



HARRISON'S

Pulmonary and Critical Care Medicine

JOSEPH LOSCALZO



HARRISON'S
Pulmonary
and Critical Care
Medicine

Derived from Harrison's Principles of Internal Medicine, 17th Edition

Editors

ANTHONY S. FAUCI, MD

Chief, Laboratory of Immunoregulation;
Director, National Institute of Allergy and Infectious Diseases,
National Institutes of Health, Bethesda

DENNIS L. KASPER, MD

William Ellery Channing Professor of Medicine, Professor of
Microbiology and Molecular Genetics, Harvard Medical School;
Director, Channing Laboratory, Department of Medicine,
Brigham and Women's Hospital, Boston

DAN L. LONGO, MD

Scientific Director, National Institute on Aging,
National Institutes of Health, Bethesda and Baltimore

EUGENE BRAUNWALD, MD

Distinguished Hersey Professor of Medicine,
Harvard Medical School; Chairman, TIMI Study Group,
Brigham and Women's Hospital, Boston

STEPHEN L. HAUSER, MD


Robert A. Fishman Distinguished Professor and Chairman,
Department of Neurology, University of California, San Francisco

J. LARRY JAMESON, MD, PhD

Professor of Medicine;
Vice President for Medical Affairs and Lewis Landsberg Dean,
Northwestern University Feinberg School of Medicine, Chicago

JOSEPH LOSCALZO, MD, PhD

Hersey Professor of Theory and Practice of Medicine,
Harvard Medical School; Chairman, Department of Medicine;
Physician-in-Chief, Brigham and Women's Hospital, Boston



HARRISON'S Pulmonary and Critical Care Medicine

Editor

Joseph Loscalzo, MD, PhD

Hersey Professor of Theory and Practice of Medicine,
Harvard Medical School; Chairman, Department of Medicine;
Physician-in-Chief, Brigham and Women's Hospital, Boston

 **Medical**

New York Chicago San Francisco Lisbon London Madrid Mexico City
Milan New Delhi San Juan Seoul Singapore Sydney Toronto

Copyright © 2010 by The McGraw-Hill Companies, Inc. All rights reserved. Except as permitted under the United States Copyright Act of 1976, no part of this publication may be reproduced or distributed in any form or by any means, or stored in a database or retrieval system, without the prior written permission of the publisher.

ISBN: 978-0-07-166338-0

MHID: 0-07-166338-X

The material in this eBook also appears in the print version of this title: ISBN: 978-0-07-166337-3, MHID: 0-07-166337-1.

All trademarks are trademarks of their respective owners. Rather than put a trademark symbol after every occurrence of a trademarked name, we use names in an editorial fashion only, and to the benefit of the trademark owner, with no intention of infringement of the trademark. Where such designations appear in this book, they have been printed with initial caps.

McGraw-Hill eBooks are available at special quantity discounts to use as premiums and sales promotions, or for use in corporate training programs. To contact a representative please e-mail us at bulksales@mcgraw-hill.com.

TERMS OF USE

This is a copyrighted work and The McGraw-Hill Companies, Inc. (“McGrawHill”) and its licensors reserve all rights in and to the work. Use of this work is subject to these terms. Except as permitted under the Copyright Act of 1976 and the right to store and retrieve one copy of the work, you may not decompile, disassemble, reverse engineer, reproduce, modify, create derivative works based upon, transmit, distribute, disseminate, sell, publish or sublicense the work or any part of it without McGraw-Hill’s prior consent. You may use the work for your own noncommercial and personal use; any other use of the work is strictly prohibited. Your right to use the work may be terminated if you fail to comply with these terms.

THE WORK IS PROVIDED “AS IS.” MCGRAW-HILL AND ITS LICENSORS MAKE NO GUARANTEES OR WARRANTIES AS TO THE ACCURACY, ADEQUACY OR COMPLETENESS OF OR RESULTS TO BE OBTAINED FROM USING THE WORK, INCLUDING ANY INFORMATION THAT CAN BE ACCESSED THROUGH THE WORK VIA HYPERLINK OR OTHERWISE, AND EXPRESSLY DISCLAIM ANY WARRANTY, EXPRESS OR IMPLIED, INCLUDING BUT NOT LIMITED TO IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. McGraw-Hill and its licensors do not warrant or guarantee that the functions contained in the work will meet your requirements or that its operation will be uninterrupted or error free. Neither McGraw-Hill nor its licensors shall be liable to you or anyone else for any inaccuracy, error or omission, regardless of cause, in the work or for any damages resulting therefrom. McGraw-Hill has no responsibility for the content of any information accessed through the work. Under no circumstances shall McGraw-Hill and/or its licensors be liable for any indirect, incidental, special, punitive, consequential or similar damages that result from the use of or inability to use the work, even if any of them has been advised of the possibility of such damages. This limitation of liability shall apply to any claim or cause whatsoever whether such claim or cause arises in contract, tort or otherwise.

CONTENTS

Contributors	vii
Preface	xi

SECTION I

DIAGNOSIS OF RESPIRATORY DISORDERS

1 Approach to the Patient with Disease of the Respiratory System	2
<i>David A. Lipson, Steven E. Weinberger</i>	
2 Dyspnea and Pulmonary Edema	7
<i>Richard M. Schwartzstein</i>	
3 Cough and Hemoptysis	14
<i>Steven E. Weinberger, David A. Lipson</i>	
4 Hypoxia and Cyanosis	20
<i>Eugene Braunwald</i>	
5 Disturbances of Respiratory Function	25
<i>Steven E. Weinberger, Ilene M. Rosen</i>	
6 Diagnostic Procedures in Respiratory Disease	36
<i>Scott Manaker, Steven E. Weinberger</i>	
7 Atlas of Chest Imaging	41
<i>Patricia A. Kritek, John J. Reilly, Jr.</i>	

SECTION II

DISEASES OF THE RESPIRATORY SYSTEM

8 Asthma	60
<i>Peter J. Barnes</i>	
9 Hypersensitivity Pneumonitis and Pulmonary Infiltrates with Eosinophilia	79
<i>Joel N. Kline, Gary W. Hunninghake</i>	
10 Environmental Lung Disease	86
<i>Frank E. Speizer, John R. Balmes</i>	
11 Pneumonia	99
<i>Lionel A. Mandell, Richard Wunderink</i>	
12 Tuberculosis	115
<i>Mario C. Raviglione, Richard J. O'Brien</i>	
13 Influenza	139
<i>Raphael Dolin</i>	

14 Common Viral Respiratory Infections and Severe Acute Respiratory Syndrome (SARS)	149
<i>Raphael Dolin</i>	
15 <i>Pneumocystis</i> Infection	161
<i>A. George Smulian, Peter D. Walzer</i>	
16 Bronchiectasis and Lung Abscess	166
<i>Gregory Tino, Steven E. Weinberger</i>	
17 Cystic Fibrosis	172
<i>Richard C. Boucher, Jr.</i>	
18 Chronic Obstructive Pulmonary Disease	178
<i>John J. Reilly, Jr., Edwin K. Silverman, Steven D. Shapiro</i>	
19 Interstitial Lung Diseases	190
<i>Talmadge E. King, Jr.</i>	
20 Deep Venous Thrombosis and Pulmonary Thromboembolism	204
<i>Samuel Z. Goldhaber</i>	
21 Disorders of the Pleura and Mediastinum	215
<i>Richard W. Light</i>	
22 Disorders of Ventilation	221
<i>Eliot A. Phillipson</i>	
23 Sleep Apnea	228
<i>Neil J. Douglas</i>	
24 Lung Transplantation	233
<i>Elbert P. Trulock</i>	
25 Infections in Lung Transplant Recipients	239
<i>Robert Finberg, Joyce Fingerth</i>	

SECTION III

GENERAL APPROACH TO THE CRITICALLY ILL PATIENT

26 Principles of Critical Care Medicine	246
<i>John P. Kress, Jesse B. Hall</i>	
27 Mechanical Ventilatory Support	258
<i>Edward P. Ingenuito</i>	
28 Approach to the Patient with Shock	266
<i>Ronald V. Maier</i>	

SECTION IV
**COMMON CRITICAL ILLNESSES
 AND SYNDROMES**

- 29** Severe Sepsis and Septic Shock. 278
Robert S. Munford
- 30** Acute Respiratory Distress Syndrome. 290
Bruce D. Levy, Steven D. Shapiro
- 31** Cardiogenic Shock and Pulmonary Edema 297
Judith S. Hochman, David H. Ingbar
- 32** Cardiovascular Collapse, Cardiac Arrest, and
 Sudden Cardiac Death. 306
Robert J. Myerburg, Agustin Castellanos
- 33** Unstable Angina and Non–ST-Elevation
 Myocardial Infarction 316
Christopher P. Cannon, Eugene Braunwald
- 34** ST-Segment Elevation Myocardial Infarction . . . 324
Elliott M. Antman, Eugene Braunwald
- 35** Coma 343
Allan H. Ropper
- 36** Neurologic Critical Care, Including Hypoxic–
 Ischemic Encephalopathy and Subarachnoid
 Hemorrhage 353
J. Claude Hemphill, III, Wade S. Smith

SECTION V
**DISORDERS COMPLICATING CRITICAL
 ILLNESSES AND THEIR MANAGEMENT**

- 37** Acute Renal Failure 370
Kathleen D. Liu, Glenn M. Chertow

- 38** Dialysis in the Treatment of Renal Failure. 386
Kathleen D. Liu, Glenn M. Chertow
- 39** Fluid and Electrolyte Disturbances 393
Gary G. Singer, Barry M. Brenner
- 40** Acidosis and Alkalosis 410
Thomas D. DuBose, Jr.
- 41** Coagulation Disorders 424
Valder Arruda, Katherine A. High
- 42** Treatment and Prophylaxis
 of Bacterial Infections 434
Gordon L. Archer, Ronald E. Polk
- 43** Antiviral Chemotherapy, Excluding
 Antiretroviral Drugs 456
Lindsey R. Baden, Raphael Dolin
- 44** Diagnosis and Treatment of
 Fungal Infections. 470
John E. Edwards, Jr.
- 45** Oncologic Emergencies. 475
Rasim Gucalp, Janice P. Dutcher
- Appendix**
 Laboratory Values of Clinical Importance 491
Alexander Kratz, Michael A. Pesce, Daniel J. Fink
- Review and Self-Assessment** 513
*Charles Wiener, Gerald Bloomfield,
 Cynthia D. Brown, Joshua Schiffer, Adam Spivak*
- Index**. 555

CONTRIBUTORS

Numbers in brackets refer to the chapter(s) written or co-written by the contributor.

GORDON L. ARCHER, MD

Professor of Medicine and Microbiology/Immunology; Associate Dean for Research, School of Medicine, Virginia Commonwealth University, Richmond [42]

VALDER ARRUDA, MD, PhD

Associate Professor of Pediatrics, University of Pennsylvania School of Medicine, Division of Hematology, The Children's Hospital of Philadelphia, Philadelphia [41]

LINDSEY R. BADEN, MD

Assistant Professor of Medicine, Harvard Medical School, Boston [43]

JOHN R. BALMES, MD

Professor of Medicine, University of California, San Francisco; Chief, Division of Occupational and Environmental Medicine, San Francisco General Hospital; Professor of Environmental Health Sciences, School of Public Health, University of California, Berkeley [10]

PETER J. BARNES, MA, DM, DSc

Professor and Head of Thoracic Medicine, National Heart & Lung Institute; Head of Respiratory Medicine, Imperial College London; Honorary Consultant Physician, Royal Brompton Hospital, London [8]

GERALD BLOOMFIELD, MD, MPH

Department of Internal Medicine, The Johns Hopkins University School of Medicine, Baltimore [Review and Self-Assessment]

RICHARD C. BOUCHER, JR., MD

William Rand Kenan Professor of Medicine, University of North Carolina at Chapel Hill; Director, University of Carolina Cystic Fibrosis Center, Chapel Hill [17]

EUGENE BRAUNWALD, MD, MA (Hon), ScD (Hon)

Distinguished Hersey Professor of Medicine, Harvard Medical School; Chairman, TIMI Study Group, Brigham and Women's Hospital, Boston [4, 33, 34]

BARRY M. BRENNER, MD, AM, DSc (Hon), DMSc (Hon), Dipl (Hon)

Samuel A. Levine Professor of Medicine, Harvard Medical School; Director Emeritus, Renal Division, Brigham and Women's Hospital, Boston [39]

CYNTHIA D. BROWN, MD

Department of Internal Medicine, The Johns Hopkins University School of Medicine, Baltimore [Review and Self-Assessment]

CHRISTOPHER P. CANNON, MD

Associate Professor of Medicine, Harvard Medical School; Associate Physician, Cardiovascular Division, Senior Investigator, TIMI Study Group, Brigham and Women's Hospital, Boston [33, 34]

AGUSTIN CASTELLANOS, MD

Professor of Medicine; Director, Clinical Electrophysiology, University of Miami Miller School of Medicine, Miami [32]

GLENN M. CHERTOW, MD

Professor of Medicine, Epidemiology and Biostatistics, University of California, San Francisco School of Medicine; Director, Clinical Services, Division of Nephrology, University of California, San Francisco Medical Center, San Francisco [37, 38]

RAPHAEL DOLIN, MD

Maxwell Finland Professor of Medicine (Microbiology and Molecular Genetics); Dean for Academic and Clinical Programs, Harvard Medical School, Boston [13, 14, 43]

NEIL J. DOUGLAS, MD

Professor of Respiratory and Sleep Medicine, University of Edinburgh; Honorary Consultant Physician, Royal Infirmary of Edinburgh, United Kingdom [23]

THOMAS D. DuBOSE, JR., MD

Tinsley R. Harrison Professor and Chair of Internal Medicine; Professor of Physiology and Pharmacology, Wake Forest University School of Medicine, Winston-Salem [40]

JANICE P. DUTCHER, MD

Professor, New York Medical College; Associate Director, Our Lady of Mercy Cancer Center, Bronx [45]

JOHN E. EDWARDS, JR., MD

Chief, Division of Infectious Diseases, Harbor/University of California, Los Angeles Medical Center; Professor of Medicine, David Geffen School of Medicine at the University of California, Los Angeles, Torrance [44]

ROBERT FINBERG, MD

Professor and Chair, Department of Medicine, University of Massachusetts Medical School, Worcester [25]

JOYCE FINGEROTH, MD

Associate Professor of Medicine, Harvard Medical School, Boston [25]

DANIEL J. FINK,[†] MD, MPH

Associate Professor of Clinical Pathology, College of Physicians and Surgeons, Columbia University, New York [Appendix]

SAMUEL Z. GOLDBABER, MD

Professor of Medicine, Harvard Medical School; Director, Venous Thromboembolism Research Group, Director, Anticoagulation Service, and Senior Staff Cardiologist, Department of Medicine, Brigham and Women's Hospital, Boston [20]

RASIM GUCALP, MD

Professor of Clinical Medicine, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx [45]

[†]Deceased.

JESSE B. HALL, MD

Professor of Medicine, Anesthesia & Critical Care; Section Chief, Pulmonary and Critical Care Medicine, University of Chicago, Chicago [26]

J. CLAUDE HEMPHILL, III, MD, MAS

Associate Professor of Clinical Neurology and Neurological Surgery, University of California, San Francisco; Director, Neurocritical Care Program, San Francisco General Hospital, San Francisco [36]

KATHERINE A. HIGH, MD

William H. Bennett Professor of Pediatrics, University of Pennsylvania School of Medicine; Investigator, Howard Hughes Medical Institute, The Children's Hospital of Philadelphia, Philadelphia [41]

JUDITH S. HOCHMAN, MD

Harold Synder Family Professor of Cardiology; Clinical Chief, the Leon H. Charney Division of Cardiology; New York University School of Medicine; Director, Cardiovascular Clinical Research, New York [31]

GARY W. HUNNINGHAKE, MD

Sterba Professor of Medicine; Director, Division of Pulmonary, Critical Care and Occupational Medicine; Director, Institute for Clinical and Translational Science; Director, Graduate Program in Translational Biomedicine; Senior Associate Dean for Clinical and Translational Science, Iowa City [9]

DAVID H. INGBAR, MD

Professor of Medicine, Physiology & Pediatrics; Director, Pulmonary, Allergy, Critical Care & Sleep Division; Executive Director, Center for Lung Science & Health, University of Minnesota School of Medicine; Co-Director, Medical ICU & Respiratory Care, University of Minnesota Medical Center, Fairview [31]

EDWARD P. INGENITO, MD, PhD

Assistant Professor, Harvard Medical School, Boston [27]

TALMADGE E. KING, JR., MD

Constance B. Wofsy Distinguished Professor and Interim Chair, Department of Medicine, University of California, San Francisco, San Francisco [19]

JOEL N. KLINE, MD, MSC

Professor, Internal Medicine and Occupational & Environmental Health; Director, University of Iowa Asthma Center, Iowa City [9]

ALEXANDER KRATZ, MD, PhD, MPH

Assistant Professor of Clinical Pathology, Columbia University College of Physicians and Surgeons; Associate Director, Core Laboratory, Columbia University Medical Center, New York-Presbyterian Hospital; Director, Allen Pavilion Laboratory, New York [Appendix]

JOHN P. KRESS, MD

Associate Professor of Medicine, Section of Pulmonary and Critical Care, University of Chicago, Chicago [26]

PATRICIA A. KRITEK, MD, EdM

Instructor in Medicine, Harvard Medical School; Co-Director, Harvard Pulmonary and Critical Care Medicine Fellowship, Brigham and Women's Hospital, Boston [7]

BRUCE D. LEVY, MD

Associate Professor of Medicine, Harvard Medical School; Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston [30]

RICHARD W. LIGHT, MD

Professor of Medicine, Vanderbilt University, Nashville [21]

DAVID A. LIPSON, MD

Assistant Professor of Medicine, Pulmonary, Allergy & Critical Care Division, University of Pennsylvania Medical Center, King of Prussia [1, 3]

KATHLEEN D. LIU, MD, PhD, MCR

Assistant Professor, Division of Nephrology, San Francisco [37, 38]

RONALD V. MAIER, MD

Jane and Donald D. Trunkey Professor and Vice Chair, Surgery, University of Washington; Surgeon-in-Chief, Harborview Medical Center, Seattle [28]

SCOTT MANAKER, MD, PhD

Associate Professor of Medicine and Pharmacology, Pulmonary and Critical Care Division, Department of Medicine, University of Pennsylvania, Philadelphia [6]

LIONEL A. MANDELL, MD

Professor of Medicine, McMaster University, Hamilton, Ontario [11]

ROBERT S. MUNFORD, MD

Jan and Henri Bromberg Chair in Internal Medicine, University of Texas Southwestern Medical Center, Dallas [29]

ROBERT J. MYERBURG, MD

Professor of Medicine and Physiology; AHA Chair in Cardiovascular Research, University of Miami Miller School of Medicine, Miami [32]

RICHARD J. O'BRIEN, MD

Head of Scientific Evaluation, Foundation for Innovative New Diagnostics, Geneva, Switzerland [12]

MICHAEL A. PESCE, PhD

Clinical Professor of Pathology, Columbia University College of Physicians and Surgeons; Director of Specialty Laboratory, New York Presbyterian Hospital, Columbia University Medical Center, New York [Appendix]

ELIOT A. PHILLIPSON, MD

Professor, Department of Medicine, University of Toronto, Toronto [22]

RONALD E. POLK, PharmD

Chair, Department of Pharmacy, Professor of Pharmacy and Medicine, School of Pharmacy, Virginia Commonwealth University, Richmond [42]

MARIO C. RAVIGLIONE, MD

Director, Stop TB Department, World Health Organization, Geneva [12]

JOHN J. REILLY, JR., MD

Associate Professor of Medicine, Harvard Medical School; Vice Chairman, Integrative Services, Department of Medicine, Brigham and Women's Hospital, Boston [7, 18]

ALLAN H. ROPPER, MD

Executive Vice-Chair, Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston [35]

ILENE M. ROSEN, MD, MSC

Associate Director, Internal Medical Residency Program; Assistant Professor of Clinical Medicine, University of Pennsylvania School of Medicine, Philadelphia [5]

JOSHUA SCHIFFER, MD

Department of Internal Medicine, The Johns Hopkins University School of Medicine, Baltimore [Review and Self-Assessment]

RICHARD M. SCHWARTZSTEIN, MD

Professor of Medicine, Harvard Medical School; Associate Chair, Pulmonary and Critical Care Medicine; Vice-President for Education, Beth Israel Deaconess Medical Center, Boston [2]

STEVEN D. SHAPIRO, MD

Jack D. Myers Professor and Chair, University of Pittsburgh, Pittsburgh [18, 30]

EDWIN K. SILVERMAN, MD, PhD

Associate Professor of Medicine, Harvard Medical School, Brigham and Women's Hospital, Boston [18]

GARY G. SINGER, MD

Assistant Professor of Clinical Medicine, Washington University School of Medicine, St. Louis [39]

WADE S. SMITH, MD, PhD

Professor of Neurology, Daryl R. Gress Endowed Chair of Neurocritical Care and Stroke; Director, University of California, San Francisco Neurovascular Service, San Francisco [36]

A. GEORGE SMULIAN, MB, BCh

Associate Professor, University of Cincinnati College of Medicine; Chief, Infectious Disease Section, Cincinnati VA Medical Center, Cincinnati [15]

FRANK E. SPEIZER, MD

Edward H. Kass Professor of Medicine, Harvard Medical School, Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Boston [10]

ADAM SPIVAK, MD

Department of Internal Medicine, The Johns Hopkins University School of Medicine, Baltimore [Review and Self-Assessment]

GREGORY TINO, MD

Associate Professor of Medicine, University of Pennsylvania School of Medicine; Chief, Pulmonary Clinical Service Hospital of the University of Pennsylvania, Philadelphia [16]

ELBERT P. TRULOCK, MD

Professor of Medicine, Rosemary and I. Jerome Flance Professor of Pulmonary Medicine, Washington University School of Medicine, St. Louis [24]

PETER D. WALZER, MD, MSC

Associate Chief of Staff for Research, Cincinnati VA Medical Center; Professor of Medicine, University of Cincinnati College of Medicine, Cincinnati [15]

STEVEN E. WEINBERGER, MD

Senior Vice President for Medical Education Division, American College of Physicians; Senior Lecturer on Medicine, Harvard Medical School; Adjunct Professor of Medicine, University of Pennsylvania School of Medicine, Philadelphia [1, 3, 5, 6, 16]

CHARLES WIENER, MD

Professor of Medicine and Physiology; Vice Chair, Department of Medicine; Director, Osler Medical Training Program, The Johns Hopkins University School of Medicine, Baltimore [Review and Self-Assessment]

RICHARD WUNDERINK, MD

Professor, Division of Pulmonary and Critical Care, Department of Medicine, Northwestern University Feinberg School of Medicine; Director, Medical Intensive Care Unit, Northwestern Memorial Hospital, Chicago [11]

This page intentionally left blank

PREFACE

Pulmonary diseases are major contributors to morbidity and mortality in the general population. Although advances in the diagnosis and treatment of many common pulmonary disorders have improved the lives of patients, these complex illnesses continue to affect a large segment of the global population. The impact of cigarette smoking cannot be underestimated in this regard, especially given the growing prevalence of tobacco use in the developing world. Pulmonary medicine is, therefore, of critical global importance to the field of internal medicine.

Pulmonary medicine is a growing subspecialty and includes a number of areas of disease focus, including reactive airways diseases, chronic obstructive lung disease, environmental lung diseases, and interstitial lung diseases. Furthermore, pulmonary medicine is linked to the field of critical care medicine, both cognitively and as a standard arm of the pulmonary fellowship training programs at most institutions. The breadth of knowledge in critical care medicine extends well beyond the respiratory system, of course, and includes selected areas of cardiology, infectious diseases, nephrology, and hematology. Given the complexity of these disciplines and the crucial role of the internist in guiding the management of patients with chronic lung diseases and in helping to guide the management of patients in the intensive care setting, knowledge of the discipline is essential for competency in the field of internal medicine.

The scientific basis of many pulmonary disorders and intensive care medicine is rapidly expanding. Novel diagnostic and therapeutic approaches, as well as prognostic assessment strategies, populate the published literature with great frequency. Maintaining updated knowledge of these evolving areas is, therefore, essential for the optimal care of patients with lung diseases and critical illness.

In view of the importance of pulmonary and critical care medicine to the field of internal medicine and the speed with which the scientific basis of the discipline is evolving, this *Sectional* was developed. The purpose of this book is to provide the readers with an overview of the field of pulmonary and critical care medicine. To achieve this end, this *Sectional* comprises the key pulmonary and critical care medicine chapters in *Harrison's Principles of Internal Medicine*, 17th edition, contributed by leading experts in the fields. This *Sectional* is designed not only for physicians-in-training, but also for medical students, practicing clinicians, and other health care professionals who seek to maintain adequately updated knowledge of this rapidly advancing field. The editors believe that this book will improve the reader's knowledge of the discipline, as well as highlight its importance to the field of internal medicine.

Joseph Loscalzo, MD, PhD

NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example, and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

Review and self-assessment questions and answers were taken from Wiener C, Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalzo J (editors) Bloomfield G, Brown CD, Schiffer J, Spivak A (contributing editors). *Harrison's Principles of Internal Medicine Self-Assessment and Board Review*, 17th ed. New York, McGraw-Hill, 2008, ISBN 978-0-07-149619-3.



The globe icons call greater attention to key epidemiologic and clinical differences in the practice of medicine throughout the world.



The genetic icons identify a clinical issue with an explicit genetic relationship.

SECTION I

DIAGNOSIS OF RESPIRATORY DISORDERS





CHAPTER 1

APPROACH TO THE PATIENT WITH DISEASE OF THE RESPIRATORY SYSTEM

David A. Lipson ■ Steven E. Weinberger

Clinical Presentation	2
Integration of the Presenting Clinical Pattern and	5
Diagnostic Studies	
■ Further Readings	6

Patients with disease of the respiratory system generally present because of symptoms, an abnormality on a chest radiograph, or both. These findings often lead to a set of diagnostic possibilities; the differential diagnosis is then refined on the basis of additional information gleaned from the history and physical examination, pulmonary function testing, additional imaging studies, and bronchoscopic examination. This chapter considers the approach to the patient based on the major patterns of presentation, focusing on the history, physical examination, and chest radiography. For further discussion of pulmonary function testing, see Chap. 5, and of other diagnostic studies, see Chap. 6.

CLINICAL PRESENTATION

History

Dyspnea (shortness of breath) and cough are nonspecific but common presenting symptoms for patients with respiratory system disease. Less common symptoms include hemoptysis (the coughing up of blood) and chest pain that often is pleuritic in nature.

■ Dyspnea

(See also Chap. 2.) When evaluating a patient with shortness of breath, one should first determine the time course over which the symptom has become manifest. Patients who were well previously and developed *acute* shortness of breath (over a period of minutes to days) may have acute disease affecting either the upper or the

intrathoracic airways (e.g., laryngeal edema or acute asthma, respectively), the pulmonary parenchyma (acute cardiogenic or noncardiogenic pulmonary edema or an acute infectious process such as bacterial pneumonia), the pleural space (a pneumothorax), or the pulmonary vasculature (a pulmonary embolus).

A *subacute* presentation (over days to weeks) may suggest an exacerbation of preexisting airways disease (asthma or chronic bronchitis), an indolent parenchymal infection (*Pneumocystis jiroveci* pneumonia in a patient with AIDS, mycobacterial or fungal pneumonia), a non-infectious inflammatory process that proceeds at a relatively slow pace (Wegener's granulomatosis, eosinophilic pneumonia, cryptogenic organizing pneumonia, and many others), neuromuscular disease (Guillain-Barré syndrome, myasthenia gravis), pleural disease (pleural effusion from a variety of possible causes), or chronic cardiac disease (congestive heart failure).

A *chronic* presentation (over months to years) often indicates chronic obstructive lung disease, chronic interstitial lung disease, or chronic cardiac disease. Chronic diseases of airways (not only chronic obstructive lung disease but also asthma) are characterized by exacerbations and remissions. Patients often have periods when they are severely limited by shortness of breath, but these may be interspersed with periods in which their symptoms are minimal or absent. In contrast, many of the diseases of the pulmonary parenchyma are characterized by slow but inexorable progression. Chronic respiratory symptoms may also be multifactorial in nature

because patients with chronic obstructive pulmonary disease may also have concomitant heart disease.

Other Respiratory Symptoms

Cough (Chap. 3) may indicate the presence of lung disease, but cough per se is not useful for the differential diagnosis. The presence of sputum accompanying the cough often suggests airway disease and may be seen in patients with asthma, chronic bronchitis, or bronchiectasis.

Hemoptysis (Chap. 3) can originate from disease of the airways, the pulmonary parenchyma, or the vasculature. Diseases of the airways can be inflammatory (acute or chronic bronchitis, bronchiectasis, or cystic fibrosis) or neoplastic (bronchogenic carcinoma or bronchial carcinoma tumors). Parenchymal diseases causing hemoptysis may be either localized (pneumonia, lung abscess, tuberculosis, or infection with *Aspergillus* spp.) or diffuse (Goodpasture's syndrome, idiopathic pulmonary hemosiderosis). Vascular diseases potentially associated with hemoptysis include pulmonary thromboembolic disease and pulmonary arteriovenous malformations.

Chest pain caused by diseases of the respiratory system usually originates from involvement of the parietal pleura. As a result, the pain is accentuated by respiratory motion and is often referred to as *pleuritic*. Common examples include primary pleural disorders, such as neoplasm or inflammatory disorders involving the pleura, or pulmonary parenchymal disorders that extend to the pleural surface, such as pneumonia or pulmonary infarction.

Additional Historic Information

Information about risk factors for lung disease should be explicitly explored to ensure a complete basis of historic data. A history of current and past smoking, especially of cigarettes, should be sought from all patients. The smoking history should include the number of years of smoking; the intensity (i.e., number of packs per day); and if the patient no longer smokes, the interval since smoking cessation. The risk of lung cancer decreases progressively in the decade after discontinuation of smoking, and loss of lung function above the expected age-related decline ceases with the discontinuation of smoking. Even though chronic obstructive lung disease and neoplasia are the two most important respiratory complications of smoking, other respiratory disorders (e.g., spontaneous pneumothorax, respiratory bronchiolitis-interstitial lung disease, pulmonary Langerhans cell histiocytosis, and pulmonary hemorrhage with Goodpasture's syndrome) are also associated with smoking. A history of significant secondhand (passive) exposure to smoke, whether in the home or at the workplace, should also be sought because it may be a risk factor for neoplasia or an exacerbating factor for airways disease.

A patient may have been exposed to other inhaled agents associated with lung disease, which act either via direct toxicity or through immune mechanisms (Chaps. 9

and 10). Such exposures can be either occupational or avocational, indicating the importance of detailed occupational and personal histories, the latter stressing exposures related to hobbies or the home environment. Important agents include the inorganic dusts associated with pneumoconiosis (especially asbestos and silica dusts) and organic antigens associated with hypersensitivity pneumonitis (especially antigens from molds and animal proteins). Asthma, which is more common in women than men, is often exacerbated by exposure to environmental allergens (dust mites, pet dander, or cockroach allergens in the home or allergens in the outdoor environment such as pollen and ragweed) or may be caused by occupational exposures (diisocyanates). Exposure to particular infectious agents can be suggested by contacts with individuals with known respiratory infections (especially tuberculosis) or by residence in an area with endemic pathogens (histoplasmosis, coccidioidomycosis, blastomycosis).

A history of coexisting nonrespiratory disease or of risk factors for or previous treatment of such diseases should be sought because they may predispose a patient to both infectious and noninfectious respiratory system complications. Common examples include systemic rheumatic diseases that are associated with pleural or parenchymal lung disease, metastatic neoplastic disease in the lung, or impaired host defense mechanisms and secondary infection, which occur in the case of immunoglobulin deficiency or with hematologic and lymph node malignancies. Risk factors for AIDS should be sought because the lungs are not only the most common site of AIDS-defining infection but may also be involved by noninfectious complications of AIDS. Treatment of patients with nonrespiratory disease may be associated with respiratory complications, either because of effects on host defense mechanisms (immunosuppressive agents, cancer chemotherapy) with resulting infection or because of direct effects on the pulmonary parenchyma (cancer chemotherapy; radiation therapy; or treatment with other agents, such as amiodarone) or on the airways (beta-blocking agents causing airflow obstruction, angiotensin-converting enzyme inhibitors causing cough) (Chap. 9).

Family history is important for evaluating diseases that have a genetic component. These include disorders such as cystic fibrosis, α_1 -antitrypsin deficiency, pulmonary hypertension, pulmonary fibrosis, and asthma.

Physical Examination

The general principles of inspection, palpation, percussion, and auscultation apply to the examination of the respiratory system. However, the physical examination should be directed not only toward ascertaining abnormalities of the lungs and thorax but also toward recognizing other findings that may reflect underlying lung disease.

4 On *inspection*, the rate and pattern of breathing as well as the depth and symmetry of lung expansion are observed. Breathing that is unusually rapid, labored, or associated with the use of accessory muscles of respiration generally indicates either augmented respiratory demands or an increased work of breathing. Asymmetric expansion of the chest is usually caused by an asymmetric process affecting the lungs, such as endobronchial obstruction of a large airway, unilateral parenchymal or pleural disease, or unilateral phrenic nerve paralysis. Visible abnormalities of the thoracic cage include kyphoscoliosis and ankylosing spondylitis, either of which may alter compliance of the thorax, increase the work of breathing, and cause dyspnea.

On *palpation*, the symmetry of lung expansion can be assessed, generally confirming the findings observed by inspection. Vibration produced by spoken sounds is transmitted to the chest wall and is assessed by the presence or absence and symmetry of tactile fremitus. Transmission of vibration is decreased or absent if pleural liquid is interposed between the lung and the chest wall or if an endobronchial obstruction alters sound transmission. In contrast, transmitted vibration may increase over an area of underlying pulmonary consolidation. Palpation may also reveal focal tenderness, as seen with costochondritis or rib fracture.

The relative resonance or dullness of the tissue underlying the chest wall is assessed by *percussion*. The normal sound of the underlying air-containing lung is resonant. In contrast, consolidated lung or a pleural effusion sounds dull, and emphysema or air in the pleural space results in a hyperresonant percussion note.

On *auscultation* of the lungs, the examiner listens for both the quality and intensity of the breath sounds and for the presence of extra, or adventitious, sounds. Normal breath sounds heard through the stethoscope at the periphery of the lung are described as *vesicular breath sounds*, in which inspiration is louder and longer than expiration. If sound transmission is impaired by endobronchial obstruction or by air or liquid in the pleural space, breath sounds are diminished in intensity or absent. When sound transmission is improved through consolidated lung, the resulting *bronchial breath sounds* have a more tubular quality and a more pronounced expiratory phase. Sound transmission can also be assessed by listening to spoken or whispered sounds; when these are transmitted through consolidated lung, *bronchophony* and *whispered pectoriloquy*, respectively, are present. The sound of a spoken E becomes more like an A, although with a nasal or bleating quality, a finding that is termed *egophony*.

The primary adventitious (abnormal) sounds that can be heard include crackles (rales), wheezes, and rhonchi. *Crackles* are the discontinuous, typically inspiratory sound created when alveoli and small airways open and close with respiration. They are often associated with

interstitial lung disease, microatelectasis, or filling of alveoli by liquid. *Wheezes*, which are generally more prominent during expiration than inspiration, reflect the oscillation of airway walls that occurs when there is air-flow limitation, as may be produced by bronchospasm, airway edema or collapse, or intraluminal obstruction by neoplasm or secretions. *Rhonchi* is the term applied to the sounds created when free liquid or mucus is present in the airway lumen; the viscous interaction between the free liquid and the moving air creates a low-pitched vibratory sound. Other adventitious sounds include pleural friction rubs and stridor. The gritty sound of a *pleural friction rub* indicates inflamed pleural surfaces rubbing against each other, often during both inspiratory and expiratory phases of the respiratory cycle. *Stridor*, which occurs primarily during inspiration, represents flow through a narrowed upper airway, as occurs in an infant with croup.

A summary of the patterns of physical findings on pulmonary examination in common types of respiratory system disease is shown in [Table 1-1](#).

A meticulous *general physical examination* is mandatory in patients with disorders of the respiratory system. Enlarged lymph nodes in the cervical and supraclavicular regions should be sought. Disturbances of mentation or even coma may occur in patients with acute carbon dioxide retention and hypoxemia. Telltale stains on the fingers point to heavy cigarette smoking; infected teeth and gums may occur in patients with aspiration pneumonia and lung abscess.

Clubbing of the digits may be found in patients with lung cancer; interstitial lung disease; and chronic infections in the thorax, such as bronchiectasis, lung abscess, and empyema. Clubbing may also be seen with congenital heart disease associated with right-to-left shunting and with a variety of chronic inflammatory or infectious diseases, such as inflammatory bowel disease and endocarditis. A number of systemic diseases, such as systemic lupus erythematosus, scleroderma, and rheumatoid arthritis, may be associated with pulmonary complications, even though their primary clinical manifestations and physical findings are not primarily related to the lungs. Conversely, patients with other diseases that most commonly affect the respiratory system, such as sarcoidosis, may have findings on physical examination not related to the respiratory system, including ocular findings (uveitis, conjunctival granulomas) and skin findings (erythema nodosum, cutaneous granulomas).

Chest Radiography

Chest radiography is often the initial diagnostic study performed to evaluate patients with respiratory symptoms, but it may also provide the initial evidence of disease in patients who are free of symptoms. Perhaps the most common example of the latter situation is the

TABLE 1-1**TYPICAL CHEST EXAMINATION FINDINGS IN SELECTED CLINICAL CONDITIONS**

CONDITION	PERCUSSION	FREMITUS	BREATH SOUNDS	VOICE TRANSMISSION	ADVENTITIOUS SOUNDS
Normal	Resonant	Normal	Vesicular (at lung bases)	Normal	Absent
Consolidation or atelectasis (with patent airway)	Dull	Increased	Bronchial	Bronchophony, whispered pectoriloquy, egophony	Crackles
Consolidation or atelectasis (with blocked airway)	Dull	Decreased	Decreased	Decreased	Absent
Asthma	Resonant	Normal	Vesicular	Normal	Wheezing
Interstitial lung disease	Resonant	Normal	Vesicular	Normal	Crackles
Emphysema	Hyperresonant	Decreased	Decreased	Decreased	Absent or wheezing
Pneumothorax	Hyperresonant	Decreased	Decreased	Decreased	Absent
Pleural effusion	Dull	Decreased	Decreased ^a	Decreased ^a	Absent or pleural friction rub

^aMay be altered by collapse of underlying lung, which increases transmission of sound.

Source: Adapted from Weinberger, with permission.

finding of one or more nodules or masses when radiography is performed for a reason other than evaluation of respiratory symptoms.

A number of diagnostic possibilities are often suggested by the radiographic pattern (Chap. 7). A localized region of opacification involving the pulmonary parenchyma may be described as a nodule (usually <3 cm in diameter), a mass (usually ≥3 cm in diameter), or an infiltrate. Diffuse disease with increased opacification is usually characterized as having an alveolar, interstitial, or nodular pattern. In contrast, increased radiolucency may be localized, as seen with a cyst or bulla, or generalized, as occurs with emphysema. Chest radiography is also particularly useful for the detection of pleural disease, especially if manifested by the presence of air or liquid in the pleural space. An abnormal appearance of the hila or the mediastinum may suggest a mass or enlargement of lymph nodes.

A summary of representative diagnoses suggested by these common radiographic patterns is presented in [Table 1-2](#), and an atlas of chest radiography and other chest images can be found in Chap. 7.

Additional Diagnostic Evaluation

Further information for clarification of radiographic abnormalities is frequently obtained with CT scanning of the chest (see Figs. 6-1, 6-2, 19-1, 19-2, 30-3). This technique is more sensitive than plain radiography in detecting subtle abnormalities and can suggest specific diagnoses based on the pattern of abnormality.

For further discussion of the use of other imaging studies, including MRI, scintigraphic studies, ultrasonography, and angiography, see Chap. 6.

Alteration in the function of the lungs as a result of respiratory system disease is assessed objectively by pulmonary function tests, and effects on gas exchange are evaluated by measurement of arterial blood gases or by oximetry (Chap. 5). As part of pulmonary function testing, quantitation of forced expiratory flow assesses the presence of obstructive physiology, which is consistent with diseases affecting the structure or function of the airways, such as asthma and chronic obstructive lung disease. Measurement of lung volumes assesses the presence of restrictive disorders seen with diseases of the pulmonary parenchyma or respiratory pump and with space-occupying processes within the pleura. Bronchoscopy is useful in some settings for visualizing abnormalities of the airways and for obtaining a variety of samples from either the airway or the pulmonary parenchyma (Chap. 6).

INTEGRATION OF THE PRESENTING CLINICAL PATTERN AND DIAGNOSTIC STUDIES

Patients with respiratory symptoms but a normal chest radiograph often have diseases affecting the airways, such as asthma or chronic obstructive pulmonary disease. However, the latter diagnosis is also commonly associated with radiographic abnormalities, such as diaphragmatic flattening, an increase in the retrosternal air space, and attenuation of vascular markings. Other disorders of the respiratory system for which the chest radiograph is normal include disorders of the respiratory pump (either the chest wall or the neuromuscular apparatus controlling the chest wall) or pulmonary circulation and occasionally interstitial lung disease. Chest examination and pulmonary

MAJOR RESPIRATORY DIAGNOSES WITH COMMON CHEST RADIOGRAPHIC PATTERNS

Solitary circumscribed density—nodule (<3 cm) or mass (≥3 cm)
 Primary or metastatic neoplasm
 Localized infection (bacterial abscess, mycobacterial or fungal infection)
 Wegener's granulomatosis (one or several nodules)
 Rheumatoid nodule (one or several nodules)
 Vascular malformation
 Bronchogenic cyst
Localized opacification (infiltrate)
 Pneumonia (bacterial, atypical, mycobacterial, or fungal infection)
 Neoplasm
 Radiation pneumonitis
 Bronchiolitis obliterans with organizing pneumonia
 Bronchocentric granulomatosis
 Pulmonary infarction
Diffuse interstitial disease
 Idiopathic pulmonary fibrosis
 Pulmonary fibrosis with systemic rheumatic disease
 Sarcoidosis
 Drug-induced lung disease
 Pneumoconiosis
 Hypersensitivity pneumonitis
 Infection (pneumocystis, viral pneumonia)
 Langerhans cell histiocytosis
Diffuse alveolar disease
 Cardiogenic pulmonary edema
 Acute respiratory distress syndrome
 Diffuse alveolar hemorrhage
 Infection (pneumocystis, viral or bacterial pneumonia)
 Sarcoidosis
Diffuse nodular disease
 Metastatic neoplasm
 Hematogenous spread of infection (bacterial, mycobacterial, fungal)
 Pneumoconiosis
 Langerhans cell histiocytosis

function tests are generally helpful in sorting out these diagnostic possibilities. Obstructive diseases associated with a normal or relatively normal chest radiograph are often characterized by findings on physical examination and pulmonary function testing that are typical for these conditions. Similarly, diseases of the respiratory pump or interstitial diseases may also be suggested by findings on physical examination or by particular patterns of restrictive disease seen on pulmonary function testing.

When respiratory symptoms are accompanied by radiographic abnormalities, diseases of the pulmonary parenchyma or the pleura are usually present. Either diffuse or localized parenchymal lung disease is generally visualized well on the radiograph, and both air and liquid in the pleural space (pneumothorax and pleural effusion, respectively) are usually readily detected by radiography.

Radiographic findings in the absence of respiratory symptoms often indicate localized disease affecting the airways or the pulmonary parenchyma. One or more nodules or masses may suggest intrathoracic malignancy, but they may also be the manifestation of a current or previous infectious process. Multiple nodules affecting only one lobe suggest an infectious cause rather than malignancy because metastatic disease would not have a predilection for only one discrete area of the lung. Patients with diffuse parenchymal lung disease on radiographic examination may be free of symptoms, as is sometimes the case in those with pulmonary sarcoidosis.

FURTHER READINGS

- AMERICAN COLLEGE OF CHEST PHYSICIANS: Diagnosis and management of cough: ACCP evidence-based clinical practice guidelines. *Chest* 129(suppl):1S, 2006
- GOODMAN L: *Felson's Principles of Chest Roentgenology. A Programmed Text*, 2d ed. Philadelphia, Saunders, 1999
- LEBLOND RF et al: *DeGowin & DeGowin's Diagnostic Examination*, 8th ed. New York, McGraw-Hill, 2004
- WEINBERGER SE: *Principles of Pulmonary Medicine*, 4th ed. Philadelphia, Saunders, 2004



CHAPTER 2

DYSPNEA AND PULMONARY EDEMA

Richard M. Schwartzstein

■ Dyspnea	7
Mechanisms of Dyspnea	7
Assessing Dyspnea	8
Differential Diagnosis	8
■ Pulmonary Edema	11
Mechanisms of Fluid Accumulation	11
■ Further Readings	12

DYSPNEA

The American Thoracic Society defines *dyspnea* as a “subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social, and environmental factors, and may induce secondary physiological and behavioral responses.” Dyspnea, a symptom, must be distinguished from the signs of increased work of breathing.

MECHANISMS OF DYSPNEA

Respiratory sensations are the consequence of interactions between the *efferent*, or outgoing, motor output from the brain to the ventilatory muscles (feed-forward) and the *afferent*, or incoming, sensory input from receptors throughout the body (feedback), as well as the integrative processing of this information that we infer must be occurring in the brain (Fig. 2-1). A given disease state may lead to dyspnea by one or more mechanisms, some of which may operate under some circumstances but not others.

Motor Efferents

Disorders of the ventilatory pump are associated with increased work of breathing or a sense of an increased effort to breathe. When the muscles are weak or fatigued, greater effort is required even though the mechanics of

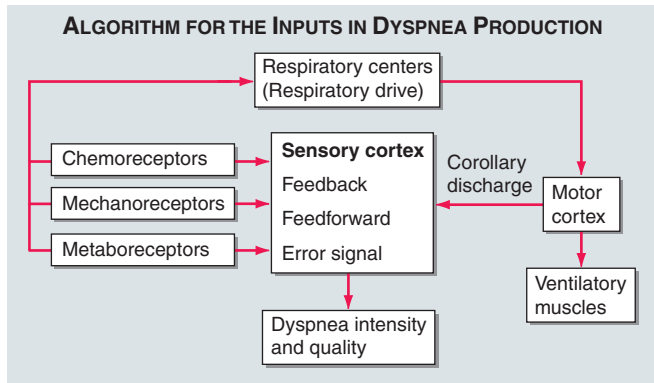
the system are normal. The increased neural output from the motor cortex is thought to be sensed because of a corollary discharge that is sent to the sensory cortex at the same time that signals are sent to the ventilatory muscles.

Sensory Afferents

Chemoreceptors in the carotid bodies and medulla are activated by hypoxemia, acute hypercapnia, and acidemia. Stimulation of these receptors, as well as others that lead to an increase in ventilation, produce a sensation of air hunger. Mechanoreceptors in the lungs, when stimulated by bronchospasm, lead to a sensation of chest tightness. J-receptors, which are sensitive to interstitial edema, and pulmonary vascular receptors, which are activated by acute changes in pulmonary artery pressure, appear to contribute to air hunger. Hyperinflation is associated with the sensation of an inability to get a deep breath or of an unsatisfying breath. It is unclear if this sensation arises from receptors in the lungs or chest wall or if it is a variant of the sensation of air hunger. Metaboreceptors, located in skeletal muscle, are believed to be activated by changes in the local biochemical milieu of the tissue active during exercise and, when stimulated, contribute to the breathing discomfort.

Integration: Efferent-Reafferent Mismatch

A discrepancy or mismatch between the feed-forward message to the ventilatory muscles and the feedback from receptors that monitor the response of the ventilatory

**FIGURE 2-1**

Hypothetical model for integration of sensory inputs in the production of dyspnea. Afferent information from the receptors throughout the respiratory system projects directly to the sensory cortex to contribute to primary qualitative sensory experiences and provide feedback on the action of the ventilatory pump. Afferents also project to the areas of the brain responsible for control of ventilation. The motor cortex, responding to input from the control centers, sends neural messages to the ventilatory muscles and a corollary discharge to the sensory cortex (feed-forward with respect to the instructions sent to the muscles). If the feed-forward and feedback messages do not match, an error signal is generated, and the intensity of dyspnea increases. (Adapted from Gillette and Schwartzstein.)

pump increases the intensity of dyspnea. This is particularly important when there is a mechanical derangement of the ventilatory pump, such as in asthma or chronic obstructive pulmonary disease (COPD).

Anxiety

Acute anxiety may increase the severity of dyspnea either by altering the interpretation of sensory data or by leading to patterns of breathing that heighten physiologic abnormalities in the respiratory system. In patients with expiratory flow limitation, for example, the increased respiratory rate that accompanies acute anxiety leads to hyperinflation, increased work of breathing, a sense of an increased effort to breathe, and a sense of an unsatisfying breath.

ASSESSING DYSPNEA

Quality of Sensation

As with pain, dyspnea assessment begins with a determination of the quality of the discomfort (Table 2-1). Dyspnea questionnaires, or lists of phrases commonly used by patients, assist those who have difficulty describing their breathing sensations.

Sensory Intensity

A modified Borg scale or visual analogue scale can be used to measure dyspnea at rest, immediately after exercise, or

TABLE 2-1

ASSOCIATION OF QUALITATIVE DESCRIPTORS AND PATHOPHYSIOLOGIC MECHANISMS OF SHORTNESS OF BREATH

DESCRIPTOR	PATHOPHYSIOLOGY
Chest tightness or constriction	Bronchoconstriction, interstitial edema (asthma, myocardial ischemia)
Increased work or effort of breathing	Airway obstruction, neuromuscular disease (COPD, moderate to severe asthma, myopathy, kyphoscoliosis)
Air hunger, need to breathe, urge to breathe	Increased drive to breathe (CHF, pulmonary embolism, moderate to severe airflow obstruction)
Cannot get a deep breath, unsatisfying breath	Hyperinflation (asthma, COPD) and restricted tidal volume (pulmonary fibrosis, chest wall restriction)
Heavy breathing, rapid breathing, breathing more	Deconditioning

Note: CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease.

Source: Adapted from Schwartzstein and Feller-Kopman.

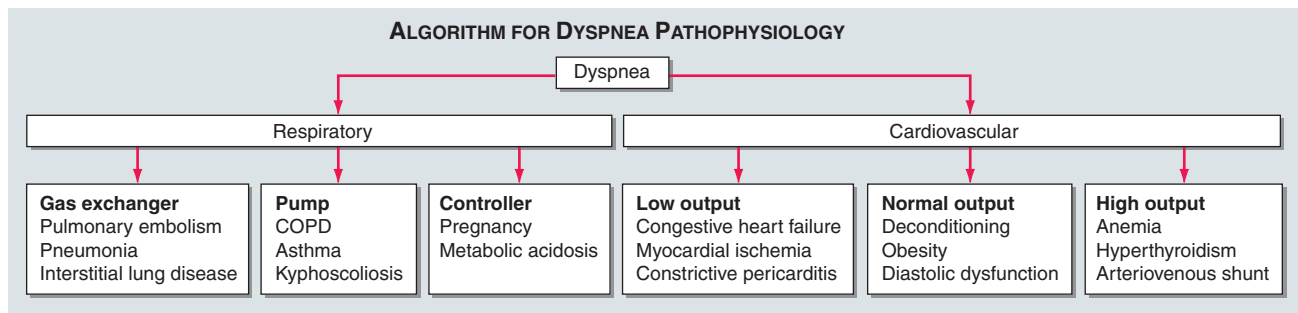
on recall of a reproducible physical task (e.g., climbing the stairs at home). An alternative approach is to inquire about the activities a patient can do (i.e., to gain a sense of the patient's disability). The Baseline Dyspnea Index and the Chronic Respiratory Disease Questionnaire are commonly used tools for this purpose.

Affective Dimension

For a sensation to be reported as a symptom, it must be perceived as unpleasant and interpreted as abnormal. We are still in the early stages of learning the best ways to assess the affective dimension of dyspnea. Some therapies for dyspnea, such as pulmonary rehabilitation, may reduce breathing discomfort, partly by altering this dimension.

DIFFERENTIAL DIAGNOSIS

Dyspnea is the consequence of deviations from normal function in the cardiopulmonary systems. Alterations in the respiratory system can be considered in the context of the controller (stimulation of breathing), the ventilatory pump (the bones and muscles that form the chest wall, the airways, and the pleura), and the gas exchanger (the alveoli, pulmonary vasculature, and surrounding lung parenchyma). Similarly, alterations in the cardiovascular system can be grouped into three categories: conditions associated with high, normal, and low cardiac output (Fig. 2-2).

**FIGURE 2-2**

Pathophysiology of dyspnea. When confronted with a patient with shortness of breath of unclear cause, it is useful to begin the analysis with a consideration of the broad

pathophysiologic categories that explain the vast majority of cases. COPD, chronic obstructive pulmonary disease. (Adapted from Schwartzstein and Feller-Kopman.)

Respiratory System Dyspnea

Contoller

Acute hypoxemia and hypercapnia are associated with increased activity in the contoller. Stimulation of pulmonary receptors, as occurs in those with acute bronchospasm, interstitial edema, and pulmonary embolism, also leads to hyperventilation and air hunger, as well as a sense of chest tightness in the case of asthma. High altitude, high progesterone states such as pregnancy, and drugs such as aspirin stimulate the contoller and may cause dyspnea even when the respiratory system is normal.

Ventilatory Pump

Disorders of the airways (e.g., asthma, emphysema, chronic bronchitis, bronchiectasis) lead to increased airway resistance and work of breathing. Hyperinflation further increases the work of breathing and can produce a sense of an inability to get a deep breath. Conditions that stiffen the chest wall, such as kyphoscoliosis, or that weaken the ventilatory muscles, such as myasthenia gravis or Guillain-Barré syndrome, are also associated with an increased effort to breathe. Large pleural effusions may contribute to dyspnea, both by increasing the work of breathing and by stimulating pulmonary receptors if associated atelectasis is present.

Gas Exchanger

Pneumonia, pulmonary edema, and aspiration all interfere with gas exchange. Pulmonary vascular and interstitial lung disease and pulmonary vascular congestion may produce dyspnea by direct stimulation of pulmonary receptors. In these cases, relief of hypoxemia typically has only a small impact on the intensity of dyspnea.

Cardiovascular System Dyspnea

High Cardiac Output

Mild to moderate anemia is associated with breathing discomfort during exercise. Left-to-right intracardiac

shunts may lead to high cardiac output and dyspnea, although in their later stages, these conditions may be complicated by the development of pulmonary hypertension, which contributes to dyspnea. The breathlessness associated with obesity is probably caused by multiple mechanisms, including high cardiac output and impaired ventilatory pump function.

Normal Cardiac Output

Cardiovascular deconditioning is characterized by early development of anaerobic metabolism and stimulation of chemoreceptors and metaboreceptors. Diastolic dysfunction—caused by hypertension, aortic stenosis, or hypertrophic cardiomyopathy—is an increasingly frequent recognized cause of exercise-induced breathlessness. Pericardial disease (e.g., constrictive pericarditis) is a relatively rare cause of chronic dyspnea.

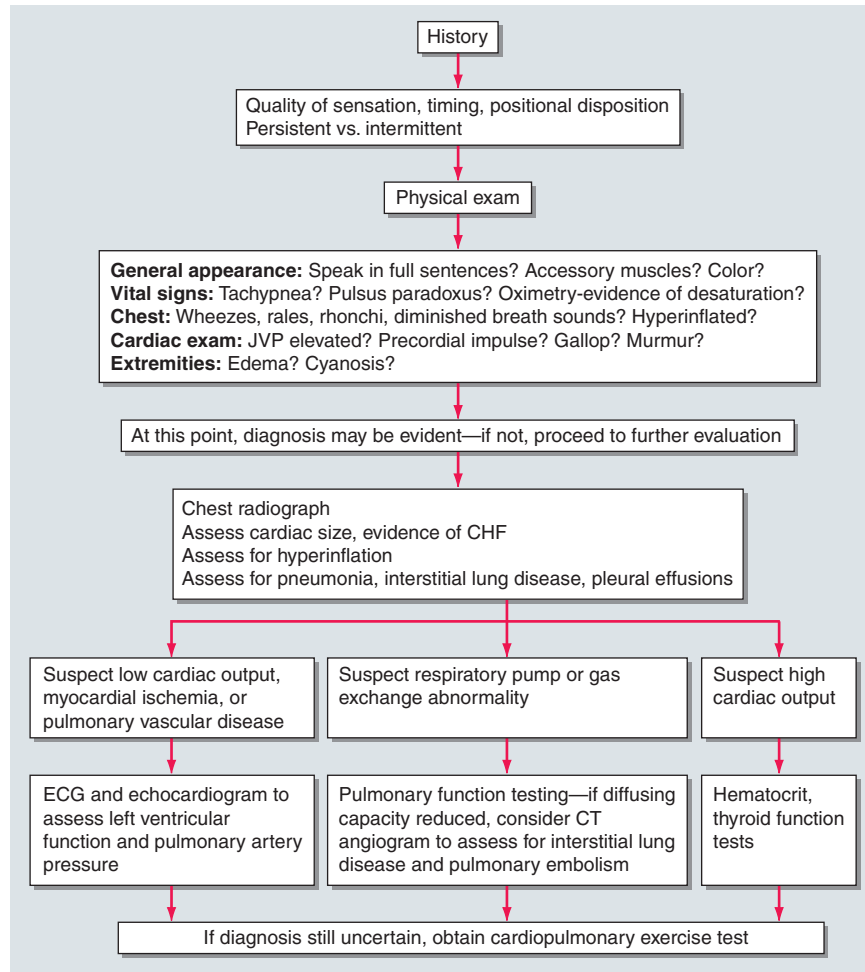
Low Cardiac Output

Diseases of the myocardium resulting from coronary artery disease and nonischemic cardiomyopathies result in a greater left ventricular end-diastolic volume and an elevation of the left ventricular end-diastolic as well as pulmonary capillary pressures. Pulmonary receptors are stimulated by the elevated vascular pressures and resultant interstitial edema, causing dyspnea.

Approach to the Patient:

DYSPNEA

In obtaining a *history*, the patient should be asked to describe in his or her own words what the discomfort feels like, as well as the effect of position, infections, and environmental stimuli on the dyspnea (Fig. 2-3). Orthopnea is a common indicator of congestive heart failure, mechanical impairment of the diaphragm associated with obesity, or asthma triggered by esophageal

**FIGURE 2-3**

An algorithm for the evaluation of the patient with dyspnea. CHF, congestive heart failure; CT, computed tomography;

ECG, electrocardiogram; JVP, jugular venous pulse. (Adapted from Schwartzstein and Feller-Kopman.)

reflux. Nocturnal dyspnea suggests congestive heart failure or asthma. Whereas acute, intermittent episodes of dyspnea are more likely to reflect episodes of myocardial ischemia, bronchospasm, or pulmonary embolism, chronic persistent dyspnea is typical of COPD and interstitial lung disease. Risk factors for occupational lung disease and for coronary artery disease should be solicited. Left atrial myxoma or hepatopulmonary syndrome should be considered when the patient complains of *platypnea*, defined as dyspnea in the upright position with relief in the supine position.

The *physical examination* should begin during the interview of the patient. A patient's inability to speak in full sentences before stopping to get a deep breath suggests a condition that leads to stimulation of the controller or an impairment of the ventilatory pump with reduced vital capacity. Evidence for increased work of breathing (supraclavicular retractions; use of

accessory muscles of ventilation; and the tripod position, characterized by sitting with one's hands braced on the knees) is indicative of disorders of the ventilatory pump, most commonly increased airway resistance or stiff lungs and chest wall. When measuring the vital signs, an accurate assessment of the respiratory rate should be obtained and examination for a pulsus paradoxus carried out; if it is above 10 mmHg, the presence of COPD should be considered. During the general examination, signs of anemia (pale conjunctivae), cyanosis, and cirrhosis (spider angiomas, gynecomastia) should be sought. Examination of the chest should focus on symmetry of movement, percussion (dullness indicative of pleural effusion, hyperresonance a sign of emphysema), and auscultation (wheezes, rales, rhonchi, prolonged expiratory phase, diminished breath sounds, which are clues to disorders of the airways, and interstitial edema or fibrosis). The cardiac examination should

focus on signs of elevated right heart pressures (jugular venous distention, edema, accentuated pulmonic component to the second heart sound), left ventricular dysfunction (S3 and S4 gallops), and valvular disease (murmurs). When examining the abdomen with the patient in the supine position, it should be noted whether there is paradoxical movement of the abdomen (inward motion during inspiration), a sign of diaphragmatic weakness. Clubbing of the digits may indicate interstitial pulmonary fibrosis, and the presence of joint swelling or deformation as well as changes consistent with Raynaud's disease may be indicative of a collagen-vascular process that may be associated with pulmonary disease.

Patients with exertional dyspnea should be asked to walk under observation to reproduce the symptoms. The patient should be examined for new findings that were not present at rest and for oxygen saturation. A "picture" of the patient while symptomatic may be worth thousands of dollars in laboratory tests.

After the history and physical examination have been performed, a *chest radiograph* should be obtained. The lung volumes should be assessed (hyperinflation indicates obstructive lung disease; low lung volumes suggest interstitial edema or fibrosis, diaphragmatic dysfunction, or impaired chest wall motion). The pulmonary parenchyma should be examined for evidence of interstitial disease and emphysema. Prominent pulmonary vasculature in the upper zones indicates pulmonary venous hypertension, and enlarged central pulmonary arteries suggest pulmonary artery hypertension. An enlarged cardiac silhouette suggests dilated cardiomyopathy or valvular disease. Bilateral pleural effusions are typical of congestive heart failure and some forms of collagen vascular disease. Unilateral effusions raise the specter of carcinoma and pulmonary embolism but may also occur in patients with heart failure. *CT of the chest* is generally reserved for further evaluation of the lung parenchyma (interstitial lung disease) and possible pulmonary embolism.

Laboratory studies should include an electrocardiogram (ECG) to look for evidence of ventricular hypertrophy and prior myocardial infarction. Echocardiography is indicated in patients in whom systolic dysfunction, pulmonary hypertension, or valvular heart disease is suspected.

DISTINGUISHING CARDIOVASCULAR FROM RESPIRATORY SYSTEM DYSPNEA If a patient has evidence of both pulmonary and cardiac disease, a cardiopulmonary exercise test should be carried out to determine which system is responsible for the exercise limitation. If, at peak exercise, the patient achieves predicted maximal ventilation, demonstrates an increase in dead space or hypoxemia (oxygen saturation <90%), or develops bronchospasm,

the respiratory system is probably the cause of the problem. Alternatively, if the heart rate is above 85% of the predicted maximum, anaerobic threshold occurs early, the blood pressure becomes excessively high or decreases during exercise, the O₂ pulse (O₂ consumption/heart rate, an indicator of stroke volume) decreases, or ischemic changes are seen on the ECG, an abnormality of the cardiovascular system is likely the explanation for the breathing discomfort.

Rx Treatment: **DYSPNEA**

The first goal is to correct the underlying problem responsible for the symptom. If this is not possible, one attempts to lessen the intensity of the symptom and its effect on the patient's quality of life. Supplemental O₂ should be administered if the resting O₂ saturation is 90% or below or if the patient's saturation decreases to these levels with activity. For patients with COPD, pulmonary rehabilitation programs have demonstrated positive effects on dyspnea, exercise capacity, and rates of hospitalization. Studies of anxiolytics and antidepressants have not demonstrated consistent benefit. Experimental interventions (e.g., cold air on the face, chest wall vibration, and inhaled furosemide) to modulate the afferent information from receptors throughout the respiratory system are being studied.

PULMONARY EDEMA

MECHANISMS OF FLUID ACCUMULATION

The extent to which fluid accumulates in the interstitium of the lung depends on the balance of hydrostatic and oncotic forces within the pulmonary capillaries and in the surrounding tissue. Hydrostatic pressure favors movement of fluid from the capillary into the interstitium. The oncotic pressure, which is determined by the protein concentration in the blood, favors movement of fluid into the vessel. Albumin, the primary protein in the plasma, may be low in patients with conditions such as cirrhosis and nephrotic syndrome. Although hypoalbuminemia favors movement of fluid into the tissue for any given hydrostatic pressure in the capillary, it is usually not sufficient by itself to cause interstitial edema. In a healthy individual, the tight junctions of the capillary endothelium are impermeable to proteins, and the lymphatics in the tissue carry away the small amounts of protein that may leak out; together these factors result in an oncotic force that maintains fluid in the capillary. Disruption of the endothelial barrier, however, allows protein to escape the capillary bed and enhances the movement of fluid into the tissue of the lung.

(See also Chap. 31) Cardiac abnormalities that lead to an increase in pulmonary venous pressure shift the balance of forces between the capillary and the interstitium. Hydrostatic pressure is increased and fluid exits the capillary at an increased rate, resulting in interstitial and, in more severe cases, alveolar edema. The development of pleural effusions may further compromise respiratory system function and contribute to breathing discomfort.

Early signs of pulmonary edema include exertional dyspnea and orthopnea. Chest radiographs show peribronchial thickening, prominent vascular markings in the upper lung zones, and Kerley B lines. As the pulmonary edema worsens, alveoli fill with fluid, and the chest radiograph shows patchy alveolar filling, typically in a perihilar distribution, which then progresses to diffuse alveolar infiltrates. Increasing airway edema is associated with rhonchi and wheezes.

Noncardiogenic Pulmonary Edema

By definition, hydrostatic pressures are normal in patients with noncardiogenic pulmonary edema. Lung water increases because of damage of the pulmonary capillary lining with leakage of proteins and other macromolecules into the tissue; fluid follows the protein as oncotic forces are shifted from the vessel to the surrounding lung tissue. This process is associated with dysfunction of the surfactant lining the alveoli, increased surface forces, and a propensity for the alveoli to collapse at low lung volumes. Physiologically, noncardiogenic pulmonary edema is characterized by intrapulmonary shunt with hypoxemia and decreased pulmonary compliance. Pathologically, hyaline membranes are evident in the alveoli, and inflammation leading to pulmonary fibrosis may be seen. Clinically, the picture ranges from mild dyspnea to respiratory failure. Auscultation of the lungs may be relatively normal despite chest radiographs that show diffuse alveolar infiltrates. CT scans demonstrate that the distribution of alveolar edema is more heterogeneous than was once thought.

It is useful to categorize the causes of noncardiogenic pulmonary edema in terms of whether the injury to the lung is likely to result from direct, indirect, or pulmonary vascular causes (Table 2-2). Direct injuries are mediated via the airways (e.g., aspiration) or as the consequence of blunt chest trauma. Indirect injury is the consequence of mediators that reach the lung via the blood stream. The third category includes conditions that may be the consequence of acute changes in pulmonary vascular pressures, possibly the result of sudden autonomic discharge in the case of neurogenic and high-altitude pulmonary edema or sudden swings of pleural pressure, as well as transient damage to the pulmonary capillaries in the case of reexpansion pulmonary edema.

TABLE 2-2

COMMON CAUSES OF NONCARDIOGENIC PULMONARY EDEMA

Direct Injury to Lung

- Chest trauma, pulmonary contusion
- Aspiration
- Smoke inhalation
- Pneumonia
- Oxygen toxicity
- Pulmonary embolism, reperfusion

Hematogenous Injury to Lung

- Sepsis
- Pancreatitis
- Nonthoracic trauma
- Leukoagglutination reactions
- Multiple transfusions
- Intravenous drug use (e.g., heroin)
- Cardiopulmonary bypass

Possible Lung Injury Plus Elevated

Hydrostatic Pressures

- High-altitude pulmonary edema
- Neurogenic pulmonary edema
- Reexpansion pulmonary edema

Distinguishing Cardiogenic from Noncardiogenic Pulmonary Edema

The *history* is essential for assessing the likelihood of underlying cardiac disease as well as for identifying one of the conditions associated with noncardiogenic pulmonary edema. The *physical examination* in cardiogenic pulmonary edema is notable for evidence of increased intracardiac pressures (S3 gallop, elevated jugular venous pulse, peripheral edema) and rales or wheezes on auscultation of the chest. In contrast, the physical examination in noncardiogenic pulmonary edema is dominated by the findings of the precipitating condition; pulmonary findings may be relatively normal in the early stages. The *chest radiograph* in cardiogenic pulmonary edema typically shows an enlarged cardiac silhouette, vascular redistribution, interstitial thickening, and perihilar alveolar infiltrates; pleural effusions are common. In noncardiogenic pulmonary edema, the heart size is normal, alveolar infiltrates are distributed more uniformly throughout the lungs, and pleural effusions are uncommon. Finally, the *hypoxemia* of cardiogenic pulmonary edema is largely attributable to ventilation-perfusion mismatch and responds to the administration of supplemental oxygen. In contrast, hypoxemia in noncardiogenic pulmonary edema is primarily attributable to intrapulmonary shunting and typically persists despite high concentrations of inhaled O₂.

FURTHER READINGS

- AARON SD et al: Overdiagnosis of asthma in obese and nonobese adults. *CMAJ* 179:1121, 2008
- ABIDOV A et al: Prognostic significance of dyspnea in patients referred for cardiac stress testing. *N Engl J Med* 353:1889, 2005

BANZETT RB et al: The affective dimension of laboratory dyspnea: Air hunger is more unpleasant than work/effort. *Am J Respir Crit Care Med* 177:1384, 2008

Dyspnea mechanisms, assessment, and management: A consensus statement. *Am Rev Respir Crit Care Med* 159:321, 1999

GILLETTE MA, SCHWARTZSTEIN RM: Mechanisms of dyspnea, in Ahmedzai SH, Muer MF (eds). *Supportive Care in Respiratory Disease*. Oxford, UK, Oxford University Press, 2005

MAHLER DA et al. Descriptors of breathlessness in cardiorespiratory diseases. *Am J Respir Crit Care Med* 154:1357, 1996

MAHLER DA, O'DONNELL DE (eds): *Dyspnea: Mechanisms, Measurement, and Management*. New York, Marcel Dekker, 2005

SCHWARTZSTEIN RM: The language of dyspnea, in Mahler DA, O'Donnell DE (eds). *Dyspnea: Mechanisms, Measurement, and Management*, New York, Marcel Dekker, 2005

———, FELLER-KOPMAN D: Shortness of breath, in Braunwald E, GOLDMAN L (eds). *Primary Care Cardiology*, 2d ed. Philadelphia, WB Saunders, 2003



CHAPTER 3

COUGH AND HEMOPTYSIS

Steven E. Weinberger ■ David A. Lipson

■ Cough	14
Mechanism	14
Etiology	14
Complications	16
■ Hemoptysis	17
Etiology	17
■ Further Readings	19

COUGH

Cough is an explosive expiration that provides a normal protective mechanism for clearing the tracheobronchial tree of secretions and foreign material. When excessive or bothersome, it is also one of the most common symptoms for which patients seek medical attention. Reasons for this include discomfort from the cough itself; interference with normal lifestyle; and concern for the cause of the cough, especially fear of cancer.

MECHANISM

Coughing may be initiated either voluntarily or reflexively. As a defensive reflex, it has both afferent and efferent pathways. The *afferent limb* includes receptors within the sensory distribution of the trigeminal, glossopharyngeal, superior laryngeal, and vagus nerves. The *efferent limb* includes the recurrent laryngeal nerve and the spinal nerves. The cough starts with a deep inspiration followed by glottic closure, relaxation of the diaphragm, and muscle contraction against a closed glottis. The resulting markedly positive intrathoracic pressure causes narrowing of the trachea. After the glottis opens, the large pressure differential between the airways and the atmosphere coupled with tracheal narrowing produces rapid flow rates through the trachea. The shearing forces that develop aid in the elimination of mucus and foreign materials.

ETIOLOGY

Cough can be initiated by a variety of irritant triggers either from an exogenous source (smoke, dust, fumes, foreign bodies) or from an endogenous origin (upper airway secretions, gastric contents). These stimuli may affect receptors in the upper airway (especially the pharynx and larynx) or in the lower respiratory tract following access to the tracheobronchial tree by inhalation or aspiration. When cough is triggered by upper airway secretions (as with postnasal drip) or gastric contents (as with gastroesophageal reflux), the initiating factor may go unrecognized, and the cough may persist. Additionally, prolonged exposure to such irritants may initiate airway inflammation, which can itself precipitate cough and sensitize the airway to other irritants. Cough associated with gastroesophageal reflux is caused only partly by irritation of upper airway receptors or by aspiration of gastric contents; a vagally mediated reflex mechanism secondary to acid in the distal esophagus may also contribute.

Any disorder resulting in inflammation, constriction, infiltration, or compression of the airways may be associated with cough. Inflammation commonly results from airway infections, ranging from viral or bacterial bronchitis to bronchiectasis. In viral bronchitis, airway inflammation sometimes persists long after resolution of the typical acute symptoms, thereby producing a prolonged cough that may last for weeks. Pertussis infection is also a possible cause of persistent cough in adults; however, diagnosis is generally made on clinical grounds. Asthma is

a common cause of cough. Although the clinical setting commonly suggests that when a cough is secondary to asthma, some patients present with cough in the absence of wheezing or dyspnea, thus making the diagnosis more subtle (“cough variant asthma”). A neoplasm infiltrating the airway wall, such as bronchogenic carcinoma or a carcinoid tumor, is commonly associated with cough. Airway infiltration with granulomas may also trigger a cough, as seen with endobronchial sarcoidosis or tuberculosis. Compression of airways results from extrinsic masses such as lymph nodes or mediastinal tumors or rarely from an aortic aneurysm.

Examples of parenchymal lung disease potentially producing cough include interstitial lung disease, pneumonia, and lung abscess. Congestive heart failure may be associated with cough, probably as a consequence of interstitial as well as peribronchial edema. A nonproductive cough complicates the use of angiotensin-converting enzyme (ACE) inhibitors in 5% to 20% of patients taking these agents. Onset is usually within 1 week of starting the drug but can be delayed up to 6 months. Although the mechanism is not known with certainty, it may relate to accumulation of bradykinin or substance P, both of which are degraded by ACE. In contrast, angiotensin II receptor antagonists do not seem to increase cough, likely because these drugs do not significantly increase bradykinin levels.

The most common causes of cough can be categorized according to the duration of the cough. Acute cough (<3 weeks) is most often caused by upper respiratory infection (especially the common cold, acute bacterial sinusitis, and pertussis), but more serious disorders, such as pneumonia, pulmonary embolus, and congestive heart failure, may also present in this fashion. Subacute cough (between 3 and 8 weeks) is commonly postinfectious, resulting from persistent airway inflammation or postnasal drip after viral infection, pertussis, or infection with *Mycoplasma* or *Chlamydia* spp. In a patient with subacute cough that is not clearly postinfectious, the varied causes of chronic cough should be considered. Chronic cough (>8 weeks) in a smoker raises the possibilities of chronic obstructive lung disease or bronchogenic carcinoma. In a nonsmoker who has a normal chest radiograph and is not taking an ACE inhibitor, the most common causes of chronic cough are postnasal drip (sometimes termed the *upper airway cough syndrome*), asthma, and gastroesophageal reflux. Eosinophilic bronchitis in the absence of asthma has also been recognized as a potential cause of chronic cough.

Approach to the Patient: COUGH

A detailed *history* frequently provides the most valuable clues for the cause of the cough. Particularly important questions include:

1. Is the cough acute, subacute, or chronic?
2. At its onset, were there associated symptoms suggestive of a respiratory infection?
3. Is it seasonal or associated with wheezing?
4. Is it associated with symptoms suggestive of postnasal drip (nasal discharge, frequent throat clearing, a “tickle in the throat”) or gastroesophageal reflux (heartburn or sensation of regurgitation)? (However, the absence of such suggestive symptoms does not exclude either of these diagnoses.)
5. Is it associated with fever or sputum? If sputum is present, what is its character?
6. Does the patient have any associated diseases or risk factors for disease (e.g., cigarette smoking, risk factors for infection with HIV, environmental exposures)?
7. Is the patient taking an ACE inhibitor?

The general *physical examination* may point to a systemic or nonpulmonary cause of cough, such as heart failure or primary nonpulmonary neoplasm. Examination of the oropharynx may provide suggestive evidence for postnasal drip, including oropharyngeal mucus or erythema, or a “cobblestone” appearance to the mucosa. Auscultation of the chest may demonstrate inspiratory stridor (indicative of upper airway disease), rhonchi or expiratory wheezing (indicative of lower airway disease), or inspiratory crackles (suggestive of a process involving the pulmonary parenchyma, such as interstitial lung disease, pneumonia, or pulmonary edema).

Chest radiography may be particularly helpful in suggesting or confirming the cause of the cough. Important potential findings include the presence of an intrathoracic mass lesion, localized pulmonary parenchymal opacification, or diffuse interstitial or alveolar disease. An area of honeycombing or cyst formation may suggest bronchiectasis, and symmetric bilateral hilar adenopathy may suggest sarcoidosis.

Pulmonary function testing (Chap. 5) is useful for assessing the functional abnormalities that accompany certain disorders that produce cough. Measurement of forced expiratory flow rates may demonstrate reversible airflow obstruction characteristic of asthma. When asthma is considered but flow rates are normal, bronchoprovocation testing with methacholine or cold-air inhalation may demonstrate hyperreactivity of the airways to a bronchoconstrictive stimulus. Measurement of lung volumes and diffusing capacity is useful primarily for demonstration of a restrictive pattern, often seen with any of the diffuse interstitial lung diseases.

If *sputum* is produced, gross and microscopic examination may provide useful information. Purulent sputum suggests chronic bronchitis, bronchiectasis,

pneumonia, or lung abscess. Blood in the sputum may be seen in the same disorders, but its presence also raises the question of an endobronchial tumor. Greater than 3% eosinophils seen on staining of induced sputum in a patient without asthma suggests the possibility of eosinophilic bronchitis. Gram and acid-fast stains and cultures may demonstrate a particular infectious pathogen, and sputum cytology may provide a diagnosis of a pulmonary malignancy.

More specialized studies are helpful in specific circumstances. *Fiberoptic bronchoscopy* is the procedure of choice for visualizing an endobronchial tumor and collecting cytologic and histologic specimens. Inspection of the tracheobronchial mucosa may demonstrate endobronchial granulomas often seen in sarcoidosis, and endobronchial biopsy of such lesions or transbronchial biopsy of the lung interstitium may confirm the diagnosis. Inspection of the airway mucosa by bronchoscopy may also demonstrate the characteristic appearance of endobronchial Kaposi's sarcoma in patients with AIDS. *High-resolution computed tomography* (HRCT) may confirm the presence of interstitial lung disease and frequently suggests a diagnosis based on the specific abnormal pattern. It is the procedure of choice for demonstrating dilated airways and confirming the diagnosis of bronchiectasis.

A diagnostic algorithm for evaluation of subacute and chronic cough is presented in Fig. 3-1.

COMPLICATIONS

Common complications of coughing include chest and abdominal wall soreness, urinary incontinence, and exhaustion. On occasion, paroxysms of coughing may precipitate syncope (cough syncope) consequent to markedly positive intrathoracic and alveolar pressures, diminished venous return, and decreased cardiac output. Although cough fractures of the ribs may occur in otherwise normal patients, their occurrence should at least raise the possibility of pathologic fractures, which are seen with multiple myeloma, osteoporosis, and osteolytic metastases.

Rx Treatment: COUGH

Definitive treatment of cough depends on determining the underlying cause and then initiating specific therapy. Elimination of an exogenous inciting agent (cigarette smoke, ACE inhibitors) or an endogenous trigger (postnasal drip, gastroesophageal reflux) is usually effective when such a precipitant can be identified.

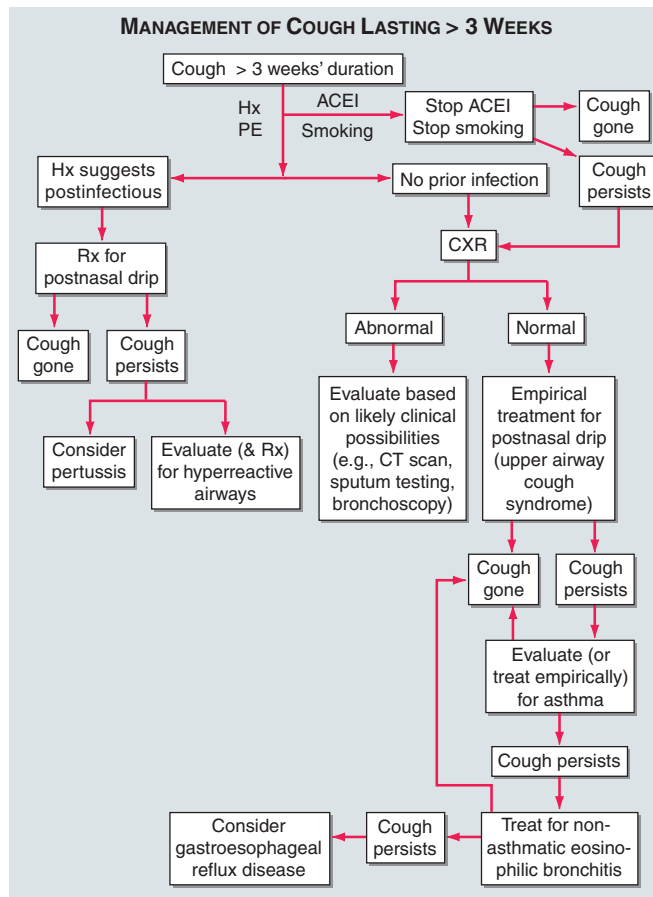


FIGURE 3-1

Algorithm for management of cough lasting more than 3 weeks. Cough lasting between 3 and 8 weeks is considered subacute; cough lasting longer than 8 weeks is considered chronic. ACEI, angiotensin-converting enzyme inhibitor; CXR, chest x-ray; Hx, history; PE, physical examination; Rx, treat.

Other important management considerations are treatment of specific respiratory tract infections, bronchodilators for potentially reversible airflow obstruction, inhaled glucocorticoids for eosinophilic bronchitis, chest physiotherapy and other methods to enhance clearance of secretions in patients with bronchiectasis, and treatment of endobronchial tumors or interstitial lung disease when such therapy is available and appropriate. In patients with chronic, unexplained cough, an empirical approach to treatment is often used for both diagnostic and therapeutic purposes, starting with an antihistamine—decongestant combination, nasal glucocorticoids, or nasal ipratropium spray to treat unrecognized postnasal drip. If ineffective, this may be followed sequentially by empirical treatment for asthma, nonasthmatic eosinophilic bronchitis, and gastroesophageal reflux.

Symptomatic or nonspecific therapy of cough should be considered when (1) the cause of the cough is not

known or specific treatment is not possible and (2) the cough performs no useful function or causes marked discomfort or sleep disturbance. An irritative, nonproductive cough may be suppressed by an antitussive agent, which increases the latency or threshold of the cough center. Such agents include codeine (15 mg qid) or nonnarcotics such as dextromethorphan (15 mg qid). These drugs provide symptomatic relief by interrupting prolonged, self-perpetuating paroxysms. However, a cough productive of significant quantities of sputum should usually not be suppressed because retention of sputum in the tracheobronchial tree may interfere with the distribution of alveolar ventilation and the ability of the lung to resist infection.

HEMOPTYSIS

Hemoptysis is defined as the expectoration of blood from the respiratory tract, a spectrum that varies from blood streaking of sputum to coughing up large amounts of pure blood. *Massive hemoptysis* is variably defined as the expectoration of more than 100 to 600 mL over a 24-h. period, although the patient's estimation of the amount of blood is notoriously unreliable. Expectoration of even relatively small amounts of blood is a frightening symptom and may be a marker for potentially serious disease, such as bronchogenic carcinoma. Massive hemoptysis, on the other hand, may represent an acutely life-threatening problem. Blood can fill the airways and the alveolar spaces, not only seriously disturbing gas exchange but also potentially causing asphyxiation.

ETIOLOGY

Because blood originating from the nasopharynx or the gastrointestinal tract can mimic blood coming from the lower respiratory tract, it is important to determine initially that the blood is not coming from one of these alternative sites. Clues that the blood is originating from the gastrointestinal tract include a dark red appearance and an acidic pH in contrast to the typical bright red appearance and alkaline pH of true hemoptysis.

An etiologic classification of hemoptysis can be based on the site of origin within the lungs (Table 3-1). The most common site of bleeding is the tracheobronchial tree, which may be affected by inflammation (acute or chronic bronchitis, bronchiectasis) or by neoplasm (bronchogenic carcinoma, endobronchial metastatic carcinoma, or bronchial carcinoid tumor). The bronchial arteries, which originate either from the aorta or from intercostal arteries and are therefore part of the high-pressure systemic circulation, are the source of bleeding in bronchitis or bronchiectasis or with endobronchial

TABLE 3-1

DIFFERENTIAL DIAGNOSIS OF HEMOPTYSIS

Source other than the lower respiratory tract
Upper airway (nasopharyngeal) bleeding
Gastrointestinal bleeding
Tracheobronchial source
Neoplasm (bronchogenic carcinoma, endobronchial metastatic tumor, Kaposi's sarcoma, bronchial carcinoid)
Bronchitis (acute or chronic)
Bronchiectasis
Broncholithiasis
Airway trauma
Foreign body
Pulmonary parenchymal source
Lung abscess
Pneumonia
Tuberculosis
Mycetoma ("fungus ball")
Goodpasture's syndrome
Idiopathic pulmonary hemosiderosis
Wegener's granulomatosis
Lupus pneumonitis
Lung contusion
Primary vascular source
Arteriovenous malformation
Pulmonary embolism
Elevated pulmonary venous pressure (especially mitral stenosis)
Pulmonary artery rupture secondary to balloon-tip pulmonary artery catheter manipulation
Miscellaneous and rare causes
Pulmonary endometriosis (catamenial hemoptysis)
Systemic coagulopathy or use of anticoagulants or thrombolytic agents

Source: Adapted from Weinberger SE: *Principles of Pulmonary Medicine*, 4th ed. Philadelphia, Saunders, 2004, with permission.

tumors. Blood originating from the pulmonary parenchyma can be either from a localized source, such as an infection (pneumonia, lung abscess, tuberculosis) or from a process diffusely affecting the parenchyma (as with a coagulopathy or with an autoimmune process such as Goodpasture's syndrome). Disorders primarily affecting the pulmonary vasculature include pulmonary embolic disease and conditions associated with elevated pulmonary venous and capillary pressures, such as mitral stenosis and left ventricular failure.

Although the relative frequency of the different causes of hemoptysis varies from series to series, most recent studies indicate that bronchitis and bronchogenic carcinoma are the two most common causes in the United States. Despite the lower frequency of tuberculosis and bronchiectasis seen in recent compared with older series, these two disorders still represent the most common causes of massive hemoptysis in several series, especially worldwide. Even after extensive evaluation,

- 18 a sizable proportion of patients ($\leq 30\%$ in some series) have no identifiable cause for their hemoptysis. These patients are classified as having idiopathic or cryptogenic hemoptysis, and subtle airway or parenchymal disease is presumably responsible for the bleeding.

Approach to the Patient: HEMOPTYSIS

The *history* is extremely valuable. Hemoptysis that is described as blood streaking of mucopurulent or purulent sputum often suggests bronchitis. Chronic production of sputum with a recent change in quantity or appearance favors an acute exacerbation of chronic bronchitis. Fever or chills accompanying blood-streaked purulent sputum suggests pneumonia, and a putrid smell to the sputum raises the possibility of lung abscess. When sputum production has been chronic and copious, the diagnosis of bronchiectasis should be considered. Hemoptysis after the acute onset of pleuritic chest pain and dyspnea is suggestive of pulmonary embolism.

A history of previous or coexisting disorders should be sought, such as renal disease (seen with Goodpasture's syndrome or Wegener's granulomatosis), lupus erythematosus (with associated pulmonary hemorrhage from lupus pneumonitis), or a previous malignancy (either recurrent lung cancer or endobronchial metastasis from a nonpulmonary primary tumor) or treatment for malignancy (with recent chemotherapy or a bone marrow transplant). In a patient with AIDS, endobronchial or pulmonary parenchymal Kaposi's sarcoma should be considered. Risk factors for bronchogenic carcinoma, particularly smoking and asbestos exposure, should be sought. Patients should be questioned about previous bleeding disorders, treatment with anticoagulants, or use of drugs that may be associated with thrombocytopenia.

The *physical examination* may also provide helpful clues to the diagnosis. For example, examination of the lungs may demonstrate a pleural friction rub (pulmonary embolism), localized or diffuse crackles (parenchymal bleeding or an underlying parenchymal process associated with bleeding), evidence of airflow obstruction (chronic bronchitis), or prominent rhonchi with or without wheezing or crackles (bronchiectasis). Cardiac examination may demonstrate findings of pulmonary arterial hypertension, mitral stenosis, or heart failure. Skin and mucosal examination may reveal Kaposi's sarcoma, arteriovenous malformations of Osler-Rendu-Weber disease, or lesions suggestive of systemic lupus erythematosus.

Diagnostic evaluation of hemoptysis starts with a chest radiograph (often followed by a CT scan) to look

for a mass lesion, findings suggestive of bronchiectasis (Chap. 16), or focal or diffuse parenchymal disease (representing either focal or diffuse bleeding or a focal area of pneumonitis). Additional initial screening evaluation often includes a complete blood count, a coagulation profile, and assessment for renal disease with a urinalysis and measurement of blood urea nitrogen and creatinine levels. When sputum is present, examination by Gram and acid-fast stains (along with the corresponding cultures) is indicated.

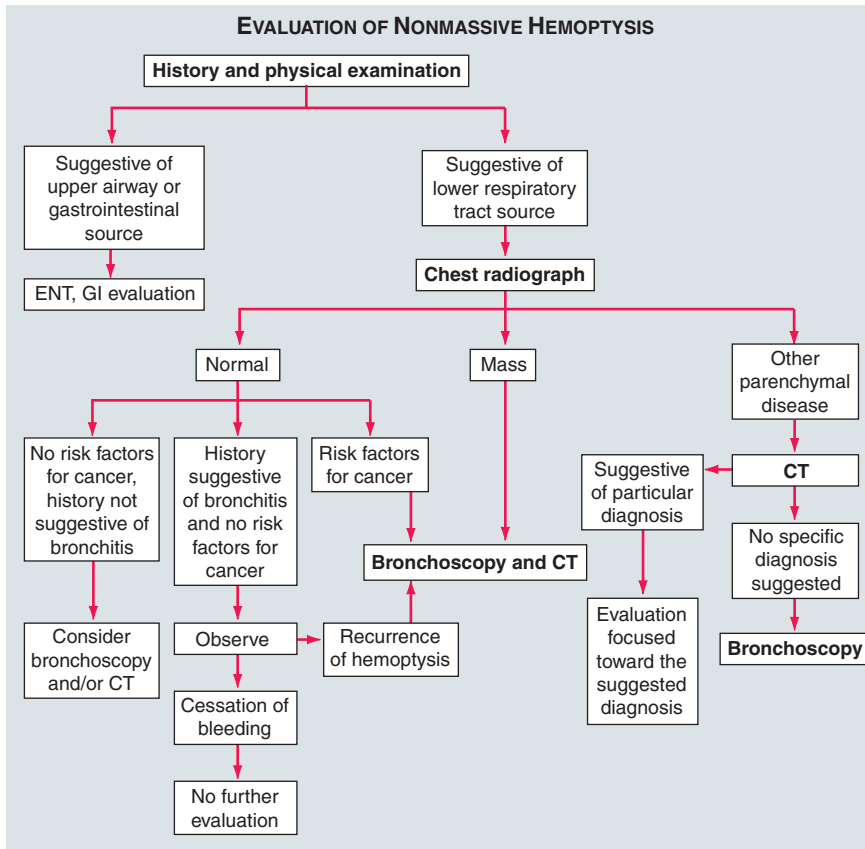
Fiberoptic bronchoscopy is particularly useful for localizing the site of bleeding and for visualization of endobronchial lesions. When bleeding is massive, rigid bronchoscopy is often preferable to fiberoptic bronchoscopy because of better airway control and greater suction capability. In patients with suspected bronchiectasis, HRCT is the diagnostic procedure of choice.

A diagnostic algorithm for evaluation of nonmassive hemoptysis is presented in [Fig. 3-2](#).

Rx Treatment: HEMOPTYSIS

The rapidity of bleeding and its effect on gas exchange determine the urgency of management. When the bleeding is confined to either blood streaking of sputum or production of small amounts of pure blood, gas exchange is usually preserved; establishing a diagnosis is the first priority. When hemoptysis is massive, maintaining adequate gas exchange, preventing blood from spilling into unaffected areas of lung, and avoiding asphyxiation are the highest priorities. Keeping the patient at rest and partially suppressing the cough may help the bleeding to subside. If the origin of the blood is known and is limited to one lung, the bleeding lung should be placed in the dependent position so that blood is not aspirated into the unaffected lung.

With massive bleeding, the need to control the airway and maintain adequate gas exchange may necessitate endotracheal intubation and mechanical ventilation. In patients in danger of flooding the lung contralateral to the side of hemorrhage despite proper positioning, isolation of the right and left mainstem bronchi from each other can be achieved by selectively intubating the nonbleeding lung (often with bronchoscopic guidance) or by using specially designed double-lumen endotracheal tubes. Another option involves inserting a balloon catheter through a bronchoscope by direct visualization and inflating the balloon to occlude the bronchus leading to the bleeding site. This technique not only prevents aspiration of blood into unaffected areas but also may promote tamponade of the bleeding site and cessation of bleeding.

**FIGURE 3-2**

An algorithm for the evaluation of nonmassive hemoptysis. CT, computed tomography; ENT, ear, nose, and throat; GI, gastrointestinal.

Other available techniques for control of significant bleeding include laser phototherapy, electrocautery, bronchial artery embolization, and surgical resection of the involved area of lung. With bleeding from an endobronchial tumor, argon plasma coagulation or the neodymium:yttrium-aluminum-garnet (Nd:YAG) laser can often achieve at least temporary hemostasis by coagulating the bleeding site. Electrocautery, which uses an electric current for thermal destruction of tissue, may be used similarly for management of bleeding from an endobronchial tumor. Bronchial artery embolization involves an arteriographic procedure in which a vessel proximal to the bleeding site is cannulated and a material such as Gelfoam is injected to occlude the bleeding vessel. Surgical resection is a therapeutic option either for the emergent therapy of life-threatening hemoptysis that fails to respond to other measures or for the elective but definitive management of localized disease subject to recurrent bleeding.

FURTHER READINGS

- AMERICAN COLLEGE OF CHEST PHYSICIANS: Diagnosis and management of cough: ACCP evidence-based clinical practice guidelines. *Chest* 129 (suppl):1S, 2006
- GIBSON PG et al: Eosinophilic bronchitis: Clinical manifestations and implications for treatment. *Thorax* 57:178, 2002
- HAQUE RA et al: Chronic idiopathic cough. A discrete clinical entity? *Chest* 127:1710, 2005
- IRWIN RS, MADISON JM: The diagnosis and treatment of cough. *N Engl J Med* 343:1715, 2000
- IRWIN RS, MADISON JM: The persistently troublesome cough. *Am J Respir Crit Care Med* 165:1469, 2002
- JEAN-BAPTISTE E: Clinical assessment and management of massive hemoptysis. *Crit Care Med* 28:1642, 2000
- KHALIL A et al: Role of MDCT in identification of the bleeding site and the vessels causing hemoptysis. *AJR Am J Roentgenol* 188:W117, 2007



CHAPTER 4

HYPOXIA AND CYANOSIS

Eugene Braunwald

■ Hypoxia	20
Effects	20
Causes of Hypoxia	21
Adaptation to Hypoxia	22
■ Cyanosis	22
Differential Diagnosis	23
■ Clubbing	24
■ Further Readings	24

HYPOXIA

The fundamental task of the cardiorespiratory system is to deliver O_2 (and substrates) to the cells and to remove CO_2 (and other metabolic products) from them. Proper maintenance of this function depends on intact cardiovascular and respiratory systems, an adequate number of red blood cells and hemoglobin, and a supply of inspired gas containing adequate O_2 .

EFFECTS

Decreased O_2 availability to cells results in an inhibition of the respiratory chain and increased anaerobic glycolysis. This switch from aerobic to anaerobic metabolism, Pasteur's effect, maintains some, albeit markedly reduced, adenosine triphosphate (ATP) production. In severe hypoxia, when ATP production is inadequate to meet the energy requirements of ionic and osmotic equilibrium, cell membrane depolarization leads to uncontrolled Ca^{2+} influx and activation of Ca^{2+} -dependent phospholipases and proteases. These events, in turn, cause cell swelling and ultimately cell necrosis.

The adaptations to hypoxia are mediated, in part, by the upregulation of genes encoding a variety of proteins, including glycolytic enzymes such as phosphoglycerate kinase and phosphofructokinase, as well as the glucose transporters Glut-1 and Glut-2; and by growth factors, such as vascular endothelial growth factor

(VEGF) and erythropoietin, which enhance erythrocyte production.

During hypoxia, systemic arterioles dilate, at least in part, by opening of K_{ATP} channels in vascular smooth muscle cells because of the hypoxia-induced reduction in ATP concentration. By contrast, in pulmonary vascular smooth muscle cells, inhibition of K^+ channels causes depolarization, which, in turn, activates voltage-gated Ca^{2+} channels, raising the cytosolic $[Ca^{2+}]$ and causing smooth muscle cell contraction. Hypoxia-induced pulmonary arterial constriction shunts blood away from poorly ventilated toward better ventilated portions of the lung; however, it also increases pulmonary vascular resistance and right ventricular afterload.

Effects on the Central Nervous System

Changes in the central nervous system (CNS), particularly the higher centers, are especially important consequences of hypoxia. Acute hypoxia causes impaired judgment, motor incoordination, and a clinical picture resembling acute alcoholism. High-altitude illness is characterized by headache secondary to cerebral vasodilatation and by gastrointestinal symptoms, dizziness, insomnia, and fatigue or somnolence. Pulmonary arterial and sometimes venous constriction cause capillary leakage and high-altitude pulmonary edema (HAPE) (Chap. 2), which intensifies hypoxia and can initiate a vicious circle. Rarely, high-altitude cerebral edema (HACE) develops.

This is manifest by severe headache and papilledema and can cause coma. As hypoxia becomes more severe, the centers of the brainstem are affected, and death usually results from respiratory failure.

CAUSES OF HYPOXIA

Respiratory Hypoxia

When hypoxia occurs consequent to respiratory failure, P_{aO_2} declines, and when respiratory failure is persistent, the hemoglobin-oxygen (Hb- O_2) dissociation curve is displaced to the right, with greater quantities of O_2 released at any level of tissue P_{O_2} . Arterial hypoxemia, that is, a reduction of O_2 saturation of arterial blood (S_{aO_2}), and consequent cyanosis are likely to be more marked when such depression of P_{aO_2} results from pulmonary disease than when the depression occurs as the result of a decline in the fraction of oxygen in inspired air (F_{iO_2}). In this latter situation, P_{aCO_2} decreases secondary to anoxia-induced hyperventilation and the Hb- O_2 dissociation curve is displaced to the left, limiting the decline in S_{aO_2} at any level of P_{aO_2} .

The most common cause of respiratory hypoxia is *ventilation-perfusion mismatch* resulting from perfusion of poorly ventilated alveoli. Respiratory hypoxemia may also be caused by *hypoventilation*, and it is then associated with an elevation of P_{aCO_2} (Chap. 5). These two forms of respiratory hypoxia are usually correctable by inspiring 100% O_2 for several minutes. A third cause is shunting of blood across the lung from the pulmonary arterial to the venous bed (*intrapulmonary right-to-left shunting*) by perfusion of nonventilated portions of the lung, as in pulmonary atelectasis or through pulmonary arteriovenous connections. The low P_{aO_2} in this situation is correctable only in part by an F_{iO_2} of 100%.

Hypoxia Secondary to High Altitude

As one ascends rapidly to 3000 m (~10,000 ft), the reduction of the O_2 content of inspired air (F_{iO_2}) leads to a decrease in alveolar P_{O_2} to about 60 mmHg and a condition termed *high-altitude illness* develops (see earlier). At higher altitudes, arterial saturation declines rapidly and symptoms become more serious, and at 5000 m, unacclimatized individuals usually cease to be able to function normally.

Hypoxia Secondary to Right-to-Left Extrapulmonary Shunting

From a physiologic viewpoint, this cause of hypoxia resembles intrapulmonary right-to-left shunting but is caused by congenital cardiac malformations such as tetralogy of Fallot, transposition of the great arteries, and Eisenmenger's syndrome. As in pulmonary right-to-left

shunting, the P_{aO_2} cannot be restored to normal with inspiration of 100% O_2 .

Anemic Hypoxia

A reduction in hemoglobin concentration of the blood is attended by a corresponding decline in the O_2 -carrying capacity of the blood. Although the P_{aO_2} is normal in anemic hypoxia, the absolute quantity of O_2 transported per unit volume of blood is diminished. As the anemic blood passes through the capillaries and the usual quantity of O_2 is removed from it, the P_{O_2} and saturation in the venous blood decline to a greater degree than normal.

Carbon Monoxide Intoxication

Hemoglobin that is combined with CO (carboxyhemoglobin, COHb) is unavailable for O_2 transport. In addition, the presence of COHb shifts the Hb- O_2 dissociation curve to the left so that O_2 is unloaded only at lower tensions, contributing further to tissue hypoxia.

Circulatory Hypoxia

As in anemic hypoxia, the P_{aO_2} is usually normal, but venous and tissue P_{O_2} values are reduced as a consequence of reduced tissue perfusion and greater tissue O_2 extraction. This pathophysiology leads to an increased arterial-mixed venous O_2 difference or ($a - \bar{v}$) gradient. Generalized circulatory hypoxia occurs in patients with heart failure and in most forms of shock (Chap. 28).

Specific Organ Hypoxia

Localized circulatory hypoxia may occur consequent to decreased perfusion secondary to organic arterial obstruction, as in localized atherosclerosis in any vascular bed, or as a consequence of vasoconstriction, as observed in Raynaud's phenomenon. Localized hypoxia may also result from venous obstruction and the resultant expansion of interstitial fluid causing arterial compression and, thereby, reduction of arterial inflow. Edema, which increases the distance through which O_2 must diffuse before it reaches cells, can also cause localized hypoxia. In an attempt to maintain adequate perfusion to more vital organs in patients with reduced cardiac output secondary to heart failure or hypovolemic shock, vasoconstriction may reduce perfusion in the limbs and skin, causing hypoxia of these regions.

Increased O_2 Requirements

If the O_2 consumption of tissues is elevated without a corresponding increase in perfusion, tissue hypoxia ensues, and the P_{O_2} in venous blood declines. Ordinarily,

22 the clinical picture of patients with hypoxia caused by an elevated metabolic rate, as in fever or thyrotoxicosis, is quite different from that in other types of hypoxia; the skin is warm and flushed owing to increased cutaneous blood flow that dissipates the excessive heat produced, and cyanosis is usually absent.

Exercise is a classic example of increased tissue O_2 requirements. These increased demands are normally met by several mechanisms operating simultaneously: (1) increasing the cardiac output and ventilation and thus O_2 delivery to the tissues; (2) preferentially directing the blood to the exercising muscles by changing vascular resistances in the circulatory beds of exercising tissues directly, reflexly, or both; (3) increasing O_2 extraction from the delivered blood and widening the arteriovenous O_2 difference; and (4) reducing the pH of the tissues and capillary blood, shifting the Hb- O_2 curve to the right and unloading more O_2 from hemoglobin. If the capacity of these mechanisms is exceeded, then hypoxia, especially of the exercising muscles, will result.

Improper Oxygen Utilization

Cyanide and several other similarly acting poisons cause cellular hypoxia. The tissues are unable to use O_2 , and as a consequence, the venous blood tends to have a high O_2 tension. This condition has been termed *histotoxic hypoxia*.

ADAPTATION TO HYPOXIA

An important component of the respiratory response to hypoxia originates in special chemosensitive cells in the carotid and aortic bodies and in the respiratory center in the brainstem. The stimulation of these cells by hypoxia increases ventilation, with a loss of CO_2 , and can lead to respiratory alkalosis. When combined with metabolic acidosis resulting from the production of lactic acid, the serum bicarbonate level declines (Chap. 40).

With the reduction of Pa_{O_2} , cerebrovascular resistance decreases, and cerebral blood flow increases in an attempt to maintain O_2 delivery to the brain. However, when the reduction of Pa_{O_2} is accompanied by hyperventilation and a reduction of Pa_{CO_2} , cerebrovascular resistance increases, cerebral blood flow decreases, and hypoxia is intensified.

The diffuse, systemic vasodilation that occurs in generalized hypoxia increases the cardiac output. In patients with underlying heart disease, the requirements of peripheral tissues for an increase of cardiac output with hypoxia may precipitate congestive heart failure. In patients with ischemic heart disease, a reduced Pa_{O_2} may intensify myocardial ischemia and further impair left ventricular function.

One of the important mechanisms of compensation for chronic hypoxia is an increase in the hemoglobin concentration and in the number of red blood cells in

the circulating blood (i.e., the development of polycythemia secondary to erythropoietin production). In persons with chronic hypoxemia secondary to prolonged residence at a high altitude (>13,000 ft or 4200 m), a condition termed *chronic mountain sickness* develops. It is characterized by a blunted respiratory drive, reduced ventilation, erythrocytosis, cyanosis, weakness, right ventricular enlargement secondary to pulmonary hypertension, and even stupor.

CYANOSIS

Cyanosis refers to a bluish color of the skin and mucous membranes resulting from an increased quantity of reduced hemoglobin or of hemoglobin derivatives in the small blood vessels of those areas. It is usually most marked in the lips, nail beds, ears, and malar eminences. Cyanosis, especially if developed recently, is more commonly detected by a family member than the patient. The florid skin characteristic of polycythemia vera must be distinguished from the true cyanosis discussed here. A cherry-colored flush, rather than cyanosis, is caused by COHb.

The degree of cyanosis is modified by the color of the cutaneous pigment and the thickness of the skin, as well as by the state of the cutaneous capillaries. The accurate clinical detection of the presence and degree of cyanosis is difficult, as proved by oximetric studies. In some instances, central cyanosis can be detected reliably when the Sa_{O_2} has decreased to 85%; in others, particularly in dark-skinned persons, it may not be detected until it has declined to 75%. In the latter case, examination of the mucous membranes in the oral cavity and the conjunctivae rather than examination of the skin is more helpful in the detection of cyanosis.

The increase in the quantity of reduced hemoglobin in the mucocutaneous vessels that produces cyanosis may be brought about either by an increase in the quantity of venous blood as a result of dilation of the venules and venous ends of the capillaries or by a reduction in the Sa_{O_2} in the capillary blood. In general, cyanosis becomes apparent when the concentration of reduced hemoglobin in capillary blood exceeds 40 g/L (4 g/dL).

It is the *absolute*, rather than the *relative*, quantity of reduced hemoglobin that is important in producing cyanosis. Thus, in a patient with severe anemia, the *relative* quantity of reduced hemoglobin in the venous blood may be very large when considered in relation to the total quantity of hemoglobin in the blood. However, because the concentration of the latter is markedly reduced, the *absolute* quantity of reduced hemoglobin may still be small; therefore, patients with severe anemia and even *marked* arterial desaturation may not display cyanosis. Conversely, the higher the total hemoglobin content, the greater the tendency toward cyanosis; thus, patients with marked polycythemia tend to be cyanotic

at higher levels of Sa_{O_2} than patients with normal hematocrit values. Likewise, local passive congestion, which causes an increase in the total quantity of reduced hemoglobin in the vessels in a given area, may cause cyanosis. Cyanosis is also observed when nonfunctional hemoglobin, such as methemoglobin or sulfhemoglobin, is present in the blood.

Cyanosis may be subdivided into central and peripheral types. In the *central* type, the Sa_{O_2} is reduced or an abnormal hemoglobin derivative is present, and the mucous membranes and skin are both affected. *Peripheral* cyanosis is caused by a slowing of blood flow and abnormally great extraction of O_2 from normally saturated arterial blood. It results from vasoconstriction and diminished peripheral blood flow, such as occurs in cold exposure, shock, congestive failure, and peripheral vascular disease. Often in these conditions, the mucous membranes of the oral cavity or those beneath the tongue may be spared. Clinical differentiation between central and peripheral cyanosis may not always be simple, and in conditions such as cardiogenic shock with pulmonary edema, there may be a mixture of both types.

DIFFERENTIAL DIAGNOSIS

Central Cyanosis

(Table 4-1) Decreased Sa_{O_2} results from a marked reduction in the Pa_{O_2} . This reduction may be brought about by a decline in the Fi_{O_2} without sufficient compensatory alveolar hyperventilation to maintain alveolar P_{O_2} . Cyanosis usually becomes manifest in an ascent to an altitude of 4000 m (13,000 ft).

Seriously *impaired pulmonary function*, through perfusion of unventilated or poorly ventilated areas of the lung or alveolar hypoventilation, is a common cause of central cyanosis (Chap. 5). This condition may occur acutely, as in extensive pneumonia or pulmonary edema, or chronically with chronic pulmonary diseases (e.g., emphysema). In the latter situation, secondary polycythemia is generally present, and clubbing of the fingers (see later) may occur. Another cause of reduced Sa_{O_2} is *shunting of systemic venous blood into the arterial circuit*. Certain forms of congenital heart disease are associated with cyanosis on this basis (see earlier).

Pulmonary arteriovenous fistulae may be congenital or acquired, solitary or multiple, and microscopic or massive. The severity of cyanosis produced by these fistulae depends on their size and number. They occur with some frequency in patients with hereditary hemorrhagic telangiectasia. Sa_{O_2} reduction and cyanosis may also occur in some patients with cirrhosis, presumably as a consequence of pulmonary arteriovenous fistulae or portal vein–pulmonary vein anastomoses.

In patients with cardiac or pulmonary right-to-left shunts, the presence and severity of cyanosis depend on

TABLE 4-1

CAUSES OF CYANOSIS

Central Cyanosis

- Decreased arterial oxygen saturation
 - Decreased atmospheric pressure—high altitude
 - Impaired pulmonary function
 - Alveolar hypoventilation
 - Uneven relationships between pulmonary ventilation and perfusion (perfusion of hypoventilated alveoli)
 - Impaired oxygen diffusion
 - Anatomic shunts
 - Certain types of congenital heart disease
 - Pulmonary arteriovenous fistulas
 - Multiple small intrapulmonary shunts
 - Hemoglobin with low affinity for oxygen
 - Hemoglobin abnormalities
 - Methemoglobinemia—hereditary, acquired
 - Sulfhemoglobinemia—acquired
 - Carboxyhemoglobinemia (not true cyanosis)

Peripheral Cyanosis

- Reduced cardiac output
- Cold exposure
- Redistribution of blood flow from extremities
- Arterial obstruction
- Venous obstruction

the size of the shunt relative to the systemic flow as well as on the Hb- O_2 saturation of the venous blood. With increased extraction of O_2 from the blood by the exercising muscles, the venous blood returning to the right side of the heart is more unsaturated than at rest, and shunting of this blood intensifies the cyanosis. Secondary polycythemia occurs frequently in patients with arterial O_2 unsaturation and contributes to the cyanosis.

Cyanosis can be caused by small quantities of circulating methemoglobin and by even smaller quantities of sulfhemoglobin. Although they are uncommon causes of cyanosis, these abnormal oxyhemoglobin derivatives should be sought by spectroscopy when cyanosis is not readily explained by malfunction of the circulatory or respiratory systems. Generally, digital clubbing does not occur with them.

Peripheral Cyanosis

Probably the most common cause of peripheral cyanosis is the normal vasoconstriction resulting from exposure to cold air or water. When cardiac output is reduced, cutaneous vasoconstriction occurs as a compensatory mechanism so that blood is diverted from the skin to more vital areas such as the CNS and heart, and cyanosis of the extremities may result even though the arterial blood is normally saturated.

Arterial obstruction to an extremity, as with an embolus, or arteriolar constriction, as in cold-induced vasospasm (Raynaud's phenomenon), generally results in pallor and coldness, and there may be associated cyanosis. Venous obstruction, as in thrombophlebitis, dilates the subpapillary venous plexuses and thereby intensifies cyanosis.

Approach to the Patient: CYANOSIS

Certain features are important in arriving at the cause of cyanosis:

1. It is important to ascertain the time of onset of cyanosis. Cyanosis present since birth or infancy is usually caused by congenital heart disease.
2. Central and peripheral cyanosis must be differentiated. Evidence of disorders of the respiratory or cardiovascular systems is helpful. Massage or gentle warming of a cyanotic extremity will increase peripheral blood flow and abolish peripheral, but not central, cyanosis.
3. The presence or absence of clubbing of the digits (see below) should be ascertained. The combination of cyanosis and clubbing is frequent in patients with congenital heart disease and right-to-left shunting and is seen occasionally in patients with pulmonary disease such as lung abscess or pulmonary arteriovenous fistulae. In contrast, peripheral cyanosis or acutely developing central cyanosis is not associated with clubbed digits.
4. Pa_{O_2} and Sa_{O_2} should be determined, and in patients with cyanosis in whom the mechanism is obscure, spectroscopic examination of the blood should be performed to look for abnormal types of hemoglobin (critical in the differential diagnosis of cyanosis).

CLUBBING

The selective bullous enlargement of the distal segments of the fingers and toes caused by proliferation of connective tissue, particularly on the dorsal surface, is termed *clubbing*; there is also increased sponginess of the

soft tissue at the base of the nail. Clubbing may be hereditary, idiopathic, or acquired and associated with a variety of disorders, including cyanotic congenital heart disease (see earlier), infective endocarditis, and a variety of pulmonary conditions (among them primary and metastatic lung cancer, bronchiectasis, lung abscess, cystic fibrosis, and mesothelioma), as well as with some gastrointestinal diseases (including inflammatory bowel disease and hepatic cirrhosis). In some instances, it is occupational (e.g., in jackhammer operators).

Clubbing in patients with primary and metastatic lung cancer, mesothelioma, bronchiectasis, and hepatic cirrhosis may be associated with *hypertrophic osteoarthropathy*. In this condition, the subperiosteal formation of new bone in the distal diaphyses of the long bones of the extremities causes pain and symmetric arthritis-like changes in the shoulders, knees, ankles, wrists, and elbows. The diagnosis of hypertrophic osteoarthropathy may be confirmed with bone radiography. Although the mechanism of clubbing is unclear, it appears to be secondary to a humoral substance that causes dilation of the vessels of the fingertip.

FURTHER READINGS

- FAWCETT RS et al: Nail abnormalities: Clues to systemic disease. *Am Fam Physician* 69:1417, 2004
- GIORDANO FJ: Oxygen, oxidative stress, hypoxia, and heart failure. *J Clin Invest* 115:500, 2005
- GRIFFEY RT et al: Cyanosis. *J Emerg Med* 18:369, 2000
- HACKETT PH, ROACH RC: Current concepts: High altitude illness. *N Engl J Med* 345:107, 2001
- LEVY MM: Pathophysiology of oxygen delivery in respiratory failure. *Chest* 128(Suppl 2):547S, 2005
- MICHIELS C: Physiological and pathological responses to hypoxia. *Am J Pathol* 164:1875, 2004
- SEMENZA GL: Involvement of oxygen-sensing pathways in physiological and pathological erythropoiesis. *Blood* 114:2015, 2009
- SPICKNALL KE et al: Clubbing: an update on diagnosis, differential diagnosis, pathophysiology, and clinical relevance. *J Am Acad Dermatol* 52:1020, 2005
- TSAI BM et al: Hypoxic pulmonary vasoconstriction in cardiothoracic surgery: Basic mechanisms to potential therapies. *Ann Thorac Surg* 78:360, 2004



CHAPTER 5

DISTURBANCES OF RESPIRATORY FUNCTION

Steven E. Weinberger ■ Ilene M. Rosen

■ Disturbances in Ventilatory Function	25	Mechanisms of Abnormal Function	30
Physiologic Features	25	Clinical Correlations	30
Measurement of Ventilatory Function	27	■ Disturbances in Gas Exchange	30
Patterns of Abnormal Function	28	Physiologic Features	30
Clinical Correlations	29	Measurement of Gas Exchange	31
■ Disturbances in the Pulmonary Circulation	29	Clinical Correlations	34
Physiologic Features	29	Further Readings	35
Methods of Measurement	29		

The respiratory system includes the lungs, the central nervous system (CNS), the chest wall (with the diaphragm and intercostal muscles), and the pulmonary circulation. The CNS controls the activity of the muscles of the chest wall, which constitute the pump of the respiratory system. Because these components of the respiratory system act in concert to achieve gas exchange, malfunction of an individual component or alteration of the relationships among components can lead to disturbances in function. In this chapter, we consider three major aspects of disturbed respiratory function: (1) disturbances in ventilatory function, (2) disturbances in the pulmonary circulation, and (3) disturbances in gas exchange. For further discussion of disorders relating to CNS control of ventilation, see Chap. 22.

DISTURBANCES IN VENTILATORY FUNCTION

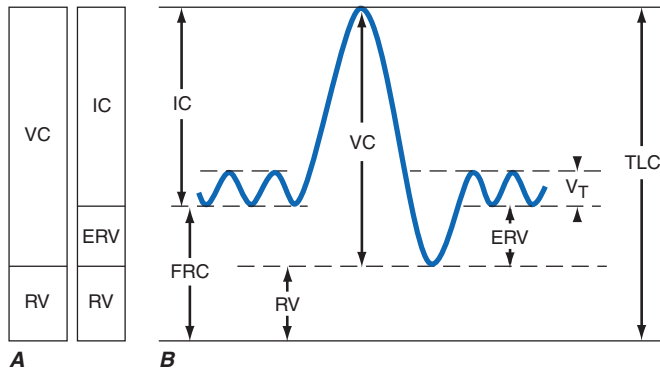
Ventilation is the process whereby the lungs replenish the gas in the alveoli. Measurements of ventilatory function in common diagnostic use consist of quantification of the gas volume contained in the lungs under certain circumstances and the rate at which gas can be expelled from the lungs. The two measurements of lung volume commonly used for respiratory diagnosis are (1) total lung capacity (TLC), which is the volume of gas contained in the lungs after a maximal inspiration, and (2) residual volume (RV),

which is the volume of gas remaining in the lungs at the end of a maximal expiration. The volume of gas that is exhaled from the lungs in going from TLC to RV is the vital capacity (VC) (Fig. 5-1).

Common clinical measurements of airflow are obtained from maneuvers in which the subject inspires to TLC and then forcibly exhales to RV. Three measurements are commonly made from a recording of forced exhaled volume versus time—i.e., a *spirogram*: (1) the volume of gas exhaled during the first second of expiration [forced expiratory volume (FEV) in 1 s, or FEV₁], (2) the total volume exhaled [forced vital capacity (FVC)], and (3) the average expiratory flow rate during the middle 50% of the VC [forced expiratory flow (FEF) between 25 and 75% of the VC, or FEF_{25-75%}, also called the maximal midexpiratory flow rate (MMFR)] (Fig. 5-2).

PHYSIOLOGIC FEATURES

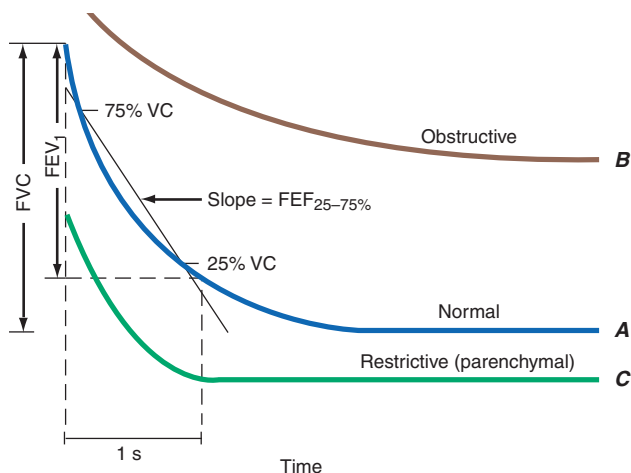
The lungs are elastic structures containing collagen and elastic fibers that resist expansion. For normal lungs to contain air, they must be distended either by a positive internal pressure—i.e., by a pressure in the airways and alveolar spaces—or by a negative external pressure—i.e., by a pressure outside the lung. The relationship between the volume of gas contained in the lungs and the distending pressure (the *transpulmonary pressure*, or P_{TP}, defined as alveolar pressure minus pleural pressure) is

**FIGURE 5-1**

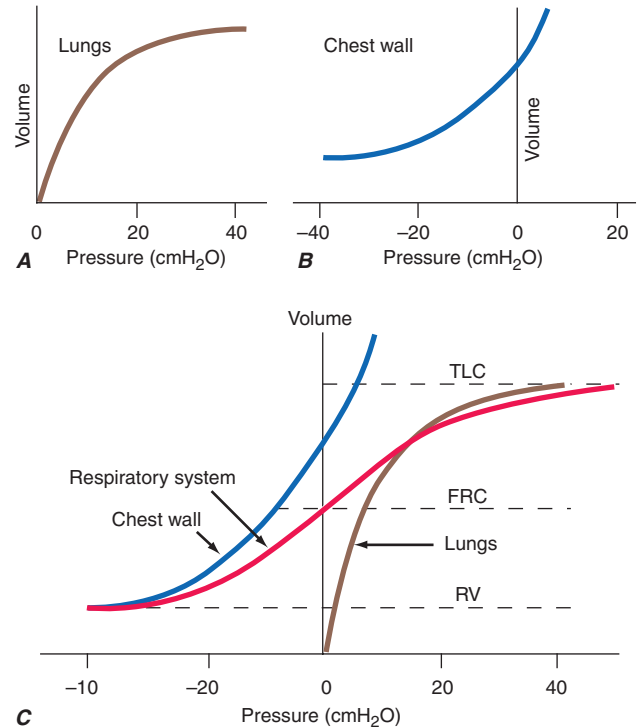
Lung volumes, shown by block diagrams (A) and by a spirometric tracing (B). ERV, expiratory reserve volume; FRC, functional residual capacity; IC, inspiratory capacity; RV, residual volume; TLC, total lung capacity; VC, vital capacity; V_T , tidal volume. (From Weinberger, with permission.)

described by the pressure-volume curve of the lungs (Fig. 5-3A).

The chest wall is also an elastic structure, with properties similar to those of an expandable and compressible spring. The relationship between the volume enclosed by the chest wall and the distending pressure for the chest wall is described by the pressure-volume curve of the chest wall (Fig. 5-3B). For the chest wall to assume a volume different from its resting volume, the internal or external pressures acting on it must be altered.

**FIGURE 5-2**

Spirometric tracings of forced expiration comparing a normal tracing (A) and tracings in obstructive (B) and parenchymal restrictive (C) disease. Calculations of FVC, FEV_1 , and $FEF_{25-75\%}$ are shown only for the normal tracing. Because there is no measure of absolute starting volume with spirometry, the curves are artificially positioned to show the relative starting lung volumes in the different conditions.

**FIGURE 5-3**

Pressure-volume curves. A. Pressure-volume curve of the lungs. B. Pressure-volume curve of the chest wall. C. Pressure-volume curve of the respiratory system showing the superimposed component curves of the lungs and the chest wall. FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity. (From Weinberger, with permission.)

At functional residual capacity (FRC), defined as the volume of gas in the lungs at the end of a normal exhalation, the tendency of the lungs to contract is opposed by the equal and opposite tendency of the chest wall to expand (Fig. 5-3C). For the lungs and the chest wall to achieve a volume other than this resting volume (FRC), either the pressures acting on them must be changed passively—e.g., by a mechanical ventilator that delivers positive pressure to the airways and alveoli—or the respiratory muscles must actively oppose the tendency of the lungs and the chest wall to return to FRC. During inhalation to volumes above FRC, the inspiratory muscles actively overcome the tendency of the respiratory system to decrease volume back to FRC. During active exhalation to volumes below FRC, expiratory muscle activity must overcome the tendency of the respiratory system to increase volume back to FRC.

At TLC, the maximal force applied by the inspiratory muscles to expand the lungs is opposed mainly by the inward recoil of the lungs. As a consequence, the major determinants of TLC are the stiffness of the lungs and inspiratory muscle strength. If the lungs become stiffer—i.e., less compliant and with increased inward recoil—TLC

is decreased. If the lungs become less stiff (more compliant and with decreased inward recoil), TLC is increased. If the inspiratory muscles are significantly weakened, they are less able to overcome the inward elastic recoil of the lungs, and TLC is lowered.

At RV, the force exerted by the expiratory muscles to further decrease lung volume is balanced by the outward recoil of the chest wall, which becomes extremely stiff at low lung volumes. Two factors influence the volume of gas contained in the lungs at RV. The first is the ability of the subject to exert a prolonged expiratory effort, which is related to muscle strength and the ability to overcome sensory stimuli from the chest wall. The second is the ability of the lungs to empty to a small volume. In normal lungs, as P_{TP} is lowered, lung volume decreases. In lungs with diseased airways, as P_{TP} is lowered, flow limitation or airway closure may limit the amount of gas that can be expired. Consequently, either weak expiratory muscles or intrinsic airways disease can result in an elevation in measured RV.

Dynamic measurements of ventilatory function are made by having the subject inhale to TLC and then perform a forced expiration to RV. If a subject performs a series of such expiratory maneuvers using increasing muscular intensity, expiratory flow rates will increase until a certain level of effort is reached. Beyond this level, additional effort at any given lung volume will not increase the forced expiratory flow rate; this phenomenon is known as the *effort independence* of FEF. The physiologic mechanisms determining the flow rates during this effort-independent phase of FEF are the elastic recoil of the lung, the airflow resistance of the airways between the alveolar zone and the physical site of flow limitation, and the airway wall compliance up to the site of flow limitation. Physical processes that decrease elastic recoil, increase airflow resistance, or increase airway wall compliance decrease the flow rate that can be achieved at any given lung volume. Conversely, processes that increase elastic recoil, decrease resistance, or stiffen airway walls increase the flow rate that can be achieved at any given lung volume.

MEASUREMENT OF VENTILATORY FUNCTION

Ventilatory function is measured under static conditions for determination of lung volumes and under dynamic conditions for determination of FEF. VC, expiratory reserve volume (ERV), and inspiratory capacity (IC) (Fig. 5-1) are measured by having the patient breathe into and out of a spirometer, a device capable of measuring expired or inspired gas volume while plotting volume as a function of time. Other volumes—specifically, RV, FRC, and TLC—cannot be measured in this way because they include the volume of gas present in the lungs even after a maximal expiration. Two techniques are

commonly used to measure these volumes: helium dilution and body plethysmography. In the helium dilution method, the subject repeatedly breathes in and out from a reservoir with a known volume of gas containing a trace amount of helium. The helium is diluted by the gas previously present in the lungs, and very little is absorbed into the pulmonary circulation. From knowledge of the reservoir volume and the initial and final helium concentrations, the volume of gas present in the lungs can be calculated. The helium dilution method may underestimate the volume of gas in the lungs if there are slowly communicating airspaces, such as bullae. In this situation, lung volumes can be measured more accurately with a body plethysmograph, a sealed box in which the patient sits while panting against a closed mouthpiece. Because there is no airflow into or out of the plethysmograph, the pressure changes in the thorax during panting cause compression and rarefaction of gas in the lungs and simultaneous rarefaction and compression of gas in the plethysmograph. By measuring the pressure changes in the plethysmograph and at the mouthpiece, the volume of gas in the thorax can be calculated using Boyle's law.

Lung volumes and measurements made during forced expiration are interpreted by comparing the values measured with the values expected given the age, height, gender, and race of the patient (Appendix, Table 14). Because there is some variability among normal individuals, values between 80 and 120% of the predicted value have traditionally been considered normal. Increasingly, calculated percentiles are used in determining normality. Specifically, values of individual measurements falling below the fifth percentile are considered to be below normal.

Obstructive lung disease is determined by a decreased FEV₁/VC ratio, where VC is defined as the largest of the FVC, SVC (slow vital capacity), or IVC (inspiratory vital capacity). Although a ratio <0.7 is typically considered abnormal, the normal value does vary with age. Historically, the FVC was the standard denominator for this ratio, and for most individuals, the FVC, SVC, and IVC are very similar. However, in individuals with airways obstruction, the SVC or IVC may be larger than the FVC. The FEV_{25-75%} is often considered a more sensitive measurement of early airflow obstruction, particularly in small airways. However, this measurement is less specific and must be interpreted cautiously in patients with abnormally small lungs (low TLC and VC). These patients exhale less air during forced expiration, and the FEV_{25-75%} may appear abnormal relative to the usual predicted value even though it is normal relative to the size of the patient's lungs.

It is also a common practice to plot expiratory flow rates against lung volume (rather than against time); the close linkage of flow rates to lung volumes produces a typical *flow-volume curve* (Fig. 5-4). In addition, the

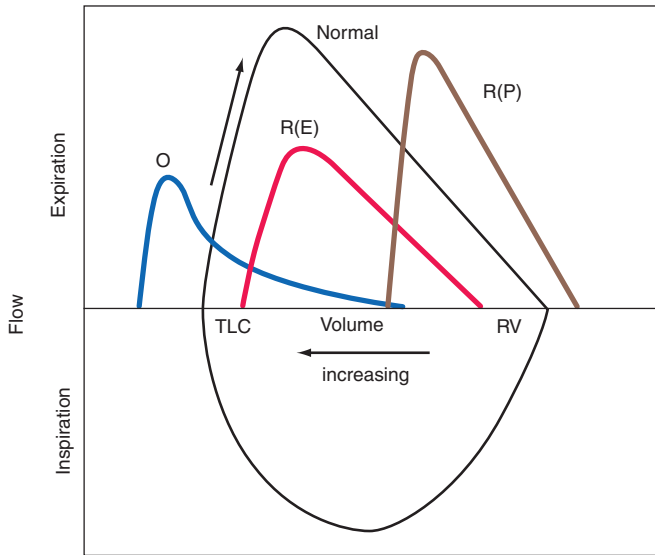


FIGURE 5-4

Flow-volume curves in different conditions: Forced expiration is plotted in all conditions; forced inspiration is shown only for the normal curve. By convention, lung volume increases to the left on the abscissa. The arrow alongside the normal curve indicates the direction of expiration from TLC to RV. TLC, total lung capacity; O, obstructive disease; R(E), extraparenchymal restrictive disease with limitation in inspiration and expiration; R(P), parenchymal restrictive disease; RV, residual volume.

spirometric values mentioned above can be calculated from the flow-volume curve. Commonly, flow rates during a maximal inspiratory effort performed as rapidly as possible are plotted as well, making the flow-volume curve into a *flow-volume loop*. At TLC, before expiratory flow starts, the flow rate is zero; after forced expiration has begun, a high peak flow rate is rapidly achieved. As expiration continues and lung volume approaches RV, the flow rate falls progressively in a nearly linear fashion as a function of lung volume for a person with normal lung function. During maximal inspiration from RV to TLC, inspiratory flow is most rapid at the midpoint of inspiration, so the inspiratory portion of the loop is U shaped or saddle shaped. The flow rates achieved during maximal expiration can be analyzed quantitatively by comparing the flow rates at specified lung volumes with the predicted values or qualitatively by analyzing the shape of the descending limb of the expiratory curve.

Assessing the strength of respiratory muscles is an additional part of the overall evaluation of some patients with respiratory dysfunction. When a patient exhales completely to RV and then tries to inspire maximally against an occluded airway, the pressure that can be generated is called the *maximal inspiratory pressure* (MIP). On the other hand, when a patient inhales to TLC and then

tries to expire maximally against an occluded airway, the pressure generated is called the *maximal expiratory pressure* (MEP). In the proper clinical setting, these studies may provide useful information regarding the cause of abnormal lung volumes and the possibility that respiratory muscle weakness may be causally related to the lung volume abnormalities.

PATTERNS OF ABNORMAL FUNCTION

The two major patterns of abnormal ventilatory function, as measured by static lung volumes and spirometry, are restrictive and obstructive patterns. In the *obstructive pattern*, the hallmark is a decrease in expiratory flow rates. With fully established disease, the ratio FEV_1/VC is decreased, as is the $FEF_{25-75\%}$ (Fig. 5-2, line B). The expiratory portion of the flow-volume loop demonstrates decreased flow rates for any given lung volume. Nonuniform emptying of airways is reflected by a coved (scooped) configuration of the descending part of the expiratory curve (Fig. 5-4). With early obstructive disease, which originates in the small airways, FEV_1/VC may be normal; the only abnormalities noted on routine testing of pulmonary function may be a depression in $FEF_{25-75\%}$ and an abnormal (i.e., coved) configuration in the terminal portion of the forced expiratory flow-volume curve.

In *obstructive* disease, the TLC is normal or increased. When helium equilibration tests are used to measure lung volumes, the measured volume may be less than the actual volume if helium was not well distributed to all regions of the lung. RV is elevated as a result of airway closure during expiration, and the ratio RV/TLC is increased. VC is frequently decreased in obstructive disease because of the striking elevations in RV with only minor changes in TLC.

The hallmark of a *restrictive pattern* is a decrease in lung volumes, primarily TLC and VC. Disorders resulting in a restrictive pattern can be broadly divided into two subgroups, depending on the location of the pathology: pulmonary parenchymal and extraparenchymal. In pulmonary parenchymal disease, RV is also generally decreased, and FEF rates are preserved. In fact, when FEV_1 is considered as a percentage of the FVC, the flow rates are often supranormal, i.e., disproportionately high relative to the size of the lungs (Fig. 5-2, line C). The flow-volume curve may graphically demonstrate this disproportionate relationship between flow rates and lung volumes because the expiratory portion of the curve appears relatively tall (preserved flow rates) but narrow (decreased lung volumes), as shown in Fig. 5-4.

With extraparenchymal disease, dysfunction can be caused by neuromuscular disease with associated respiratory muscle weakness or by disorders of the chest wall or pleura (Table 5-1). In the extraparenchymal diseases, TLC is decreased caused by inspiratory muscle weakness,

TABLE 5-1

ALTERATIONS IN VENTILATORY FUNCTION					
	TLC	RV	VC	FEV ₁ /VC	MIP
Obstructive	N to ↑	↑	↓ or N	↓	N
Restrictive					
Pulmonary parenchymal	↓	↓	↓	N to ↑	N
Extraparenchymal					
Neuromuscular weakness	↓	Variable ^a	↓	Variable ^a	↓
Chest wall deformity	↓	Variable ^b	↓	N	N

^aDepends on expiratory muscle strength.

^bDepends on specific chest wall disorder.

a stiff chest wall, or a space-occupying process within the pleura. If inspiratory muscle weakness is the cause of this pattern, then RV is often not significantly affected, expiratory flow rates are preserved, and MIP is decreased. Alternatively, if the restrictive pattern is caused by a deformed chest wall that is abnormally rigid at volumes below FRC, the ability to expire to a normal RV is also limited. Consequently, RV is often elevated, unlike the pattern observed in the other restrictive subcategories.

CLINICAL CORRELATIONS

Table 5-1 summarizes the typical patterns of altered ventilatory function as indicated by pulmonary function testing. This information can then be useful in diagnosis, as outlined in [Table 5-2](#).

DISTURBANCES IN THE PULMONARY CIRCULATION

PHYSIOLOGIC FEATURES

The pulmonary vasculature must handle the entire output of the right ventricle (i.e., ~5 L/min in a normal adult at rest). The comparatively thin-walled vessels of the pulmonary arterial system provide relatively little resistance to flow and are capable of handling this large volume of blood at perfusion pressures that are low compared with those of the systemic circulation. The normal mean pulmonary artery pressure is 15 mmHg compared with ~95 mmHg for the normal mean aortic pressure. Regional blood flow in the lung is dependent on vascular geometry and on hydrostatic forces. In an upright person, perfusion is least at the apex of the lung and greatest at the base. When cardiac output increases, as occurs during exercise, the pulmonary vasculature is capable of recruiting previously unperfused vessels and distending underperfused vessels, thus responding to the increase in flow with a decrease in pulmonary vascular

resistance. In consequence, the increase in mean pulmonary arterial pressure (PAP), even with a three- to fourfold increase in cardiac output, is small.

METHODS OF MEASUREMENT

Assessment of circulatory function in the pulmonary vasculature depends on measuring pulmonary vascular pressures and cardiac output. Clinically, these measurements are commonly made in intensive care units capable of invasive monitoring and in cardiac catheterization laboratories. With a flow-directed pulmonary arterial

TABLE 5-2

COMMON RESPIRATORY DISEASES BY DIAGNOSTIC CATEGORIES

Obstructive

- Asthma
- Chronic obstructive lung disease (chronic bronchitis, emphysema)
- Bronchiectasis
- Cystic fibrosis
- Bronchiolitis

Restrictive—Parenchymal

- Sarcoidosis
- Idiopathic pulmonary fibrosis
- Pneumoconiosis
- Drug- or radiation-induced interstitial lung disease

Restrictive—Extraparenchymal

- Neuromuscular
 - Diaphragmatic weakness or paralysis
 - Myasthenia gravis
 - Guillain-Barré syndrome
 - Muscular dystrophies
 - Cervical spine injury
- Chest wall
 - Kyphoscoliosis
 - Obesity
 - Ankylosing spondylitis

30 (Swan-Ganz) catheter, PAP and pulmonary capillary wedge pressure can be measured directly, and cardiac output can be obtained by the thermodilution method. Pulmonary vascular resistance (PVR) can then be calculated according to the equation

$$\text{PVR} = 80(\text{PAP} - \text{PCW})/\text{CO}$$

where PVR = pulmonary vascular resistance ($\text{dyn} \cdot \text{s}/\text{cm}^5$); PAP = mean pulmonary arterial pressure (mmHg); PCW = pulmonary capillary wedge pressure (mmHg); and CO = cardiac output (L/min).

The normal value for pulmonary vascular resistance is approximately 50 to 150 $\text{dyn} \cdot \text{s}/\text{cm}^5$.

MECHANISMS OF ABNORMAL FUNCTION

PVR may increase by a variety of mechanisms. Pulmonary arterial and arteriolar vasoconstriction is a prominent response to alveolar hypoxia. PVR also increases if intraluminal thrombi or proliferation of smooth muscle in vessel walls diminishes the luminal cross-sectional area. If small pulmonary vessels are destroyed, either by scarring or by loss of alveolar walls (as in chronic obstructive lung disease), the total cross-sectional area of the pulmonary vascular bed diminishes, and PVR increases. When PVR is elevated, either PAP increases to maintain normal cardiac output or cardiac output decreases if PAP does not increase.

CLINICAL CORRELATIONS

Disturbances in the function of the pulmonary vasculature as a result of primary cardiac disease, either congenital heart disease or conditions that elevate left atrial pressure, such as mitral stenosis, are beyond the scope of this chapter. Instead, the focus will be on the pulmonary vasculature as its function is affected by diseases primarily involving the respiratory system, including the pulmonary vessels themselves.

All diseases of the respiratory system causing hypoxemia are potentially capable of increasing PVR because alveolar hypoxia is a very potent stimulus for pulmonary vasoconstriction. The more prolonged and intense the hypoxic stimulus, the more likely it is that a significant increase in PVR producing pulmonary hypertension will result. In practice, patients with hypoxemia caused by chronic obstructive lung disease, interstitial lung disease, chest wall disease, and the obesity hypoventilation–sleep apnea syndrome are particularly prone to developing pulmonary hypertension. If there are additional structural changes in the pulmonary vasculature secondary to the underlying process, these will increase the likelihood of developing pulmonary hypertension.

With diseases directly affecting the pulmonary vessels, a decrease in the cross-sectional area of the pulmonary

vascular bed is primarily responsible for increased PVR, and hypoxemia generally plays a lesser role. In the case of recurrent pulmonary emboli, parts of the pulmonary arterial system are occluded by intraluminal thrombi originating in the systemic venous system. With primary pulmonary hypertension or pulmonary vascular disease secondary to scleroderma, the small pulmonary arteries and arterioles are affected by a generalized obliterative process that narrows and occludes these vessels. PVR increases and significant pulmonary hypertension often results.

DISTURBANCES IN GAS EXCHANGE

PHYSIOLOGIC FEATURES

The primary functions of the respiratory system are to remove the appropriate amount of CO_2 from blood entering the pulmonary circulation and to provide adequate O_2 to blood leaving the pulmonary circulation. For these functions to be carried out properly, there must be adequate provision of fresh air to the alveoli for delivery of O_2 and removal of CO_2 (ventilation), adequate circulation of blood through the pulmonary vasculature (perfusion), adequate movement of gas between alveoli and pulmonary capillaries (diffusion), and appropriate contact between alveolar gas and pulmonary capillary blood (ventilation–perfusion matching).

A normal individual at rest inspires ~12 to 16 times per minute, each breath having a tidal volume of ~500 mL. A portion (~30%) of the fresh air inspired with each breath does not reach the alveoli but remains in the conducting airways of the lung. This component of each breath, which is not generally available for gas exchange, is called the *anatomic dead space* component. The remaining 70% reaches the alveolar zone, mixes rapidly with the gas already there, and can participate in gas exchange. In this example, the total ventilation each minute is ~7 L, composed of 2 L/min of dead space ventilation and 5 L/min of alveolar ventilation. In certain diseases, some alveoli are ventilated but not perfused, so some ventilation in addition to the anatomic dead space component is wasted. If total dead space ventilation is increased but total minute ventilation is unchanged, then alveolar ventilation must decrease correspondingly.

Gas exchange is dependent on alveolar ventilation rather than total minute ventilation, as outlined below. The partial pressure of CO_2 in arterial blood (Pa_{CO_2}) is directly proportional to the amount of CO_2 produced per minute (\dot{V}_{CO_2}) and inversely proportional to alveolar ventilation (\dot{V}_A), according to the relationship

$$\text{Pa}_{\text{CO}_2} = 0.863 \times \dot{V}_{\text{CO}_2} / \dot{V}_A$$

where \dot{V}_{CO_2} is expressed in mL/min and \dot{V}_A in L/min, and Pa_{CO_2} in mmHg. At fixed \dot{V}_{CO_2} , when alveolar ventilation increases, Pa_{CO_2} decreases, and when alveolar

ventilation decreases, P_{aCO_2} increases. Maintaining a normal level of O_2 in the alveoli (and consequently in arterial blood) also depends on provision of adequate alveolar ventilation to replenish alveolar O_2 . This principle will become more apparent from consideration of the alveolar gas equation below.

Diffusion of O_2 and CO_2

Both O_2 and CO_2 diffuse readily down their respective concentration gradients through the alveolar wall and pulmonary capillary endothelium. Under normal circumstances, this process is rapid, and equilibration of both gases is complete within one-third of the transit time of erythrocytes through the pulmonary capillary bed. Even in disease states in which diffusion of gases is impaired, the impairment is unlikely to be severe enough to prevent equilibration of CO_2 and O_2 . Consequently, a diffusion abnormality rarely results in arterial hypoxemia at rest. If erythrocyte transit time in the pulmonary circulation is shortened, as occurs with exercise, and diffusion is impaired, then diffusion limitation may contribute to hypoxemia. Exercise testing can often demonstrate such physiologically significant abnormalities due to impaired diffusion. Even though diffusion limitation rarely makes a clinically significant contribution to resting hypoxemia, clinical measurements of what is known as *diffusing capacity* (see later) can be a useful measure of the integrity of the alveolar-capillary membrane.

Ventilation-Perfusion Matching

In addition to the absolute levels of alveolar ventilation and perfusion, gas exchange depends critically on the proper matching of ventilation and perfusion. The spectrum of possible ventilation-perfusion (\dot{V}/\dot{Q}) ratios in an alveolar-capillary unit ranges from zero, in which ventilation is totally absent and the unit behaves as a shunt, to infinity, in which perfusion is totally absent and the unit behaves as dead space. The P_{O_2} and P_{CO_2} of blood leaving each alveolar-capillary unit depend on the gas tension (of blood and air) entering that unit and on the particular \dot{V}/\dot{Q} ratio of the unit. At one extreme, when an alveolar-capillary unit has a \dot{V}/\dot{Q} ratio of 0 and behaves as a shunt, blood leaving the unit has the composition of mixed venous blood entering the pulmonary capillaries, i.e., $P_{\bar{v}O_2} \approx 40$ mmHg and $P_{\bar{v}CO_2} \approx 46$ mmHg. At the other extreme, when an alveolar-capillary unit has a high \dot{V}/\dot{Q} ratio, it behaves almost like dead space, and the small amount of blood leaving the unit has partial pressures of O_2 and CO_2 ($P_{O_2} \approx 150$ mmHg, $P_{CO_2} \approx 0$ mmHg while breathing room air) approaching the composition of inspired gas.

In the ideal situation, all alveolar-capillary units have equal matching of ventilation and perfusion (i.e., a ratio of ~ 1 when each is expressed in L/min). However, even

in the normal individual, some \dot{V}/\dot{Q} mismatching is present because there is normally an increasing gradient of blood flow from the apices to the bases of the lungs. There is a similar gradient of ventilation from the apices to the bases, but it is less marked than the perfusion gradient. As a result, ventilation-perfusion ratios are higher at the lung apices than at the lung bases. Therefore, blood coming from the apices has a higher P_{O_2} and lower P_{CO_2} than blood coming from the bases. The net P_{O_2} and P_{CO_2} of the blood mixture coming from all areas of the lung is a flow-weighted average of the individual components, which reflects both the relative amount of blood from each unit and the O_2 and CO_2 content of the blood coming from each unit. Because of the sigmoid shape of the oxyhemoglobin dissociation curve, it is important to distinguish between the partial pressure and the content of O_2 in blood. Hemoglobin is almost fully ($\sim 90\%$) saturated at a P_{O_2} of 60 mmHg, and little additional O_2 is carried by hemoglobin even with a substantial elevation of $P_{O_2} > 60$ mmHg. On the other hand, significant O_2 desaturation of hemoglobin occurs after P_{O_2} to < 60 mmHg and onto the steep descending limb of the curve. As a result, blood coming from regions of the lung with a high \dot{V}/\dot{Q} ratio and a high P_{O_2} has only a small elevation in O_2 content and cannot compensate for blood coming from regions with a low \dot{V}/\dot{Q} ratio and a low P_{O_2} , which has a significantly decreased O_2 content. Although \dot{V}/\dot{Q} mismatching can influence P_{CO_2} , this effect is less marked and is often overcome by an increase in overall minute ventilation.

MEASUREMENT OF GAS EXCHANGE

Arterial Blood Gases

The most commonly used measures of gas exchange are the partial pressures of O_2 and CO_2 in arterial blood (i.e., P_{aO_2} and P_{aCO_2} , respectively). These partial pressures do not measure directly the quantity of O_2 and CO_2 in blood but rather the driving pressure for the gas in blood. The actual quantity or content of a gas in blood also depends on the solubility of the gas in plasma and the ability of any component of blood to react with or bind the gas of interest. Because hemoglobin is capable of binding large amounts of O_2 , oxygenated hemoglobin is the primary form in which O_2 is transported in blood. The actual content of O_2 in blood therefore depends both on the hemoglobin concentration and on the P_{aO_2} . The P_{aO_2} determines what percentage of hemoglobin is saturated with O_2 , based on the position on the oxyhemoglobin dissociation curve. Oxygen content in normal blood (at 37°C , pH 7.4) can be determined by adding the amount of O_2 dissolved in plasma to the amount bound to hemoglobin, according to the equation

$$O_2 \text{ content} = 1.34 \times [\text{hemoglobin}] \\ \times \text{saturation} + 0.0031 \times P_{O_2}$$

32 because each gram of hemoglobin is capable of carrying 1.34 mL O₂ when fully saturated and the amount of O₂ that can be dissolved in plasma is proportional to the P_{O₂}, with 0.0031 mL O₂ dissolved per deciliter of blood per mmHg P_{O₂}. In arterial blood, the amount of O₂ transported dissolved in plasma (~0.3 mL O₂ per deciliter of blood) is trivial compared with the amount bound to hemoglobin (~20 mL O₂ per deciliter of blood).

Most commonly, P_{O₂} is the measurement used to assess the effect of respiratory disease on the oxygenation of arterial blood. Direct measurement of O₂ saturation in arterial blood by oximetry is also important in selected clinical conditions. For example, in patients with carbon monoxide intoxication, carbon monoxide preferentially displaces O₂ from hemoglobin, essentially making a portion of hemoglobin unavailable for binding to O₂. In this circumstance, carbon monoxide saturation is high and O₂ saturation is low, even though the driving pressure for O₂ to bind to hemoglobin, reflected by P_{O₂}, is normal. Measurement of O₂ saturation is also important for the determination of O₂ content when mixed venous blood is sampled from a pulmonary arterial catheter to calculate cardiac output by the Fick technique. In mixed venous blood, the P_{O₂} is normally ~40 mmHg, but small changes in P_{O₂} may reflect relatively large changes in O₂ saturation.

A useful calculation in the assessment of oxygenation is the alveolar-arterial O₂ difference (P_{A_{O₂}} - P_{a_{O₂}}), commonly called the *alveolar-arterial O₂ gradient* (or A - a gradient). This calculation takes into account the fact that alveolar and, hence, arterial P_{O₂} can be expected to change depending on the level of alveolar ventilation, reflected by the arterial P_{CO₂}. When a patient hyperventilates and has a low P_{CO₂} in arterial blood and alveolar gas, alveolar and arterial P_{O₂} will increase; conversely, hypoventilation and a high P_{CO₂} are accompanied by a decrease in alveolar and arterial P_{O₂}. These changes in arterial P_{O₂} are independent of abnormalities in O₂ transfer at the alveolar-capillary level and reflect only the dependence of alveolar P_{O₂} on the level of alveolar ventilation.

To determine the alveolar-arterial O₂ difference, the alveolar P_{O₂} (P_{A_{O₂}}) must first be calculated. The equation most commonly used for this purpose, a simplified form of the alveolar gas equation, is

$$P_{A_{O_2}} = F_{I_{O_2}} \times (P_B - P_{H_2O}) - P_{a_{CO_2}}/R$$

where F_{I_{O₂}} = fractional concentration of inspired O₂ (0.21 when breathing room air); P_B = barometric pressure (~760 mmHg at sea level); P_{H₂O} = water vapor pressure (47 mmHg when air is fully saturated at 37°C); and R = respiratory quotient (the ratio of CO₂ production to O₂ consumption, usually assumed to be 0.8). If the preceding values are substituted into the equation for the patient breathing air at sea level, the equation becomes

$$P_{A_{O_2}} = 150 - 1.25 \times P_{a_{CO_2}}$$

The alveolar-arterial O₂ difference can then be calculated by subtracting measured P_{a_{O₂}} from calculated P_{A_{O₂}}. In a healthy young person breathing room air, the P_{A_{O₂}} - P_{a_{O₂}} is normally <15 mmHg; this value increases with age and may be as high as 30 mmHg in elderly patients.

The adequacy of CO₂ elimination is measured by the partial pressure of CO₂ in arterial blood (i.e., P_{a_{CO₂}}). A more complete understanding of the mechanisms and chronicity of abnormal levels of P_{CO₂} also requires measurement of pH or bicarbonate (HCO₃⁻) because P_{CO₂} and the patient's acid-base status are so closely intertwined (Chap. 40).

Pulse Oximetry

Because measurement of P_{a_{O₂}} requires arterial puncture, it is not ideal either for office use or for routine or frequent measurement in the inpatient setting. Additionally, because it provides intermittent rather than continuous data about the patient's oxygenation, it is not ideal for close monitoring of unstable patients. Pulse oximetry, an alternative method for assessing oxygenation, is readily available in many clinical settings. Using a probe usually clipped over a patient's finger, the pulse oximeter calculates oxygen saturation (rather than P_{a_{O₂}}) based on measurements of absorption of two wavelengths of light by hemoglobin in pulsatile, cutaneous arterial blood. Because of differential absorption of the two wavelengths of light by oxygenated and nonoxygenated hemoglobin, the percentage of hemoglobin that is saturated with oxygen (i.e., the S_{a_{O₂}}) can be calculated and displayed instantaneously.

Although the pulse oximeter is widely used in the noninvasive assessment and monitoring of oxygenation, there are several issues and potential problems concerning its use. First, the clinician must be aware of the relationship between oxygen saturation and tension as shown by the oxyhemoglobin dissociation curve. Because the curve becomes relatively flat above an arterial P_{O₂} of 60 mmHg (corresponding to S_{a_{O₂}} = 90%), the oximeter is relatively insensitive to changes in P_{a_{O₂}} above this level. In addition, the position of the curve and therefore the specific relationship between P_{a_{O₂}} and S_{a_{O₂}} may change depending on factors such as temperature, pH, and the erythrocyte concentration of 2,3-diphosphoglycerate. Second, when cutaneous perfusion is decreased (e.g., owing to low cardiac output or the use of vasoconstrictors), the signal from the oximeter may be less reliable or even unobtainable. Third, other forms of hemoglobin, such as carboxyhemoglobin and methemoglobin, are indistinguishable from oxyhemoglobin when only two wavelengths of light are used. The S_{a_{O₂}} values reported by the pulse oximeter are not reliable in the presence of significant amounts of either of these forms of hemoglobin. In contrast, the device used to measure

oxygen saturation in samples of arterial blood, called the CO-oximeter, uses at least four wavelengths of light and is capable of distinguishing oxyhemoglobin, deoxygenated hemoglobin, carboxyhemoglobin, and methemoglobin. Finally, the clinician must remember that the often-used goal of Sa_{O_2} of 90% or above does not indicate anything about CO_2 elimination and therefore does not ensure a clinically acceptable P_{CO_2} .

Diffusing Capacity

The ability of gas to diffuse across the alveolar-capillary membrane is ordinarily assessed by the diffusing capacity of the lung for carbon monoxide (DL_{CO}). In this test, a small concentration of carbon monoxide (0.3%) is inhaled, usually in a single breath that is held for ~10 s. During the breath hold, the carbon monoxide is diluted by the gas already present in the alveoli and is also taken up by hemoglobin as the erythrocytes course through the pulmonary capillary system. The concentration of carbon monoxide is then measured in the gas exhaled after the breath hold, and DL_{CO} is calculated as the quantity of carbon monoxide absorbed per minute per mmHg pressure gradient from the alveoli to the pulmonary capillaries. The value obtained for DL_{CO} depends on the alveolar-capillary surface area available for gas exchange and on the pulmonary capillary blood volume. In addition, the thickness of the alveolar-capillary membrane, the degree of \dot{V}/\dot{Q} mismatching, and the patient's hemoglobin level will affect the measurement. Because of this effect of hemoglobin levels on DL_{CO} , the measured DL_{CO} is frequently corrected to take the patient's hemoglobin level into account. The value for DL_{CO} , ideally corrected for hemoglobin, can then be compared with a predicted value based either on age, height, and gender or on the alveolar volume (VA) at which the value was obtained. Alternatively, the DL_{CO} can be divided by VA and the resulting value for DL_{CO}/VA compared with a predicted value.

Approach to the Patient: DISTURBANCE OF RESPIRATORY FUNCTION

Arterial Blood Gases Hypoxemia is a common manifestation of a variety of diseases affecting the lungs or other parts of the respiratory system. The broad clinical problem of hypoxemia is often best characterized according to the underlying mechanism. The four basic, and not mutually exclusive, mechanisms of hypoxemia are (1) a decrease in inspired P_{O_2} , (2) hypoventilation, (3) shunting, and (4) \dot{V}/\dot{Q} mismatching. A fifth potential mechanism of hypoxemia, due to decreased diffusion, occurs only under selected clinical circumstances and is not usually included among the general categories

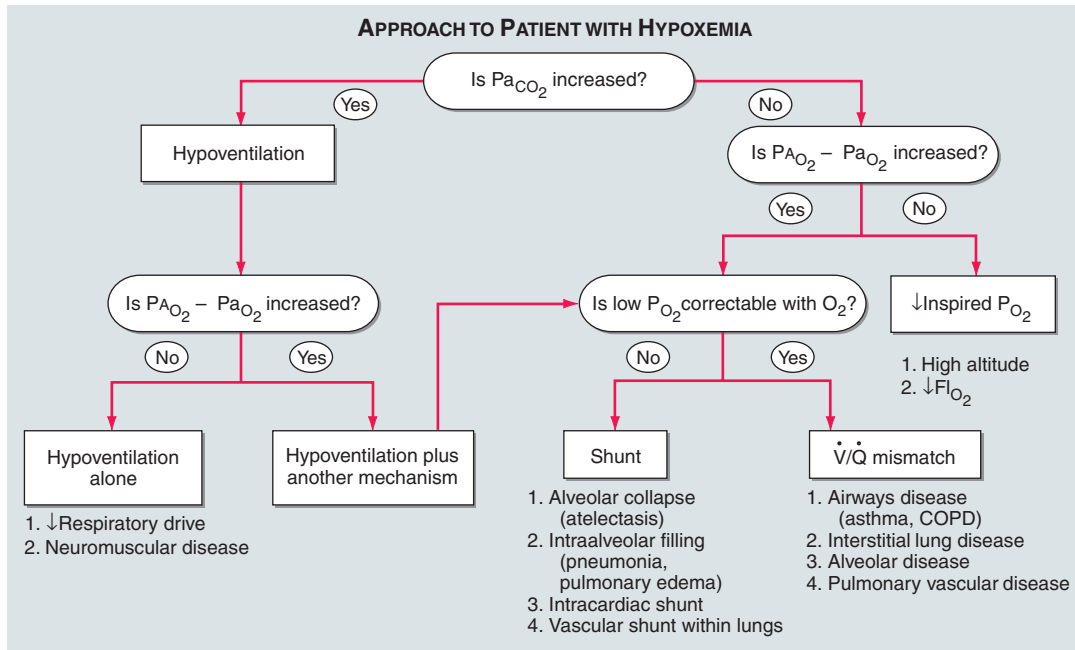
of hypoxemia. Determining the underlying mechanism for hypoxemia depends on measurement of the P_{aCO_2} , calculation of $P_{A_{O_2}} - P_{a_{O_2}}$, and knowledge of the response to supplemental O_2 . A flowchart summarizing the approach to the hypoxemic patient is given in Fig. 5-5. (See also Chap. 4.)

A decrease in the inspired P_{O_2} and hypoventilation both cause hypoxemia by lowering $P_{A_{O_2}}$ and therefore $P_{a_{O_2}}$. In each case, gas exchange at the alveolar-capillary level occurs normally, and $P_{A_{O_2}} - P_{a_{O_2}}$ is not elevated. Hypoxemia due to decreased inspired P_{O_2} can be diagnosed from knowledge of the clinical situation. Inspired P_{O_2} is lowered either because the patient is at a high altitude, where barometric pressure is low, or much less commonly, because the patient is breathing a gas mixture containing <21% O_2 . The hallmark of hypoventilation as a cause of hypoxemia is an elevation in P_{aCO_2} . This is associated with an increase in P_{ACO_2} and a decrease in $P_{A_{O_2}}$. When hypoxemia is due purely to a low inspired P_{O_2} or to alveolar hypoventilation, $P_{A_{O_2}} - P_{a_{O_2}}$ is normal. If $P_{A_{O_2}} - P_{a_{O_2}}$ and P_{aCO_2} are both elevated, then an additional mechanism, such as \dot{V}/\dot{Q} mismatching or shunting, is contributing to hypoxemia.

Shunting is a cause of hypoxemia when desaturated blood effectively bypasses oxygenation at the alveolar-capillary level. This situation occurs either because a structural problem allows desaturated blood to bypass the normal site of gas exchange or because perfused alveoli are not ventilated. Shunting is associated with an elevation in the $P_{A_{O_2}} - P_{a_{O_2}}$ value. When shunting is an important contributing factor to hypoxemia, the lowered $P_{a_{O_2}}$ is relatively refractory to improvement by supplemental O_2 .

Finally, the largest clinical category of hypoxemia is \dot{V}/\dot{Q} mismatching. With \dot{V}/\dot{Q} mismatching, regions with low \dot{V}/\dot{Q} ratios contribute blood with a low P_{O_2} and a low O_2 content. Corresponding regions with high \dot{V}/\dot{Q} ratios contribute blood with a high P_{O_2} . However, because blood is already almost fully saturated at a normal P_{O_2} , elevation of the P_{O_2} to a high value does not significantly increase O_2 saturation or content and therefore cannot compensate for the reduction of O_2 saturation and content in blood coming from regions with a low \dot{V}/\dot{Q} ratio. When \dot{V}/\dot{Q} mismatch is the primary cause of hypoxemia, $P_{A_{O_2}} - P_{a_{O_2}}$ is elevated, and P_{CO_2} generally is normal. Supplemental O_2 corrects the hypoxemia by increasing the P_{O_2} in blood coming from regions with a low \dot{V}/\dot{Q} ratio; this response distinguishes hypoxemia due to \dot{V}/\dot{Q} mismatching from that due to true shunt.

The essential mechanism underlying all cases of hypercapnia is alveolar ventilation that is inadequate for the amount of CO_2 produced. It is conceptually useful to further characterize CO_2 retention based on

**FIGURE 5-5**

Flow diagram outlining the diagnostic approach to the patient with hypoxemia ($P_{aO_2} < 80$ mmHg). $P_{A_{O_2}} - P_{a_{O_2}}$ is usually < 15 mmHg for subjects ≤ 30 years old and younger and

increases by ~ 3 mmHg per decade after age 30 years. COPD, chronic obstructive pulmonary disease.

a more detailed examination of the potential contributing factors. These include (1) increased CO_2 production; (2) decreased ventilatory drive (“won’t breathe”); (3) malfunction of the respiratory pump or increased airways resistance, which makes it more difficult to sustain adequate ventilation (“can’t breathe”); and (4) inefficiency of gas exchange (increased dead space or \dot{V}/\dot{Q} mismatch) necessitating a compensatory increase in overall minute ventilation. In practice, more than one of these mechanisms is commonly responsible for hypercapnia because increased minute ventilation is capable of compensating for increased CO_2 production and for inefficiencies of gas exchange.

Diffusing Capacity Although abnormalities in diffusion are rarely responsible for hypoxemia, clinical measurement of diffusing capacity is frequently used to assess the functional integrity of the alveolar-capillary membrane, which includes the pulmonary capillary bed. Whereas diseases that affect solely the airways generally do not lower DL_{CO} , diseases that affect the alveolar walls or the pulmonary capillary bed do have an effect on DL_{CO} . Even though DL_{CO} is a useful marker for assessing whether disease affecting the alveolar-capillary bed is present, an abnormal DL_{CO} does not necessarily imply that diffusion limitation is responsible for hypoxemia in a particular patient.

CLINICAL CORRELATIONS

Useful clinical correlations can be made with the mechanisms underlying hypoxemia (Fig. 5-5). A lowered inspired P_{O_2} contributes to hypoxemia if either the patient is at high altitude or the concentration of inspired O_2 is $< 21\%$. The latter problem occurs if a patient receiving anesthesia or ventilatory support is inadvertently given a gas mixture to breathe containing $< 21\%$ O_2 or if O_2 is consumed from the ambient gas, as can occur during smoke inhalation from a fire. The primary feature of hypoventilation as a cause of hypoxemia is an elevation in arterial P_{CO_2} .

For further discussion of the clinical correlations with hypoventilation, see Chap. 22.

Shunting as a cause of hypoxemia can reflect transfer of blood from the right to the left side of the heart without passage through the pulmonary circulation, as occurs with an intracardiac shunt. This problem is most common in the setting of cyanotic congenital heart disease, when an interatrial or interventricular septal defect is associated with pulmonary hypertension so that shunting is in the right-to-left rather than the left-to-right direction. Shunting of blood through the pulmonary parenchyma is most frequently due to disease causing absence of ventilation to perfused alveoli. This can occur if the alveoli are atelectatic or if they are filled with fluid, as in pulmonary edema (both cardiogenic

and noncardiogenic), or with extensive intraalveolar exudation of fluid due to pneumonia. Less commonly, vascular anomalies with arteriovenous shunting in the lung can cause hypoxemia. These anomalies can be hereditary, as found with hereditary hemorrhagic telangiectasia (Osler-Rendu-Weber syndrome), or acquired, as in pulmonary vascular malformations secondary to hepatic cirrhosis, which are similar to the commonly recognized cutaneous vascular malformations (“spider hemangiomas”).

Ventilation-perfusion mismatch is the most common cause of hypoxemia clinically. Most of the processes affecting either the airways or the pulmonary parenchyma are distributed unevenly throughout the lungs and do not necessarily affect ventilation and perfusion equally. Whereas some areas of lung may have good perfusion and poor ventilation, others may have poor perfusion and relatively good ventilation. Important examples of airways diseases in which \dot{V}/\dot{Q} mismatch causes hypoxemia are asthma and chronic obstructive lung disease. Parenchymal lung diseases causing \dot{V}/\dot{Q} mismatch and hypoxemia include interstitial lung disease and pneumonia.

Clinically important alterations in CO_2 elimination range from excessive ventilation and hypocapnia to inadequate CO_2 elimination and hypercapnia.

For further discussion of these clinical problems, see Chap. 22.

Diffusing Capacity

Measurement of DL_{CO} may be useful for assessing disease affecting the alveolar-capillary bed or the pulmonary vasculature. In practice, three main categories of disease are associated with lowered DL_{CO} : interstitial lung disease, emphysema, and pulmonary vascular disease. With interstitial lung disease, scarring of alveolar-capillary units diminishes the area of the alveolar-capillary bed as well as pulmonary blood volume. With emphysema, alveolar walls are destroyed, so the surface area of the alveolar-capillary bed is again diminished. In patients with disease causing a decrease in the cross-sectional area and volume of the pulmonary vascular bed, such as recurrent pulmonary

emboli or primary pulmonary hypertension, DL_{CO} is commonly diminished.

Diffusing capacity may be elevated if pulmonary blood volume is increased, as may be seen in congestive heart failure. However, after interstitial and alveolar edema ensues, the net DL_{CO} depends on the opposing influences of increased pulmonary capillary blood volume elevating DL_{CO} and pulmonary edema decreasing it. Finding an elevated DL_{CO} may be useful in the diagnosis of alveolar hemorrhage, as in Goodpasture’s syndrome. Hemoglobin contained in erythrocytes in the alveolar lumen is capable of binding carbon monoxide, so the exhaled carbon monoxide concentration is diminished, and the measured DL_{CO} is increased.

ACKNOWLEDGMENT

We acknowledge the contribution of Dr. Jeffrey M. Drazen to this chapter in previous editions of Harrison’s Principles of Internal Medicine.

FURTHER READINGS

- BRUSASCO V et al: ATS/ERS Task Force Standardization of lung function testing: Standardization of measurements of lung volumes. *Eur Respir J* 26:511, 2005
- et al: ATS/ERS Task Force Standardization of lung function testing: Standardization of spirometry. *Eur Respir J* 26:319, 2005
- et al: ATS/ERS Task Force Standardization of lung function testing: Standardization of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 26:720, 2005
- CELLI BR: The importance of spirometry in COPD and asthma: Effect on approach to management. *Chest* 117(Suppl):15S, 2000
- CHUPP GL (ed): Pulmonary function testing. *Clin Chest Med* 22:599, 2001
- PELLEGRINO R et al: Interpretative strategies for lung function tests. *Eur Respir J* 26:948, 2005
- ROSE BD, Post T: *Clinical Physiology of Acid-Base and Electrolyte Disorders*, 5th ed. New York, McGraw-Hill, 2000
- SCHWARTZSTEIN RM, PARKER MJ: *Respiratory Physiology: A Clinical Approach*. Philadelphia, Lippincott Williams & Wilkins, 2006
- WEINBERGER SE: *Principles of Pulmonary Medicine*, 4th ed. Philadelphia, Saunders, 2004



CHAPTER 6

DIAGNOSTIC PROCEDURES IN RESPIRATORY DISEASE

Scott Manaker ■ Steven E. Weinberger

Imaging Studies	36
Techniques for Obtaining Biologic Specimens	38
■ Further Readings	40

The diagnostic modalities available for assessing a patient with suspected or known respiratory system disease include imaging studies and techniques for acquiring biologic specimens, some of which involve direct visualization of part of the respiratory system. Methods to characterize the functional changes developing as a result of disease, including pulmonary function tests and measurements of gas exchange, are discussed in Chap. 5.

IMAGING STUDIES

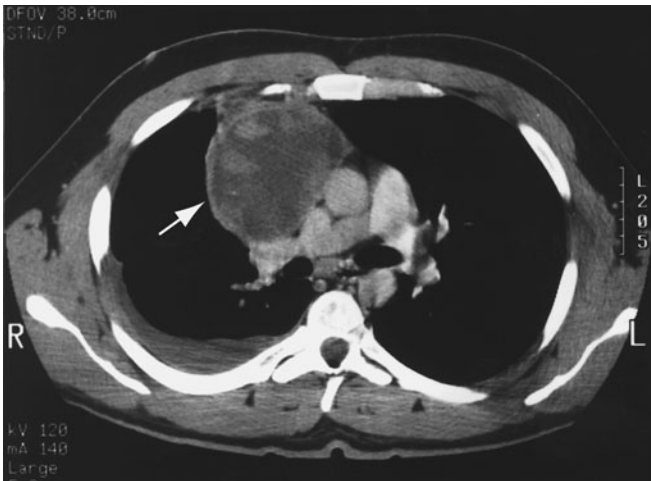
Routine Radiography

Routine chest radiography, generally including both posteroanterior and lateral views, is an integral part of the diagnostic evaluation of diseases involving the pulmonary parenchyma; the pleura; and, to a lesser extent, the airways and the mediastinum (Chap. 7). Whereas lateral decubitus views are often useful for determining whether pleural abnormalities represent freely flowing fluid, apical lordotic views can often visualize disease at the lung apices better than the standard posteroanterior view. Portable equipment, which is often used for acutely ill patients who either cannot be transported to a radiology suite or cannot stand for posteroanterior and lateral views, generally yields a single radiograph taken in the anteroposterior direction. Common radiographic patterns and their clinical correlates are reviewed in Chap. 7.

Computed Tomography

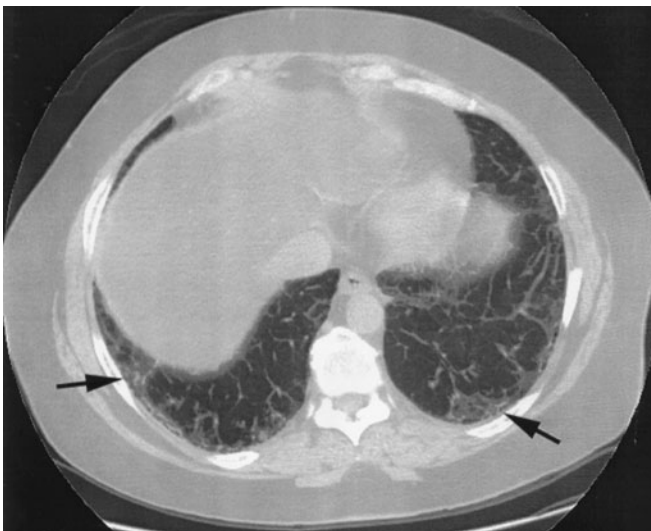
CT offers several advantages over routine chest radiography (Figs. 6-1 and 6-2; see also Figs. 19-3, 19-4, and 30-4). First, the use of cross-sectional images allows distinction between densities that would be superimposed on plain radiographs. Second, CT is far better than routine radiographic studies at characterizing tissue density, distinguishing subtle density differences between adjacent structures, and providing accurate size assessment of lesions. As a result, CT is particularly valuable in assessing hilar and mediastinal disease (which is often poorly characterized by plain radiography), identifying and characterizing disease adjacent to the chest wall or spine (including pleural disease), and identifying areas of fat density or calcification in pulmonary nodules (see Fig. 6-1). Its utility in the assessment of mediastinal disease has made CT an important tool in the staging of lung cancer because an assessment of tumor involvement of mediastinal lymph nodes is critical to proper staging. With the additional use of contrast material, CT also makes it possible to distinguish vascular from nonvascular structures, which is particularly important in distinguishing lymph nodes and masses from vascular structures primarily in the mediastinum.

Helical CT scanning allows the collection of continuous data over a larger volume of lung during a single breath-holding maneuver than is possible with conventional CT. With CT angiography, in which IV contrast is administered and images are acquired rapidly by helical

**FIGURE 6-1**

CT scan demonstrating a mediastinal mass of heterogeneous density (arrow). CT is superior to plain radiography for the detection of abnormal mediastinal densities and the distinction of masses from adjacent vascular structures.

scanning, pulmonary emboli can be detected in segmental and larger pulmonary arteries. With high-resolution CT (HRCT), the thickness of individual cross-sectional images is ~1 to 2 mm rather than the usual 7 to 10 mm, and the images are reconstructed using high-spatial-resolution algorithms. The visible detail on HRCT scans allows better recognition of subtle parenchymal and airway disease, such as bronchiectasis, emphysema, and

**FIGURE 6-2**

High-resolution CT scan from a patient with idiopathic pulmonary fibrosis. There are scattered reticular densities (arrows point to examples) that are especially prominent at the periphery of the lungs. This particular cross-section is from the base of the lungs, where the findings in idiopathic pulmonary fibrosis tend to be most marked.

diffuse parenchymal disease (Fig. 6-2). Certain characteristic patterns have now been recognized for many of the interstitial lung diseases, such as lymphangitic carcinoma, idiopathic pulmonary fibrosis, sarcoidosis, and eosinophilic granuloma; however, it is not yet clear in what settings these patterns obviate the need for obtaining lung tissue.

Recent advances in computer processing of helical scanning data have provided the opportunity to display images in views and planes other than the traditional cross-sectional view, including sophisticated three-dimensional reconstructions, to produce images (called *virtual bronchoscopy*) mimicking direct visualization through a bronchoscope.

Magnetic Resonance Imaging

The role of MRI in the evaluation of respiratory system disease is less well defined than that of CT. Because MRI generally provides a less detailed view of the pulmonary parenchyma as well as poorer spatial resolution, its usefulness in the evaluation of parenchymal lung disease is limited at present. However, MRIs can be reconstructed in sagittal and coronal as well as transverse planes, so the technique is well suited for imaging abnormalities near the lung apex, spine, and thoracoabdominal junction. MRIs depend on tissue characteristics other than density, unlike CT scanning. Therefore, in selected circumstances, MRIs can better suggest the nature of abnormal tissue than can density-determined CT images. Finally, MRI is particularly well suited to evaluating intrathoracic cardiovascular pathology and to distinguishing vascular from nonvascular structures without the need for contrast. Flowing blood does not produce a signal on MRI, so vessels appear as hollow tubular structures. This feature can be useful in determining whether abnormal hilar or mediastinal densities are vascular in origin and in defining aortic lesions, such as aneurysms or dissection. In addition, gadolinium can be used as an intravascular contrast agent for MR angiography.

Scintigraphic Imaging

Radioactive isotopes, administered by either IV or inhaled routes, allow the lungs to be imaged with a gamma camera. In the past, scintigraphic imaging in the form of ventilation-perfusion lung scanning was commonly performed for evaluation of pulmonary embolism. However, with advances in CT scanning, scintigraphic imaging has largely been replaced by CT angiography in patients with suspected pulmonary embolism. When injected intravenously, albumin macroaggregates labeled with technetium 99m become lodged in pulmonary capillaries; therefore, the distribution of the trapped radioisotope follows the distribution of blood flow. When inhaled, radiolabeled xenon gas can be used to

38 demonstrate the distribution of ventilation. For example, pulmonary thromboembolism usually produces one or more regions of ventilation-perfusion mismatch (i.e., regions in which there is a defect in perfusion that follows the distribution of a vessel and that is not accompanied by a corresponding defect in ventilation) (Chap. 20). Another common use of such radioisotope scans is in a patient with impaired lung function who is being considered for lung resection. The distribution of the isotope(s) can be used to assess the regional distribution of blood flow and ventilation, allowing the physician to estimate the level of postoperative lung function.

Positron Emission Tomographic Scanning

Positron emission tomographic (PET) scanning is increasingly being used to identify malignant lesions in the lung based on their increased uptake and metabolism of glucose. The technique involves injection of a radiolabeled glucose analogue, [^{18}F]-fluoro-2-deoxyglucose (FDG), which is taken up by metabolically active malignant cells. However, FDG is trapped within the cell after phosphorylation, and the unstable fluorine 18 decays by emission of positrons, which can be detected by a specialized PET camera or by a gamma camera that has been adapted for imaging of positron-emitting nuclides. This technique has been used in the evaluation of solitary pulmonary nodules and as an aid to staging lung cancer through identification of mediastinal lymph node involvement by malignancy.

Pulmonary Angiography

The pulmonary arterial system can be visualized by pulmonary angiography, in which radiopaque contrast medium is injected through a catheter previously placed in the pulmonary artery. When performed in cases of pulmonary embolism, pulmonary angiography demonstrates the consequences of an intravascular thrombus—either a defect in the lumen of a vessel (a “filling defect”) or an abrupt termination (“cutoff”) of the vessel. Other less common indications for pulmonary angiography include visualization of a suspected pulmonary arteriovenous malformation and assessment of pulmonary arterial invasion by a neoplasm. However, with advances in CT scanning, traditional pulmonary angiography has largely been replaced by CT angiography. The latter allows rapid acquisition of images with a less invasive procedure because the radiocontrast material is injected intravenously rather than into a pulmonary artery.

Ultrasonography

Because ultrasound energy is rapidly dissipated in air, ultrasound imaging is not useful for evaluation of the

pulmonary parenchyma. However, ultrasonography is helpful in the detection and localization of pleural abnormalities and is often used as a guide to placement of a needle for sampling of pleural liquid (i.e., for thoracentesis). Endobronchial ultrasonography, in which the ultrasound probe is passed through a bronchoscope, is emerging as a valuable adjunct to bronchoscopy, allowing identification and localization of pathology adjacent to airway walls or within the mediastinum.

TECHNIQUES FOR OBTAINING BIOLOGIC SPECIMENS

Collection of Sputum

Sputum can be collected either by spontaneous expectoration or after inhalation of an irritating aerosol, such as hypertonic saline. The latter method, called *sputum induction*, is commonly used to obtain sputum for diagnostic studies, either because sputum is not spontaneously being produced or because of an expected higher yield of certain types of findings. Knowledge of the appearance and quality of the sputum specimen obtained is especially important when one is interested in Gram's staining and culture. Because sputum consists mainly of secretions from the tracheobronchial tree rather than the upper airway, the finding of alveolar macrophages and other inflammatory cells is consistent with a lower respiratory tract origin of the sample, whereas the presence of squamous epithelial cells in a “sputum” sample indicates contamination by secretions from the upper airways.

In addition to processing for routine bacterial pathogens by Gram's staining and culture, sputum can be processed for a variety of other pathogens, including staining and culture for mycobacteria or fungi, culture for viruses, and staining for *Pneumocystis jiroveci*. In the specific case of sputum obtained for evaluation of *P. jiroveci* pneumonia in a patient infected with HIV, for example, sputum should be collected by induction rather than spontaneous expectoration, and an immunofluorescent stain should be used to detect the organisms. Cytologic staining of sputum for malignant cells using the traditional Papanicolaou method allows noninvasive evaluation for suspected lung cancer. Traditional stains and cultures are now also being supplemented in some cases by immunologic techniques and by molecular biologic methods, including the use of polymerase chain reaction amplification and DNA probes.

Percutaneous Needle Aspiration

A needle can be inserted through the chest wall into a pulmonary lesion to aspirate material for analysis by cytologic or microbiologic techniques. The procedure is usually carried out under CT guidance to assist positioning

of the needle and assure localization in the lesion. The low potential risk of this procedure (intrapulmonary bleeding or creation of a pneumothorax with collapse of the underlying lung) in experienced hands is usually acceptable owing to the information obtained. However, a limitation of the technique is sampling error due to the small size of the tissue sample. Thus, findings other than a specific cytologic or microbiologic diagnosis are of limited clinical value.

Thoracentesis

Sampling of pleural liquid by thoracentesis is commonly performed for diagnostic purposes or, in the case of a large effusion, for palliation of dyspnea. Diagnostic sampling, either by blind needle aspiration or after localization by ultrasonography, allows the collection of liquid for microbiologic and cytologic studies. Analysis of the fluid obtained for its cellular composition and chemical constituents, including glucose, protein, and lactate dehydrogenase, allows the effusion to be classified as either exudative or transudative (Chap. 21).

Bronchoscopy

Bronchoscopy is the process of direct visualization of the tracheobronchial tree. Although bronchoscopy is now performed almost exclusively with flexible fiberoptic instruments, rigid bronchoscopy, generally performed in an operating room on a patient under general anesthesia, still has a role in selected circumstances, primarily because of a larger suction channel and the fact that the patient can be ventilated through the bronchoscope channel. These situations include the retrieval of a foreign body and the suctioning of a massive hemorrhage, for which the small suction channel of the bronchoscope may be insufficient.

Flexible Fiberoptic Bronchoscopy

This outpatient procedure is usually performed in an awake but sedated patient. The bronchoscope is passed through either the mouth or the nose, between the vocal cords, and into the trachea. The ability to flex the scope makes it possible to visualize virtually all airways to the level of subsegmental bronchi. The bronchoscopist is able to identify endobronchial pathology, including tumors, granulomas, bronchitis, foreign bodies, and sites of bleeding. Samples from airway lesions can be taken by several methods, including washing, brushing, and biopsy. Washing involves instillation of sterile saline through a channel of the bronchoscope and onto the surface of a lesion. A portion of the liquid is collected by suctioning through the bronchoscope, and the recovered material can be analyzed for cells (cytology) or organisms (by standard stains and cultures). Brushing or biopsy of the surface of the lesion, using a small brush or biopsy

forceps at the end of a long cable inserted through a channel of the bronchoscope, allows recovery of cellular material or tissue for analysis by standard cytologic and histopathologic methods.

The bronchoscope can be used to sample material not only from the regions that can be directly visualized (i.e., the airways) but also from the more distal pulmonary parenchyma. With the bronchoscope wedged into a subsegmental airway, aliquots of sterile saline can be instilled through the scope, allowing sampling of cells and organisms even from alveolar spaces. This procedure, called *bronchoalveolar lavage*, has been particularly useful for the recovery of organisms such as *P. jiroveci* in patients with HIV infection.

Brushing and biopsy of the distal lung parenchyma can also be performed with the same instruments that are used for endobronchial sampling. These instruments can be passed through the scope into small airways, where they penetrate the airway wall, allowing biopsy of peribronchial alveolar tissue. This procedure, called *transbronchial biopsy*, is used when there is either relatively diffuse disease or a localized lesion of adequate size. With the aid of fluoroscopic imaging, the bronchoscopist is able to determine not only whether and when the instrument is in the area of abnormality but also the proximity of the instrument to the pleural surface. If the forceps are too close to the pleural surface, there is a risk of violating the visceral pleura and creating a pneumothorax; the other potential complication of transbronchial biopsy is pulmonary hemorrhage. The incidence of these complications is less than several percent.

Another procedure involves use of a hollow-bore needle passed through the bronchoscope for sampling of tissue adjacent to the trachea or a large bronchus. The needle is passed through the airway wall, and cellular material can be aspirated from mass lesions or enlarged lymph nodes, generally in a search for malignant cells. This procedure can facilitate the staging of lung cancer by identifying mediastinal lymph node involvement and in some cases obviates the need for a more invasive procedure. Other promising new techniques that are not yet widely available include fluorescence bronchoscopy (to detect early endobronchial malignancy) and endobronchial ultrasonography (to better identify and localize peribronchial and mediastinal pathology).

The bronchoscope may provide the opportunity for treatment as well as diagnosis. For example, an aspirated foreign body may be retrieved with an instrument passed through the scope, and bleeding may be controlled with a similarly introduced balloon catheter. Newer interventional techniques performed through a bronchoscope include methods for achieving and maintaining patency of airways that are partially or completely occluded, especially by tumors. These techniques include laser therapy, cryotherapy, argon plasma coagulation, electrocautery, and stent placement.

Advances in video technology have allowed the development of thoracoscopy, or video-assisted thoracic surgery (VATS), for the diagnosis and management of pleural as well as parenchymal lung disease. This procedure involves the passage of a rigid scope with a distal lens through a trocar inserted into the pleura. A high-quality image is shown on a monitor screen, allowing the operator to manipulate instruments passed into the pleural space through separate small intercostal incisions. With these instruments, the operator can biopsy lesions of the pleura under direct vision. In addition, this procedure is now used commonly to biopsy peripheral lung tissue or to remove peripheral nodules for both diagnostic and therapeutic purposes. This much less invasive procedure has largely supplanted the traditional “open lung biopsy” performed by thoracotomy.

Thoracotomy

Although frequently replaced by VATS, thoracotomy remains an option for the diagnostic sampling of lung tissue. It provides the largest amount of material, and it can be used to biopsy or excise lesions that are too deep or too close to vital structures for removal by VATS. The choice between VATS and thoracotomy needs to be made on a case-by-case basis.

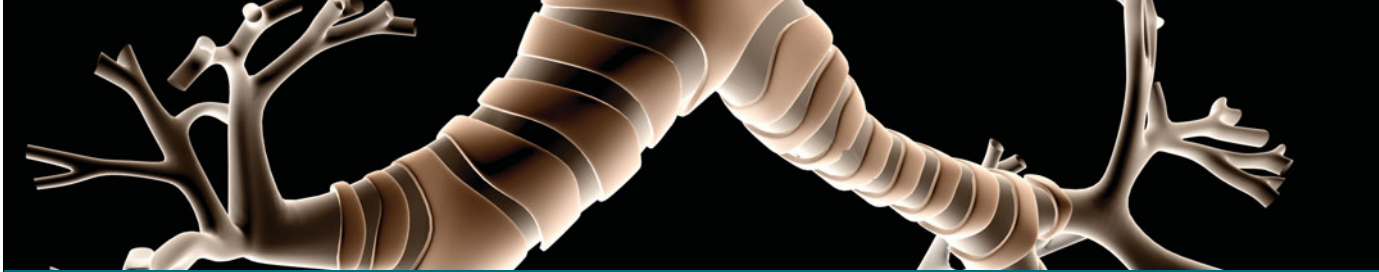
Mediastinoscopy and Mediastinotomy

Tissue biopsy is often critical for the diagnosis of mediastinal masses or enlarged mediastinal lymph nodes. Although CT and PET scanning are useful for determining the size and nature of mediastinal lymph nodes as part of the staging of lung cancer, confirmation that enlarged lymph nodes are actually involved with a tumor generally

requires biopsy and histopathologic examination. The two major procedures used to obtain specimens from masses or nodes in the mediastinum are mediastinoscopy (via a suprasternal approach) and mediastinotomy (via a parasternal approach). Both procedures are performed under general anesthesia by a qualified surgeon. In the case of suprasternal mediastinoscopy, a rigid mediastinoscope is inserted at the suprasternal notch and passed into the mediastinum along a pathway just anterior to the trachea. Tissue can be obtained with biopsy forceps passed through the scope, sampling masses or nodes that are in a paratracheal or pretracheal position. Left paratracheal and aortopulmonary lymph nodes are not accessible by this route and thus are commonly sampled by parasternal mediastinotomy (the Chamberlain procedure). This approach involves either a right or a left parasternal incision and dissection directly down to a mass or node that requires biopsy.

FURTHER READINGS

- DETTERTBECK FC et al: Seeking a home for a PET. Defining the appropriate place for positron emission tomography imaging in the diagnosis of pulmonary nodules or masses. *Chest* 125:2294, 2300, 2004
- DE WEVER W et al: Multidetector CT-generated virtual bronchoscopy: An illustrated review of the potential clinical indications. *Eur Respir J* 23:776, 2004
- ERNST A et al: Interventional pulmonary procedures: Guidelines from the American College of Chest Physicians. *Chest* 123:1693, 2003
- FELLER-KOPMAN D et al: Autofluorescence bronchoscopy and endobronchial ultrasound: A practical review. *Ann Thorac Surg* 80:2395, 2005
- LIN J, IANNETTONI MD: The role of thoracoscopy in the management of lung cancer. *Surgical Oncol* 12:195, 2003
- PATEL S, KAZEROONI EA: Helical CT for the evaluation of acute pulmonary embolism. *AJR Am J Roentgenol* 185:135, 2005
- WEINBERGER SE: *Principles of Pulmonary Medicine*, 4th ed. Philadelphia, Saunders, 2004



CHAPTER 7

ATLAS OF CHEST IMAGING

Patricia A. Kritek ■ John J. Reilly, Jr.

This atlas of chest imaging is a collection of interesting chest radiographs and computed tomograms of the chest. The readings of the films are meant to be illustrative

of specific, major findings. The associated text is not intended as a comprehensive assessment of the images.

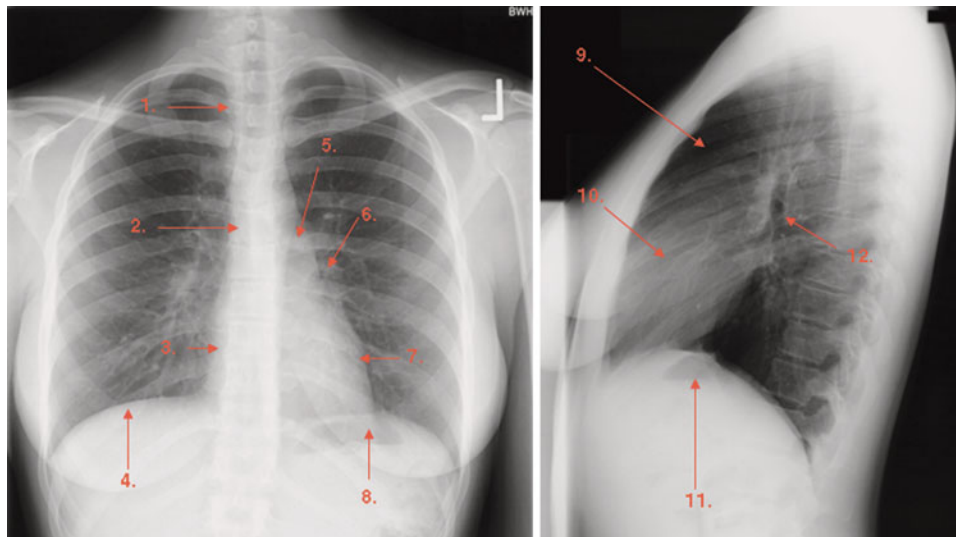
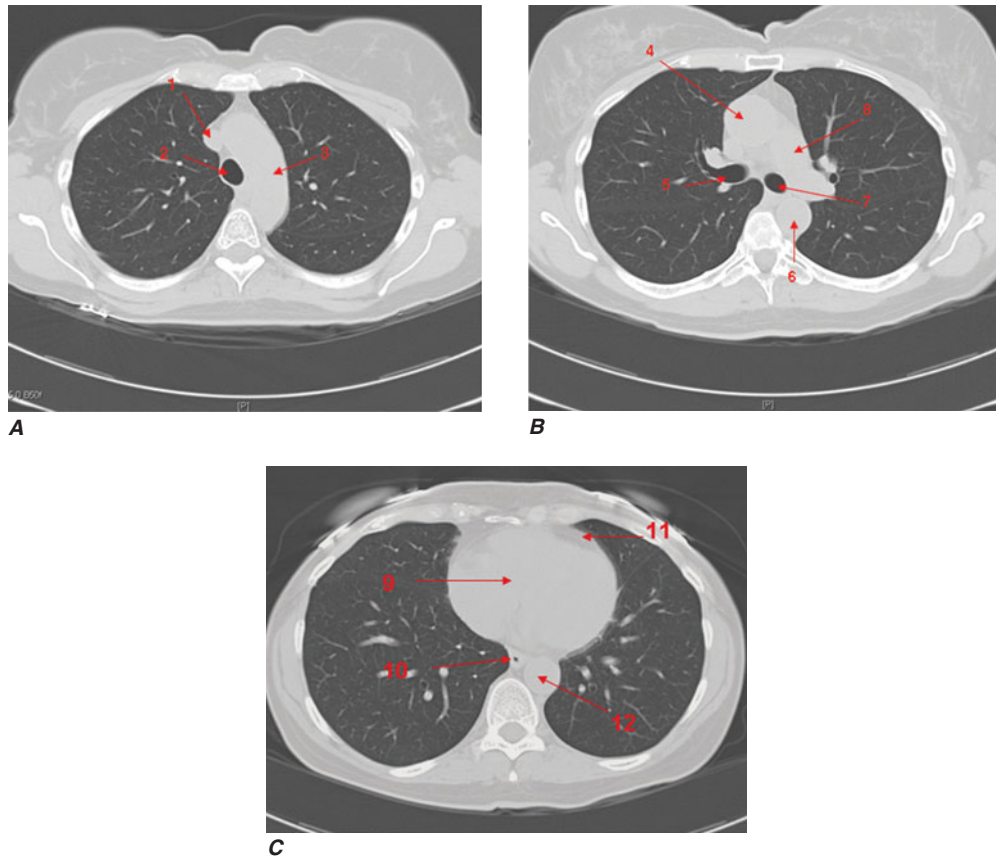


FIGURE 7-1

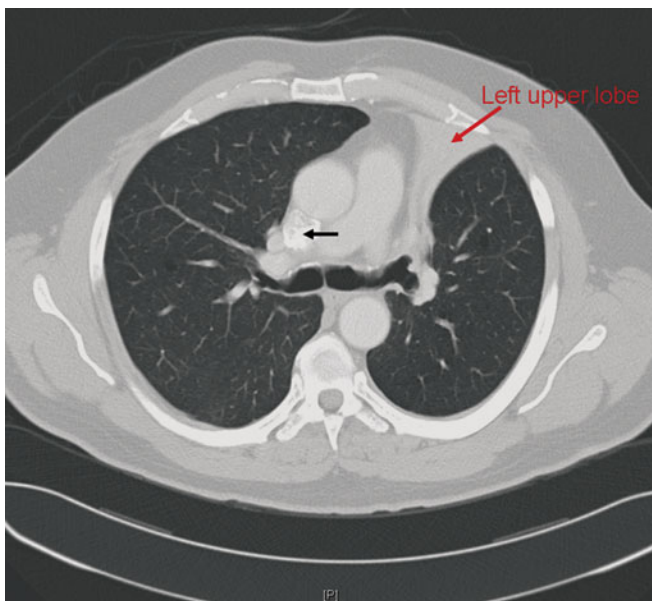
Normal chest radiograph—review of anatomy. 1. Trachea. 2. Carina. 3. Right atrium. 4. Right hemi-diaphragm. 5. Aortic knob. 6. Left hilum. 7. Left ventricle. 8. Left hemi-diaphragm

(with stomach bubble). 9. Retrosternal clear space. 10. Right ventricle. 11. Left hemi-diaphragm (with stomach bubble). 12. Left upper lobe bronchus.

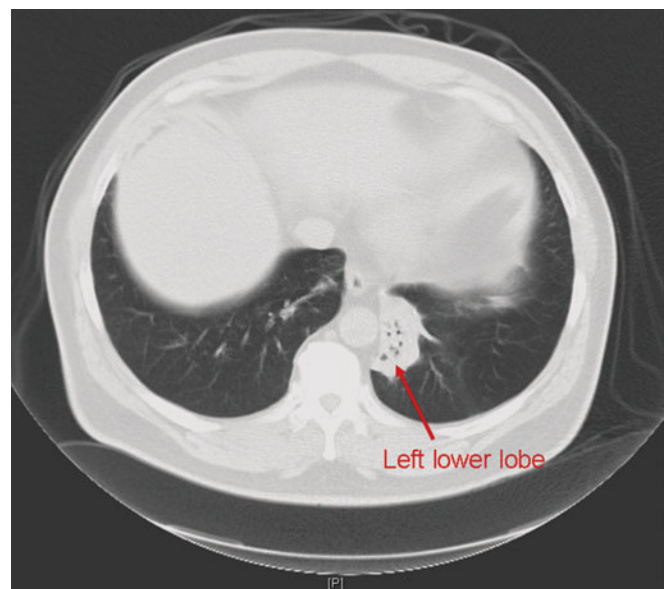
**FIGURE 7-2**

Normal chest tomogram—note anatomy. 1. Superior vena cava. 2. Trachea. 3. Aortic arch. 4. Ascending aorta. 5. Right mainstem bronchus. 6. Descending aorta. 7. Left mainstem

bronchus. 8. Main pulmonary artery. 9. Heart. 10. Esophagus. 11. Pericardium. 12. Descending aorta.

**FIGURE 7-3**

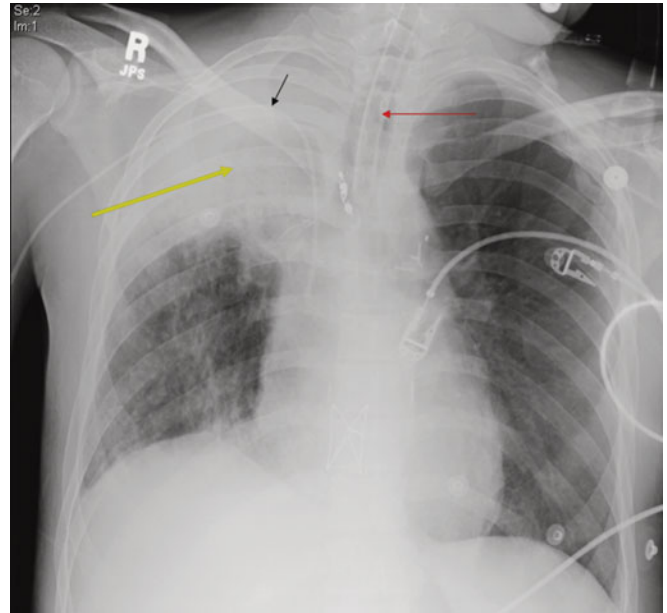
CT scan demonstrating left upper lobe collapse. The patient was found to have an endobronchial lesion (not visible on the CT scan) resulting in this finding. The superior vena cava (*black arrow*) is partially opacified by IV contrast.

**FIGURE 7-4**

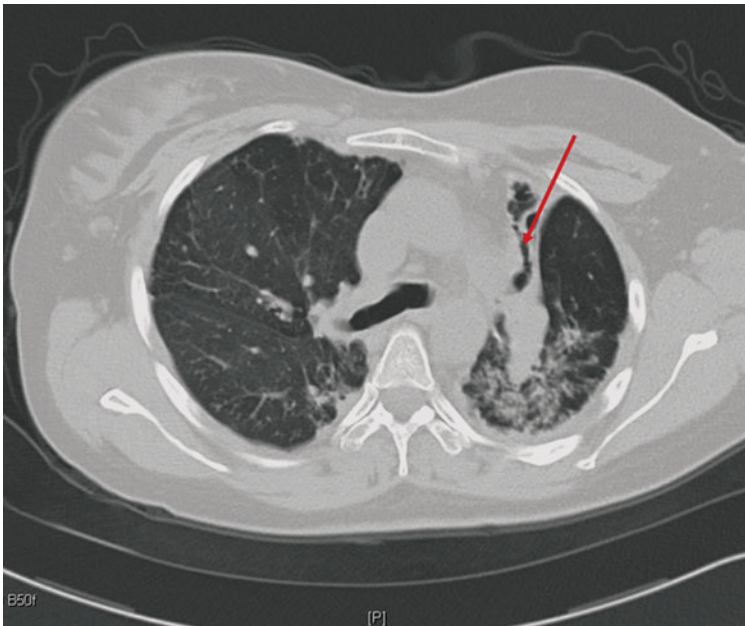
CT scan revealing chronic left lower lobe collapse. Note dramatic volume loss with minimal aeration. There is subtle mediastinal shift to the left.

**FIGURE 7-5**

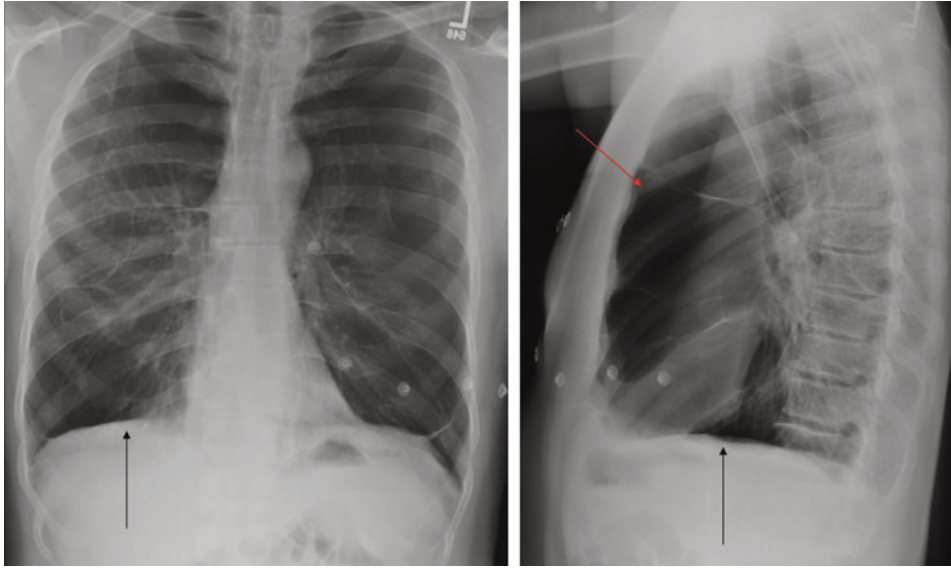
Left upper lobe scarring with hilar retraction with less prominent scarring in right upper lobe as well. These findings are consistent with previous tuberculosis infection. The patient was an immigrant from Ecuador.

**FIGURE 7-7**

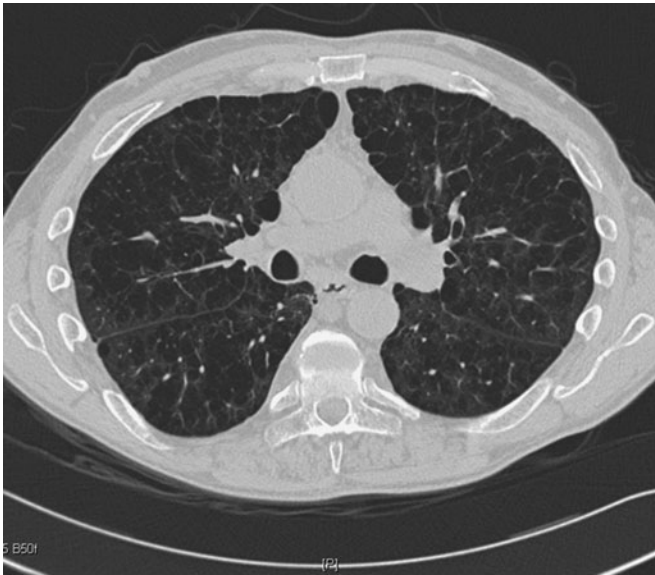
Chest x-ray (CXR) demonstrating right upper lobe collapse (yellow arrow). Note the volume loss as demonstrated by the elevated right hemi-diaphragm as well as mediastinal shift to the right. Also apparent on the film are an endotracheal tube (red arrow) and a central venous catheter (black arrow).

**FIGURE 7-6**

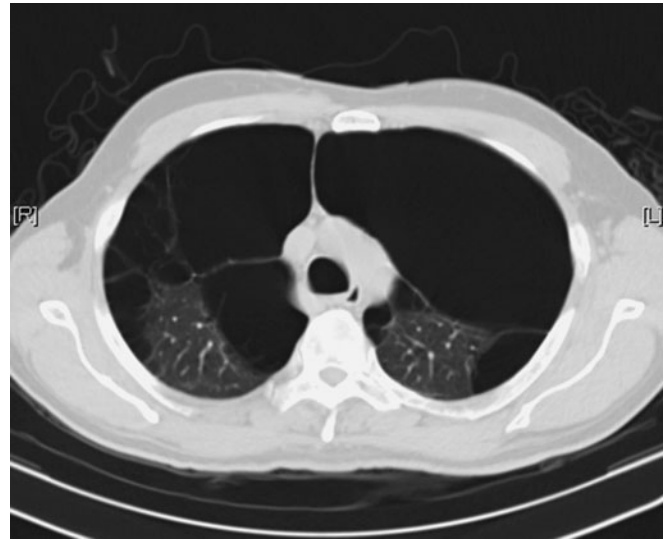
Apical scarring, traction bronchiectasis (red arrow), and **decreased lung volume** consistent with previous tuberculosis infection. The findings are more significant in the left lung.

**FIGURE 7-8**

Emphysema with increased lucency, flattened diaphragms (*black arrows*), increased anteroposterior (AP) diameter, and increased retrosternal clear space (*red arrow*).

**FIGURE 7-9**

CT scan of diffuse, bilateral emphysema.

**FIGURE 7-10**

CT scan of bullous emphysema.

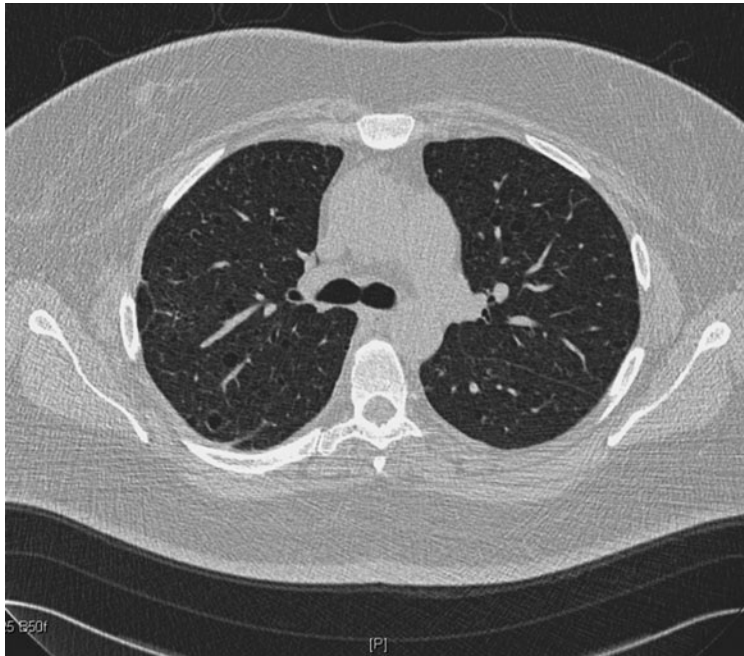


FIGURE 7-11
Multiple, thin-walled cysts consistent with lymphangioleiomyomatosis.

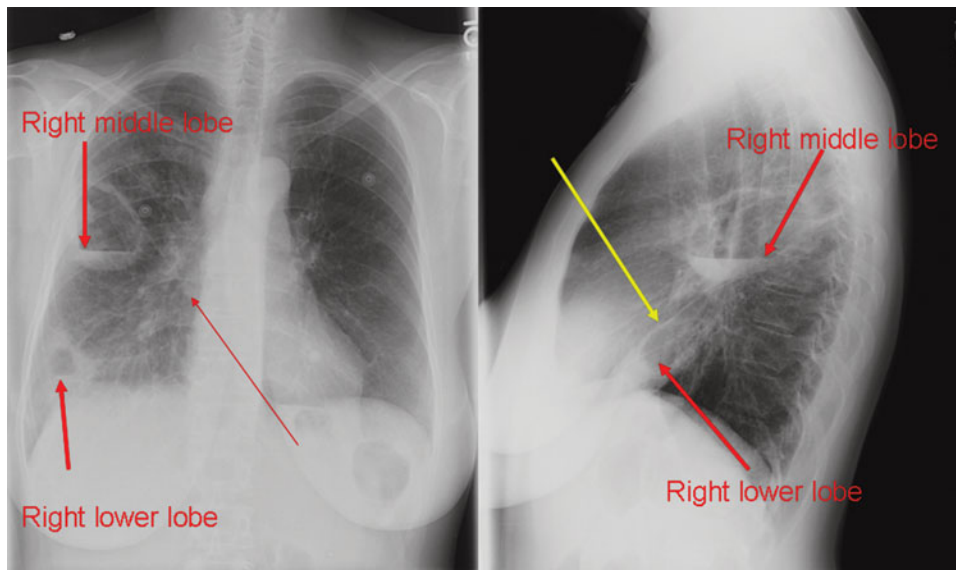


FIGURE 7-12
Two cavities on posteroanterior (PA) and lateral CXR. Cavities and air-fluid levels are identified by *red arrows*. The smaller cavity is in the right lower lobe (located below the major fissure, identified with the *yellow arrow*) and the larger

cavity is located in the right middle lobe, which is located between the minor (*red arrow*) and major fissures. An area of consolidation associated with the cavity is seen in the right lower lobe.



FIGURE 7-13
CT scan of parenchymal cavity.



FIGURE 7-15
Pulmonary edema. Note indistinct vasculature, perihilar opacities, and peripheral interstitial reticular opacities. Although, this is an AP film, making cardiac size more difficult to assess, the cardiac silhouette still appears enlarged.

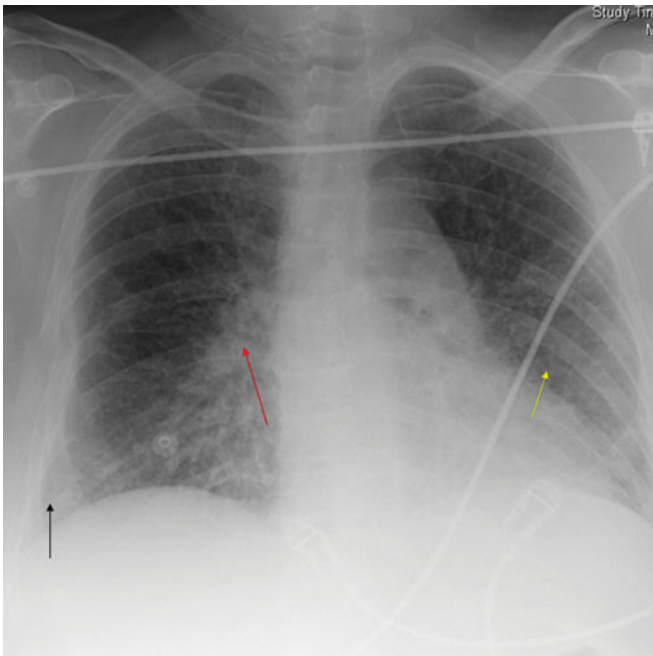
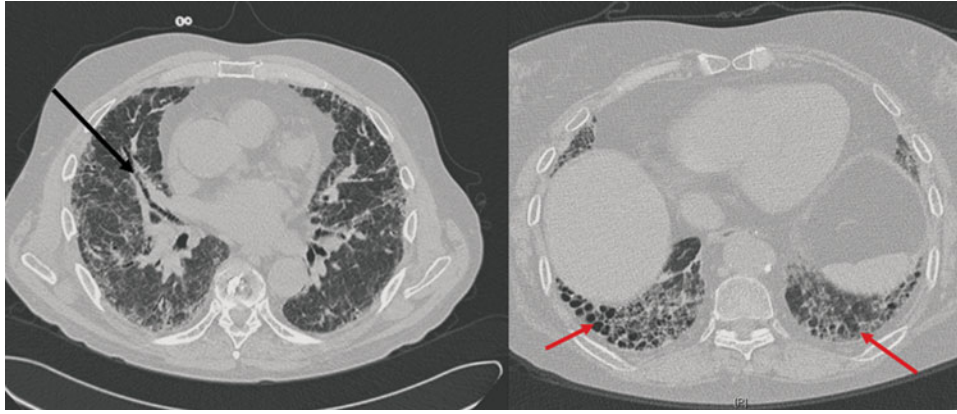


FIGURE 7-14
Mild congestive heart failure. Note the Kerley B lines (*black arrow*) and perivascular cuffing (*yellow arrow*) as well as the pulmonary vascular congestion (*red arrow*).



FIGURE 7-16
CXR demonstrating reticular nodular opacities bilaterally with small lung volumes consistent with usual interstitial pneumonitis (UIP) on pathology. Clinically, *UIP* is used interchangeably with *idiopathic pulmonary fibrosis* (IPF).

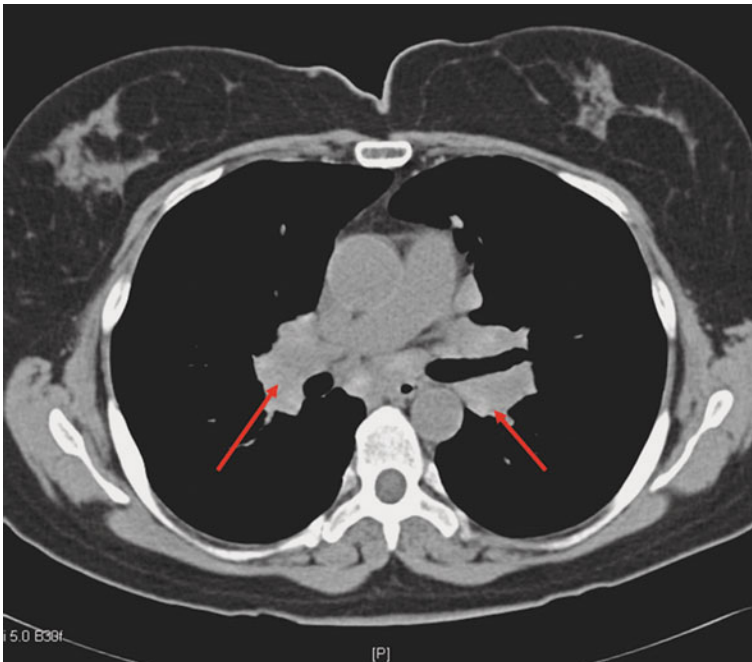
**FIGURE 7-17**

CT scan of usual interstitial pneumonitis (UIP), also known as idiopathic pulmonary fibrosis (IPF). Classic findings include traction bronchiectasis (*black arrow*) and honeycombing

(*red arrows*). Note the subpleural, basilar predominance of the honeycombing.

**FIGURE 7-18**

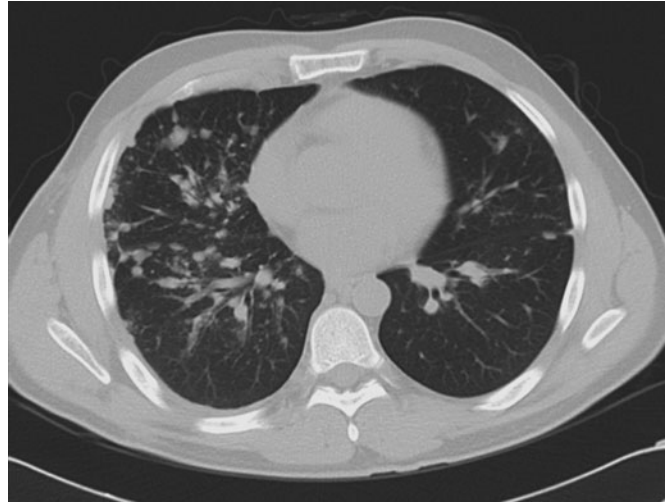
Sarcoid—CXR of stage I (hilar lymphadenopathy without parenchymal infiltrates).

**FIGURE 7-19**

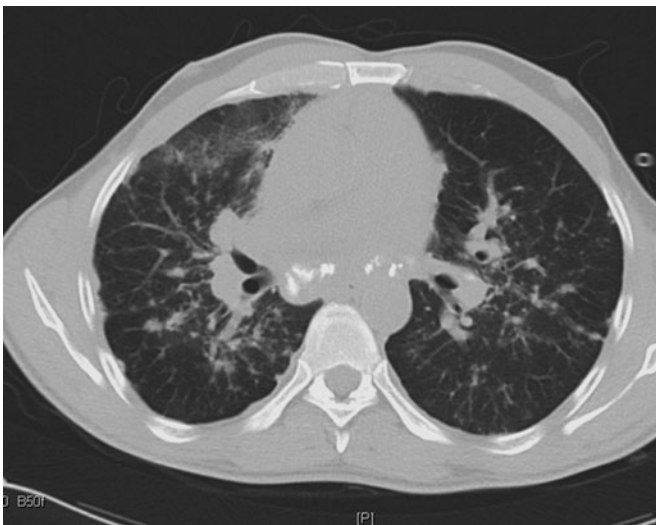
Sarcoid—CT scan of stage I demonstrating bulky hilar and mediastinal lymphadenopathy (*red arrows*) without parenchymal infiltrates.

**FIGURE 7-20**

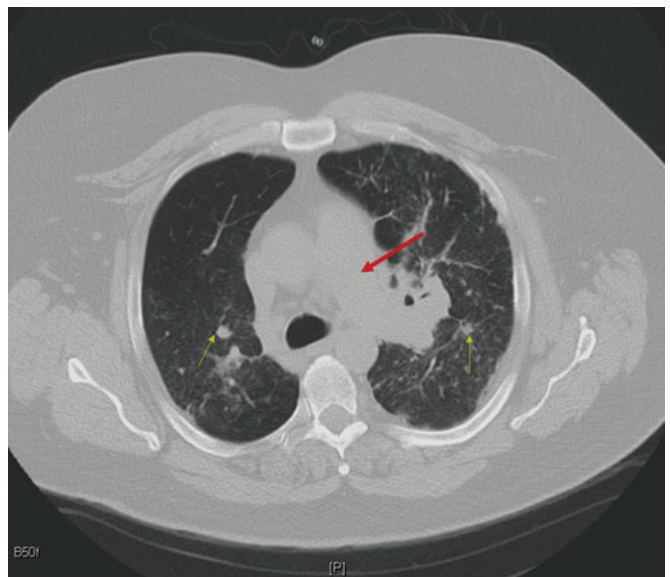
Sarcoid—CXR of stage II (lymphadenopathy with parenchymal changes). Note the apical predominance of the disease. The diaphragms are also flattened, suggesting hyperinflation.

**FIGURE 7-22**

Sarcoid—CT scan of stage II (nodular opacities tracking along bronchovascular bundles).

**FIGURE 7-21**

Sarcoid—CT scan of stage II (calcified lymphadenopathy, parenchymal infiltrates).

**FIGURE 7-23**

Sarcoid—stage III with nodular parenchymal infiltrates (yellow arrows) and no lymphadenopathy. Also note the large pulmonary artery (red arrow).



FIGURE 7-24
Sarcoid—stage IV (fibrotic lung disease).

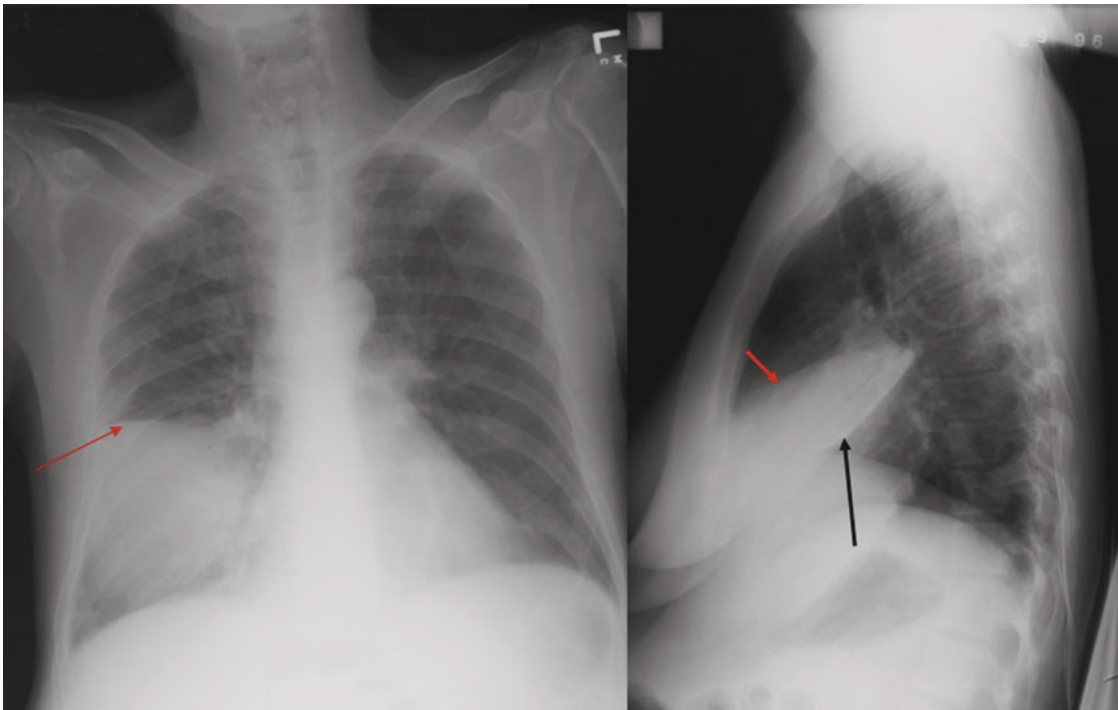
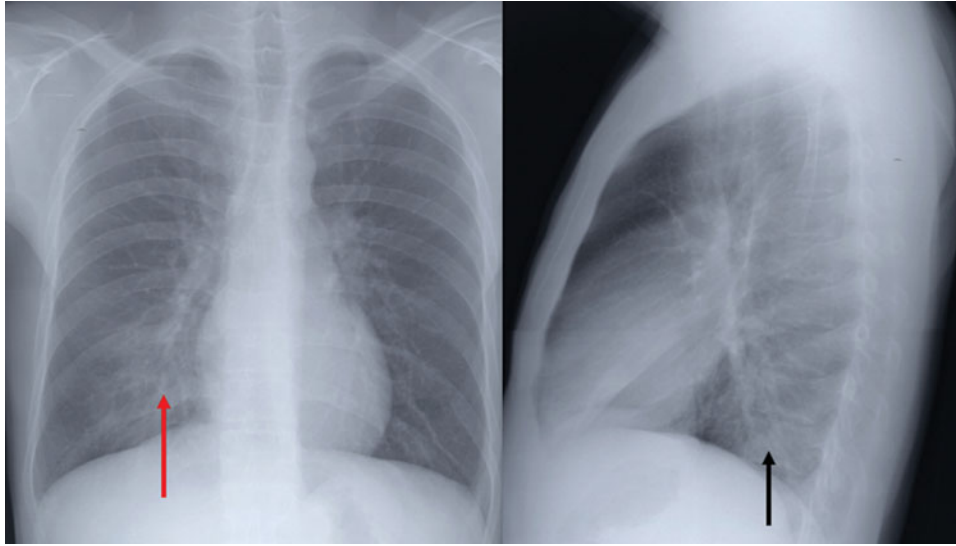
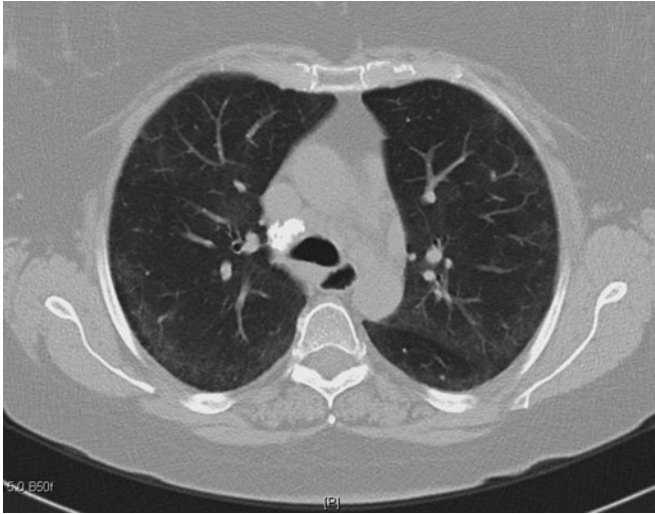


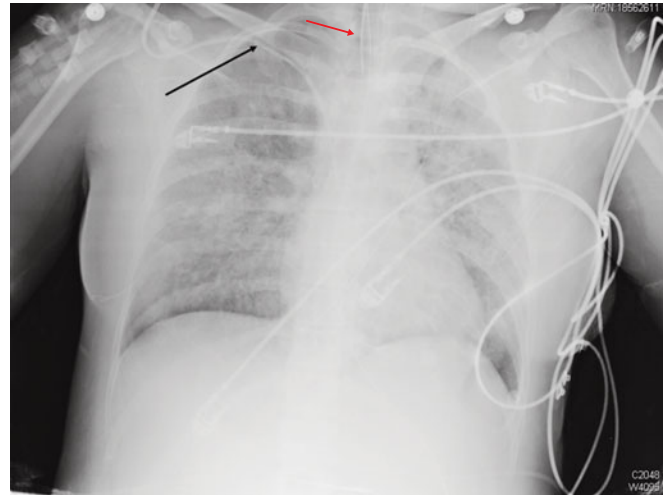
FIGURE 7-25
Right middle lobe opacity illustrating major (*black arrow*) and minor fissures (*red arrows*) as well as the “silhouette sign” on the right heart border.

**FIGURE 7-26**

Right lower lobe pneumonia. There is subtle opacity on the PA film (*red arrow*), and the lateral film illustrates the “spine sign” (*black arrow*) where the lower spine does not become more lucent.

**FIGURE 7-27**

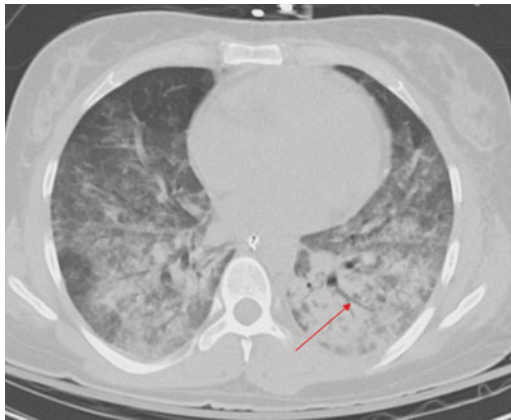
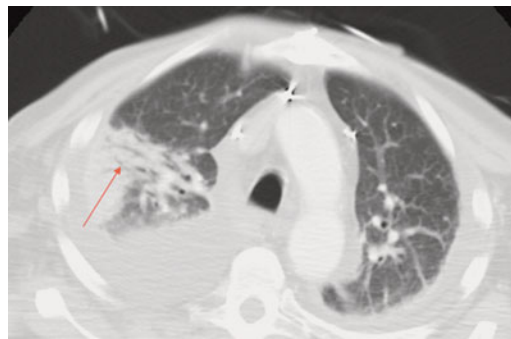
CT scan of diffuse, bilateral “ground-glass” infiltrates. This finding is consistent with fluid density in the alveolar space.

**FIGURE 7-28**

CXR revealing diffuse, bilateral alveolar infiltrates without pleural effusions consistent with acute respiratory distress syndrome (ARDS). Note that the patient has an endotracheal tube (*red arrow*) and a central venous catheter (*black arrow*).

**FIGURE 7-29**

CT scan of acute respiratory distress syndrome (ARDS) demonstrates ground-glass infiltrates with more consolidated areas in the dependent lung zones.

**A****B****C****FIGURE 7-30**

(A) to (C) Three examples of air bronchograms (red arrows) on chest CT.



FIGURE 7-31
Cystic fibrosis with bronchiectasis, apical disease.

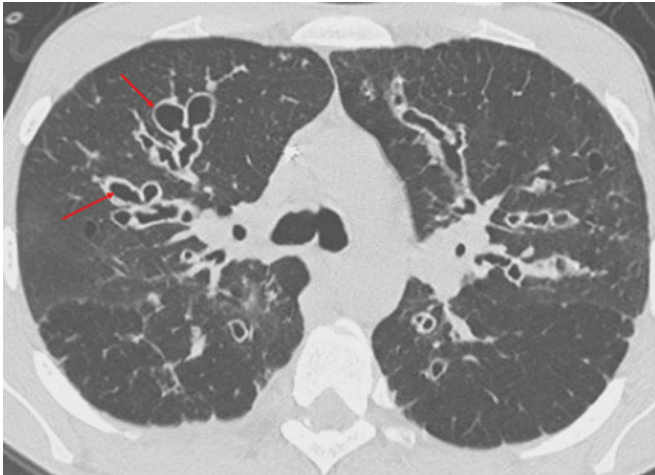


FIGURE 7-32
CT scan of diffuse, cystic bronchiectasis (*red arrows*) in a patient with cystic fibrosis.

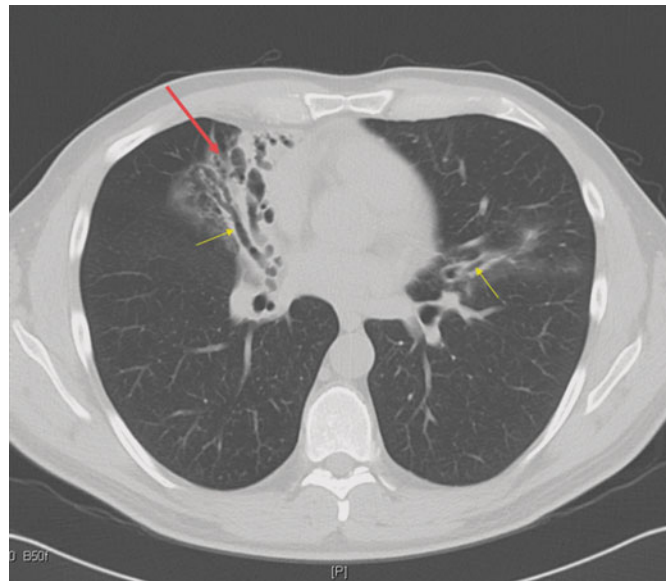
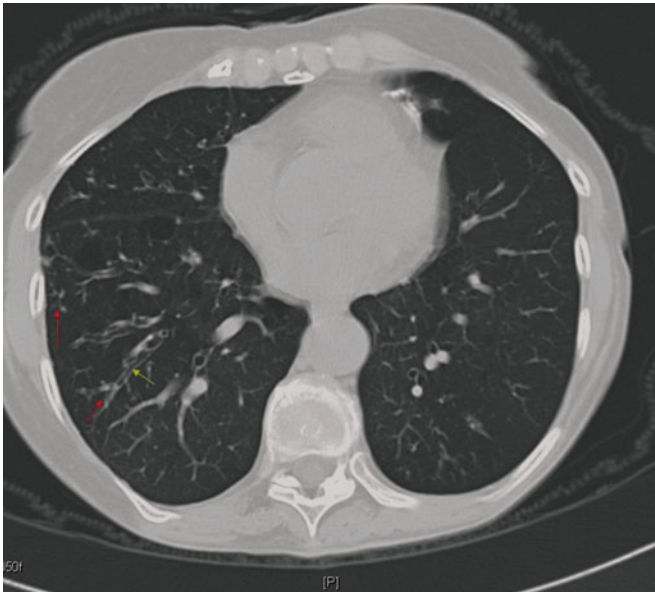
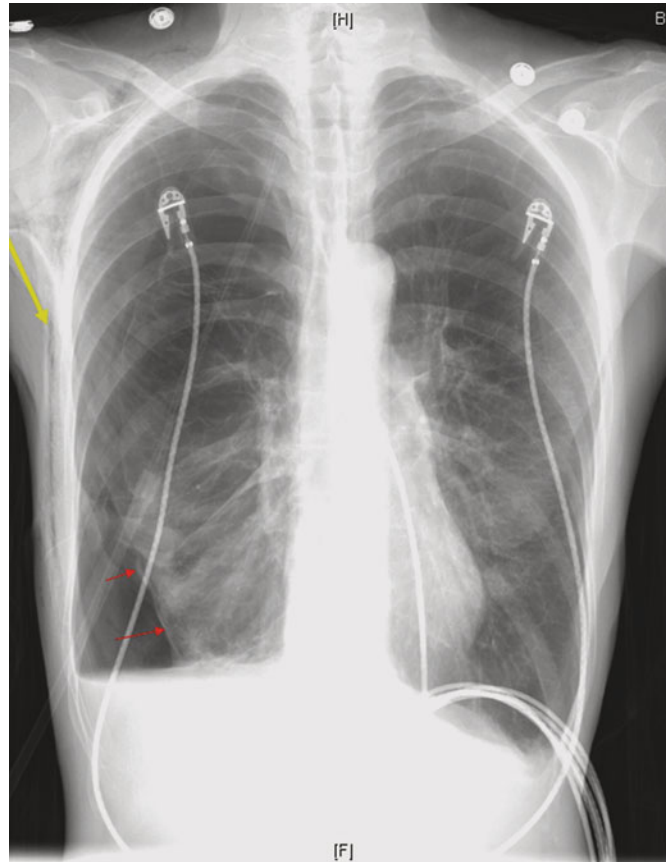


FIGURE 7-33
CT scan of focal right middle lobe and lingular bronchiectasis (*yellow arrows*). Note that there is near total collapse of the right middle lobe (*red arrow*).

**FIGURE 7-34**

“Tree in bud” opacities (*red arrows*) and bronchiectasis (*yellow arrow*) consistent with atypical mycobacterial infection. “Tree in bud” refers to small nodules clustered around the centrilobular arteries as well as increased prominence of the centrilobular branching. These findings are consistent with bronchiolitis.

**FIGURE 7-36**

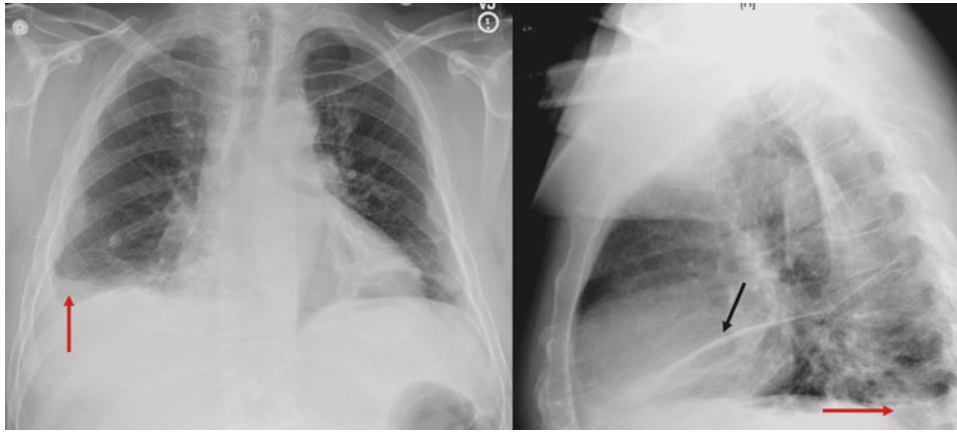
Basilar pneumothorax with visible pleural reflection (*red arrows*). Also note that the patient has subcutaneous emphysema (*yellow arrow*).

**FIGURE 7-35**

Large right pneumothorax with near complete collapse of the right lung. Pleural reflection highlighted with *red arrows*.

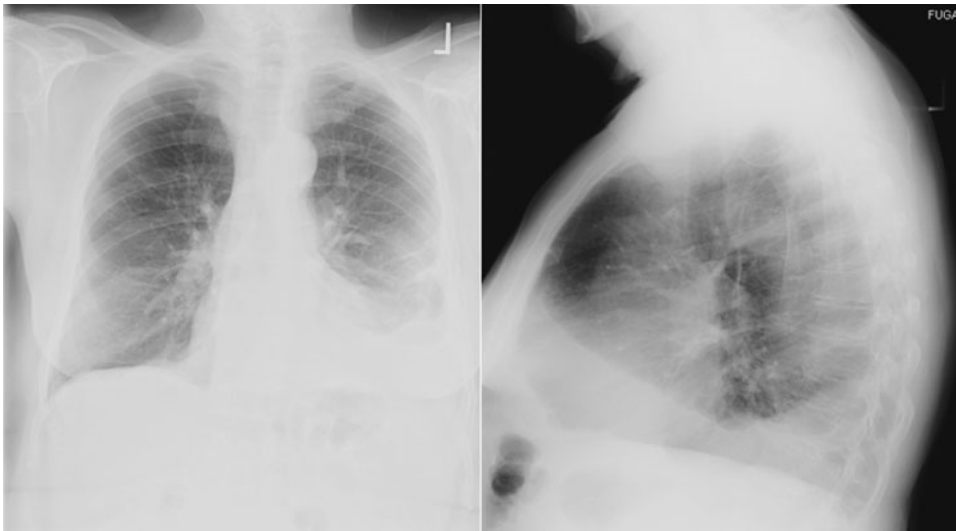
**FIGURE 7-37**

CT scan of large right-sided pneumothorax. Note the significant collapse of the right lung with adhesion to the anterior chest wall. Pleural reflection is highlighted with *red arrows*. The patient has severe underlying emphysema.

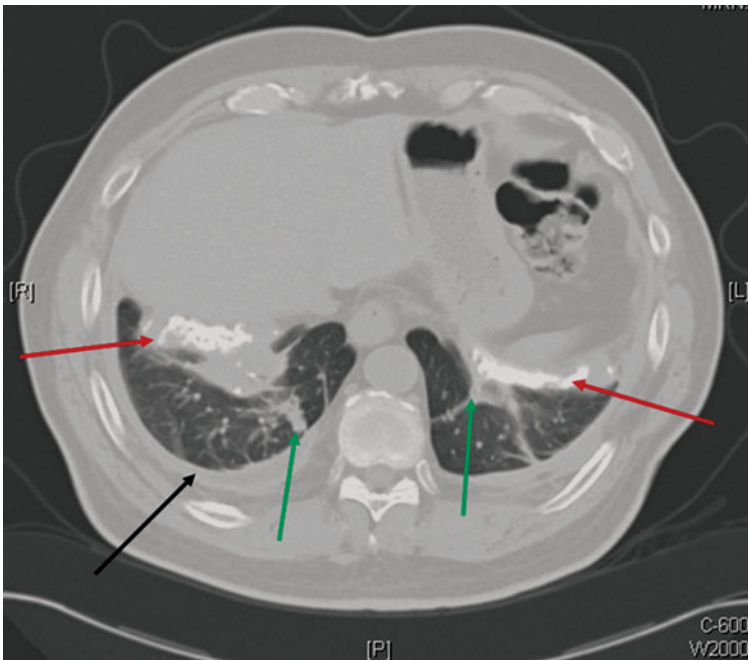
**FIGURE 7-38**

Small right pleural effusion (*red arrows* highlight blunted right costophrenic angles) with associated pleural thickening.

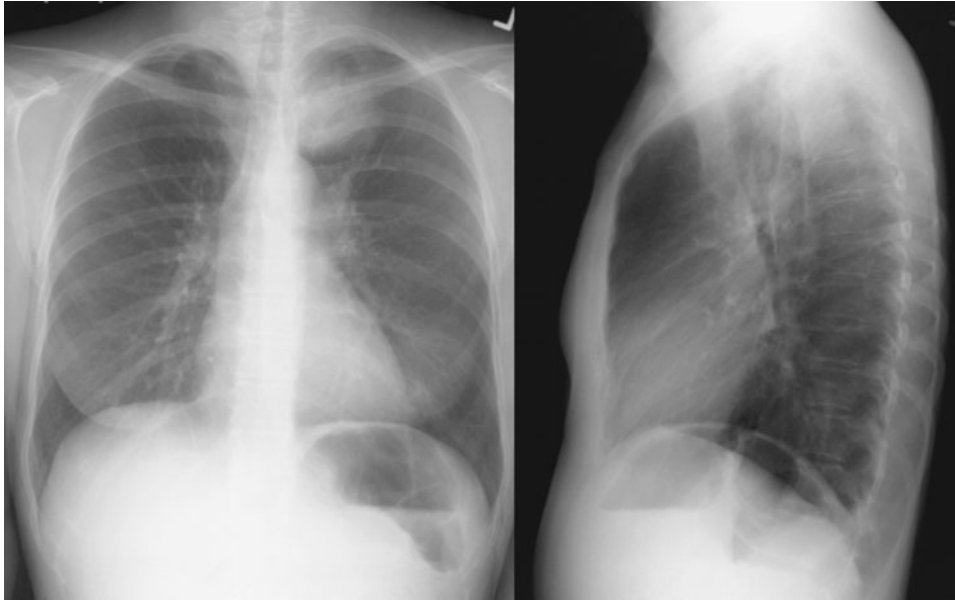
Note fluid in the major fissure (*black arrow*) visible on the lateral film as well as the meniscus of the right pleural effusion.

**FIGURE 7-39**

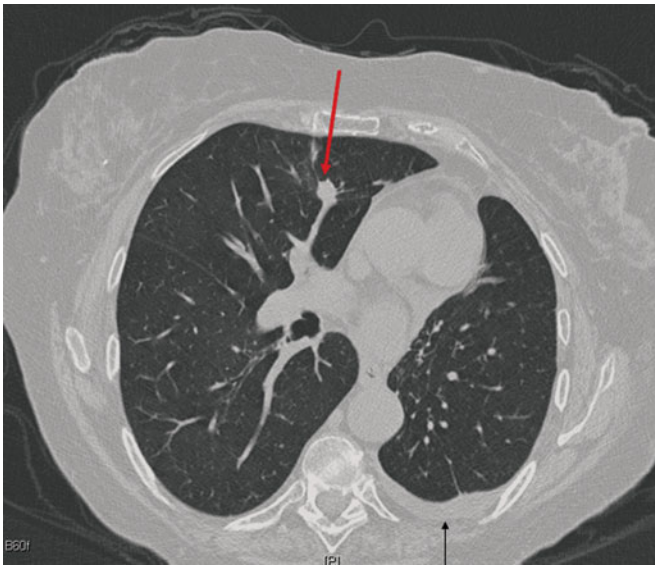
Left pleural effusion with clear meniscus seen on both PA and lateral chest radiographs.

**FIGURE 7-40**

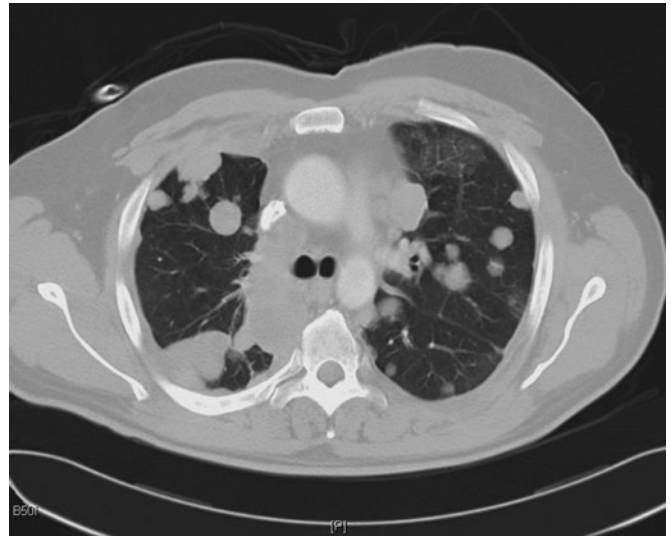
Asbestosis. Note calcified pleural plaques (*red arrows*), pleural thickening (*black arrow*), and subpleural atelectasis (*green arrows*).

**FIGURE 7-41**

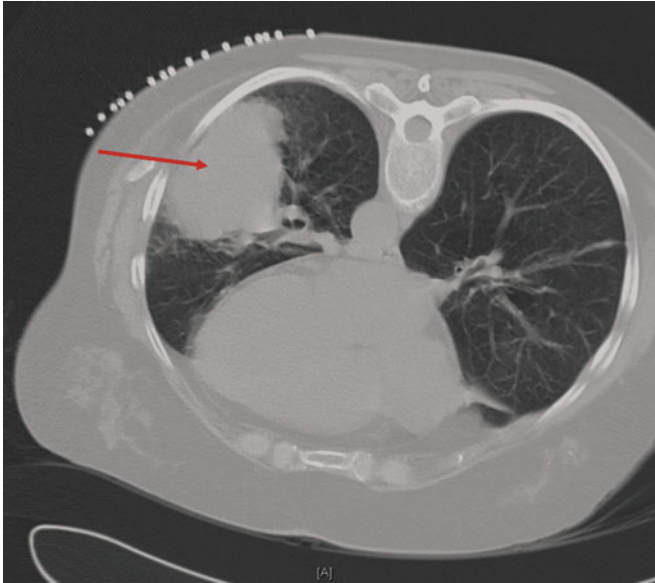
Left upper lobe mass, which biopsy revealed to be squamous cell carcinoma.

**FIGURE 7-42**

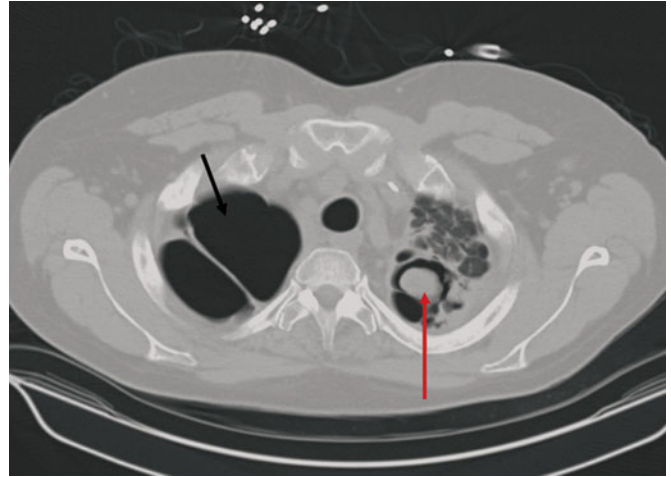
Solitary pulmonary nodule on the right (*red arrow*) with a spiculated pattern concerning for lung cancer. Note also that the patient has had a left upper lobectomy with resultant volume loss and associated effusion (*black arrow*).

**FIGURE 7-43**

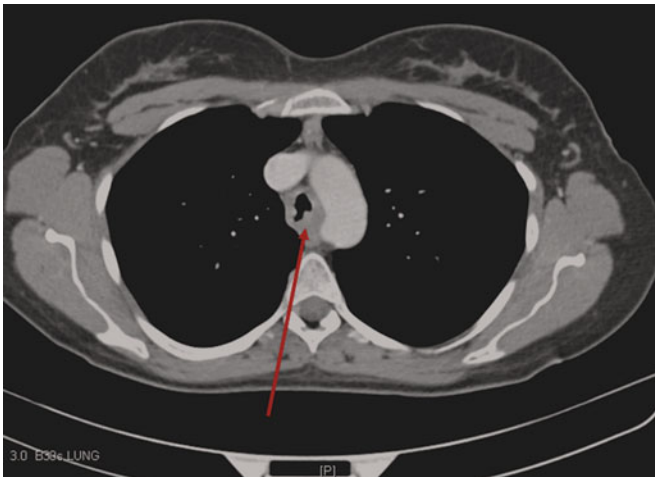
Metastatic sarcoma. Note the multiple, well-circumscribed nodules of different sizes.

**FIGURE 7-44**

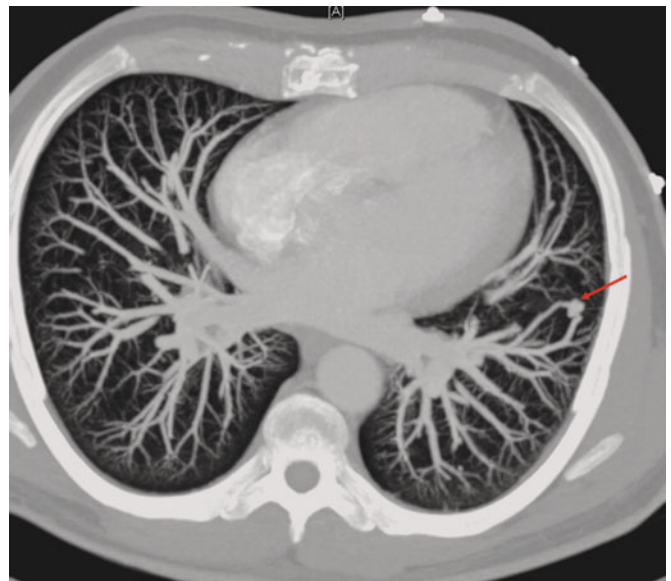
Left lower lobe lung mass (*red arrow*) abutting the pleura. Biopsy demonstrated small cell lung cancer.

**FIGURE 7-46**

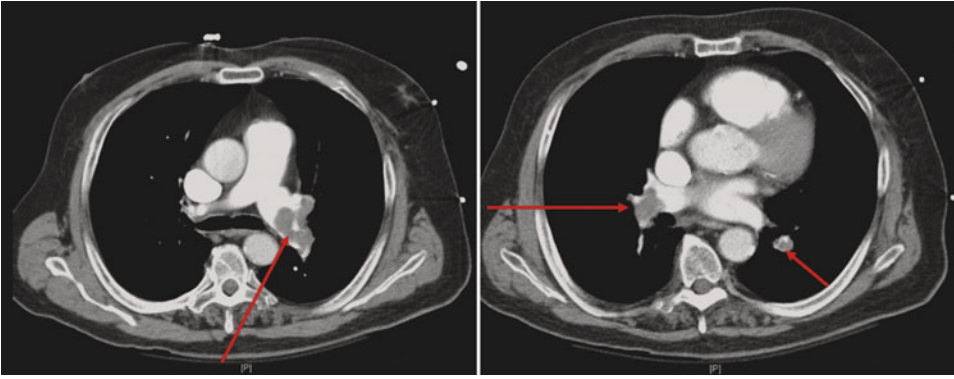
Mycetoma. Fungal ball (*red arrow*) growing in a preexisting cavity on the left. The right upper lobe has a large bulla (*black arrow*).

**FIGURE 7-45**

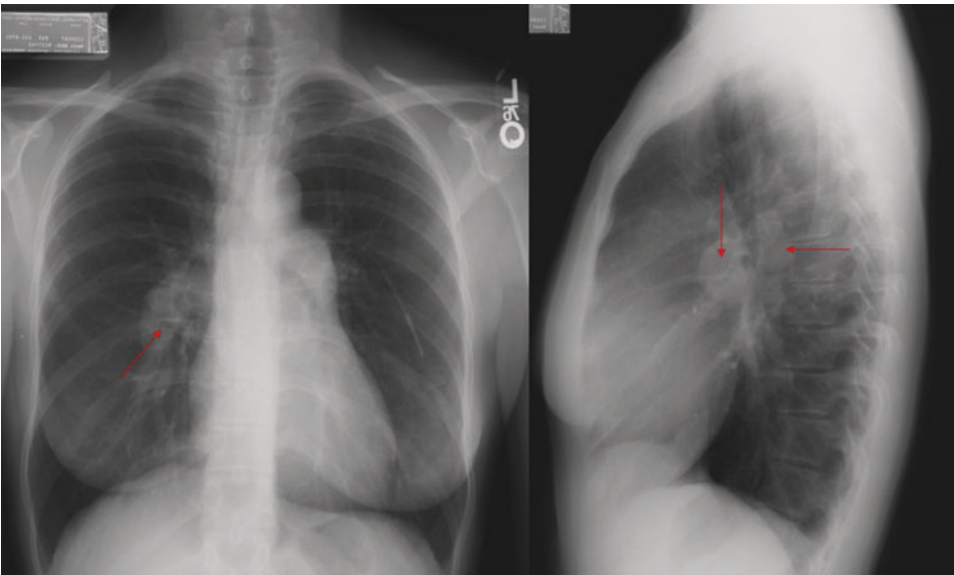
CT scan of soft tissue mass encircling the trachea (*red arrow*) and invading the tracheal lumen. Biopsy demonstrated adenoid cystic carcinoma (cylindroma).

**FIGURE 7-47**

Pulmonary arteriovenous malformation (AVM) demonstrated on a reformatted CT angiogram (*red arrow*).

**FIGURE 7-48**

Large bilateral pulmonary emboli (intravascular filling defects in the contrast scan are identified by *red arrows*).

**FIGURE 7-49**

CXR of a patient with severe pulmonary hypertension. Note the enlarged pulmonary arteries (*red arrows*) visible on both the PA and lateral films.

**FIGURE 7-50**

CT scan of the same patient as in Fig. 7-49. Note the markedly enlarged pulmonary arteries (*red arrow*).

This page intentionally left blank

SECTION II

DISEASES OF THE RESPIRATORY SYSTEM





CHAPTER 8

ASTHMA

Peter J. Barnes

■ Prevalence	60	Hormonal Factors	69
■ Etiology	61	Gastroesophageal Reflux	69
Atopy	61	Stress	69
Intrinsic Asthma	61	■ Pathophysiology	69
Infections	62	Airway Hyperresponsiveness	69
Genetic Considerations	62	■ Clinical Features and Diagnosis	69
Environmental Factors	62	Diagnosis	69
Other Factors	63	Differential Diagnosis	70
■ Pathogenesis	63	■ Acute Severe Asthma	75
Pathology	63	Clinical Features	75
Inflammation	64	■ Refractory Asthma	75
Inflammatory Mediators	65	Mechanisms	76
Effects of Inflammation	66	Differential Diagnosis	76
Airway Remodeling	67	Corticosteroid-Resistant Asthma	76
■ Asthma Triggers	68	Brittle Asthma	76
Allergens	68	■ Special Considerations	77
Virus Infections	68	Aspirin-Sensitive Asthma	77
Pharmacologic Agents	68	Asthma in the Elderly	77
Exercise	68	Pregnancy	77
Physical Factors	68	Cigarette Smoking	77
Food	68	Surgery	78
Air Pollution	69	Bronchopulmonary Aspergillosis	78
Occupational Factors	69	■ Further Readings	78

Asthma is a syndrome characterized by airflow obstruction that varies markedly, both spontaneously and with treatment. Asthmatics harbor a special type of inflammation in the airways that makes them more responsive than nonasthmatics to a wide range of triggers, leading to excessive narrowing with consequent reduced airflow and symptomatic wheezing and dyspnea. Narrowing of the airways is usually reversible, but in some patients with chronic asthma, there may be an element of irreversible airflow obstruction. The increasing global prevalence of asthma, the large burden it now imposes on patients, and the high health care costs have led to extensive research into its mechanisms and treatment.

PREVALENCE

Asthma is one of the most common chronic diseases globally and currently affects ~300 million people. The prevalence of asthma has risen in affluent countries over the past 30 years but now appears to have stabilized, with ~10–12% of adults and 15% of children affected by the disease. In developing countries where the prevalence of asthma had been much lower, there is a rising incidence that appears to be associated with increased urbanization. The prevalence of atopy and other allergic diseases has also increased over the same time, suggesting that the reasons for the increase are likely to be systemic rather than confined to the lungs. This epidemiologic

observation suggests that there is a maximum number of individuals in the community who are liable to be affected by asthma, likely by genetic predisposition. Most patients with asthma in affluent countries are atopic, with allergic sensitization to the house dust mite *Dermatophagoides pteronyssinus* and other environmental allergens.

Asthma is both common and frequently complicated by the effects of smoking on the lungs; hence, it is difficult to be certain about the natural history of the disease in adults. Asthma can present at any age with a peak age of 3 years. In childhood, twice as many boys as girls are asthmatic, but by adulthood, the gender ratio has equalized. The commonly held belief that children “grow out of their asthma” is justified to some extent. Long-term studies that have followed children until they reach the age of 40 years suggest that many with asthma become asymptomatic during adolescence but that asthma returns in some during adult life, particularly in children with persistent symptoms and severe asthma. Adults with asthma, including those with onset during adulthood, rarely become permanently asymptomatic. The severity of asthma does not vary significantly within a given patient; those with mild asthma rarely progress to more severe disease, whereas those with severe asthma usually have severe disease at the onset.

Deaths from asthma are uncommon and have been steadily declining in many affluent countries over the past decade. An increase in asthma mortality seen in several countries during the 1960s was associated with increased use of short-acting β_2 -adrenergic agonists (as rescue therapy), but there is now compelling evidence that the more widespread use of inhaled corticosteroids (ICSs) in patients with persistent asthma is responsible for the decrease in mortality in recent years. Major risk factors for asthma deaths are poorly controlled disease with frequent use of bronchodilator inhalers, lack of corticosteroid therapy, and previous admissions to the hospital with near-fatal asthma.

It has proven difficult to agree on a definition of asthma, but there is good agreement on the description of the clinical syndrome and disease pathology. Until the etiologic mechanisms of the disease are better understood, it will be difficult to provide an accurate definition.

ETIOLOGY

Asthma is a heterogeneous disease with interplay between genetic and environmental factors. Several risk factors have been implicated (Table 8-1).

ATOPY

Atopy is the major risk factor for asthma, and nonatopic individuals have a very low risk of developing asthma.

TABLE 8-1

RISK FACTORS AND TRIGGERS INVOLVED IN ASTHMA

RISK FACTORS

Endogenous Factors	Environmental Factors
Genetic predisposition	Indoor allergens
Atopy	Outdoor allergens
Airway hyperresponsiveness	Occupational sensitizers
Gender	Passive smoking
Ethnicity?	Respiratory infections
	Obesity?
	Early viral infections?

TRIGGERS

Allergens
Upper respiratory tract viral infections
Exercise and hyperventilation
Cold air
Sulfur dioxide
Drugs (β -blockers, aspirin)
Stress
Irritants (household sprays, paint fumes)

Patients with asthma commonly have other atopic diseases, particularly allergic rhinitis, which may be found in more than 80% of asthmatic patients, and atopic dermatitis (eczema). Atopy may be found in 40–50% of the population in affluent countries, with only a proportion of atopic individuals becoming asthmatic. This observation suggests that some other environmental or genetic factor(s) predispose to the development of asthma in atopic individuals. The allergens that lead to sensitization are usually proteins that have protease activity, and the commonest allergens are derived from house dust mites, cat and dog fur, cockroaches, grass and tree pollens, and rodents (in laboratory workers). Atopy is caused by the genetically determined production of a specific IgE antibody, with many patients showing a family history of allergic diseases.

INTRINSIC ASTHMA

A minority of asthmatic patients (approximately 10%) have negative skin test results to common inhalant allergens and normal serum concentrations of IgE. These patients with nonatopic or intrinsic asthma usually show a later onset of disease (adult-onset asthma), commonly have concomitant nasal polyps, and may be aspirin sensitive. They usually have more severe, persistent asthma. Little is understood about the mechanism, but the immunopathology in bronchial biopsies and sputum appears to be identical to that found in atopic asthma. There is recent evidence for increased local production of IgE in the airways, suggesting that there may be common IgE-mediated mechanisms.

Although viral infections are common as triggers of asthma exacerbations, it is uncertain whether they play a role in the cause. There is some association between respiratory syncytial virus infection in infancy and the development of asthma, but the specific pathogenesis is difficult to elucidate because this infection is very common in children. More recently, atypical bacteria such as *Mycoplasma* and *Chlamydia* spp. have been implicated in the mechanism of severe asthma, but thus far, evidence of a true association is not very convincing.

GENETIC CONSIDERATIONS



The familial association of asthma and a high degree of concordance for asthma in identical twins indicate a genetic predisposition to the disease; however, whether or not the genes predisposing to asthma are similar or in addition to those predisposing to atopy is not yet clear. It now seems likely that different genes may also contribute to asthma specifically, and increasing evidence suggests that the severity of asthma is also genetically determined. Genetic screens with classical linkage analysis and single nucleotide polymorphisms of various candidate genes indicate that asthma is polygenic, with each gene identified having a small effect that is often not replicated in different populations. This observation suggests that the interaction of many genes is important, and these may differ in different populations. The most consistent findings have been associations with polymorphisms of genes on chromosome 5q, including the T helper 2 (T_H2) cells interleukin (IL) 4, IL-5, IL-9, and IL-13, which are associated with atopy. There is increasing evidence for a complex interaction between genetic polymorphisms and environmental factors that will require very large population studies to unravel. Novel genes that have been associated with asthma, including *ADAM-33*, *DPP-10*, and *GPR4*, have also been identified by positional cloning, but their function in disease pathogenesis is thus far obscure. Genetic polymorphisms may also be important in determining the response to asthma therapy. For example, the Arg-Gly-16 variant in the β_2 -receptor is associated with reduced response to β_2 -agonists, and repeats of an Sp1 recognition sequence in the promoter region of 5-lipoxygenase may affect the response to antileukotrienes.

ENVIRONMENTAL FACTORS

It is likely that environmental factors in early life determine which atopic individuals become asthmatic. The increasing prevalence of asthma, particularly in developing countries, over the past few decades also indicates the importance of environmental mechanisms interacting with a genetic predisposition.

Hygiene Hypothesis

The observation that allergic sensitization and asthma were less common in children with older siblings first suggested that lower levels of infection may be a factor in affluent societies that increase the risks of asthma. This “hygiene hypothesis” proposes that lack of infections in early childhood preserves the T_H2 cell bias at birth, but exposure to infections and endotoxin results in a shift toward a predominant protective T_H1 response. Children brought up on farms who are exposed to a high level of endotoxin are less likely to develop allergic sensitization than children raised on dairy farms. Intestinal parasite infection may also be associated with a reduced risk of asthma. Although there is considerable epidemiologic support for the hygiene hypothesis, it cannot account for the parallel increase in T_H1 -driven diseases, such as diabetes mellitus, over the same period.

Diet

The role of dietary factors is controversial. Observational studies have shown that diets low in antioxidants, such as vitamin C and vitamin A, magnesium, selenium, and omega-3 polyunsaturated fats (fish oil), or high in sodium and omega-6 polyunsaturates are associated with an increased risk of asthma. However, interventional studies have not supported an important role for these dietary factors. Obesity is also an independent risk factor for asthma, particularly in women, but the mechanisms thus far are unknown.

Air Pollution

There is no doubt that air pollutants, such as sulfur dioxide, ozone, and diesel particulates, may trigger asthma symptoms, but the role of different air pollutants in the cause of the disease is much less certain. Most evidence argues against an important role for air pollution because asthma is no more prevalent in cities with a high ambient level of traffic pollution than in rural areas with low levels of pollution. Asthma had a much lower prevalence in East Germany than West Germany despite a much higher level of air pollution, but since reunification, these differences have decreased as eastern Germany has become more affluent. Indoor air pollution may be more important with exposure to nitrogen oxides from cooking stoves and exposure to passive cigarette smoke. There is some evidence that maternal smoking is a risk factor for asthma, but it is difficult to dissociate this from an increased risk of respiratory infections.

Allergens

Inhaled allergens are common triggers of asthma symptoms and have also been implicated in allergic

sensitization. Exposure to house dust mites in early childhood is a risk factor for allergic sensitization and asthma, but rigorous allergen avoidance has not shown any evidence for a reduced risk of developing asthma. The increase in house dust mites in centrally heated, poorly ventilated homes with fitted carpets has been implicated in the increasing prevalence of asthma in affluent countries. Domestic pets, particularly cats, have also been associated with allergic sensitization, but early exposure to cats in the home may be protective through the induction of tolerance.

Occupational Exposure

Occupational asthma is relatively common and may affect up to 10% of young adults. More than 200 sensitizing agents have been identified. Chemicals, such as toluene diisocyanate and trimellitic anhydride, may lead to sensitization independent of atopy. Individuals may also be exposed to allergens in the workplace, such as small animal allergens in laboratory workers and fungal amylase in wheat flour in bakers.

OTHER FACTORS

Several other factors have been implicated in the cause of asthma, including lower maternal age, duration of breastfeeding, prematurity and low birth weight, and inactivity, but are unlikely to contribute to the recent global increase in asthma prevalence. There is also an association with acetaminophen (paracetamol) consumption, which remains unexplained.

PATHOGENESIS

Asthma is associated with a specific chronic inflammation of the mucosa of the lower airways. One of the main aims of treatment is to reduce this inflammation.

PATHOLOGY

The pathology of asthma has been revealed through examining the lungs at autopsy in patients who have died of asthma and from bronchial biopsies in patients with usually mild asthma. The airway mucosa is infiltrated with activated eosinophils and T lymphocytes, and there is activation of mucosal mast cells. The degree of inflammation is poorly related to disease severity and may be found in atopic patients without asthma symptoms. The inflammation is reduced by treatment with ICSs. A characteristic finding is thickening of the basement membrane caused by subepithelial collagen deposition. This feature is also found in patients with eosinophilic bronchitis presenting as cough who do not have asthma; it is therefore likely to be a marker of eosinophilic inflammation in the airway because eosinophils release fibrogenic factors. The epithelium is often shed or friable, with reduced attachments to the airway wall and increased numbers of epithelial cells in the lumen. The airway wall itself may be thickened and edematous, particularly in fatal asthma. Another common finding in fatal asthma is occlusion of the airway lumen by a mucus plug, which is composed of mucus glycoproteins secreted from goblet cells and plasma proteins from leaky bronchial vessels (Fig. 8-1). There is also vasodilatation and increased numbers of blood vessels (angiogenesis). Direct observation by bronchoscopy indicates that the airways may be narrowed, reddened, and edematous. The pathology of asthma is remarkably uniform in different types of asthma, including atopic, nonatopic, occupational, aspirin-sensitive, and pediatric asthma. These pathologic changes are found in all airways but do not extend to the lung parenchyma; small airway inflammation is found particularly in patients with severe asthma. The involvement of airways may be patchy, and this is consistent with bronchographic findings of uneven narrowing of the airways.

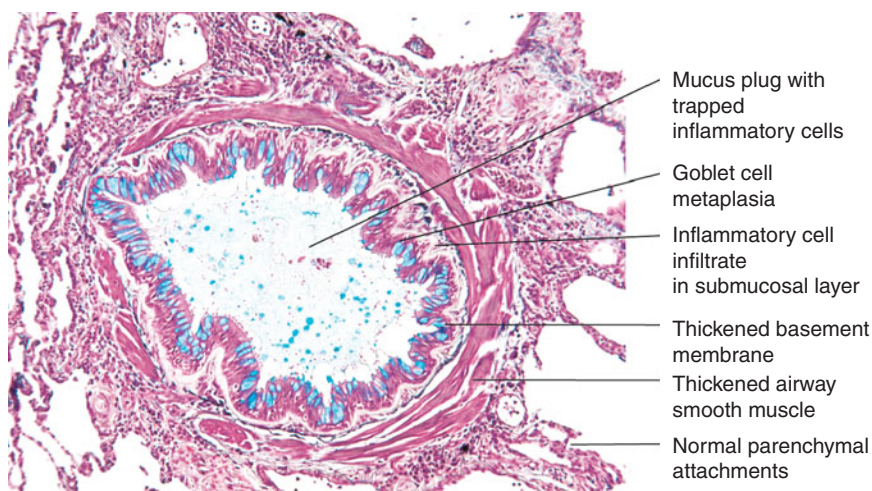


FIGURE 8-1

Histopathology of a small airway in fatal asthma. The lumen is occluded with a mucus plug, goblet cell metaplasia is present, and the airway wall is thickened, with an increase in basement membrane thickness and airway smooth muscle. (Courtesy of Dr. J. Hogg, University of British Columbia, with permission.)

There is inflammation in the respiratory mucosa from trachea to terminal bronchioles but with a predominance in the bronchi (cartilaginous airways). Considerable research has identified the major cellular components of inflammation, but it is still uncertain how inflammatory cells interact and how inflammation translates into the symptoms of asthma (Fig. 8-2). There is good evidence that the specific pattern of airway inflammation in asthma is associated with airway hyperresponsiveness (AHR), the physiologic abnormality of asthma that is correlated with variable airflow obstruction. The pattern of inflammation in asthma is characteristic of allergic diseases, with similar inflammatory cells seen in the nasal mucosa in rhinitis. However, an indistinguishable pattern of inflammation is found in intrinsic asthma, although this may reflect local rather than systemic IgE production. Although most attention has focused on the acute inflammatory changes seen in asthma, this is a chronic condition, with inflammation persisting over many years in most patients. The mechanisms involved in persistence of inflammation in asthma are still poorly understood. Superimposed on this chronic inflammatory state are acute inflammatory episodes, which correspond to exacerbations of asthma. Many inflammatory cells are known to be involved in asthma, with no predominant key cell (Fig. 8-3).

Mast Cells

Mast cells are important in initiating the acute bronchoconstrictor responses to allergens and several other indirectly acting stimuli, such as exercise and hyperventilation (via osmolality or thermal changes), as well as fog. In biopsies from asthmatic patients, mast cells are localized to

the airway smooth muscle layer; they are not found in normal subjects or in patients with eosinophilic cough. Mast cells are activated by allergens through an IgE-dependent mechanism, and binding of specific IgE to mast cells renders them more sensitive to activation. The importance of IgE in the pathophysiology of asthma has been highlighted by clinical studies with humanized anti-IgE antibodies, which inhibit IgE-mediated effects, reduce asthma symptoms, and prevent exacerbations. There are, however, uncertainties about the role of mast cells in more chronic allergic inflammatory events. Mast cells release several bronchoconstrictor mediators, including histamine and cysteinyl-leukotrienes, but also several cytokines, chemokines, growth factors, and neurotrophins.

Macrophages and Dendritic Cells

Macrophages, which are derived from blood monocytes, may traffic into the airways in asthma and may be activated by allergens via low-affinity IgE receptors (FcεRII). Macrophages have the capacity to initiate a type of inflammatory response via the release of a certain pattern of cytokines, but these cells also release anti-inflammatory mediators, such as IL-10, and thus their role in asthma is uncertain. Dendritic cells are specialized macrophage-like cells in the airway epithelium, which are the major antigen-presenting cells. Dendritic cells take up allergens, process them to peptides, and migrate to local lymph nodes, where they present the allergenic peptides to uncommitted T-lymphocytes to program the production of allergen-specific T cells. Immature dendritic cells in the respiratory tract promote T_H2 cell differentiation and require cytokines, such as IL-12 and tumor necrosis factor α (TNF α), to promote the normally preponderant T_H1 response.

Eosinophils

Eosinophil infiltration is a characteristic feature of asthmatic airways. Allergen inhalation results in a marked increase in activated eosinophils in the airways at the time of the late reaction. Eosinophils are linked to the development of AHR through the release of basic proteins and oxygen-derived free radicals. Eosinophil recruitment involves adhesion of eosinophils to vascular endothelial cells in the airway circulation due to interaction between adhesion molecules, migration into the submucosa under the direction of chemokines, and their subsequent activation and prolonged survival. Blocking antibodies to IL-5 cause a profound and prolonged reduction in circulating and sputum eosinophils, but they are not associated with reduced AHR or asthma symptoms, thus questioning the pivotal role of eosinophils in asthma. Furthermore, eosinophilic inflammation is also found in patients with chronic cough who do not have any clinical features of asthma or AHR. Increasing evidence suggests that

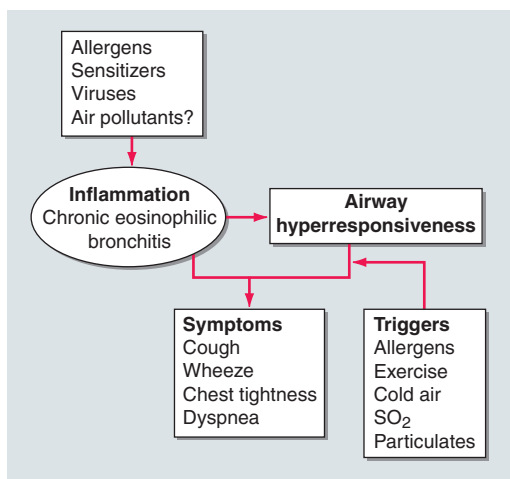
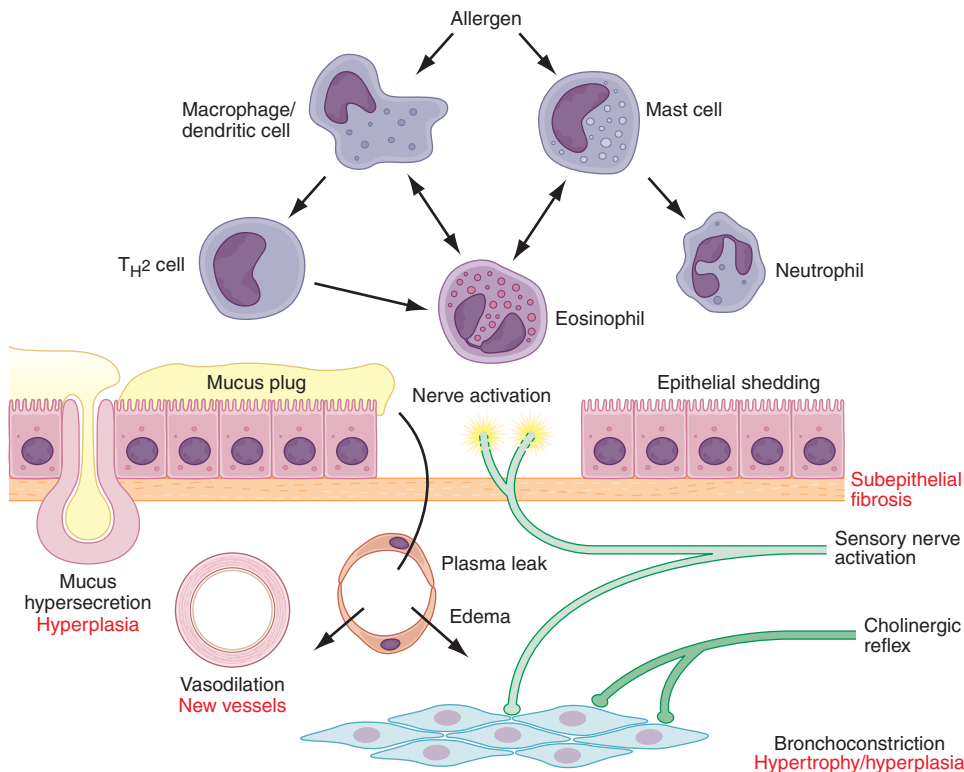


FIGURE 8-2

Inflammation in the airways of asthmatic patients leads to airway hyperresponsiveness and symptoms.

**FIGURE 8-3**

The pathophysiology of asthma is complex, with participation of several interacting inflammatory cells, resulting in acute and chronic inflammatory effects on the airway.

eosinophils may be more important in release of growth factors involved in airway remodeling than in AHR.

Neutrophils

Increased numbers of activated neutrophils are found in the sputum and airways of some patients with severe asthma and during exacerbations, although there is a proportion of patients even with mild or moderate asthma that have a predominance of neutrophils. The role of neutrophils in asthma, which are resistant to the anti-inflammatory effects of corticosteroids, is currently unknown.

T Lymphocytes

T lymphocytes play a very important role in coordinating the inflammatory response in asthma through the release of specific patterns of cytokines, resulting in the recruitment and survival of eosinophils and in the maintenance of a mast cell population in the airways. Whereas the naïve immune system and the immune system of asthmatics are skewed to express the T_H2 phenotype, in normal airways, T_H1 cells predominate. Through the release of IL-5, T_H2 cells are associated with eosinophilic inflammation and, through the release of IL-4 and IL-13, are associated with increased IgE formation. Recently, bronchial biopsies have demonstrated a preponderance of natural killer CD4+ T lymphocytes, which express high levels of IL-4. Regulatory T cells

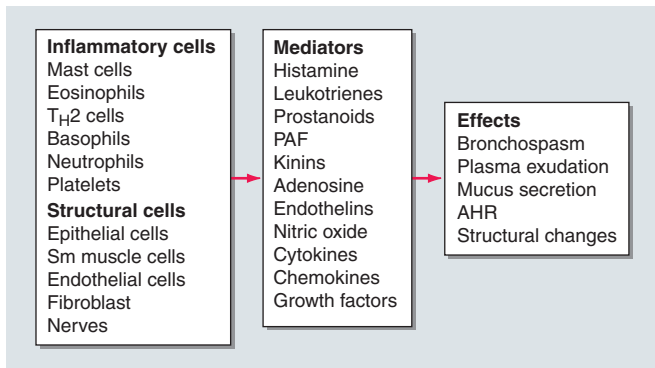
play an important role in determining the expression of other T cells, and there is evidence for a reduction in a certain subset of regulatory T cells (CD4+CD25+) in asthma, which is associated with increased T_H2 cells.

Structural Cells

Structural cells of the airways, including epithelial cells, fibroblasts, and airway smooth muscle cells, are also an important source of inflammatory mediators, such as cytokines and lipid mediators, in asthma. Indeed, because structural cells far outnumber inflammatory cells, they may become the major source of mediators driving chronic inflammation in asthmatic airways. In addition, epithelial cells may have a key role in translating inhaled environmental signals into an airway inflammatory response and are probably a major target cell for ICSs.

INFLAMMATORY MEDIATORS

Many different mediators have been implicated in asthma, and they may have a variety of effects on the airways that could account for the pathologic features of asthma (Fig. 8-4). Mediators such as histamine, prostaglandins, and cysteinyl-leukotrienes contract airway smooth muscle, increase microvascular leakage, increase airway mucus secretion, and attract other inflammatory cells. Because each mediator has many effects, the role of individual mediators in the pathophysiology of asthma is not yet clear. Although the multiplicity of mediators

**FIGURE 8-4**

Many cells and mediators are involved in asthma and lead to several effects on the airways. AHR, hyperresponsiveness; PAF, platelet-activating factor.

makes it unlikely that preventing the synthesis or action of a single mediator will have a major impact in clinical asthma, recent clinical studies with antileukotrienes suggest that cysteinyl-leukotrienes have a clinically important effect.

Cytokines

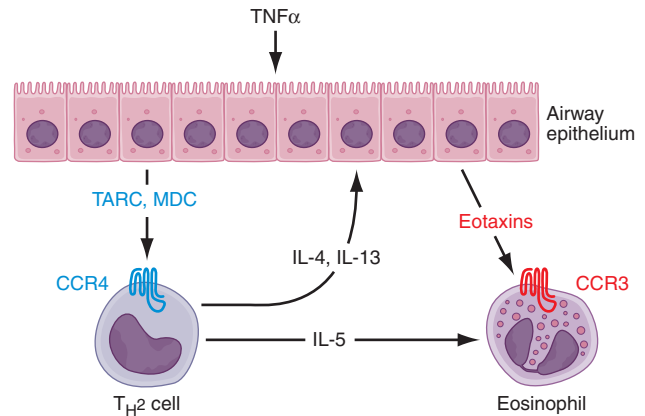
Multiple cytokines regulate the chronic inflammation of asthma. The T_H2 cytokines IL-4, IL-5, and IL-13 mediate allergic inflammation, whereas proinflammatory cytokines, such as TNF α and IL-1 β , amplify the inflammatory response and play a role in more severe disease. Thymic stromal lymphopoietin is an upstream cytokine released from epithelial cells of asthmatics that orchestrates the release of chemokines, which selectively attract T_H2 cells. Some cytokines, such as IL-10 and IL-12, are anti-inflammatory and may be deficient in individuals with asthma.

Chemokines

Chemokines are involved in attracting inflammatory cells from the bronchial circulation into the airways. Whereas eotaxin (CCL11) is selectively attractant to eosinophils via CCR3 and is expressed by epithelial cells of asthmatics, CCL17 (TARC) and CCL22 (MDC) from epithelial cells attract T_H2 cells via CCR4 (Fig. 8-5).

Oxidative Stress

There is increased oxidative stress in asthma as activated inflammatory cells, such as macrophages and eosinophils, produce reactive oxygen species. Evidence for increased oxidative stress in asthma is provided by the increased concentrations of 8-isoprostane (a product of oxidized arachidonic acid) in exhaled breath condensates and increased ethane (a product of lipid peroxidation) in the

**FIGURE 8-5**

Chemokines in asthma. Tumor necrosis factor α (TNF α) and other triggers of airway epithelial cells release thymus and activation-regulated chemokine (TARC, CCL17) and macrophage-derived chemokine (MDC, CCL22) from epithelial cells, which attract T_H2 cells via activation of their CCR4 receptors. These promote eosinophilic inflammation directly through the release of interleukin 5 (IL-5) and indirectly via the release of IL-4 and IL-13, which induce eotaxin (CCL11) formation in airway epithelial cells.

expired air of asthmatic patients. Increased oxidative stress is related to disease severity, may amplify the inflammatory response, and may reduce responsiveness to corticosteroids.

Nitric Oxide

Nitric oxide (NO) is produced by several cells in the airway by NO synthases, particularly airway epithelial cells and macrophages. The level of NO in the expired air of patients with asthma is higher than normal and is related to the eosinophilic inflammation. Increased NO may contribute to the bronchial vasodilation observed in asthma. Exhaled NO is increasingly used in the diagnosis and monitoring of asthmatic inflammation, although it is not used routinely in clinical practice.

Transcription Factors

Proinflammatory transcription factors, such as nuclear factor κ B (NF κ B) and activator protein 1 (AP-1), are activated in asthmatic airways and orchestrate the expression of multiple inflammatory genes. More-specific transcription factors that are involved include nuclear factor of activated T cells and GATA-3, which regulate the expression of T_H2 cytokines in T cells.

EFFECTS OF INFLAMMATION

The chronic inflammatory response has several effects on the target cells of the airways, resulting in the characteristic

pathophysiologic changes associated with asthma. Asthma may be regarded as a disease with continuous inflammation and repair proceeding simultaneously. Important advances continue to be made in our understanding of these changes, but despite these new insights, the relationship between chronic inflammatory processes and asthma symptoms is often not clear.

Airway Epithelium

Airway epithelial shedding may be important in contributing to AHR and may explain how several mechanisms, such as ozone exposure, virus infections, chemical sensitizers, and allergen exposure, can lead to its development because all of these stimuli may lead to epithelial disruption. Epithelial damage may contribute to AHR in a number of ways, including loss of its barrier function to allow penetration of allergens; loss of enzymes (e.g., neutral endopeptidase) that normally degrade inflammatory mediators; loss of a relaxant factor (so called epithelial-derived relaxant factor); and exposure of sensory nerves, which may lead to reflex neural effects on the airway.

Fibrosis

In all asthmatic patients, the basement membrane is apparently thickened due to subepithelial fibrosis with deposition of types III and V collagen below the true basement membrane, and it is associated with eosinophil infiltration, presumably through the release of profibrotic mediators, such as transforming growth factor β . Mechanical manipulations can alter the phenotype of airway epithelial cells in a profibrotic fashion. In patients with more severe asthma, there is also fibrosis within the airway wall, which may contribute to irreversible narrowing of the airways.

Airway Smooth Muscle

There is still debate about the role of abnormalities in airway smooth muscle in asthmatic airways. In vitro airway smooth muscle from asthmatic patients usually shows no increased responsiveness to constrictors. Reduced responsiveness to β -agonists has also been reported in post-mortem or surgically removed bronchi from asthmatics, although the number of β -receptors is not reduced, suggesting that β -receptors have been uncoupled. These abnormalities of airway smooth muscle may be secondary to the chronic inflammatory process. Inflammatory mediators may modulate the ion channels that serve to regulate the resting membrane potential of airway smooth muscle cells, thus altering the level of excitability of these cells. In asthmatic airways, there is also a characteristic hypertrophy and hyperplasia of airway smooth muscle, which is presumably the result of stimulation of airway

smooth muscle cells by various growth factors, such as platelet-derived growth factor or endothelin 1, released from inflammatory or epithelial cells.

Vascular Responses

There is increased airway mucosal blood flow in asthma. The bronchial circulation may play an important role in regulating airway caliber because an increase in the vascular volume may contribute to airway narrowing. Increased airway blood flow may be important in removing inflammatory mediators from the airway and may play a role in the development of exercise-induced asthma (EIA). There is an increase in the number of blood vessels in asthmatic airways as a result of angiogenesis in response to growth factors, particularly vascular-endothelial growth factor. Microvascular leakage from postcapillary venules in response to inflammatory mediators is observed in asthma, resulting in airway edema and plasma exudation into the airway lumen.

Mucus Hypersecretion

Increased mucus secretion contributes to the viscid mucus plugs that occlude asthmatic airways, particularly in fatal asthma. There is evidence for hyperplasia of submucosal glands that are confined to large airways and of increased numbers of epithelial goblet cells. IL-4 and IL-13 induce mucus hypersecretion in experimental models of asthma.

Neural Effects

Various defects in autonomic neural control may contribute to AHR in asthma, but these are likely to be secondary to the disease rather than primary defects. Cholinergic pathways, through the release of acetylcholine acting on muscarinic receptors, cause bronchoconstriction and may be activated reflexly in asthma. Inflammatory mediators may activate sensory nerves, resulting in reflex cholinergic bronchoconstriction or release of inflammatory neuropeptides. Inflammatory products may also sensitize sensory nerve endings in the airway epithelium, such that the nerves become hyperalgesic. Neurotrophins, which may be released from various cell types in peripheral tissues, may cause proliferation and sensitization of airway sensory nerves. Airway nerves may also release neurotransmitters, such as substance P, which have inflammatory effects.

AIRWAY REMODELING

Several changes in the structure of the airway are characteristically found in asthma, and these may lead to irreversible narrowing of the airways. Population studies have shown a greater decline in lung function over time

68 than in normal subjects; however, most patients with asthma preserve normal or near-normal lung function throughout life if appropriately treated. This observation suggests that the accelerated decline in lung function occurs in a smaller proportion of people with asthma, and these are usually patients with more severe disease. There is debate about whether the early use of ICSs may reduce the decline in lung function. The characteristic structural changes are increased airway smooth muscle, fibrosis, angiogenesis, and mucus hyperplasia.

ASTHMA TRIGGERS

Several stimuli trigger airway narrowing, wheezing, and dyspnea in asthmatic patients. Although the previous view held that these should be avoided, it is now seen as evidence for poor control and an indicator of the need to increase controller therapy.

ALLERGENS

Inhaled allergens are able to activate mast cells with bound IgE directly leading to the immediate release of bronchoconstrictor mediators, resulting in the early response reversed by bronchodilators. Often, experimental allergen challenge is followed by a late response when there is airway edema and an acute inflammatory response with increased eosinophils and neutrophils that is not very reversible with bronchodilators. The most common allergen to trigger asthma is *Dermatophagoides* spp., and environmental exposure leads to low-grade chronic symptoms that are perennial. Perennial allergens are derived from cats and other domestic pets, as well as cockroaches. Other allergens, including grass pollen, ragweed, tree pollen, and fungal spores, are seasonal. Pollens usually cause allergic rhinitis rather than asthma, but in thunderstorms, the pollen grains are disrupted, and the particles that may be released can trigger severe asthma exacerbations (thunderstorm asthma).

VIRUS INFECTIONS

Upper respiratory tract virus infections, such as rhinovirus, respiratory syncytial virus, and coronavirus, are the commonest triggers of acute severe exacerbations. The mechanism whereby these viruses cause exacerbations is poorly understood, but there is an increase in airway inflammation with increased numbers of eosinophils and neutrophils. There is evidence for reduced production of type I interferons by epithelial cells from asthmatic patients, resulting in increased susceptibility to these viral infections and a greater inflammatory response.

PHARMACOLOGIC AGENTS

Several drugs may trigger asthma. β -Adrenergic blockers commonly worsen asthma, and their use may be fatal.

The mechanisms are not clear but are mediated through increased cholinergic bronchoconstriction. All β -blockers need to be avoided in patients with asthma, and even selective β_2 blocker or topical application (e.g., timolol eye drops) may be dangerous. Angiotensin-converting enzyme inhibitors are theoretically detrimental because they inhibit breakdown of kinins, which are bronchoconstrictors; however, they rarely worsen asthma, and the characteristic cough is no more frequent in asthmatics than nonasthmatics. Aspirin may worsen asthma in some patients (aspirin-sensitive asthma is discussed below under “Special Considerations”).

EXERCISE

Exercise is a common trigger of asthma, particularly in children. The mechanism is linked to hyperventilation, which results in increased osmolality in airway lining fluids and triggers mast cell mediator release, resulting in bronchoconstriction. EIA typically begins after exercise has ended and recovers spontaneously within about 30 min. EIA is worse in cold, dry climates than in hot, humid conditions. It is therefore more common in sports such as cross-country running in cold weather, overland skiing, and ice hockey than in swimming. It may be prevented by prior administration of β_2 -agonists and antileukotrienes but is best prevented by regular treatment with inhaled glucocorticoids, which reduce the population of surface mast cells required for this response.

PHYSICAL FACTORS

Cold air and hyperventilation may trigger asthma through the same mechanisms as exercise. Laughter may also be a trigger. Many patients report worsening of asthma in hot weather and when the weather changes. Some asthmatics become worse when exposed to strong smells or perfumes, but the mechanism of this response is uncertain.

FOOD

There is little evidence that allergic reactions to food lead to increased asthma symptoms despite the belief of many patients that their symptoms are triggered by particular food constituents. Exclusion diets are usually unsuccessful at reducing the frequency of episodes. Some foods, such as shellfish and nuts, may induce anaphylactic reactions that may include wheezing. Patients with aspirin-induced asthma may benefit from a salicylate-free diet, but these diets are difficult to maintain. Certain food additives may trigger asthma. Metabisulfite, which is used as a food preservative, may trigger asthma through the release of sulfur dioxide gas in the stomach. Tartrazine, a food yellow-coloring agent, was believed to be a trigger for asthma, but there is little convincing evidence for this.

AIR POLLUTION

Increased ambient levels of sulfur dioxide, ozone, and nitrogen oxides are associated with increased asthma symptoms.

OCCUPATIONAL FACTORS

Several substances found in the workplace may act as sensitizing agents, as discussed above, but may also act as triggers of asthma symptoms. Occupational asthma is characteristically associated with symptoms at work with relief on weekends and holidays. If removed from exposure within the first 6 months of symptoms, there is usually complete recovery. More persistent symptoms lead to irreversible airway changes, so early detection and avoidance are important.

HORMONAL FACTORS

Some women show premenstrual worsening of asthma, which can occasionally be very severe. The mechanisms are not completely understood but are related to a decrease in progesterone and in severe cases may be improved by treatment with high doses of progesterone or gonadotropin-releasing factors. Thyrotoxicosis and hypothyroidism can both worsen asthma, although the mechanisms are uncertain.

GASTROESOPHAGEAL REFLUX

Gastroesophageal reflux is common in asthmatic patients because it is increased by bronchodilators. Although acid reflux might trigger reflex bronchoconstriction, it rarely causes asthma symptoms, and anti-reflux therapy fails to reduce asthma symptoms in most patients.

STRESS

Many people with asthma report worsening of symptoms with stress. There is no doubt that psychological factors can induce bronchoconstriction through cholinergic reflex pathways. Paradoxically, very severe stress, such as bereavement, usually does not worsen, and may even improve, asthma symptoms.

PATHOPHYSIOLOGY

Limitation of airflow is mainly caused by bronchoconstriction, but airway edema, vascular congestion, and luminal occlusion with exudate may also contribute. This results in a reduction in forced expiratory volume in 1 s (FEV_1), FEV_1 /forced vital capacity (FVC) ratio, and peak expiratory flow (PEF), as well as an increase in airway resistance. Early closure of peripheral airway results in

lung hyperinflation (air trapping) and increased residual volume, particularly during acute exacerbations. In more severe asthma, reduced ventilation and increased pulmonary blood flow result in mismatching of ventilation and perfusion and in bronchial hyperemia. Ventilatory failure is very uncommon, even in patients with severe asthma, and arterial Pa_{CO_2} tends to be low because of increased ventilation.

AIRWAY HYPERRESPONSIVENESS

AHR is the characteristic physiologic abnormality of asthma and describes the excessive bronchoconstrictor response to multiple inhaled triggers that would have no effect on normal airways. The increase in AHR is linked to the frequency of asthma symptoms; thus, an important aim of therapy is to reduce AHR. Increased bronchoconstrictor responsiveness is seen with *direct* bronchoconstrictors, such as histamine and methacholine, which contract airway smooth muscle, but it is characteristically also seen with many *indirect* stimuli, which release bronchoconstrictors from mast cells or activate sensory neural reflexes. Most of the triggers for asthma symptoms appear to act indirectly, including allergens, exercise, hyperventilation, fog (via mast cell activation), irritant dusts, and sulfur dioxide (via cholinergic reflex).

CLINICAL FEATURES AND DIAGNOSIS

The characteristic symptoms of asthma are wheezing, dyspnea, and coughing, which are variable, both spontaneously and with therapy. Symptoms may be worse at night, and patients typically awake in the early morning hours. Patients may report difficulty in filling their lungs with air. There is increased mucus production in some patients, with typically tenacious mucus that is difficult to expectorate. There may be increased ventilation and use of accessory muscles of ventilation. Prodromal symptoms may precede an attack, with itching under the chin, discomfort between the scapulae, or inexplicable fear (impending doom).

Typical physical signs are inspiratory, and to a great extent expiratory, rhonchi throughout the chest, and there may be hyperinflation. Some patients, particularly children, may present with a predominant non-productive cough (cough-variant asthma). There may be no abnormal physical findings when asthma is under control.

DIAGNOSIS

The diagnosis of asthma is usually apparent from the symptoms of variable and intermittent airways obstruction but is usually confirmed by objective measurements of lung function.

Simple spirometry confirms airflow limitation with a reduced FEV₁, FEV₁/FVC ratio, and PEF. Reversibility is demonstrated by a >12% and 200-mL increase in FEV₁ 15 min after an inhaled short-acting β_2 -agonist or, in some patients, by a 2- to 4-week trial of oral glucocorticoids (prednisone or prednisolone 30–40 mg daily). Measurements of PEF twice daily may confirm the diurnal variations in airflow obstruction. Flow-volume loops show reduced peak flow and reduced maximum expiratory flow. Further lung function tests are rarely necessary, but whole-body plethysmography shows increased airway resistance and may show increased total lung capacity and residual volume. Gas diffusion is usually normal, but there may be a small increase in gas transfer in some patients.

Airway Responsiveness

The increased AHR is normally measured by methacholine or histamine challenge with calculation of the provocative concentration that reduces FEV₁ by 20% (PC₂₀). This is rarely useful in clinical practice but can be used in the differential diagnosis of chronic cough and when the diagnosis is in doubt in the setting of normal pulmonary function tests. Occasionally, exercise testing is done to demonstrate the post-exercise bronchoconstriction if there is a predominant history of EIA. Allergen challenge is rarely necessary and should only be undertaken by a specialist if specific occupational agents are to be identified.

Hematologic Tests

Blood tests are not usually helpful. Total serum IgE and specific IgE to inhaled allergens (RAST) may be measured in some patients.

Imaging

Chest roentgenography is usually normal but may show hyperinflated lungs in more severe patients. In exacerbations, there may be evidence of a pneumothorax. Lung shadowing usually indicates pneumonia or eosinophilic infiltrates in patients with bronchopulmonary aspergillosis (BPA). High-resolution CT may show areas of bronchiectasis in patients with severe asthma, and there may be thickening of the bronchial walls, but these changes are not diagnostic of asthma.

Skin Tests

Skin prick tests to common inhalant allergens are positive in allergic asthma and negative in intrinsic asthma but are not helpful in diagnosis. Positive skin responses may be useful in persuading patients to undertake allergen avoidance measures.

DIFFERENTIAL DIAGNOSIS

It is usually not difficult to differentiate asthma from other conditions that cause wheezing and dyspnea. Upper airway obstruction by a tumor or laryngeal edema can mimic severe asthma, but patients typically present with stridor localized to large airways. The diagnosis is confirmed by a flow-volume loop, which shows a reduction in inspiratory as well as expiratory flow, and bronchoscopy to demonstrate the site of upper airway narrowing. Persistent wheezing in a specific area of the chest may indicate endobronchial obstruction with a foreign body. Left ventricular failure may mimic the wheezing of asthma, but basilar crackles are present in contrast to asthma.

Eosinophilic pneumonias and systemic vasculitis, including Churg-Strauss syndrome and polyarteritis nodosa, may be associated with wheezing. Chronic obstructive pulmonary disease (COPD) is usually easy to differentiate from asthma because symptoms show less variability, never completely remit, and show much less (or no) reversibility to bronchodilators. Approximately 10% of COPD patients have features of asthma, with increased sputum eosinophils and a response to oral corticosteroids; these patients probably have both diseases concomitantly.

Rx Treatment: ASTHMA

The treatment of asthma is straightforward, and the majority of patients are now managed by internists with effective and safe therapies. There are several aims of therapy (Table 8-2). Most emphasis has been placed on drug therapy, but several nonpharmacologic approaches have also been used. The main drugs for asthma can be divided into *bronchodilators*, which give rapid relief of symptoms mainly through relaxation of airway smooth muscle, and *controllers*, which inhibit the underlying inflammatory process.

TABLE 8-2

AIMS OF ASTHMA THERAPY

Minimal (ideally no) chronic symptoms, including nocturnal
Minimal (infrequent) exacerbations
No emergency visits
Minimal (ideally no) use of as-required β_2 -agonist
No limitations on activities, including exercise
PEF circadian variation <20%
(Near) normal PEF
Minimal (or no) adverse effects from medicine

Note: PEF, peak expiratory flow.

Bronchodilator Therapies Bronchodilators act primarily on airway smooth muscle to reverse the bronchoconstriction of asthma. This gives rapid relief of symptoms but has little or no effect on the underlying inflammatory process. Thus, bronchodilators are not sufficient to control asthma in patients with persistent symptoms. There are three classes of bronchodilator in current use: β_2 -adrenergic agonists, anticholinergics, and theophylline; of these, β_2 -agonists are by far the most effective.

β_2 -Agonists β_2 -Agonists activate β_2 -adrenergic receptors, which are widely expressed in the airways. β_2 -Receptors are coupled through a stimulatory G protein to adenylyl cyclase, resulting in increased intracellular cyclic AMP, which relaxes smooth muscle cells and inhibits certain inflammatory cells.

Mode of action The primary action of β_2 -agonists is to relax airway smooth muscle cells of all airways, where they act as functional antagonists, reversing and preventing contraction of airway smooth muscle cells by all known bronchoconstrictors. This generalized action is likely to account for their great efficacy as bronchodilators in asthma. There are also additional non-bronchodilator effects that may be clinically useful, including inhibition of mast cell mediator release, reduction in plasma exudation, and inhibition of sensory nerve activation (Table 8-3). Inflammatory cells express small numbers of β_2 -receptors, but these are rapidly downregulated with β_2 -agonist activation so that, in contrast to corticosteroids, there are no effects on inflammatory cells in the airways, and there is no reduction in AHR.

Clinical use β_2 -Agonists are usually given by inhalation to reduce side effects. Short-acting β_2 -agonists (SABAs), such as albuterol and terbutaline, have a duration of action of 3 to 6 hours. They have a rapid onset of bronchodilation and are therefore used as needed for symptom relief. Increased use of SABAs indicates that asthma is not controlled. They are also useful in preventing EIA if taken before exercise. SABAs are used in high

doses by nebulizer or via a metered dose inhaler with a spacer. Long-acting β_2 -agonists (LABAs) include salmeterol and formoterol, both of which have a duration of action over 12 hours and are given twice daily. LABAs have replaced the regular use of SABAs, but LABAs should not be given in the absence of ICS therapy because they do not control the underlying inflammation. They do, however, improve asthma control and reduce exacerbations when added to ICS, which allows asthma to be controlled at lower doses of corticosteroids. This observation has led to the widespread use of fixed combination inhalers that contain a corticosteroid and a LABA, which have proven to be highly effective in the control of asthma.

Side effects Adverse effects are not usually a problem with β_2 -agonists when given by inhalation. The most common side effects are muscle tremor and palpitations, which are seen more commonly in elderly patients. There is a small decrease in plasma potassium because of increased uptake by skeletal muscle cells, but this effect does not usually cause a clinical problem.

Tolerance Tolerance is a potential problem with any agonist given chronically, but although there is downregulation of β_2 -receptors, this does not reduce the bronchodilator response because there is a large receptor reserve in airway smooth muscle cells. By contrast, mast cells become rapidly tolerant, but their tolerance may be prevented by concomitant administration of ICS.

Safety The safety of β_2 -agonists has been an important issue. There is an association between asthma mortality and the amount of SABA used, but careful analysis demonstrates that the increased use of rescue SABAs reflects poor asthma control, which is a risk factor for asthma death. The slight excess in mortality that has been associated with the use of LABAs is related to the lack of use of concomitant ICS because LABA therapy does not deal with the underlying inflammation. This highlights the importance of always using an ICS when LABAs are given, which is most conveniently achieved by using a combination inhaler.

Anticholinergics Muscarinic receptor antagonists, such as ipratropium bromide, prevent cholinergic nerve-induced bronchoconstriction and mucus secretion. They are much less effective than β_2 -agonists in asthma therapy because they inhibit only the cholinergic reflex component of bronchoconstriction, β_2 -agonists prevent all bronchoconstrictor mechanisms. Anticholinergics are therefore only used as an additional bronchodilator in patients with asthma that is not controlled on other inhaled medications. High doses may be given by nebulizer in treating acute severe asthma but should only be given after β_2 -agonists because they have a slower onset of bronchodilation.

TABLE 8-3

EFFECTS OF β -ADRENERGIC AGONISTS ON AIRWAYS

Relaxation of airway smooth muscle (proximal and distal airways)
Inhibition of mast cell mediator release
Inhibition of plasma exudation and airway edema
Increased mucociliary clearance
Increased mucus secretion
Decreased cough
No effect on chronic inflammation

Side effects are not usually a problem because there is little or no systemic absorption. The most common side effect is dry mouth; in elderly patients, urinary retention and glaucoma may also be observed.

Theophylline Theophylline was widely prescribed as an oral bronchodilator several years ago, especially because it was inexpensive. It has now fallen out of favor because side effects are common and inhaled β_2 -agonists are much more effective as bronchodilators. The bronchodilator effect is caused by inhibition of phosphodiesterases in airway smooth muscle cells, which increases cyclic AMP, but doses required for bronchodilation commonly cause side effects that are mediated mainly by phosphodiesterase inhibition. Increasing evidence suggests that theophylline at lower doses has anti-inflammatory effects, and these are likely to be mediated through different molecular mechanisms. There is evidence that theophylline activates the key nuclear enzyme histone deacetylase-2, which is a critical mechanism for switching off activated inflammatory genes.

Clinical use Oral theophylline is usually given as a slow-release preparation once or twice daily because this gives more stable plasma concentrations than normal theophylline tablets. It may be used as an additional bronchodilator in patients with severe asthma when plasma concentrations of 10–20 mg/L are required, although these concentrations are often associated with side effects. Low doses of theophylline, giving plasma concentrations of 5–10 mg/L, have additive effects to ICSs and are particularly useful in patients with severe asthma. Indeed, withdrawal of theophylline from these patients may result in marked deterioration in asthma control. The drug is well tolerated at low doses. IV aminophylline (a soluble salt of theophylline) was used for the treatment of patients with severe asthma but has now been largely supplemented by inhaled SABAs, which are more effective and have fewer side effects. Aminophylline is occasionally used (via slow IV infusion) in patients with severe exacerbations that are refractory to high-dose SABAs.

Side effects Oral theophylline is well absorbed and is largely inactivated in the liver. Side effects are related to plasma concentrations; measurement of plasma theophylline may be useful in determining the correct dose. The most common side effects—nausea, vomiting, and headaches—are caused by phosphodiesterase inhibition. Diuresis and palpitations may also occur, and at high concentrations, cardiac arrhythmias, epileptic seizures, and death may occur because of adenosine receptor antagonism. Theophylline's side effects are related to plasma concentration and are rarely observed at plasma concentrations below 10 mg/L. Theophylline is metabolized by CYP450 in the liver, and thus plasma

concentrations may be elevated by drugs that block CYP450, such as erythromycin and allopurinol. Other drugs may also reduce clearance by other mechanisms leading to increased plasma concentrations (Table 8-4).

Controller Therapies

Inhaled Corticosteroids ICSs are by far the most effective controllers for asthma, and their early use has revolutionized asthma therapy.

Mode of action ICSs are the most effective anti-inflammatory agents used in asthma therapy, reducing the number of inflammatory cells and their activation in the airways. ICSs reduce eosinophils in the airways and sputum and numbers of activated T lymphocytes and surface mast cells in the airway mucosa. These effects may account for the reduction in AHR that is seen with chronic ICS therapy.

The molecular mechanism of action of corticosteroids involves several effects on the inflammatory process. The major effect of corticosteroids is to switch off the transcription of multiple activated genes that encode inflammatory proteins, such as cytokines, chemokines, adhesion molecules, and inflammatory enzymes. This effect involves several mechanisms, including inhibition of the transcription factors NF κ B and AP-1, but an important mechanism is recruitment of histone deacetylase-2 to the inflammatory gene complex, which reverses the histone acetylation associated with increased gene transcription. Corticosteroids also activate anti-inflammatory genes, such as mitogen-activated protein (MAP) kinase phosphatase-1, and increase the expression of β_2 -receptors. Most of the metabolic and endocrine side effects of corticosteroids are also mediated through transcriptional activation.

TABLE 8-4

FACTORS AFFECTING CLEARANCE OF THEOPHYLLINE

Increased Clearance

- Enzyme induction (rifampicin, phenobarbitone, ethanol)
- Smoking (tobacco, marijuana)
- High-protein, low-carbohydrate diet
- Barbecued meat
- Childhood

Decreased Clearance

- Enzyme inhibition (cimetidine, erythromycin, ciprofloxacin, allopurinol, zileuton, zafirlukast)
- Congestive heart failure
- Liver disease
- Pneumonia
- Viral infection and vaccination
- High-carbohydrate diet
- Old age

Clinical use ICSs are by far the most effective controllers in the management of asthma and are beneficial in treating asthma of any severity and age. ICSs are usually given twice daily, but some may be effective once daily in mildly symptomatic patients. ICSs rapidly improve the symptoms of asthma, and lung function improves over several days. ICSs are effective in preventing asthma symptoms, such as EIA and nocturnal exacerbations, but they also prevent severe exacerbations. ICSs reduce AHR, but maximal improvement may take several months of therapy. Early treatment with ICSs appears to prevent irreversible changes in airway function that occur with chronic asthma. Withdrawal of ICSs results in slow deterioration of asthma control, indicating that they suppress inflammation and symptoms but do not cure the underlying condition. ICSs are now given as first-line therapy for patients with persistent asthma, but if they do not control symptoms at low doses, it is usual to add a LABA as the next step.

Side effects Local side effects include hoarseness (dysphonia) and oral candidiasis, which may be reduced with the use of a large-volume spacer device. There has been concern about systemic side effects from lung absorption, but many studies have demonstrated that ICSs have minimal systemic effects (Fig. 8-6). At the highest recommended doses, there may be some suppression of plasma and urinary cortisol concentrations, but there is no convincing evidence that long-term treatment leads to impaired growth in children or to osteoporosis in adults. Indeed, effective control of asthma with ICSs reduces the number of courses of oral corticosteroids that are needed and thus reduces systemic exposure to ICSs.

Systemic Corticosteroids Corticosteroids (hydrocortisone or methylprednisolone) are used intravenously for the treatment of acute severe asthma,

although several studies now show that oral corticosteroids are as effective and easier to administer. A course of oral corticosteroids (usually prednisone or prednisolone 30–45 mg od for 5–10 days) is used to treat acute exacerbations of asthma; no tapering of the dose is needed. Approximately 1% of asthma patients may require maintenance treatment with oral corticosteroids; the lowest dose necessary to maintaining control needs to be determined. Systemic side effects, including truncal obesity, bruising, osteoporosis, diabetes, hypertension, gastric ulceration, proximal myopathy, depression, and cataracts may be a major problem, and steroid-sparing therapies may be considered if side effects are a significant problem. If patients require maintenance treatment with oral corticosteroids, it is important to monitor bone density so that preventive treatment with bisphosphonates (or estrogen in postmenopausal women) may be initiated if bone density is low. IM triamcinolone acetonide is a depot preparation that is occasionally used in noncompliant patients, but proximal myopathy is a major problem with this therapy.

Antileukotrienes Cysteinyl-leukotrienes are potent bronchoconstrictors, cause microvascular leakage, and increase eosinophilic inflammation through the activation of cys-LT₁-receptors. These inflammatory mediators are produced predominantly by mast cells and, to a lesser extent, eosinophils in asthma. Antileukotrienes, such as montelukast and zafirlukast, block cys-LT₁-receptors and provide a modest clinical benefit in asthma. They are less effective than ICSs in controlling asthma and have less effect on airway inflammation but are useful as an add-on therapy in some patients not controlled with low doses of ICSs (although they are less effective than LABAs). They are given orally once or twice daily and are well tolerated. Some patients show a better response than others to antileukotrienes, but this

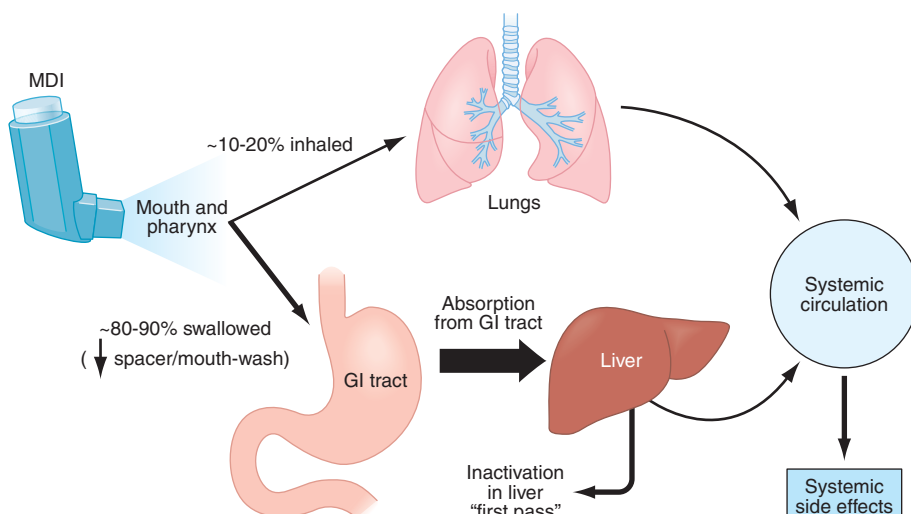


FIGURE 8-6 Pharmacokinetics of inhaled corticosteroids. GI, gastrointestinal; MDI, metered dose inhaler.

has not been convincingly linked to any genomic differences in the leukotriene pathway.

Cromones Cromolyn sodium and nedocromil sodium are asthma controller drugs that appear to inhibit mast cell and sensory nerve activation and are therefore effective in blocking trigger-induced asthma, such as EIA, and allergen- and sulfur dioxide—induced symptoms. Cromones have relatively little benefit in the long-term control of asthma because of their short duration of action (they are needed at least four times daily by inhalation). They are very safe, and although they were popular in the treatment of childhood asthma, low doses of ICSs are now preferred because they are more effective and have a proven safety profile.

Steroid-Sparing Therapies Various immunomodulatory treatments have been used to reduce the requirement for oral corticosteroids in patients with severe asthma who have serious side effects with this therapy. Methotrexate, cyclosporine, azathioprine, gold, and IV gamma globulin have all been used as steroid-sparing therapies, but none of these treatments has any long-term benefit, and each is associated with a relatively high risk of side effects.

Anti-IgE Omalizumab is a blocking antibody that neutralizes circulating IgE without binding to cell-bound IgE; it thus inhibits IgE-mediated reactions. This treatment has been shown to reduce the number of exacerbations in patients with severe asthma and may improve asthma control. However, the treatment is very expensive and only suitable for highly selected patients who are not controlled on maximal doses of inhaled therapy and have a circulating IgE within a specified range. Patients should be given a 3- to 4-month trial of therapy to show objective benefit. Omalizumab is usually given as a subcutaneous injection every 2 to 4 weeks and appears not to have significant side effects.

Immunotherapy Specific immunotherapy using injected extracts of pollens or house dust mite has not been very effective in controlling asthma and may cause anaphylaxis. Side effects may be reduced by sublingual dosing. It is not recommended in most asthma treatment guidelines because of lack of evidence of clinical efficacy.

Alternative Therapies Nonpharmacologic treatments, including hypnosis, acupuncture, chiropraxy, breathing control, yoga, and speleotherapy, may be popular with some patients. However, placebo-controlled studies have shown that each of these treatments lacks efficacy and cannot be recommended. However, they are not detrimental and may be used as long as conventional pharmacologic therapy is continued.

Future Therapies It has proven very difficult to discover novel pharmaceutical therapies, particularly because current therapy with corticosteroids and β_2 -agonists is so effective in the majority of patients. However, there is a need for the development of new therapies for patients with refractory asthma who have side effects with systemic corticosteroids. Antagonists of specific mediators have little or no benefit in asthma, apart from antileukotrienes, which have a rather weak effect, presumably reflecting the fact that multiple mediators are involved. Antagonists of chemokine receptors, particularly CCR3, are in development and may be more effective. Novel anti-inflammatory treatments that are in clinical development include inhibitors of phosphodiesterase-4, NF κ B, p38 MAP kinase, and phosphoinositide-3 kinase. However, these drugs, which act on signal transduction pathways common to many cells, are likely to have troublesome side effects, necessitating their delivery by inhalation. Safer and more effective immunotherapy using T cell peptide fragments of allergens or DNA vaccination are also being investigated. Bacterial products, such as CpG oligonucleotides that stimulate T_H1 immunity or regulatory T cells, are also currently under evaluation.

MANAGEMENT OF CHRONIC ASTHMA

There are several aims of chronic therapy in asthma (see Table 8-2). It is important to establish the diagnosis objectively using spirometry or PEF measurements at home. Triggers that worsen asthma control, such as allergens or occupational agents, should be avoided, but triggers such as exercise and fog, which result in transient symptoms, provide an indication that more controller therapy is needed.

Stepwise Therapy For patients with mild, intermittent asthma, a short-acting β_2 -agonist is all that is required (Fig. 8-7). However, use of a reliever medication more than three times a week indicates the need for

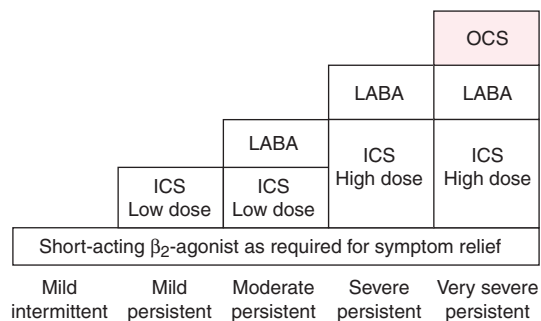


FIGURE 8-7

Step-wise approach to asthma therapy according to the severity of asthma and ability to control symptoms. ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; OCS, oral corticosteroid.

regular controller therapy. The treatment of choice for all patients is an ICS given twice daily. It is usual to start with an intermediate dose (e.g., 200 µg bid of beclomethasone dipropionate or equivalent) and to decrease the dose if symptoms are controlled after 3 months. If symptoms are not controlled, an LABA should be added, most conveniently by switching to a combination inhaler. The dose of controller should be adjusted accordingly, as judged by the need for a rescue inhaler. Low doses of theophylline or an antileukotriene may also be considered as an add-on therapy, but these are less effective than LABAs. In patients with severe asthma, low-dose oral theophylline is also helpful, and when there is irreversible airway narrowing, the long-acting anticholinergic tiotropium bromide may be tried. If asthma is not controlled despite the maximal recommended dose of inhaled therapy, it is important to check compliance and inhaler technique. In these patients, maintenance treatment with an oral corticosteroid may be needed, and the lowest dose that maintains control should be used. Occasionally, omalizumab may be tried in steroid-dependent asthmatics who are not well controlled. After asthma is controlled, it is important to slowly decrease therapy to find the optimal dose to control symptoms.

Education Patients with asthma need to understand how to use their medications and the difference between reliever and controller therapies. Education may improve compliance, particularly with ICSs. All patients should be taught how to use their inhalers correctly. In particular, they need to understand how to recognize worsening of asthma and how to step up therapy. Written action plans have been shown to reduce hospital admissions and morbidity in adults and children and are recommended particularly in patients with unstable disease who have frequent exacerbations.

ACUTE SEVERE ASTHMA

Exacerbations of asthma are feared by patients and may be life threatening. One of the main aims of controller therapy is to prevent exacerbations; in this respect, ICS and combination inhalers are very effective.

CLINICAL FEATURES

Patients are aware of increasing chest tightness, wheezing, and dyspnea that are often not or poorly relieved by their usual reliever inhaler. In severe exacerbations, patients may be so breathless that they are unable to complete sentences and may become cyanotic. Examination usually shows increased ventilation, hyperinflation, and tachycardia. Pulsus paradoxus may be present,

but this is rarely a useful clinical sign. There is a marked decrease in spirometric values and PEF. Arterial blood gases on air show hypoxia and P_{aCO_2} is usually low because of hyperventilation. A normal or increasing P_{aCO_2} is an indication of impending respiratory failure and requires immediate monitoring and therapy. Chest radiography is not usually informative but may show pneumonia or pneumothorax.

Rx Treatment: ACUTE SEVERE ASTHMA

A high concentration of oxygen should be given by face mask to achieve oxygen saturation of above 90%. The mainstay of treatment is high doses of short-acting inhaled β_2 -agonists that are given either by nebulizer or via a metered dose inhaler with a spacer. In severely ill patients with impending respiratory failure, IV β_2 -agonists may be given. An inhaled anticholinergic agent may be added if there is not a satisfactory response to β_2 -agonists alone because there are additive effects. In patients who are refractory to inhaled therapies, a slow infusion of aminophylline may be effective, but it is important to monitor blood levels especially if patients have already been treated with oral theophylline. Magnesium sulfate given IV or by nebulizer has also been shown to be effective when added to inhaled β_2 -agonists, and is relatively well tolerated but is not routinely recommended. Prophylactic intubation may be indicated for impending respiratory failure when the P_{aCO_2} is normal or increases. For patients with respiratory failure, it is necessary to intubate and institute ventilation. These patients may benefit from an anesthetic, such as halothane, if they have not responded to conventional bronchodilators. Sedatives should never be given because they may depress ventilation. Antibiotics should not be used routinely unless there are signs of pneumonia.

REFRACTORY ASTHMA

Although asthma is easily controlled in most patients with appropriate medication, the disease is difficult to control in a small proportion of patients (~5% of asthmatics) despite maximal inhaled therapy. Some of these patients require maintenance treatment with oral corticosteroids. In managing these patients, it is important to investigate and correct any mechanisms that may be aggravating asthma. There are two major patterns of difficult asthma: some patients have persistent symptoms and poor lung function despite appropriate therapy, and others may have normal or near-normal lung function but intermittent, severe (sometimes life-threatening) exacerbations.

The most common reason for poor control of asthma is noncompliance with medication, particularly ICS. Compliance with ICS may be low because patients do not feel any immediate clinical benefit or may be concerned about side effects. Compliance with ICS is difficult to monitor because there are no useful plasma measurements that can be made. Compliance may be improved by giving the ICS as a combination with a LABA that gives symptom relief. Compliance with oral corticosteroids may be measured by suppression of plasma cortisol and the expected concentration of prednisone or prednisolone in the plasma. There are several factors that may make asthma more difficult to control, including exposure to high ambient levels of allergens or unidentified occupational agents. Severe rhinosinusitis may make asthma more difficult to control; upper airway disease should be vigorously treated. Gastroesophageal reflux is common among asthmatics because of bronchodilator therapy, but there is little evidence that it is a significant factor in worsening asthma, and treatment of the reflux is not usually effective at improving asthma symptoms. Some patients may have chronic infection with *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* and benefit from treatment with a macrolide antibiotic. Drugs such as β -adrenergic blockers, aspirin, and other cyclooxygenase (COX) inhibitors may worsen asthma. Some women develop severe premenstrual worsening of asthma, which is unresponsive to corticosteroids and requires treatment with progesterone or gonadotropin-releasing factors. Few systemic diseases make asthma more difficult to control, but hyper- and hypothyroidism may increase asthma symptoms and should be investigated if suspected.

Relatively little is known about the pathology of refractory asthma because biopsy studies are more difficult in these patients. Some patients show the typical eosinophilic pattern of inflammation, but others have a predominantly neutrophilic pattern. There may be an increase in T_H1 cells and CD8 lymphocytes compared with mild asthma and increased expression of TNF α . Structural changes in the airway, including fibrosis, angiogenesis, and airway smooth muscle thickening, are more commonly seen in these patients.

DIFFERENTIAL DIAGNOSIS

Some patients who apparently have difficult-to-control asthma also have vocal cord dysfunction, resulting in wheezing or stridor. This symptom is thought to be an attention-seeking hysterical conversion syndrome and may lead to escalating doses of asthma therapy, with some patients taking high doses of oral corticosteroids. It may be recognized by the characteristic discrepancy between tests of forced expiration, such as FEV₁ and

PEF, and relatively normal airway resistance. Direct inspection by laryngoscopy may confirm adduction of the vocal cords at the time of symptoms. This condition is usually difficult to manage, but it is important that patients be weaned off oral and ICSs. Speech therapy is sometimes beneficial. Some patients with COPD may be diagnosed as asthmatic and may show the characteristic poor response to corticosteroids and bronchodilators, but this situation is complicated by the fact that some patients with COPD also have concomitant asthma.

CORTICOSTEROID-RESISTANT ASTHMA

A few patients with asthma show a poor response to corticosteroid therapy and may have various molecular abnormalities that impair the anti-inflammatory action of corticosteroids. Complete resistance to corticosteroids is extremely uncommon and affects fewer than one in 1000 patients. It is defined by a failure to respond to a high dose of oral prednisone or prednisolone (40 mg od over 2 weeks), ideally with a 2-week run-in with matched placebo. More common is reduced responsiveness to corticosteroids in which control of asthma requires oral corticosteroids (corticosteroid-dependent asthma). In all patients with poor responsiveness to corticosteroids, there is a reduction in the response of circulating monocytes and lymphocytes to the anti-inflammatory effects of corticosteroids in vitro and reduced skin blanching in response to topical corticosteroids. Several mechanisms have been described, including an excess of the transcription factor AP-1, an increase in the alternatively spliced form of the glucocorticoid receptor GR- β , an abnormal pattern of histone acetylation in response to corticosteroids, a defect in IL-10 production, and a reduction in histone deacetylase activity (as in COPD). These observations suggest that there are likely to be heterogeneous mechanisms for corticosteroid resistance; whether these mechanisms are genetically determined has yet to be determined.

BRITTLE ASTHMA

Some patients show chaotic variations in lung function despite taking appropriate therapy. Some show a persistent pattern of variability and may require oral corticosteroids or, at times, continuous infusion of β_2 -agonists (type I brittle asthma), and others have generally normal or near-normal lung function but precipitous, unpredictable decreases in lung function that may result in death (type 2 brittle asthma). These latter patients are difficult to manage because they do not respond well to corticosteroids, and the worsening of asthma does not reverse well with inhaled bronchodilators. The most effective therapy is subcutaneous epinephrine, which suggests that the worsening is likely to be a localized airway anaphylactic reaction with edema. Some of these

patients may be allergic to specific foods. These patients should be taught to self-administer epinephrine and should carry a medical warning accordingly.

Rx Treatment: **REFRACTORY ASTHMA**

Refractory asthma is difficult to control, by definition. It is important to check compliance and the correct use of inhalers and to identify and eliminate any underlying triggers. Low doses of theophylline may be helpful in some patients, and theophylline withdrawal has been found to worsen many patients' symptoms. Most of these patients require maintenance treatment with oral corticosteroids, and the minimal dose that achieves satisfactory control should be determined by careful dose titration. Steroid-sparing therapies are rarely effective. In some patients with allergic asthma, omalizumab is effective, particularly when there are frequent exacerbations. There is some evidence that anti-TNF therapy may be effective, but this is controversial and very expensive. A few patients may benefit from infusions of β_2 -agonists. New therapies are needed for these patients, who currently consume a disproportionate amount of health care spending.

SPECIAL CONSIDERATIONS

Although asthma is usually straightforward to manage, there are some situations that may require additional investigation and different therapy.

ASPIRIN-SENSITIVE ASTHMA

A small proportion (~1%) of patients with asthma have worse disease with aspirin and other COX inhibitors, although this is much more commonly seen in severe patients and in those with frequent hospital admission. Aspirin-sensitive asthma is a well-defined subtype of asthma that is usually preceded by perennial rhinitis and nasal polyps in nonatopic patients with a late onset of the disease. Aspirin, even in small doses, characteristically provokes rhinorrhea, conjunctival irritation, facial flushing, and wheezing. There is a genetic predisposition to increased production of cysteinyl-leukotrienes with functional polymorphism of cys-leukotriene synthase. Asthma is triggered by COX inhibitors but is persistent even in their absence. All nonselective COX inhibitors should be avoided, but selective COX-2 inhibitors are apparently safe to use when an anti-inflammatory analgesic is needed. Patients with aspirin-sensitive asthma respond to usual therapy with an ICS. Although

antileukotrienes should be effective in these patients, they are no more effective than in those with allergic asthma. Occasionally, aspirin desensitization is necessary, but this should only be undertaken in specialized centers.

ASTHMA IN THE ELDERLY

Asthma may start at any age, including in elderly patients. The principles of management are the same as in other asthmatics, but side effects of therapy may be a problem, including muscle tremor with β_2 -agonists and more systemic side effects with ICSs. Comorbidities are more frequent in this age group, and interactions with drugs such as β_2 blockers, COX inhibitors, and agents that may affect theophylline metabolism need to be considered. COPD is more likely in elderly patients and may coexist with asthma. A trial of oral corticosteroids may be very useful in documenting the steroid responsiveness of asthma.

PREGNANCY

Approximately one-third of asthmatic patients who are pregnant improve during the course of a pregnancy, one-third deteriorate, and one-third are unchanged. It is important to maintain good control of asthma because poor control may have adverse effects on fetal development. Compliance may be a problem because there is often concern about the effects of anti-asthma medications on fetal development. The drugs that have been used for many years in asthma therapy have now been shown to be safe and without teratogenic potential. These drugs include short-acting β_2 -agonists, ICSs, and theophylline; there is less safety information about newer classes of drugs such as LABAs, antileukotrienes, and anti-IgE. If an oral corticosteroid is needed, it is better to use prednisone rather than prednisolone because it cannot be converted to the active prednisolone by the fetal liver, thus protecting the fetus from systemic effects of the corticosteroid. There is no contraindication to breast-feeding when patients are using these drugs.

CIGARETTE SMOKING

Approximately 20% of asthmatics smoke, which may adversely affect asthma in several ways. Smoking asthmatics have more severe disease, more frequent hospital admissions, a faster decline in lung function, and a higher risk of death from asthma than nonsmoking asthmatics. There is evidence that smoking interferes with the anti-inflammatory actions of corticosteroids, necessitating higher doses for asthma control. Smoking cessation improves lung function and reverses the steroid resistance; thus, vigorous smoking cessation strategies should be used. Some patients report a temporary worsening of asthma when they first stop smoking, which

78 may be caused by the loss of the bronchodilating effect of NO in cigarette smoke.

SURGERY

If asthma is well controlled, there is no contraindication to general anesthesia and intubation. Patients who are treated with oral corticosteroids will have adrenal suppression and should be treated with an increased dose of oral corticosteroid immediately before surgery. Patients with FEV₁ below 80% of their normal levels should also be given a boost of oral corticosteroids before surgery. High maintenance doses of corticosteroids may be a contraindication to surgery because of increased risks of infection and delayed wound healing.

BRONCHOPULMONARY ASPERGILLOSIS

BPA is uncommon and results from an allergic pulmonary reaction to inhaled spores of *Aspergillus fumigatus* and, occasionally, other *Aspergillus* spp. A skin prick test to *A. fumigatus* is always positive, but serum *Aspergillus* precipitins are low or undetectable. Characteristically, there are fleeting eosinophilic infiltrates in the lungs, particularly in the upper lobes. As airways become blocked with mucoid plugs rich in eosinophils, patients may cough up brown plugs and have hemoptysis. BPA may result in bronchiectasis, particularly affecting central airways, if not suppressed by corticosteroids. Asthma is controlled in the usual way by ICSs, but it is necessary to give a course of oral corticosteroids if there is any sign of worsening or pulmonary shadowing is found. Treatment with the oral antifungal itraconazole is beneficial in preventing exacerbations.

FURTHER READINGS

- ADCOCK IM et al: New targets for drug development in asthma. *Lancet* 372:1073, 2008
- ASHER MI et al: Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 368:733, 2006

- BARNES PJ: Immunology of asthma and chronic obstructive pulmonary disease. *Nat Immunol Rev* 8:183, 2000
- , New drugs for asthma. *Nat Rev Drug Discov* 3:831, 2004
- , How corticosteroids control inflammation. *Br J Pharmacol* 148:245, 2006
- , Cytokine networks in asthma and chronic obstructive pulmonary disease. *J Clin Invest* 118:3546, 2008
- , ADCOCK IM: How do corticosteroids work in asthma? *Ann Intern Med* 139:359, 2003
- et al: Inflammatory mediators of asthma: An update. *Pharmacol Rev* 50:515, 1998
- et al: *Asthma and COPD*. London, Academic Press, 2002
- et al: *Asthma and COPD*, 2d ed. Amsterdam, Elsevier, 2009
- BATEMAN ED et al: Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 31:143, 2008
- BUSSE WW, LEMANSKE RF: Asthma. *N Engl J Med* 344:350, 2001
- COOKSON W, MOFFATT M: Making sense of asthma genes. *N Engl J Med* 351:1794, 2004
- EDER W et al: The asthma epidemic. *N Engl J Med* 355:2226, 2006
- FANTA CH: Asthma. *N Engl J Med* 360:1002, 2009
- FAROOQUE SP, LEE TH: Aspirin-sensitive respiratory disease. *Ann Rev Physiol* 71:465, 2009
- HAMID Q, TULIC M: Immunobiology of asthma. *Ann Rev Physiol* 71:489, 2009
- HEANEY LG, ROBINSON DS: Severe asthma treatment: Need for characterising patients. *Lancet* 365:974, 2005
- MAPP CE et al: Occupational asthma. *Am J Respir Crit Care Med* 172:280, 2005
- O'BYRNE PM, PARAMESWARAN K: Pharmacological management of mild or moderate persistent asthma. *Lancet* 368:794, 2006
- SZCZEKLIK A, STEVENSON DD: Aspirin-induced asthma: Advances in pathogenesis, diagnosis, and management. *J Allergy Clin Immunol* 111:913, 2003
- WENZEL SE: Asthma: Defining of the persistent adult phenotypes. *Lancet* 368:804, 2006
- , BUSSE WW: Severe asthma: Lessons from the Severe Asthma Research Program. *J Allergy Clin Immunol* 119:14, 2007



CHAPTER 9

HYPERSENSITIVITY PNEUMONITIS AND PULMONARY INFILTRATES WITH EOSINOPHILIA

Joel N. Kline ■ Gary W. Hunninghake

■ Hypersensitivity Pneumonitis	79
Etiology	79
Pathogenesis	79
Clinical Presentation	81
Diagnosis	81
Differential Diagnosis	83
■ Pulmonary Infiltrates with Eosinophilia	84
■ Global Picture of Hypersensitivity Pneumonitis and Pulmonary Infiltrates with Eosinophilia	85
■ Further Readings	85

HYPERSENSITIVITY PNEUMONITIS

First described in 1874, hypersensitivity pneumonitis (HP), or extrinsic allergic alveolitis, is an inflammatory disorder of the lung involving alveolar walls and terminal airways that is induced in a susceptible host by repeated inhalation of a variety of organic agents. Factors responsible for the expression of HP include both those related to the host (susceptibility) and the inciting agent. Causes of HP are typically designated with colorful names denoting the occupational or avocational risk associated with the disease; for example, “farmer’s lung” is the term most commonly used for HP caused by inhalation of antigens present in moldy hay, such as thermophilic actinomyces, *Micropolyspora faeni*, and *Aspergillus* spp. The frequency of HP varies with the environmental exposure and the specific antigen involved.

ETIOLOGY

Agents implicated as causes of HP are diverse and include those listed in [Table 9-1](#). In the United States, the most common types of HP are farmer’s lung, bird fancier’s

lung, and chemical worker’s lung. In *farmer’s lung*, inhalation of proteins such as thermophilic bacteria and fungal spores that are present in moldy bedding and feed are most commonly responsible for the development of HP. These antigens are probably also responsible for the etiology of *mushroom worker’s disease* (moldy composted growth medium is the source of the proteins) and *bagassosis* (moldy sugar cane is the source). *Bird fancier’s lung* (and the related disorders of duck fever, turkey handler’s lung, and dove pillow’s lung) is a response to inhalation of proteins from feathers and droppings. *Chemical worker’s lung* is an example of how simple chemicals, such as isocyanates, may also cause immune-mediated diseases.

PATHOGENESIS

The finding that precipitating antibodies against extracts of moldy hay were demonstrable in most patients with farmer’s lung led to the early conclusion that HP was an immune complex–mediated reaction. Subsequent investigations of HP in human beings and animal models provided evidence for the importance of cell-mediated hypersensitivity. The very early (acute) reaction is

SELECTED EXAMPLES OF HYPERSENSITIVITY PNEUMONITIS (HP)

DISEASE	ANTIGEN	SOURCE OF ANTIGEN
Bagassosis	Thermophilic actinomycetes ^a	"Moldy" bagasse (sugar cane)
Bird fancier's, breeder's, or handler's lung ^b	Parakeet, pigeon, chicken, turkey proteins	Avian droppings or feathers
<i>Cephalosporium</i> HP	Contaminated basement (sewage)	<i>Cephalosporium</i> spp.
Cheese washer's lung	<i>Penicillium casei</i>	Moldy cheese
Chemical worker's lung ^b	Isocyanates	Polyurethane foam, varnishes, lacquer
Coffee worker's lung	Coffee bean dust	Coffee beans
Compost lung	<i>Aspergillus</i> spp.	Compost
Detergent worker's disease	<i>Bacillus subtilis</i> enzymes (subtilisins)	Detergent
Familial HP	<i>Bacillus subtilis</i>	Contaminated wood dust in walls
Farmer's lung ^b	Thermophilic actinomycetes ^a	"Moldy" hay, grain, silage
Fish food lung	Unknown	Fish food
Fish meal worker's lung	Fish meal dust	Fish meal
Furrier's lung	Animal fur dust	Animal pelts
Hot tub lung	<i>Cladosporium</i> spp., <i>Mycobacterium avium</i> complex	Mold on ceiling; contaminated water
Humidifier or air-conditioner lung (ventilation pneumonitis)	<i>Aureobasidium pullulans</i> , <i>Candida albicans</i> , Thermophilic actinomycetes, ^a mycobacterium spp., other microorganisms	Contaminated water in humidification or forced-air air-conditioning systems
Japanese summer-type HP	<i>Trichosporon cutaneum</i> , <i>T. asahii</i> , and <i>T. mucoides</i>	House dust? Bird droppings
Laboratory worker's HP	Male rat urine	Laboratory rat
Lycoperdonosis	<i>Lycoperdon</i> puffballs	Puffball spores
Malt worker's lung	<i>Aspergillus fumigatus</i> or <i>A. clavatus</i>	Moldy barley
Maple bark disease	<i>Cryptostroma corticale</i>	Maple bark
Metalworking fluid lung	Mycobacterium spp., <i>Pseudomonas</i> spp.	Contaminated metalworking fluid
Miller's lung	<i>Sitophilus granarius</i> (wheat weevil)	Infested wheat flour
Miscellaneous medications	Amiodarone, bleomycin, efavirenz, gemcitabine, hydralazine, hydroxyurea, isoniazid, methotrexate, paclitaxel, penicillin, procarbazine, propranolol, riluzole, sirolimus, sulfasalazine	Medication
Mushroom worker's lung	Thermophilic actinomycetes, ^a <i>Hypsizygus marmoreus</i> , <i>Bunashimeji</i> spp., and other exotic mushrooms	Mushroom compost; mushrooms
Pituitary snuff taker's lung	Animal proteins	Heterologous pituitary snuff
Potato riddler's lung	Thermophilic actinomycetes, ^a <i>Aspergillus</i> spp.	"Moldy" hay around potatoes
Sauna taker's lung	<i>Aureobasidium</i> spp., other	Contaminated sauna water
Sausage worker's lung	<i>Penicillium nalgiovense</i>	Dry sausage mold
Sequoiosis	<i>Aureobasidium</i> spp., <i>Graphium</i> spp.	Redwood sawdust
<i>Streptomyces albus</i> HP	<i>Streptomyces albus</i>	Contaminated fertilizer
Suberosis	<i>Penicillium glabrum</i> and <i>Chrysonilia sitophila</i>	Cork dust
Tap water lung	<i>Mycobacteria</i> spp.	Contaminated tap water
Thatched roof disease	<i>Saccharomonospora viridis</i>	Dried grasses and leaves
Tobacco worker's disease	<i>Aspergillus</i> spp.	Mold on tobacco
Winegrower's lung	<i>Botrytis cinerea</i>	Mold on grapes
Wood trimmer's disease	<i>Rhizopus</i> spp., <i>Mucor</i> spp.	Contaminated wood trimmings
Woodman's disease	<i>Penicillium</i> spp.	Oak and maple trees
Woodworker's lung	Wood dust, <i>Alternaria</i>	Oak, cedar, pine, and mahogany dusts

^aThermophilic actinomycetes species include *Micropolyspora faeni*, *Thermoactinomyces vulgaris*, *T. saccharii*, *T. viridis*, and *T. candidus*.^bMost common causes of hypersensitivity pneumonitis in the United States.

characterized by an increase in polymorphonuclear leukocytes in the alveoli and small airways. This early lesion is followed by an influx of mononuclear cells into the lung and the formation of granulomas that appear to be the result of a classic delayed (T cell–mediated) hypersensitivity reaction to repeated inhalation of antigen and adjuvant-active materials. Studies in animal models suggest that the disease is a T_H1 –mediated immune response to antigen, with interferon γ , interleukin (IL) 12, and possibly IL-18 contributing to disease expression. Most likely, multiple cytokines [including also IL-1 β , transforming growth factor (TGF) β , tumor necrosis factor (TNF) α and others] interact to promote HP; their source includes both alveolar macrophages and T lymphocytes in the lung. Recent data support a genetic predisposition to the development of HP; certain polymorphisms of the TNF- α promoter region reportedly confer an enhanced susceptibility to pigeon breeder's disease.

The attraction and accumulation of inflammatory cells in the lung may be caused by one or more of the following mechanisms: induction of the adhesion molecules L-selectin and E-selectin, elaboration by dendritic cells of CC chemokine 1 (DC-CK-1/CCL18), and increased expression of CXCR3/CXCL10 by CD4⁺ and CD8⁺ lymphocytes. Increased levels of Fas protein and FasL in the lung (which would be expected to suppress inflammation by induction of T cell apoptosis) is counterbalanced by increased expression of the inducible antiapoptotic gene Bcl-xL, resulting in a lower overall level of pulmonary lymphocyte apoptosis in HP patients.

Bronchoalveolar lavage (BAL) in patients with HP consistently demonstrates an increase in T lymphocytes in lavage fluid (a finding that is also observed in patients with other granulomatous lung disorders). Patients with recent or continual exposure to antigen may have an increase in polymorphonuclear leukocytes in lavage fluid; this has been associated with lung fibrosis. A role for oxidant injury has been proposed in HP. Several markers of oxidative stress are reported to be increased during exacerbation of HP and are reduced by treatment with glucocorticoids.

CLINICAL PRESENTATION

The clinical picture is that of an interstitial pneumonitis, which varies from patient to patient and seems related to the frequency and intensity of exposure to the causative antigen and perhaps other host factors. The presentation can be acute, subacute, or chronic. In the *acute* form, symptoms such as cough, fever, chills, malaise, and dyspnea may occur 6–8 h after exposure to the antigen and usually clear within a few days if there is no further exposure to antigen. The *subacute* form often appears insidiously over a period of weeks marked by cough and dyspnea and may progress to cyanosis and severe dyspnea requiring

hospitalization. In some patients, a subacute form of the disease may persist after an acute presentation of the disorder, especially if there is continued exposure to antigen. In most patients with the acute or subacute form of HP, the symptoms, signs, and other manifestations of HP disappear within days, weeks, or months if the causative agent is no longer inhaled. Transformation to a chronic form of the disease may occur in patients with continued antigen exposure, but the frequency of such progression is uncertain.

The *chronic* form of HP may be clinically indistinguishable from pulmonary fibrosis due to a wide variety of causes. Physical examination may reveal clubbing. This stage may progressively worsen, resulting in dependence on supplemental oxygen, pulmonary hypertension, and respiratory failure. Pulmonary fibrosis is the clinical manifestation of HP with the greatest predictive value for mortality. An indolent, gradually progressive form of the disease can be associated with cough and exertional dyspnea without a history consistent with acute or subacute manifestations. Such a gradual onset frequently occurs with low-dose exposure to the antigen.

DIAGNOSIS

All forms of the disease may be associated with elevations in erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, and serum immunoglobulins. After acute exposure to antigen, neutrophilia and lymphopenia are frequently present. Eosinophilia is not a feature. Examination for *serum precipitins* against suspected antigens, such as those listed in Table 9–1, is an important part of the diagnostic workup and should be performed on any patient with interstitial lung disease, especially if a suggestive exposure history is elicited. If found, precipitins indicate sufficient exposure to the causative agent for generation of an immunologic response. The diagnosis of HP is not established solely by the presence of precipitins, however, because precipitins are found in sera of many individuals exposed to appropriate antigens who demonstrate no other evidence of HP. False-negative results may occur because of poor-quality antigens or an inappropriate choice of antigens. Extraction of antigens from the suspected source may at times be helpful.

The chest x-ray shows no specific or distinctive changes in HP. It can be normal even in symptomatic patients. The acute or subacute phases may be associated with poorly defined, patchy, or diffuse infiltrates or with discrete, nodular infiltrates. In the chronic phase, the chest x-ray usually shows a diffuse reticulonodular infiltrate. Honeycombing may eventually develop as the condition progresses. Apical sparing is common, suggesting that disease severity correlates with inhaled antigen load, but no particular distribution or pattern is classic for HP. Abnormalities rarely seen in HP include pleural effusion or thickening and hilar adenopathy. High-resolution

82 chest CT has become the procedure of choice for imaging of HP, and a consensus is developing as to the typical appearance of the disease. Although pathognomonic features have not been identified, acute HP may appear with confluent alveolar opacification. In subacute disease, centrilobular nodules and “ground-glass” changes predominate in the lower lobes, and expiratory views may demonstrate air trapping; this pattern is more common in individuals whose exposure to antigen continues rather than those in whom removal from antigen exposure has occurred. In chronic HP, patchy emphysema is seen more often than interstitial fibrosis; subpleural linear opacities and honeycombing are common, and these changes may be found throughout the lung. Hilar or mediastinal adenopathy is not associated with HP (Fig. 9-1).

Pulmonary function studies in all forms of HP may show a restrictive or an obstructive pattern with loss of lung volumes, impaired diffusion capacity, decreased compliance, and exercise-induced hypoxemia. Resting hypoxemia may also be found. Bronchospasm and bronchial hyperreactivity are sometimes found in acute HP. With antigen avoidance, the pulmonary function abnormalities are usually reversible, but they may gradually increase in severity or may occur rapidly after acute or subacute exposure to antigen.

BAL is used in some centers to aid in diagnostic evaluation. A marked lymphocytic alveolitis on BAL is almost universal, although not pathognomonic. Lymphocytes typically have a decreased helper/suppressor ratio and are activated. Alveolar neutrophilia is also prominent acutely but tends to fade in the absence of

recurrent exposure. Bronchoalveolar mastocytosis may correlate with disease activity.

Lung biopsy, obtained through flexible bronchoscopy, open-lung procedures, or thoracoscopy, may be diagnostic. Although the histopathology is distinctive, it may not be pathognomonic of HP (Fig. 9-2). When the biopsy is taken during the active phase of disease, typical findings include an interstitial alveolar infiltrate consisting of plasma cells, lymphocytes, and occasional eosinophils and neutrophils, usually accompanied by loose, noncaseating peribronchial granulomas. Interstitial fibrosis may be present but most often is mild in earlier stages of the disease. Some degree of bronchiolitis is found in about half of cases. Rarely, bronchiolitis obliterans with organizing pneumonia (BOOP) (Chap. 19) may be present. The triad of mononuclear bronchiolitis; interstitial infiltrates of lymphocytes and plasma cells; and single, nonnecrotizing, and randomly scattered parenchymal granulomas without mural vascular involvement is consistent with but not specific for HP.

A *prediction rule* for the clinical diagnosis of HP has been developed by the International Hypersensitivity Pneumonitis Study Group. Six significant predictors of HP (exposure to a known antigen, positive predictive antibodies to the antigen, recurrent episodes of symptoms, inspiratory crackles, symptoms developing 4–8 hours after exposure, and weight loss) were retrospectively developed and then validated in a separate cohort. This diagnostic paradigm has a high predictive value in the diagnosis of HP without the need for invasive testing. In cases where only a subset of the criteria are fulfilled, the diagnosis is less clearly established. It is clear, however, that the diagnosis of HP is established by (1) consistent symptoms, physical



FIGURE 9-1
Chest CT scan of a patient with acute hypersensitivity pneumonitis in which scattered regions of ground-glass and nodular infiltrates are seen bilaterally. (Courtesy of JS Wilson, with permission.)

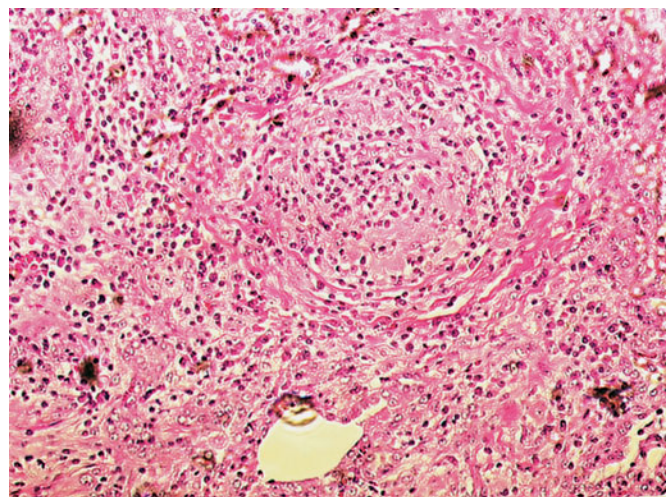


FIGURE 9-2
Open-lung biopsy from a patient with acute hypersensitivity pneumonitis demonstrating loose, nonnecrotizing granulomas and thickened interstitium with an associated interstitial inflammatory response. (Courtesy of B DeYoung, with permission.)

findings, pulmonary function tests, and radiographic tests; (2) a history of exposure to a recognized antigen; and (3) ideally, identification of an antibody to that antigen. In some circumstances, BAL, lung biopsy, or both may be needed. The most important tool in diagnosing HP continues to be a high index of suspicion!

DIFFERENTIAL DIAGNOSIS

Chronic HP may often be difficult to distinguish from a number of other interstitial lung disorders (Chap. 19). A negative history for use of relevant drugs and no evidence of a systemic disorder usually exclude the presence of drug-induced lung disease or a collagen vascular disorder. BAL often shows predominance of neutrophils in idiopathic pulmonary fibrosis (IPF) and a predominance of CD4+ lymphocytes in sarcoidosis. Hilar or paratracheal lymphadenopathy or evidence of multisystem involvement also favors the diagnosis of sarcoidosis. In some patients, a lung biopsy may be required to differentiate chronic HP from other interstitial diseases. The lung disease associated with acute or subacute HP may clinically resemble other disorders that present with systemic symptoms and recurrent pulmonary infiltrates, including the allergic bronchopulmonary mycoses and other eosinophilic pneumonias. Gene cluster analysis of DNA from lung biopsies of patients with fibrotic lung disease has shown a significantly different gene expression profile in HP and IPF. Whereas HP biopsies expressed T cell and other genes related to inflammation, the IPF patients had greater expression of genes associated with pulmonary remodeling, especially epithelial and myofibroblast genes. Although, this finding may be related to the disease stage in which the disorders were diagnosed, they suggest that such analyses may be clinically useful in the future.

Eosinophilic pneumonia is often associated with asthma and is typified by peripheral eosinophilia; neither of these is a feature of HP. Allergic bronchopulmonary aspergillosis (ABPA) is the most common example of the allergic bronchopulmonary mycoses and is sometimes confused with HP because of the presence of precipitating antibodies to *Aspergillus fumigatus*. ABPA is associated with allergic (atopic) asthma. Acute HP may be confused with *organic dust toxic syndrome* (ODTS), a condition that is more common than HP. ODTS occurs after heavy exposure to organic dusts and is characterized by transient fever and muscle aches with or without dyspnea and cough. Serum precipitins are absent, and the chest x-ray is usually normal. This distinction is important because ODTS is a self-limited disorder without significant long-term sequelae, but continued antigen exposure in patients with HP can result in permanent disability. Massive exposure to moldy silage may result in a syndrome termed *pulmonary mycotoxicosis*, with fever, chills, and cough and the presence of pulmonary

infiltrates within a few hours of exposure. No previous sensitization is required, and precipitins are absent to *Aspergillus* spp., the suspected causative agent.

Rx Treatment: HYPERSENSITIVITY PNEUMONITIS

Because effective treatment depends largely on avoiding the antigen, identification of the causative agent and its source is essential. This is usually possible if the physician takes a careful environmental and occupational history or, if necessary, visits the patient's environment. The simplest way to avoid the incriminated agent is to remove the patient from the environment or the source of the agent from the patient's environment. This recommendation cannot be taken lightly when it completely changes the lifestyle or livelihood of the patient. In many cases, however, the source of exposure (birds, humidifiers) can easily be removed. Pollen masks, personal dust respirators, airstream helmets, and ventilated helmets with a supply of fresh air are increasingly efficient means of purifying inhaled air. If symptoms recur or physiologic abnormalities progress despite these measures, then more effective measures to avoid antigen exposure must be pursued. The chronic form of HP typically results from low-grade or recurrent exposure over many months to years, and the lung disease may already be partially or completely irreversible. These patients are usually advised to avoid all possible contact with the offending agent.

Patients with the *acute*, recurrent form of HP usually recover without need for glucocorticoids. *Subacute* HP may be associated with severe symptoms and marked physiologic impairment and may continue to progress for several days despite hospitalization. Urgent establishment of the diagnosis and prompt institution of glucocorticoid treatment are indicated in such patients. Prednisone at a dosage of 1 mg/kg per day or its equivalent is continued for 7–14 days and then tapered over the ensuing 2–6 weeks at a rate that depends on the patient's clinical status. Patients with *chronic* HP may gradually recover without therapy after environmental control. In many patients, however, a trial of prednisone may be useful to obtain maximal reversibility of the lung disease. After initial prednisone therapy (1 mg/kg per day for 2–4 weeks), the drug is tapered to the lowest dosage that will maintain the functional status of the patient. Many patients will not require or benefit from long-term therapy if there is no further exposure to the antigen. Regrettably, available studies demonstrate no effect of glucocorticoid therapy on long-term prognosis of patients with farmer's lung.

PULMONARY INFILTRATES WITH EOSINOPHILIA

Pulmonary infiltrates with eosinophilia (PIE, eosinophilic pneumonias) include distinct individual syndromes characterized by eosinophilic pulmonary infiltrates and, commonly, peripheral blood eosinophilia. Since Loeffler's initial description of a transient, benign syndrome of migratory pulmonary infiltrates and peripheral blood eosinophilia of unknown cause, this group of disorders has been enlarged to include several diseases of both known and unknown etiology (Table 9-2). These diseases may be considered as immunologically mediated lung diseases but are not to be confused with HP, in which eosinophilia is *not* a feature.

When an eosinophilic pneumonia is associated with bronchial asthma, it is important to determine if the patient has atopic asthma and has wheal-and-flare skin reactivity to *Aspergillus* spp. or other relevant fungal antigens. If so, other criteria should be sought for the diagnosis of ABPA (Table 9-3) or other, rarer examples of allergic bronchopulmonary mycosis such as those caused by *Penicillium*, *Candida*, *Curvularia*, or *Helminthosporium* spp. *A. fumigatus* is the most common cause of ABPA. The chest radiograph in ABPA may show transient, recurrent infiltrates or may suggest the presence of proximal bronchiectasis. High-resolution chest CT is a sensitive, noninvasive technique for the recognition of proximal bronchiectasis. The bronchial asthma of ABPA likely involves an IgE-mediated hypersensitivity, whereas the bronchiectasis associated with this disorder is thought to result from a deposition of immune complexes in proximal airways. Adequate treatment usually requires the long-term use of systemic glucocorticoids.

A travel history or evidence of recent immigration should prompt the consideration of parasite-associated disorders. *Tropical eosinophilia* is usually caused by filarial infection; however, eosinophilic pneumonias also occur with other parasites such as *Ascaris* spp., *Ancylostoma* spp., *Toxocara* spp., and *Strongyloides stercoralis*. Tropical

TABLE 9-2

PULMONARY INFILTRATES WITH EOSINOPHILIA

Etiology Known

- Allergic bronchopulmonary mycoses
- Parasitic infestations
- Drug reactions
- Eosinophilia-myalgia syndrome

Idiopathic

- Loeffler's syndrome
- Acute eosinophilic pneumonia
- Chronic eosinophilic pneumonia
- Allergic granulomatosis of Churg and Strauss
- Hypereosinophilic syndrome

TABLE 9-3

DIAGNOSTIC FEATURES OF ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (ABPA)

Main Diagnostic Criteria

- Bronchial asthma
- Pulmonary infiltrates
- Peripheral eosinophilia (>1000/ μ L)
- Immediate wheal-and-flare response to *Aspergillus fumigatus*
- Serum precipitins to *A. fumigatus*
- Elevated serum IgE
- Central bronchiectasis

Other Diagnostic Features

- History of brownish plugs in sputum
- Culture of *A. fumigatus* from sputum
- Elevated IgE (and IgG) class antibodies specific for *A. fumigatus*

eosinophilia caused by *Wuchereria bancrofti* or *Wuchereria malayi* infection occurs most commonly in southern Asia, Africa, and South America and is treated successfully with diethylcarbamazine. Even in cases of known foreign travel, identification of the causative agent is not always possible, as exemplified by 18 cases (two fatal) of acute eosinophilic pneumonia reported among U.S. military personnel deployed in Iraq.

In the United States, *drug-induced eosinophilic pneumonias* are the most common cause of eosinophilic pulmonary infiltrates. These are exemplified by acute reactions to nitrofurantoin, which may begin 2 h to 10 days after nitrofurantoin is started, with symptoms of dry cough, fever, chills, and dyspnea; an eosinophilic pleural effusion accompanying patchy or diffuse pulmonary infiltrates may also occur. Other drugs associated with eosinophilic pneumonias include sulfonamides, penicillin, chlorpropamide, thiazides, tricyclic antidepressants, hydralazine, gold salts, isoniazid, indomethacin, and others. One report has identified anti-TNF α monoclonal antibody therapy as a cause of eosinophilic pneumonitis. Treatment consists of withdrawal of the incriminated drugs and the use of glucocorticoids, if necessary.

The group of idiopathic eosinophilic pneumonias consists of diseases of varying severity. *Loeffler's syndrome* was originally reported as a benign, acute eosinophilic pneumonia of unknown cause characterized by migrating pulmonary infiltrates and minimal clinical manifestations. In some patients, these clinical characteristics may prove to be secondary to parasites or drugs. *Acute eosinophilic pneumonia* is an idiopathic acute febrile illness of less than 7 days' duration with severe hypoxemia, pulmonary infiltrates, and no history of asthma. *Chronic eosinophilic pneumonia* presents with significant systemic symptoms, including fever, chills, night sweats, cough, anorexia, and weight loss of several weeks' to months'

duration. The chest x-ray classically shows peripheral infiltrates. Some patients also have bronchial asthma of the intrinsic or nonallergic type. Dramatic clearing of symptoms and chest x-rays is often noted within 48 hours after initiation of glucocorticoid therapy.

The *hypereosinophilic syndrome* is characterized by the presence of >1500 eosinophils per microliter of peripheral blood for 6 months or longer; lack of evidence for parasitic, allergic, or other known causes of eosinophilia; and signs or symptoms of multisystem organ dysfunction. Consistent features are blood and bone marrow eosinophilia with tissue infiltration by relatively mature eosinophils. The heart may be involved with tricuspid valve abnormalities or endomyocardial fibrosis and a restrictive, biventricular cardiomyopathy. Other organs affected typically include the lungs, liver, spleen, skin, and nervous system. Therapy for patients with the disorder consists of glucocorticoids, hydroxyurea, or both plus therapy as needed for cardiac dysfunction, which is frequently responsible for much of the morbidity and mortality associated with this syndrome. Pulmonary eosinophilia has also been associated with T cell lymphoma and has been reported after *lung* and *bone marrow transplantation*.

GLOBAL PICTURE OF HYPERSENSITIVITY PNEUMONITIS AND PULMONARY INFILTRATES WITH EOSINOPHILIA



HP is more prevalent outside of the United States, and the range of antigen responses is somewhat different. Internationally, bird breeder's lung is the most common form of HP. Rather than being associated with avocational exposures, bird-raising practices, highlighted by the emerging threat of avian influenza, led to substantial exposure to workers involved in poultry husbandry and processing. This increases antigen exposure enormously compared with U.S. workers and enhances the risk of HP. Importantly, it is the most common cause of pediatric HP and has been reported in individuals as young as 4 years, when it has presented as a chronic cough.

Farmer's lung, one of the earliest reported causes of HP, is now more prevalent outside the United States, but it appears to be waning worldwide. This is likely in response to changing agricultural practices; increased use of impermeable barriers in hay storage has reduced the proliferation of thermophilic bacteria and thus HP.

In certain cases, the international manifestations of HP resemble those of the U.S. disease. Many industrialized nations have increasingly reported HP caused by mycobacteria and pseudomonads in contaminated

metalworking fluids; the prevalence of these environmental contaminants greatly depends on workplace hygiene practices. Some forms of HP are almost exclusively geographically limited; an example of this is summer-type HP in Japan. Likewise, cork worker's pneumonitis (suberosis), caused by exposure to contaminated corks, is almost exclusively seen in Spain and southern Europe because of the regional cork industry. However, one of the causative antigens (*Chrysonilia sitophila*) is also reported to be an antigen in lung diseases associated with logging in Canada. In Spain, esparto, a member of the grass family, is used as a fiber for the weaving of mats, baskets, and ropes; it is also incorporated into traditional plaster construction. In both of its uses, it has been associated with HP (most likely due to contamination with *A. fumigatus*), again geographically limited because of the utility of the product, though not of the underlying fungal antigen. Exposure to exotic mushrooms is greater in Asia than in the United States and has recently been linked to cases of HP.

PIE is also a greater international than U.S. health burden. In this case, parasitic infestation is far more common than drug-induced lung disease, but the manifestations are similar.

FURTHER READINGS

- ALLEN JN: Drug-induced eosinophilic lung disease. *Clin Chest Med* 25:77, 2004
- BECKETT W et al: Hypersensitivity pneumonitis associated with environmental mycobacteria. *Environ Health Perspect* 113:767, 2005
- COORAY JH, ISMAIL MM: Re-examination of the diagnostic criteria of tropical pulmonary eosinophilia. *Respir Med* 93:655, 1999
- CORMIER Y et al: High-resolution computed tomographic characteristics in acute farmer's lung and in its follow-up. *Eur Resp J* 16:56, 2000
- FINK JN et al: Needs and opportunities for research in hypersensitivity pneumonitis. *Am J Respir Crit Care Med* 171:792, 2005
- LACASSE Y et al: Clinical diagnosis of hypersensitivity pneumonitis. *Am J Respir Crit Care Med* 168:962, 2003
- MIZAZAKI Y et al: Clinical predictors and histologic appearance of acute exacerbations in chronic hypersensitivity pneumonitis. *Chest* 134:1265, 2008
- SELMAN M: Hypersensitivity pneumonitis: a multifaceted deceiving disorder. *Clin Chest Med* 25:531, 2004
- et al: Gene expression profiles distinguish idiopathic pulmonary fibrosis from hypersensitivity pneumonitis. *Am J Respir Crit Care Med* 173:188, 2006
- SHORR AF et al: Acute eosinophilic pneumonia among U.S. military personnel deployed in or near Iraq. *JAMA* 292:2997, 2004
- SILVA CI et al: Hypersensitivity pneumonitis: Spectrum of high-resolution CT and pathologic findings. *Am J Roentgenol* 188:334, 2007
- ZACHARISEN MC et al: The long-term outcome in acute, subacute, and chronic forms of pigeon breeder's disease hypersensitivity pneumonitis. *Ann Allergy Asthma Immunol* 88:175, 2002



CHAPTER 10

ENVIRONMENTAL LUNG DISEASE

Frank E. Speizer ■ John R. Balmes

History and Physical Examination	86	Toxic Chemicals	93
Pulmonary Function Tests and Chest Imaging	87	Environmental Respiratory Carcinogens	95
Measurement of Exposure	87	Assessment of Disability	95
■ Occupational Exposures and Pulmonary Disease	88	■ General Environmental Exposures	96
Asbestos-Related Diseases	88	Outdoor Air Pollution	96
Silicosis	90	Indoor Exposures	96
Coal Worker's Pneumoconiosis	91	Portal of Entry	97
Chronic Beryllium Disease	92	Global Considerations	97
Other Inorganic Dusts	92	■ Further Readings	97
Organic Dusts	92		

This chapter provides perspectives on ways to assess pulmonary diseases for which environmental or occupational causes are suspected. This assessment is important because removal of the patient from harmful exposure is often the only intervention that might prevent further significant deterioration or lead to improvement in a patient's condition. Furthermore, the identification of an environment-associated disease in a single patient may lead to primary preventive strategies affecting other similarly exposed people who have not yet developed disease.

The exact magnitude of the problem is unknown, but there is no question that large numbers of individuals are at risk for developing serious respiratory disease as a result of occupational or environmental exposures. For example, for populations over age 15 years, 15–20% of the burden of asthma and chronic obstructive pulmonary disease (COPD) has been estimated to be caused by occupational factors.

HISTORY AND PHYSICAL EXAMINATION

The patient's history is of paramount importance in assessing any potential occupational or environmental exposure. Inquiry into specific work practices should include questions about specific contaminants involved, the availability and use of personal respiratory protection devices, the size and ventilation of workspaces, and whether coworkers have

similar complaints. The temporal association of exposure at work and symptoms may provide clues to occupation-related disease. In addition, the patient must be questioned about alternative sources for exposure to potentially toxic agents, including hobbies, home characteristics, exposure to secondhand smoke, and proximity to traffic or industrial facilities. Short- and long-term exposures to potential toxic agents in the distant past must also be considered.

Many employees are aware of the potential hazards in their workplaces, and many states require that employees be informed about potentially hazardous exposures. These requirements include the provision of specific information about potential hazardous agents in products being used (Material Safety Data Sheets) and training in personal protective equipment and environmental control procedures. Reminders posted in the workplace may warn workers about hazardous substances. Protective clothing, lockers, and shower facilities may be considered necessary parts of the job. However, the introduction of new processes or new chemical compounds may change exposure significantly, and often only the employee on the production line is aware of the change. For the physician who regularly sees patients from a particular industry, a visit to the work site can be very instructive. Alternatively, physicians can request inspections by appropriate federal and/or state authorities.

The physical examination of patients with environment-related lung diseases may help to determine the nature and severity of the pulmonary condition. Unfortunately, these findings do not typically point to the specific causative agent, and other types of information must be used to arrive at an etiologic diagnosis.

PULMONARY FUNCTION TESTS AND CHEST IMAGING

Many mineral dusts produce characteristic alterations in the mechanics of breathing and lung volumes that clearly indicate a restrictive pattern (Chap. 5). Similarly, exposures to a number of organic dusts or chemical agents may result in occupational asthma or COPD. Measurement of change in forced expiratory volume in 1 s (FEV₁) before and after a work shift can be used to detect an acute bronchoconstrictive or inflammatory response. For example, an acute decrement of FEV₁ over the first work shift of the week is a characteristic feature of cotton textile workers with byssinosis (an obstructive airway disorder with features of both asthma and chronic bronchitis).

The chest radiograph is useful in detecting and monitoring the pulmonary response to mineral dusts, certain metals, and organic dusts capable of inducing hypersensitivity pneumonitis. The International Labour Organisation (ILO) International Classification of Radiographs of Pneumoconioses classifies chest radiographs according to the nature and size of opacities seen and the extent of involvement of the parenchyma. In general, small, rounded opacities are seen in silicosis and coal worker's pneumoconiosis (CWP), and small, linear opacities are seen in asbestosis. The profusion of such opacities is rated using a 12-point scheme. Although useful for epidemiologic studies and screening large numbers of workers, the ILO system can be problematic when applied to an individual worker's chest radiograph. With dusts causing rounded opacities, the degree of involvement on the chest radiograph may be extensive, but pulmonary function may be only minimally impaired. In contrast, in pneumoconiosis causing linear, irregular opacities like those seen in asbestosis, the radiograph may lead to underestimation of the severity of the impairment until relatively late in the disease. For the individual patient with a history of exposure, conventional CT and high-resolution CT (HRCT) have improved the sensitivity of identifying diffuse parenchymal abnormalities of the lung as well as pleural thickening characteristic of asbestos exposure.

Other procedures that may be of use in identifying the role of environment exposures in causing lung disease include evaluation of heavy metal concentrations in urine (cadmium in battery plant workers), skin prick testing or specific IgE antibody titers for evidence of

immediate hypersensitivity to agents capable of inducing occupational asthma (flour antigens in bakery workers), specific IgG precipitating antibody titers for agents capable of causing hypersensitivity pneumonitis (pigeon antigens in bird handlers), or assays for specific cell-mediated immune responses (beryllium lymphocyte proliferation testing in nuclear workers or tuberculin skin testing in health care workers). Sometimes, a bronchoscopy to obtain bronchoalveolar lavage (BAL) fluid and transbronchial biopsy of lung tissue may be required for histologic diagnosis [chronic beryllium disease (CBD)]. Rarely, video-assisted thoracoscopic surgery to obtain a larger sample of lung tissue may be required to determine the specific diagnosis of environment-induced lung disease (hypersensitivity pneumonitis or giant cell interstitial pneumonitis caused by cobalt exposure).

MEASUREMENT OF EXPOSURE

If reliable environmental sampling data are available, this information should be used in assessing a patient's exposure. Because many of the chronic diseases result from exposure over many years, current environmental measurements should be combined with work histories to arrive at estimates of past exposure.

In situations in which individual exposure to specific agents—either in a work setting or via ambient air pollutants—has been determined, the chemical and physical characteristics of these agents affect both inhaled dose and site of deposition in the respiratory tract. Water-soluble gases such as ammonia or sulfur dioxide are absorbed in the lining fluid of the upper and proximal airways and thus tend to produce irritative and bronchoconstrictive responses. In contrast, nitrogen dioxide and phosgene, which are less soluble, may penetrate to the bronchioles and alveoli in sufficient quantities to produce acute chemical pneumonitis that can be life threatening (acute respiratory distress syndrome with noncardiogenic pulmonary edema).

Particle size of air contaminants must also be considered. Particles larger than 10–15 μm in diameter, because of their settling velocities in air, do not penetrate beyond the upper airways. Particles smaller than 10 μm in size are deposited below the larynx and are primarily created by the burning of fossil fuels or high-temperature industrial processes resulting in condensation products from gases, fumes, or vapors. These particles are divided into three size fractions on the basis of their size characteristics and sources. Particles of approximately 2.5–10 μm (coarse-mode fraction) contain crustal elements, such as silica, aluminum, and iron. These particles mostly deposit relatively high in the tracheobronchial tree. Although the total mass of an ambient sample is dominated by these larger respirable particles, the number of particles, and therefore

88 the surface area on which potential toxic agents can deposit and be carried to the lower airways, is dominated by particles <2.5 μm (fine-mode fraction). The smallest particles, those <0.1 μm in size, represent the ultrafine fraction and make up the largest number of particles, which tend to remain in the airstream and deposit in the lung only on a random basis as they come into contact with the alveolar walls. Besides the size characteristics of particles and the solubility of gases, the actual chemical composition, mechanical properties, and immunogenicity or infectivity of inhaled material largely determine the nature of the diseases found among exposed persons.

OCCUPATIONAL EXPOSURES AND PULMONARY DISEASE

Table 10-1 provides broad categories of exposure in the workplace and diseases associated with chronic exposure in these industries.

ASBESTOS-RELATED DISEASES

Asbestos is a generic term for several different mineral silicates, including chrysolite, amosite, anthophyllite, and crocidolite. In addition to workers involved in the production of asbestos products (mining, milling, and

TABLE 10-1

CATEGORIES OF OCCUPATIONAL EXPOSURE AND ASSOCIATED RESPIRATORY CONDITIONS

OCCUPATIONAL EXPOSURES	NATURE OF RESPIRATORY RESPONSES	COMMENT
Inorganic Dusts		
Asbestos: mining, processing, construction, ship repair	Fibrosis (asbestosis), pleural disease, cancer, mesothelioma	Virtually all new mining and construction with asbestos done in developing countries
Silica: mining, stone cutting, sandblasting, quarrying Coal dust: mining	Fibrosis (silicosis), PMF, cancer, silicotuberculosis, COPD Fibrosis (coal workers' pneumoconiosis), PMF, COPD	Improved protection in United States, persistent risk in developing countries Risk decreasing in United States, increasing where new mines open
Beryllium: processing alloys for high-tech industries	Acute pneumonitis, chronic granulomatous disease, lung cancer (highly suspect)	Risk in high-tech industries persists
Other metals: aluminum, chromium, cobalt, nickel, titanium, tungsten carbide, or "hard metal" (contains cobalt)	Wide variety of conditions from acute pneumonitis to lung cancer and asthma	New diseases appear with new process development
Organic Dusts		
Cotton dust: milling, processing	Byssinosis (an asthma-like syndrome), chronic bronchitis, COPD	Increasing risk in developing countries with a decrease in United States as jobs shift overseas
Grain dust: elevator agents, dock workers, milling, bakers Other agricultural dusts: fungal spores, vegetable products, insect fragments, animal dander, bird and rodent feces, endotoxins, microorganisms, pollens	Asthma, chronic bronchitis, COPD Hypersensitivity pneumonitis (farmers' lung), asthma, chronic bronchitis	Risk shifting more to migrant labor pool Important in migrant labor pool but also resulting from in-home exposures
Toxic chemicals: wide variety of industries; see Table 10-2	Chronic bronchitis, COPD, hypersensitivity pneumonitis, pneumoconiosis, and cancer	Reduced risk with recognized hazards; increasing risk in developing countries where controlled labor practices are less stringent
Other respiratory environmental agents (proven or highly suspect): uranium and radon daughters, environmental tobacco smoke, polycyclic hydrocarbons, biomass fuels, diesel exhaust, welding fumes, woods or wood-finishing products	Estimates vary from ~3 to 10% of all lung cancers; in addition chronic bronchitis, COPD, and fibrosis	In-home exposures important; in developing countries, disease rates as high or higher in females than males

manufacturing), many workers in the ship-building and construction trades, including pipe fitters and boiler-makers, were occupationally exposed because asbestos was widely used for its thermal and electrical insulation properties. Asbestos also was used in the manufacture of fire-smothering blankets and safety garments; as filler for plastic materials; in cement and floor tiles; and in friction materials, such as brake and clutch linings.

Exposure to asbestos is not limited to persons who directly handle the material. Cases of asbestos-related diseases have been encountered in individuals with only bystander exposure, such as the painter or electrician who worked alongside the insulation worker in a shipyard. Community exposure resulted from the use of asbestos-containing mine or mill tailings as landfill, road surface, and playground material. Finally, exposure can also occur from the disturbance of naturally occurring asbestos (e.g., from increasing residential development in the foothills of the Sierra Mountains in California).

Asbestos was first used extensively in the 1930s. Starting in 1975, it was mostly replaced with synthetic mineral fibers, such as fiberglass or slag wool, but it continues to be used increasingly in the developing world. Despite current regulations mandating adequate training for any worker potentially exposed to asbestos, exposure continues among inadequately trained and protected demolition workers. The major health effects from exposure to asbestos are pleural and pulmonary fibrosis and cancers of the respiratory tract, the pleura, and (in rare cases) the peritoneum.

Asbestosis is a diffuse interstitial fibrosing disease of the lung that is directly related to the intensity and duration of exposure. The disease resembles other forms of diffuse interstitial fibrosis (Chap. 19). Usually, moderate to severe

exposure has taken place for at least 10 years before the disease becomes manifest and may occur after exposure to any of the asbestiform fiber types.

Physiologic studies reveal a restrictive pattern with a decrease in both lung volumes and diffusing capacity. There may also be evidence of mild airflow obstruction (caused by peribronchiolar fibrosis).

The fibrotic lesions are the end result of oxidative injury caused by the generation of reactive oxygen species by the transition metals on the surface of the fibers as well as from cells engaged in phagocytosis.

Diagnosis

The chest radiograph can be used to detect a number of manifestations of asbestos exposure. Past exposure is specifically indicated by pleural plaques, which are characterized either by thickening or calcification along the parietal pleura, particularly along the lower lung fields, the diaphragm, and the cardiac border. Without additional manifestations, pleural plaques imply only exposure, not pulmonary impairment. Benign pleural effusions may also occur. The fluid is typically a serous or bloody exudate. The effusion may be slowly progressive or may resolve spontaneously. Irregular or linear opacities, usually first noted in the lower lung fields and spreading into the middle and upper lung fields, occur as the disease progresses. An indistinct heart border or a “ground-glass” appearance in the lung fields is seen in some cases. In cases in which the x-ray changes are less obvious, HRCT may show distinct changes of subpleural curvilinear lines 5–10 mm in length that appear to be parallel to the pleural surface (**Fig. 10-1**).

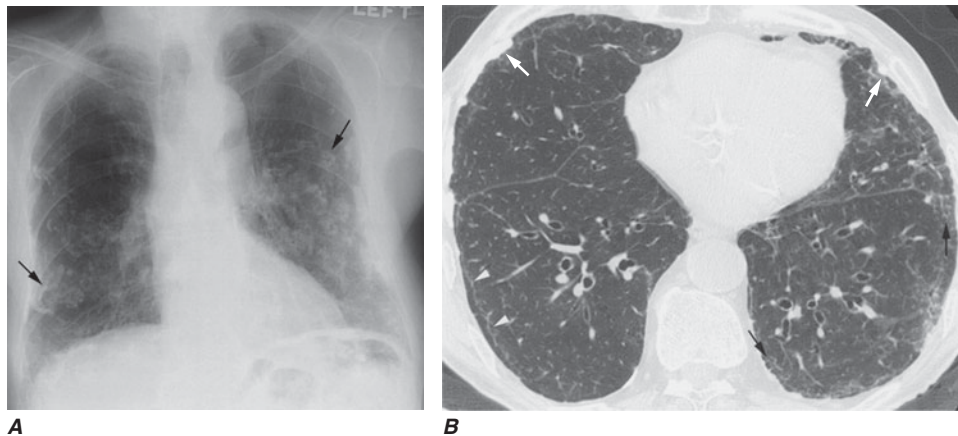


FIGURE 10-1

Asbestosis. **A.** Frontal chest radiograph showing bilateral calcified pleural plaques consistent with asbestos-related pleural disease. Poorly defined linear and reticular abnormalities are seen in the lower lobes bilaterally. **B.** Axial high-resolution CT of the thorax obtained through the lung bases showing bilateral, subpleural reticulation (*black arrows*),

representing fibrotic lung disease caused by asbestosis. Subpleural lines are also present (*arrowheads*), characteristic of, although not specific for, asbestosis. Calcified pleural plaques representing asbestos-related pleural disease (*white arrows*) are also evident.

90 No specific therapy is available for the management of patients with asbestosis. The supportive care is the same as that given to any patient with diffuse interstitial fibrosis from any cause. In general, newly diagnosed cases will have resulted from exposure levels that were present many years before and, despite the patients' having left the industry, are attributable to that former exposure. Because the patient may be eligible for compensation within a specific time frame after the diagnosis of an asbestos-related disease is made, the physician making the diagnosis should be certain to inform the patient promptly. On occasion, the physician may have reason to suspect ongoing exposure from a patient's current job description. Such a patient needs to wear appropriate respiratory protective gear according to federal regulation. Casual, nonoccupational exposure to undisturbed sources of asbestos-containing materials—e.g., in walls of schools or other buildings—represents virtually no hazard of asbestosis.

Lung cancer is the most frequent cancer associated with asbestos exposure. The excess frequency of lung cancer (all histologic types) in asbestos workers is associated with a minimum latency of 15–19 years between first exposure and development of the disease. Persons with more exposure are at greater risk of disease. In addition, there is a significant multiplicative effect of smoking and asbestos exposure than would be expected from the additive effect of each factor. The use of HRCT in such at-risk individuals to detect lung cancer at an earlier stage is currently under investigation.

Mesotheliomas (Chap. 21), both pleural and peritoneal, are also associated with asbestos exposure. In contrast to lung cancers, these tumors do not appear to be associated with smoking. Relatively short-term asbestos exposures of 1–2 years or less, occurring up to 40 years in the past, have been associated with the development of mesotheliomas (an observation that emphasizes the importance of obtaining a complete environmental exposure history). Although the risk of mesothelioma is much less than for lung cancer among asbestos-exposed workers, more than 2000 cases were reported in the United States per year at the start of the 21st century.

Although ~50% of mesotheliomas metastasize, the tumor generally is locally invasive, and death usually results from local extension. Most patients present with effusions that may obscure the underlying pleural tumor. In contrast to the findings in effusion due to other causes, because of the restriction placed on the chest wall, no shift of mediastinal structures toward the opposite side of the chest will be seen. The major diagnostic problem is differentiation from peripherally spreading pulmonary adenocarcinoma or from adenocarcinoma metastasized to pleura from an extrathoracic primary site. Although cytologic examination of pleural fluid may suggest the diagnosis, biopsy of pleural tissue, generally with video-assisted thoracic surgery, and special

immunohistochemical staining is usually required. There is no effective therapy.

Because epidemiologic studies have shown that more than 80% of mesotheliomas may be associated with asbestos exposure, documented mesothelioma in a patient with occupational or environmental exposure to asbestos may be compensable.

SILICOSIS

Despite the technical adequacy of existing protective equipment, *free silica* (SiO_2), or crystalline quartz, is still a major occupational hazard. The major occupational exposures include mining; stonecutting; employment in abrasive industries, such as stone, clay, glass, and cement manufacturing; foundry work; packing of silica flour; and quarrying, particularly of granite. Most often, pulmonary fibrosis caused by silica exposure (silicosis) occurs in a dose-response fashion after many years of exposure.

Workers heavily exposed through sandblasting in confined spaces, tunneling through rock with high quartz content (15–25%), or the manufacture of abrasive soaps may develop acute silicosis with as little as 10 months' exposure. The clinical and pathological features of acute silicosis are similar to those of pulmonary alveolar proteinosis (Chap. 19). The chest radiograph may show profuse miliary infiltration or consolidation, and there is a characteristic HRCT pattern known as "crazy paving" (Fig. 10-2). The disease may be quite severe and progressive despite the discontinuation of exposure. Whole-lung lavage may provide symptomatic relief and slow progression.

With long-term, less intense exposure, small, rounded opacities in the upper lobes may appear on the chest radiograph after 15–20 years of exposure (*simple silicosis*). Calcification of hilar nodes may occur in as many as 20% of cases and produces a characteristic "eggshell" pattern. Silicotic nodules may be identified more readily by HRCT (Fig. 10-3). The nodular fibrosis may be progressive in the absence of further exposure, with coalescence and formation of nonsegmental conglomerates of irregular masses >1 cm in diameter (*complicated silicosis*). These masses can become quite large, and when this occurs, the term *progressive massive fibrosis* (PMF) is applied. Significant functional impairment with both restrictive and obstructive components may be associated with this form of silicosis.

Because silica is cytotoxic to alveolar macrophages, patients with silicosis are at greater risk of acquiring lung infections that involve these cells as a primary defense (*Mycobacterium tuberculosis*, atypical mycobacteria and fungi). Because of the increased risk of active tuberculosis, the recommended treatment of latent tuberculosis in these patients is longer. Another potential clinical complication of silicosis is autoimmune connective

**FIGURE 10-2**

Acute silicosis. The high-resolution CT scan shows multiple small nodules consistent with silicosis but also diffuse ground-glass densities with thickened intralobular and interlobular septa, producing polygonal shapes. This has been referred to as “crazy paving.”

tissue disorders such as rheumatoid arthritis and scleroderma. In addition, there are sufficient epidemiologic data that the International Agency for Research on Cancer lists silica as a probable lung carcinogen.

Other less hazardous silicates include Fuller’s earth, kaolin, mica, diatomaceous earths, silica gel, soapstone, carbonate dusts, and cement dusts. The production of

fibrosis in workers exposed to these agents is believed to be related either to the free silica content of these dusts or, for substances that contain no free silica, to the potentially large dust loads to which these workers may be exposed.

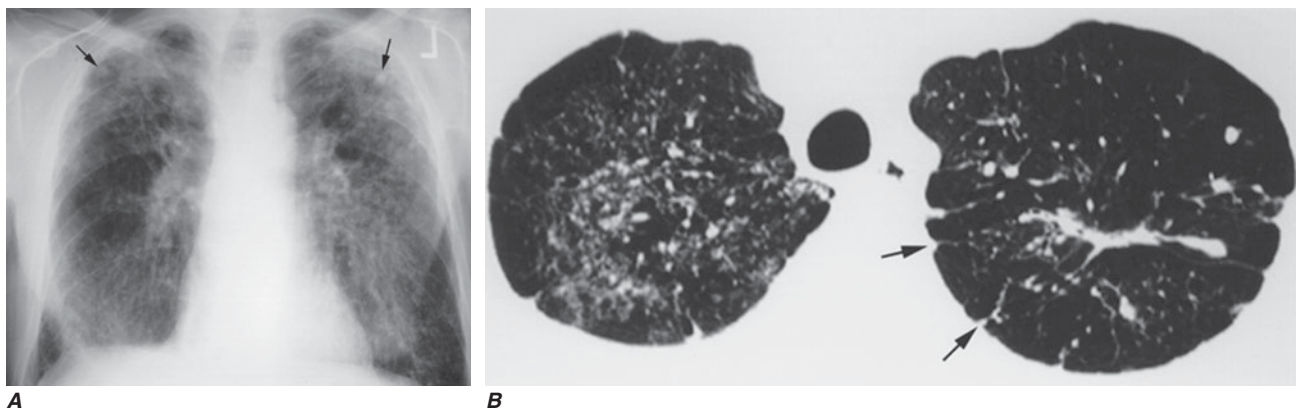
Other silicates, including *talc dusts*, may be contaminated with asbestos or free silica. Fibrosis and pleural or lung cancer have been associated with chronic exposure to commercial talc.

COAL WORKER’S PNEUMOCONIOSIS

Occupational exposure to *coal dust* can lead to CWP, which has enormous social, economic, and medical significance in every nation in which coal mining is an important industry. Simple radiographically identified CWP is seen in about 10% of all coal miners and in as many as 50% of anthracite miners with more than 20 years’ work on the coal face. The prevalence of disease is lower in workers in bituminous coal mines. Because much western U.S. coal is bituminous, CWP is less prevalent in that region.

With prolonged exposure to coal dust (i.e., 15–20 years), small, rounded opacities similar to those of silicosis may develop. As in silicosis, the presence of these nodules (*simple CWP*) is not usually associated with pulmonary impairment. Much of the symptomatology associated with simple CWP appears to be due to the effects of coal dust on the development of chronic bronchitis and COPD (Chap. 18). The effects of coal dust are additive to those of cigarette smoking.

Complicated CWP is manifested by the appearance on the chest radiograph of nodules ranging from 1 cm in diameter to the size of an entire lobe, generally confined to the upper half of the lungs. As in silicosis, this condition can progress to PMF, which is accompanied by

**FIGURE 10-3**

Chronic silicosis. **A.** Frontal chest radiograph in a patient with silicosis showing variably sized, poorly defined nodules (*arrows*) predominating in the upper lobes. **B.** Axial thoracic

CT image through the lung apices showing numerous small nodules that are more pronounced in the right upper lobe. A number of the nodules are subpleural in location (*arrows*).

92 severe lung function deficits and associated with premature mortality.

Caplan's syndrome, first described in coal miners but subsequently found in patients with silicosis, includes seropositive rheumatoid arthritis with characteristic pneumoconiotic nodules. Silica has immunoadjuvant properties and is often present in anthracitic coal dust.

CHRONIC BERYLLIUM DISEASE

Beryllium is a lightweight metal with tensile strength, has good electrical conductivity, and is valuable in the control of nuclear reactions through its ability to quench neutrons. Although beryllium may produce an acute pneumonitis, it is far more commonly associated with a chronic granulomatous inflammatory disease that is similar to sarcoidosis. Unless one inquires specifically about occupational exposures to beryllium in the manufacture of alloys, ceramics, or high-technology electronics in a patient with sarcoidosis, one may miss entirely the etiologic relationship to the occupational exposure. What distinguishes CBD from sarcoidosis is evidence of a specific cell-mediated immune response (i.e., delayed hypersensitivity) to beryllium.

The test that usually provides this evidence is the beryllium lymphocyte proliferation test (BeLPT). The BeLPT uses the *in vitro* proliferation of lymphocytes from blood or BAL in the presence of beryllium salts compared with that of unstimulated cells. Proliferation is usually measured by lymphocyte uptake of radiolabeled thymidine.

Chest imaging findings are similar to those of sarcoidosis (nodules along septal lines) except that hilar adenopathy is somewhat less common. Similar to sarcoidosis, pulmonary function test results may show restrictive or obstructive ventilatory deficits and decreased diffusing capacity. With early disease, both chest imaging studies and pulmonary function test results may be normal. Fiberoptic bronchoscopy with transbronchial lung biopsy is usually required to make the diagnosis of CBD. In a beryllium-sensitized individual, the presence of noncaseating granulomas or monocytic infiltration in lung tissue establishes the diagnosis. Accumulation of beryllium-specific CD4+ T cells occurs in the granulomatous inflammation seen on lung biopsy.

Chronic beryllium disease is one of the best studied examples of gene–environment interaction. Susceptibility to CBD is highly associated with HLA-DP alleles possessing a glutamic acid in position 69 of the β chain. In addition, there is also evidence that a polymorphism in position 308 of the promoter region of tumor necrosis factor α is involved in mediating the severity of the inflammatory response in patients with CBD.

Other metals, including aluminum and titanium dioxide, have been rarely associated with a sarcoid-like reaction in lung tissue. Exposure to dust containing tungsten carbide, also known as “hard metal,” may produce

giant cell interstitial pneumonitis. Cobalt is a constituent of tungsten carbide and is the likely etiologic agent of both the interstitial pneumonitis and the occupational asthma that may occur. The most common exposures to tungsten carbide occur in tool and dye, saw blade, and drill bit manufacture. Diamond polishing may also involve exposure to cobalt dust. The same Glu69 polymorphism of the HLA-DP β chain that confers increased risk of CBD also appears to increase risk of cobalt-induced giant cell interstitial pneumonitis.

In patients with interstitial lung disease, one should always inquire about exposure to metal fumes or dusts. Especially when sarcoidosis appears to be the diagnosis, one should always consider possible CBD.

OTHER INORGANIC DUSTS

Most of the inorganic dusts discussed thus far are associated with the production of either dust macules or interstitial fibrotic changes in the lung. Other inorganic and organic dusts (see categories in Table 10-1), along with some of the dusts previously discussed, are associated with chronic mucus hypersecretion (chronic bronchitis), with or without reduction of expiratory flow rates. Cigarette smoking is the major cause of these conditions, and any effort to attribute some component of the disease to occupational and environmental exposures must take cigarette smoking into account. Most studies suggest an additive effect of dust exposure and smoking. The pattern of the irritant dust effect is similar to that of cigarette smoking, suggesting that small airway inflammation may be the initial site of pathologic response in those cases, and continued exposure may lead to chronic bronchitis and COPD.

ORGANIC DUSTS

Some of the specific diseases associated with organic dusts are discussed in detail in the chapters on asthma (Chap. 8) and hypersensitivity pneumonitis (Chap. 9). Many of these diseases are named for the specific setting in which they are found (e.g., farmer's lung, malt worker's disease, mushroom worker's disease). Often the temporal relation of symptoms to exposure furnishes the best evidence for the diagnosis. Three occupational groups are singled out for discussion because they represent the largest proportion of people affected by the diseases resulting from organic dusts.

Cotton Dust (Byssinosis)

Many persons are exposed occupationally to cotton, flax, or hemp in the production of yarns for cotton, linen, and rope making. Although this discussion focuses

on cotton, the same syndrome—albeit somewhat less severe—has been reported in association with exposure to flax, hemp, and jute.

Exposure occurs throughout the manufacturing process but is most pronounced in those portions of the factory involved with the treatment of the cotton before spinning—i.e., blowing, mixing, and carding (straightening of fibers). Risk of byssinosis is associated with both cotton dust and endotoxin levels in the workplace environment. Attempts to control dust levels by use of exhaust hoods, general increases in ventilation, and wetting procedures in some settings have been highly successful. However, respiratory protective equipment appears to be required during certain operations to prevent workers from being exposed to levels of cotton dust that exceed the current U.S. permissible exposure level.

Byssinosis is characterized clinically as occasional (early stage) and then regular (late stage) chest tightness toward the end of the first day of the workweek (“Monday chest tightness”). In epidemiologic studies, depending on the level of exposure via the carding room air, up to 80% of employees may show a significant decrease in their FEV₁ over the course of a Monday shift.

Initially, the symptoms do not recur on subsequent days of the week. However, in 10–25% of workers, the disease may be progressive, with chest tightness recurring or persisting throughout the workweek. After >10 years of exposure, workers with recurrent symptoms are more likely to have an obstructive pattern on pulmonary function testing. The highest grades of impairment are generally seen in smokers.

Reduction of dust exposure is of primary importance to the management of byssinosis. All workers with persistent symptoms or significantly reduced levels of pulmonary function should be moved to areas of lower risk of exposure. Regular surveillance of pulmonary function in cotton dust–exposed workers using spirometry before and after the work shift is required by the Occupational Safety and Health Administration (OSHA) of the U.S. government.

Grain Dust

Although the exact number of workers at risk in the United States is not known, at least 500,000 people work in grain elevators, and >2 million farmers are potentially exposed to grain dust. The presentation of obstructive airway disease in grain dust–exposed workers is virtually identical to the characteristic findings in cigarette smokers (i.e., persistent cough, mucous hypersecretion, wheeze and dyspnea on exertion, and reduced FEV₁ and FEV₁/FVC ratio) (Chap. 5).

Dust concentrations in grain elevators vary greatly but appear to be >10,000 µg/m³; approximately one-third of the particles, by weight, are in the respirable range. The effect of grain dust exposure is additive to

that of cigarette smoking, with about 50% of workers who smoke having symptoms. Among nonsmoking grain elevator operators, approximately 25% have mucus hypersecretion, about five times the number that would be expected in unexposed nonsmokers. Smoking grain dust–exposed workers are more likely to have obstructive ventilatory deficits on pulmonary function testing. As in byssinosis, endotoxin may play a role in grain dust–induced chronic bronchitis and COPD.

Farmer’s Lung

This condition results from exposure to moldy hay containing spores of thermophilic actinomycetes that produce a hypersensitivity pneumonitis (Chap. 9). There are few good population–based estimates of the frequency of occurrence of this condition in the United States. However, among farmers in Great Britain, the rate of disease ranges from approximately 10–50 per 1000. The prevalence of disease varies in association with rainfall, which determines the amount of fungal growth, and with differences in agricultural practices related to turning and stacking hay.

The patient with acute farmer’s lung presents 4–8 h after exposure with fever, chills, malaise, cough, and dyspnea without wheezing. The history of exposure is obviously essential to distinguish this disease from influenza or pneumonia with similar symptoms. In the chronic form of the disease, the history of repeated attacks after similar exposure is important in differentiating this syndrome from other causes of patchy fibrosis (e.g., sarcoidosis).

A wide variety of other organic dusts are associated with the occurrence of hypersensitivity pneumonitis (Chap. 9). For patients who present with hypersensitivity pneumonitis, specific and careful inquiry about occupations, hobbies, or other home environmental exposures is necessary to uncover the source of the etiologic agent.

TOXIC CHEMICALS

Exposure to toxic chemicals affecting the lung generally involves gases and vapors. A common accident is one in which the victim is trapped in a confined space where the chemicals have accumulated to toxic levels. In addition to the specific toxic effects of the chemical, the victim will often sustain considerable anoxia, which can play a dominant role in determining whether the individual survives.

Table 10-2 lists a variety of toxic agents that can produce acute and sometimes life-threatening reactions in the lung. All of these agents in sufficient concentrations have been demonstrated, at least in animal studies, to affect the lower airways and disrupt alveolar architecture, either acutely or as a result of chronic exposure. Some of these agents may be generated acutely in the environment (see later).

SELECTED COMMON TOXIC CHEMICAL AGENTS AFFECTING THE LUNG

AGENT(S)	SELECTED EXPOSURES	ACUTE EFFECTS FROM HIGH OR ACCIDENTAL EXPOSURE	CHRONIC EFFECTS FROM RELATIVELY LOW EXPOSURE
Acid fumes: H ₂ SO ₄ , HNO ₃	Manufacture of fertilizers, chlorinated organic compounds, dyes, explosives, rubber products, metal etching, plastics	Mucous membrane irritation followed by chemical pneumonitis 2–3 days later	Bronchitis and suggestion of mildly reduced pulmonary function in children with lifelong residential exposure to high levels; clinical significance unknown
Acrolein and other aldehydes Ammonia	Byproduct of burning plastics, woods, tobacco smoke Refrigeration; petroleum refining; manufacture of fertilizers, explosives, plastics, and other chemicals	Mucous membrane irritant, decrease in lung function Same as for acid fumes	Mutagen in animals, no human data Chronic bronchitis
Anhydrides	Manufacture of resin esters, polyester resins, thermoactivated adhesives	Nasal irritation, cough	Asthma, chronic bronchitis, hypersensitivity pneumonitis
Cadmium fumes	Smelting, soldering, battery production	Mucous membrane irritant, ARDS	COPD
Formaldehyde	Manufacture of resins, leathers, rubber, metals, and woods; laboratory workers, embalmers; emission from urethane foam insulation	Same as for acid fumes	Cancers in one species; no data on humans
Halides and acid salts (Cl, Br, F)	Bleaching in pulp, paper, textile industry; manufacture of chemical compounds; synthetic rubber, plastics, disinfectant, rocket fuel, gasoline	Mucous membrane irritation, pulmonary edema; possible reduced FVC 1–2 yrs after exposure	Dryness of mucous membranes, epistaxis, dental fluorosis, tracheobronchitis
Hydrogen sulfide	Byproduct of many industrial processes, oil, other petroleum processes and storage	Increase in respiratory rate followed by respiratory arrest, lactic acidosis, pulmonary edema, death	Conjunctival irritation, chronic bronchitis, recurrent pneumonitis
Isocyanates (TDI, HDI, MDI)	Production of polyurethane foams, plastics, adhesives, surface coatings	Mucous membrane irritation, dyspnea, cough, wheeze, pulmonary edema	Upper respiratory tract irritation, cough, asthma, allergic alveolitis
Nitrogen dioxide	Silage, metal etching, explosives, rocket fuels, welding, byproduct of burning fossil fuels	Cough, dyspnea, pulmonary edema may be delayed 4–12 h; possible result from acute exposure: bronchiolitis obliterans in 2–6 wks	Emphysema in animals, ? chronic bronchitis, associated with reduced lung function in children with lifelong residential exposure, clinical significance unknown
Ozone	Arc welding, flour bleaching, deodorizing, emissions from copying equipment, photochemical air pollutant	Mucous membrane irritant, pulmonary hemorrhage and edema, reduced pulmonary function transiently in children and adults, and increased hospitalization with exposure to summer haze	Chronic eye irritation and slight excess in cardiopulmonary mortality in susceptible individuals
Phosgene	Organic compound, metallurgy, volatilization of chlorine-containing compounds	Delayed onset of bronchiolitis and pulmonary edema	Chronic bronchitis
Sulfur dioxide	Manufacture of sulfuric acid, bleaches, coating of nonferrous metals, food processing, refrigerant, burning of fossil fuels, wood pulp industry	Mucous membrane irritant, epistaxis	Chronic bronchitis

Firefighters and fire victims are at risk of *smoke inhalation*, a numerically important cause of acute cardiorespiratory failure. Smoke inhalation kills more fire victims than does thermal injury. Carbon monoxide poisoning with resulting significant hypoxemia can be life threatening. The use of synthetic materials (plastic, polyurethanes), which, when burned, may release a variety of other toxic agents (e.g., cyanide, hydrochloric acid), must be considered when evaluating smoke inhalation victims. Exposed victims may have some degree of lower respiratory tract inflammation, pulmonary edema, or both.

Exposure to certain highly reactive, low-molecular-weight agents used in the manufacture of synthetic polymers, paints, and coatings (e.g., *diisocyanates* in polyurethanes; *aromatic amines* and *acid anhydrides* in epoxies) are associated with a high risk of occupational asthma. Although this occupational asthma manifests clinically as if sensitization has occurred, there is little evidence that an IgE antibody-mediated mechanism is involved. Hypersensitivity pneumonitis-like reactions also have been described in diisocyanate and acid anhydride-exposed workers.

Fluoropolymers, such as Teflon, which produce no reaction at normal temperatures, become volatilized upon heating. The inhaled agents cause a characteristic syndrome of fever, chills, malaise, and occasionally mild wheezing leading to the diagnosis of *polymer fume fever*. A similar self-limited, influenza-like syndrome—*metal fume fever*—results from acute exposure to fumes or smoke containing zinc oxide. The syndrome may begin several hours after work and resolves within 24 h, only to return on repeated exposure. Welding of galvanized steel is the most common exposure leading to metal fume fever.

Two other agents have been recently associated with potentially severe interstitial lung disease. Occupational exposure to nylon flock has been shown to induce lymphocytic bronchiolitis, and workers exposed to diacetyl used to provide “butter” flavor in the manufacture of microwave popcorn have developed bronchiolitis obliterans (Chap. 19).

World Trade Center Disaster

A consequence of the attack on the World Trade Center (WTC) on September 11, 2001, was relatively heavy exposure of a large number of firefighters and other rescue workers to the dust generated by the collapse of the buildings. Environmental monitoring and chemical characterization of WTC dust has revealed a wide variety of potentially toxic constituents, although much of the dust was pulverized cement. Possibly because of the high alkalinity of WTC dust significant cough, wheeze, and phlegm production occurred among firefighters and clean-up crews. New cough and wheeze syndromes also occurred among local residents. Initial longitudinal follow-up of New York firefighters suggests that heavier

exposure to WTC dust is associated with an accelerated decline of lung function.

ENVIRONMENTAL RESPIRATORY CARCINOGENS

In addition to asbestos exposures, other occupational exposures associated with either proven or suspected respiratory carcinogens include those to acrylonitrile, arsenic compounds, beryllium, bis(chloromethyl) ether, chromium (hexavalent), formaldehyde (nasal), isopropyl oil (nasal sinuses), mustard gas, the various ores used to produce pure nickel, polyaromatic hydrocarbons (coke oven emissions and diesel exhaust), secondhand tobacco smoke, silica (both mining and processing), talc (possible asbestos contamination in both mining and milling), vinyl chloride (sarcomas), wood (nasal cancer only), and uranium. The occurrence of excess cancers in uranium miners raises the possibility that a large number of workers are at risk by virtue of exposure to similar radiation hazards. This number includes not only workers involved in processing uranium but also workers exposed in underground mining operations where radon daughters may be emitted from rock formations.

ASSESSMENT OF DISABILITY

Patients who have lung disease may have difficulty continuing to work in their usual jobs because of respiratory symptoms. Such patients frequently seek assistance from their physicians in obtaining compensation for loss of income. *Disability* is the term used to describe the decreased ability to work because of the effects of a medical condition. Physicians are generally able to assess physiologic dysfunction, or *impairment*, but the rating of disability also involves non-medical factors such as the education and employability of the individual. The disability rating scheme differs with the compensation-granting agency. For example, the U.S. Social Security Administration requires that an individual be unable to do any work (i.e., *total disability*) before he or she will receive income replacement payments. Many state workers' compensation systems allow for payments for *partial disability*. In the Social Security scheme, no determination of cause is done, but work-relatedness must be established in workers' compensation systems.

Most commonly the need for disability assessment comes about because of the patient's complaint of shortness of breath. It is important to remember that dyspnea may result from cardiac, hematologic, or neuromuscular diseases in addition to respiratory diseases. For respiratory disability, resting pulmonary function tests (spirometry and diffusing capacity) are used as the initial assessment tool, with cardiopulmonary exercise testing (to assess maximal oxygen consumption) used if the results of the resting tests do not correlate with the patient's symptoms.

96 Methacholine challenge (to assess airways reactivity) can also be useful in patients with asthma who have normal spirometry results when evaluated. Some compensation agencies (e.g., Social Security) have proscribed disability classification schemes based on pulmonary function test results. When no specific scheme is proscribed, the *Guidelines of the American Medical Association* should be used.

Evaluating relation to work exposure requires a detailed work history, as previously discussed in this chapter. Occasionally, as with some cases of suspected occupational asthma, challenge to the putative agent in the work environment with repeated pulmonary function measures may be required.

GENERAL ENVIRONMENTAL EXPOSURES

OUTDOOR AIR POLLUTION

In 1971, the U.S. government established national air quality standards for several pollutants believed to be responsible for excess cardiorespiratory diseases. Primary standards regulated by the Environmental Protection Agency (EPA) designed to protect the public health with an adequate margin of safety exist for sulfur dioxide, particulates matter, nitrogen dioxide, ozone, lead, and carbon monoxide. Standards for each of these pollutants are updated regularly through an extensive review process conducted by the EPA. (For details on current standards, see <http://www.epa.gov/air/criteria.html>.)

Pollutants are generated from both stationary sources (power plants and industrial complexes) and mobile sources (automobiles), and none of the pollutants occurs in isolation. Furthermore, pollutants may be changed by chemical reactions after being emitted. For example, reducing agents, such as sulfur dioxide and particulate matter from a power plant stack, may react in air to produce acid sulfates and aerosols, which can be transported long distances in the atmosphere. Oxidizing substances, such as oxides of nitrogen and oxidants from automobile exhaust, may react with sunlight to produce ozone. Although originally a problem confined to the southwestern part of the United States, in recent years, at least during the summertime, elevated ozone and acid aerosol levels have been documented throughout the United States. Both acute and chronic effects of these exposures have been documented in large population studies.

The symptoms and diseases associated with air pollution are the same as conditions commonly associated with cigarette smoking. In addition, respiratory illness in early childhood has been associated with chronic exposure to only modestly elevated levels of traffic-related gases and respirable particles. Multiple population-based time-series studies within cities have demonstrated excess cardiopulmonary hospitalizations and mortality.

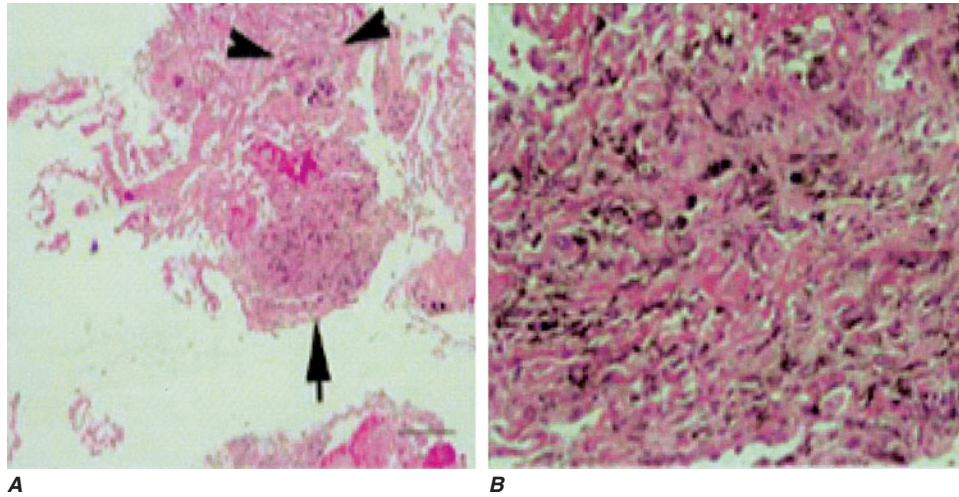
In addition, cohort studies comparing cities that have relatively high levels of particulate exposures with less polluted communities suggest excess morbidity and mortality from cardiorespiratory conditions in long-term residents of the former. These findings have led to stricter U.S. ambient air quality standards for particulate matter as well as greater emphasis on publicizing pollution alerts to encourage individuals with significant cardiopulmonary impairment to stay indoors during high pollution episodes.

INDOOR EXPOSURES

Environmental tobacco smoke, radon gas, wood smoke, and other biologic agents generated indoors need to be considered. Several studies have shown that the respirable particulate load in any household is directly proportional to the number of cigarette smokers living in the home. Increases in prevalence of respiratory illnesses and reduced levels of pulmonary function measured with simple spirometry have been found in children of smoking parents in a number of studies. Recent meta-analyses for lung cancer and cardiopulmonary diseases, combining data from the best of the environmental tobacco smoke exposure studies, suggest an approximate 25% increase in relative risk for each condition, even after adjustment for major potential confounders.

Radon gas is believed to be a risk factor for lung cancer. The main radon product (radon 222) is a gas that results from the decay series of uranium 238, with the immediate precursor being radium 226. The amount of radium in earth materials determines how much radon gas will be emitted. Outdoors, the concentrations are trivial. Indoors, levels are dependent on the sources, the ventilation rate of the space, and the size of the space into which the gas is emitted. Levels associated with excess lung cancer risk may be present in as many as 10% of the houses in the United States. When smokers reside in the household, the problem is potentially greater because the molecular size of radon particles allows them to readily attach to smoke particles that are inhaled. Fortunately, technology is available for assessing and reducing the level of exposure.

Other indoor exposures associated with an increased risk of atopy and asthma include those to such specific recognized putative biologic agents as cockroach antigen, dust mites, and pet dander. Other indoor chemical agents include formaldehyde, perfumes, and latex particles. Nonspecific responses associated with “tight-building syndrome,” in which no particular agent has been implicated, have included a wide variety of complaints, among them respiratory symptoms that are relieved only by avoiding exposure in the building in question. The degree to which “smells” or other sensory stimuli are involved in the triggering of potentially incapacitating psychological or physical responses has yet to be

**FIGURE 10-4**

Histopathologic features of biomass smoke-induced interstitial lung disease. **A.** Anthracitic pigment is seen accumulating along alveolar septae (*arrowheads*) and within

a pigmented dust macule (*single arrow*). **B.** A high-power photomicrograph contains a mixture of fibroblasts and carbon-laden macrophages.

determined, and the long-term consequences of such environmental exposures are as yet unknown.

PORTAL OF ENTRY

The lung is a primary point of entry into the body for a number of toxic agents that affect other organ systems. For example, the lung is a route of entry for benzene (bone marrow), carbon disulfide (cardiovascular and nervous systems), cadmium (kidney), and metallic mercury (kidney, central nervous system). Thus, in any disease state of obscure origin, it is important to consider the possibility of inhaled environmental agents. Such consideration can sometimes furnish the clue needed to identify a specific external cause for a disorder that might otherwise be labeled “idiopathic.”

GLOBAL CONSIDERATIONS



Indoor exposure to *biomass smoke* (wood, dung, crop residues, charcoal) is estimated to be responsible for 2.7% of worldwide disability adjusted life-years (DALYs) lost caused by acute lower respiratory infections in children and COPD and lung cancer in women. This burden of disease places indoor exposure to biomass smoke as the second leading environmental hazard for poor health, just behind unsafe water, sanitation, and hygiene, and is 3.5 times larger than the burden attributed to outdoor air pollution.

More than 50% of the world’s population uses biomass fuel for cooking, heating, or baking. This occurs predominantly in the rural areas of developing countries. Because many families burn biomass fuels in open stoves, which are highly inefficient, and inside homes

with poor ventilation, women and young children are exposed on a daily basis to high levels of smoke. In these homes, 24-h mean levels of fine particulate matter, a component of biomass smoke, have been reported to be two to 30 times higher than the National Ambient Air Quality Standards set by the U.S. EPA.

Epidemiologic studies have consistently shown associations between exposure to biomass smoke and both chronic bronchitis and COPD, with odds ratios ranging between 3 and 10 and increasing with longer exposures. In addition to the common occupational exposure to biomass smoke of women in developing countries, men from such countries may also be occupationally exposed. Because of increased migration to the United States from developing countries, clinicians need to be aware of the chronic respiratory effects of exposure to biomass smoke, which can also include interstitial lung disease ([Fig. 10-4](#)).

FURTHER READINGS

- BALMES JR et al: ATS Statement: Occupational contribution to the burden of airway disease. *Am J Respir Crit Care Med* 167:787, 2003
- CASTRANOVA V, VALLYATHAN V: Silicosis and coal workers’ pneumoconiosis. *Environ Health Perspect* 108(Suppl 4):675, 2000
- CHEN TM et al: Outdoor air pollution: Overview and historical perspective. *Am J Med Sci* 333:230, 2007
- DIAZ JV et al: A case of wood smoke-related pulmonary disease. *Environ Health Perspect* 114:759, 2006
- D’MANNETJE A et al: Exposure-response analysis and risk assessment for silica and silicosis mortality in a pooled analysis of six cohorts. *Occup Environ Med* 59:723, 2002
- EKICI A et al: Obstructive airway diseases in women exposed to biomass smoke. *Environ Res* 99:93, 2005

- 98 FONTENOT AP, MAIER LA: Genetic susceptibility and immune-mediated destruction in beryllium-induced disease. *Trends Immunol* 26:543, 2005
- KUSAKA Y et al (eds): *International Classification of HRCT for Occupational and Environmental Respiratory Diseases*. New York, Springer, 2005, 145
- LANDRIGAN PJ et al: Health and environmental consequences of the World Trade Center disaster. *Environ Health Perspect* 112:731, 2004
- NEWMAN LS et al: Beryllium sensitization progresses to chronic beryllium disease: A longitudinal study of disease risk. *Am J Respir Crit Care Med* 171:54, 2005
- O'REILLY KM et al: Asbestos-related lung disease. *Am Fam Physician* 75:683, 2007
- POPE CA III et al: Cardiovascular mortality and long-term exposure to particulate air pollution: Epidemiological evidence of general pathophysiological pathways of disease. *Circulation* 109:71, 2004



CHAPTER 11

PNEUMONIA

Lionel A. Mandell ■ Richard Wunderink

Definition	99	Diagnosis	103
Pathophysiology	99	Prognosis	108
Pathology	100	Prevention	108
■ Community-Acquired Pneumonia	101	■ Health Care–Associated Pneumonia	108
Etiology	101	Ventilator-Associated Pneumonia	108
Epidemiology	101	Hospital-Acquired Pneumonia	113
Clinical Manifestations	102	■ Further Readings	114

DEFINITION

Pneumonia is an infection of the pulmonary parenchyma. Despite being the cause of significant morbidity and mortality, pneumonia is often misdiagnosed, mistreated, and underestimated. In the past, pneumonia was typically classified as community-acquired (CAP), hospital-acquired (HAP), or ventilator-associated (VAP) pneumonia. Over the past decade or two, however, patients presenting to the hospital have often been found to be infected with multidrug-resistant (MDR) pathogens previously associated with hospital-acquired pneumonia. Factors responsible for this phenomenon include the development and widespread use of potent oral antibiotics, earlier transfer of patients out of acute-care hospitals to their homes or various lower-acuity facilities, increased use of outpatient IV antibiotic therapy, general aging of the population, and more extensive immunomodulatory therapies. The potential involvement of these MDR pathogens has led to a revised classification system in which infection is categorized as either CAP or health care–associated pneumonia (HCAP), with subcategories of HCAP including HAP and VAP. The conditions associated with HCAP and the likely pathogens are listed in [Table 11-1](#).

Although the new classification system has been helpful in designing empirical antibiotic strategies, it has some disadvantages. For instance, not all MDR pathogens are associated with all risk factors (Table 11-1). Therefore, this

system represents a distillation of multiple risk factors, and each patient must be considered individually. For example, the risk of infection with MDR pathogens for a nursing home resident with dementia who can independently dress, ambulate, and eat is quite different from the risk for a patient who is in a chronic vegetative state with a tracheostomy and a percutaneous feeding tube in place. In addition, risk factors for MDR infection do not preclude the development of pneumonia caused by the usual CAP pathogens.

This chapter deals with pneumonia in patients who are not considered to be immunocompromised.

PATHOPHYSIOLOGY

Pneumonia results from the proliferation of microbial pathogens at the alveolar level and the host's response to those pathogens. Microorganisms gain access to the lower respiratory tract in several ways. The most common way is by aspiration from the oropharynx. Small-volume aspiration occurs frequently during sleep (especially in the elderly) and in patients with decreased levels of consciousness. Many pathogens are inhaled as contaminated droplets. Rarely, pneumonia occurs via hematogenous spread (e.g., from tricuspid endocarditis) or by contiguous extension from an infected pleural or mediastinal space.

Mechanical factors are critically important in host defense. The hairs and turbinates of the nares catch larger inhaled particles before they reach the lower respiratory

TABLE 11-1

**CLINICAL CONDITIONS ASSOCIATED WITH AND LIKELY PATHOGENS IN HEALTH CARE—
ASSOCIATED PNEUMONIA**

CONDITION	PATHOGEN			
	MRSA	<i>PSEUDOMONAS AERUGINOSA</i>	<i>ACINETOBACTER SPP.</i>	MDR ENTEROBACTERIACEAE
Hospitalization for ≥ 48 h	X	X	X	X
Hospitalization for ≥ 2 days in prior 3 months	X	X	X	X
Nursing home or extended- care facility residence	X	X	X	X
Antibiotic therapy in preceding 3 months		X		X
Chronic dialysis	X			
Home infusion therapy	X			
Home wound care	X			
Family member with MDR infection	X			X

Note: MDR, multidrug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*.

tract, and the branching architecture of the tracheo-bronchial tree traps particles on the airway lining, where mucociliary clearance and local antibacterial factors either clear or kill the potential pathogen. The gag reflex and the cough mechanism offer critical protection from aspiration. In addition, the normal flora adhering to mucosal cells of the oropharynx, whose components are remarkably constant, prevent pathogenic bacteria from binding, thereby decreasing the risk of pneumonia caused by these more virulent bacteria.

When these barriers are overcome or when the microorganisms are small enough to be inhaled to the alveolar level, resident alveolar macrophages are extremely efficient at clearing and killing pathogens. Macrophages are assisted by local proteins (e.g., surfactant proteins A and D) that have intrinsic opsonizing properties or antibacterial or antiviral activity. After they have been engulfed, the pathogens—even if they are not killed by macrophages—are eliminated via either the mucociliary elevator or the lymphatics and no longer represent an infectious challenge. Only when the capacity of the alveolar macrophages to ingest or kill the microorganisms is exceeded does clinical pneumonia become manifest. In that situation, the alveolar macrophages initiate the inflammatory response to bolster lower respiratory tract defenses. The host inflammatory response, rather than the proliferation of microorganisms, triggers the clinical syndrome of pneumonia. The release of inflammatory mediators, such as interleukin (IL) 1 and tumor necrosis factor (TNF), results in fever. Chemokines, such as IL-8 and granulocyte colony-stimulating factor, stimulate the release of neutrophils and their attraction to the lung, producing both peripheral leukocytosis and increased

purulent secretions. Inflammatory mediators released by macrophages and the newly recruited neutrophils create an alveolar capillary leak equivalent to that seen in acute respiratory distress syndrome (ARDS), although in pneumonia, this leak is localized (at least initially). Even erythrocytes can cross the alveolar-capillary membrane, with consequent hemoptysis. The capillary leak, results in a radiographic infiltrate and rales detectable on auscultation, and hypoxemia results from alveolar filling. Moreover, some bacterial pathogens appear to interfere with the hypoxic vasoconstriction that would normally occur with fluid-filled alveoli, and this interference can result in severe hypoxemia. Increased respiratory drive in systemic inflammatory response syndrome (SIRS) leads to respiratory alkalosis. Decreased compliance caused by capillary leak, hypoxemia, increased respiratory drive, increased secretions, and occasionally infection-related bronchospasm all lead to dyspnea. If severe enough, the changes in lung mechanics secondary to reductions in lung volume and compliance and the intrapulmonary shunting of blood may cause the patient's death.

PATHOLOGY

Classic pneumonia evolves through a series of pathologic changes. The initial phase is one of *edema*, with the presence of a proteinaceous exudate—and often of bacteria—in the alveoli. This phase is rarely evident in clinical or autopsy specimens because it is so rapidly followed by a *red hepatization* phase. The presence of erythrocytes in the cellular intraalveolar exudate gives this second stage its name, but neutrophils are also present and are important from the standpoint of host defense.

Bacteria are occasionally seen in cultures of alveolar specimens collected during this phase. In the third phase, *gray hepatization*, no new erythrocytes are extravasating, and those already present have been lysed and degraded. The neutrophil is the predominant cell, fibrin deposition is abundant, and bacteria have disappeared. This phase corresponds with successful containment of the infection and improvement in gas exchange. In the final phase, *resolution*, the macrophage is the dominant cell type in the alveolar space, and the debris of neutrophils, bacteria, and fibrin has been cleared, as has the inflammatory response.

This pattern has been described best for pneumococcal pneumonia and may not apply to pneumonias of all etiologies, especially viral or *Pneumocystis* pneumonia. In VAP, respiratory bronchiolitis may precede the development of a radiologically apparent infiltrate. Because of the microaspiration mechanism, a bronchopneumonia pattern is most common in nosocomial pneumonias, but a lobar pattern is more common in bacterial CAP. Despite the radiographic appearance, viral and *Pneumocystis* pneumonias represent alveolar rather than interstitial processes.

COMMUNITY-ACQUIRED PNEUMONIA

ETIOLOGY

The extensive list of potential etiologic agents in CAP includes bacteria, fungi, viruses, and protozoa. Newly identified pathogens include hantaviruses, metapneumoviruses, the coronavirus responsible for severe acute respiratory syndrome (SARS), and community-acquired strains of methicillin-resistant *Staphylococcus aureus* (MRSA). Most cases of CAP, however, are caused by relatively few pathogens (Table 11-2). Although *Streptococcus pneumoniae*

is most common, other organisms must also be considered in light of the patient's risk factors and severity of illness. In most cases, it is most useful to think of the potential causes as either "typical" bacterial pathogens or "atypical" organisms. The former category includes *S. pneumoniae*, *Haemophilus influenzae*, and (in selected patients) *S. aureus* and gram-negative bacilli such as *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. The "atypical" organisms include *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella* spp. as well as respiratory viruses such as influenza viruses, adenoviruses, and respiratory syncytial viruses (RSVs). Data suggest that a virus may be responsible in up to 18% of cases of CAP that require admission to the hospital. The atypical organisms cannot be cultured on standard media, nor can they be seen on Gram's stain. The frequency and importance of atypical pathogens such as *M. pneumoniae* and *C. pneumoniae* in outpatients and *Legionella* spp. in inpatients have significant implications for therapy. These organisms are intrinsically resistant to all β -lactam agents and must be treated with a macrolide, a fluoroquinolone, or a tetracycline. In the ~10–15% of CAP cases that are polymicrobial, the etiology often includes a combination of typical and atypical pathogens.

Anaerobes play a significant role only when an episode of aspiration has occurred days to weeks before presentation for pneumonia. The combination of an unprotected airway (e.g., in patients with alcohol or drug overdose or a seizure disorder) and significant gingivitis constitutes the major risk factor. Anaerobic pneumonias are often complicated by abscess formation and significant empyemas or parapneumonic effusions.

S. aureus pneumonia is well known to complicate influenza infection. Recently, however, MRSA strains have been reported as primary causes of CAP. Although this entity is still relatively uncommon, clinicians must be aware of its potentially serious consequences, such as necrotizing pneumonia. Two important developments have led to this problem: the spread of MRSA from the hospital setting to the community and the emergence of genetically distinct strains of MRSA in the community. These novel community-acquired MRSA (CA-MRSA) strains have infected healthy individuals who have had no association with health care.

Unfortunately, despite a careful history and physical examination as well as routine radiographic studies, it is usually impossible to predict the pathogen in a case of CAP with any degree of certainty; in more than half of cases, a specific etiology is never determined. Nevertheless, it is important to consider epidemiologic and risk factors that might suggest certain pathogens (Table 11-3).

TABLE 11-2

MICROBIAL CAUSES OF COMMUNITY-ACQUIRED PNEUMONIA, BY SITE OF CARE

OUTPATIENTS	HOSPITALIZED PATIENTS	
	NON-ICU	ICU
<i>Streptococcus pneumoniae</i>	<i>S. pneumoniae</i>	<i>S. pneumoniae</i>
<i>Mycoplasma pneumoniae</i>	<i>M. pneumoniae</i>	<i>Staphylococcus aureus</i>
<i>Haemophilus influenzae</i>	<i>Chlamydophila pneumoniae</i>	<i>Legionella</i> spp.
<i>C. pneumoniae</i>	<i>H. influenzae</i>	Gram-negative bacilli
Respiratory viruses ^a	<i>Legionella</i> spp. Respiratory viruses ^a	<i>H. influenzae</i>

^aInfluenza A and B viruses, adenoviruses, respiratory syncytial viruses, parainfluenza viruses.

Note: Pathogens are listed in descending order of frequency. ICU, intensive care unit.

EPIDEMIOLOGY

In the United States, about 80% of the 4 million CAP cases that occur annually are treated on an outpatient

EPIDEMIOLOGIC FACTORS SUGGESTING POSSIBLE CAUSES OF COMMUNITY-ACQUIRED PNEUMONIA

FACTOR	POSSIBLE PATHOGEN(S)
Alcoholism	<i>Streptococcus pneumoniae</i> , oral anaerobes, <i>Klebsiella pneumoniae</i> , <i>Acinetobacter</i> spp., <i>Mycobacterium tuberculosis</i>
COPD or smoking	<i>Haemophilus influenzae</i> , <i>Pseudomonas aeruginosa</i> , <i>Legionella</i> spp., <i>S. pneumoniae</i> , <i>Moraxella catarrhalis</i> , <i>Chlamydomphila pneumoniae</i>
Structural lung disease (e.g., bronchiectasis)	<i>P. aeruginosa</i> , <i>Burkholderia cepacia</i> , <i>Staphylococcus aureus</i>
Dementia, stroke, decreased level of consciousness	Oral anaerobes, gram-negative enteric bacteria
Lung abscess	CA-MRSA, oral anaerobes, endemic fungi, <i>M. tuberculosis</i> , atypical mycobacteria
Travel to Ohio or St. Lawrence River valleys	<i>Histoplasma capsulatum</i>
Travel to southwestern United States	Hantavirus, <i>Coccidioides</i> spp.
Travel to Southeast Asia	<i>Burkholderia pseudomallei</i> , avian influenza virus
Stay in hotel or on cruise ship in previous 2 weeks	<i>Legionella</i> spp.
Local influenza activity	Influenza virus, <i>S. pneumoniae</i> , <i>S. aureus</i>
Exposure to bats or birds	<i>H. capsulatum</i>
Exposure to birds	<i>Chlamydomphila psittaci</i>
Exposure to rabbits	<i>Francisella tularensis</i>
Exposure to sheep, goats, parturient cats	<i>Coxiella burnetii</i>

Note: CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*; COPD, chronic obstructive pulmonary disease.

basis, and about 20% are treated in the hospital. CAP results in more than 600,000 hospitalizations, 64 million days of restricted activity, and 45,000 deaths annually. The overall yearly cost associated with CAP is estimated at \$9 to \$10 billion (U.S.). The incidence rates are highest at the extremes of age. Although the overall annual figure in the United States is 12 cases per 1000 persons, the figure is 12 to 18 per 1000 among children younger than 4 years of age and 20 per 1000 among persons older than 60 years of age.

The risk factors for CAP in general and for pneumococcal pneumonia in particular have implications for

treatment regimens. Risk factors for CAP include alcoholism, asthma, immunosuppression, institutionalization, and an age of 70 years or older versus 60 to 69 years. Risk factors for pneumococcal pneumonia include dementia, seizure disorders, heart failure, cerebrovascular disease, alcoholism, tobacco smoking, chronic obstructive pulmonary disease, and HIV infection. CA-MRSA infection is more likely in Native Americans, homeless youths, men who have sex with men, prison inmates, military recruits, children in daycare centers, and athletes such as wrestlers. The Enterobacteriaceae tend to affect patients who have recently been hospitalized or received antibiotic therapy or who have comorbidities such as alcoholism, heart failure, or renal failure. *P. aeruginosa* may also infect these patients as well as those with severe structural lung disease. Risk factors for *Legionella* infection include diabetes, hematologic malignancy, cancer, severe renal disease, HIV infection, smoking, male gender, and a recent hotel stay or ship cruise. (Many of these risk factors would now reclassify as HCAP some cases that were previously designated CAP.)

CLINICAL MANIFESTATIONS

CAP can vary from indolent to fulminant in presentation and from mild to fatal in severity. The various signs and symptoms, which depend on the progression and severity of the infection, include both constitutional findings and manifestations limited to the lung and its associated structures. In light of the pathobiology of the disease, many of the findings are to be expected.

The patient is frequently febrile with a tachycardic response and may have chills or sweats and cough that is either nonproductive or productive of mucoid, purulent, or blood-tinged sputum. In accordance with the severity of infection, the patient may be able to speak in full sentences or may be very short of breath. If the pleura is involved, the patient may experience pleuritic chest pain. Up to 20% of patients may have gastrointestinal symptoms such as nausea, vomiting, or diarrhea. Other symptoms may include fatigue, headache, myalgias, and arthralgias.

Findings on physical examination vary with the degree of pulmonary consolidation and the presence or absence of a significant pleural effusion. An increased respiratory rate and use of accessory muscles of respiration are common. Palpation may reveal increased or decreased tactile fremitus, and the percussion note can vary from dull to flat, reflecting underlying consolidated lung and pleural fluid, respectively. Crackles, bronchial breath sounds, and possibly a pleural friction rub may be heard on auscultation. The clinical presentation may not be so obvious in the elderly, who may initially display new-onset or worsening confusion and few other manifestations. Severely ill patients who have septic shock secondary to CAP are hypotensive and may have evidence of organ failure.

DIAGNOSIS

When confronted with possible CAP, the physician must ask two questions: Is this pneumonia, and, if so, what is the etiology? Whereas the former question is typically answered by clinical and radiographic methods, the latter requires the aid of laboratory techniques.

Clinical Diagnosis

The differential diagnosis includes both infectious and noninfectious entities such as acute bronchitis, acute exacerbations of chronic bronchitis, heart failure, pulmonary embolism, and radiation pneumonitis. The importance of a careful history cannot be overemphasized. For example, known cardiac disease may suggest worsening pulmonary edema, and underlying carcinoma may suggest lung injury secondary to radiation. Epidemiologic clues, such as recent travel to areas with known endemic pathogens, may alert the physician to specific possibilities (Table 11-3).

Unfortunately, the sensitivity and specificity of the findings on physical examination are less than ideal, averaging 58% and 67%, respectively. Therefore, chest radiography is often necessary to help differentiate CAP from other conditions. Radiographic findings serve as a baseline and may include risk factors for increased severity (e.g., cavitation or multilobar involvement). Occasionally, radiographic results suggest an etiologic diagnosis. For example, pneumatoceles suggest infection with *S. aureus*, and an upper-lobe cavitating lesion suggests tuberculosis. CT is rarely necessary but may be of value in a patient with suspected postobstructive pneumonia caused by a tumor or foreign body. For patients managed on an outpatient basis, the clinical and radiologic assessment is usually all that is done before treatment is started because most laboratory test results are not available soon enough to influence initial management. In certain cases, however (e.g., influenza virus infection), the availability of rapid point-of-care diagnostic tests and access to specific drugs for treatment and prevention can be very important.

Etiologic Diagnosis

The cause of pneumonia usually cannot be determined on the basis of clinical presentation; instead, the physician must rely on the laboratory for support. Except for the 2% of CAP patients who are admitted to the intensive care unit (ICU), no data exist to show that treatment directed at a specific pathogen is statistically superior to empirical therapy. The benefits of establishing a microbial etiology can therefore be questioned, particularly in light of the cost of diagnostic testing. However, a number of reasons can be advanced for attempting an etiologic diagnosis. Identification of an unexpected pathogen allows narrowing of the initial empirical regimen, which decreases antibiotic selection pressure and may lessen the

risk of resistance. Pathogens with important public safety implications, such as *Mycobacterium tuberculosis* and influenza virus, may be found in some cases. Finally, without culture and susceptibility data, trends in resistance cannot be followed accurately, and appropriate empirical therapeutic regimens are harder to devise.

Gram's Stain and Culture of Sputum

The main purpose of the sputum Gram's stain is to ensure that a sample is suitable for culture. However, Gram's staining may also help to identify certain pathogens (e.g., *S. pneumoniae*, *S. aureus*, and gram-negative bacteria) by their characteristic appearance. To be adequate for culture, a sputum sample must have >25 neutrophils and <10 squamous epithelial cells per low-power field. The sensitivity and specificity of the sputum Gram's stain and culture are highly variable; even in cases of proven bacteremic pneumococcal pneumonia; the yield of positive cultures from sputum samples is $\leq 50\%$.

Some patients, particularly elderly individuals, may not be able to produce an appropriate expectorated sputum sample. Others may already have started a course of antibiotics, which can interfere with results, at the time a sample is obtained. The inability to produce sputum can be a consequence of dehydration, and the correction of this condition may result in increased sputum production and a more obvious infiltrate on chest radiography. For patients admitted to the ICU and intubated, a deep-suction aspirate or bronchoalveolar lavage sample should be sent to the microbiology laboratory as soon as possible. Because the causes in severe CAP are somewhat different from those in milder disease (Table 11-2), the greatest benefit of staining and culturing respiratory secretions is to alert the physician of unsuspected or resistant pathogens and to permit appropriate modification of therapy. Other stains and cultures may be useful as well. For suspected tuberculosis or fungal infection, specific stains are available. Cultures of pleural fluid obtained from effusions >1 cm in height on a lateral decubitus chest radiograph may also be helpful.

Blood Cultures

The yield from blood cultures, even those obtained before antibiotic therapy, is disappointingly low. Only ~5–14% of cultures of blood from patients hospitalized with CAP are positive, and the most frequently isolated pathogen is *S. pneumoniae*. Because recommended empirical regimens all provide pneumococcal coverage, a blood culture positive for this pathogen has little, if any, effect on clinical outcome. However, susceptibility data may allow a switch from a broader-spectrum regimen (e.g., a fluoroquinolone or β -lactam plus a macrolide) to penicillin in appropriate cases. Because of the low yield and the lack of significant impact on outcome, blood cultures are no longer considered *de rigueur* for all hospitalized CAP patients. Certain high-risk patients—including

104 those with neutropenia secondary to pneumonia, asplenia, or complement deficiencies; chronic liver disease; or severe CAP—should have their blood cultured.

Antigen Tests

Two commercially available tests detect pneumococcal and certain *Legionella* antigens in urine. The test for *Legionella pneumophila* detects only serogroup 1, but this serogroup accounts for most community-acquired cases of Legionnaires' disease. The sensitivity and specificity of the *Legionella* urine antigen test are as high as 90% and 99%, respectively. The pneumococcal urine antigen test is also quite sensitive and specific (80% and >90%, respectively). Although false-positive results can be obtained with samples from colonized children, the test is generally reliable. Both tests can detect antigen even after the initiation of appropriate antibiotic therapy and after weeks of illness. Other antigen tests include a rapid test for influenza virus and direct fluorescent antibody tests for influenza virus and RSV, although the test for RSV is only poorly sensitive.

Polymerase Chain Reaction

Polymerase chain reaction (PCR) tests are available for a number of pathogens, including *L. pneumophila* and mycobacteria. In addition, a multiplex PCR can detect the nucleic acid of *Legionella* spp., *M. pneumoniae*, and *C. pneumoniae*. However, the use of these PCR assays is generally limited to research studies.

Serology

A fourfold increase in specific IgM antibody titer between acute- and convalescent-phase serum samples is generally considered diagnostic of infection with the pathogen in question. In the past, serologic tests were used to help identify atypical pathogens as well as some typical but relatively unusual organisms, such as *Coxiella burnetii*. Recently, however, they have fallen out of favor because of the time required to obtain a final result for the convalescent-phase sample.

Rx Treatment: COMMUNITY-ACQUIRED PNEUMONIA

SITE OF CARE The decision to hospitalize a patient with CAP must take into consideration the diminishing health care resources and the rising costs of treatment. The cost of inpatient management exceeds that of outpatient treatment by a factor of 20 and accounts for most CAP-related expenditures. Certain patients clearly can be managed at home, and others clearly require treatment in the hospital, but the choice is sometimes difficult. Tools that objectively assess the risk of adverse outcomes, including severe illness and death, may

minimize unnecessary hospital admissions and help to identify patients who will benefit from hospital care. There are currently two sets of criteria: the Pneumonia Severity Index (PSI), a prognostic model used to identify patients at low risk of dying, and the CURB-65 criteria, a severity-of-illness score.

To determine the PSI, points are given for 20 variables, including age, coexisting illness, and abnormal physical and laboratory findings. On the basis of the resulting score, patients are assigned to one of five classes with the following mortality rates: class 1, 0.1%; class 2, 0.6%; class 3, 2.8%; class 4, 8.2%; and class 5, 29.2%. Clinical trials have demonstrated that routine use of the PSI results in lower admission rates for class 1 and class 2 patients. Patients in classes 4 and 5 should be admitted to the hospital, and those in class 3 should ideally be admitted to an observation unit until a further decision can be made.

The CURB-65 criteria include five variables: confusion (C); urea >7 mmol/L (U); respiratory rate ≥ 30 /min (R); blood pressure, systolic ≤ 90 mmHg or diastolic ≤ 60 mmHg (B); and age ≥ 65 years (65). Patients with a score of 0, among whom the 30-day mortality rate is 1.5%, can be treated outside the hospital. With a score of 2, the 30-day mortality rate is 9.2%, and patients should be admitted to the hospital. Among patients with scores of ≥ 3 , mortality rates are 22% overall; these patients may require admission to an ICU.

At present, it is difficult to say which assessment tool is superior. The PSI is less practical in a busy emergency department setting because of the need to assess 20 variables. Although the CURB-65 criteria are easily remembered, they have not been studied as extensively. Whichever system is used, these objective criteria must always be tempered by careful consideration of factors relevant to individual patients, including the ability to comply reliably with an oral antibiotic regimen and the resources available to the patient outside the hospital.

RESISTANCE Antimicrobial resistance is a significant problem that threatens to diminish our therapeutic armamentarium. Misuse of antibiotics results in increased antibiotic selection pressure that can affect resistance locally or even globally by clonal dissemination. For CAP, the main resistance issues currently involve *S. pneumoniae* and CA-MRSA.

S. pneumoniae In general, pneumococcal resistance is acquired by (1) direct DNA incorporation and remodeling resulting from contact with closely related oral commensal bacteria, (2) the process of natural transformation, or (3) mutation of certain genes.

Pneumococcal strains are classified as sensitive to penicillin if the minimal inhibitory concentration (MIC) is ≤ 0.06 $\mu\text{g/mL}$, as intermediate if the MIC is 0.1–1.0 $\mu\text{g/mL}$, and as resistant if the MIC is ≥ 2 $\mu\text{g/mL}$. Strains resistant

to drugs from three or more antimicrobial classes with different mechanisms of action are considered MDR isolates. Pneumococcal resistance to β -lactam drugs is solely caused by the presence of low-affinity penicillin-binding proteins. The propensity for pneumococcal resistance to penicillin to be associated with reduced susceptibility to other drugs, such as macrolides, tetracyclines, and trimethoprim-sulfamethoxazole (TMP-SMX), is of concern. In the United States, 58.9% of penicillin-resistant pneumococcal isolates from blood cultures are also resistant to macrolides. Penicillin is an appropriate agent for the treatment of pneumococcal infection caused by strains with MICs of ≤ 1 $\mu\text{g}/\text{mL}$. For infections caused by pneumococcal strains with penicillin MICs of 2–4 $\mu\text{g}/\text{mL}$, the data are conflicting; some studies suggest no increase in treatment failure with penicillin, but others suggest increased rates of death or complications. For strains of *S. pneumoniae* with intermediate levels of resistance, higher doses of the drug should be used. Risk factors for drug-resistant pneumococcal infection include recent antimicrobial therapy, an age of <2 years or >65 years, attendance at a daycare center, recent hospitalization, and HIV infection. Fortunately, resistance to penicillin appears to be reaching a plateau.

In contrast, resistance to macrolides is increasing through several mechanisms, including target-site modification and the presence of an efflux pump. Target-site modification is caused by ribosomal methylation in 23S rRNA encoded by the *ermB* gene and results in resistance to macrolides, lincosamides, and streptogramin B-type antibiotics. This *MLS_B* phenotype is associated with high-level resistance, with typical MICs of ≥ 64 $\mu\text{g}/\text{mL}$. The efflux mechanism encoded by the *mef* gene (*M* phenotype) is usually associated with low-level resistance (MICs, 1–32 $\mu\text{g}/\text{mL}$). These two mechanisms account for $\sim 45\%$ and $\sim 65\%$, respectively, of resistant pneumococcal isolates in the United States. Some pneumococcal isolates with both the *erm* and *mef* genes have been identified, but the exact significance of this finding is unknown. High-level resistance to macrolides is more common in Europe, and lower-level resistance seems to predominate in North America. Although clinical failures with macrolides have been reported, many experts think that these drugs still have a role to play in the management of pneumococcal pneumonia in North America.

Pneumococcal resistance to fluoroquinolones (e.g., ciprofloxacin and levofloxacin) has been reported. Changes can occur in one or both target sites (topoisomerases II and IV); changes in these two sites usually result from mutations in the *gyrA* and *parC* genes, respectively. The increasing number of pneumococcal isolates that, although susceptible to fluoroquinolones, already have a mutation in one target site is of concern.

Such organisms may be more likely to undergo a second-step mutation that will render them fully resistant to fluoroquinolones. In addition, an efflux pump may play a role in pneumococcal resistance to fluoroquinolones.

CA-MRSA CAP due to MRSA may be caused by infection with the classic hospital-acquired strains or with the more recently identified genotypically and phenotypically distinct community-acquired strains. Most infections with the former strains have been acquired either directly or indirectly by contact with the health care environment and, although classified as HAP in the past, would now be classified as HCAP. In some hospitals, CA-MRSA strains are displacing the classic hospital-acquired strains—a trend suggesting that the newer strains may be more robust.

Methicillin resistance in *S. aureus* is determined by the *mecA* gene, which encodes for resistance to all β -lactam drugs. At least five *staphylococcal chromosomal cassette mec* (*SCCmec*) types have been described. Whereas the typical hospital-acquired strain usually has type II or III, CA-MRSA has a type IV *SCCmec* element. CA-MRSA isolates tend to be less resistant than the older hospital-acquired strains and are often susceptible to TMP-SMX, clindamycin, and tetracycline in addition to vancomycin and linezolid. However, CA-MRSA strains may also carry genes for superantigens, such as enterotoxins B and C and Panton-Valentine leukocidin, a membrane-tropic toxin that can create cytolytic pores in polymorphonuclear neutrophils, monocytes, and macrophages.

Gram-Negative Bacilli A detailed discussion of resistance among gram-negative bacilli is beyond the scope of this chapter. Fluoroquinolone resistance among isolates of *Escherichia coli* from the community appears to be increasing. *Enterobacter* spp. are typically resistant to cephalosporins; the drugs of choice for use against these bacteria are usually fluoroquinolones or carbapenems. Similarly, when infections caused by bacteria producing extended-spectrum β -lactamases (ESBLs) are documented or suspected, a fluoroquinolone or a carbapenem should be used; these MDR strains are more likely to be involved in HCAP.

INITIAL ANTIBIOTIC MANAGEMENT Because the physician rarely knows the etiology of CAP at the outset of treatment, initial therapy is usually empirical and is designed to cover the most likely pathogens (Table 11-4). In all cases, antibiotic treatment should be initiated as expeditiously as possible.

The CAP treatment guidelines in the United States (summarized in Table 11-4) represent joint statements from the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS); the Canadian guidelines come from the Canadian Infectious Disease Society and the Canadian Thoracic Society. In these

EMPIRICAL ANTIBIOTIC TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA

Outpatients

Previously healthy and no antibiotics in the past 3 months:

- A macrolide [clarithromycin (500 mg PO bid) or azithromycin (500 mg PO once then 250 mg od)] **or**
- Doxycycline (100 mg PO bid)

Comorbidities or antibiotics in the past 3 months:

select an alternative from a different class:

- A respiratory fluoroquinolone [moxifloxacin (400 mg PO od), gemifloxacin (320 mg PO od), levofloxacin (750 mg PO od)] **or**
- A β -lactam [preferred: high-dose amoxicillin (1 g tid) or amoxicillin/clavulanate (2 g bid); alternatives: ceftriaxone (1–2 g IV od), cefpodoxime (200 mg PO bid), cefuroxime (500 mg PO bid)] **plus** a macrolide^a

In regions with a high rate of “high-level” pneumococcal macrolide resistance,^b consider the alternatives listed above for patients with comorbidities.

Inpatients, Non-ICU

- A respiratory fluoroquinolone [moxifloxacin (400 mg PO or IV od), gemifloxacin (320 mg PO od), levofloxacin (750 mg PO or IV od)]
- A β -lactam^c [cefotaxime (1–2 g IV q8h), ceftriaxone (1–2 g IV od), ampicillin (1–2 g IV q4–6h), ertapenem (1 g IV od in selected patients)] **plus** a macrolide^d oral clarithromycin or azithromycin [as listed above for previously healthy patients or IV azithromycin (1 g once, then 500 mg od)]

Inpatients, ICU

- A β -lactam^e [cefotaxime (1–2 g IV q8h), ceftriaxone (2 g IV od), ampicillin-sulbactam (2 g IV q8h)] **plus**
- Azithromycin or a fluoroquinolone (as listed above for inpatients, non-ICU)

Special Concerns

If *Pseudomonas* infection is a consideration:

- An antipseudomoccal, antipseudomonal β -lactam [piperacillin/tazobactam (4.5 g IV q6h), cefepime (1–2 g IV q12h), imipenem (500 mg IV q6h), meropenem (1 g IV q8h)] **plus** either ciprofloxacin (400 mg IV q12h) or levofloxacin (750 mg IV od)
- The above β -lactams **plus** an aminoglycoside [amikacin (15 mg/kg od) or tobramycin (1.7 mg/kg od) and azithromycin]
- The above β -lactams^f **plus** an aminoglycoside **plus** an antipseudomoccal fluoroquinolone

If CA-MRSA is a consideration:

- Add linezolid (600 mg IV q12h) or vancomycin (1 g IV q12h)

^aDoxycycline (100 mg PO bid) is an alternative to the macrolide.

^bMinimal inhibitory concentrations of >16 μ g/mL in 25% of isolates.

^cA respiratory fluoroquinolone should be used for penicillin-allergic patients.

^dDoxycycline (100 mg IV q12h) is an alternative to the macrolide.

^eFor penicillin-allergic patients, use a respiratory fluoroquinolone and aztreonam (2 g IV q8h).

^fFor penicillin-allergic patients, substitute aztreonam.

Note: CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*; ICU, intensive care unit.

guidelines, coverage is always provided for the pneumococcus and the atypical pathogens. In contrast, guidelines from some European countries do not always include atypical coverage based on local epidemiologic data. The U.S.–Canadian approach is supported by retrospective data from almost 13,000 patients >65 years of age. Atypical pathogen coverage provided by a macrolide or a fluoroquinolone has been associated with a significant reduction in mortality rates compared with those for β -lactam coverage alone.

Therapy with a macrolide or a fluoroquinolone within the previous 3 months is associated with an increased likelihood of infection with a macrolide- or fluoroquinolone-resistant strain of *S. pneumoniae*. For this reason, a fluoroquinolone-based regimen should be used for patients recently given a macrolide and vice versa (Table 11-4). Telithromycin, a ketolide derived from the macrolide class, differs from the macrolides in that it binds to bacteria more avidly and at two sites rather than one. This drug is active against pneumococci resistant to penicillins, macrolides, and fluoroquinolones. Its future role in the outpatient management of CAP will depend on the evaluation of its safety by the U.S. Food and Drug Administration.

After the etiologic agent(s) and susceptibilities are known, therapy may be altered to target the specific pathogen(s). However, this decision is not always straightforward. If blood cultures yield *S. pneumoniae* sensitive to penicillin after 2 days of treatment with a macrolide plus a β -lactam or a fluoroquinolone, should therapy be switched to penicillin? Penicillin alone would not be effective in the potential 15% of cases with atypical co-infection. No standard approach exists. Some experts would argue that pneumococcal coverage by a switch to penicillin is appropriate, but others would opt for continued coverage of both the pneumococcus and atypical pathogens. One compromise is to continue atypical coverage with either a macrolide or a fluoroquinolone for a few more days and then to complete the treatment course with penicillin alone. In all cases, the individual patient and the various risk factors must be considered.

Management of bacteremic pneumococcal pneumonia is also controversial. Data from nonrandomized studies suggest that combination therapy (e.g., with a macrolide and a β -lactam) is associated with a lower mortality rate than monotherapy, particularly in severely ill patients. The exact reason is unknown, but explanations include possible atypical co-infection or the immunomodulatory effects of the macrolides.

For patients with CAP who are admitted to the ICU, the risk of infection with *P. aeruginosa* or CA-MRSA is increased, and coverage should be considered when a patient has risk factors or a Gram's stain suggestive of these pathogens (see Table 11-4). The main risk factors

for *P. aeruginosa* infection are structural lung disease (e.g., bronchiectasis) and recent treatment with antibiotics or glucocorticoids. If CA-MRSA infection is suspected, either linezolid or vancomycin should be added to the initial empirical regimen.

Although hospitalized patients have traditionally received initial therapy by the IV route, some drugs—particularly the fluoroquinolones—are very well absorbed and can be given orally from the outset to select patients. For patients initially treated IV, a switch to oral treatment is appropriate as long as the patient can ingest and absorb the drugs, is hemodynamically stable, and is showing clinical improvement.

The duration of treatment for CAP has recently generated considerable interest. Patients have usually been treated for 10–14 days, but recent studies with fluoroquinolones and telithromycin suggest that a 5-day course is sufficient for otherwise uncomplicated CAP. A longer course is required for patients with bacteremia; metastatic infection; or infection with a particularly virulent pathogen, such as *P. aeruginosa* or CA-MRSA. Longer-term therapy should also be considered if initial treatment was ineffective and in most cases of severe CAP. Data from studies with azithromycin, which suggest 3–5 days of treatment for outpatient-managed CAP, cannot be extrapolated to other drugs because of the extremely long half-life of azithromycin.

Patients may be discharged from the hospital after they are clinically stable and have no active medical problems requiring ongoing hospital care. The site of residence after discharge (in a nursing home, at home with family, at home alone) is an important consideration, particularly for elderly patients.

GENERAL CONSIDERATIONS In addition to appropriate antimicrobial therapy, certain general considerations apply in dealing with either CAP or HAP. Adequate hydration, oxygen therapy for hypoxemia, and assisted ventilation (when necessary) are critical to the success of therapy. Patients with severe CAP who remain hypotensive despite fluid resuscitation may have adrenal insufficiency and may respond to glucocorticoid treatment. Immunomodulatory therapy in the form of drotrecogin alfa (activated) should be considered for CAP patients with persistent septic shock and APACHE II scores of 25 or above, particularly if the infection is caused by *S. pneumoniae*.

Failure to Improve Patients who are slow to respond to therapy should be reevaluated at about day 3 (sooner if their condition is worsening rather than simply not improving), and a number of possible scenarios should be considered. (1) Is it a noninfectious condition? (2) If it is an infection, is the correct pathogen being targeted? (3) Is it a superinfection with a new nosocomial pathogen? A number of noninfectious conditions can

mimic pneumonia, including pulmonary edema, pulmonary embolism, lung carcinoma, radiation and hypersensitivity pneumonitis, and connective tissue disease involving the lungs. If the patient has CAP and treatment is aimed at the correct pathogen, the lack of response may be explained in a number of ways. The pathogen may be resistant to the drug selected, or a sequestered focus (e.g., a lung abscess or empyema) may be blocking access of the antibiotic(s) to the pathogen. Alternatively, the patient may be getting either the wrong drug or the correct drug at the wrong dose or frequency of administration. It is also possible that CAP is the correct diagnosis but that a different pathogen (e.g., *M. tuberculosis* or a fungus) is the cause. In addition, nosocomial superinfections—both pulmonary and extrapulmonary—are possible explanations for persistence. In all cases of delayed response or deteriorating condition, the patient must be carefully reassessed and appropriate studies initiated. These studies may include such diverse procedures as CT and bronchoscopy.

Complications As in other severe infections, common complications of severe CAP include respiratory failure, shock and multiorgan failure, bleeding diatheses, and exacerbation of comorbid illnesses. Three particularly noteworthy conditions are metastatic infection, lung abscess, and complicated pleural effusion. Metastatic infection (e.g., brain abscess or endocarditis), although unusual, deserves immediate attention by the physician, with a detailed workup and proper treatment. Lung abscess may occur in association with aspiration or with infection caused by a single CAP pathogen, such as CA-MRSA, *P. aeruginosa*, or (rarely) *S. pneumoniae*. Aspiration pneumonia is typically a mixed polymicrobial infection involving both aerobes and anaerobes. In either scenario, drainage should be established, and antibiotics that cover the known or suspected pathogens should be administered. A significant pleural effusion should be tapped for both diagnostic and therapeutic purposes. If the fluid has a pH of <7, a glucose level of <2.2 mmol/L, and a lactate dehydrogenase concentration of >1000 U/L, or if bacteria are seen or cultured, then the fluid should be drained, and a chest tube is usually required.

Follow-Up Fever and leukocytosis usually resolve within 2 and 4 days, respectively, in otherwise healthy patients with CAP, but physical findings may persist longer. Chest radiographic abnormalities are slowest to resolve and may require 4–12 weeks to clear, with the speed of clearance depending on the patient's age and underlying lung disease. For a patient whose condition is improving and who (if hospitalized) has been discharged, a follow-up radiograph can be done ~4–6 weeks later. If relapse or recurrence is documented, particularly in the same lung segment, the possibility of an underlying neoplasm must be considered.

The prognosis of CAP depends on the patient's age, comorbidities, and site of treatment (inpatient or outpatient). Young patients without comorbidity do well and usually recover fully after ~2 weeks. Older patients and those with comorbid conditions can take several weeks longer to recover fully. The overall mortality rate for the outpatient group is <1%. For patients requiring hospitalization, the overall mortality rate is estimated at 10%, with ~50% of the deaths directly attributable to pneumonia.

PREVENTION

The main preventive measure is vaccination. The recommendations of the Advisory Committee on Immunization Practices should be followed for influenza and pneumococcal vaccines. In the event of an influenza outbreak, unprotected patients at risk from complications should be vaccinated immediately and given chemoprophylaxis with either oseltamivir or zanamivir for 2 weeks—i.e., until vaccine-induced antibody levels are sufficiently high. Because of an increased risk of pneumococcal infection, even among patients without obstructive lung disease, smokers should be strongly encouraged to stop smoking.

HEALTH CARE–ASSOCIATED PNEUMONIA

VENTILATOR-ASSOCIATED PNEUMONIA

Most research on VAP has focused on illness in the hospital setting. However, the information and principles based on this research can be applied to HCAP not associated with ventilator use as well. The main rationale for the new designation *HCAP* is that the pathogens and treatment strategies for VAP are more similar to those for HAP than to those for pure CAP. The greatest difference between VAP and HCAP or HAP—and the greatest similarity of VAP to CAP—is the return to dependence on expectorated sputum for a microbiologic diagnosis, which is further complicated by the frequent colonization with pathogens among patients in the hospital or other health care–associated settings.

Etiology

Potential etiologic agents of VAP include both MDR and non-MDR bacterial pathogens (Table 11-5). The non-MDR group is nearly identical to the pathogens found in severe CAP (see Table 11-2); it is not surprising that such pathogens predominate if VAP develops in the first 5–7 days of the hospital stay. However, if patients have other risk factors for HCAP, MDR pathogens are a consideration, even early in the hospital course. The

TABLE 11-5

MICROBIOLOGIC CAUSES OF VENTILATOR-ASSOCIATED PNEUMONIA

NON-MDR PATHOGENS	MDR PATHOGENS
<i>Streptococcus pneumoniae</i>	<i>Pseudomonas aeruginosa</i>
Other <i>Streptococcus</i> spp.	MRSA
<i>Haemophilus influenzae</i>	<i>Acinetobacter</i> spp.
MSSA	Antibiotic-resistant Enterobacteriaceae
Antibiotic-sensitive Enterobacteriaceae	<i>Enterobacter</i> spp.
<i>Escherichia coli</i>	ESBL-positive strains
<i>Klebsiella pneumoniae</i>	<i>Klebsiella</i> spp.
<i>Proteus</i> spp.	<i>Legionella pneumophila</i>
<i>Enterobacter</i> spp.	<i>Burkholderia cepacia</i>
<i>Serratia marcescens</i>	<i>Aspergillus</i> spp.

Note: ESBL, extended-spectrum β -lactamase; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *S. aureus*.

relative frequency of individual MDR pathogens can vary significantly from hospital to hospital and even between different critical care units within the same institution. Many hospitals have problems with *P. aeruginosa* and MRSA, but other MDR pathogens are often institution specific.

Less commonly, fungal and viral pathogens cause VAP, most frequently affecting severely immunocompromised patients. Rarely, community-associated viruses cause mini epidemics, usually when introduced by ill health care workers.

Epidemiology

Pneumonia is a common complication among patients requiring mechanical ventilation. Prevalence estimates vary between six and 52 cases per 100 patients, depending on the population studied. On any given day in the ICU, an average of 10% of patients will have pneumonia—VAP in the overwhelming majority of cases. The frequency of diagnosis is not static but changes with the duration of mechanical ventilation, with the highest hazard ratio in the first 5 days and a plateau in additional cases (1% per day) after ~2 weeks. However, the cumulative rate among patients who remain ventilated for as long as 30 days is as high as 70%. These rates often do not reflect the recurrence of VAP in the same patient. After a ventilated patient has been transferred to a chronic care facility or to home, the incidence of pneumonia decreases significantly, especially in the absence of other risk factors for pneumonia.

Three factors are critical in the pathogenesis of VAP: colonization of the oropharynx with pathogenic microorganisms, aspiration of these organisms from the oropharynx into the lower respiratory tract, and

compromise of the normal host defense mechanisms. Most risk factors and their corresponding prevention strategies pertain to one of these three factors (Table 11-6).

The most obvious risk factor is the endotracheal tube (ET), which bypasses the normal mechanical factors, preventing aspiration. Although the presence of an ET may prevent large-volume aspiration, microaspiration is actually enhanced by secretions pooling above the cuff. The ET and the concomitant need for suctioning can damage the tracheal mucosa, thereby facilitating tracheal colonization. In addition, pathogenic bacteria can form a glycocalyx biofilm on the ET surface that protects them from both antibiotics and host defenses. The bacteria can also be dislodged during suctioning and can reinoculate the trachea, or tiny fragments of glycocalyx can embolize to distal airways, carrying bacteria with them.

In a high percentage of critically ill patients, the normal oropharyngeal flora is replaced by pathogenic microorganisms. The most important risk factors are antibiotic selection pressure, cross-infection from other infected or colonized patients or contaminated equipment, and malnutrition.

How the lower respiratory tract defenses become overwhelmed remains poorly understood. Almost all intubated patients experience microaspiration and are at least transiently colonized with pathogenic bacteria. However, only around one-third of colonized patients develop VAP. Severely ill patients with sepsis and trauma appear to enter a state of immunoparalysis several days after admission to the ICU—a time that corresponds to the greatest risk of developing VAP. The mechanism of this immunosuppression is not clear, although several factors have been suggested. Hyperglycemia affects neutrophil function, and recent trials suggest that keeping the blood sugar close to normal with exogenous insulin may have beneficial effects, including a decreased risk of infection. More frequent transfusions, especially of leukocyte-depleted red blood cells, also affect the immune response positively.

Clinical Manifestations

The clinical manifestations of VAP are generally the same as for all other forms of pneumonia: fever, leukocytosis, increase in respiratory secretions, and pulmonary

TABLE 11-6

PATHOGENIC MECHANISMS AND CORRESPONDING PREVENTION STRATEGIES FOR VENTILATOR-ASSOCIATED PNEUMONIA

PATHOGENIC MECHANISM	PREVENTION STRATEGY
Oropharyngeal colonization with pathogenic bacteria	Avoidance of prolonged antibiotic courses
Elimination of normal flora	Short course of prophylactic antibiotics for comatose patients ^a
Large-volume oropharyngeal aspiration around time of intubation	
Gastroesophageal reflux	Postpyloric enteral feeding ^b ; avoidance of high gastric residuals, prokinetic agents
Bacterial overgrowth of stomach	Avoidance of GI bleeding caused by prophylactic agents that increase gastric pH ^b ; selective decontamination of the digestive tract with nonabsorbable antibiotics ^b
Cross-infection from other colonized patients	Hand washing, especially with an alcohol-based hand rub; intensive infection control education ^a ; isolation; proper cleaning of reusable equipment
Large-volume aspiration	Endotracheal intubation; avoidance of sedation; decompression of small-bowel obstruction
Microaspiration around the endotracheal tube	
Endotracheal intubation	Noninvasive ventilation ^a
Prolonged duration of ventilation	Daily awakening from sedation, ^a weaning protocols ^a
Abnormal swallowing function	Early percutaneous tracheostomy ^a
Secretions pooled above the ET	Head of bed elevated ^a ; continuous aspiration of subglottic secretions with specialized ET ^a ; avoidance of reintubation; minimization of sedation and patient transport
Altered lower respiratory host defenses	Tight glycemic control ^b ; lowering of hemoglobin transfusion threshold; specialized enteral feeding formula

^aStrategies demonstrated to be effective in at least one randomized controlled trial.

^bStrategies with negative randomized trials or conflicting results.

Note: ET, endotracheal tube; GI, gastrointestinal.

110 consolidation on physical examination, along with a new or changing radiographic infiltrate. The frequency of abnormal chest radiographs before the onset of pneumonia in intubated patients and the limitations of portable radiographic technique make interpretation of radiographs more difficult than in patients who are not intubated. Other clinical features may include tachypnea, tachycardia, worsening oxygenation, and increased minute ventilation.

Diagnosis

No single set of criteria is reliably diagnostic of pneumonia in a ventilated patient. The inability to identify such patients compromises efforts to prevent and treat VAP and even calls into question estimates of the impact of VAP on mortality rates.

Application of clinical criteria consistently results in overdiagnosis of VAP, largely because of three common findings in at-risk patients: (1) tracheal colonization with pathogenic bacteria in patients with ETs, (2) multiple alternative causes of radiographic infiltrates in mechanically ventilated patients, and (3) the high frequency of other sources of fever in critically ill patients. The differential diagnosis of VAP includes a number of entities, such as atypical pulmonary edema, pulmonary contusion or hemorrhage, hypersensitivity pneumonitis, ARDS, and pulmonary embolism. Clinical findings in ventilated patients with fever or leukocytosis may have alternative causes, including antibiotic-associated diarrhea, sinusitis, urinary tract infection, pancreatitis, and drug fever. Conditions mimicking pneumonia are often documented in patients in whom VAP has been ruled out by accurate diagnostic techniques. Most of these alternative diagnoses do not require antibiotic treatment; require antibiotics different from those used to treat VAP; or require some additional intervention, such as surgical drainage or catheter removal, for optimal management.

This diagnostic dilemma has led to debate and controversy. The major question is whether a quantitative-culture approach as a means of eliminating false-positive clinical diagnoses is superior to the clinical approach enhanced by principles learned from quantitative-culture studies. The recent IDSA/ATS guidelines for HCAP suggest that either approach is clinically valid.

Quantitative-Culture Approach

The essence of the quantitative-culture approach is to discriminate between colonization and true infection by determining the bacterial burden. The more distal in the respiratory tree the diagnostic sampling, the more specific the results and therefore the lower the threshold of growth necessary to diagnose pneumonia and exclude colonization. For example, a quantitative endotracheal aspirate yields proximate samples, and the diagnostic

threshold is 10^6 cfu/mL. The protected specimen brush method, in contrast, obtains distal samples and has a threshold of 10^3 cfu/mL. Conversely, sensitivity declines as more distal secretions are obtained, especially when they are collected blindly (i.e., by a technique other than bronchoscopy). Additional tests that may increase the diagnostic yield include Gram's stain, differential cell counts, staining for intracellular organisms, and detection of local protein levels elevated in response to infection.

Several studies have compared patient cohorts managed by the various quantitative-culture methods. Although these studies documented issues of relative sensitivity and specificity, outcomes were not significantly different for the various groups of patients. The IDSA/ATS guidelines have suggested that all these methods are appropriate and that the choice depends on availability and local expertise.

The Achilles heel of the quantitative approach is the effect of antibiotic therapy. With sensitive microorganisms, a single antibiotic dose can reduce colony counts below the diagnostic threshold. Recent changes in antibiotic therapy are the most significant. After ≥ 3 days of consistent antibiotic therapy for another infection before suspicion of pneumonia, the accuracy of diagnostic tests for pneumonia is unaffected. Conversely, colony counts above the diagnostic threshold during antibiotic therapy suggest that the current antibiotics are ineffective. Even the normal host response may be sufficient to reduce quantitative-culture counts below the diagnostic threshold by the time of sampling. In short, expertise in quantitative-culture techniques is critical, with a specimen obtained as soon as pneumonia is suspected and before antibiotic therapy is initiated or changed.

In a study comparing the quantitative with the clinical approach, use of bronchoscopic quantitative cultures resulted in significantly less antibiotic use at 14 days after study entry and lower rates of mortality and severity-adjusted mortality at 28 days. In addition, more alternative sites of infection were found in patients randomized to the quantitative-culture strategy. A critical aspect of this study was that antibiotic treatment was initiated only in patients whose gram-stained respiratory sample was positive or who displayed signs of hemodynamic instability. Fewer than half as many patients were treated for pneumonia in the bronchoscopy group, and only one-third as many microorganisms were cultured.

Clinical Approach

The lack of specificity of a clinical diagnosis of VAP has led to efforts to improve the diagnostic criteria. The Clinical Pulmonary Infection Score (CPIS) was developed by weighting of the various clinical criteria usually used for the diagnosis of VAP (Table 11-7). Use of the CPIS allows the selection of low-risk patients who may need only short-course antibiotic therapy or no treatment at all. Moreover, studies have demonstrated that

TABLE 11-7

CLINICAL PULMONARY INFECTION SCORE (CPIS)	
CRITERION	SCORE
Fever (°C)	
≥38.5 but ≤38.9	1
>39 or <36	2
Leukocytosis	
<4000 or >11,000/μL	1
Bands >50%	1 (additional)
Oxygenation (mmHg)	
PaO ₂ /Fio ₂ <250 and no ARDS	2
Chest radiograph	
Localized infiltrate	2
Patchy or diffuse infiltrate	1
Progression of infiltrate (no ARDS or CHF)	2
Tracheal aspirate	
Moderate or heavy growth	1
Same morphology on Gram's stain	1 (additional)
Maximal score ^a	12

^aThe progression of the infiltrate is unknown, and tracheal aspirate culture results are often unavailable at the time of the original diagnosis; thus, the maximal score is initially 8 to 10.

Note: ARDS, acute respiratory distress syndrome; CHF, congestive heart failure.

the absence of bacteria in gram-stained endotracheal aspirates makes pneumonia an unlikely cause of fever or pulmonary infiltrates. These findings, coupled with a heightened awareness of the alternative diagnoses possible in patients with suspected VAP, can prevent inappropriate treatment for this disease. Furthermore, data show that the absence of an MDR pathogen in tracheal aspirate cultures eliminates the need for MDR coverage when empirical antibiotic therapy is narrowed. Because the most likely explanations for the mortality benefit of bronchoscopic quantitative cultures are decreased antibiotic selection pressure (which reduces the risk of subsequent infection with MDR pathogens) and identification of alternative sources of infection, a clinical diagnostic approach that incorporates such principles may result in similar outcomes.

Rx Treatment: **VENTILATOR-ASSOCIATED PNEUMONIA**

Many studies have demonstrated higher mortality rates with inappropriate than with appropriate empirical antibiotic therapy. The key to appropriate antibiotic management of VAP is an appreciation of the patterns of resistance of the most likely pathogens in any given patient.

RESISTANCE If it were not for the risk of infection with MDR pathogens (see Table 11-1), VAP could be treated with the same antibiotics used for severe CAP.

However, antibiotic selection pressure leads to the frequent involvement of MDR pathogens by selecting either for drug-resistant isolates of common pathogens (MRSA and ESBL-positive Enterobacteriaceae) or for intrinsically resistant pathogens (*P. aeruginosa* and *Acinetobacter* spp.). Frequent use of β-lactam drugs, especially cephalosporins, appears to be the major risk factor for infection with MRSA and ESBL-positive strains.

P. aeruginosa has demonstrated the ability to develop resistance to all routinely used antibiotics. Unfortunately, even if initially sensitive, *P. aeruginosa* isolates have also shown a propensity to develop resistance during treatment. Occasionally, derepression of resistance genes may be the cause of the selection of resistant clones within the large bacterial inoculum associated with most pneumonias. *Acinetobacter* spp., *Stenotrophomonas maltophilia*, and *Burkholderia cepacia* are intrinsically resistant to many of the empirical antibiotic regimens listed in Table 11-8. VAP caused by these pathogens emerges during treatment of other infections, and resistance is always evident at initial diagnosis.

EMPIRICAL THERAPY Recommended options for empirical therapy are listed in Table 11-8. Treatment should be started after diagnostic specimens have been obtained. The major factor in the selection of agents is the presence of risk factors for MDR pathogens. Choices

TABLE 11-8

EMPIRICAL ANTIBIOTIC TREATMENT OF HEALTH CARE—ASSOCIATED PNEUMONIA

Patients without Risk Factors for MDR Pathogens

Ceftriaxone (2 g IV q24h) **or**
Moxifloxacin (400 mg IV q24h), ciprofloxacin (400 mg IV q8h), or levofloxacin (750 mg IV q24h) **or**
Ampicillin/sulbactam (3 g IV q6h) **or**
Ertapenem (1 g IV q24h)

Patients with Risk Factors for MDR Pathogens

1. A β-lactam:
Ceftazidime (2 g IV q8h) or cefepime (2 g IV q8–12h) **or**
Piperacillin/tazobactam (4.5 g IV q6h), imipenem (500 mg IV q6h or 1 g IV q8h), or meropenem (1 g IV q8h) **plus**
2. A second agent active against gram-negative bacterial pathogens:
Gentamicin or tobramycin (7 mg/kg IV q24h) **or**
amikacin (20 mg/kg IV q24h) **or**
Ciprofloxacin (400 mg IV q8h) or levofloxacin (750 mg IV q24h) **plus**
3. An agent active against gram-positive bacterial pathogens:
Linezolid (600 mg IV q12h) **or**
Vancomycin (15 mg/kg, up to 1 g IV, q12h)

Note: MDR, multidrug-resistant.

among the various options listed depend on local patterns of resistance and the patient's prior antibiotic exposure.

The majority of patients *without* risk factors for MDR infection can be treated with a single agent. The major difference from CAP is the markedly lower incidence of atypical pathogens in VAP; the exception is *Legionella* spp., which can be a nosocomial pathogen, especially when there are deficiencies in the treatment of a hospital's potable water supply.

The standard recommendation for patients *with* risk factors for MDR infection is for three antibiotics: two directed at *P. aeruginosa* and one at MRSA. The choice of a β -lactam agent provides the greatest variability in coverage, yet the use of the broadest-spectrum agent—a carbapenem—still represents inappropriate initial therapy in 10–15% of cases.

SPECIFIC TREATMENT After an etiologic diagnosis has been made, broad-spectrum empirical therapy can be modified to address the known pathogen specifically. For patients with MDR risk factors, antibiotic regimens can be reduced to a single agent in more than 50% of cases and to a two-drug combination in more than 20%. Only a minority of cases require a complete course with three drugs. A negative tracheal-aspirate culture or growth below the threshold for quantitative cultures, especially if the sample was obtained before any antibiotic change, strongly suggests that antibiotics should be discontinued. Identification of other confirmed or suspected sites of infection may require ongoing antibiotic therapy, but the spectrum of pathogens (and the corresponding antibiotic choices) may be different from those for VAP. If the CPIS decreases over the first 3 days, antibiotics should be stopped after 8 days. An 8-day course of therapy is just as effective as a 2-week course and is associated with less frequent emergence of antibiotic-resistant strains.

The major controversy regarding specific therapy for VAP concerns the need for ongoing combination treatment of *Pseudomonas* infection. No randomized, controlled trials have demonstrated a benefit of combination therapy with a β -lactam and an aminoglycoside, nor have subgroup analyses in other trials found a survival benefit with such a regimen. The unacceptably high rates of clinical failure and death for VAP caused by *P. aeruginosa* despite combination therapy (see "Failure to Improve" below) indicate that better regimens are needed—including, perhaps, aerosolized antibiotics.

VAP caused by MRSA is associated with a 40% clinical failure rate when treated with standard-dose vancomycin. One proposed solution is the use of high-dose individualized treatment, but the risk-to-benefit ratio of this approach is unknown. Linezolid appears to be more efficacious than the standard dose of vancomycin, especially in patients with renal insufficiency.

FAILURE TO IMPROVE Treatment failure is not uncommon in VAP, especially in that caused by MDR pathogens. In addition to the 40% failure rate for MRSA infection treated with vancomycin, VAP caused by *Pseudomonas* infection has a 50% failure rate, no matter what the regimen. The causes of clinical failure vary with the pathogen(s) and the antibiotic(s). Inappropriate therapy can usually be minimized by use of the recommended triple-drug regimen (Table 11-8). However, the emergence of β -lactam resistance during therapy is an important problem, especially in infection with *Pseudomonas* and *Enterobacter* spp. Recurrent VAP caused by the same pathogen is possible because the biofilm on ETs allows reintroduction of the microorganism. However, studies of VAP caused by *Pseudomonas* spp. show that approximately 50% of recurrent cases are caused by a new strain. Inadequate local levels of vancomycin are the likely cause of treatment failure in VAP caused by MRSA.

Treatment failure is very difficult to diagnose. Pneumonia caused by a new superinfection, the presence of extrapulmonary infection, and drug toxicity must be considered in the differential diagnosis of treatment failure. Whereas serial CPIS appears to track the clinical response accurately, repeat quantitative cultures may clarify the microbiologic response. A persistently elevated or increasing CPIS value by day 3 of therapy is likely to indicate failure. The most sensitive component of the CPIS is improvement in oxygenation.

COMPLICATIONS Apart from death, the major complication of VAP is prolongation of mechanical ventilation, with corresponding increases in length of stay in the ICU and in the hospital. In most studies, an additional week of mechanical ventilation because of VAP is common. The additional expense of this complication warrants costly and aggressive efforts at prevention.

In rare cases, some types of necrotizing pneumonia (e.g., that caused by *P. aeruginosa* infection) result in significant pulmonary hemorrhage. More commonly, necrotizing infections result in the long-term complications of bronchiectasis and parenchymal scarring, leading to recurrent pneumonias. The long-term complications of pneumonia are underappreciated. Pneumonia results in a catabolic state in a patient already nutritionally at risk. The muscle loss and general debilitation from an episode of VAP often require prolonged rehabilitation and, in the elderly, commonly result in an inability to return to independent function and the need for nursing home placement.

FOLLOW-UP Clinical improvement, if it occurs, is usually evident within 48 to 72 hours of the initiation of antimicrobial treatment. Because findings on chest radiography often worsen initially during treatment, they are less helpful than clinical criteria as an indicator of

clinical response in severe pneumonia. Although no hard and fast rules govern the frequency of follow-up chest radiography in seriously ill patients with pneumonia, assessment every few days in a responding patient seems appropriate. After the patient has improved substantially and has stabilized, follow-up radiographs may not be necessary for a few weeks.

Prognosis

VAP is associated with significant mortality. Crude mortality rates of 50–70% have been reported, but the real issue is attributable mortality. Many patients with VAP have underlying diseases that would result in death even if VAP did not occur. Attributable mortality exceeded 25% in one matched-cohort study. Patients who develop VAP are at least twice as likely to die as those who do not. Some of the variability in reported figures is clearly related to the type of patient and ICU studied. VAP in trauma patients is not associated with attributable mortality, possibly because many of the patients were otherwise healthy before being injured. However, the causative pathogen also plays a major role. Generally, MDR pathogens are associated with significantly greater attributable mortality than non-MDR pathogens. Pneumonia caused by some pathogens (e.g., *S. maltophilia*) is simply a marker for a patient whose immune system is so compromised that death is almost inevitable.

Prevention

(Table 11-6) Because of the significance of the ET as a risk factor for VAP, the most important preventive intervention is to avoid endotracheal intubation or at least to minimize its duration. Successful use of noninvasive ventilation via a nasal or full-face mask avoids many of the problems associated with ETs. Strategies that minimize the duration of ventilation have also been highly effective in preventing VAP.

Unfortunately, a tradeoff in risks is sometimes required. Aggressive attempts to extubate early may result in reintubation(s), which pose a risk of VAP. Heavy continuous sedation increases the risk, but self-extubation, because of too little sedation, is also a risk. The tradeoff is probably best illustrated by antibiotic therapy. Short-course antibiotic prophylaxis can decrease the risk of VAP in comatose patients requiring intubation, and data suggest that antibiotics decrease VAP rates in general. However, the major benefit appears to be a decrease in the incidence of early-onset VAP, which is usually caused by the less pathogenic non-MDR microorganisms. Conversely, prolonged courses of antibiotics consistently increase the risk of VAP caused by the more lethal MDR pathogens. Despite its virulence and associated mortality, VAP caused by

Pseudomonas spp. is rare among patients who have not recently received antibiotics.

Minimizing the amount of microaspiration around the ET cuff is also a strategy for avoidance of VAP. Simply elevating the head of the bed (at least 30° above horizontal but preferably 45°) decreases VAP rates. Specially modified ETs that allow removal of the secretions pooled above the cuff may also prevent VAP. The risk-to-benefit ratio of transporting the patient outside the ICU for diagnostic tests or procedures should be carefully considered because VAP rates are increased among transported patients.

Emphasis on the avoidance of agents that increase gastric pH and on oropharyngeal decontamination has been diminished by the equivocal and conflicting results of more recent clinical trials. The role in the pathogenesis of VAP that is played by the overgrowth of bacterial components of the bowel flora in the stomach has also been downplayed. MRSA and the nonfermenters *P. aeruginosa* and *Acinetobacter* spp. are not normally part of the bowel flora but reside primarily in the nose and on the skin, respectively. Therefore, an emphasis on controlling overgrowth of the bowel flora may be relevant only in certain populations, such as liver transplant recipients and patients who have undergone other major intraabdominal procedures or who have bowel obstruction.

In outbreaks of VAP caused by specific pathogens, the possibility of a breakdown in infection control measures (particularly contamination of reusable equipment) should be investigated. Even high rates of pathogens that are already common in a particular ICU may be a result of cross-infection. Education and reminders of the need for consistent infection control practices can minimize this risk.

HOSPITAL-ACQUIRED PNEUMONIA

Although significantly less well studied than VAP, HAP in nonintubated patients, both inside and outside the ICU, is similar to VAP. The main differences are in the higher frequency of non-MDR pathogens and the better underlying host immunity in nonintubated patients. The lower frequency of MDR pathogens allows monotherapy in a larger proportion of cases of HAP than of VAP.

The only pathogens that may be more common in the non-VAP population are anaerobes. The greater risk of macroaspiration by nonintubated patients and the lower oxygen tensions in the lower respiratory tract of these patients increase the likelihood of a role for anaerobes. As in the management of CAP, specific therapy targeting anaerobes probably is not indicated unless gross aspiration is a concern.

Diagnosis is even more difficult for HAP in nonintubated patients than for VAP. Lower respiratory tract samples appropriate for culture are considerably more difficult to obtain from nonintubated patients. Many of

114 the underlying diseases that predispose a patient to HAP are also associated with an inability to cough adequately. Because blood cultures are infrequently positive (<15% of cases), the majority of patients with HAP do not have culture data on which antibiotic modifications can be based. Therefore, de-escalation of therapy is less likely in patients with risk factors for MDR pathogens. Despite these difficulties, the better host defenses in non-ICU patients result in lower mortality rates than are documented for VAP. In addition, the risk of antibiotic failure is lower in those with HAP.

FURTHER READINGS

AARTS MA et al: Empiric antibiotic therapy for suspected ventilator-associated pneumonia: A systematic review and meta-analysis of randomized trials. *Crit Care Med* 36:108, 2008 [PMID:18007262]
AMERICAN THORACIC SOCIETY/INFECTIOUS DISEASES SOCIETY OF AMERICA: Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 171:388, 2005

CHASTRE J, FAGON JY: Ventilator-associated pneumonia. *Am J Respir Crit Care Med* 165:867, 2002
FAGON JY et al: Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. *Ann Intern Med* 132:621, 2000
FINE MJ et al: A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 336:243, 1997
KLOMPAS M: Does this patient have ventilator-associated pneumonia? *JAMA* 297:1583, 2007 [PMID:17426278]
LIM WS et al: Defining community acquired pneumonia severity on presentation to hospital: An international derivation and validation study. *Thorax* 58:377, 2003
MANDELL LA et al: Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 44(Suppl 2): S27, 2007 [PMID:17278083]
SINGH N et al: Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. *Am J Respir Crit Care Med* 162:505, 2000
VANDERKOOI OG et al: Predicting antimicrobial resistance in invasive pneumococcal infections. *Clin Infect Dis* 40:1288, 2005



CHAPTER 12

TUBERCULOSIS

Mario C. Raviglione ■ Richard J. O'Brien

■ Etiologic Agent	115	Pulmonary Tuberculosis	121
■ Epidemiology	116	Extrapulmonary Tuberculosis	122
From Exposure to Infection	117	HIV-Associated Tuberculosis	126
From Infection to Disease	118	■ Diagnosis of Tuberculosis	127
■ Natural History of Disease	118	Acid-Fast Bacillimicroscopy	127
■ Pathogenesis and Immunity	119	Mycobacterial Culture	127
Infection and Macrophage Invasion	119	Nucleic Acid Amplification	127
Virulence of Tubercle Bacilli	119	Drug Susceptibility Testing	127
Innate Resistance to Infection	119	Radiographic Procedures	128
The Host Response	119	Additional Diagnostic Procedures	128
Granuloma Formation	119	Serologic and Other Diagnostic Tests	
The Macrophage-Activating Response	120	for Active Tuberculosis	128
The Delayed-Type Hypersensitivity Reaction	120	Diagnosis of Latent <i>M. Tuberculosis</i> Infection	128
Role of Macrophages and Monocytes	120	■ Prevention	134
Role of T Lymphocytes	120	Bacille Calmette-Guérin Vaccination	135
Mycobacterial Lipids and Proteins	120	■ Principles of Tuberculosis Control	136
Skin Test Reactivity	121	■ Further Readings	138
■ Clinical Manifestations	121		

Tuberculosis, one of the oldest diseases known to affect humans, is a major cause of death worldwide. This disease, which is caused by bacteria of the *Mycobacterium tuberculosis* complex, usually affects the lungs, although other organs are involved in up to one-third of cases. If properly treated, tuberculosis caused by drug-susceptible strains is curable in virtually all cases. If untreated, the disease may be fatal within 5 years in 50–65% of cases. Transmission usually takes place through the airborne spread of droplet nuclei produced by patients with infectious pulmonary tuberculosis.

ETIOLOGIC AGENT

Mycobacteria belong to the family Mycobacteriaceae and the order Actinomycetales. Of the pathogenic species belonging to the *M. tuberculosis* complex, the most common and important agent of human disease is *M. tuberculosis*. The complex includes *M. bovis* (the bovine tubercle bacillus—characteristically resistant to pyrazinamide, once an important cause of tuberculosis

transmitted by unpasteurized milk, and currently the cause of a small percentage of cases worldwide), *M. caprae* (related to *M. bovis*), *M. africanum* (isolated from cases in West, Central, and East Africa), *M. microti* (the “vole” bacillus, a less virulent and rarely encountered organism), *M. pinnipedii* (a bacillus infecting seals and sea lions in the southern hemisphere and recently isolated from humans), and *M. canettii* (a rare isolate from East African cases that produces unusual smooth colonies on solid media and is considered closely related to a supposed progenitor type).

M. tuberculosis is a rod-shaped, non-spore-forming, thin aerobic bacterium measuring 0.5 μm by 3 μm . Mycobacteria, including *M. tuberculosis*, are often neutral on Gram’s staining. However, after they have been stained, the bacilli cannot be decolorized by acid alcohol; this characteristic justifies their classification as acid-fast bacilli (AFB; Fig. 12-1). Acid fastness is mainly attributable to the organisms’ high content of mycolic acids, long-chain cross-linked fatty acids, and other cell-wall lipids. Microorganisms other than mycobacteria

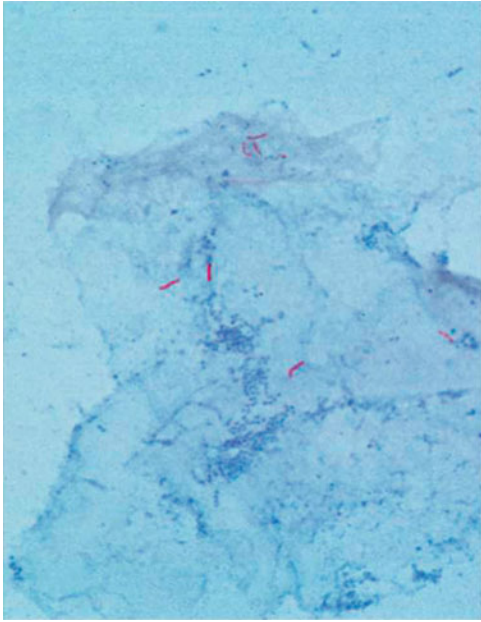


FIGURE 12-1
Acid-fast bacillus smear showing *M. tuberculosis* bacilli.
(Courtesy of the CDC, Atlanta.)

that display some acid fastness include species of *Nocardia* and *Rhodococcus*, *Legionella micdadei*, and the protozoa *Isospora* and *Cryptosporidium*. In the mycobacterial cell wall, lipids (e.g., mycolic acids) are linked to underlying arabinogalactan and peptidoglycan. This structure confers very low permeability of the cell wall, thus reducing

the effectiveness of most antibiotics. Another molecule in the mycobacterial cell wall, lipoarabinomannan, is involved in the pathogen–host interaction and facilitates the survival of *M. tuberculosis* within macrophages. The complete genome sequence of *M. tuberculosis* comprises 4043 genes encoding 3993 proteins and 50 genes encoding RNAs; its high guanine–plus–cytosine content (65.6%) is indicative of an aerobic lifestyle. A large proportion of genes are devoted to the production of enzymes involved in cell wall metabolism.

EPIDEMIOLOGY



More than 5 million new cases of tuberculosis (all forms, both pulmonary and extrapulmonary) were reported to the World Health Organization (WHO) in 2005; >90% of cases were reported from developing countries. However, because of insufficient case detection and incomplete notification, reported cases represent only ~60% of total estimated cases. The WHO estimated that 8.8 million new cases of tuberculosis occurred worldwide in 2005, with 95% of them in developing countries of Asia (4.9 million), Africa (2.6 million), the Middle East (0.6 million), and Latin America (0.4 million). It is further estimated that 1.6 million deaths from tuberculosis occurred in 2005, 95% of them in developing countries. Estimates of tuberculosis incidence rates (per 100,000 population) and numbers of tuberculosis-related deaths in 2005 are depicted in Figs. 12-2 and 12-3, respectively.

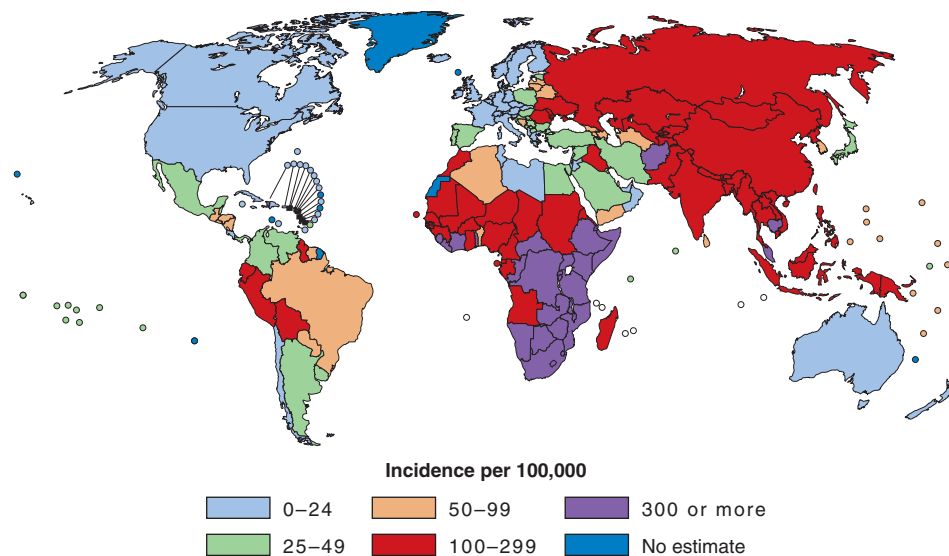
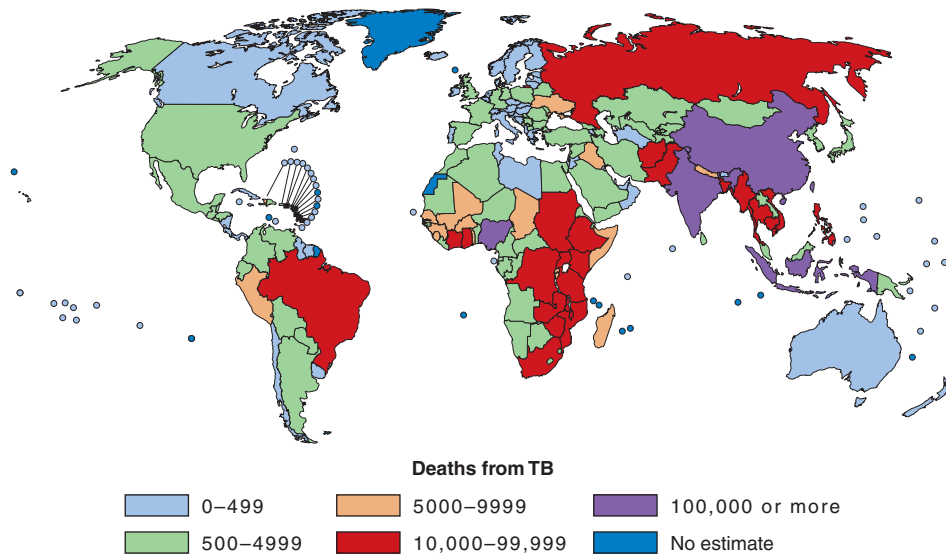


FIGURE 12-2
Estimated tuberculosis incidence rates (per 100,000 population) in 2005. The designations employed and the presentation of material on this map do not imply the expression of any opinion whatsoever on the part of the WHO concerning the legal status of any country, territory, city, or area

or of its authorities or concerning the delimitation of its frontiers or boundaries. *White lines* on maps represent approximate border lines for which there may not yet be full agreement. (Courtesy of the Stop TB Department, WHO, with permission.)

**FIGURE 12-3**

Estimated numbers of tuberculosis-related deaths in 2005. (See also disclaimer in Fig. 12-2. Courtesy of the Stop TB Department, WHO, with permission.)

During the late 1980s and early 1990s, numbers of reported cases of tuberculosis increased in industrialized countries. These increases were related largely to immigration from countries with a high prevalence of tuberculosis; infection with HIV; social problems, such as increased urban poverty, homelessness, and drug abuse; and dismantling of tuberculosis services. During the past few years, numbers of reported cases have begun to decline again or stabilized in industrialized nations. In the United States, with the implementation of stronger control programs, the decrease resumed in 1993. In 2005, 14,097 cases of tuberculosis (4.8 cases per 100,000 population) were reported to the Centers for Disease Control and Prevention (CDC).

In the United States, tuberculosis is uncommon among young adults of European descent, who have only rarely been exposed to *M. tuberculosis* infection during recent decades. In contrast, because of a high risk in the past, the prevalence of *M. tuberculosis* infection is relatively high among elderly white people, who remain at increased risk of developing active tuberculosis. Tuberculosis in the United States is also a disease of young adult members of the HIV-infected, immigrant, and disadvantaged or marginalized populations. Similarly, in Europe, tuberculosis has reemerged as an important public health problem, mainly as a result of cases among immigrants from high-prevalence countries.

Recent data on trends indicate that in 2005, the incidence of tuberculosis was stable or decreasing in most regions; the result is a small decline globally from figures in previous years. This global reduction is largely attributable to an apparent peaking in sub-Saharan Africa, where incidence had risen steeply since the 1980s as a result of

the HIV epidemic and the paucity of health services. In eastern Europe, the incidence increased during the 1990s because of deterioration in socioeconomic conditions and the health care infrastructure; however, after peaking in 2001, the incidence has recently stabilized.

FROM EXPOSURE TO INFECTION

M. tuberculosis is most commonly transmitted from a person with infectious pulmonary tuberculosis to others by droplet nuclei, which are aerosolized by coughing, sneezing, or speaking. The tiny droplets dry rapidly; the smallest (<5–10 μm in diameter) may remain suspended in the air for several hours and may reach the terminal air passages when inhaled. There may be as many as 3000 infectious nuclei per cough. Other routes of transmission of tubercle bacilli (e.g., through the skin or the placenta) are uncommon and of no epidemiologic significance.

The probability of contact with a person who has an infectious form of tuberculosis, the intimacy and duration of that contact, the degree of infectiousness of the case, and the shared environment in which the contact takes place are all important determinants of the likelihood of transmission. Several studies of close-contact situations have clearly demonstrated that tuberculosis patients whose sputum contains AFB visible by microscopy are the most likely to transmit the infection. The most infectious patients have cavitary pulmonary disease or, much less commonly, laryngeal tuberculosis and produce sputum containing as many as 10^5 – 10^7 AFB/mL. Patients with sputum smear-negative/culture-positive tuberculosis are

118 less infectious, and those with culture-negative pulmonary disease and extrapulmonary tuberculosis are essentially noninfectious. Because persons with both HIV infection and tuberculosis are less likely to have cavitations, they may be less infectious than persons without HIV co-infection. Crowding in poorly ventilated rooms is one of the most important factors in the transmission of tubercle bacilli because it increases the intensity of contact with a case.

In short, the risk of acquiring *M. tuberculosis* infection is determined mainly by exogenous factors. Because of delays in seeking care and in making a diagnosis, it is estimated that in high-prevalence settings, up to 20 contacts may be infected by each AFB-positive case before the index case is found to have tuberculosis.

FROM INFECTION TO DISEASE

Unlike the risk of acquiring infection with *M. tuberculosis*, the risk of developing disease after being infected depends largely on endogenous factors, such as the individual's innate immunologic and nonimmunologic defenses and level of function of cell-mediated immunity (CMI). Clinical illness directly after infection is classified as *primary tuberculosis* and is common among children up to 4 years of age and among immunocompromised persons. Although primary tuberculosis may be severe and disseminated, it is not generally associated with high-level transmissibility. When infection is acquired later in life, the chance is greater that the mature immune system will contain it at least temporarily. The majority of infected individuals who ultimately develop tuberculosis do so within the first year or two after infection. Dormant bacilli, however, may persist for years before reactivating to produce *secondary* (or *postprimary*) *tuberculosis*, which, because of frequent cavitation, is more often infectious than is primary disease. Overall, it is estimated that up to 10% of infected persons will eventually develop active tuberculosis in their lifetime. The risk is much higher among HIV-infected persons. Reinfection of a previously infected individual, which is common in areas with high rates of tuberculosis transmission, may also favor the development of disease. At the height of the tuberculosis resurgence in the United States in the early 1990s, molecular typing and comparison of strains of *M. tuberculosis* suggested that up to one-third of cases of active tuberculosis in some inner-city communities were caused by recent transmission rather than to reactivation of latent infection.

Age is an important determinant of the risk of disease after infection. Among infected persons, the incidence of tuberculosis is highest during late adolescence and early adulthood; the reasons are unclear. The incidence among women peaks at 25–34 years of age. In this age group, rates among women may be higher than those among

TABLE 12-1

RISK FACTORS FOR ACTIVE TUBERCULOSIS AMONG PERSONS WHO HAVE BEEN INFECTED WITH TUBERCLE BACILLI

FACTOR	RELATIVE RISK/ODDS ^a
Recent infection (<1 year)	12.9
Fibrotic lesions (spontaneously healed)	2–20
Comorbidity	
HIV infection	100
Silicosis	30
Chronic renal failure or hemodialysis	10–25
Diabetes	2–4
IV drug use	10–30
Immunosuppressive treatment	10
Gastrectomy	2–5
Jejunioileal bypass	30–60
Posttransplantation period (renal, cardiac)	20–70
Malnutrition and severe underweight	2

^aOld infection = 1.

men; at older ages, the opposite is true. The risk may increase in elderly individuals, possibly because of waning immunity and comorbidity.

A variety of diseases and conditions favor the development of active tuberculosis (Table 12-1). The most potent risk factor for tuberculosis among infected individuals is clearly HIV co-infection, which suppresses cellular immunity. The risk that latent *M. tuberculosis* infection will proceed to active disease is directly related to the patient's degree of immunosuppression. In a study of HIV-infected, tuberculin skin test (TST)-positive persons, this risk varied from 2.6 to 13.3 cases per 100 person-years and increased as the CD4+ T cell count decreased.

NATURAL HISTORY OF DISEASE

Studies conducted in various countries before the advent of chemotherapy showed that untreated tuberculosis is often fatal. About one-third of patients died within 1 year after diagnosis, and one-half died within 5 years. The 5-year mortality rate among sputum smear-positive cases was 65%. Of the survivors at 5 years, ~60% had undergone spontaneous remission; the remainders were still excreting tubercle bacilli.

With effective, timely, and proper chemotherapy, patients have a very high chance of being cured. However, improper use of antituberculosis drugs, while reducing mortality rates, may also result in large numbers of chronic infectious cases, often with drug-resistant bacilli.

INFECTION AND MACROPHAGE INVASION

The interaction of *M. tuberculosis* with the human host begins when droplet nuclei containing microorganisms from infectious patients are inhaled. Although the majority of inhaled bacilli are trapped in the upper airways and expelled by ciliated mucosal cells, a fraction (usually <10%) reach the alveoli. There, alveolar macrophages that have not yet been activated phagocytize the bacilli. Invasion of macrophages by mycobacteria results largely from binding of the bacterial cell wall with a variety of macrophage cell-surface molecules, including complement receptors, mannose receptor, immunoglobulin G Fc γ receptor, and type A scavenger receptors. Phagocytosis is enhanced by complement activation, leading to opsonization of bacilli with C3 activation products such as C3b. After a phagosome forms, the survival of *M. tuberculosis* within it seems to depend on reduced acidification because of lack of accumulation of vesicular proton-adenosine triphosphatase. A complex series of events is probably generated by the bacterial cell-wall glycolipid lipoarabinomannan (LAM). LAM inhibits the intracellular increase of Ca²⁺. Thus, the Ca²⁺/calmodulin pathway (leading to phagosome-lysosome fusion) is impaired, and the bacilli may survive within the phagosomes. If the bacilli are successful in arresting phagosome maturation, then replication begins, and the macrophage eventually ruptures and releases its bacillary contents.

VIRULENCE OF TUBERCLE BACILLI

Several genes thought to confer virulence to *M. tuberculosis* have been identified. The *katG* gene encodes for catalase/oxidase enzymes that protect against oxidative stress; *rpoV* is the main sigma factor initiating transcription of several genes. Defects in these two genes result in loss of virulence. The *erp* gene, encoding a protein required for multiplication, also contributes to virulence. Strains of the Beijing/W genotype family have been identified in outbreak conditions in a variety of settings worldwide and have been associated with higher mortality rates and occasionally with multidrug resistance.

INNATE RESISTANCE TO INFECTION

Several observations suggest that genetic factors play a key role in innate nonimmune resistance to infection with *M. tuberculosis* and the development of disease. The existence of this resistance, which is polygenic in nature, is suggested by the differing degrees of susceptibility to tuberculosis in different populations. In mice, a gene called *Nramp1* (natural resistance-associated macrophage protein 1) plays a regulatory role in resistance/susceptibility to mycobacteria. The human homologue NRAMP1,

which maps to chromosome 2q, may play a role in determining susceptibility to tuberculosis, as suggested by a study among West Africans. Polymorphisms in multiple genes, such as those encoding for histocompatibility leukocyte antigen (HLA), interferon γ (IFN- γ), T cell growth factor β (TGF- β), interleukin (IL) 10, mannose-binding protein, IFN- γ receptor, Toll-like receptor (TLR) 2, vitamin D receptor, and IL-1, have been associated with susceptibility to tuberculosis.

THE HOST RESPONSE

In the initial stage of host-bacterium interaction, either fusion between phagosomes and lysosomes occurs, preventing bacillary survival, or the bacilli begin to multiply, ultimately killing the macrophage. A variety of chemoattractants that are released after cell lysis (e.g., complement components, bacterial molecules, and cytokines) recruit additional immature monocyte-derived macrophages, including dendritic cells, which migrate to the draining lymph nodes and present mycobacterial antigens to T lymphocytes. At this point, the development of CMI and humoral immunity begins. These initial stages of infection are usually asymptomatic.

About 2–4 weeks after infection, two host responses to *M. tuberculosis* develop: a macrophage-activating CMI response and a tissue-damaging response. The *macrophage-activating response* is a T cell-mediated phenomenon resulting in the activation of macrophages that are capable of killing and digesting tubercle bacilli. The *tissue-damaging response* is the result of a delayed-type hypersensitivity (DTH) reaction to various bacillary antigens; it destroys unactivated macrophages that contain multiplying bacilli but also causes caseous necrosis of the involved tissues (see later). Although both of these responses can inhibit mycobacterial growth, it is the balance between the two that determines the form of tuberculosis that will develop subsequently.

GRANULOMA FORMATION

With the development of specific immunity and the accumulation of large numbers of activated macrophages at the site of the primary lesion, granulomatous lesions (tubercles) are formed. These lesions consist of accumulations of lymphocytes and activated macrophages that evolve toward epithelioid and giant cell morphologies. Initially, the tissue-damaging response can limit mycobacterial growth within macrophages. As stated above, this response, mediated by various bacterial products, not only destroys macrophages but also produces early solid necrosis in the center of the tubercle. Although *M. tuberculosis* can survive, its growth is inhibited within this necrotic environment by low oxygen tension and low pH. At this point, some lesions may heal by fibrosis with subsequent calcification, but inflammation and necrosis occur in other lesions.

CMI is critical at this early stage. In the majority of infected individuals, local macrophages are activated when bacillary antigens processed by macrophages stimulate T lymphocytes to release a variety of lymphokines. These activated macrophages aggregate around the lesion's center and effectively neutralize tubercle bacilli without causing further tissue destruction. In the central part of the lesion, the necrotic material resembles soft cheese (*caseous necrosis*)—a phenomenon that may also be observed in other conditions, such as neoplasms. Even when healing takes place, viable bacilli may remain dormant within macrophages or in the necrotic material for many years. These “healed” lesions in the lung parenchyma and hilar lymph nodes may later undergo calcification.

THE DELAYED-TYPE HYPERSENSITIVITY REACTION

In a minority of cases, the macrophage-activating response is weak, and mycobacterial growth can be inhibited only by intensified DTH reactions, which lead to lung tissue destruction. The lesion tends to enlarge further, and the surrounding tissue is progressively damaged. At the center of the lesion, the caseous material liquefies. Bronchial walls as well as blood vessels are invaded and destroyed, and cavities are formed. The liquefied caseous material, containing large numbers of bacilli, is drained through bronchi. Within the cavity, tubercle bacilli multiply, spill into the airways, and are discharged into the environment through expiratory maneuvers such as coughing and talking.

In the early stages of infection, bacilli are usually transported by macrophages to regional lymph nodes, from which they gain access to the bloodstream and disseminate widely throughout the body. The resulting lesions may undergo the same evolution as those in the lungs, although most tend to heal. In young children with poor natural immunity, hematogenous dissemination may result in fatal miliary tuberculosis or tuberculous meningitis.

ROLE OF MACROPHAGES AND MONOCYTES

Although CMI confers partial protection against *M. tuberculosis*, humoral immunity plays a less well-defined role in protection (although evidence is accumulating on the existence of LAM antibodies, which may prevent dissemination of infection in children). In the case of CMI, two types of cells are essential: macrophages, which directly phagocytize tubercle bacilli, and T cells (mainly CD4+ T lymphocytes), which induce protection through the production of cytokines, especially IFN- γ .

After infection with *M. tuberculosis*, alveolar macrophages secrete various cytokines responsible for a number of

events (e.g., the formation of granulomas) as well as systemic effects (e.g., fever and weight loss). Monocytes and macrophages attracted to the site are key components of the immune response. Their primary mechanism is probably related to production of nitric oxide, which has antimycobacterial activity and increases synthesis of cytokines such as tumor necrosis factor α (TNF α) and IL-1, which in turn regulate release of reactive nitrogen intermediates. In addition, macrophages can undergo apoptosis—a defensive mechanism to prevent release of cytokines and bacilli via their sequestration in the apoptotic cell.

ROLE OF T LYMPHOCYTES

Alveolar macrophages, monocytes, and dendritic cells are also critical in processing and presenting antigens to T lymphocytes, primarily CD4+ and CD8+ T cells; the result is the activation and proliferation of CD4+ T lymphocytes, which are crucial to the host's defense against *M. tuberculosis*. Qualitative and quantitative defects of CD4+ T cells explain the inability of HIV-infected individuals to contain mycobacterial proliferation. Activated CD4+ T lymphocytes can differentiate into cytokine-producing T_H1 or T_H2 cells. T_H1 cells produce IFN- γ —an activator of macrophages and monocytes—and IL-2. T_H2 cells produce IL-4, IL-5, IL-10, and IL-13 and may promote humoral immunity. The interplay of these various cytokines and their cross-regulation determine the host's response. The role of cytokines in promoting intracellular killing of mycobacteria, however, has not been entirely elucidated. IFN- γ may induce the generation of reactive nitrogen intermediates and regulate genes involved in bactericidal effects. TNF α also seems to be important.

Observations made originally in transgenic knockout mice and more recently in humans suggest that other T cell subsets, especially CD8+ T cells, may play an important role. CD8+ T cells have been associated with protective activities via cytotoxic responses and lysis of infected cells as well as with production of IFN- γ and TNF α . Finally, natural killer cells act as co-regulators of CD8+ T cell lytic activities, and $\gamma\delta$ T cells are increasingly thought to be involved in protective responses in humans.

MYCOBACTERIAL LIPIDS AND PROTEINS

Lipids have been involved in mycobacterial recognition by the innate immune system, and lipoproteins (e.g., 19-kDa lipoprotein) have been proven to trigger potent signals through TLRs present in blood dendritic cells. *M. tuberculosis* possesses various protein antigens. Some are present in the cytoplasm and cell wall; others are secreted. That the latter are more important in eliciting a

T lymphocyte response is suggested by experiments documenting the appearance of protective immunity in animals after immunization with live, protein-secreting mycobacteria. Among the antigens that may play a protective role are the 30-kDa (or 85B) and ESAT-6 antigens. Protective immunity is probably the result of reactivity to many different mycobacterial antigens.

SKIN TEST REACTIVITY

Coincident with the appearance of immunity, DTH to *M. tuberculosis* develops. This reactivity is the basis of the TST, which is used primarily for the detection of *M. tuberculosis* infection in persons without symptoms. The cellular mechanisms responsible for TST reactivity are related mainly to previously sensitized CD4+ T lymphocytes, which are attracted to the skin-test site. There, they proliferate and produce cytokines.

Although DTH is associated with protective immunity (with TST-positive persons being less susceptible to a new *M. tuberculosis* infection than TST-negative persons), it by no means guarantees protection against reactivation. In fact, cases of active tuberculosis are often accompanied by strongly positive skin-test reactions. There is also evidence of reinfection with a new strain of *M. tuberculosis* in patients previously treated for active disease. This evidence underscores the fact that previous latent or active tuberculosis may not confer fully protective immunity.

CLINICAL MANIFESTATIONS

Tuberculosis is classified as pulmonary, extrapulmonary, or both. Before the advent of HIV infection, ~80% of all new cases of tuberculosis were limited to the lungs. However, up to two-thirds of HIV-infected patients with tuberculosis may have both, pulmonary and extrapulmonary disease or extrapulmonary disease alone.

PULMONARY TUBERCULOSIS

Pulmonary tuberculosis can be categorized as primary or postprimary (secondary).

Primary Disease

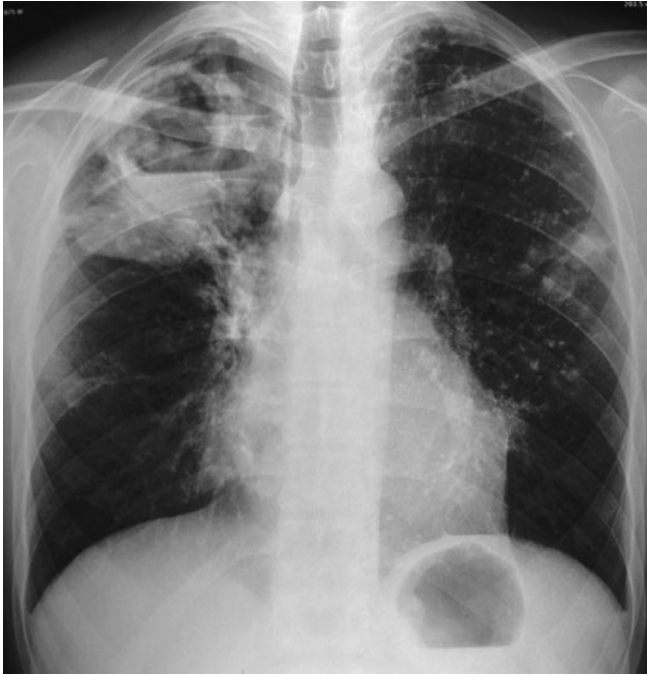
Primary pulmonary tuberculosis occurs soon after the initial infection with tubercle bacilli. In areas of high tuberculosis transmission, this form of disease is often seen in children. Because most inspired air is distributed to the middle and lower lung zones, these areas of the lungs are most commonly involved in primary tuberculosis. The lesion forming after infection is usually peripheral and accompanied in more than half of cases by hilar or paratracheal lymphadenopathy, which may not be detectable on chest radiography. In the majority

of cases, the lesion heals spontaneously and may later be evident as a small calcified nodule (*Ghon lesion*).

In children and in persons with impaired immunity (e.g., those with malnutrition or HIV infection), primary pulmonary tuberculosis may progress rapidly to clinical illness. The initial lesion increases in size and can evolve in different ways. Pleural effusion, which is found in up to two-thirds of cases, results from the penetration of bacilli into the pleural space from an adjacent subpleural focus. In severe cases, the primary site rapidly enlarges, its central portion undergoes necrosis, and cavitation develops (*progressive primary tuberculosis*). Tuberculosis in young children is almost invariably accompanied by hilar or mediastinal lymphadenopathy caused by the spread of bacilli from the lung parenchyma through lymphatic vessels. Enlarged lymph nodes may compress bronchi, causing obstruction and subsequent segmental or lobar collapse. Partial obstruction may cause obstructive emphysema, and bronchiectasis may also develop. Hematogenous dissemination, which is common and often asymptomatic, may result in the most severe manifestations of primary *M. tuberculosis* infection. Bacilli reach the bloodstream from the pulmonary lesion or the lymph nodes and disseminate into various organs, where they may produce granulomatous lesions. Although healing frequently takes place, immunocompromised persons (e.g., patients with HIV infection) may develop miliary tuberculosis, tuberculous meningitis, or both.

Postprimary Disease

Also called *adult-type, reactivation, or secondary tuberculosis*, postprimary disease results from endogenous reactivation of latent infection and is usually localized to the apical and posterior segments of the upper lobes, where the substantially higher mean oxygen tension (compared with that in the lower zones) favors mycobacterial growth. In addition, the superior segments of the lower lobes are frequently involved. The extent of lung parenchymal involvement varies greatly, from small infiltrates to extensive cavitary disease. With cavity formation, liquefied necrotic contents are ultimately discharged into the airways, resulting in satellite lesions within the lungs that may in turn undergo cavitation (**Figs. 12-4 and 12-5**). Massive involvement of pulmonary segments or lobes, with coalescence of lesions, produces tuberculous pneumonia. Although up to one-third of untreated patients reportedly succumb to severe pulmonary tuberculosis within a few weeks or months after onset (the classical “galloping consumption” of the past), others undergo a process of spontaneous remission or proceed along a chronic, progressively debilitating course (“consumption”). Under these circumstances, some pulmonary lesions become fibrotic and may later calcify, but cavities persist in other parts of the lungs. Individuals with such chronic disease continue to discharge tubercle

**FIGURE 12-4**

Chest radiograph showing a right upper-lobe infiltrate and a cavity with an air-fluid level in a patient with active tuberculosis. (Courtesy of Dr. Andrea Gori, Department of Infectious Diseases, S. Paolo University Hospital, Milan, Italy, with permission.)

bacilli into the environment. Most patients respond to treatment, with defervescence, decreasing cough, weight gain, and a general improvement in well-being within several weeks.

Early in the course of disease, symptoms and signs are often nonspecific and insidious, consisting mainly of

**FIGURE 12-5**

CT scan showing a large cavity in the right lung of a patient with active tuberculosis. (Courtesy of Dr. Enrico Girardi, National Institute for Infectious Diseases, Spallanzani Hospital, Rome, Italy, with permission.)

fever and night sweats, weight loss, anorexia, general malaise, and weakness. However, in the majority of cases, cough eventually develops—often initially nonproductive and subsequently accompanied by the production of purulent sputum, sometimes with blood streaking. Massive hemoptysis may ensue as a consequence of the erosion of a blood vessel in the wall of a cavity. Hemoptysis, however, may also result from rupture of a dilated vessel in a cavity (*Rasmussen's aneurysm*) or from aspergilloma formation in an old cavity. Pleuritic chest pain sometimes develops in patients with subpleural parenchymal lesions. Extensive disease may produce dyspnea and, in rare instances, adult respiratory distress syndrome (ARDS).

Physical findings are of limited use in pulmonary tuberculosis. Many patients have no abnormalities detectable by chest examination, but others have detectable rales in the involved areas during inspiration, especially after coughing. Occasionally, rhonchi caused by partial bronchial obstruction and classic amphoric breath sounds in areas with large cavities may be heard. Systemic features include fever (often low-grade and intermittent) in up to 80% of cases and wasting. Absence of fever, however, does not exclude tuberculosis. In some cases, pallor and finger clubbing develop. The most common hematologic findings are mild anemia and leukocytosis. Hyponatremia caused by the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) has also been reported.

EXTRAPULMONARY TUBERCULOSIS

In order of frequency, the extrapulmonary sites most commonly involved in tuberculosis are the lymph nodes, pleura, genitourinary tract, bones and joints, meninges, peritoneum, and pericardium. However, virtually all organ systems may be affected. As a result of hematogenous dissemination in HIV-infected individuals, extrapulmonary tuberculosis is seen more commonly today than in the past.

Lymph-Node Tuberculosis (Tuberculous Lymphadenitis)

The most common presentation of extrapulmonary tuberculosis (>40% of cases in the United States in recent series), lymph-node disease is particularly frequent among HIV-infected patients. In the United States, children and women (particularly non-whites) also seem to be especially susceptible. Once caused mainly by *M. bovis*, tuberculous lymphadenitis is today largely caused by *M. tuberculosis* infection. Lymph-node tuberculosis presents as painless swelling of the lymph nodes, most commonly at posterior cervical and supraclavicular sites (a condition historically referred to as *scrofula*). Lymph nodes are usually discrete and nontender in early disease but may be inflamed and have a fistulous tract draining caseous material. Associated pulmonary disease is seen in

>40% of cases. Systemic symptoms are usually limited to HIV-infected patients. The diagnosis is established only by fine-needle aspiration or surgical biopsy. AFB are seen in up to 50% of cases, cultures are positive in 70–80%, and histologic examination shows granulomatous lesions. Among HIV-infected patients, granulomas usually are not seen. The differential diagnosis includes a variety of infectious conditions; neoplastic diseases such as lymphomas or metastatic carcinomas; and rare disorders such as Kikuchi disease (necrotizing histiocytic lymphadenitis), Kimura's disease, and Castleman's disease.

Pleural Tuberculosis

Involvement of the pleura, which accounts for ~20% of extrapulmonary cases in the United States, is common in primary tuberculosis and may result from either contiguous spread of parenchymal inflammation or, as in many cases of pleurisy accompanying postprimary disease, actual penetration by tubercle bacilli into the pleural space. Depending on the extent of reactivity, the effusion may be small, remain unnoticed, and resolve spontaneously or may be sufficiently large to cause symptoms such as fever, pleuritic chest pain, and dyspnea. Physical findings are those of pleural effusion: dullness to percussion and absence of breath sounds. A chest radiograph reveals the effusion and, in up to one-third of cases, also shows a parenchymal lesion. Thoracentesis is required to ascertain the nature of the effusion and to differentiate it from manifestations of other etiologies. The fluid is straw colored and at times hemorrhagic; it is an exudate with a protein concentration >50% of that in serum (usually ~4–6 g/dL), a normal to low glucose concentration, a pH of ~7.3 (occasionally <7.2), and detectable white blood cells (usually 500–6000/μL). Neutrophils may predominate in the early stage, and mononuclear cells are the typical finding later. Mesothelial cells are generally rare or absent. AFB are seen on direct smear in only 10–25% of cases, but cultures may be positive for *M. tuberculosis* in 25–75% of cases; positive cultures are more common among postprimary cases. Determination of the pleural concentration of adenosine deaminase (ADA) is a useful screening test: tuberculosis is virtually excluded if the value is very low. Needle biopsy of the pleura is often required for diagnosis and reveals granulomas or yields a positive culture in up to 80% of cases. This form of pleural tuberculosis responds well to chemotherapy and may resolve spontaneously. The usefulness of glucocorticoid administration is doubtful.

Tuberculous empyema is a less common complication of pulmonary tuberculosis. It is usually the result of the rupture of a cavity, with spillage of a large number of organisms into the pleural space. This process may create a bronchopleural fistula with evident air in the pleural space. A chest radiograph shows hydropneumothorax

with an air-fluid level. The pleural fluid is purulent and thick and contains large numbers of lymphocytes. Acid-fast smears and mycobacterial cultures are often positive. Surgical drainage is usually required as an adjunct to chemotherapy. Tuberculous empyema may result in severe pleural fibrosis and restrictive lung disease. Removal of the thickened visceral pleura (decortication) is occasionally necessary to improve lung function.

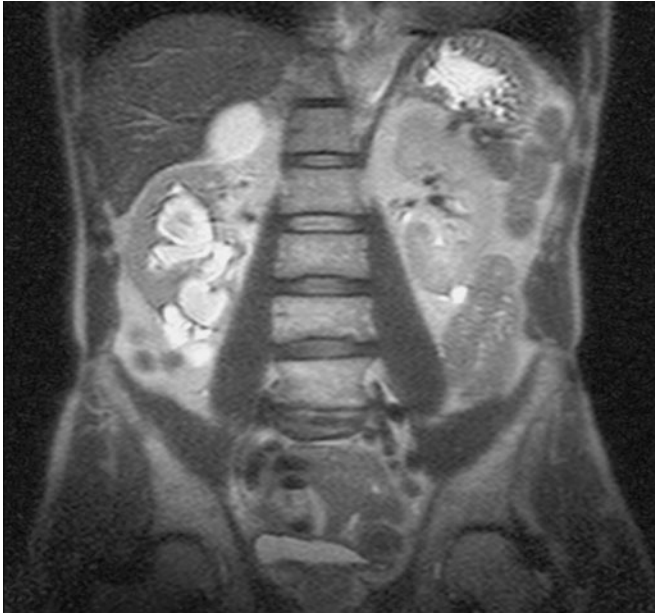
Tuberculosis of the Upper Airways

Nearly always a complication of advanced cavitary pulmonary tuberculosis, tuberculosis of the upper airways may involve the larynx, pharynx, and epiglottis. Symptoms include hoarseness, dysphonia, and dysphagia in addition to chronic productive cough. Findings depend on the site of involvement, and ulcerations may be seen on laryngoscopy. Acid-fast smear of the sputum is often positive, but biopsy may be necessary in some cases to establish the diagnosis. Carcinoma of the larynx may have similar features but is usually painless.

Genitourinary Tuberculosis

Genitourinary tuberculosis, which accounts for ~15% of all extrapulmonary cases in the United States, may involve any portion of the genitourinary tract. Local symptoms predominate, and up to one-third of patients may concomitantly have pulmonary disease. Urinary frequency, dysuria, nocturia, hematuria, and flank or abdominal pain are common presentations. However, patients may be asymptomatic and the disease discovered only after severe destructive lesions of the kidneys have developed. Urinalysis gives abnormal results in 90% of cases, revealing pyuria and hematuria. The documentation of culture-negative pyuria in acidic urine raises the suspicion of tuberculosis. IV pyelography, abdominal CT, or MRI (**Fig. 12-6**) may show deformities and obstructions, and calcifications and ureteral strictures are suggestive findings. Culture of three morning urine specimens yields a definitive diagnosis in nearly 90% of cases. Severe ureteral strictures may lead to hydronephrosis and renal damage.

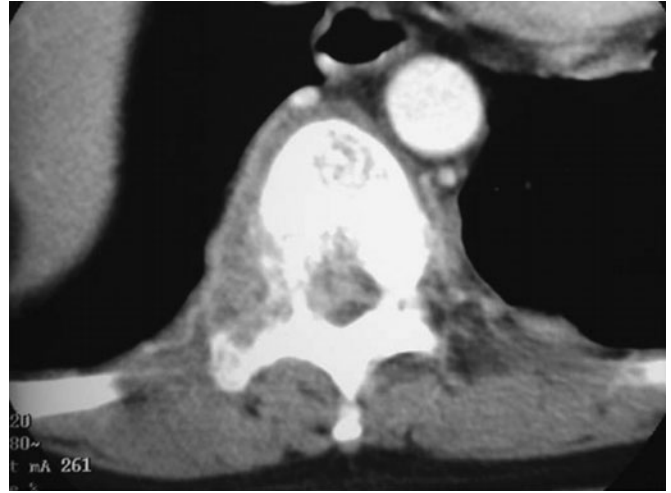
Genital tuberculosis is diagnosed more commonly in female than in male patients. In female patients, it affects the fallopian tubes and the endometrium and may cause infertility, pelvic pain, and menstrual abnormalities. Diagnosis requires biopsy or culture of specimens obtained by dilatation and curettage. In male patients, tuberculosis preferentially affects the epididymis, producing a slightly tender mass that may drain externally through a fistulous tract; orchitis and prostatitis may also develop. In almost half of cases of genitourinary tuberculosis, urinary tract disease is also present. Genitourinary tuberculosis responds well to chemotherapy.

**FIGURE 12-6**

MRI of culture-confirmed renal tuberculosis. T2-weighted coronal plane: coronal sections showing several renal lesions in both the cortical and the medullary tissues of the right kidney. (Courtesy of Dr. Alberto Matteelli, Department of Infectious Diseases, University of Brescia, Italy, with permission.)

Skeletal Tuberculosis

In the United States, tuberculosis of the bones and joints is responsible for about 10% of extrapulmonary cases. In bone and joint disease, pathogenesis is related to reactivation of hematogenous foci or to spread from adjacent paravertebral lymph nodes. Weight-bearing joints (the spine in 40% of cases, the hips in 13%, and the knees in 10%) are most commonly affected. Spinal tuberculosis (Pott's disease or tuberculous spondylitis; **Fig. 12-7**) often involves two or more adjacent vertebral bodies. Although the upper thoracic spine is the most common site of spinal tuberculosis in children, the lower thoracic and upper lumbar vertebrae are usually affected in adults. From the anterior superior or inferior angle of the vertebral body, the lesion slowly reaches the adjacent body, later affecting the intervertebral disk. With advanced disease, collapse of vertebral bodies results in kyphosis (*gibbus*). A paravertebral "cold" abscess may also form. In the upper spine, this abscess may track to and penetrate the chest wall, presenting as a soft tissue mass; in the lower spine, it may reach the inguinal ligaments or present as a psoas abscess. CT or MRI reveals the characteristic lesion and suggests its etiology. The differential diagnosis includes tumors and other infections. Pyogenic bacterial osteomyelitis, in particular, involves the disk very early and produces rapid sclerosis. Aspiration of the abscess or bone biopsy confirms the tuberculous etiology because cultures are usually positive and histologic find-

**FIGURE 12-7**

CT scan demonstrating destruction of the right pedicle of T10 due to Pott's disease. The patient, a 70-year-old Asian woman, presented with back pain and weight loss and had biopsy-proven tuberculosis. (Courtesy of Charles L. Daley, M.D., University of California, San Francisco, with permission.)

ings highly typical. A catastrophic complication of Pott's disease is paraplegia, which is usually caused by an abscess or a lesion compressing the spinal cord. Paraparesis caused by a large abscess is a medical emergency and requires rapid drainage. Tuberculosis of the hip joints, usually involving the head of the femur, causes pain; tuberculosis of the knee produces pain and swelling. If the disease goes unrecognized, the joints may be destroyed. Diagnosis requires examination of the synovial fluid, which is thick in appearance, with a high protein concentration and a variable cell count. Although synovial fluid culture is positive in a high percentage of cases, synovial biopsy and tissue culture may be necessary to establish the diagnosis. Skeletal tuberculosis responds to chemotherapy, but severe cases may require surgery.

Tuberculous Meningitis and Tuberculoma

Tuberculosis of the central nervous system (CNS) accounts for ~5% of extrapulmonary cases in the United States. It is seen most often in young children but also develops in adults, especially those infected with HIV. Tuberculous meningitis results from the hematogenous spread of primary or postprimary pulmonary disease or from the rupture of a subependymal tubercle into the subarachnoid space. In more than half of cases, evidence of old pulmonary lesions or a miliary pattern is found on chest radiography. The disease often presents subtly as headache and slight mental changes after a prodrome of weeks of low-grade fever, malaise, anorexia, and irritability. If not recognized, tuberculous meningitis may evolve acutely with severe headache, confusion, lethargy,

altered sensorium, and neck rigidity. Typically, the disease evolves over 1–2 weeks, a course longer than that of bacterial meningitis. Paresis of the cranial nerves (ocular nerves in particular) is a frequent finding, and the involvement of the cerebral arteries may produce focal ischemia. The ultimate evolution is toward coma, with hydrocephalus and intracranial hypertension.

Lumbar puncture is the cornerstone of diagnosis. In general, examination of the cerebrospinal fluid (CSF) reveals a high leukocyte count (up to 1000/ μ L), usually with a predominance of lymphocytes but sometimes with a predominance of neutrophils in the early stage; a protein content of 1–8 g/L (100–800 mg/dL); and a low glucose concentration. However, any of these three parameters can be within the normal range. AFB are seen on direct smear of CSF sediment in up to one-third of cases, but repeated lumbar punctures increase the yield. Culture of CSF is diagnostic in up to 80% of cases and remains the gold standard. Polymerase chain reaction (PCR) has a sensitivity of up to 80%, but rates of false-positivity reach 10%. The ADA concentration may be a sensitive test but has low specificity. Imaging studies (CT and MRI) may show hydrocephalus and abnormal enhancement of basal cisterns or ependyma.

If unrecognized, tuberculous meningitis is uniformly fatal. This disease responds to chemotherapy; however, neurologic sequelae are documented in 25% of treated cases, in most of which the diagnosis has been delayed. Clinical trials have demonstrated that patients given adjunctive glucocorticoids may experience faster resolution of CSF abnormalities and elevated CSF pressure. In a recent study, adjunctive dexamethasone (0.4 mg/kg per day given IV and tapering by 0.1 mg/kg per week until the fourth week, when 0.1 mg/kg per day was administered; followed by 4 mg/d given by mouth and tapering by 1 mg per week until the fourth week, when 1 mg/d was administered) significantly enhanced the chances of survival among persons >14 years of age but did not reduce the frequency of neurologic sequelae.

Tuberculoma, an uncommon manifestation of CNS tuberculosis, presents as one or more space-occupying lesions and usually causes seizures and focal signs. CT or MRI reveals contrast-enhanced ring lesions, but biopsy is necessary to establish the diagnosis.

Gastrointestinal Tuberculosis

Gastrointestinal tuberculosis is uncommon, making up 3.5% of extrapulmonary cases in the United States. Various pathogenetic mechanisms are involved: swallowing of sputum with direct seeding, hematogenous spread, or (largely in developing areas) ingestion of milk from cows affected by bovine tuberculosis. Although any portion of the gastrointestinal tract may be affected, the terminal ileum and the cecum are the most commonly involved sites. Abdominal pain (at times similar to that associated with

appendicitis) and swelling, obstruction, hematochezia, and a palpable mass in the abdomen are common findings at presentation. Fever, weight loss, anorexia, and night sweats are also common. With intestinal wall involvement, ulcerations and fistulae may simulate Crohn's disease; the differential diagnosis with this entity is always difficult. Anal fistulae should prompt an evaluation for rectal tuberculosis. Because surgery is required in most cases, the diagnosis can be established by histologic examination and culture of specimens obtained intraoperatively.

Tuberculous peritonitis follows either the direct spread of tubercle bacilli from ruptured lymph nodes and intraabdominal organs (e.g., genital tuberculosis in women) or hematogenous seeding. Nonspecific abdominal pain, fever, and ascites should raise the suspicion of tuberculous peritonitis. The coexistence of cirrhosis in patients with tuberculous peritonitis complicates the diagnosis. In tuberculous peritonitis, paracentesis reveals an exudative fluid with a high protein content and leukocytosis that is usually lymphocytic (although neutrophils occasionally predominate). The yield of direct smear and culture is relatively low; culture of a large volume of ascitic fluid can increase the yield, but peritoneal biopsy (with a specimen best obtained by laparoscopy) is often needed to establish the diagnosis.

Pericardial Tuberculosis (Tuberculous Pericarditis)

Because of direct progression of a primary focus within the pericardium to reactivation of a latent focus or to rupture of an adjacent subcarinal lymph node, pericardial tuberculosis has often been a disease of the elderly in countries with low tuberculosis prevalence but also develops frequently in HIV-infected patients. Case-fatality rates are as high as 40% in some series. The onset may be subacute, although an acute presentation, with dyspnea, fever, dull retrosternal pain, and a pericardial friction rub, is possible. An effusion eventually develops in many cases; cardiovascular symptoms and signs of cardiac tamponade may ultimately appear. In the presence of effusion, tuberculosis must be suspected if the patient belongs to a high-risk population (HIV infected, originating in a high-prevalence country); if there is evidence of previous tuberculosis in other organs; or if echocardiography, CT, or MRI shows effusion and thickness across the pericardial space. A definitive diagnosis can be obtained by pericardiocentesis under echocardiographic guidance. The pericardial fluid must be submitted for biochemical, cytologic, and microbiologic study. The effusion is exudative in nature, with a high count of leukocytes (predominantly mononuclear cells). Hemorrhagic effusion is frequent. Direct smear examination is very rarely positive. Whereas culture of pericardial fluid reveals *M. tuberculosis* in up to two-thirds of cases, pericardial biopsy has a higher yield. High levels of ADA and IFN- γ may also suggest a tuberculous etiology.

Without treatment, pericardial tuberculosis is usually fatal. Even with treatment, complications may develop, including chronic constrictive pericarditis with thickening of the pericardium, fibrosis, and sometimes calcification, which may be visible on a chest radiograph. A course of glucocorticoid treatment (e.g., prednisone, 20–60 mg/d for up to 6 weeks) is useful in the management of acute disease, reducing effusion, facilitating hemodynamic recovery, and thus decreasing mortality rates. Progression to chronic constrictive pericarditis, however, seems unaffected by such therapy.

Miliary or Disseminated Tuberculosis

Miliary tuberculosis is caused by hematogenous spread of tubercle bacilli. Although it is often the consequence of primary infection in children, it may be caused by either recent infection or reactivation of old disseminated foci in adults. The lesions are usually yellowish granulomas 1–2 mm in diameter that resemble millet seeds (thus the term *miliary*, coined by nineteenth-century pathologists).

The clinical manifestations are nonspecific and protean, depending on the predominant site of involvement. Fever, night sweats, anorexia, weakness, and weight loss are presenting symptoms in the majority of cases. At times, patients have a cough and other respiratory symptoms caused by pulmonary involvement as well as abdominal symptoms. Physical findings include hepatomegaly, splenomegaly, and lymphadenopathy. Eye examination may reveal choroidal tubercles, which are pathognomonic of miliary tuberculosis, in up to 30% of cases. Meningismus occurs in <10% of cases.

A high index of suspicion is required for the diagnosis of miliary tuberculosis. Frequently, chest radiography reveals a miliary reticulonodular pattern (more easily seen on underpenetrated film), although no radiographic abnormality may be evident early in the course and among HIV-infected patients. Other radiologic findings include large infiltrates, interstitial infiltrates (especially in HIV-infected patients), and pleural effusion. Sputum smear microscopy results are negative in 80% of cases. Various hematologic abnormalities may be seen, including anemia with leukopenia, lymphopenia, neutrophilic leukocytosis and leukemoid reactions, and polycythemia. Disseminated intravascular coagulation has been reported. Elevation of alkaline phosphatase levels and other abnormal values in liver function tests are detected in patients with severe hepatic involvement. The TST may be negative in up to half of cases, but reactivity may be restored during chemotherapy. Bronchoalveolar lavage (BAL) and transbronchial biopsy are more likely to provide bacteriologic confirmation, and granulomas are evident in liver or bone marrow biopsy specimens from many patients. If it goes unrecognized, miliary tuberculosis is lethal; with proper early treatment, however, it is amenable to cure. Glucocorticoid therapy has not proved beneficial.

A rare presentation seen in the elderly is *cryptic miliary tuberculosis*, which has a chronic course characterized by mild intermittent fever, anemia, and—ultimately—meningeal involvement preceding death. An acute septicemic form, *nonreactive miliary tuberculosis*, occurs very rarely and is caused by massive hematogenous dissemination of tubercle bacilli. Pancytopenia is common in this form of disease, which is rapidly fatal. At postmortem examination, multiple necrotic but nongranulomatous (“nonreactive”) lesions are detected.

Less Common Extrapulmonary Forms

Tuberculosis may cause chorioretinitis, uveitis, panophthalmitis, and painful hypersensitivity-related phlyctenular conjunctivitis. Tuberculous otitis is rare and presents as hearing loss, otorrhea, and tympanic membrane perforation. In the nasopharynx, tuberculosis may simulate Wegener’s granulomatosis. Cutaneous manifestations of tuberculosis include primary infection caused by direct inoculation, abscesses and chronic ulcers, scrofuloderma, lupus vulgaris (a smoldering disease with nodules, plaques, and fissures), miliary lesions, and erythema nodosum. Adrenal tuberculosis is a manifestation of disseminated disease presenting rarely as adrenal insufficiency. Finally, congenital tuberculosis results from transplacental spread of tubercle bacilli to the fetus or from ingestion of contaminated amniotic fluid. This rare disease affects the liver, spleen, lymph nodes, and various other organs.

HIV-ASSOCIATED TUBERCULOSIS

Tuberculosis is one of the most common diseases among HIV-infected persons worldwide. In some African countries, the rate of HIV infection among tuberculosis patients reaches 70–80% in certain urban settings. A person with a positive TST result who acquires HIV infection has a 3–13% annual risk of developing active tuberculosis. A new tuberculosis infection acquired by an HIV-infected individual may evolve to active disease in a matter of weeks rather than months or years.

Tuberculosis can appear at any stage of HIV infection, and its presentation varies with the stage. When CMI is only partially compromised, pulmonary tuberculosis presents in a typical manner (Figs. 12-4 and 12-5), with upper-lobe infiltrates and cavitation and without significant lymphadenopathy or pleural effusion. In late stages of HIV infection, a primary tuberculosis-like pattern, with diffuse interstitial or miliary infiltrates, little or no cavitation, and intrathoracic lymphadenopathy, is more common. Overall, sputum smears may be positive less frequently among tuberculosis patients with HIV infection than among those without; thus, the diagnosis of tuberculosis may be unusually difficult, especially in view of the variety of HIV-related pulmonary conditions mimicking tuberculosis.

Extrapulmonary tuberculosis is common among HIV-infected patients. In various series, extrapulmonary tuberculosis—alone or in association with pulmonary disease—has been documented in 40–60% of all cases in HIV-co-infected individuals. The most common forms are lymphatic, disseminated, pleural, and pericardial. Mycobacteremia and meningitis are also frequent, particularly in patients with advanced HIV disease.

The diagnosis of tuberculosis in HIV-infected patients may be difficult not only because of the increased frequency of sputum-smear negativity (up to 40% in culture-proven pulmonary cases) but also because of atypical radiographic findings, a lack of classic granuloma formation in the late stages, and a negative TST result. Delays in treatment may prove fatal.

Recommendations for the prevention and treatment of tuberculosis in HIV-infected individuals are provided below.

DIAGNOSIS OF TUBERCULOSIS

The key to the diagnosis of tuberculosis is a high index of suspicion. Diagnosis is not difficult with a high-risk patient—e.g., a homeless alcoholic who presents with typical symptoms and a classic chest radiograph showing upper-lobe infiltrates with cavities (Fig. 12-4). On the other hand, the diagnosis can easily be missed in an elderly nursing home resident or a teenager with a focal infiltrate.

Often, the diagnosis is first entertained when the chest radiograph of a patient being evaluated for respiratory symptoms is abnormal. If the patient has no complicating medical conditions that cause immunosuppression, the chest radiograph may show typical upper-lobe infiltrates with cavitation (Fig. 12-4). The longer the delay between the onset of symptoms and the diagnosis, the more likely is the finding of cavitory disease. In contrast, immunosuppressed patients, including those with HIV infection, may have “atypical” findings on chest radiography (e.g., lower-zone infiltrates without cavity formation).

ACID-FAST BACILLIMICROSCOPY

A presumptive diagnosis is commonly based on the finding of AFB on microscopic examination of a diagnostic specimen, such as a smear of expectorated sputum or of tissue (e.g., a lymph node biopsy). Although rapid and inexpensive, AFB microscopy has relatively low sensitivity (40–60%) in confirmed cases of pulmonary tuberculosis. Most modern laboratories processing large numbers of diagnostic specimens use auramine-rhodamine staining and fluorescence microscopy. The more traditional method—light microscopy of specimens stained with Kinyoun or Ziehl-Neelsen basic fuchsin dyes—is satisfactory, although

more time consuming. For patients with suspected pulmonary tuberculosis, three sputum specimens, preferably collected early in the morning, should be submitted to the laboratory for AFB smear and mycobacterial culture. If tissue is obtained, it is critical that the portion of the specimen intended for culture not be put in formaldehyde. The use of AFB microscopy on urine or gastric lavage fluid is limited by the presence of commensal mycobacteria that can cause false-positive results.

MYCOBACTERIAL CULTURE

Definitive diagnosis depends on the isolation and identification of *M. tuberculosis* from a clinical specimen or the identification of specific sequences of DNA in a nucleic acid amplification test (see below). Specimens may be inoculated onto egg- or agar-based medium (e.g., Löwenstein-Jensen or Middlebrook 7H10) and incubated at 37°C (under 5% CO₂ for Middlebrook medium). Because most species of mycobacteria, including *M. tuberculosis*, grow slowly, 4–8 weeks may be required before growth is detected. Although *M. tuberculosis* may be presumptively identified on the basis of growth time and colony pigmentation and morphology, a variety of biochemical tests have traditionally been used to speciate mycobacterial isolates. In modern, well-equipped laboratories, the use of broth-based culture for isolation and speciation by molecular methods or high-pressure liquid chromatography of mycolic acids has replaced isolation on solid media and identification by biochemical tests. These new methods have decreased the time required for bacteriologic confirmation to 2–3 weeks.

NUCLEIC ACID AMPLIFICATION

Several test systems based on amplification of mycobacterial nucleic acid are available. These systems permit the diagnosis of tuberculosis in as little as several hours, with high specificity and sensitivity approaching that of culture. These tests are most useful for the rapid confirmation of tuberculosis in persons with AFB-positive specimens but also have utility for the diagnosis of AFB-negative pulmonary and extrapulmonary tuberculosis.

DRUG SUSCEPTIBILITY TESTING

In general, the initial isolate of *M. tuberculosis* should be tested for susceptibility to isoniazid, rifampin, and ethambutol. In addition, expanded susceptibility testing is mandatory when resistance to one or more of these drugs is found or the patient either fails to respond to initial therapy or has a relapse after the completion of treatment (see “Treatment Failure and Relapse” below). Susceptibility testing may be conducted directly (with the clinical specimen) or indirectly (with mycobacterial cultures) on solid or liquid medium. Results are obtained

128 most rapidly by direct susceptibility testing on liquid medium, with an average reporting time of 3 weeks. With indirect testing on solid medium, results may be unavailable for ≥ 8 weeks. Molecular methods for the rapid identification of genetic mutations known to be associated with resistance to rifampin and isoniazid have been developed but are not marketed in the United States.

RADIOGRAPHIC PROCEDURES

As noted above, the initial suspicion of pulmonary tuberculosis is often based on abnormal chest radiographic findings in a patient with respiratory symptoms. Although the “classic” picture is that of upper-lobe disease with infiltrates and cavities (Fig. 12-4), virtually any radiographic pattern—from a normal film or a solitary pulmonary nodule to diffuse alveolar infiltrates in a patient with ARDS—may be seen. In the era of AIDS, no radiographic pattern can be considered pathognomonic. CT (Fig. 12-5) may be useful in interpreting questionable findings on plain chest radiography and may be helpful in diagnosing some forms of extrapulmonary tuberculosis [e.g., Pott’s disease; (Fig. 12-7)]. MRI is useful in the diagnosis of intracranial tuberculosis.

ADDITIONAL DIAGNOSTIC PROCEDURES

Other diagnostic tests may be used when pulmonary tuberculosis is suspected. Sputum induction by ultrasonic nebulization of hypertonic saline may be useful for patients who cannot produce a sputum specimen spontaneously. Frequently, patients with radiographic abnormalities that are consistent with other diagnoses (e.g., bronchogenic carcinoma) undergo fiberoptic bronchoscopy with bronchial brushings and endobronchial or transbronchial biopsy of the lesion. BAL of a lung segment containing an abnormality may also be performed. In all cases, it is essential that specimens be submitted for AFB smear and mycobacterial culture. For the diagnosis of primary pulmonary tuberculosis in children, who often do not expectorate sputum, specimens from early-morning gastric lavage may yield positive cultures.

Invasive diagnostic procedures are indicated for patients with suspected extrapulmonary tuberculosis. In addition to testing of specimens from involved sites (e.g., CSF for tuberculous meningitis, pleural fluid and biopsy samples for pleural disease), biopsy and culture of bone marrow and liver tissue have a good diagnostic yield in disseminated (miliary) tuberculosis, particularly in HIV-infected patients, who also have a high frequency of positive blood cultures.

In some cases, cultures are negative, but a clinical diagnosis of tuberculosis is supported by consistent epidemiologic evidence (e.g., a history of close contact with an infectious patient), a positive TST result, and a compatible clinical and radiographic response to treatment. In the

United States and other industrialized countries with low rates of tuberculosis, some patients with limited abnormalities on chest radiographs and sputum positive for AFB are infected with nontuberculous mycobacteria, most commonly organisms of the *M. avium* complex (MAC) or *M. kansasii*. Factors favoring the diagnosis of nontuberculous mycobacterial disease over tuberculosis include an absence of risk factors for tuberculosis, a negative TST result, and underlying chronic pulmonary disease.

Patients with HIV-associated tuberculosis pose several diagnostic problems (see “HIV-Associated Tuberculosis” above). Moreover, HIV-infected patients with sputum culture-positive, AFB-positive tuberculosis may present with a normal chest radiograph. With the advent of highly active antiretroviral therapy, the occurrence of disseminated MAC disease that can be confused with tuberculosis has become much less common.

SEROLOGIC AND OTHER DIAGNOSTIC TESTS FOR ACTIVE TUBERCULOSIS

A number of serologic tests based on detection of antibodies to a variety of mycobacterial antigens are marketed in developing countries but not in the United States. Careful independent assessments of these tests suggest that they are not useful as diagnostic aids, especially in persons with a low probability of tuberculosis. Various methods aimed at detection of mycobacterial antigens in diagnostic specimens are being investigated but are limited at present by low sensitivity. Determination of ADA levels in pleural fluid may be useful in the diagnosis of pleural tuberculosis; the utility of this test in the diagnosis of other forms of extrapulmonary tuberculosis (e.g., pericardial, peritoneal, and meningeal) is less clear.

DIAGNOSIS OF LATENT *M. TUBERCULOSIS* INFECTION

Tuberculin Skin Testing

In 1891, Robert Koch discovered that components of *M. tuberculosis* in a concentrated liquid culture medium, subsequently named “old tuberculin” (OT), were capable of eliciting a skin reaction when injected subcutaneously into patients with tuberculosis. In 1932, Seibert and Munday purified this product by ammonium sulfate precipitation to produce an active protein fraction known as *tuberculin purified protein derivative (PPD)*. In 1941, PPD-S, developed by Seibert and Glenn, was chosen as the international standard. Later, the WHO and UNICEF sponsored large-scale production of a master batch of PPD (RT23) and made it available for general use. The greatest limitation of PPD is its lack of mycobacterial species specificity, a property caused by the large number of proteins in this product that are highly conserved in the various species. In addition, subjectivity of the skin-reaction interpretation, deterioration

of the product, and batch-to-batch variations limit the usefulness of PPD.

Skin testing with tuberculin-PPD (TST) is most widely used in screening for latent *M. tuberculosis* infection (LTBI). The test is of limited value in the diagnosis of active tuberculosis because of its relatively low sensitivity and specificity and its inability to discriminate between latent infection and active disease. False-negative reactions are common in immunosuppressed patients and in those with overwhelming tuberculosis. False-positive reactions may be caused by infections with nontuberculous mycobacteria and by bacille Calmette-Guérin (BCG) vaccination.

IFN- γ Release Assays (IGRAs)

Recently, two in vitro assays that measure T cell release of IFN- γ in response to stimulation with the highly tuberculosis-specific antigens ESAT-6 and CFP-10 have become commercially available. QuantiFERON-TB Gold[®] (Cellestis Ltd., Carnegie, Australia) is a whole-blood enzyme-linked immunosorbent assay (ELISA) for measurement of IFN- γ , and T-SPOT.TB[®] (Oxford Immunotec, Oxford, UK) is an enzyme-linked immunospot (ELISpot) assay.

IGRAs are more specific than the TST as a result of less cross-reactivity because of BCG vaccination and sensitization by nontuberculous mycobacteria. IGRAs also appear to be at least as sensitive as the TST for active tuberculosis (used as a surrogate for LTBI). Although diagnostic sensitivity for LTBI cannot be directly estimated because of the absence of a gold standard, these tests have shown better correlation than the TST with exposure to *M. tuberculosis* in contact investigations in low-incidence settings.

Other potential advantages of IGRAs include logistical convenience, the need for fewer patient visits to complete testing, the avoidance of unreliable and somewhat subjective measurements such as skin induration, and the ability to perform serial testing without inducing the boosting phenomenon (a spurious TST conversion due to boosting of reactivity on subsequent TSTs among BCG-vaccinated persons and those infected with other mycobacteria). Because of the high specificity and other potential advantages, IGRAs are likely to replace the TST for LTBI diagnosis in low-incidence, high-income settings where cross-reactivity because of BCG might adversely impact the interpretation and utility of the TST. Direct comparative studies in routine practice thus far suggest that the ELISpot has a lower rate of indeterminate results and probably a higher degree of diagnostic sensitivity than the whole-blood ELISA. Further studies are under way to assess the performance of these tests in contact investigations and in persons with suspected tuberculosis disease, health care workers, HIV-infected individuals, persons with iatrogenic immunosuppression, and children.

R_x Treatment: TUBERCULOSIS

The two aims of tuberculosis treatment are to interrupt tuberculosis transmission by rendering patients noninfectious and to prevent morbidity and death by curing patients with tuberculosis. Chemotherapy for tuberculosis became possible with the discovery of streptomycin in the mid-1940s. Randomized clinical trials clearly indicated that the administration of streptomycin to patients with chronic tuberculosis reduced mortality rates and led to cure in the majority of cases. However, monotherapy with streptomycin was frequently associated with the development of resistance to this drug and the attendant failure of treatment. With the discovery of para-aminosalicylic acid (PAS) and isoniazid, it became axiomatic that cure of tuberculosis required the concomitant administration of at least two agents to which the organism was susceptible. Furthermore, early clinical trials demonstrated that a long period of treatment (i.e., 12–24 months) was required to prevent recurrence.

The introduction of rifampin in the early 1970s heralded the era of effective short-course chemotherapy, with a treatment duration of <12 months. The discovery that pyrazinamide, which was first used in the 1950s, augmented the potency of isoniazid/rifampin regimens led to the use of a 6-month course of this triple-drug regimen as standard therapy.

DRUGS Four major drugs are considered the first-line agents for the treatment of tuberculosis: isoniazid, rifampin, pyrazinamide, and ethambutol (Table 12-2). These drugs are well absorbed after oral administration, with peak serum levels at 2–4 h and nearly complete elimination within 24 h. These agents are recommended on the basis of their bactericidal activity (i.e., their ability to rapidly reduce the number of viable organisms and render patients noninfectious), their sterilizing activity (i.e., their ability to kill all bacilli and thus sterilize the affected tissues, measured in terms of the ability to prevent relapses), and their low rate of induction of drug resistance. Rifapentine and rifabutin, two drugs related to rifampin, are also available in the United States and are useful for selected patients.

Because of a lower degree of efficacy and a higher degree of intolerability and toxicity, six classes of second-line drugs are generally used only for the treatment of patients with tuberculosis resistant to first-line drugs. Included in this group are the injectable aminoglycosides streptomycin (formerly a first-line agent), kanamycin, and amikacin; the injectable polypeptide capreomycin; the oral agents ethionamide, cycloserine, and PAS; and the fluoroquinolone antibiotics. Of the quinolones, third-generation agents are preferred: levofloxacin, gatifloxacin (no longer marketed in the United States), and moxifloxacin. Amithiozone (thiacetazone) is still used in some

RECOMMENDED DOSAGE^a FOR INITIAL TREATMENT OF TUBERCULOSIS IN ADULTS^b

DRUG	DOSAGE	
	DAILY DOSE	THRICE-WEEKLY DOSE ^c
Isoniazid	5 mg/kg, max 300 mg	15 mg/kg, max 900 mg
Rifampin	10 mg/kg, max 600 mg	10 mg/kg, max 600 mg
Pyrazinamide	20–25 mg/kg, max 2 g	30–40 mg/kg, max 3 g
Ethambutol ^d	15–20 mg/kg	25–30 mg/kg

^aThe duration of treatment for individual drugs varies by regimen, as detailed in Table 12-3.

^bDosages for children are similar, except that some authorities recommend higher doses of isoniazid (10–15 mg/kg/d; 20–30 mg/kg intermittent) and rifampin (10–20 mg/kg).

^cDosages for twice-weekly administration are the same for isoniazid and rifampin but are higher for pyrazinamide (50 mg/kg, with a maximum of 4 g/d) and ethambutol (40–50 mg/d).

^dIn certain settings, streptomycin (15 mg/kg/d, with a maximum dose of 1 g; or 25–30 mg/kg thrice weekly, with a maximum dose of 1.5 g) can replace ethambutol in the initial phase of treatment. However, streptomycin is no longer considered a first-line drug by the American Thoracic Society, the Infectious Diseases Society of America, or the Centers for Disease Control and Prevention.

Source: Based on recommendations of the American Thoracic Society, the Infectious Diseases Society of America, and the Centers for Disease Control and Prevention.

developing countries but is associated with severe and sometimes even fatal skin reactions among HIV-infected patients. Other drugs of unproven efficacy that have been used in the treatment of patients with resistance to most of the first- and second-line agents include clofazimine, amoxicillin/clavulanic acid, and linezolid.

REGIMENS Standard short-course regimens are divided into an initial, or bactericidal, phase and a continuation, or sterilizing, phase. During the initial phase, the majority of the tubercle bacilli are killed, symptoms resolved, and the patient usually becomes noninfectious. The continuation phase is required to eliminate persisting mycobacteria and prevent relapse.

The treatment regimen of choice for virtually all forms of tuberculosis in both adults and children consists of a 2-month initial phase of isoniazid, rifampin, pyrazinamide, and ethambutol followed by a 4-month continuation phase of isoniazid and rifampin (Table 12-3). Treatment may be given daily throughout the course or intermittently (either three times weekly throughout the course or twice weekly after an initial phase of daily therapy, although the twice-weekly option is not recommended by the WHO). A continuation phase of once-weekly rifapentine and isoniazid is equally

effective for HIV-seronegative patients with noncavitary pulmonary tuberculosis who have negative sputum cultures at 2 months. Intermittent treatment is especially useful for patients whose therapy is being directly observed (see later). Patients with cavitary pulmonary tuberculosis and delayed sputum-culture conversion (i.e., those who remain culture-positive at 2 months) should have the continuation phase extended by 3 months, for a total course of 9 months. For patients with sputum culture-negative pulmonary tuberculosis, the duration of treatment may be reduced to a total of 4 months. To prevent isoniazid-related neuropathy, pyridoxine (10–25 mg/d) should be added to the regimen given to persons at high risk of vitamin B6 deficiency (e.g., alcoholics; malnourished persons; pregnant and lactating women; and patients with conditions such as chronic renal failure, diabetes, and HIV infection, which are also associated with neuropathy). A full course of therapy (completion of treatment) is defined more accurately by the total number of doses taken than by the duration of treatment. Specific recommendations on the required numbers of doses for each of the various treatment regimens have been published jointly by the American Thoracic Society, the Infectious Diseases Society of America, and the CDC. In some developing countries where the ability to ensure compliance with treatment is limited, a continuation-phase regimen of daily isoniazid and ethambutol for 6 months is acceptable. However, this regimen is associated with a higher rate of relapse and failure, especially among HIV-infected patients.

Lack of adherence to treatment is recognized worldwide as the most important impediment to cure. Moreover, the tubercle bacilli infecting patients who do not adhere to the prescribed regimen are likely to become drug resistant. Both patient- and provider-related factors may affect compliance. Patient-related factors include a lack of belief that the illness is significant or that treatment will have a beneficial effect; the existence of concomitant medical conditions (notably substance abuse); lack of social support; and poverty, with attendant joblessness and homelessness. Provider-related factors that may promote compliance include the education and encouragement of patients, the offering of convenient clinic hours, and the provision of incentives and enablers such as meals and travel vouchers.

In addition to specific measures addressing noncompliance, two other strategic approaches are used: direct observation of treatment and provision of fixed-drug-combination (FDC) products. Because it is difficult to predict which patients will adhere to the recommended treatment, all patients should have their therapy directly supervised, especially during the initial phase. In the United States, personnel to supervise therapy are usually available through tuberculosis control programs of local public health departments. Supervision increases

TABLE 12-3

RECOMMENDED ANTITUBERCULOSIS TREATMENT REGIMENS

INDICATION	INITIAL PHASE		CONTINUATION PHASE	
	DURATION, MONTHS	DRUGS	DURATION, MONTHS	DRUGS
New smear- or culture-positive cases	2	HRZE ^{a,b}	4	HR ^{a,c,d}
New culture-negative cases	2	HRZE ^a	2	HR ^a
Pregnancy	2	HRE ^e	7	HR
Failure and relapse ^f	—	—	—	—
Resistance (or intolerance) to H	Throughout (6)	RZE ^g		
Resistance to H + R	Throughout (12–18)	ZEQ + S (or another injectable agent ^h)		
Resistance to all first-line drugs	Throughout (24)	1 injectable agent ^h + 3 of these 4: ethionamide, cycloserine, Q, PAS		
Standardized retreatment (susceptibility testing unavailable)	3	HRZES ⁱ	5	HRE
Drug intolerance to R	Throughout (12) ^j	HZE		
Drug intolerance to Z	2	HRE	7	HR

^aAll drugs can be given daily or intermittently (three times weekly throughout or twice weekly after 2–8 weeks of daily therapy during the initial phase).

^bStreptomycin can be used in place of ethambutol but is no longer considered to be a first-line drug by the American Thoracic Society, the Infectious Diseases Society of America, or the Centers for Disease Control and Prevention.

^cThe continuation phase should be extended to 7 months for patients with cavitary pulmonary tuberculosis who remain sputum culture positive after the initial phase of treatment.

^dHIV-negative patients with noncavitary pulmonary tuberculosis who have negative sputum AFB smears after the initial phase of treatment can be given once-weekly rifapentine/isoniazid in the continuation phase.

^eThe 6-month regimen with pyrazinamide can probably be used safely during pregnancy and is recommended by the World Health Organization and the International Union Against Tuberculosis and Lung Disease. If pyrazinamide is not included in the initial treatment regimen, the minimum duration of therapy is 9 months.

^fRegimen is tailored according to the results of drug susceptibility tests.

^gA fluoroquinolone may strengthen the regimen for patients with extensive disease.

^hAmikacin, kanamycin, or capreomycin. All these agents should be discontinued after 2 to 6 months, depending on tolerance and response.

ⁱStreptomycin should be discontinued after 2 months. This regimen is less effective for patients in whom treatment has failed, who have an increased probability of rifampin-resistant disease. In such cases, the retreatment regimen might include second-line drugs chosen in light of the likely pattern of drug resistance.

^jStreptomycin for the initial 2 months or a fluoroquinolone might strengthen the regimen for patients with extensive disease.

Note: E, ethambutol; H, isoniazid; PAS, para-aminosalicylic acid; Q, a quinolone antibiotic; R, rifampin; S, streptomycin; Z, pyrazinamide.

the proportion of patients completing treatment and greatly lessens the chances of relapse and acquired drug resistance. FDC products (e.g., isoniazid/rifampin, isoniazid/rifampin/pyrazinamide, and isoniazid/rifampin/pyrazinamide/ethambutol) are available (except, in the United States, for the four-drug FDC) and are strongly recommended as a means of minimizing the likelihood of prescription error and of the development of drug resistance as the result of monotherapy. In some formulations of these combination products, the bioavailability of rifampin has been found to be substandard. In North America and Europe, regulatory authorities ensure that combination products are of good quality; however, this type of quality assurance cannot be assumed to take place in less affluent countries. Alternative regimens for patients who exhibit drug intolerance or adverse reactions are listed in Table 12-3. However, severe side

effects prompting discontinuation of any of the first-line drugs and use of these alternative regimens are uncommon.

MONITORING TREATMENT RESPONSE AND DRUG TOXICITY

Bacteriologic evaluation is the preferred method of monitoring the response to treatment for tuberculosis. Patients with pulmonary disease should have their sputum examined monthly until cultures become negative. With the recommended regimen, >80% of patients will have negative sputum cultures at the end of the second month of treatment. By the end of the third month, virtually all patients should be culture negative. In some patients, especially those with extensive cavitary disease and large numbers of organisms, AFB smear conversion may lag behind culture conversion. This phenomenon is presumably

caused by the expectoration and microscopic visualization of dead bacilli. As noted above, patients with cavitory disease who do not achieve sputum culture conversion by 2 months require extended treatment. When a patient's sputum cultures remain positive at ≥ 3 months, treatment failure and drug resistance or poor adherence with the regimen should be suspected (see later). A sputum specimen should be collected by the end of treatment to document cure. If mycobacterial cultures are not practical, then monitoring by AFB smear examination should be undertaken at 2, 5, and 6 months. Smears that are positive after 5 months of treatment in a patient known to be adherent are indicative of treatment failure.

Bacteriologic monitoring of patients with extrapulmonary tuberculosis is more difficult and often not feasible. In these cases, the response to treatment must be assessed clinically and radiographically.

Monitoring of the response to treatment during chemotherapy by serial chest radiographs is not recommended because radiographic changes may lag behind bacteriologic response and are not highly sensitive. After the completion of treatment, neither sputum examination nor chest radiography is recommended for routine follow-up purposes. However, a chest radiograph obtained at the end of treatment may be useful for comparative purposes if the patient develops symptoms of recurrent tuberculosis months or years later. Patients should be instructed to report promptly for medical assessment if they develop any such symptoms.

During treatment, patients should be monitored for drug toxicity. The most common adverse reaction of significance is hepatitis. Patients should be carefully educated about the signs and symptoms of drug-induced hepatitis (e.g., dark urine, loss of appetite) and should be instructed to discontinue treatment promptly and see their health care provider if these symptoms occur. Although biochemical monitoring is not routinely recommended, all adult patients should undergo baseline assessment of liver function (e.g., measurement of serum levels of hepatic aminotransferases and serum bilirubin). Older patients, those with concomitant diseases, those with a history of hepatic disease (especially hepatitis C), and those using alcohol daily should be monitored especially closely (i.e., monthly), with repeated measurements of aminotransferases, during the initial phase of treatment. Up to 20% of patients have small increases in aspartate aminotransferase (up to three times the upper limit of normal) that are not accompanied by symptoms and are of no consequence. For patients with symptomatic hepatitis and those with marked (five- to sixfold) elevations in serum levels of aspartate aminotransferase, treatment should be stopped and drugs reintroduced one at a time after liver function has returned to normal.

Hypersensitivity reactions usually require the discontinuation of all drugs and rechallenge to determine which agent is the culprit. Because of the variety of regimens available, it is usually not necessary—although it is possible—to desensitize patients. Hyperuricemia and arthralgia caused by pyrazinamide can usually be managed by the administration of acetylsalicylic acid; however, pyrazinamide treatment should be stopped if the patient develops gouty arthritis. Individuals who develop autoimmune thrombocytopenia secondary to rifampin therapy should not receive the drug thereafter. Similarly, the occurrence of optic neuritis with ethambutol is an indication for permanent discontinuation of this drug. Other common manifestations of drug intolerance, such as pruritus and gastrointestinal upset, can generally be managed without the interruption of therapy.

TREATMENT FAILURE AND RELAPSE As stated above, treatment failure should be suspected when a patient's sputum cultures remain positive after 3 months or when AFB smears remain positive after 5 months. In the management of such patients, it is imperative that the current isolate be tested for susceptibility to first- and second-line agents. When the results of susceptibility testing are expected to become available within a few weeks, changes in the regimen can be postponed until that time. However, if the patient's clinical condition is deteriorating, an earlier change in regimen may be indicated. A cardinal rule in the latter situation is to always add more than one drug at a time to a failing regimen—at least two and preferably three drugs that have never been used and to which the bacilli are likely to be susceptible should be added. The patient may continue to take isoniazid and rifampin along with these new agents pending the results of susceptibility tests.

The mycobacterial strains infecting patients who experience a relapse after apparently successful treatment are less likely to have acquired drug resistance (see below) than are strains from patients in whom treatment has failed. However, if the regimen administered initially does not contain rifampin, the probability of isoniazid resistance is high. Acquired resistance is uncommon among strains from patients who relapse after completing a standard short-course regimen. However, it is prudent to begin the treatment of all patients who have relapsed with all four first-line drugs plus streptomycin, pending the results of susceptibility testing. In less affluent countries and other settings where facilities for culture and drug susceptibility testing are not available, a standard regimen should be used in all instances of relapse and treatment failure (Table 12-3).

DRUG-RESISTANT TUBERCULOSIS Strains of *M. tuberculosis* resistant to individual drugs arise by spontaneous point mutations in the mycobacterial

genome, which occur at low but predictable rates. Because there is no cross-resistance among the commonly used drugs, the probability that a strain will be resistant to two drugs is the product of the probabilities of resistance to each drug and thus is low. The development of drug-resistant tuberculosis is invariably the result of monotherapy—i.e., the failure of the health care provider to prescribe at least two drugs to which tubercle bacilli are susceptible or of the patient to take properly prescribed therapy.

Drug-resistant tuberculosis may be either primary or acquired. Primary drug resistance is that in a strain infecting a patient who has not previously been treated. Acquired resistance develops during treatment with an inappropriate regimen. In North America and Europe, rates of primary resistance are generally low, and isoniazid resistance is most common. In the United States, although primary isoniazid resistance was stable at ~7–8% between 1993 and 2002, the rate of primary multidrug-resistant (MDR) tuberculosis (defined as tuberculosis caused by a strain resistant at least to isoniazid and rifampin) declined from 2.5% to 1%. Resistance rates are higher among foreign-born and HIV-infected patients. Worldwide, MDR tuberculosis is a serious problem in some regions, especially in the former Soviet Union and parts of Asia (Fig. 12-8). As noted above, drug-resistant tuberculosis can be prevented by adherence to the principles of sound therapy—the inclusion of at least two bactericidal drugs to which the organism is susceptible, the use of FDC products, and the verification that patients complete the prescribed course.

Although the 6-month regimen described in Table 12-3 is generally effective for patients with initial isoniazid-resistant disease, it is prudent to include ethambutol and pyrazinamide for the full 6 months. In such cases, isoniazid probably does not contribute to a successful outcome and should be omitted. MDR tuberculosis is more difficult to manage than is disease caused by a drug-susceptible organism, especially because resistance to other first-line drugs as well as to isoniazid and rifampin is common. For strains resistant to isoniazid and rifampin, combinations of a fluoroquinolone, ethambutol, pyrazinamide, and streptomycin (or, for strains resistant to streptomycin as well, another injectable agent such as amikacin or kanamycin), given for 18–24 months and for at least 9 months after sputum culture conversion, may be effective. For patients with bacilli resistant to all of the first-line agents, cure may be attained with a combination of four second-line drugs, including one injectable agent (Table 12-3). The optimal duration of treatment in this situation is unknown; however, a duration of 24 months is recommended. MDR strains of *M. tuberculosis* that are also resistant to at least the fluoroquinolones and one or more of the injectable drugs amikacin, kanamycin, or capreomycin [extensive drug-resistant (XDR) strains] have fewer treatment options and a much poorer prognosis. For patients with localized disease and sufficient pulmonary reserve, lobectomy or pneumonectomy may be helpful. Because the management of patients with MDR and XDR tuberculosis is complicated by both social and medical factors, care of these patients should

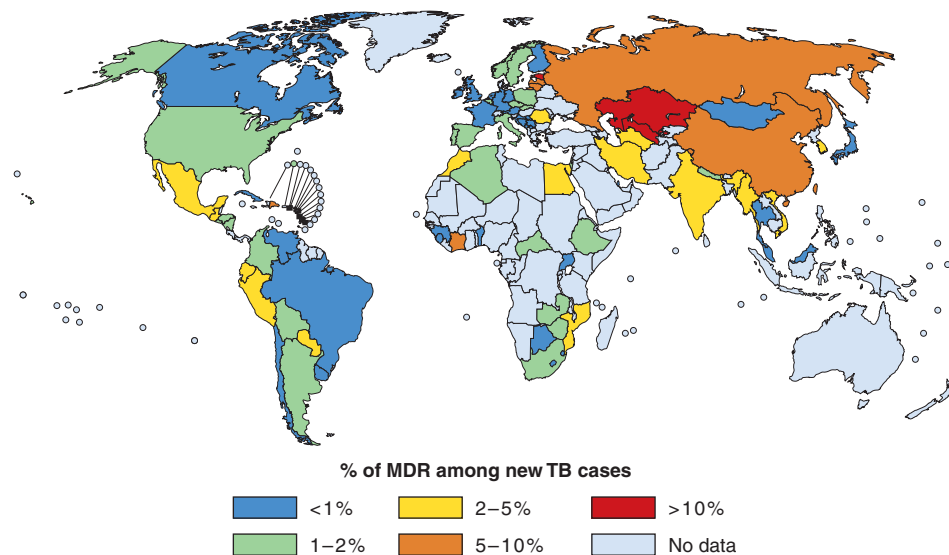


FIGURE 12-8

Percentage of new tuberculosis (TB) cases exhibiting multidrug resistance (MDR) in all countries surveyed by the WHO/Union Global Drug Resistance Surveillance Project from

1994 to 2005. (See also disclaimer in Fig. 12-2. Courtesy of the Stop TB Department, WHO, with permission.)

be restricted to tuberculosis control programs with resources and capacity and to specialized centers.

HIV-ASSOCIATED TUBERCULOSIS In general, the standard treatment regimens are equally efficacious in HIV-negative and HIV-positive patients. However, adverse drug effects may be more pronounced in HIV-infected patients. Because these effects may include serious or even fatal skin reactions to amithiozone (thiacetazone), this drug, which has been used in place of ethambutol in developing countries, is no longer recommended by the WHO.

Three important considerations are relevant to tuberculosis treatment in HIV-infected patients: an increased frequency of paradoxical reactions, drug interactions between antiretroviral therapy and rifamycins, and development of rifampin monoresistance with widely spaced intermittent treatment. Exacerbations in symptoms, signs, and laboratory or radiographic manifestations of tuberculosis—termed the *immune reconstitution inflammatory syndrome* (IRIS)—have been associated with the administration of antiretroviral regimens. IRIS is more common among patients with advanced immunosuppression and extrapulmonary tuberculosis. The presumed pathogenesis of IRIS is an immune response that is elicited by antigens released as bacilli are killed during effective chemotherapy and that is temporally associated with improving immune function. The first priority in the management of a possible case of IRIS is to ensure that the clinical syndrome does not represent a failure of tuberculosis treatment or the development of another infection. Mild paradoxical reactions can be managed with symptom-based treatment. Glucocorticoids have been used for more severe reactions, although their use in this setting has not been formally evaluated in clinical trials.

Most HIV-infected tuberculosis patients are candidates for antiretroviral therapy, although the optimal timing of this treatment is not known. Rifampin, a potent inducer of enzymes of the cytochrome P450 system, lowers serum levels of many HIV protease inhibitors and some nonnucleoside reverse transcriptase inhibitors—essential drugs used in antiretroviral regimens. In such cases, rifabutin, which has much less enzyme-inducing activity, has been recommended in place of rifampin. However, dosage adjustment for rifabutin, the antiretroviral drugs, or both may be necessary. Because recommendations are frequently updated, consultation of the CDC website is advised (www.cdc.gov/tb/TB_HIV_Drugs/default.htm).

Several clinical trials of HIV-associated tuberculosis have found that patients with advanced immunosuppression (CD4+ T cell counts of <100/ μ L) are prone to treatment failure and relapse with rifampin-resistant organisms when treated with “highly intermittent” (i.e., once- or twice-weekly) rifamycin-containing regimens.

Consequently, it is recommended that these patients receive daily or thrice-weekly therapy for the entire course.

SPECIAL CLINICAL SITUATIONS Although comparative clinical trials of treatment for extrapulmonary tuberculosis are limited, the available evidence indicates that most forms of disease can be treated with the 6-month regimen recommended for patients with pulmonary disease. The American Academy of Pediatrics recommends that children with bone and joint tuberculosis, tuberculous meningitis, or miliary tuberculosis receive 9–12 months of treatment.

Treatment for tuberculosis may be complicated by underlying medical problems that require special consideration. As a rule, patients with chronic renal failure should not receive aminoglycosides and should receive ethambutol only if serum levels can be monitored. Isoniazid, rifampin, and pyrazinamide may be given in the usual doses in cases of mild to moderate renal failure, but the dosages of isoniazid and pyrazinamide should be reduced for all patients with severe renal failure except those undergoing hemodialysis. Patients with hepatic disease pose a special problem because of the hepatotoxicity of isoniazid, rifampin, and pyrazinamide. Patients with severe hepatic disease may be treated with ethambutol, streptomycin, and possibly another drug (e.g., a fluoroquinolone); if required, isoniazid and rifampin may be administered under close supervision. The use of pyrazinamide by patients with liver failure should be avoided. Silicotuberculosis necessitates the extension of therapy by at least 2 months.

The regimen of choice for pregnant women (Table 12-3) is 9 months of treatment with isoniazid and rifampin supplemented by ethambutol for the first 2 months. Although the WHO has recommended routine use of pyrazinamide in pregnant women, this drug has not been recommended in the United States because of insufficient data documenting its safety in pregnancy. Streptomycin is contraindicated because it is known to cause eighth cranial nerve damage in fetuses. Treatment for tuberculosis is not a contraindication to breast-feeding; most of the drugs administered are present in small quantities in breast milk, albeit at concentrations far too low to provide any therapeutic or prophylactic benefit to the child.

Medical consultation on difficult-to-manage cases is provided by the CDC Regional Training and Medical Consultation Centers (<http://www.cdc.gov/tb/rtmcc.htm>).

PREVENTION

By far the best way to prevent tuberculosis is to diagnose and isolate infectious cases rapidly and administer appropriate treatment until patients are rendered noninfectious

and the disease is cured. Additional strategies include BCG vaccination and treatment of persons with latent tuberculosis infection who are at high risk of developing active disease.

BACILLE CALMETTE-GUÉRIN VACCINATION

BCG was derived from an attenuated strain of *M. bovis* and first administered to humans in 1921. Many BCG vaccines are available worldwide; all are derived from the original strain, but the vaccines vary in efficacy, ranging from 80% to nil in randomized, placebo-controlled trials. A similar range of efficacy was found in recent observational studies (case-control, historic cohort, and cross-sectional) in areas where infants are vaccinated at birth. These studies also found higher rates of efficacy in the protection of infants and young children from relatively serious forms of tuberculosis, such as tuberculous meningitis and miliary tuberculosis.

BCG vaccine is safe and rarely causes serious complications. The local tissue response begins 2–3 weeks after vaccination, with scar formation and healing within 3 months. Side effects—most commonly, ulceration at the vaccination site and regional lymphadenitis—occur in 1–10% of vaccinated persons. Some vaccine strains have caused osteomyelitis (~1 case per million doses administered). Disseminated BCG infection and death have occurred in 1–10 cases per 10 million doses administered, although this problem is restricted almost exclusively to persons with impaired immunity, such as children with severe combined immunodeficiency syndrome or adults with HIV infection. BCG vaccination induces TST reactivity, which tends to wane with time. The presence or size of TST reactions after vaccination does not predict the degree of protection afforded.

BCG vaccine is recommended for routine use at birth in countries with high tuberculosis prevalence. However, because of the low risk of transmission of tuberculosis in the United States, the unreliable protection afforded by BCG, and its impact on the TST, the vaccine has never been recommended for general use in the United States. The CDC has recommended that HIV-infected adults and children not receive BCG vaccine, although the WHO has recommended that asymptomatic HIV-infected children residing in tuberculosis-endemic areas receive BCG.

Rx Treatment: LATENT TUBERCULOSIS INFECTION

Treatment of selected persons with LTBI aims at preventing active disease. This intervention (formerly called *preventive chemotherapy* or *chemoprophylaxis*) is based

on the results of a large number of randomized, placebo-controlled clinical trials demonstrating that a 6- to 12-month course of isoniazid reduces the risk of active tuberculosis in infected people by up to 90%. Analysis of available data indicates that the optimal duration of treatment is 9–10 months. In the absence of reinfection, the protective effect is believed to be life-long. Clinical trials have shown that isoniazid reduces rates of tuberculosis among TST-positive persons with HIV infection. Studies in HIV-infected patients have also demonstrated the effectiveness of shorter courses of rifampin-based treatment.

In most cases, candidates for treatment of LTBI (Table 12-4) are identified by the TST of persons in defined high-risk groups. For skin testing, 5 tuberculin units of polysorbate-stabilized PPD should be injected intradermally into the volar surface of the forearm (Mantoux method). Multipuncture tests are not recommended. Reactions are read at 48–72 h as the transverse diameter (in millimeters) of induration; the diameter of erythema is not considered. In some persons, TST reactivity wanes with time but can be recalled by a second skin test administered ≥ 1 week after the first (i.e., two-step testing). For persons periodically undergoing the TST, such as health care workers and individuals admitted to long-term care institutions, initial two-step testing may preclude subsequent misclassification of persons with boosted reactions as TST converters.

TABLE 12-4

TUBERCULIN REACTION SIZE AND TREATMENT OF LATENT TUBERCULOSIS INFECTION

RISK GROUP	TUBERCULIN REACTION SIZE, MM
HIV-infected persons or persons receiving immunosuppressive therapy	≥ 5
Close contacts of tuberculosis patients	$\geq 5^a$
Persons with fibrotic lesions on chest radiography	≥ 5
Recently infected persons (≤ 2 years)	≥ 10
Persons with high-risk medical conditions ^b	≥ 10
Low-risk persons ^c	≥ 15

^aTuberculin-negative contacts, especially children, should receive prophylaxis for 2 to 3 months after contact ends and should then undergo a repeat tuberculin skin test (TST). Those whose results remain negative should discontinue prophylaxis. HIV-infected contacts should receive a full course of treatment regardless of TST results.

^bIncludes diabetes mellitus, some hematologic and reticuloendothelial diseases, injection drug use (with HIV seronegativity), end-stage renal disease, and clinical situations associated with rapid weight loss.

^cExcept for employment purposes in which longitudinal TST screening is anticipated, TST is not indicated for these low-risk persons. A decision to treat should be based on individual risk–benefit considerations.

The cutoff for a positive TST result (and thus for treatment) is related both to the probability that the reaction represents true infection and to the likelihood that the individual, if truly infected, will develop tuberculosis (Table 12-4). Thus, positive reactions for close contacts of infectious cases, persons with HIV infection, persons receiving drugs that suppress the immune system, and previously untreated persons whose chest radiographs are consistent with healed tuberculosis are defined as an area of induration 5 mm or more in diameter. A 10-mm cutoff is used to define positive reactions in most other at-risk persons. For persons with a very low risk of developing tuberculosis if infected, a cutoff of 15 mm is used. (Except for employment purposes in which longitudinal screening is anticipated, the TST is not indicated for these low-risk persons.) Treatment should be considered for persons from tuberculosis-endemic countries who have a history of BCG vaccination. A positive reaction in an IGRA is not based on the degree of response (i.e., the level of IFN- γ induced).

Some TST-negative individuals are also candidates for treatment. Infants and children who have come into contact with infectious cases should be treated and should have a repeat skin test 2 or 3 months after contact ends. Those whose test results remain negative should discontinue treatment. HIV-infected persons who have been exposed to an infectious tuberculosis patient should receive treatment regardless of the TST result.

Isoniazid is administered at a daily dose of 5 mg/kg (up to 300 mg/d) for 9 months (Table 12-5). On the basis of cost-benefit analyses, a 6-month period of treatment has been recommended in the past and may be considered for HIV-negative adults with normal chest radiographs when financial considerations are important. When supervised treatment is desirable and feasible, isoniazid may be given at a dose of 15 mg/kg (up to 900 mg) twice weekly. An alternative regimen for adults is 4 months of daily rifampin. A 3-month regimen of isoniazid and rifampin is recommended in the United Kingdom for both adults and children. A previously recommended regimen of 2 months of rifampin and pyrazinamide has been associated with serious and fatal hepatotoxicity and is now generally not recommended. The rifampin regimen should be considered for persons who are likely to have been infected with an isoniazid-resistant strain.

Isoniazid should not be given to persons with active liver disease. All persons at increased risk of hepatotoxicity (e.g., those abusing alcohol daily and those with a history of liver disease) should undergo baseline and then monthly assessment of liver function. All patients should be carefully educated about hepatitis and instructed to discontinue use of the drug immediately if any symptoms develop. Moreover, patients should be seen and questioned monthly during therapy about

adverse reactions and should be given no more than 1 month's supply of drug at each visit.

It may be more difficult to ensure compliance when treating persons with latent infection than when treating those with active tuberculosis. If family members of active cases are being treated, compliance and monitoring may be easier. When feasible, twice-weekly supervised therapy may increase the likelihood of completion. As in active cases, the provision of incentives may also be helpful.

PRINCIPLES OF TUBERCULOSIS CONTROL

The highest priority in any tuberculosis control program is the prompt detection of cases and the provision of short-course chemotherapy to all tuberculosis patients under proper case-management conditions, including directly observed therapy. In addition, in low-prevalence countries with adequate resources, screening of high-risk groups (e.g., immigrants from high-prevalence countries, migratory workers, prisoners, homeless people, substance abusers, and HIV-seropositive persons) is recommended. TST-positive high-risk persons should be treated for latent infection. Contact investigation is an important component of efficient tuberculosis control. In the United States, a great deal of attention has been given to the transmission of tuberculosis (particularly in association with HIV infection) in institutional settings such as hospitals, homeless shelters, and prisons. Measures to limit such transmission include respiratory isolation of persons with suspected tuberculosis until they are proven to be noninfectious (i.e., by sputum AFB smear negativity), proper ventilation in rooms of patients with infectious tuberculosis, use of ultraviolet irradiation in areas of increased risk of tuberculosis transmission, and periodic screening of personnel who may come into contact with known or unsuspected cases of tuberculosis. In the past, radiographic surveys, especially those conducted with portable equipment and miniature films, were advocated for case finding. Today, however, the prevalence of tuberculosis in industrialized countries is sufficiently low that "mass miniature radiography" is not cost effective.

In high-prevalence countries, many tuberculosis control programs have made good progress in reducing morbidity and mortality during the past decade by adopting and implementing the DOTS strategy promoted by the WHO. This strategy consists of (1) political commitment with increased and sustained financing; (2) case detection through quality-assured bacteriology (starting with microscopic examination of sputum from patients with cough of >2–3 weeks' duration); (3) administration of standardized treatment, with supervision and patient support; (4) an effective drug supply and management system; and

TABLE 12-5

REVISED DRUG REGIMENS FOR TREATMENT OF LATENT TUBERCULOSIS INFECTION (LTBI) IN ADULTS

DRUG	INTERVAL AND DURATION	COMMENTS ^a	RATING ^b (EVIDENCE ^c)	
			HIV NEGATIVE	HIV INFECTED
Isoniazid	Daily for 9 months ^{d,e}	In HIV-infected persons, isoniazid may be administered concurrently with nucleoside reverse transcriptase inhibitors, protease inhibitors, or nonnucleoside reverse transcriptase inhibitors (NNRTIs).	A (II)	A (II)
	Twice weekly for 9 months ^{d,e}	Directly observed therapy (DOT) must be used with twice-weekly dosing.	B (II)	B (II)
	Daily for 6 months ^e	Regimen is not indicated for HIV-infected persons, those with fibrotic lesions on chest radiographs, or children.	B (I)	C (I)
	Twice weekly for 6 months ^e	DOT must be used with twice-weekly dosing.	B (II)	C (I)
Rifampin ^f	Daily for 4 months	Regimen is used for contacts of patients with isoniazid-resistant, rifampin-susceptible tuberculosis. In HIV-infected persons, most protease inhibitors and delavirdine should not be administered concurrently with rifampin. Rifabutin, with appropriate dose adjustments, can be used with protease inhibitors (saquinavir should be augmented with ritonavir) and NNRTIs (except delavirdine). Clinicians should consult Web-based updates for the latest specific recommendations.	B (II)	B (III)
Rifampin plus pyrazinamide (RZ)	Daily for 2 months	Regimen generally should not be offered for treatment of LTBI in either HIV-infected or HIV-negative persons.	D (II)	D (II)
	Twice weekly for 2–3 months		D (III)	D (III)

^aInteractions with HIV-related drugs are updated frequently and are available at <http://www.aidsinfo.nih.gov/guidelines>.

^bStrength of the recommendation: A. Both strong evidence of efficacy and substantial clinical benefit support recommendation for use. Should always be offered. B. Moderate evidence for efficacy or strong evidence for efficacy but only limited clinical benefit supports recommendation for use. Should generally be offered. C. Evidence for efficacy is insufficient to support a recommendation for or against use, or evidence for efficacy might not outweigh adverse consequences (e.g., drug toxicity, drug interactions) or cost of the treatment or alternative approaches. Optional. D. Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should generally not be offered. E. Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should never be offered.

^cQuality of evidence supporting the recommendation: I. Evidence from at least one properly randomized controlled trial. II. Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), from multiple time-series studies, or from dramatic results in uncontrolled experiments. III. Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

^dRecommended regimen for persons aged <18 years.

^eRecommended regimen for pregnant women.

^fThe substitution of rifapentine for rifampin is not recommended because rifapentine's safety and effectiveness have not been established for patients with LTBI.

Source: Adapted from CDC: Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR 49(RR-6), 2000.

(5) a monitoring and evaluation system, with impact measurement (including assessment of treatment outcomes—e.g., cure, completion of treatment without bacteriologic proof of cure, death, treatment failure, and default—in all cases registered and notified). In 2006, the WHO indicated that although DOTS remains the essential component of any control strategy, additional steps must be undertaken to reach the 2015 tuberculosis control targets set within

the United Nations Millennium Development Goals. Thus, a new “Stop TB Strategy” with six components has been promoted: (1) pursue high-quality DOTS expansion and enhancement; (2) address HIV-associated tuberculosis, MDR tuberculosis, and other special challenges; (3) contribute to health system strengthening; (4) engage all care providers; (5) empower people with tuberculosis and communities; and (6) enable and promote research. As part of

138 the fourth component, new evidence-based International Standards for Tuberculosis Care, focused on diagnosis, treatment, and public health responsibilities, have recently been introduced for wide adoption by medical and professional societies, academic institutions, and all practitioners worldwide.

FURTHER READINGS

AMERICAN THORACIC SOCIETY, CENTERS FOR DISEASE CONTROL AND PREVENTION: Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med* 161:S221, 2000

AMERICAN THORACIC SOCIETY, INFECTIOUS DISEASES SOCIETY OF AMERICA, CENTERS FOR DISEASE CONTROL AND PREVENTION: Treatment of tuberculosis. *Am J Respir Crit Care Med* 167:603, 2003

CENTERS FOR DISEASE CONTROL AND PREVENTION: Control of tuberculosis in the United States: Recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. *MMWR* 54:RR1, 2005

HOPEWELL PC et al: International standards for tuberculosis care. *Lancet Infect Dis* 6:710, 2006

MENZIES D et al: Meta-analysis: New tests for the diagnosis of latent tuberculosis infection: Areas of uncertainty and recommendations for research. *Ann Intern Med* 146:340, 2007 [PMID:17339619]

NAHID P et al: Treatment outcomes of patients with HIV and tuberculosis. *Am J Respir Crit Care Med* 175:1199, 2007 [PMID:17290042]

ONYEBUJOH PC et al: Treatment options for HIV-associated tuberculosis. *J Infect Dis* 196(Suppl 1):S35, 2007 [PMID:17726832]

PAI M et al: New tools and emerging technologies for the diagnosis of tuberculosis. Part I: Latent tuberculosis. Part II: Active tuberculosis and drug resistance. *Expert Rev Mol Diagn* 6:413, 2006

RAVIGLIONE MC, SMITH IM: XDR tuberculosis—Implications for global public health. *N Engl J Med* 356:656, 2007 [PMID:17301295]

——, UPLEKAR M: WHO's new Stop TB Strategy. *Lancet* 367:952, 2006

REID A et al: Towards universal access to HIV prevention, treatment, care and support: The role of tuberculosis/HIV collaboration. *Lancet Infect Dis* 6:483, 2006

VOLMINK J, GARNER P: Directly observed therapy for treating tuberculosis. *Cochrane Database Syst Rev* Oct 17(4):CD003343, 2007 [PMID:17943789]

WORLD HEALTH ORGANIZATION: Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, WHO, 2006

WRIGHT A et al: Global project on anti-tuberculosis drug resistance surveillance. Epidemiology of antituberculosis drug resistance 2002–07: An updated analysis of the Global Project on Anti-Tuberculosis Drug Resistance Surveillance. *Lancet* 373:186, 2009



CHAPTER 13

INFLUENZA

Raphael Dolin

Definition	139
Etiologic Agent	139
Epidemiology	140
Avian Influenza	140
Pathogenesis and Immunity	142
Clinical Manifestations	143
Complications	143
Laboratory Findings and Diagnosis	145
Differential Diagnosis	145
Prophylaxis	146
■ Further Readings	148

DEFINITION

Influenza is an acute respiratory illness caused by infection with influenza viruses. The illness affects the upper or lower respiratory tract (or both) and is often accompanied by systemic signs and symptoms such as fever, headache, myalgia, and weakness. Outbreaks of illness of variable extent and severity occur nearly every winter. Such outbreaks result in significant morbidity in the general population and in increased mortality rates among certain high-risk patients, mainly as a result of pulmonary complications.

ETIOLOGIC AGENT

Influenza viruses are members of the Orthomyxoviridae family, of which influenza A, B, and C viruses constitute three separate genera. The designation of influenza viruses as type A, B, or C is based on antigenic characteristics of the nucleoprotein (NP) and matrix (M) protein antigens. Influenza A viruses are further subdivided (subtyped) on the basis of the surface hemagglutinin (H) and neuraminidase (N) antigens (see later); individual strains are designated according to the site of origin, isolate number, year of isolation, and subtype—for example, influenza A/Hiroshima/52/2005 (H3N2). Influenza A has 16 distinct H subtypes and nine distinct N subtypes, of which

only H1, H2, H3, N1, and N2 have been associated with epidemics of disease in humans. Influenza B and C viruses are similarly designated, but H and N antigens from these viruses do not receive subtype designations because intratypic variations in influenza B antigens are less extensive than those in influenza A viruses and may not occur with influenza C virus.

Influenza A and B viruses are major human pathogens and the most extensively studied of the Orthomyxoviridae. Type A and type B viruses are morphologically similar. The virions are irregularly shaped spherical particles, measure 80 to 120 nm in diameter, and have a lipid envelope from the surface of which the H and N glycoproteins project (**Fig. 13-1**). Whereas the hemagglutinin is the site by which the virus binds to sialic acid cell receptors, the neuraminidase degrades the receptor and plays a role in the release of the virus from infected cells after replication has taken place. Influenza viruses enter cells by receptor-mediated endocytosis, forming a virus-containing endosome. The viral hemagglutinin mediates fusion of the endosomal membrane with the virus envelope, and viral nucleocapsids are subsequently released into the cytoplasm. Whereas immune responses to the H antigen are the major determinants of protection against infection with influenza virus, those to the N antigen limit viral spread and contribute to reduction of the infection. The lipid envelope of influenza A virus also

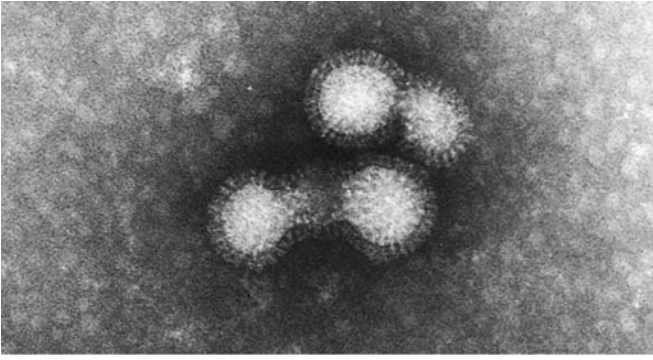


FIGURE 13-1
An electron micrograph of influenza A virus ($\times 40,000$).

contains the M proteins M1 and M2, which are involved in stabilization of the lipid envelope and in virus assembly. The virion also contains the NP antigen, which is associated with the viral genome, as well as three polymerase (P) proteins that are essential for transcription and synthesis of viral RNA. Two nonstructural proteins function as an interferon antagonist and posttranscriptional regulator (NS1) and a nuclear export factor (NS2 or NEP).

The genomes of influenza A and B viruses consist of eight single-stranded RNA segments, which code for the structural and nonstructural proteins. Because the genome is segmented, the opportunity for gene reassortment during infection is high; reassortment often occurs during infection of cells with more than one influenza A virus.

EPIDEMIOLOGY

Influenza outbreaks are recorded virtually every year, although their extent and severity vary widely. Localized outbreaks take place at variable intervals, usually every 1–3 years. Global pandemics have occurred at variable intervals but much less frequently than interpandemic outbreaks (Table 13-1). The most recent pandemic occurred in 1977—some 30 years ago as of this writing; because of this relatively long interval, concern exists that the next pandemic may be imminent.

Influenza A Virus

Antigenic Variation and Influenza Outbreaks

The most extensive and severe outbreaks are caused by influenza A viruses, in part because of the remarkable propensity of the H and N antigens of these viruses to undergo periodic antigenic variation. Major antigenic variations, called *antigenic shifts*, may be associated with pandemics and are restricted to influenza A viruses. Minor variations are called *antigenic drifts*. These types of antigenic variation may involve the hemagglutinin alone or both the hemagglutinin and the neuraminidase. An example of an antigenic shift involving both the

TABLE 13-1

EMERGENCE OF ANTIGENIC SUBTYPES OF INFLUENZA A VIRUS ASSOCIATED WITH PANDEMIC OR EPIDEMIC DISEASE

YEARS	SUBTYPE	EXTENT OF OUTBREAK
1889–1890	H2N8 ^a	Severe pandemic
1900–1903	H3N8 ^a	Moderate epidemic
1918–1919	H1N1 ^b	Severe pandemic
	(formerly HswN1)	
1933–1935	H1N1 ^b	Mild epidemic
	(formerly H0N1)	
1946–1947	H1N1	Mild epidemic
1957–1958	H2N2	Severe pandemic
1968–1969	H3N2	Moderate pandemic
1977–1978 ^c	H1N1	Mild pandemic

^aAs determined by retrospective serologic survey of individuals alive during those years (“seroarcheology”).

^bHemagglutinins formerly designated as Hsw and H0 are now classified as variants of H1.

^cFrom this time until the present (2006–2007), viruses of the H1N1 and H3N2 subtypes have circulated either in alternating years or concurrently.

hemagglutinin and the neuraminidase is that of 1957, when the predominant influenza A virus subtype shifted from H1N1 to H2N2; this shift resulted in a severe pandemic, with an estimated 70,000 excess deaths (i.e., deaths in excess of the number expected without an influenza epidemic) in the United States alone. In 1968, an antigenic shift involving only the hemagglutinin occurred (H2N2 to H3N2); the subsequent pandemic was less severe than that of 1957. In 1977, an H1N1 virus emerged and caused a pandemic that primarily affected younger individuals (i.e., those born after 1957). As can be seen in Table 13-1, H1N1 viruses circulated from 1918 to 1956; thus, individuals born before 1957 are expected to have some degree of immunity to H1N1 viruses. During most outbreaks of influenza A, a single subtype has circulated at a time. However, since 1977, H1N1 and H3N2 viruses have circulated simultaneously, resulting in outbreaks of varying severity. In some outbreaks, influenza B viruses have also circulated simultaneously with influenza A viruses.

AVIAN INFLUENZA



In 1997, human cases of influenza caused by avian influenza viruses (A/H5N1) were detected in Hong Kong during an extensive outbreak of influenza in poultry. Between that time and January 2007, 261 cases of avian influenza in humans were reported in 10 countries in Asia and the Middle East. Nearly all of these cases were associated with contact with infected poultry.

Efficient person-to-person transmission has not been observed to date. Mortality rates have been high (60%), and clinical manifestations have differed somewhat from those associated with “typical” outbreaks of influenza (see below). Transmission of avian influenza A/H7N7 viruses from infected poultry to humans has been observed in The Netherlands, resulting predominantly in cases of conjunctivitis and some respiratory illnesses. Infection with avian A/H9N2 viruses along with mild respiratory illness has been reported in children in Hong Kong. Because of the absence of widespread immunity to the H5, H7, and H9 viruses, concern has been raised that avian-to-human transmission may be the basis for the emergence of pandemic strains.

The origin of actual pandemic influenza A virus strains has now been partially elucidated with molecular virologic techniques. It appears that the pandemic strains of 1957 and 1968 resulted from a genetic reassortment between human viruses and avian viruses with novel surface glycoproteins (H2N2, H3). The influenza virus responsible for the most severe pandemic of modern times (1918–1919) appears to have represented an adaptation of an avian virus to efficient infection of humans. Close molecular surveillance of the avian viruses currently infecting humans is being conducted to provide early detection of possible pandemic strains.

Features of Pandemic and Interpandemic Influenza A

Pandemics provide the most dramatic evidence of the impact of influenza A. However, illnesses occurring between pandemics (i.e., interpandemic disease) account for extensive mortality and morbidity, albeit over a longer period. In the United States, influenza was associated with at least 19,000 excess deaths per season from 1976 to 1990 and with 36,000 excess deaths per season from 1990 to 1999. On average, there were 226,000 influenza-associated hospitalizations per year in this country from 1979 to 2001.

Influenza A viruses that circulate between pandemics demonstrate antigenic drifts in the H antigen. These antigenic drifts result from point mutations involving the RNA segment that codes for the hemagglutinin, which occur most frequently in five hypervariable regions. Epidemiologically significant strains—i.e., those with the potential to cause widespread outbreaks—exhibit changes in amino acids in at least two of the major antigenic sites in the hemagglutinin molecule. Because two point mutations are unlikely to occur simultaneously, it is believed that antigenic drifts result from point mutations occurring sequentially during the spread of virus from person to person. Antigenic drifts have been reported nearly annually since 1977 for H1N1 viruses and since 1968 for H3N2 viruses.

Influenza A epidemics begin abruptly, peak over a 2- to 3-week period, generally last for 2 to 3 months, and

often subside almost as rapidly as they began. The first indication of influenza activity in a community is an increase in the number of children with febrile respiratory illnesses who present for medical attention. This increase is followed by increases in rates of influenza-like illnesses among adults and eventually by an increase in hospital admissions for patients with pneumonia, worsening of congestive heart failure, and exacerbations of chronic pulmonary disease. Rates of absence from work and school also increase at this time. An increase in the number of deaths caused by pneumonia and influenza is generally a late observation in an outbreak. Attack rates have been highly variable from outbreak to outbreak but most commonly are in the range of 10–20% of the general population. During the pandemic of 1957, it was estimated that the attack rate of clinical influenza exceeded 50% in urban populations and that an additional 25% or more of individuals in these populations may have been subclinically infected with influenza A virus. Among institutionalized populations and in semi-closed settings with many susceptible individuals, even higher attack rates have been reported.

Epidemics of influenza A occur almost exclusively during the winter months in the temperate zones of the northern and southern hemispheres. In those locations, it is highly unusual to detect influenza A virus at other times, although increases in serum antibody titer or even outbreaks have been noted rarely during the warm months. In contrast, influenza virus infections occur throughout the year in the tropics. Where or how influenza A virus persists between outbreaks in temperate zones is unknown. It is possible that influenza A viruses are maintained in the human population on a worldwide basis by person-to-person transmission and that large population clusters support a low level of interepidemic transmission. Alternatively, human strains may persist in animal reservoirs. Convincing evidence to support either explanation is not available. In the modern era, rapid transportation may contribute to the transmission of viruses among widespread geographic locales.

The factors that result in the inception and termination of outbreaks of influenza A are incompletely understood. A major determinant of the extent and severity of an outbreak is the level of immunity in the population at risk. With the emergence of an antigenically novel influenza virus to which little or no immunity is present in a community, extensive outbreaks may occur. When the absence of immunity is worldwide, epidemic disease may spread around the globe, resulting in a pandemic. Such pandemic waves can continue for several years until immunity in the population reaches a high level. In the years after pandemic influenza, antigenic drifts among influenza viruses result in outbreaks of variable severity in populations with high levels of immunity to the pandemic strain that circulated earlier. This situation persists until another antigenically novel pandemic strain

142 emerges. On the other hand, outbreaks sometimes end despite the persistence of a large pool of susceptible individuals in the population. It has been suggested that certain influenza A viruses, such as recently circulating A/H1N1 strains, may be intrinsically less virulent and cause less severe disease than other variants, even in immunologically virgin subjects. If so, then other (undefined) factors besides the level of preexisting immunity must play a role in the epidemiology of influenza.

SECTION II

Diseases of the Respiratory System

Influenza B and C Viruses

Influenza B virus causes outbreaks that are generally less extensive and are associated with less severe disease than those caused by influenza A virus. The hemagglutinin and neuraminidase of influenza B virus undergo less frequent and less extensive variation than those of influenza A viruses; this characteristic may account, in part, for the lesser extent of disease. Influenza B outbreaks are seen most frequently in schools and military camps, although outbreaks in institutions in which elderly individuals reside have also been noted on occasion. The most serious complication of influenza B virus infection is Reye's syndrome.

In contrast to influenza A and B viruses, influenza C virus appears to be a relatively minor cause of disease in humans. It has been associated with common cold-like symptoms and occasionally with lower respiratory tract illness. Serum antibody to this virus is widely prevalent and indicates that asymptomatic infection may be common.

Influenza-Associated Morbidity and Mortality

The morbidity and mortality caused by influenza outbreaks continue to be substantial. Most individuals who die in this setting have underlying diseases that place them at high risk for complications of influenza. Excess hospitalizations for groups of adults and children with high-risk medical conditions ranged from 56 to 1900 per 100,000 during outbreaks of influenza from 1973 to 1993. The most prominent high-risk conditions are chronic cardiac and pulmonary diseases and old age. Mortality rates among individuals with chronic metabolic or renal disease or certain immunosuppressive diseases have also been elevated, albeit lower than those among patients with chronic cardiopulmonary diseases. The morbidity attributable to influenza in the general population is considerable. It is estimated that interpandemic outbreaks of influenza currently incur annual costs of more than \$12 billion in the United States. If a pandemic were to occur, it is estimated that annual costs would range from \$71 to \$167 billion for attack rates of 15–35%.

PATHOGENESIS AND IMMUNITY

The initial event in influenza is infection of the respiratory epithelium with influenza virus acquired from

respiratory secretions of acutely infected individuals. In all likelihood, the virus is transmitted via aerosols generated by coughs and sneezes, although hand-to-hand contact, other personal contact, and even fomite transmission may take place. Experimental evidence suggests that infection by a small-particle aerosol (particle diameter, $<10\ \mu\text{m}$) is more efficient than that by larger droplets. Initially, viral infection involves the ciliated columnar epithelial cells, but it may also involve other respiratory tract cells, including alveolar cells, mucous gland cells, and macrophages. In infected cells, virus replicates within 4–6 h, after which infectious virus is released to infect adjacent or nearby cells. In this way, infection spreads from a few foci to a large number of respiratory cells over several hours. In experimentally induced infection, the incubation period of illness has ranged from 18 to 72 h, depending on the size of the viral inoculum. Histopathologic study reveals degenerative changes, including granulation, vacuolization, swelling, and pyknotic nuclei, in infected ciliated cells. The cells eventually become necrotic and desquamate; in some areas, previously columnar epithelium is replaced by flattened and metaplastic epithelial cells. The severity of illness is correlated with the quantity of virus shed in secretions; thus, the degree of viral replication itself may be an important factor in pathogenesis. Despite the frequent development of systemic signs and symptoms such as fever, headache, and myalgias, influenza virus has only rarely been detected in extrapulmonary sites (including the bloodstream). Evidence suggests that the pathogenesis of systemic symptoms in influenza may be related to the induction of certain cytokines, particularly tumor necrosis factor α , interferon α , interleukin 6, and interleukin 8, in respiratory secretions and in the bloodstream.

The host response to influenza infections involves a complex interplay of humoral antibody, local antibody, cell-mediated immunity, interferon, and other host defenses. Serum antibody responses, which can be detected by the second week after primary infection, are measured by a variety of techniques: hemagglutination inhibition (HI), complement fixation (CF), neutralization, enzyme-linked immunosorbent assay (ELISA), and antineuraminidase antibody assay. Antibodies to the hemagglutinin appear to be the most important mediators of immunity; in several studies, HI titers of ≥ 40 have been associated with protection from infection. Secretory antibodies produced in the respiratory tract are predominantly of the IgA class and also play a major role in protection against infection. Secretory antibody neutralization titers of ≥ 4 have also been associated with protection. A variety of cell-mediated immune responses, both antigen-specific and antigen-nonspecific, can be detected early after infection and depend on the prior immune status of the host. These responses include T cell proliferative, T cell cytotoxic, and natural killer cell

activity. In humans, CD8+ HLA class I–restricted cytotoxic T lymphocytes (CTLs) are directed at conserved regions of internal proteins (NP, M, and polymerases) as well as against the surface proteins (H and N). Interferons can be detected in respiratory secretions shortly after the shedding of virus has begun, and increases in interferon titers coincide with decreases in virus shedding.

The host defense factors responsible for cessation of virus shedding and resolution of illness have not been defined specifically. Virus shedding generally stops within 2 to 5 days after symptoms first appear, at a time when serum and local antibody responses often are not detectable by conventional techniques (although antibody increases may be detected earlier by use of highly sensitive techniques, particularly in individuals with previous immunity to the virus). It has been suggested that interferon, cell-mediated immune responses, or nonspecific inflammatory responses all contribute to the resolution of illness. CTL responses may be particularly important in this regard.

CLINICAL MANIFESTATIONS

Influenza has most frequently been described as an illness characterized by the abrupt onset of systemic symptoms, such as headache, feverishness, chills, myalgia, or malaise, and accompanying respiratory tract signs, particularly cough and sore throat. In many cases, the onset is so abrupt that patients can recall the precise time they became ill. However, the spectrum of clinical presentations is wide, ranging from a mild, afebrile respiratory illness similar to the common cold (with either a gradual or an abrupt onset) to severe prostration with relatively few respiratory signs and symptoms. In most of the cases that come to a physician's attention, the patient has a fever, with a temperature of 38°–41°C (100.4°–105.8°F). A rapid temperature increase within the first 24 h of illness is generally followed by gradual defervescence over 2–3 days, although, on occasion, fever may last as long as 1 week. Patients report a feverish feeling and chilliness, but true rigors are rare. Headache, either generalized or frontal, is often particularly troublesome. Myalgias may involve any part of the body but are most common in the legs and lumbosacral area. Arthralgias may also develop.

Respiratory symptoms often become more prominent as systemic symptoms subside. Many patients have a sore throat or persistent cough, which may last for ≥ 1 week and which is often accompanied by substernal discomfort. Ocular signs and symptoms include pain on motion of the eyes, photophobia, and burning of the eyes.

Physical findings are usually minimal in uncomplicated influenza. Early in the illness, the patient appears flushed, and the skin is hot and dry, although diaphoresis and mottled extremities are sometimes evident, particularly in older patients. Examination of the pharynx may

yield surprisingly unremarkable results despite a severe sore throat, but injection of the mucous membranes and postnasal discharge are apparent in some cases. Mild cervical lymphadenopathy may be noted, especially in younger individuals. The results of chest examination are largely negative in uncomplicated influenza, although rhonchi, wheezes, and scattered rales have been reported with variable frequency in different outbreaks. Frank dyspnea, hyperpnea, cyanosis, diffuse rales, and signs of consolidation indicate pulmonary complications. Patients with apparently uncomplicated influenza have been reported to have a variety of mild ventilatory defects and increased alveolar–capillary diffusion gradients; thus, subclinical pulmonary involvement may be more common than is appreciated.

In uncomplicated influenza, the acute illness generally resolves over 2–5 days, and most patients have largely recovered in 1 week, although cough may persist 1–2 weeks longer. In a significant minority (particularly the elderly), however, symptoms of weakness or lassitude (postinfluenza asthenia) may persist for several weeks and may prove troublesome for persons who wish to resume their full level of activity promptly. The pathogenetic basis for this asthenia is unknown, although pulmonary function abnormalities may persist for several weeks after uncomplicated influenza.

COMPLICATIONS

Complications of influenza occur most frequently in patients >64 years and in those with certain chronic disorders, including cardiac or pulmonary diseases, diabetes mellitus, hemoglobinopathies, renal dysfunction, and immunosuppression. Pregnancy in the second or third trimester also predisposes to complications with influenza. Children younger than age 2 years (especially infants) are also at high risk for complications.

Pulmonary Complications

■ Pneumonia

The most significant complication of influenza is pneumonia: “primary” influenza viral pneumonia, secondary bacterial pneumonia, or mixed viral and bacterial pneumonia.

■ Primary Influenza Viral Pneumonia

Primary influenza viral pneumonia is the least common but most severe of the pneumonic complications. It presents as acute influenza that does not resolve but instead progresses relentlessly, with persistent fever, dyspnea, and eventual cyanosis. Sputum production is generally scanty, but the sputum can contain blood. Few physical signs may be evident early in the illness. In more advanced cases, diffuse rales may be noted, and chest x-ray findings consistent with diffuse interstitial infiltrates

144 or acute respiratory distress syndrome may be present. In such cases, arterial blood gas determinations show marked hypoxia. Viral cultures of respiratory secretions and lung parenchyma, especially if samples are taken early in illness, yield high titers of virus. In fatal cases of primary viral pneumonia, histopathologic examination reveals a marked inflammatory reaction in the alveolar septa, with edema and infiltration by lymphocytes, macrophages, occasional plasma cells, and variable numbers of neutrophils. Fibrin thrombi in alveolar capillaries, along with necrosis and hemorrhage, have also been noted. Eosinophilic hyaline membranes can be found lining alveoli and alveolar ducts.

Primary influenza viral pneumonia has a predilection for individuals with cardiac disease, particularly those with mitral stenosis, but has also been reported in otherwise healthy young adults as well as in older individuals with chronic pulmonary disorders. In some epidemics of influenza (notably those of 1918 and 1957), pregnancy increased the risk of primary influenza pneumonia. Subsequent epidemics of influenza have been associated with increased rates of hospitalization among pregnant women.

Secondary Bacterial Pneumonia

Secondary bacterial pneumonia occurs after acute influenza. Improvement of the patient's condition over 2–3 days is followed by a reappearance of fever along with clinical signs and symptoms of bacterial pneumonia, including cough, production of purulent sputum, and physical and x-ray signs of consolidation. The most common bacterial pathogens in this setting are *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae*—organisms that can colonize the nasopharynx and that cause infection in the wake of changes in bronchopulmonary defenses. The etiology can often be determined by Gram's staining and culture of an appropriately obtained sputum specimen. Secondary bacterial pneumonia occurs most frequently in high-risk individuals with chronic pulmonary and cardiac disease and in elderly individuals. Patients with secondary bacterial pneumonia often respond to antibiotic therapy when it is instituted promptly.

Mixed Viral and Bacterial Pneumonia

Perhaps the most common pneumonic complications during outbreaks of influenza have mixed features of viral and bacterial pneumonia. Patients may experience a gradual progression of their acute illness or may show transient improvement followed by clinical exacerbation, with eventual manifestation of the clinical features of bacterial pneumonia. Sputum cultures may contain both influenza A virus and one of the bacterial pathogens described above. Patchy infiltrates or areas of consolidation may be detected by physical examination and chest x-ray. Patients with mixed viral and bacterial pneumonia generally have less widespread involvement

of the lung than those with primary viral pneumonia, and their bacterial infections may respond to appropriate antibacterial drugs. Mixed viral and bacterial pneumonia occurs primarily in patients with chronic cardiovascular and pulmonary diseases.

Other Pulmonary Complications

Other pulmonary complications associated with influenza include worsening of chronic obstructive pulmonary disease and exacerbation of chronic bronchitis and asthma. In children, influenza infection may present as croup. Sinusitis as well as otitis media (the latter occurring particularly often in children) may also be associated with influenza.

Extrapulmonary Complications

In addition to the pulmonary complications of influenza, a number of extrapulmonary complications may occur. These include *Reye's syndrome*, a serious complication in children that is associated with influenza B and to a lesser extent with influenza A virus infection as well as with varicella-zoster virus infection. An epidemiologic association between Reye's syndrome and aspirin therapy for the antecedent viral infection has been noted, and the syndrome's incidence has decreased markedly with widespread warnings regarding aspirin use by children with acute viral respiratory infections.

Myositis, rhabdomyolysis, and myoglobinuria are occasional complications of influenza infection. Although myalgias are exceedingly common in influenza, true myositis is rare. Patients with acute myositis have exquisite tenderness of the affected muscles, most commonly in the legs, and may not be able to tolerate even the slightest pressure, such as the touch of bedsheets. In the most severe cases, there is frank swelling and boggy muscles. Serum levels of creatine phosphokinase and aldolase are markedly elevated, and an occasional patient develops renal failure from myoglobinuria. The pathogenesis of influenza-associated myositis is also unclear, although the presence of influenza virus in affected muscles has been reported.

Myocarditis and pericarditis were reported in association with influenza virus infection during the 1918–1919 pandemic; these reports were based largely on histopathologic findings, and these complications have been reported only infrequently since that time. Electrocardiographic changes during acute influenza are common among patients who have cardiac disease but have been ascribed most often to exacerbations of the underlying cardiac disease rather than to direct involvement of the myocardium with influenza virus.

Central nervous system (CNS) diseases, including encephalitis, transverse myelitis, and Guillain-Barré syndrome, have been reported during influenza. The etiologic relationship of influenza virus to such CNS illnesses

remains uncertain. Toxic shock syndrome associated with *S. aureus* or group A streptococcal infection after acute influenza infection has also been reported.

In addition to complications involving the specific organ systems described above, influenza outbreaks include a number of cases in which elderly and other high-risk individuals develop influenza and subsequently experience a gradual deterioration of underlying cardiovascular, pulmonary, or renal function—changes that occasionally are irreversible and lead to death. These deaths contribute to the overall excess mortality rate associated with influenza A outbreaks.

Complications of Avian Influenza

Cases of influenza caused by avian A/H5N1 virus are reportedly associated with high rates of pneumonia (>50%) and extrapulmonary manifestations such as diarrhea and CNS involvement. Deaths have been associated with multisystem dysfunction, including cardiac and renal failure.

LABORATORY FINDINGS AND DIAGNOSIS

During acute influenza, virus may be detected in throat swabs, nasopharyngeal washes, or sputum. The virus can be isolated by use of tissue culture—or, less commonly, chick embryos—within 48–72 h after inoculation. Most commonly, the laboratory diagnosis is established with rapid viral tests that detect viral nucleoprotein or neuraminidase by means of immunologic or enzymatic techniques that are highly sensitive and 60–90% as specific as tissue culture. Viral nucleic acids can also be detected in clinical samples by reverse transcriptase polymerase chain reaction. The type of the infecting influenza virus (A or B) may be determined by either immunofluorescence or HI techniques, and the hemagglutinin subtype of influenza A virus (H1, H2, or H3) may be identified by HI with use of subtype-specific antisera. Serologic methods for diagnosis require comparison of antibody titers in sera obtained during the acute illness with those in sera obtained 10–14 days after the onset of illness and are useful primarily in retrospect. Fourfold or greater titer increases as detected by HI or CF or significant increases as measured by ELISA are diagnostic of acute infection. CF tests are generally less sensitive than other serologic techniques, but because they detect type-specific antigens, they may be particularly useful when subtype-specific reagents are not available.

Other laboratory tests generally are not helpful in the specific diagnosis of influenza virus infection. Leukocyte counts are variable, frequently being low early in illness and normal or slightly elevated later. Severe leukopenia has been described in overwhelming viral or bacterial infection, and leukocytosis with >15,000 cells/ μ L raises the suspicion of secondary bacterial infection.

DIFFERENTIAL DIAGNOSIS

During a community-wide outbreak, a clinical diagnosis of influenza can be made with a high degree of certainty in patients who present to a physician's office with the typical febrile respiratory illness described above. In the absence of an outbreak (i.e., in sporadic or isolated cases), influenza may be difficult to differentiate on clinical grounds alone from an acute respiratory illness caused by any of a variety of respiratory viruses or by *Mycoplasma pneumoniae*. Severe streptococcal pharyngitis or early bacterial pneumonia may mimic acute influenza, although bacterial pneumonias generally do not run a self-limited course. Purulent sputum in which a bacterial pathogen can be detected by Gram's staining is an important diagnostic feature in bacterial pneumonia.

Rx Treatment: INFLUENZA

In uncomplicated cases of influenza, symptom-based therapy with acetaminophen for the relief of headache, myalgia, and fever may be considered, but the use of salicylates should be avoided in children <18 years of age because of the possible association of salicylates with Reye's syndrome. Because cough is ordinarily self-limited, treatment with cough suppressants generally is not indicated, although codeine-containing compounds may be used if the cough is particularly troublesome. Patients should be advised to rest and maintain hydration during acute illness and to return to full activity only gradually after illness has resolved, especially if it has been severe.

Specific antiviral therapy is available for influenza (**Table 13-2**): the neuraminidase inhibitors zanamivir and oseltamivir for both influenza A and influenza B and the adamantane agents amantadine and rimantadine for influenza A (Chap. 43). In 2005 to 2006, resistance to amantadine was reported in >90% of A/H3N2 viral isolates; thus, amantadine and rimantadine are no longer recommended, but their use may be reconsidered if sensitivity becomes reestablished.

Oseltamivir (administered orally at a dose of 75 mg twice a day for 5 days) or zanamivir (which must be given by an oral inhalation device; 10 mg twice a day for 5 days) reduces the duration of signs and symptoms of influenza by 1–1.5 days if treatment is started within 2 days of the onset of illness. Zanamivir may exacerbate bronchospasm in asthmatic patients, and oseltamivir has been associated with nausea and vomiting, whose frequency can be reduced by administration of the drug with food. Oseltamivir has also been associated with neuropsychiatric side effects in children.

If begun within 48 h of the onset of illness caused by sensitive influenza A virus strains, treatment with

ANTIVIRAL MEDICATIONS FOR TREATMENT AND PROPHYLAXIS OF INFLUENZA

ANTIVIRAL DRUG	AGE GROUP (YEARS)		
	CHILDREN (≤12)	13–64	≥65
Oseltamivir			
Treatment, influenza A and B	Age 1–12, dose varies by weight ^a	75 mg PO bid	75 mg PO bid
Prophylaxis, influenza A and B	Age 1–12, dose varies by weight ^b	75 PO qd	75 mg PO qd
Zanamivir			
Treatment, influenza A and B	Age 7–12, 10 mg bid by inhalation	10 mg bid by inhalation	10 mg bid by inhalation
Prophylaxis, influenza A and B	Age 5–12, 10 mg qd by inhalation	10 mg qd by inhalation	10 mg qd by inhalation
Amantadine ^c			
Treatment, influenza A	Age 1–9, 5 mg/kg in 2 divided doses, ≤150 mg/d	Age ≥10, 100 mg PO bid	≤100 mg/d
Prophylaxis, influenza A	Age 1–9, 5 mg/kg in 2 divided doses, ≤150 mg/d	Age ≥10, 100 mg PO bid	≤100 mg/d
Rimantadine ^c			
Treatment, influenza A	Not approved	100 mg PO bid	100–200 mg/d
Prophylaxis, influenza A	Age 1–9, 5 mg/kg in 2 divided doses, ≤150 mg/d	Age ≥10, 100 mg PO bid	100–200 mg/d

^a<15 kg: 30 mg bid; >15–23 kg: 45 mg bid; >23–40 kg: 60 mg bid; >40 kg: 75 mg bid.

^b<15 kg: 30 mg qd; >15–23 kg: 45 mg qd; >23–40 kg: 60 mg qd; >40 kg: 75 mg qd.

^cAmantadine and rimantadine are not currently recommended (2006–2007) because of widespread resistance in influenza A/H3N2 viruses. Their use may be reconsidered if viral susceptibility is reestablished.

amantadine or rimantadine reduces the duration of systemic and respiratory symptoms of influenza by ~50%. Of individuals who receive amantadine, 5–10% experience mild CNS side effects, primarily jitteriness, anxiety, insomnia, or difficulty concentrating. These side effects disappear promptly upon cessation of therapy. Rimantadine appears to be equally efficacious and is associated with less frequent CNS side effects than is amantadine. In adults, the usual dose of amantadine or rimantadine is 200 mg/d for 3–7 days. Because both drugs are excreted via the kidney, the dose should be reduced to ≤100 mg/d in elderly patients and in patients with renal insufficiency. Resistant viruses emerge frequently during treatment with amantadine or rimantadine and can be transmitted among family members. Development of resistance to zanamivir or oseltamivir appears to be less common but can occur. Ribavirin is a nucleoside analogue with activity against influenza A and B viruses in vitro. It has been reported to be variably effective against influenza when administered as an aerosol but ineffective when administered orally. Its efficacy in the treatment of influenza A or B is unestablished.

Studies demonstrating the therapeutic efficacy of antiviral compounds in influenza have primarily involved young adults with uncomplicated disease. A meta-analysis of studies with oseltamivir suggests that treatment may reduce the likelihood of some lower respiratory tract complications of influenza. However, it is not known whether antiviral agents are themselves effective in the treatment of influenza pneumonia or of

other complications of influenza. Therapy for primary influenza pneumonia is directed at maintaining oxygenation and is most appropriately undertaken in an intensive care unit, with aggressive respiratory and hemodynamic support as needed. Bypass membrane oxygenators have been used in this setting with variable results. When an acute respiratory distress syndrome develops, fluids must be administered cautiously, with close monitoring of blood gases and hemodynamic function.

Antibacterial drugs should be reserved for the treatment of bacterial complications of acute influenza, such as secondary bacterial pneumonia. The choice of antibiotics should be guided by Gram's staining and culture of appropriate specimens of respiratory secretions, such as sputum or transtracheal aspirates. If the etiology of a case of bacterial pneumonia is unclear from an examination of respiratory secretions, empirical antibiotics effective against the most common bacterial pathogens in this setting (*S. pneumoniae*, *S. aureus*, and *H. influenzae*) should be selected.

PROPHYLAXIS

Inactivated and live attenuated vaccines against influenza are available, and their use represents the major public health measure for prevention of influenza. The vast majority of currently used vaccines are inactivated (“killed”) preparations derived from influenza A and B viruses that

circulated during the previous influenza season. If the vaccine virus and the currently circulating viruses are closely related, 50–80% protection against influenza would be expected from inactivated vaccines. The available inactivated vaccines have been highly purified and are associated with few reactions. Up to 5% of individuals experience low-grade fever and mild systemic symptoms 8–24 h after vaccination and up to one-third develop mild redness or tenderness at the vaccination site. Because the vaccine is produced in eggs, individuals with true hypersensitivity to egg products either should be desensitized or should not be vaccinated. Although the 1976 swine influenza vaccine appears to have been associated with an increased frequency of Guillain-Barré syndrome, influenza vaccines administered since 1976 generally have not been. Possible exceptions were noted during the 1992–1993 and 1993–1994 influenza seasons, when there may have been an excess risk of Guillain-Barré syndrome of slightly more than one case per million vaccine recipients. However, the overall health risk after influenza outweighs the potential risk associated with vaccination.

The U.S. Public Health Service recommends the administration of inactivated influenza vaccine to individuals who, because of age or underlying disease, are at increased risk for complications of influenza and to the contacts of these individuals (Table 13-3). Inactivated vaccines may be administered safely to immunocompromised patients. Influenza vaccination is not associated with exacerbations of chronic CNS diseases such as multiple sclerosis. Vaccine should be administered early in the autumn before influenza outbreaks occur and should then be given annually to maintain immunity against the most current influenza virus strains.

A live attenuated influenza vaccine that is administered by intranasal spray is also available. The vaccine is generated by reassortment between currently circulating strains of influenza A and B virus and a cold-adapted, attenuated master strain. The cold-adapted vaccine is well tolerated and highly efficacious (92% protective) in young children; in one study, it provided protection against a circulating influenza virus that had drifted antigenically away from the vaccine strain. Live attenuated vaccine is approved for use in healthy persons 5–49 years of age.

Antiviral drugs may also be used as chemoprophylaxis against influenza (see Table 13-2). Chemoprophylaxis with oseltamivir (75 mg/d by mouth) or zanamivir (10 mg/d inhaled) has been 84–89% efficacious against influenza A and B. Chemoprophylaxis with amantadine or rimantadine is no longer recommended because of reports of widespread resistance to these drugs. In earlier studies with sensitive viruses, prophylaxis with amantadine or rimantadine (100–200 mg/d) was 70–100% effective against illness associated with influenza A. Chemoprophylaxis is most likely to be used for high-risk individuals who have not received influenza vaccine or

TABLE 13-3

PERSONS FOR WHOM ANNUAL INFLUENZA VACCINATION IS RECOMMENDED

Children 6–59 months old
Women who will be pregnant during the influenza season
Persons ≥50 years old
Children and adolescents (6 months–18 years old) who are receiving long-term aspirin therapy and therefore may be at risk for developing Reye's syndrome after influenza
Adults and children who have chronic disorders of the pulmonary or cardiovascular systems, including asthma ^a
Adults and children who have required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunodeficiency (including immunodeficiency caused by medications or by HIV)
Adults and children who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or can increase the risk of aspiration
Residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions
Persons who live with or care for persons at high risk for influenza-related complications, including healthy household contacts of and caregivers for children from birth through 59 months of age
Health care workers

^aHypertension itself is not considered a chronic disorder for which influenza vaccination is recommended.

Source: Centers for Disease Control and Prevention: Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 55(RR-11):1, 2006.

in a situation where the vaccines previously administered are relatively ineffective because of antigenic changes in the circulating virus. During an outbreak, antiviral chemoprophylaxis can be administered simultaneously with inactivated vaccine, since the drugs do not interfere with an immune response to the vaccine. In fact, evidence suggests that the protective effects of chemoprophylaxis and inactivated vaccine may be additive. However, concurrent administration of chemoprophylaxis and the live attenuated vaccine may interfere with the immune response to the latter. Antiviral drugs should not be administered until at least 2 weeks after administration of live vaccine, and vaccination with live vaccine should not begin until at least 48 h after antiviral drug administration has been stopped. Chemoprophylaxis may also be used to control nosocomial outbreaks of influenza. For that purpose, prophylaxis should be instituted promptly when influenza activity is detected and must be continued daily for the duration of the outbreak.

148 FURTHER READINGS

- BEIGEL JH et al: Avian influenza A (H5N1) infection in humans. *N Engl J Med* 353:1374, 2005
- BELSHE RB et al: The efficacy of live attenuated, cold adapted trivalent, intranasal influenza vaccine in children. *N Engl J Med* 38:1405, 1998
- CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC): Prevention and control of influenza. *MMWR* 55(RR-11):1, 2006
- : Severe Methicillin-Resistant *Staphylococcus aureus* Community-Acquired Pneumonia Associated with Influenza. Louisiana and Georgia, December 2006–January 2007
- COOPER NJ et al: Effectiveness of neuraminidase inhibitors in treatment and prevention of influenza A and B: Systematic review and meta-analysis of randomized controlled trials. *BMJ* 326:1235, 2003
- DOLIN R: Interpandemic as well as pandemic disease. *N Engl J Med* 353:2535, 2005
- FIGLIORE AE et al: Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2007. *MMWR Recomm Rep* 56:1, 2007 [PMID:17625497]
- HATAKEYAMA S et al: Emergence of influenza B viruses with reduced sensitivity to neuraminidase inhibitors. *JAMA* 297:1435, 2007 [PMID:17405969]
- HAYDEN FG et al: Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. *N Engl J Med* 341:1336, 1999
- MELTZER MI et al: The economic impact of pandemic influenza in the United States: Priorities for intervention. *Emerg Infect Dis* 5:659, 1999
- MIST [MANAGEMENT OF INFLUENZA IN THE SOUTHERN HEMISPHERE TRIALISTS] STUDY GROUP: Randomized trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B infections. *Lancet* 352:1871, 1998
- NEUZIL KM et al: Influenza-associated morbidity and mortality in young and middle-aged women. *JAMA* 281:901, 1999
- NOVEL SWINE-ORIGIN INFLUENZA A (H1N1) VIRUS INVESTIGATION TEAM et al: Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *N Engl J Med*, 360(25), 2009, pp 2605–15
- ROTHBERG MB, HAESSLER SD, BROWN RB: Complications of viral influenza. *Am J Med* 121:258, 2008 [PMID:18374680]
- SHINDE V et al: Triple-reassortant swine influenza A (H1) in humans in the United States, 2005–2009. *N Engl J Med*, 360(25), 2009, pp 2616–25
- SIMONSEN L et al: Pandemic vs epidemic mortality: A pattern of changing age distribution. *J Infect Dis* 178:53, 1998
- TREANOR JJ: Influenza virus, in *Principles and Practice of Infectious Diseases*, 6th ed, GL Mandell et al (eds). Philadelphia, Elsevier, 2005, pp 2201–2203
- WRITING COMMITTEE OF THE SECOND WORLD HEALTH ORGANIZATION CONSULTATION ON CLINICAL ASPECTS OF HUMAN INFECTION WITH AVIAN INFLUENZA A (H5N1) VIRUS et al: Update on avian influenza A (H5N1) virus infection in humans. *N Engl J Med* 358:261, 2008 [PMID:18199865]



CHAPTER 14

COMMON VIRAL RESPIRATORY INFECTIONS AND SEVERE ACUTE RESPIRATORY SYNDROME (SARS)

Raphael Dolin

General Considerations	149	Prevention	156
■ Rhinovirus Infections	150	■ Human Metapneumovirus Infections	157
Etiologic Agent	150	Etiologic Agent	157
Epidemiology	151	Epidemiology	157
Pathogenesis	151	Clinical Manifestations	157
Clinical Manifestations	151	Diagnosis	157
Diagnosis	152	Prevention	157
Prevention	152	■ Parainfluenza Virus Infections	157
■ Coronavirus Infections, Including SARS	152	Etiologic Agent	157
Etiologic Agent	152	Epidemiology	157
Epidemiology	152	Pathogenesis	158
Pathogenesis	153	Clinical Manifestations	158
Clinical Manifestations	153	Laboratory Findings and Diagnosis	158
Laboratory Findings and Diagnosis	153	Prevention	158
Prevention	154	■ Adenovirus Infections	158
■ Human Respiratory Syncytial Virus Infections	155	Etiologic Agent	158
Etiologic Agent	155	Epidemiology	159
Epidemiology	155	Clinical Manifestations	159
Pathogenesis	155	Laboratory Findings and Diagnosis	159
Clinical Manifestations	156	Prevention	160
Laboratory Findings and Diagnosis	156	■ Further Readings	160

GENERAL CONSIDERATIONS

Acute viral respiratory illnesses are among the most common of human diseases, accounting for one-half or more of all acute illnesses. The incidence of acute respiratory disease in the United States is 3 to 5.6 cases per person per year. The rates are highest among children <1 year old (6.1–8.3 cases per year) and remain high until age 6 years, when a progressive decrease begins. Adults have three to four cases per person per year. Morbidity from acute respiratory illnesses accounts for 30–50% of time lost from work by adults and for 60–80% of time lost from school by children. The use of antibacterial agents to treat viral respiratory infections represents a major source of abuse of that category of drugs.

It has been estimated that two-thirds to three-fourths of cases of acute respiratory illnesses are caused by viruses. More than 200 antigenically distinct viruses from 10 genera have been reported to cause acute respiratory illness, and it is likely that additional agents will be described in the future. The vast majority of these viral infections involve the upper respiratory tract, but lower respiratory tract disease can also develop, particularly in younger age groups, in the elderly, and in certain epidemiologic settings.

The illnesses caused by respiratory viruses traditionally have been divided into multiple distinct syndromes, such as the “common cold,” pharyngitis, croup (laryngotracheobronchitis), tracheitis, bronchiolitis, bronchitis, and pneumonia. Each of these general categories of

150 illness has a certain epidemiologic and clinical profile; for example, croup occurs exclusively in very young children and has a characteristic clinical course. Some types of respiratory illness are more likely to be associated with certain viruses (e.g., the common cold with rhinoviruses), but others occupy characteristic epidemiologic niches (e.g., adenovirus infections in military recruits). The syndromes most commonly associated with infections with the major respiratory virus groups are summarized in **Table 14-1**. Most respiratory viruses clearly have the potential to cause more than one type of respiratory illness, and features of several types of illness may be found in the same patient. Moreover, the clinical illnesses induced by these viruses are rarely sufficiently distinctive to permit an etiologic diagnosis on clinical grounds alone, although the epidemiologic setting increases the likelihood that one group of viruses rather than another is involved. In general, laboratory methods must be relied on to establish a specific viral diagnosis.

This chapter reviews viral infections caused by six of the major groups of respiratory viruses: rhinoviruses, coronaviruses, respiratory syncytial viruses, metapneumoviruses, parainfluenza viruses, and adenoviruses. The extraordinary outbreaks of lower respiratory tract disease associated with coronaviruses (severe acute respiratory syndrome, or SARS) in 2002 to 2003 are also discussed. Influenza viruses, which are a major cause of death as well as morbidity, are reviewed in Chap. 13. Herpesviruses occasionally cause pharyngitis and also cause lower respiratory tract disease in immunosuppressed patients. Enteroviruses account for occasional respiratory illnesses during the summer months.

RHINOVIRUS INFECTIONS

ETIOLOGIC AGENT

Rhinoviruses are members of the Picornaviridae family, small (15–30 nm) nonenveloped viruses that contain a

TABLE 14-1
ILLNESSES ASSOCIATED WITH RESPIRATORY VIRUSES

VIRUS	FREQUENCY OF RESPIRATORY SYNDROMES		
	MOST FREQUENT	OCCASIONAL	INFREQUENT
Rhinoviruses	Common cold	Exacerbation of chronic bronchitis and asthma	Pneumonia in children
Coronaviruses ^a	Common cold	Exacerbation of chronic bronchitis and asthma	Pneumonia and bronchiolitis
Human respiratory syncytial virus	Pneumonia and bronchiolitis in young children	Common cold in adults	Pneumonia in elderly and immunosuppressed patients
Parainfluenza viruses	Croup and lower respiratory tract disease in young children	Pharyngitis and common cold	Tracheobronchitis in adults; lower respiratory tract disease in immunosuppressed patients
Adenoviruses	Common cold and pharyngitis in children	Outbreaks of acute respiratory disease in military recruits ^b	Pneumonia in children; lower respiratory tract and disseminated disease in immunosuppressed patients
Influenza A viruses	Influenza ^c	Pneumonia and excess mortality in high-risk patients	Pneumonia in healthy individuals
Influenza B viruses	Influenza ^c	Rhinitis or pharyngitis alone	Pneumonia
Enteroviruses	Acute undifferentiated febrile illnesses ^d	Rhinitis or pharyngitis alone	Pneumonia
Herpes simplex viruses	Gingivostomatitis in children; pharyngotonsillitis in adults	Tracheitis and pneumonia in immunocompromised patients	Disseminated infection in immunocompromised patients
Human metapneumoviruses ^e	Lower respiratory tract disease in children	Upper respiratory tract illness in adults	Pneumonia in elderly and immunosuppressed patients

^aSevere acute respiratory syndrome–associated coronavirus (SARS-CoV) caused epidemics of pneumonia from November 2002 to July 2003 (see text).

^bSerotypes 4 and 7.

^cFever, cough, myalgia, malaise.

^dMay or may not have a respiratory component.

^eNewly recognized human metapneumoviruses cause upper and lower respiratory tract illnesses; their relative frequency is under investigation.

single-stranded RNA genome. In contrast to other members of the picornavirus family, such as enteroviruses, rhinoviruses are acid labile and are almost completely inactivated at $\text{pH} \leq 3$. Rhinoviruses grow preferentially at $33^{\circ}\text{--}34^{\circ}\text{C}$ (the temperature of the human nasal passages) rather than at 37°C (the temperature of the lower respiratory tract). Of the 102 recognized serotypes of rhinovirus, 91 use intercellular adhesion molecule 1 (ICAM-1) as a cellular receptor and constitute the “major” receptor group, 10 use the low-density lipoprotein receptor and constitute the “minor” receptor group, and one uses decay-accelerating factor.

EPIDEMIOLOGY

Rhinoviruses are a prominent cause of the common cold and have been detected in up to 50% of common cold-like illnesses by tissue culture and polymerase chain reaction (PCR) techniques. Overall rates of rhinovirus infection are higher among infants and young children and decrease with increasing age. Rhinovirus infections occur throughout the year, with seasonal peaks in early fall and spring in temperate climates. These infections are most often introduced into families by preschool or grade-school children <6 years old. Of initial illnesses in family settings, 25–70% are followed by secondary cases, with the highest attack rates among the youngest siblings at home. Attack rates also increase with family size.

Rhinoviruses appear to spread through direct contact with infected secretions, usually respiratory droplets. In some studies of volunteers, transmission was most efficient by hand-to-hand contact, with subsequent self-inoculation of the conjunctival or nasal mucosa. Other studies demonstrated transmission by large- or small-particle aerosol. Virus can be recovered from plastic surfaces inoculated 1–3 hours previously; this observation suggests that environmental surfaces contribute to transmission. In studies of married couples in which neither partner had detectable serum antibody, transmission was associated with prolonged contact (≥ 122 h) during a 7-day period. Transmission was infrequent unless (1) virus was recoverable from the donor’s hands and nasal mucosa, (2) at least 1000 TCID₅₀ of virus was present in nasal washes from the donor, and (3) the donor was at least moderately symptomatic with the “cold.” Despite anecdotal observations, exposure to cold temperatures, fatigue, and sleep deprivation have not been associated with increased rates of rhinovirus-induced illness in volunteers, although some studies have suggested that psychologically defined “stress” may contribute to development of symptoms.

Infection with rhinoviruses is worldwide in distribution. By adulthood, nearly all individuals have neutralizing antibodies to multiple serotypes, although the prevalence of antibody to any one serotype varies widely. Multiple serotypes circulate simultaneously, and generally no single

serotype or group of serotypes has been more prevalent than the others.

PATHOGENESIS

Rhinoviruses infect cells through attachment to specific cellular receptors; as mentioned above, most serotypes attach to ICAM-1, but a few use the low-density lipoprotein receptor. Relatively limited information is available on the histopathology and pathogenesis of acute rhinovirus infections in humans. Examination of biopsy specimens obtained during experimentally induced and naturally occurring illness indicates that the nasal mucosa is edematous, is often hyperemic, and—during acute illness—is covered by a mucoid discharge. There is a mild infiltrate with inflammatory cells, including neutrophils, lymphocytes, plasma cells, and eosinophils. Mucus-secreting glands in the submucosa appear hyperactive; the nasal turbinates are engorged, a condition that may lead to obstruction of nearby openings of sinus cavities. Several mediators—e.g., bradykinin; lysylbradykinin; prostaglandins; histamine; interleukins 1 β , 6, and 8; and tumor necrosis factor α —have been linked to the development of signs and symptoms in rhinovirus-induced colds.

The incubation period for rhinovirus illness is short, generally 1–2 days. Virus shedding coincides with the onset of illness or may begin shortly before symptoms develop. The mechanisms of immunity to rhinovirus are not well worked out. In some studies, the presence of homotypic antibody has been associated with significantly reduced rates of subsequent infection and illness, but data conflict regarding the relative importance of serum and local antibody in protection from rhinovirus infection.

CLINICAL MANIFESTATIONS

The most common clinical manifestations of rhinovirus infections are those of the common cold. Illness usually begins with rhinorrhea and sneezing accompanied by nasal congestion. The throat is frequently sore, and in some cases, sore throat is the initial complaint. Systemic signs and symptoms, such as malaise and headache, are mild or absent, and fever is unusual. Illness generally lasts for 4–9 days and resolves spontaneously without sequelae. In children, bronchitis, bronchiolitis, and bronchopneumonia have been reported; nevertheless, it appears that rhinoviruses are not major causes of lower respiratory tract disease in children. Rhinoviruses may cause exacerbations of asthma and chronic pulmonary disease in adults. The vast majority of rhinovirus infections resolve without sequelae, but complications related to obstruction of the eustachian tubes or sinus ostia, including otitis media or acute sinusitis, can develop. In immunosuppressed patients, particularly bone marrow transplant recipients, severe and even fatal pneumonias have been associated with rhinovirus infections.

Although rhinoviruses are the most frequently recognized cause of the common cold, similar illnesses are caused by a variety of other viruses, and a specific viral etiologic diagnosis cannot be made on clinical grounds alone. Rather, rhinovirus infection is diagnosed by isolation of the virus from nasal washes or nasal secretions in tissue culture. In practice, this procedure is rarely undertaken because of the benign, self-limited nature of the illness. In most settings, detection of rhinovirus RNA by PCR is more sensitive than that by tissue culture; however, PCR for rhinoviruses is largely a research procedure. Given the many serotypes of rhinovirus, diagnosis by serum antibody tests is currently impractical. Likewise, common laboratory tests, such as white blood cell count and erythrocyte sedimentation rate, are not helpful.

Rx Treatment: **RHINOVIRUS INFECTIONS**

Because rhinovirus infections are generally mild and self-limited, treatment is not usually necessary. Therapy in the form of first-generation antihistamines and nonsteroidal antiinflammatory drugs may be beneficial in patients with particularly pronounced symptoms, and an oral decongestant may be added if nasal obstruction is particularly troublesome. Reduction of activity is prudent in instances of significant discomfort or fatigability. Antibacterial agents should be used only if bacterial complications such as otitis media or sinusitis develop. Specific antiviral therapy is not available.

PREVENTION

Intranasal application of interferon sprays has been effective in the prophylaxis of rhinovirus infections but is also associated with local irritation of the nasal mucosa. Studies of the prevention of rhinovirus infection by administration of antibodies to ICAM-1 or by the soluble purified receptors themselves have yielded disappointing results. Experimental vaccines to certain rhinovirus serotypes have been generated, but their usefulness is questionable because of the myriad serotypes and the uncertainty about mechanisms of immunity. Thorough hand washing, environmental decontamination, and protection against autoinoculation may help to reduce rates of transmission of infection.

CORONAVIRUS INFECTIONS, INCLUDING SARS

ETIOLOGIC AGENT

Coronaviruses are pleomorphic, single-stranded RNA viruses that measure 100–160 nm in diameter. The

name derives from the crownlike appearance produced by the club-shaped projections that stud the viral envelope. Coronaviruses infect a wide variety of animal species and have been divided into three antigenic groups. Previously recognized coronaviruses that infect humans fell into two of these groups (serogroups I and II), which include human isolates HCoV-229E and HCoV-OC43, respectively. The coronavirus associated with SARS (SARS-CoV) was first believed to represent a novel group but now is considered to be a distantly related member of group II (Fig. 14-1). To date, the SARS-CoV strains that have been fully sequenced have shown only minimal variation.

In general, human coronaviruses have been difficult to cultivate *in vitro*, and some strains grow only in human tracheal organ cultures rather than in tissue culture. SARS-CoV is an exception whose ready growth in African green monkey kidney (Vero E6) cells greatly facilitates its study.

EPIDEMIOLOGY



Generally, human coronavirus infections are present throughout the world. Seroprevalence studies of strains HCoV-229E and HCoV-OC43 have demonstrated that serum antibodies are acquired early in life and increase in prevalence with advancing age, so

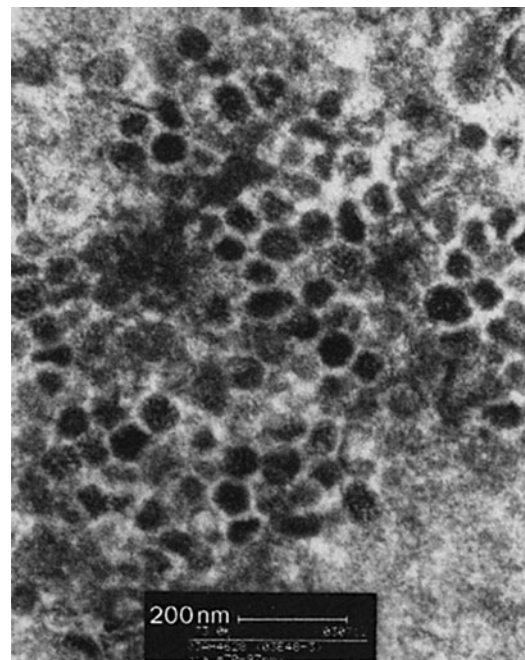


FIGURE 14-1

Electron micrograph of severe acute respiratory syndrome (SARS)-associated coronavirus (SARS-CoV) isolated in fetal rhesus kidney tissue culture from a lung biopsy sample from a patient with SARS. Viral particles are 55–90 nm in diameter. [Reprinted with permission from Elsevier (JSM Peiris et al., *Lancet* 361:1319, 2003).]

that >80% of adult populations have antibodies as measured by enzyme-linked immunosorbent assay (ELISA). Overall, coronaviruses account for 10–35% of common colds, depending on the season. Coronavirus infections appear to be particularly prevalent in the late fall, winter, and early spring—times when rhinovirus infections are less common.

An extraordinary outbreak of the coronavirus-associated illness known as SARS occurred in 2002–2003. The outbreak apparently began in southern China and eventually resulted in 8096 recognized cases in 28 countries in Asia, Europe, and North and South America; ~90% of cases occurred in China and Hong Kong. The natural reservoir of SARS-CoV appears to be the horseshoe bat, and the outbreak may have originated from human contact with infected semidomesticated animals such as the palm civet. In most cases, however, the infection was transmitted from human to human. Case-fatality rates varied among the outbreaks, with an overall figure of ~9.5%. The disease appeared to be somewhat milder in cases in the United States and was clearly less severe among children. The outbreak ceased in 2003; 17 cases were detected in 2004, mostly in laboratory-associated settings, and no cases were reported in 2005 or 2006.

The mechanisms of transmission of SARS are incompletely understood. Clusters of cases suggest that spread may occur by both large and small aerosols and perhaps by the fecal–oral route as well. The outbreak of illness in a large apartment complex in Hong Kong suggested that environmental sources, such as sewage or water, may also play a role in transmission. Some ill individuals (“super-spreaders”) appeared to be hyperinfectious and were capable of transmitting infection to 10–40 contacts, although most infections resulted in spread either to no one or to three or fewer individuals.

PATHOGENESIS

Coronaviruses that cause the common cold (e.g., strains HCoV-229E and HCoV-OC43) infect ciliated epithelial cells in the nasopharynx via the aminopeptidase N receptor (group I) or a sialic acid receptor (group II). Viral replication leads to damage of ciliated cells and induction of chemokines and interleukins, with consequent common-cold symptoms similar to those induced by rhinoviruses.

SARS-CoV infects cells of the respiratory tract via the angiotensin-converting enzyme 2 receptor. The result is a systemic illness in which virus is also found in the bloodstream, in the urine, and (for ≤ 2 months) in the stool. Virus persists in the respiratory tract for 2–3 weeks, and titers peak ~10 days after the onset of systemic illness. Pulmonary pathology consists of hyaline membrane formation, desquamation of pneumocytes in alveolar spaces, and an interstitial infiltrate made up of lymphocytes and mononuclear cells. Giant cells are frequently

seen, and coronavirus particles have been detected in type II pneumocytes. Elevated levels of proinflammatory cytokines and chemokines have been detected in sera from patients with SARS.

CLINICAL MANIFESTATIONS

After an incubation period that generally lasts 2–7 days (range, 1–14 days), SARS usually begins as a systemic illness marked by the onset of fever, which is often accompanied by malaise, headache, and myalgias and is followed in 1–2 days by a nonproductive cough and dyspnea. Approximately 25% of patients have diarrhea. Chest x-rays show a variety of infiltrates, including patchy areas of consolidation—most frequently in peripheral and lower lung fields—or interstitial infiltrates, which can progress to diffuse involvement (Fig. 14-2).

In severe cases, respiratory function may worsen during the second week of illness and progress to frank adult respiratory distress syndrome (ARDS) accompanied by multiorgan dysfunction. Risk factors for severe disease include an age older than 50 years and comorbidities such as cardiovascular disease, diabetes, or hepatitis. Illness in pregnant women may be particularly severe, but SARS-CoV infection appears to be milder in children than in adults.

The clinical features of common colds caused by human coronaviruses are similar to those of illness caused by rhinoviruses. In studies of volunteers, the mean incubation period of colds induced by coronaviruses (3 days) is somewhat longer than that of illness caused by rhinoviruses, and the duration of illness is somewhat shorter (mean, 6–7 days). In some studies, the amount of nasal discharge was greater in colds induced by coronaviruses than in those induced by rhinoviruses. Coronaviruses other than SARS-CoV have been recovered occasionally from infants with pneumonia and from military recruits with lower respiratory tract disease and have been associated with worsening of chronic bronchitis. Two novel coronaviruses, HCoV-NL63 (group I) and HCoV-HKU1 (group II), have recently been isolated from patients hospitalized with acute respiratory illness. Their role as causes of human respiratory disease remains to be determined.

LABORATORY FINDINGS AND DIAGNOSIS

Laboratory abnormalities in SARS include lymphopenia, which is present in ~50% of cases and which mostly affects CD4+ T cells but also involves CD8+ T cells and natural killer (NK) cells. Total white blood cell counts are normal or slightly low, and thrombocytopenia may develop as the illness progresses. Elevated serum levels of aminotransferases, creatine kinase, and lactate dehydrogenase have been reported.

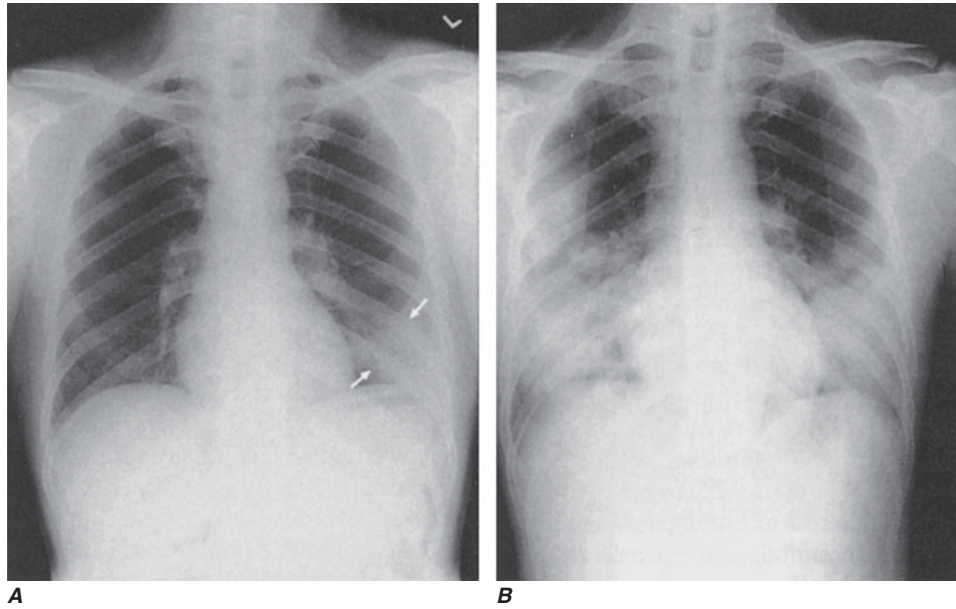


FIGURE 14-2
Chest x-rays of a 46-year-old man with severe acute respiratory syndrome. The left lower lung infiltrate seen initially (**A**) progressed to multiple bilateral opacities (**B**). (Reprinted

with permission from N Lee et al. © 2003 Massachusetts Medical Society.)

A rapid diagnosis of SARS-CoV infection can be made by reverse-transcriptase PCR (RT-PCR) of respiratory tract samples and plasma early in illness and of urine and stool later on. SARS-CoV can also be grown from respiratory tract samples by inoculation into Vero E6 tissue culture cells, in which a cytopathic effect is seen within days. RT-PCR appears to be more sensitive than tissue culture, but only around one-third of cases are positive by PCR at initial presentation. Serum antibodies can be detected by ELISA or immunofluorescence, and nearly all patients develop detectable serum antibodies within 28 days after the onset of illness.

Laboratory diagnosis of coronavirus-induced colds is rarely required. Coronaviruses that cause those illnesses are frequently difficult to cultivate *in vitro* but can be detected in clinical samples by ELISA or immunofluorescence assays or by RT-PCR for viral RNA. These research procedures can be used to detect coronaviruses in unusual clinical settings.

Rx Treatment: **CORONAVIRUS INFECTIONS**

There is no specific therapy of established efficacy for SARS. Although ribavirin has frequently been used, it has little, if any, activity against SARS-CoV *in vitro*, and no beneficial effect on the course of illness has been demonstrated. Because of suggestions that immunopathology may contribute to the disease, glucocorticoids have also

been widely used, but their benefit, if any, is likewise unestablished. Supportive care to maintain pulmonary and other organ system functions remains the mainstay of therapy.

The approach to the treatment of common colds caused by coronaviruses is similar to that discussed above for rhinovirus-induced illnesses.

PREVENTION



The recognition of SARS led to a worldwide mobilization of public health resources to apply infection-control practices to contain the disease. Case definitions were established, travel advisories were proposed, and quarantines were imposed in certain locales. As of this writing, no additional cases of SARS have been reported since 2004. However, it remains unknown whether the disappearance of cases is a result of control measures, whether it is part of a seasonal or otherwise unexplained epidemiologic pattern of SARS, or when or whether SARS might reemerge. The U.S. Centers for Disease Control and Prevention and the World Health Organization maintain recommendations for surveillance and assessment of potential cases of SARS (www.cdc.gov/ncidod/sars/). The frequent transmission of the disease to health care workers makes it mandatory that strict infection-control practices be used by health care facilities to prevent airborne, droplet, and contact transmission from any suspected cases of SARS. Health care workers who enter areas in which patients

with SARS may be present should don gowns, gloves, and eye and respiratory protective equipment (e.g., an N95 filtering facepiece respirator certified by the National Institute for Occupational Safety and Health).

Vaccines have been developed against several animal coronaviruses but not against known human coronaviruses. The emergence of SARS-CoV has stimulated interest in the development of vaccines against such agents.

HUMAN RESPIRATORY SYNCYTIAL VIRUS INFECTIONS

ETIOLOGIC AGENT

Human respiratory syncytial virus, previously referred to as RSV and now designated HRSV, is a member of the Paramyxoviridae family (genus *Pneumovirus*). HRSV, an enveloped virus ~150–350 nm in diameter, is so named because its replication in vitro leads to the fusion of neighboring cells into large multinucleated syncytia. The single-stranded RNA genome codes for 11 virus-specific proteins. Viral RNA is contained in a helical nucleocapsid surrounded by a lipid envelope bearing two glycoproteins: the G protein, by which the virus attaches to cells, and the F (fusion) protein, which facilitates entry of the virus into the cell by fusing host and viral membranes. HRSV was once considered to be of a single antigenic type, but two distinct subgroups (A and B) and multiple subtypes within each subgroup have now been described. Antigenic diversity is reflected by differences in the G protein, and the F protein is highly conserved. Both antigenic groups can circulate simultaneously in outbreaks, although there are typically alternating patterns in which one subgroup predominates over 1- to 2-year periods. Infections with group B viruses may be somewhat milder than those with group A viruses.

EPIDEMIOLOGY

HRSV is a major respiratory pathogen of young children and the foremost cause of lower respiratory disease in infants. Infection with HRSV is seen throughout the world in annual epidemics that occur in the late fall, winter, or spring and last up to 5 months. The virus is rarely encountered during the summer. Rates of illness are highest among infants 1–6 months of age, peaking at 2–3 months of age. The attack rates among susceptible infants and children are extraordinarily high, approaching 100% in settings such as day care centers where large numbers of susceptible infants are present. By age 2 years, virtually all children will have been infected with HRSV. HRSV accounts for 20–25% of hospital admissions of young infants and children for pneumonia and for up to 75% of cases of bronchiolitis in this age group. It has been estimated that more than 50% of infants

who are at risk will become infected during an HRSV epidemic.

In older children and adults, reinfection with HRSV is frequent, but the disease is milder than in infancy. A common cold-like syndrome is the illness most commonly associated with HRSV infection in adults. Severe lower respiratory tract disease with pneumonitis can occur in elderly (often institutionalized) adults and in patients with immunocompromising disorders or treatment, including recipients of stem cell and solid-organ transplants. HRSV is also an important nosocomial pathogen; during an outbreak, it can infect pediatric patients and up to 25–50% of the staff on pediatric wards. The spread of HRSV among families is efficient: up to 40% of siblings may become infected when the virus is introduced into the family setting.

HRSV is transmitted primarily by close contact with contaminated fingers or fomites and by self-inoculation of the conjunctiva or anterior nares. The virus may also be spread by coarse aerosols produced by coughing or sneezing, but it is inefficiently spread by fine-particle aerosols. The incubation period is ~4–6 days, and virus shedding may last for ≥ 2 weeks in children and for shorter periods in adults. In immunosuppressed patients, shedding can continue for weeks.

PATHOGENESIS

Little is known about the histopathology of minor HRSV infection. Severe bronchiolitis or pneumonia is characterized by necrosis of the bronchiolar epithelium and a peribronchiolar infiltrate of lymphocytes and mononuclear cells. Inter-alveolar thickening and filling of alveolar spaces with fluid can also be found. The correlates of protective immunity to HRSV are incompletely understood. Because reinfection occurs frequently and is often associated with illness, the immunity that develops after single episodes of infection clearly is not complete or long lasting. However, the cumulative effect of multiple reinfections is to temper subsequent disease and to provide some temporary measure of protection against infection. Studies of experimentally induced disease in healthy volunteers indicate that the presence of nasal IgA neutralizing antibody correlates more closely with protection than does the presence of serum antibody. Studies in infants, however, suggest that maternally acquired antibody provides some protection from lower respiratory tract disease, although illness can be severe even in infants who have moderate levels of maternally derived serum antibody. The relatively severe disease observed in immunosuppressed patients and experimental animal models indicates that cell-mediated immunity is an important mechanism of host defense against HRSV. Evidence suggests that class I MHC-restricted cytotoxic T cells may be particularly important in this regard.

HRSV infection leads to a wide spectrum of respiratory illnesses. In infants, 25–40% of infections result in lower respiratory tract involvement, including pneumonia, bronchiolitis, and tracheobronchitis. In this age group, illness begins most frequently with rhinorrhea, low-grade fever, and mild systemic symptoms, often accompanied by cough and wheezing. Most patients recover gradually over 1–2 weeks. In more severe illness, tachypnea and dyspnea develop, and eventually frank hypoxia, cyanosis, and apnea can ensue. Physical examination may reveal diffuse wheezing, rhonchi, and rales. Chest radiography shows hyperexpansion, peribronchial thickening, and variable infiltrates ranging from diffuse interstitial infiltrates to segmental or lobar consolidation. Illness may be particularly severe in children born prematurely and in those with congenital cardiac disease, bronchopulmonary dysplasia, nephrotic syndrome, or immunosuppression. One study documented a 37% mortality rate among infants with HRSV pneumonia and congenital cardiac disease.

In adults, the most common symptoms of HRSV infection are those of the common cold, with rhinorrhea, sore throat, and cough. Illness is occasionally associated with moderate systemic symptoms such as malaise, headache, and fever. HRSV has also been reported to cause lower respiratory tract disease with fever in adults, including severe pneumonia in the elderly—particularly in nursing-home residents, among whom its impact can rival that of influenza. HRSV pneumonia can be a significant cause of morbidity and death among patients undergoing stem cell and solid-organ transplantation, whose case-fatality rates of 20–80% have been reported. Sinusitis, otitis media, and worsening of chronic obstructive and reactive airway disease have also been associated with HRSV infection.

LABORATORY FINDINGS AND DIAGNOSIS

The diagnosis of HRSV infection can be suspected on the basis of a suggestive epidemiologic setting—i.e., severe illness among infants during an outbreak of HRSV in the community. Infections in older children and adults cannot be differentiated with certainty from those caused by other respiratory viruses. The specific diagnosis is established by detection of HRSV in respiratory secretions, such as sputum, throat swabs, or nasopharyngeal washes. Virus can be isolated in tissue culture and is identified specifically by immunofluorescence, ELISA, or other immunologic techniques. Rapid viral diagnosis is available by immunofluorescence techniques or ELISA of nasopharyngeal washes, aspirates, and (less satisfactorily) nasopharyngeal swabs. With specimens from children, these techniques have sensitivities and specificities of 80–95%; they are somewhat less sensitive with specimens from adults. Serologic diagnosis may be made by comparison of

acute- and convalescent-phase serum specimens by ELISA or by neutralization or complement-fixation tests. These tests may be useful in older children and adults but are less sensitive in children <4 months of age.

R_x Treatment: **HUMAN RESPIRATORY SYNCYTIAL VIRUS INFECTIONS**

Treatment of upper respiratory tract HRSV infection is aimed primarily at the alleviation of symptoms and is similar to that for other viral infections of the upper respiratory tract. For lower respiratory tract infections, respiratory therapy, including hydration, suctioning of secretions, and administration of humidified oxygen and antibronchospastic agents, is given as needed. In severe hypoxia, intubation and ventilatory assistance may be required. Studies of infants with HRSV infection who were given aerosolized ribavirin, a nucleoside analogue active in vitro against HRSV, demonstrated a modest beneficial effect on the resolution of lower respiratory tract illness, including alleviation of blood-gas abnormalities. The American Academy of Pediatrics recommends that treatment with aerosolized ribavirin “may be considered” for infants who are severely ill or who are at high risk for complications of HRSV infection; included are premature infants and those with bronchopulmonary dysplasia, congenital heart disease, or immunosuppression. The efficacy of ribavirin against HRSV pneumonia in older children and adults, including those with immunosuppression, has not been established. Administration of standard immunoglobulin, immunoglobulin with high titers of antibody to HRSV (RSVlg), or chimeric mouse-human monoclonal IgG antibody to HRSV (palivizumab) has not been found to be beneficial in the treatment of HRSV pneumonia. Combined therapy with aerosolized ribavirin and palivizumab is being evaluated in immunosuppressed patients with HRSV pneumonia.

PREVENTION

Monthly administration of RSVlg or palivizumab has been approved as prophylaxis against HRSV for children <2 years of age who have bronchopulmonary dysplasia or cyanotic heart disease or who were born prematurely. Considerable interest exists in the development of vaccines against HRSV. Inactivated whole-virus vaccines have been ineffective; in one study, they actually potentiated disease in infants. Other approaches include immunization with purified F and G surface glycoproteins of HRSV or generation of stable, live attenuated virus vaccines. In settings such as pediatric wards where rates of transmission are high, barrier methods for the protection of hands and conjunctivae may be useful in reducing the spread of virus.

HUMAN METAPNEUMOVIRUS INFECTIONS

ETIOLOGIC AGENT

Human metapneumovirus (HMPV) is a recently described viral respiratory pathogen that has been assigned to the Paramyxoviridae family (genus *Metapneumovirus*). Its morphology and genomic organization are similar to those of avian metapneumoviruses, which are recognized respiratory pathogens of turkeys. HMPV particles may be spherical, filamentous, or pleomorphic in shape and measure 150–600 nm in diameter. Particles contain 15-nm projections from the surface that are similar in appearance to those of other Paramyxoviridae. The single-stranded RNA genome codes for nine proteins that, except for the absence of nonstructural proteins, generally correspond to those of HRSV. There is only one antigenic type; two closely related genetic subgroups (A and B) have been described.

EPIDEMIOLOGY

HMPV infections are worldwide in distribution, are most frequent during the winter, and occur early in life, so that serum antibodies to the virus are present in nearly all children by age of 5 years. HMPV infections have been detected in older age groups, including elderly adults, and in both immunocompetent and immunosuppressed hosts. To date, studies indicate that HMPV infections account for 4% of respiratory tract illnesses requiring hospitalization of children, 12% of outpatient lower respiratory illnesses, and 2–4% of acute respiratory illnesses in ambulatory adults and elderly patients. HMPV has been detected in a few cases of SARS, but its role (if any) in these illnesses has not been established. Assessment of the overall significance of HMPV infections awaits the conduct of large-scale epidemiologic studies.

CLINICAL MANIFESTATIONS

The spectrum of clinical illnesses associated with HMPV is similar to that associated with HRSV and includes both upper and lower respiratory tract illnesses, such as bronchiolitis, croup, and pneumonia. Reinfection with HMPV is common in older children and adults and has manifestations ranging from subclinical infections to common cold syndromes and occasionally pneumonia, which is seen primarily in elderly patients and those with cardiopulmonary diseases. Serious HMPV infections occur in immunocompromised patients, including those with neoplasia and stem cell transplants.

DIAGNOSIS

HMPV can be detected in nasal aspirates and respiratory secretions by PCR or by growth in rhesus monkey kidney

(LLC-MK2) tissue cultures. Rapid immunodetection methods are under development. A serologic diagnosis can be made by ELISA, which uses HMPV-infected tissue culture lysates as sources of antigens.

R_x Treatment: HUMAN METAPNEUMOVIRUS INFECTIONS

Treatment for HMPV infections is primarily supportive and symptom based. Ribavirin and RSVIg are both active against HMPV in vitro, but their efficacy in vivo is unknown.

PREVENTION


Vaccines against HMPV are in the early stages of development.

PARAINFLUENZA VIRUS INFECTIONS

ETIOLOGIC AGENT

Parainfluenza viruses belong to the Paramyxoviridae family (genera *Respirovirus* and *Rubulavirus*). They are 150–200 nm in diameter, are enveloped, and contain a single-stranded RNA genome. The envelope is studded with two glycoproteins: one possesses both hemagglutinin and neuraminidase activity, and the other contains fusion activity. The viral RNA genome is enclosed in a helical nucleocapsid and codes for six structural and several accessory proteins. There are four distinct serotypes of parainfluenza virus, all of which share certain antigens with other members of the Paramyxoviridae family, including mumps and Newcastle disease viruses.

EPIDEMIOLOGY

 Parainfluenza viruses are distributed throughout the world; infection with type 4 (subtypes 4A and 4B) has been reported less widely, probably because type 4 is more difficult to grow in tissue culture. Infection is acquired in early childhood, so that by 5 years of age most children have antibodies to serotypes 1, 2, and 3. Types 1 and 2 cause epidemics during the fall, often occurring in an alternate-year pattern. Type 3 infection has been detected during all seasons of the year, but epidemics have occurred annually in the spring.

The contribution of parainfluenza infections to respiratory disease varies with both the location and the year. In studies conducted in the United States, parainfluenza virus infections have accounted for 4.3–22% of respiratory illnesses in children. In adults, parainfluenza infections are generally mild and account for <10% of respiratory illnesses. The major importance of parainfluenza viruses

158 is as a cause of respiratory illness in young children, in whom they rank second only to HRSV as causes of lower respiratory tract illness. Parainfluenza virus type 1 is the most frequent cause of croup (laryngotracheobronchitis) in children; serotype 2 causes similar, although generally less severe, disease. Type 3 is an important cause of bronchiolitis and pneumonia in infants, but illnesses associated with type 4 have generally been mild. Unlike types 1 and 2, type 3 frequently causes illness during the first month of life, when passively acquired maternal antibody is still present. Parainfluenza viruses are spread through infected respiratory secretions, primarily by person-to-person contact or by large droplets. The incubation period has varied from 3 to 6 days in experimental infections but may be somewhat shorter for naturally occurring disease in children.

PATHOGENESIS

Immunity to parainfluenza viruses is incompletely understood, but evidence suggests that immunity to infections with serotypes 1 and 2 is mediated by local IgA antibodies in the respiratory tract. Passively acquired serum neutralizing antibodies also confer some protection against infection with types 1, 2, and (to a lesser degree) 3. Studies in experimental animal models and in immunosuppressed patients suggest that T cell-mediated immunity may also be important in parainfluenza virus infections.

CLINICAL MANIFESTATIONS

Parainfluenza virus infections occur most frequently among children, in whom initial infection with serotype 1, 2, or 3 is associated with an acute febrile illness 50–80% of the time. Children may present with coryza, sore throat, hoarseness, and cough that may or may not be croupy. In severe croup, fever persists, with worsening coryza and sore throat. A brassy or barking cough may progress to frank stridor. Most children recover over the next 1 or 2 days, although progressive airway obstruction and hypoxia ensue occasionally. If bronchiolitis or pneumonia develops, progressive cough accompanied by wheezing, tachypnea, and intercostal retractions may occur. In this setting, sputum production increases modestly. Physical examination shows nasopharyngeal discharge and oropharyngeal injection, along with rhonchi, wheezes, or coarse breath sounds. Chest x-rays can show air trapping and occasionally interstitial infiltrates.

In older children and adults, parainfluenza infections tend to be milder, presenting most frequently as a common cold or as hoarseness, with or without cough. Lower respiratory tract involvement in older children and adults is uncommon, but tracheobronchitis in adults has been reported. Severe, prolonged, and even fatal parainfluenza infection has been reported in children and adults with severe immunosuppression, including stem cell and solid-organ transplant recipients.

LABORATORY FINDINGS AND DIAGNOSIS

The clinical syndromes caused by parainfluenza viruses (with the possible exception of croup in young children) are not sufficiently distinctive to be diagnosed on clinical grounds alone. A specific diagnosis is established by detection of virus in respiratory tract secretions, throat swabs, or nasopharyngeal washings. Viral growth in tissue culture is detected either by hemagglutination or by a cytopathic effect. Rapid viral diagnosis may be made by identification of parainfluenza antigens in exfoliated cells from the respiratory tract with immunofluorescence or ELISA, although these techniques appear to be less sensitive than tissue culture. Highly specific and sensitive PCR assays have also been developed. Serologic diagnosis can be established by hemagglutination inhibition, complement-fixation, or neutralization tests of acute- and convalescent-phase specimens. However, because frequent heterotypic responses occur among the parainfluenza serotypes, the serotype causing illness often cannot be identified by serologic techniques alone.

Acute epiglottitis caused by *Haemophilus influenzae* type B must be differentiated from viral croup. Influenza A virus is also a common cause of croup during epidemic periods.

Rx Treatment: PARAINFLUENZA VIRUS INFECTIONS

For upper respiratory tract illness, symptoms can be treated as discussed for other viral respiratory tract illnesses. If complications such as sinusitis, otitis, or superimposed bacterial bronchitis develop, appropriate antibacterial antibiotics should be administered. Mild cases of croup should be treated with bed rest and moist air generated by vaporizers. More severe cases require hospitalization and close observation for the development of respiratory distress. If acute respiratory distress develops, humidified oxygen and intermittent racemic epinephrine are usually administered. Aerosolized or systemically administered glucocorticoids are beneficial; the latter have a more profound effect. No specific antiviral therapy is available, although ribavirin is active against parainfluenza viruses in vitro and anecdotal reports describe its use clinically, particularly in immunosuppressed patients.

PREVENTION

Vaccines against parainfluenza viruses are under development.

ADENOVIRUS INFECTIONS

ETIOLOGIC AGENT

Adenoviruses are complex DNA viruses that measure 70–80 nm in diameter. Human adenoviruses belong to

the genus *Mastadenovirus*, which includes 51 serotypes. Adenoviruses have a characteristic morphology consisting of an icosahedral shell composed of 20 equilateral triangular faces and 12 vertices. The protein coat (capsid) consists of hexon subunits with group-specific and type-specific antigenic determinants and penton subunits at each vertex primarily containing group-specific antigens. A fiber with a knob at the end projects from each penton; this fiber contains type-specific and some group-specific antigens. Human adenoviruses have been divided into six subgenera (A through F) on the basis of the homology of DNA genomes and other properties. The adenovirus genome is a linear double-stranded DNA that codes for structural and nonstructural polypeptides. The replicative cycle of adenovirus may result either in lytic infection of cells or in the establishment of a latent infection (primarily involving lymphoid cells). Some adenovirus types can induce oncogenic transformation, and tumor formation has been observed in rodents; however, despite intensive investigation, adenoviruses have not been associated with tumors in humans.

EPIDEMIOLOGY

Adenovirus infections most frequently affect infants and children. Infections occur throughout the year but are most common from the fall to the spring. Adenoviruses account for ~10% of acute respiratory infections in children but for <2% of respiratory illnesses in civilian adults. Nearly 100% of adults have serum antibody to multiple serotypes—a finding indicating that infection is common in childhood. Types 1, 2, 3, and 5 are the most frequent isolates from children. Certain adenovirus serotypes—particularly 4 and 7 but also 3, 14, and 21—are associated with outbreaks of acute respiratory disease in military recruits in the winter and spring. Adenovirus infection can be transmitted by inhalation of aerosolized virus, by inoculation of virus into conjunctival sacs, and probably by the fecal–oral route as well. Type-specific antibody generally develops after infection and is associated with protection, albeit incomplete, against infection with the same serotype.

CLINICAL MANIFESTATIONS

In children, adenoviruses cause a variety of clinical syndromes. The most common is an acute upper respiratory tract infection with prominent rhinitis. On occasion, lower respiratory tract disease, including bronchiolitis and pneumonia, also develops. Adenoviruses, particularly types 3 and 7, cause pharyngoconjunctival fever, a characteristic acute febrile illness of children that occurs in outbreaks, most often in summer camps. The syndrome is marked by bilateral conjunctivitis in which the bulbar and palpebral conjunctivae have a granular appearance. Low-grade fever is frequently present for the first 3–5 days, and rhinitis, sore throat, and cervical adenopathy

develop. The illness generally lasts for 1–2 weeks and resolves spontaneously. Febrile pharyngitis without conjunctivitis has also been associated with adenovirus infection. Adenoviruses have been isolated from cases of whooping cough with or without *Bordetella pertussis*; the significance of adenovirus in that disease is unknown.

In adults, the most frequently reported illness has been acute respiratory disease caused by adenovirus types 4 and 7 in military recruits. This illness is marked by a prominent sore throat and the gradual onset of fever, which often reaches 39°C (102.2°F) on the second or third day of illness. Cough is almost always present, and coryza and regional lymphadenopathy are frequently seen. Physical examination may show pharyngeal edema, injection, and tonsillar enlargement with little or no exudate. If pneumonia has developed, auscultation and x-ray of the chest may indicate areas of patchy infiltration.

Adenoviruses have been associated with a number of non-respiratory tract diseases, including acute diarrheal illness caused by types 40 and 41 in young children and hemorrhagic cystitis caused by types 11 and 21. Epidemic keratoconjunctivitis, caused most frequently by types 8, 19, and 37, has been associated with contaminated common sources such as ophthalmic solutions and roller towels. Adenoviruses have also been implicated in disseminated disease and pneumonia in immunosuppressed patients, including recipients of solid-organ or stem cell transplants. In stem cell transplant recipients, adenovirus infections have manifested as pneumonia, hepatitis, nephritis, colitis, encephalitis, and hemorrhagic cystitis. In solid-organ transplant recipients, adenovirus infection may involve the organ transplanted (e.g., hepatitis in liver transplants, nephritis in renal transplants) but can disseminate to other organs as well. In patients with AIDS, high-numbered and intermediate adenovirus serotypes have been isolated, usually in the setting of low CD4+ T cell counts, but their isolation often has not been clearly linked to disease manifestations. Adenovirus nucleic acids have been detected in myocardial cells from patients with “idiopathic” cardiomyopathies, and adenoviruses have been suggested as causative agents in some cases.

LABORATORY FINDINGS AND DIAGNOSIS

Adenovirus infection should be suspected in the epidemiologic setting of acute respiratory disease in military recruits and in certain of the clinical syndromes (e.g., pharyngoconjunctival fever or epidemic keratoconjunctivitis) in which outbreaks of characteristic illnesses occur. In most cases, however, illnesses caused by adenovirus infection cannot be differentiated from those caused by a number of other viral respiratory agents and *Mycoplasma pneumoniae*. A definitive diagnosis of adenovirus infection is established by detection of the virus in tissue culture (as evidenced by cytopathic changes) and by specific identification with immunofluorescence or other immunologic techniques. Rapid viral diagnosis

160 can be established by immunofluorescence or ELISA of nasopharyngeal aspirates, conjunctival or respiratory secretions, urine, or stool. Highly sensitive and specific PCR assays and nucleic acid hybridization are also available. Adenovirus types 40 and 41, which have been associated with diarrheal disease in children, require special tissue-culture cells for isolation, and these serotypes are most commonly detected by direct ELISA of stool. Serum antibody rises can be demonstrated by complement-fixation or neutralization tests, ELISA, radioimmunoassay, or (for adenoviruses that hemagglutinate red cells) hemagglutination inhibition tests.

Rx Treatment: **ADENOVIRUS INFECTIONS**

Only symptom-based treatment and supportive therapy are available for adenovirus infections, and clinically useful antiviral therapy has not been established. Ribavirin and cidofovir have activity in vitro against certain adenoviruses. Retrospective studies and anecdotes describe the use of these agents in disseminated adenovirus infections, but definitive efficacy data from controlled studies are not available.

PREVENTION

Live vaccines have been developed against adenovirus types 4 and 7 and have been used to control illness among military recruits. These vaccines consist of live, unattenuated virus administered in enteric-coated capsules. Infection of the gastrointestinal tract with types 4 and 7 does not

cause disease but stimulates local and systemic antibodies that are protective against subsequent acute respiratory disease caused by those serotypes. This vaccine has not been produced since 1999, and outbreaks of acute respiratory illness caused by adenovirus types 4 and 7 have reemerged among military recruits. Therefore, a program to redevelop type 4 and 7 vaccines is under way. Adenoviruses are also being studied as live-virus vectors for the delivery of vaccine antigens and for gene therapy.

FURTHER READINGS

- AMERICAN ACADEMY OF PEDIATRICS: Diagnosis and management of bronchiolitis. *Pediatrics* 118:1774, 2006
- CHANOCK RM et al: Serious respiratory tract disease caused by respiratory syncytial virus: Prospects for improved therapy and effective immunization. *Pediatrics* 90:137, 1992
- CHRISTIAN MD et al: Severe acute respiratory syndrome. *Clin Infect Dis* 38:1420, 2004
- GRAHAM BS et al: Respiratory syncytial virus immunobiology and pathogenesis. *Virology* 297:1, 2002
- GWALTNEY JM: Rhinoviruses, in *Principles and Practice of Infectious Diseases*, 6th ed, GF Mandell et al (eds). Philadelphia, Elsevier, 2005, pp 2185–2193
- LEE N et al: A major outbreak of severe acute respiratory syndrome in Hong Kong. *N Engl J Med* 348:1986, 2003
- PEIRIS JS et al: Severe acute respiratory syndrome. *Nat Med* 10:S88, 2004
- PERET T et al: Characterization of human metapneumoviruses isolated from patients in North America. *J Infect Dis* 185:1660, 2002
- STOCKTON J et al: Human metapneumovirus as a cause of community-acquired respiratory illness. *Emerg Infect Dis* 8:897, 2002
- WHEELER AP, BERNARD GR: Acute lung injury and the acute respiratory distress syndrome: A clinical review. *Lancet* 369:1553, 2007
- WRIGHT PF: Parainfluenza viruses, in *Viral Infections of the Respiratory Tract*, R Dolin, PF Wright (eds). New York, Marcel Dekker, 1999



CHAPTER 15

PNEUMOCYSTIS INFECTION

A. George Smulian ■ Peter D. Walzer

Definition and Description	161
Epidemiology	161
Pathogenesis and Pathology	161
Clinical Features	162
Diagnosis	162
Course and Prognosis	163
Prevention	164
■ Further Readings	164

DEFINITION AND DESCRIPTION

Pneumocystis is an opportunistic fungal pulmonary pathogen that is an important cause of pneumonia in the immunocompromised host. Although organisms within the *Pneumocystis* genus are morphologically very similar, they are genetically diverse and host specific. Whereas *P. jirovecii* infects humans, *P. carinii*—the original species described in 1909—infects rats. For clarity, only the genus designation *Pneumocystis* will be used in this chapter.

Developmental stages of the organism include the trophic form, the cyst, and the precyst (an intermediate stage). The life cycle of *Pneumocystis* probably involves sexual and asexual reproduction, although definitive proof awaits the development of a reliable culture system. *Pneumocystis* contains several different antigen groups, the most prominent of which is the 95- to 140-kDa major surface glycoprotein (MSG). MSG plays a central role in the interaction of *Pneumocystis* with its host.

EPIDEMIOLOGY

Serologic surveys have demonstrated that *Pneumocystis* has a worldwide distribution and that most healthy children have been exposed to the organism by 3–4 years of age. Airborne transmission of *Pneumocystis* has been documented in animal studies; person-to-person transmission has been suggested by hospital outbreaks of *Pneumocystis* pneumonia (PcP) and by molecular epidemiologic analysis

of isolates. *Pneumocystis* colonization of immunocompetent individuals has been detected by polymerase chain reaction (PCR) techniques.

PATHOGENESIS AND PATHOLOGY

The host factors that predispose to the development of PcP include defects in cellular and humoral immunity. The risk of PcP among HIV-infected patients increases markedly when circulating CD4+ T cell counts decrease below 200/ μ L. Other persons at risk for PcP are patients receiving immunosuppressive agents (particularly glucocorticoids) for cancer and organ transplantation; those receiving biologic agents such as infliximab and etanercept for rheumatoid arthritis and inflammatory bowel disease; children with primary immunodeficiency diseases; and premature malnourished infants.

The principal host effector cells against *Pneumocystis* are alveolar macrophages, which ingest and kill the organism, releasing a variety of inflammatory mediators. Proliferating organisms remain extracellular within the alveolus, attaching tightly to type I cells. Alveolar damage results in increased alveolar-capillary permeability and surfactant abnormalities, including a decrease in phospholipids and an increase in surfactant proteins A and D. The host inflammatory response to lung injury leads to increases in levels of interleukin 8 and in neutrophil counts in bronchoalveolar lavage (BAL) fluid. These changes correlate with disease severity.

162 On lung sections stained with hematoxylin and eosin, the alveoli are filled with a typical foamy, vacuolated exudate. Severe disease may include interstitial edema, fibrosis, and hyaline membrane formation. The host inflammatory changes usually consist of hypertrophy of alveolar type II cells, a typical reparative response, and a mild mononuclear cell interstitial infiltrate. Malnourished infants display an intense plasma cell infiltrate that gave the disease its early name: interstitial plasma cell pneumonia.

CLINICAL FEATURES

Patients with PcP develop dyspnea, fever, and nonproductive cough. HIV-infected patients are usually ill for several weeks and may have relatively subtle manifestations. Symptoms in non-HIV-infected patients are of shorter duration and often begin after the glucocorticoid dose has been tapered. A high index of suspicion and a thorough history are key factors in early detection.

Physical findings include tachypnea, tachycardia, and cyanosis, but lung auscultation reveals few abnormalities. Reduced arterial oxygen pressure (PaO_2), increased alveolar-arterial oxygen gradient ($PAO_2 - PaO_2$), and respiratory alkalosis are evident. Diffusion capacity is reduced, and heightened uptake with nonspecific nuclear imaging techniques (gallium scan) may be noted. Elevated serum concentrations of lactate dehydrogenase, reflecting lung parenchymal damage, have been reported; however, the increase is not specific for PcP.

The classic findings on chest radiography consist of bilateral diffuse infiltrates beginning in the perihilar

regions (Fig. 15-1A), but various atypical manifestations (nodular densities, cavitory lesions) have also been reported. Pneumothorax occurs, and its management is often difficult. Early in the course of PcP, the chest radiograph may be normal, although high-resolution CT of the lung may reveal ground-glass opacities at this stage (Fig. 15-1B).

Although *Pneumocystis* usually remains confined to the lungs, cases of disseminated infection have occurred in both HIV-infected and non-HIV-infected patients. Common sites of involvement include the lymph nodes, spleen, liver, and bone marrow.

DIAGNOSIS

Because of the nonspecific nature of the clinical picture, the diagnosis must be based on specific identification of the organism. A definitive diagnosis is made by histopathologic staining. Whereas traditional cell wall stains such as methenamine silver selectively stain the wall of *Pneumocystis* cysts, reagents such as Wright-Giemsa stain the nuclei of all developmental stages. Immunofluorescence with monoclonal antibodies is more sensitive and specific than histologic staining. DNA amplification by PCR may become part of routine diagnostics but may not distinguish colonization from infection.

The successful diagnosis of PcP depends on the collection of proper specimens. In general, the yield from different diagnostic procedures is higher in HIV-infected patients than in non-HIV-infected patients because of the higher organism burden in the former group. Sputum

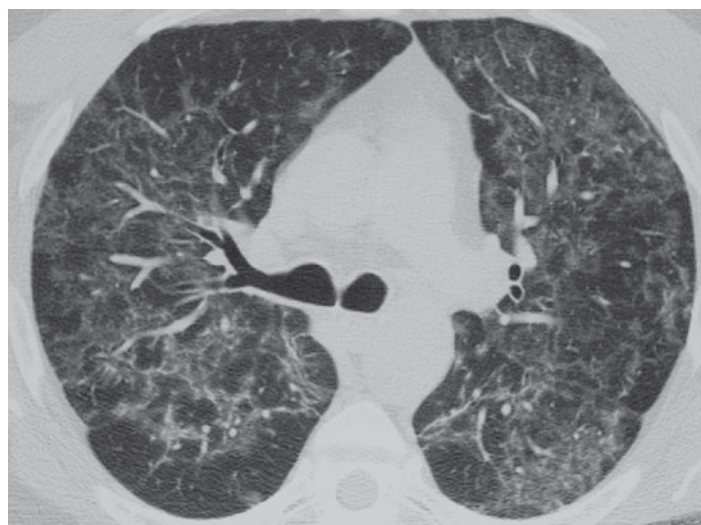


A

FIGURE 15-1

A. Chest radiograph depicting diffuse infiltrates in an HIV-infected patient with *Pneumocystis pneumonia* (PcP).

B. High-resolution CT of the lung showing ground-glass



B

opacification in an HIV-infected patient with PcP. (Courtesy of Dr. Christopher Meyer, with permission.)

induction and oral washes have gained popularity as simple, noninvasive techniques; however, these procedures require trained and dedicated personnel. Fiberoptic bronchoscopy with BAL, which provides information about the organism burden, the host inflammatory response, and the presence of other opportunistic infections, continues to be the mainstay of *Pneumocystis* diagnosis. Trans-bronchial biopsy and open lung biopsy, the most invasive procedures, are used only when a diagnosis cannot be made by BAL.

COURSE AND PROGNOSIS

In the typical case of untreated PcP, progressive respiratory embarrassment leads to death. Therapy is most effective when instituted early before extensive alveolar damage occurs. If examination of induced sputum is nondiagnostic and BAL cannot be performed in a timely manner, empirical therapy for PcP is reasonable. However, this practice does not eliminate the need for a specific etiologic diagnosis. With improved management of HIV and its complications, mortality from PcP is 15–20% at 1 month and 50–55% at 1 year. Rates of early death remain high among patients who require mechanical ventilation (60%) and among non-HIV-infected patients (40%).

Rx Treatment: PNEUMOCYSTIS INFECTION

Trimethoprim-sulfamethoxazole (TMP-SMX), which acts by inhibiting folic acid synthesis, is considered the drug of choice for all forms of PcP (Table 15-1). Therapy is continued for 14 days in non-HIV-infected patients and for 21 days in persons infected with HIV. Because HIV-infected patients respond more slowly than non-HIV-infected patients, it is prudent to wait at least 7 days after the initiation of treatment before concluding that therapy has failed. TMP-SMX is well tolerated by non-HIV-infected patients, whereas more than half of HIV-infected patients experience serious adverse reactions.

Several alternative regimens are available for the treatment of mild to moderate cases of PcP (a PaO₂ of >70 mmHg or a PAO₂ – PaO₂ of <35 mmHg on breathing room air). TMP plus dapsone and clindamycin plus primaquine are about as effective as TMP-SMX. Dapsone and primaquine should not be administered to patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Atovaquone is less effective than TMP-SMX but is better tolerated. Because *Pneumocystis* lacks ergosterol, it is not susceptible to antifungal agents that inhibit ergosterol synthesis.

TABLE 15-1

TREATMENT OF PNEUMOCYSTOSIS	
DRUG(S), DOSE, ROUTE	ADVERSE EFFECTS
First Choice^a	
TMP-SMX (5 mg/kg TMP, 25 mg/kg SMX ^b) q6–8 h PO or IV	Fever, rash, cytopenias, hepatitis, hyperkalemia, GI disturbances
Other Agents^a	
TMP, 5 mg/kg q6–8h, plus dapsone, 100 mg qd PO	Hemolysis (G6PD deficiency), methemoglobinemia, fever, rash, GI disturbances
Atovaquone, 750 mg bid PO	Rash, fever, GI and hepatic disturbances
Clindamycin, 300–450 mg q6h PO or 600 mg q6–8h IV, plus primaquine, 15–30 mg qd PO	Hemolysis (G6PD deficiency), methemoglobinemia, rash, colitis, neutropenia
Pentamidine, 3–4 mg/kg qd IV	Hypotension, azotemia, cardiac arrhythmias, pancreatitis, dysglycemias, hypocalcemia, neutropenia, hepatitis
Trimetrexate, 45 mg/m ² qd IV, plus leucovorin, ^c 20 mg/kg q6h PO or IV	Cytopenias, peripheral neuropathy, hepatic disturbances
Adjunctive Agent	
Prednisone, 40 mg bid × 5 d, 40 mg qd × 5 d, 20 mg qd × 11 d; PO or IV	Immunosuppression, peptic ulcer, hyperglycemia, mood changes, hypertension

^aTherapy is administered for 14 days to non-HIV-infected patients and for 21 days to HIV-infected patients.

^bEquivalent of 2 double-strength (DS) tablets. (One DS tablet contains 160 mg of TMP and 800 mg of SMX.)

^cLeucovorin prevents bone marrow toxicity from trimetrexate.

Note: GI, gastrointestinal; G6PD, glucose-6-phosphate dehydrogenase; TMP-SMX, trimethoprim-sulfamethoxazole.

TABLE 15-2

PROPHYLAXIS OF PNEUMOCYSTOSIS^a

DRUG(S), DOSE, ROUTE	COMMENTS
First Choice	
TMP-SMX, 1 DS tablet or 1 SS tablet qd PO ^b	TMP-SMX can be safely reintroduced in some patients who have experienced mild to moderate side effects.
Other Agents	
Dapsone, 50 mg bid or 100 mg qd PO	—
Dapsone, 50 mg qd PO, plus pyrimethamine, 50 mg weekly PO, plus leucovorin, 25 mg weekly PO	Leucovorin prevents bone marrow toxicity from pyrimethamine.
Dapsone, 200 mg weekly PO, plus pyrimethamine, 75 mg weekly PO, plus leucovorin, 25 mg weekly PO	Leucovorin prevents bone marrow toxicity from pyrimethamine.
Pentamidine, 300 mg monthly via Respigard II nebulizer	Adverse reactions include cough and bronchospasm.
Atovaquone, 1500 mg qd PO	—
TMP-SMX, 1 DS tablet three times weekly PO	TMP-SMX can be safely reintroduced in some patients who have experienced mild to moderate side effects.

^aFor list of adverse effects, see Table 15-1.

^bOne DS tablet contains 160 mg of TMP and 800 mg of SMX.

Note: DS, double strength; SS, single strength; TMP-SMX, trimethoprim-sulfamethoxazole.

Alternative regimens that are recommended for the treatment of moderate to severe PcP (a P_{aO_2} of ≤ 70 mmHg or a $PA_{O_2} - P_{aO_2}$ of ≥ 35 mmHg) are parenteral pentamidine, parenteral clindamycin plus primaquine, or trimethoprim plus leucovorin. Parenteral clindamycin plus primaquine may be more efficacious than pentamidine.

Molecular evidence of resistance to sulfonamides and to atovaquone has emerged among human *Pneumocystis* isolates. Although prior sulfonamide exposure is a risk factor, this resistance has also occurred in HIV-infected patients who have never received sulfonamides. The outcome of therapy appears to be linked more strongly to traditional measures—e.g., high Acute Physiology, Age, and Chronic Health Evaluation III (APACHE III) scores, need for positive-pressure ventilation, delayed intubation, and development of pneumothorax—than to the presence of molecular markers of sulfonamide resistance. HIV-infected patients frequently experience deterioration of respiratory function shortly after receiving anti-*Pneumocystis* drugs. The adjunctive administration of tapering doses of glucocorticoids to HIV-infected patients with moderate to severe PcP can prevent this problem and improve the rate of survival (see Table 15-1). For maximal benefit, this adjunctive therapy should be started early in the course of the illness. The use of steroids as adjunctive therapy in HIV-infected patients with mild PcP or in non-HIV-infected patients remains to be evaluated.

PREVENTION

Prophylaxis is indicated for HIV-infected patients with CD4+ T cell counts of $<200/\mu\text{L}$ or a history of oropharyngeal candidiasis and for both HIV-infected and non-HIV-infected patients who have recovered from PcP. Prophylaxis may be discontinued in HIV-infected patients after CD4+ T cell counts have risen to $>200/\mu\text{L}$ and remained at that level for ≥ 3 months. Primary prophylaxis guidelines for immunocompromised hosts not infected with HIV are less clear.

TMP-SMX is the drug of choice for primary and secondary prophylaxis (Table 15-2). This agent also provides protection against toxoplasmosis and some bacterial infections. Alternative regimens are available for individuals intolerant of TMP-SMX (Table 15-2). Although there are no specific recommendations for preventing the spread of *Pneumocystis* in health care facilities, it seems prudent to prevent direct contact between patients with PcP and other susceptible hosts.

FURTHER READINGS

CENTERS FOR DISEASE CONTROL AND PREVENTION: Treating opportunistic infections among HIV-infected adults and adolescents: Recommendations from the CDC, the National Institutes of Health and the HIV Medicine Association/Infectious Diseases Society of America. *MMWR* 53(RR-15):1, 2004

DALY KR et al: Antibody responses to the *Pneumocystis jirovecii* major surface glycoprotein. *Emerg Infect Dis* 12:1231, 2006

FESTIC E et al: Acute respiratory failure due to *Pneumocystis* pneumonia in patients without human immunodeficiency virus infection: Outcome and associated features. *Chest* 128:573, 2005

MEDRANO FJ et al: *Pneumocystis jirovecii* in general population. *Emerg Infect Dis* 11:245, 2005

MILLER RF et al: Improved survival for HIV infected patients with severe *Pneumocystis jirovecii* pneumonia is independent of highly active antiretroviral therapy. *Thorax* 61:716, 2006

REDHEAD SA et al: *Pneumocystis* and *Trypanosoma cruzi*: Nomenclature and typifications. *J Eukaryot Microbiol* 53:1, 2006

THOMAS CF JR, LEMPER AH: *Pneumocystis* pneumonia. *N Engl J Med* 350:2487, 2004

ZAR HJ: Pneumonia in HIV-infected and HIV-uninfected children in developing countries: Epidemiology, clinical features, and management. *Curr Opin Pulm Med* 10:176, 2004



CHAPTER 16

BRONCHIECTASIS AND LUNG ABSCESS

Gregory Tino ■ Steven E. Weinberger

■ Bronchiectasis	166
Definition	166
Pathology	166
Etiology and Pathogenesis	166
Clinical Manifestations	168
Radiographic and Laboratory Findings	168
■ Lung Abscess	169
Microbiology	169
Clinical Manifestations	170
Diagnosis	170
■ Further Readings	171

BRONCHIECTASIS

DEFINITION

Bronchiectasis is an abnormal and permanent dilatation of bronchi. It may be either focal, involving airways supplying a limited region of pulmonary parenchyma, or diffuse, involving airways in a more widespread distribution. Recent studies have estimated there to be about 110,000 patients with bronchiectasis in the United States. It is a disorder that typically affects older individuals; approximately two-thirds of patients are women.

PATHOLOGY

The bronchial dilatation of bronchiectasis is associated with destructive and inflammatory changes in the walls of medium-sized airways, often at the level of segmental or subsegmental bronchi. Airway inflammation is primarily mediated by neutrophils and results in up-regulation of enzymes such as elastase and matrix metalloproteinases. The normal structural components of the wall, including cartilage, muscle, and elastic tissue, are destroyed and may be replaced by fibrous tissue. The dilated airways frequently contain pools of thick, purulent material, and the more peripheral airways are often occluded by

secretions or obliterated and replaced by fibrous tissue. Additional microscopic features include bronchial and peribronchial inflammation and fibrosis, ulceration of the bronchial wall, squamous metaplasia, and mucous gland hyperplasia. The parenchyma normally supplied by the affected airways is abnormal, containing varying combinations of fibrosis, emphysema, bronchopneumonia, and atelectasis. As a result of the inflammation, vascularity of the bronchial wall increases, with associated enlargement of the bronchial arteries and anastomoses between the bronchial and pulmonary arterial circulations.

Three different patterns of bronchiectasis have been described. In *cylindrical bronchiectasis*, the involved bronchi appear uniformly dilated and end abruptly at the point that smaller airways are obstructed by secretions. In *varicose bronchiectasis*, the affected bronchi have an irregular or beaded pattern of dilatation resembling varicose veins. In *saccular (cystic) bronchiectasis*, the bronchi have a ballooned appearance at the periphery, ending in blind sacs without recognizable bronchial structures distal to the sacs.

ETIOLOGY AND PATHOGENESIS

Bronchiectasis is a consequence of inflammation and destruction of the structural components of the bronchial wall. Infection is the usual cause of the inflammation;

microorganisms such as *Pseudomonas aeruginosa* and *Haemophilus influenzae* produce pigments, proteases, and other toxins that injure the respiratory epithelium and impair mucociliary clearance. The host inflammatory response induces epithelial injury, largely as a result of mediators released from neutrophils. As protection against infection is compromised, the dilated airways become more susceptible to colonization and growth of bacteria. Thus, a reinforcing cycle can result, with inflammation producing airway damage, impaired clearance of microorganisms, and further infection, which then completes the cycle by inciting more inflammation.

Infectious Causes

Adenovirus and influenza virus are the main viruses that cause bronchiectasis in association with lower respiratory tract involvement. Virulent bacterial infections, especially with potentially necrotizing organisms such as *Staphylococcus aureus*, *Klebsiella* spp., and anaerobes, remain important causes of bronchiectasis when antibiotic treatment of a pneumonia is not given or is significantly delayed. Infection with *Bordetella pertussis*, particularly in childhood, has also been classically associated with chronic suppurative airways disease. Bronchiectasis has been reported in patients with HIV infection, perhaps at least partly because of recurrent bacterial infections. Tuberculosis, a major cause of bronchiectasis worldwide, can produce airway dilatation by a necrotizing effect on pulmonary parenchyma and airways and indirectly as a consequence of airway obstruction from bronchostenosis or extrinsic compression by lymph nodes. Nontuberculous mycobacteria are frequently cultured from patients with bronchiectasis, often as secondary infections or colonizing organisms. However, it has also been recognized that these organisms, especially those of the *Mycobacterium avium* complex, can serve as primary pathogens associated with the development or progression of bronchiectasis.

Impaired host defense mechanisms are often involved in the predisposition to recurrent infections. The major cause of localized impairment of host defenses is endobronchial obstruction. Bacteria and secretions cannot be cleared adequately from the obstructed airway, which develops recurrent or chronic infection. Slowly growing endobronchial neoplasms such as carcinoid tumors may be associated with bronchiectasis. Foreign-body aspiration is another important cause of endobronchial obstruction, particularly in children. Airway obstruction can also result from bronchostenosis, from impacted secretions, or from extrinsic compression by enlarged lymph nodes.

Generalized impairment of pulmonary defense mechanisms occurs with immunoglobulin deficiency, primary ciliary disorders, or cystic fibrosis (CF). Infections and bronchiectasis are therefore often more diffuse. With panhypogammaglobulinemia, the best described of the

immunoglobulin disorders associated with recurrent infection and bronchiectasis, patients often also have a history of sinus or skin infections. Selective deficiency of an IgG subclass, especially IgG2, has also been described in a small number of patients with bronchiectasis.

The primary disorders associated with ciliary dysfunction, termed *primary ciliary dyskinesia*, are responsible for 5–10% of cases of bronchiectasis. Primary ciliary dyskinesia is inherited in an autosomal recessive fashion. Numerous defects are encompassed under this category, including structural abnormalities of the dynein arms, radial spokes, and microtubules; mutations in heavy and intermediate chain dynein have been described in a small number of patients. The cilia become dyskinetic; their coordinated, propulsive action is diminished, and bacterial clearance is impaired. The clinical effects include recurrent upper and lower respiratory tract infections, such as sinusitis, otitis media, and bronchiectasis. Because normal sperm motility also depends on proper ciliary function, men are generally infertile. Additionally, because visceral rotation during development depends on proper ciliary motion, the positioning of normally lateralized organs becomes random. As a result, approximately half of patients with primary ciliary dyskinesia fall into the subgroup of *Kartagener's syndrome*, in which situs inversus accompanies bronchiectasis and sinusitis.

In CF (Chap. 17), the tenacious secretions in the bronchi are associated with impaired bacterial clearance, resulting in colonization and recurrent infection with a variety of organisms, particularly mucoid strains of *P. aeruginosa* but also *S. aureus*, *H. influenzae*, *Escherichia coli*, and *Burkholderia cepacia*.

Noninfectious Causes

Some cases of bronchiectasis are associated with exposure to a toxic substance that incites a severe inflammatory response. Examples include inhalation of a toxic gas such as ammonia or aspiration of acidic gastric contents, although the latter problem is often also complicated by aspiration of bacteria. An immune response in the airway may also trigger inflammation, destructive changes, and bronchial dilatation. This mechanism is presumably important for bronchiectasis with allergic bronchopulmonary aspergillosis (ABPA), which is caused at least partly by an immune response to *Aspergillus* organisms that have colonized the airway (Chap. 9).

In α_1 -antitrypsin deficiency, the usual respiratory complication is the early development of panacinar emphysema, but affected individuals may occasionally have bronchiectasis. In the *yellow nail syndrome*, which is caused by hypoplastic lymphatics, the triad of lymphedema, pleural effusion, and yellow discoloration of the nails is accompanied by bronchiectasis in approximately 40% of patients.

Patients typically present with persistent or recurrent cough and purulent sputum production. Repeated, purulent respiratory tract infections should raise clinical suspicion for bronchiectasis. Hemoptysis occurs in 50–70% of cases and can be caused by bleeding from friable, inflamed airway mucosa (Chap. 3). More significant, even massive bleeding is often a consequence of bleeding from hypertrophied bronchial arteries. Systemic symptoms such as fatigue, weight loss, and myalgias can also occur.

When a specific infectious episode initiates bronchiectasis, patients may describe a severe pneumonia followed by chronic cough and sputum production. Alternatively, patients without a dramatic initiating event often describe the insidious onset of symptoms. In some cases, patients are either asymptomatic or have a nonproductive cough, often associated with “dry” bronchiectasis in an upper lobe. Dyspnea or wheezing generally reflects either widespread bronchiectasis or underlying chronic obstructive pulmonary disease. With exacerbations of infection, the amount of sputum increases, and it becomes more purulent and often more bloody; systemic symptoms, including fever, may also be prominent.

Physical examination of the chest overlying an area of bronchiectasis is quite variable. Any combination of crackles, rhonchi, and wheezes may be heard, all of which reflect the damaged airways containing significant secretions. As with other types of chronic intrathoracic infection, clubbing may be present. Patients with severe diffuse disease, particularly those with chronic hypoxemia, may have associated cor pulmonale and right ventricular failure.

RADIOGRAPHIC AND LABORATORY FINDINGS

Although the chest radiograph is important in the evaluation of suspected bronchiectasis, the findings are often nonspecific. At one extreme, the radiograph may be normal with mild disease. Alternatively, patients with saccular bronchiectasis may have prominent cystic spaces, either with or without air-liquid levels, corresponding to the dilated airways. These may be difficult to distinguish from enlarged airspaces because of bullous emphysema or from regions of honeycombing in patients with severe interstitial lung disease. Other findings are caused by dilated airways with thickened walls, which result from peribronchial inflammation. These dilated airways are often crowded together in parallel. When seen longitudinally, the airways appear as “tram tracks”; when seen in cross-section, they produce “ring shadows.” Because the dilated airways may be filled with secretions, the lumen may appear dense rather



FIGURE 16-1

High-resolution CT scan of bronchiectasis showing dilated airways in both lower lobes and in the lingula. When seen in cross-section, the dilated airways have a ringlike appearance. (From SE Weinberger: *Principles of Pulmonary Medicine*, 4th ed. Philadelphia, Saunders, 2004, with permission.)

than radiolucent, producing an opaque tubular or branched tubular structure.

CT, especially with high-resolution images 1.0–1.5 mm thick, provides an excellent view of dilated airways (Fig. 16-1). Consequently, it is now the standard technique for detecting or confirming the diagnosis of bronchiectasis.

Examination of sputum often reveals an abundance of neutrophils and colonization or infection with a variety of possible organisms. Appropriate staining and culturing of sputum often provide a guide to antibiotic therapy.

When bronchiectasis is focal, fiberoptic bronchoscopy may reveal an underlying endobronchial obstruction. In other cases, upper lobe involvement may be suggestive of either tuberculosis or ABPA. With more widespread disease, measurement of sweat chloride levels for CF, structural or functional assessment of nasal or bronchial cilia or sperm for primary ciliary dyskinesia, and quantitative assessment of immunoglobulins may explain recurrent airway infection.

Pulmonary function tests may demonstrate airflow obstruction as a consequence of diffuse bronchiectasis or associated chronic obstructive lung disease. Bronchial hyperreactivity (e.g., to methacholine challenge) and some reversibility of the airflow obstruction with inhaled bronchodilators are relatively common.

Figure 16-2 illustrates a diagnostic approach based on clinical suspicion and radiographic findings. Because the differential diagnosis for focal versus diffuse bronchiectasis is different, the radiographic distribution of disease can serve as a starting point of the diagnostic workup. This algorithm should not imply that all studies be obtained in all patients with bronchiectasis. Rather, the workup

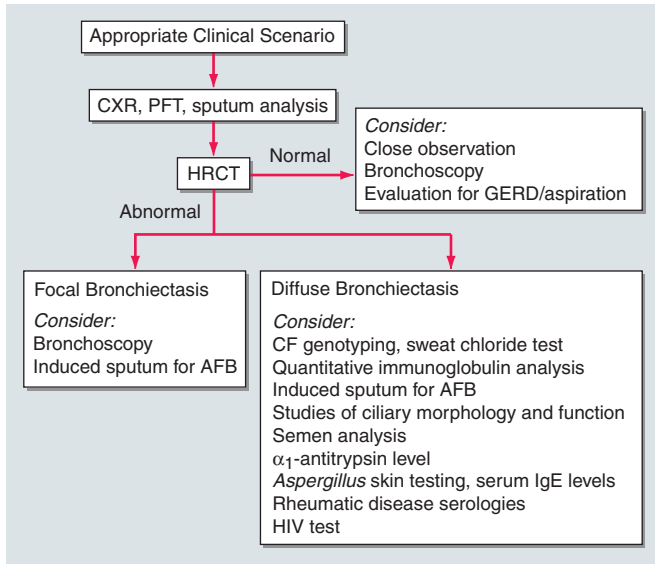


FIGURE 16-2

Diagnostic approach to bronchiectasis. AFB, acid-fast bacilli; CXR, chest x-ray; GERD, gastroesophageal reflux disease; HRCT, high-resolution computed tomography; PFT, pulmonary function testing.

should be dictated by a careful assessment of the clinical scenario. In a patient with focal bronchiectasis, for example, documentation of a prior pneumonia in the same location may suffice. Evaluation for immunoglobulin deficiency and CF should be considered for young patients with bronchiectasis and sinopulmonary disease.

Rx Treatment: **BRONCHIECTASIS**

Therapy has several major goals: (1) treatment of infection, particularly during acute exacerbations; (2) improved clearance of tracheobronchial secretions; (3) reduction of inflammation; and (4) treatment of an identifiable underlying problem.

Antibiotics are the cornerstone of bronchiectasis management. For patients with infrequent exacerbations characterized by an increase in quantity and purulence of the sputum, antibiotics are used only during acute episodes. Although choice of an antibiotic should be guided by Gram's stain and culture of sputum, empiric coverage (e.g., with amoxicillin, trimethoprim-sulfamethoxazole, or levofloxacin) is often given initially. Infection with *P. aeruginosa* is of particular concern because it appears to be associated with greater rate of deterioration of lung function and worse quality of life. When *Pseudomonas* spp. is present, oral therapy with a

quinolone or parenteral therapy with an aminoglycoside, carbapenem, or third-generation cephalosporin is appropriate based on antibiotic sensitivity patterns. There are no firm guidelines for length of therapy, but a 10- to 14-day course or longer is typically administered.

A variety of mechanical methods and devices accompanied by appropriate positioning can facilitate drainage in patients with copious secretions. Although commonly used and probably beneficial, these airway-clearance techniques have been poorly studied, and their efficacy is not proven. Pharmacologic agents are also used to promote bronchopulmonary hygiene. Mucolytic agents to thin secretions and allow better clearance are controversial. Aerosolized recombinant DNase, which decreases viscosity of sputum by breaking down DNA released from neutrophils, has been shown to improve pulmonary function in patients with CF but may be deleterious and should be avoided in bronchiectasis that is not associated with CF. Bronchodilators to improve obstruction and aid clearance of secretions are particularly useful in patients with airway hyperreactivity and reversible air-flow obstruction.

Although surgical therapy was common in the past, more effective antibiotic and supportive therapy has largely replaced surgery. However, when bronchiectasis is localized and the morbidity is substantial despite adequate medical therapy, surgical resection of the involved region of lung should be considered.

When massive hemoptysis, often originating from the hypertrophied bronchial circulation, does not resolve with conservative therapy, including rest and antibiotics, therapeutic options are either surgical resection or bronchial arterial embolization (Chap. 3). Although resection may be successful if the disease is localized, embolization is preferable with widespread disease.

LUNG ABSCESS

Lung abscess is defined as pulmonary parenchymal necrosis and cavitation resulting from infection. The development of a lung abscess implies a high microorganism burden as well as inadequate microbial clearance from the airways. Aspiration is the most common cause; factors that portend an increased risk of aspiration include esophageal dysmotility, seizure disorders, and neurologic conditions causing bulbar dysfunction. Other predisposing conditions for lung abscess include periodontal disease and alcoholism.

MICROBIOLOGY

Anaerobic bacteria are the most common causative organisms for lung abscess. Aerobic or facultative bacteria such as *S. aureus*, *Klebsiella pneumoniae*, *Nocardia* spp., and

170 gram-negative organisms, as well as nonbacterial pathogens such as fungi and parasites, may also cause abscess formation. In an immunocompromised host, aerobic bacteria and opportunistic pathogens may predominate. Multiple isolates are more commonly seen in all patients when anaerobic and aerobic cultures are done.

CLINICAL MANIFESTATIONS

The symptoms of lung abscess are typical of pulmonary infection in general and may include cough, purulent sputum production, pleuritic chest pain, fever, and hemoptysis. In anaerobic infection, the clinical course may evolve over an extended period of time, and some patients may be asymptomatic. More acute presentations are typical of infection with aerobic bacteria.

Physical examination is often unrevealing. Rales or evidence of consolidation may be present. Fetid breath and poor dentition may be diagnostic clues. Clubbing or hypertrophic pulmonary osteoarthropathy may occur in chronic cases.

The chest radiograph classically reveals one or two thick-walled cavities in dependent areas of the lung, particularly the upper lobes and posterior segments of the lower lobes (Fig. 16-3). An air-fluid level is often present. CT of the chest is helpful in defining the size and location of the abscess, as well as to evaluate for additional cavities and the presence of pleural disease. Cavitory lesions in nondependent regions such as the right middle lobe or anterior segments of the upper lobes should raise the possibility of other causes, including malignancy.

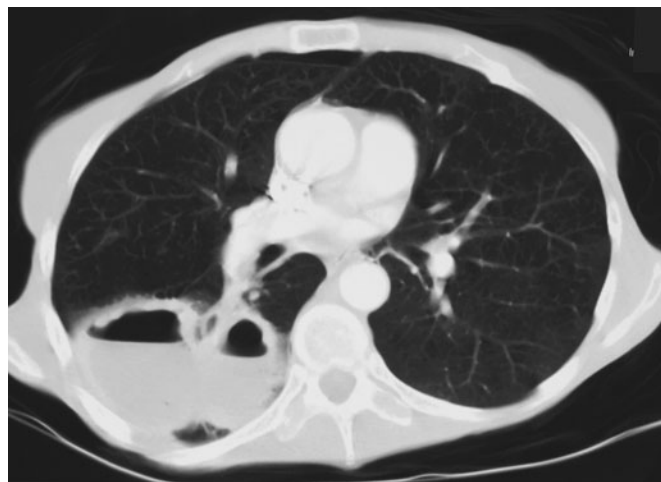


FIGURE 16-3

Cross-sectional CT image from a patient with an anaerobic lung abscess showing two contiguous thick-walled cavitary lesions in the right lower lobe with air-fluid levels. (From WT Miller Jr: *Diagnostic Thoracic Imaging*. New York, McGraw-Hill, 2006, with permission.)

Laboratory studies may reveal leukocytosis, anemia, and an elevated erythrocyte sedimentation rate.

DIAGNOSIS

The diagnosis of lung abscess is based on clinical symptoms, identification of predisposing conditions, and chest radiographic findings. The differential diagnosis includes mycobacterial infection, pulmonary sequestration, malignancy, pulmonary infarction, and an infected bulla.

Identification of a causative organism is an ideal but challenging goal. Anaerobic bacteria are particularly difficult to isolate. Blood, sputum cultures, and (when appropriate) pleural fluid cultures should be obtained from patients with lung abscess. The role of fiberoptic bronchoscopy with bronchoalveolar lavage or protected-specimen brush for diagnosis or drainage of lung abscess is controversial. The relatively low yield, especially with anaerobic lung abscess, should be balanced against the risk of rupture of the abscess cavity with spillage into the airways. Bronchoscopy is perhaps most useful to rule out airway obstruction, mycobacterial infection, or malignancy. Other less commonly used methods for microbiologic sampling are transtracheal or transthoracic aspiration.

Rx Treatment: LUNG ABSCESS

For many years, penicillin was the mainstay of empiric antibiotic therapy for lung abscess. Because of the emergence of β -lactamase-producing organisms, clindamycin (150–300 mg q6 h) is now standard therapy. Other agents, such as carbapenems and β -lactam/ β -lactamase inhibitor combinations, may be useful in selected cases. Metronidazole alone is associated with a high treatment failure rate. When possible, the choice of antibiotics should be guided by microbiologic results.

The duration of treatment for lung abscess is controversial. Four to 6 weeks of antibiotic therapy is typically used, although a more extended course is favored by some experts. Treatment failure suggests the possibility of a noninfectious etiology.

Although surgery has had a limited role in treatment in the antibiotic era, indications include refractory hemoptysis, inadequate response to medical therapy, or the need for a tissue diagnosis when there is concern for a noninfectious etiology.

In general, outcomes for patients with classic anaerobic lung abscess are favorable, with a 90%–95% cure rate. Higher mortality rates have been reported in immunocompromised patients; those with significant comorbidities; and those with infection with *P. aeruginosa*, *S. aureus*, and *K. pneumoniae*.

FURTHER READINGS

- BARKER AF: Bronchiectasis. *N Engl J Med* 346:1383, 2002
- MANSHARAMANI N et al: Lung abscess in adults: Clinical comparison of immunocompromised to non-immunocompromised patients. *Respir Med* 96:178, 2002
- MANSHARAMANI N, KOZIEL H: Chronic lung sepsis: Lung abscess, bronchiectasis, and empyema. *Curr Opin Pulm Med* 9:181, 2003
- NOONE PG et al: Primary ciliary dyskinesia: Diagnostic and phenotypic features. *Am J Respir Crit Care Med* 169:459, 2004
- PASTEUR MC et al: An investigation into causative factors in patients with bronchiectasis. *Am J Respir Crit Care Med* 162:1277, 2000
- ROSEN MJ: Chronic cough due to bronchiectasis. ACCP evidence-based clinical practice guidelines. *Chest* 129:122S, 2006
- SCHEINBERG P, SHORE E: A pilot study of the safety and efficacy of tobramycin solution for inhalation in patients with severe bronchiectasis. *Chest* 127:1420, 2005
- WEYCKER D et al: Prevalence and economic burden of bronchiectasis. *Clin Pulm Med* 12:205, 2005
- WILLS P, GREENSTONE M: Inhaled hyperosmolar agents for bronchiectasis. *Cochrane Database Syst Rev* 2:CD002996, 2006



CHAPTER 17

CYSTIC FIBROSIS

Richard C. Boucher, Jr.

■ Pathogenesis	172
Genetic Considerations	172
CFTR Protein	172
Epithelial Dysfunction	173
Organ-Specific Pathophysiology	173
■ Clinical Features	174
Respiratory Tract	174
Gastrointestinal Tract	175
Genitourinary System	175
■ Diagnosis	175
■ Further Readings	177

Cystic fibrosis (CF) is a monogenic disorder that presents as a multisystem disease. The first signs and symptoms typically occur in childhood, but about 5% of patients in the United States are diagnosed as adults. Because of improvements in therapy, >41% of patients are now adults (≥ 18 years old) and 13% are past the age of 30 years. The median survival is >41 years for patients with CF. Thus, CF is no longer only a pediatric disease, and internists must be prepared to recognize and treat its many complications. This disease is characterized by chronic bacterial infection of the airways that ultimately leads to bronchiectasis and bronchiolectasis, exocrine pancreatic insufficiency and intestinal dysfunction, abnormal sweat gland function, and urogenital dysfunction.

PATHOGENESIS

GENETIC CONSIDERATIONS



CF is an autosomal recessive disease resulting from mutations in the gene that encodes the CF transmembrane conductance regulator (CFTR) protein located on chromosome 7. The mutations in the *CFTR* gene fall into four major classes, as depicted in [Fig. 17-1](#). Class I to III mutations are considered “severe,” as indexed by pancreatic insufficiency and high sweat NaCl values (see below). Class IV mutations can be “mild,” i.e.,

associated with pancreatic sufficiency and intermediate or normal sweat NaCl values. Of note, Class I mutations that encode for premature stop codons are important to identify because they may in the future be treated with agents that promote “read-through” of the stop codon with production of functional CFTR.

The prevalence of CF varies with the ethnic origin of a population. CF is detected in approximately one in 3000 live births in the white population of North America and northern Europe, one in 17,000 live births of African Americans, and one in 90,000 live births of the Asian population of Hawaii. The most common mutation in the CF gene (~70% of CF chromosomes) is a 3-bp deletion (a Class III mutation) that results in an absence of phenylalanine at amino acid position 508 (ΔF_{508}) of the CF gene protein product, known as CFTR. The large number (>1400) of relatively uncommon (<2% each) mutations identified in the CF gene makes it difficult to use DNA diagnostic technologies for identifying heterozygotes in populations at large.

CFTR PROTEIN

The CFTR protein is a single polypeptide chain containing 1480 amino acids that appears to function both

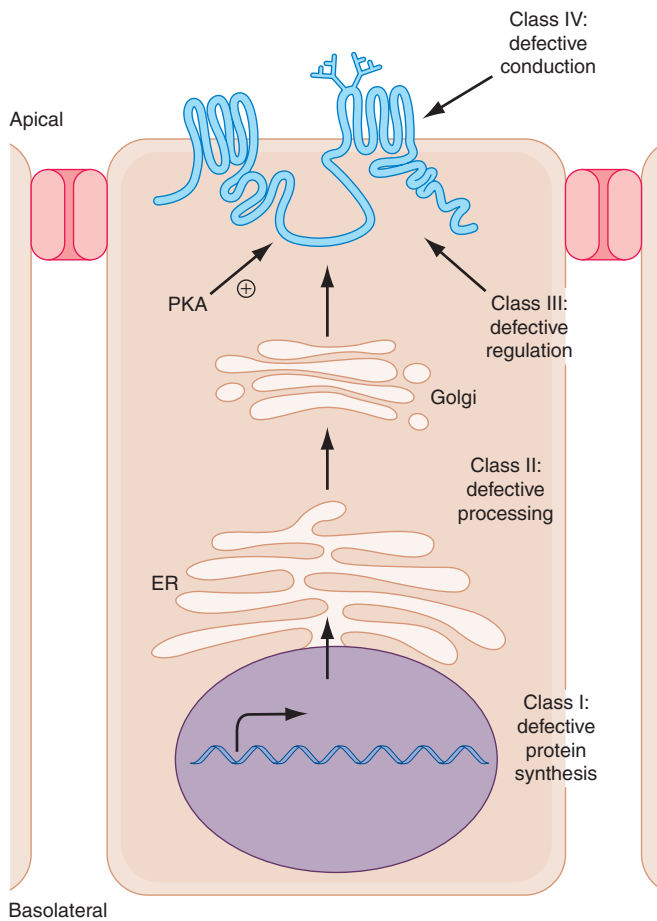


FIGURE 17-1
Schema describing classes of genetic mutations in *CFTR* gene and effects on CFTR protein/function. Note the ΔF_{508} mutation is a class II mutation and, similar to class I mutations, would be predicted to produce no mature CFTR protein in the apical membrane. CFTR, cystic fibrosis transmembrane conductance regulator.

as a cyclic AMP (cAMP)–regulated Cl^- channel and, as its name implies, a regulator of other ion channels. The fully processed form of CFTR is found in the plasma membrane in normal epithelia. Biochemical studies indicate that the ΔF_{508} mutation leads to improper processing and intracellular degradation of the CFTR protein. Thus, absence of CFTR in the plasma membrane is central to the molecular pathophysiology of the ΔF_{508} mutation and other Class I–II mutations. However, Class III/IV mutations produce CFTR proteins that are fully processed but are nonfunctional or only partially functional in the plasma membrane.

EPITHELIAL DYSFUNCTION

The epithelia affected by CF exhibit different functions in their native state, i.e., whereas some are volume absorbing (airways and distal intestinal epithelia), and some are

salt but not volume absorbing (sweat duct), others are volume secretory (proximal intestine and pancreas). Given this diversity of native activities, it is not surprising that CF produces organ-specific effects on electrolyte and water transport. However, the unifying concept is that all affected tissues express abnormal ion transport function.

ORGAN-SPECIFIC PATHOPHYSIOLOGY

Lung

The diagnostic biophysical hallmark of CF airway epithelia is the increased transepithelial electric potential difference (PD). The transepithelial PD reflects both the rate of active ion transport and epithelial resistance to ion flow. CF airway epithelia exhibit abnormalities in both active Na^+ absorption and active Cl^- secretion (Fig. 17-2). The Cl^- secretory defect reflects the absence of cAMP–dependent kinase and protein kinase C–regulated Cl^- transport mediated by CFTR itself. An important observation is that there is also a molecularly distinct Ca^{2+} –activated Cl^- channel (CaCC) expressed in the apical membrane. This channel can substitute for CFTR with regard to Cl^- secretion and may be a potential therapeutic target.

Abnormal regulation of Na^+ absorption is a key feature of CF airway epithelia. This abnormality reflects a second function of CFTR, its function as a tonic inhibitor of the epithelial Na^+ channel. The molecular mechanisms mediating this action of CFTR remain unknown.

Mucus clearance is the primary innate airways defense mechanism against infection by inhaled bacteria. Normal airways vary the rates of active Na^+ absorption and Cl^- secretion to adjust the volume of liquid (water), i.e., “hydration,” on airway surfaces for efficient mucus clearance. The central hypothesis of CF airways pathophysiology is that the faulty regulation of Na^+ absorption and inability to secrete Cl^- via CFTR reduce the volume of liquid on airway surfaces (i.e., they are “dehydrated”). Both the thickening of mucus and the depletion of the periciliary liquid lead to adhesion of mucus to the airway surface. Mucus adhesion leads to a failure to clear mucus from the airways both by ciliary and airflow-dependent (cough) mechanisms. The absence of a strict correspondence between gene mutation class and severity of lung disease suggests important roles for modifier genes and gene–environmental interactions.

The infection that characterizes CF airways involves the mucus layer rather than epithelial or airway wall invasion. The predisposition of CF airways to chronic infection by *Staphylococcus aureus* and *Pseudomonas aeruginosa* is consistent with failure to clear mucus. Recently, it has been demonstrated that the O_2 tension is very low in the mucus of individuals with CF, and adaptations to

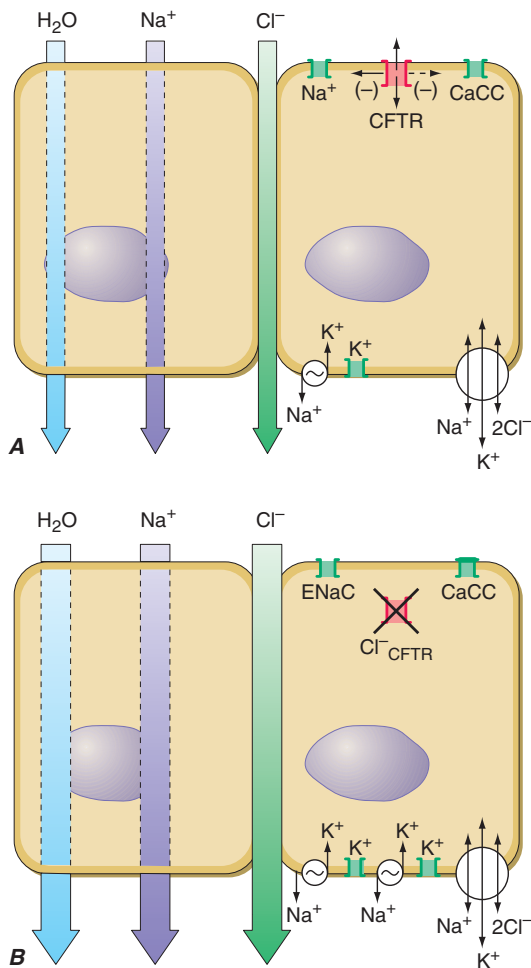


FIGURE 17-2

Comparison of ion transport properties of normal (A) and cystic fibrosis (CF) (B) airway epithelia. The vectors describe routes and magnitudes of Na⁺ and Cl⁻ transport that is accompanied by osmotically driven water flow. The normal basal pattern for ion transport is absorption of Na⁺ from the lumen via an amiloride-sensitive Na⁺ channel. This process is accelerated in CF. The capacity to initiate cyclic AMP-mediated Cl⁻ secretion is diminished in CF airway epithelia because of absence or dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) Cl⁻ channel. The accelerated Na⁺ absorption in CF reflects the absence of CFTR inhibitory effects on Na⁺ channels.

hypoxia are important determinants of the physiology of bacteria in the CF lung. Indeed, both mucus stasis and mucus hypoxia may contribute to the propensity for *Pseudomonas* spp. to grow in biofilm colonies within mucus plaques adherent to CF airway surfaces.

Gastrointestinal Tract

The gastrointestinal effects of CF are diverse. In the exocrine pancreas, the absence of the CFTR Cl⁻ channel in the apical membrane of pancreatic ductal epithelia limits the function of an apical membrane Cl⁻-HCO₃⁻

exchanger to secrete bicarbonate and Na⁺ (by a passive process) into the duct. The failure to secrete Na⁺ HCO₃⁻ and water leads to retention of enzymes in the pancreas and ultimately destruction of virtually all pancreatic tissue. The CF intestinal epithelium, because of the lack of Cl⁻ and water secretion, fails to flush secreted mucins and other macromolecules from intestinal crypts. The diminished CFTR-mediated secretion of liquid may be exacerbated by excessive absorption of liquid, reflecting abnormalities of CFTR-mediated regulation of Na⁺ absorption (both mediated by Na⁺ channels and possibly other Na⁺ transporters, e.g., Na⁺-H⁺ exchangers). Both dysfunctions lead to desiccated intraluminal contents and obstruction of both the small and large intestine. In the hepatobiliary system, defective hepatic ductal salt (Cl⁻) and water secretion causes thickened biliary secretions, focal biliary cirrhosis, and bile duct proliferation in approximately 25–30% of patients with CF. The inability of the CF gallbladder epithelium to secrete salt and water can lead to both chronic cholecystitis and cholelithiasis.

Sweat Gland

CF patients secrete nearly normal volumes of sweat in the sweat acinus. However, CF patients are not able to absorb NaCl from sweat as it moves through the sweat duct because of the inability to absorb Cl⁻ across the ductal epithelial cells. This dysfunction in the sweat gland is typically measured by collecting sweat after iontophoresing a cholinergic agonist into the forearm.

CLINICAL FEATURES

Most patients with CF present with signs and symptoms of the disease in childhood. Approximately 20% of patients present within the first 24 hours of life with gastrointestinal obstruction, termed *meconium ileus*. Other common presentations within the first year or two of life include respiratory tract symptoms, most prominently cough or recurrent pulmonary infiltrates, and failure to thrive. A significant proportion of patients (~5%), however, are diagnosed after age 18 years.

RESPIRATORY TRACT

Upper respiratory tract disease is almost universal in patients with CF. Chronic sinusitis is common in childhood and leads to nasal obstruction and rhinorrhea. The occurrence of nasal polyps approaches 25% and often requires treatment with topical steroids, surgery, or both.

In the lower respiratory tract, the first symptom of CF is cough. With time, the cough becomes persistent and produces viscous, purulent, often greenish-colored sputum. Inevitably, periods of clinical stability are interrupted by “exacerbations,” defined by increased cough,

weight loss, low-grade fever, increased sputum volume, and decrements in pulmonary function. Over the course of years, the exacerbations become more frequent and the recovery of lost lung function incomplete, leading to respiratory failure.

CF patients exhibit characteristic sputum microbiology. *Haemophilus influenzae* and *S. aureus* are often the first organisms recovered from lung secretions in newly diagnosed patients with CF. *P. aeruginosa*, often mucoid and antibiotic resistant, is typically cultured from lower respiratory tract secretions thereafter. *Burkholderia* spp. (formerly *Pseudomonas cepacia*) is also recovered from CF sputum and is pathogenic. Patient-to-patient spread of certain strains of this organism mandates strict infection control in the hospital. Other gram-negative rods recovered from CF sputum include *Alcaligenes xylosoxidans*; *B. gladioli*; and occasionally mucoid forms of *Proteus*, *Escherichia coli*, and *Klebsiella* spp. Up to 50% of CF patients have *Aspergillus fumigatus* in their sputum, and up to 10% of these patients exhibit the syndrome of allergic bronchopulmonary aspergillosis. *Mycobacterium tuberculosis* is rare in patients with CF. However, 10–20% of adult patients with CF have sputum cultures positive for nontuberculous mycobacteria and in some patients, these microorganisms are associated with disease.

The first lung-function abnormalities observed in CF children, increased ratios of residual volume to total lung capacity, suggest that small-airways disease is the first functional lung abnormality in CF. As the disease progresses, both reversible and irreversible changes in forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV₁) develop. The reversible component reflects the accumulation of intraluminal secretions or airway reactivity, which occurs in 40–60% of patients with CF. The irreversible component reflects chronic destruction of the airway wall and bronchiolitis.

The earliest chest x-ray change in CF lungs is hyperinflation, reflecting small-airways obstruction. Later, signs of luminal mucus impaction, bronchial cuffing, and finally bronchiectasis (e.g., ring shadows) are noted. For reasons that remain speculative, the right upper lobe displays the earliest and most severe changes.

CF pulmonary disease is associated with many intermittent complications. Pneumothorax is common (>10% of patients). The production of small amounts of blood in sputum is common in CF patients with advanced pulmonary disease. Massive hemoptysis is life threatening. With advanced lung disease, digital clubbing appears in virtually all patients with CF. As late events, respiratory failure and cor pulmonale are prominent features of CF.

GASTROINTESTINAL TRACT

The syndrome of meconium ileus in infants presents with abdominal distension, failure to pass stool, and emesis. The abdominal flat plate can be diagnostic, with

small intestinal air-fluid levels, a granular appearance representing meconium, and a small colon. In children and young adults, a syndrome termed *meconium ileus equivalent* or *distal intestinal obstruction syndrome* (DIOS) occurs. The syndrome presents with right lower quadrant pain, loss of appetite, occasionally emesis, and often a palpable mass. The syndrome can be confused with appendicitis, whose frequency is not increased in CF patients.

Exocrine pancreatic insufficiency occurs in >90% of patients with CF. Insufficient pancreatic enzyme secretion yields the typical pattern of protein and fat malabsorption, with frequent, bulky, foul-smelling stools. Signs and symptoms of malabsorption of fat-soluble vitamins, including vitamins E and K, are also noted. Pancreatic beta cells are spared early, but its function decreases with age. This effect, plus inflammation-induced insulin resistance, causes hyperglycemia and a requirement for insulin in >15% of older patients with CF (age >35 years).

GENITOURINARY SYSTEM

Late onset of puberty is common in both boys and girls with CF. The delayed maturational pattern is likely secondary to the effects of chronic lung disease and inadequate nutrition on reproductive endocrine function. More than 95% of male patients with CF are azoospermic, reflecting obliteration of the vas deferens caused by defective liquid secretion. Some 20% of CF women are infertile because of effects of chronic lung disease on the menstrual cycle; thick, tenacious cervical mucus that blocks sperm migration; and possibly fallopian tube or uterine wall abnormalities in liquid transport. Most pregnancies produce viable infants, and women with CF are able to breastfeed infants normally.

DIAGNOSIS

The diagnosis of CF rests on the combination of clinical criteria and abnormal CFTR function as demonstrated by sweat tests, nasal PD measurements, and CFTR mutation analysis. Elevated sweat Cl⁻ values are nearly pathognomonic for CF. The values for the Cl⁻ (and Na⁺) concentrations in sweat vary with age, but typically in adults, a Cl⁻ concentration of >70 meq/L discriminates between patients with CF and those with other lung diseases. DNA analysis of the most common mutations can identify CF mutations in >90% of affected patients. The nasal PD measurement can document CFTR dysfunction if the sweat Cl⁻ test is normal or borderline and two CF mutations are not identified. DNA analysis is performed routinely in patients with CF because pancreatic genotype-phenotype relationships have been identified, and mutation class-specific treatments are being developed.

Between 1 and 2% of patients with the clinical syndrome of CF have normal sweat Cl⁻ values. In most of

176 these patients, the nasal transepithelial PD is raised into the diagnostic range for CF, and sweat acini do not secrete in response to injected β -adrenergic agonists. A single mutation of the CFTR gene, 3849 + 10 kb C→T, is associated with most CF patients with normal sweat Cl^- values.

Rx Treatment: **CYSTIC FIBROSIS**

The major objectives of therapy for CF are to promote clearance of secretions and control infection in the lung, provide adequate nutrition, and prevent intestinal obstruction. Ultimately, therapies that restore the processing of misfolded mutant CFTR or gene therapy may be the treatments of choice.

LUNG DISEASE More than 95% of CF patients die of complications resulting from lung infection. Theoretically, increasing clearance of adherent mucus should both treat and prevent progression of CF lung disease, whereas antibiotics principally reduce the bacterial burden in the CF lung.

The time-honored techniques for clearing pulmonary secretions are breathing exercises, flutter valves, and chest percussion. Regular use of these maneuvers is effective in preserving lung function. A major advance has been the demonstrated efficacy of inhaled hypertonic saline (7%) in restoring mucus clearance and pulmonary function in short-term studies and its efficacy in reducing acute exacerbations in long-term (1 year) studies. Hypertonic saline is safe but can produce bronchoconstriction in some patients, which can be prevented with coadministered bronchodilators. Studies are ongoing to establish whether inhaled hypertonic saline should be the base therapy for all CF patients.

Pharmacologic agents for increasing mucus clearance are in use and in development. An important adjunct to secretion clearance can be recombinant human DNAse, which degrades the concentrated DNA in CF sputum, increases airflow during short-term administration, and increases the time between pulmonary exacerbations. Most patients receive a therapeutic trial of DNAse for several months to test for efficacy. Clinical trials of experimental drugs aimed at restoring salt and water content of secretions are underway, but these drugs are not yet available for clinical use.

Antibiotics are used for treating lung infection, and their use is guided by sputum culture results. It should be noted, however, that because routine hospital microbiologic cultures are performed under conditions that do not mimic conditions in the CF lung (e.g., hypoxia), clinical efficacy often does not correlate with sensitivity testing. Because of increased total-body clearance and volume of distribution of antibiotics in CF patients, the required doses are higher for patients with CF.

Early intervention with antibiotics in infants with infection may eradicate *P. aeruginosa* for extended periods. In older patients with established infection, suppression of bacterial growth is the therapeutic goal. Azithromycin (250 mg/day or 500 mg three times weekly) is often used chronically, although it is unclear whether its actions are antimicrobial or antiinflammatory. Inhaled aminoglycosides (e.g., tobramycin 300 mg bid) for alternating monthly intervals are also used. "Mild exacerbations," as defined by increased cough and mucus production, are treated with additional oral antibiotics. Oral agents used to treat *Staphylococcus* infection include a semisynthetic penicillin or a cephalosporin. Oral ciprofloxacin may reduce pseudomonal bacterial counts and control symptoms, but its clinical utility may be limited by rapid emergence of resistant organisms. Accordingly, it is often used with an inhaled antibiotic, either tobramycin or colistin (75 mg bid). More severe exacerbations, or exacerbations associated with bacteria resistant to oral antibiotics, require IV antibiotics. IV therapy is given both in the hospital and in the outpatient setting. Usually, two drugs with different mechanisms of action (e.g., a cephalosporin and an aminoglycoside) are used to treat *P. aeruginosa* to minimize emergence of resistant organisms. Drug dosage should be monitored so that levels for gentamicin or tobramycin peak at ranges of ~10 $\mu\text{g/mL}$ and exhibit troughs of <2 $\mu\text{g/mL}$. Antibiotics directed at *Staphylococcus*, *H. influenzae*, or both are added, depending on culture results.

Inhaled β -adrenergic agonists can be useful to control airways constriction, but long-term benefit has not been shown. Oral glucocorticoids may reduce airways inflammation, but their long-term use is limited by adverse side effects; however, they may be useful for treating allergic bronchopulmonary aspergillosis.

The chronic damage to airway walls partly reflects the destructive activities of inflammatory enzymes generated in part by inflammatory cells. Specific therapies with antiproteases have not been developed. However, a subset of adolescents with CF may benefit from long-term, high-dose nonsteroidal (ibuprofen) therapy.

A number of pulmonary complications require acute interventions. Atelectasis requires treatment with inhaled hypertonic saline, chest physiotherapy, and antibiotics. Pneumothoraces involving $\leq 10\%$ of the lung can be observed, but chest tubes are required to expand collapsed, diseased lung. Small-volume hemoptysis typically requires treatment of lung infection and assessment of coagulation and vitamin K status. For massive hemoptysis, bronchial artery embolization should be performed. The most ominous complications of CF are respiratory failure and cor pulmonale. The most effective conventional therapy for these conditions is vigorous medical management of the lung disease and O_2 supplementation. Ultimately, the only effective treatment for respiratory

failure in CF is lung transplantation (Chap. 24). The 2-year survival for lung transplantation exceeds 60%, and transplant patient deaths result principally from graft rejection, often involving obliterative bronchiolitis. The transplanted lungs do not develop a CF-specific phenotype.

GASTROINTESTINAL DISEASE Maintenance of adequate nutrition is critical for the health of patients with CF. Most (>90%) CF patients require pancreatic enzyme replacement. Capsules generally contain between 4000 and 20,000 units of lipase. The dose of enzymes (typically no more than 2500 units/kg per meal, to avoid risk of fibrosing colonopathy) should be adjusted on the basis of weight, abdominal symptomatology, and stool character. Replacement of fat-soluble vitamins, particularly vitamins E and K, is usually required. Hyperglycemia most often becomes manifest in adulthood and typically requires insulin treatment.

For treatment of the distal intestinal obstruction syndrome, megalodiatrizoate or other hypertonic radiocontrast materials delivered by enema to the terminal ileum are used. For control of symptoms, adjustment of pancreatic enzymes and use of salt solutions containing osmotically active agents (e.g. propyleneglycol) is recommended. Persistent symptoms may indicate a diagnosis of gastrointestinal malignancy, which is increased in incidence in patients with CF.

Cholestatic liver disease occurs in about 8% of CF patients. Treatment with urodeoxycholic acid is typically initiated if there is an increase in alkaline phosphatase and gammaglutamyl transpeptidase (GGT) (3 x normal), but this treatment has not been shown to influence the course of hepatic disease. End-stage liver disease occurs in about 5% of CF patients and can be treated by transplantation.

OTHER ORGAN COMPLICATIONS Dehydration caused by heat-induced salt loss from sweat ducts occurs more readily in CF patients. CF patients also have an increased incidence of osteoarthritis, renal stones, and osteoporosis, particularly after transplant.

Psychosocial Factors CF imposes a tremendous burden on patients, and depression is common. Health insurance, career options, family planning, and life expectancy become major issues. Thus, assisting patients with the psychosocial adjustments required by CF is critical.

FURTHER READINGS

- BOUCHER RC: Airway surface dehydration in cystic fibrosis: Pathogenesis and therapy. *Ann Rev Med* 58:157, 2007
- DAVIES JC et al: Cystic fibrosis. *Br Med J* 335:1255, 2007
- DAVIS PB: Cystic fibrosis since 1938. *Am J Respir Crit Care Med* 173:475, 2006
- FLUME PA, STENBIT A: Making the diagnosis of cystic fibrosis. *Am J Med Sci* 335:51, 2008
- GROMAN JD et al: Phenotypic and genetic characterization of patients with features of “nonclassic” forms of cystic fibrosis. *J Pediatr* 146:675, 2006
- GUGGINO WB, STANTON BA: New insights into cystic fibrosis: Molecular switches that regulate CFTR. *Nat Rev Mol Cell Biol* 7:426, 2006
- PRINCE AS: Biofilms, antimicrobial resistance, and airway infection. *N Engl J Med* 347:1110, 2002
- ROWE SM et al: Cystic fibrosis. *N Engl J Med* 352:1992, 2005
- WORLITSCH D et al: Effects of reduced mucus oxygen concentration in airway pseudomonas infections of cystic fibrosis patients. *J Clin Invest* 109:317, 2002



CHAPTER 18

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

John J. Reilly, Jr. ■ Edwin K. Silverman ■ Steven D. Shapiro

Risk Factors	178
■ Genetic Considerations	180
Natural History	180
Pathophysiology	181
Pathology	182
Pathogenesis	183
Clinical Presentation	184
■ Further Readings	189

Chronic obstructive pulmonary disease (COPD) has been defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), an international collaborative effort to improve awareness, diagnosis, and treatment of COPD, as a disease state characterized by airflow limitation that is not fully reversible (<http://www.goldcopd.com/>). COPD includes *emphysema*, an anatomically defined condition characterized by destruction and enlargement of the lung alveoli; *chronic bronchitis*, a clinically defined condition with chronic cough and phlegm; and *small airways disease*, a condition in which small bronchioles are narrowed. COPD is present only if chronic airflow obstruction occurs; chronic bronchitis *without* chronic airflow obstruction is *not* included within COPD.

COPD is the fourth leading cause of death and affects >16 million persons in the United States. COPD is also a disease of increasing public health importance around the world. GOLD estimates suggest that COPD will increase from the sixth to the third most common cause of death worldwide by 2020.

RISK FACTORS

Cigarette Smoking

By 1964, the Advisory Committee to the Surgeon General of the United States had concluded that cigarette smoking

was a major risk factor for mortality from chronic bronchitis and emphysema. Subsequent longitudinal studies have shown accelerated decline in the volume of air exhaled within the first second of the forced expiratory volume in 1 second (FEV₁) in a dose-response relationship to the intensity of cigarette smoking, which is typically expressed as pack-years (average number of packs of cigarettes smoked per day multiplied by the total number of years of smoking). This dose-response relationship between reduced pulmonary function and cigarette smoking intensity accounts for the higher prevalence rates for COPD with increasing age. The historically higher rate of smoking among men is the likely explanation for the higher prevalence of COPD among men; however, the prevalence of COPD among women is increasing because the gender gap in smoking rates has diminished in the past 50 years.

Although the causal relationship between cigarette smoking and the development of COPD has been absolutely proven, there is considerable variability in the response to smoking. Although pack-years of cigarette smoking is the most highly significant predictor of FEV₁ (Fig. 18-1), only 15% of the variability in FEV₁ is explained by pack-years. This finding suggests that additional environmental or genetic factors (or both) contribute to the impact of smoking on the development of airflow obstruction.

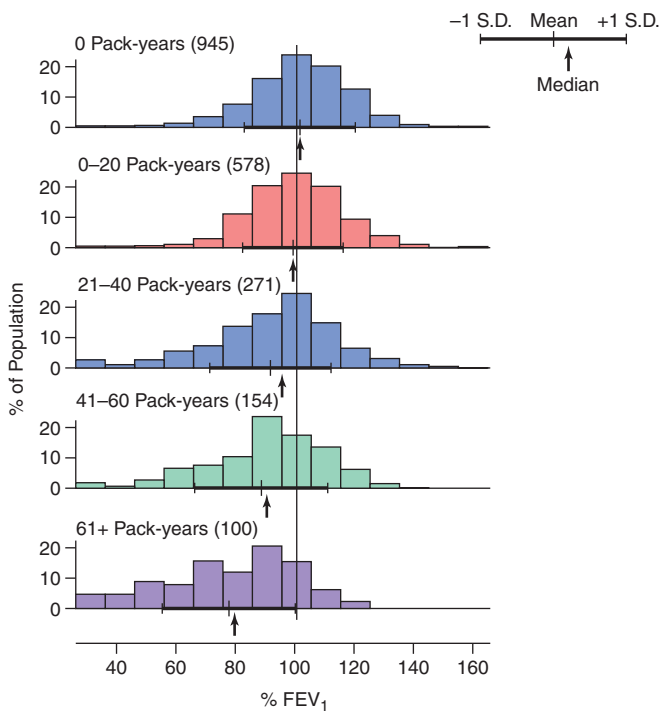


FIGURE 18-1
Distributions of forced expiratory volume in 1 s (FEV_1) values in a general population sample, stratified by pack-years of smoking. Means, medians, and ± 1 standard deviation of percent predicted FEV_1 are shown for each smoking group. Although a dose-response relationship between smoking intensity and FEV_1 was found, marked variability in pulmonary function was observed among subjects with similar smoking histories. (From R Burrows et al: *Am Rev Respir Dis* 115:95, 1977, with permission.)

Although cigar and pipe smoking may also be associated with the development of COPD, the evidence supporting such associations is less compelling, likely related to the lower dose of inhaled tobacco by-products during cigar and pipe smoking.

Airway Responsiveness and COPD

A tendency for increased bronchoconstriction in response to a variety of exogenous stimuli, including methacholine and histamine, is one of the defining features of asthma (Chap. 8). However, many patients with COPD also share this feature of airway hyperresponsiveness. The considerable overlap between persons with asthma and those with COPD in airway responsiveness, airflow obstruction, and pulmonary symptoms led to the formulation of the Dutch hypothesis. This suggests that asthma, chronic bronchitis, and emphysema are variations of the same basic disease, which is modulated by environmental and genetic factors to produce these pathologically distinct entities. The alternative British hypothesis contends that asthma and COPD are fundamentally different diseases: asthma is viewed as largely an allergic phenomenon, but COPD results from

smoking-related inflammation and damage. Determination of the validity of the Dutch hypothesis versus the British hypothesis awaits identification of the genetic predisposing factors for asthma and COPD, as well as the interactions between these postulated genetic factors and environmental risk factors.

Longitudinal studies that compared airway responsiveness at the beginning of the study with subsequent decline in pulmonary function have demonstrated that increased airway responsiveness is clearly a significant predictor of subsequent decline in pulmonary function. Thus, airway hyperresponsiveness is a risk factor for COPD.

Respiratory Infections

These have been studied as potential risk factors for the development and progression of COPD in adults; childhood respiratory infections have also been assessed as potential predisposing factors for the eventual development of COPD. The impact of adult respiratory infections on decline in pulmonary function is controversial, but significant long-term reductions in pulmonary function are not typically seen after an episode of bronchitis or pneumonia. The impact of the effects of childhood respiratory illnesses on the subsequent development of COPD has been difficult to assess because of a lack of adequate longitudinal data. Thus, although respiratory infections are important causes of exacerbations of COPD, the association of both adult and childhood respiratory infections to the development and progression of COPD remains to be proven.

Occupational Exposures

Increased respiratory symptoms and airflow obstruction have been suggested as resulting from general exposure to dust at work. Several specific occupational exposures, including coal mining, gold mining, and cotton textile dust, have been suggested as risk factors for chronic airflow obstruction. However, although nonsmokers in these occupations developed some reductions in FEV_1 , the importance of dust exposure as a risk factor for COPD, independent of cigarette smoking, is not certain. Among workers exposed to cadmium (a specific chemical fume), FEV_1 , FEV_1/FVC (forced vital capacity), and DL_{CO} (carbon monoxide diffusing capacity of the lung) were significantly reduced (Chap. 5), consistent with airflow obstruction and emphysema. Although several specific occupational dusts and fumes are likely risk factors for COPD, the magnitude of these effects appears to be substantially less important than the effect of cigarette smoking.

Ambient Air Pollution

Some investigators have reported increased respiratory symptoms in those living in urban compared with rural areas, which may relate to increased pollution in the

180 urban settings. However, the relationship of air pollution to chronic airflow obstruction remains unproven. Prolonged exposure to smoke produced by biomass combustion—a common mode of cooking in some countries—also appears to be a significant risk factor for COPD among women in those countries. However, in most populations, ambient air pollution is a much less important risk factor for COPD than cigarette smoking.

Passive, or Second-Hand, Smoking Exposure

Exposure of children to maternal smoking results in significantly reduced lung growth. In utero tobacco smoke exposure also contributes to significant reductions in postnatal pulmonary function. Although passive smoke exposure has been associated with reductions in pulmonary function, the importance of this risk factor in the development of the severe pulmonary function reductions in COPD remains uncertain.

GENETIC CONSIDERATIONS



Although cigarette smoking is the major environmental risk factor for the development of COPD, the development of airflow obstruction in smokers is highly variable. Severe α_1 antitrypsin (α_1 AT) deficiency is a proven genetic risk factor for COPD; increasing evidence suggests that other genetic determinants also exist.

α_1 Antitrypsin Deficiency

Many variants of the protease inhibitor (PI or SERPINA1) locus that encodes α_1 AT have been described. The common M allele is associated with normal α_1 AT levels. The S allele, associated with slightly reduced α_1 AT levels, and the Z allele, associated with markedly reduced α_1 AT levels, also occur with frequencies >1% in most white populations. Rare individuals inherit null alleles, which lead to the absence of any α_1 AT production through a heterogeneous collection of mutations. Individuals with two Z alleles or one Z and one null allele are referred to as Pi^Z , which is the most common form of severe α_1 AT deficiency.

Although only 1–2% of COPD patients are found to have severe α_1 AT deficiency as a contributing cause of COPD, these patients demonstrate that genetic factors can have a profound influence on the susceptibility for developing COPD. Pi^Z individuals often develop early-onset COPD, but the ascertainment bias in the published series of Pi^Z individuals—which have usually included many Pi^Z subjects who were tested for α_1 AT deficiency because they had COPD—means that the fraction of Pi^Z individuals who will develop COPD and the age-of-onset distribution for the development of COPD in Pi^Z subjects remain unknown. Approximately one in 3000 individuals in the United States inherits severe α_1 AT deficiency, but only a small minority of these individuals has been

recognized. The clinical laboratory test used most frequently to screen for α_1 AT deficiency is measurement of the immunologic level of α_1 AT in serum (see “Laboratory Findings” later in the chapter).

A significant percentage of the variability in pulmonary function among Pi^Z individuals is explained by cigarette smoking; cigarette smokers with severe α_1 AT deficiency are more likely to develop COPD at early ages. However, the development of COPD in Pi^Z subjects, even among current or ex-smokers, is not absolute. Among Pi^Z nonsmokers, impressive variability has been noted in the development of airflow obstruction. Other genetic and environmental factors likely contribute to this variability.

Specific treatment in the form of α_1 AT augmentation therapy is available for severe α_1 AT deficiency as a weekly IV infusion (see “Treatment” later in the chapter).

The risk of lung disease in heterozygous Pi^{MZ} individuals, who have intermediate serum levels of α_1 AT (~60% of Pi^{MM} levels), is controversial. Although previous general population surveys have not typically shown increased rates of airflow obstruction in Pi^{MZ} compared with Pi^{MM} individuals, case-control studies that compared COPD patients with control subjects have usually found an excess of Pi^{MZ} genotypes in the COPD patient group. Several recent large population studies have suggested that Pi^{MZ} subjects are at slightly increased risk for the development of airflow obstruction, but it remains unclear if all Pi^{MZ} subjects are at slightly increased risk for COPD or if a subset of Pi^{MZ} subjects are at substantially increased risk for COPD because of other genetic or environmental factors.

Other Genetic Risk Factors

Studies of pulmonary function measurements performed in general population samples have suggested that genetic factors other than PI type influence variation in pulmonary function. Familial aggregation of airflow obstruction within families of COPD patients has also been demonstrated.

Association studies have compared the distribution of variants in genes hypothesized to be involved in the development of COPD in COPD patients and control subjects. However, the results have been quite inconsistent, and no genetic determinants of COPD other than severe α_1 AT deficiency have been definitively proven using this approach. Genome scan linkage analyses of early-onset COPD families have found evidence for linkage of spirometric phenotypes to several chromosomal regions, but the specific genetic determinants in those regions have yet to be definitively identified.

NATURAL HISTORY

The effects of cigarette smoking on pulmonary function appear to depend on the intensity of smoking exposure, the timing of smoking exposure during growth, and the

baseline lung function of the individual; other environmental factors may have similar effects. Although rare individuals may demonstrate precipitous declines in pulmonary function, most individuals follow a steady trajectory of increasing pulmonary function with growth during childhood and adolescence followed by a gradual decline with aging. Individuals appear to track in their quartile of pulmonary function based on environmental and genetic factors that put them on different tracks. The risk of eventual mortality from COPD is closely associated with reduced levels of FEV₁. A graphic depiction of the natural history of COPD is shown as a function of the influences on tracking curves of FEV₁ in Fig. 18-2. Death or disability from COPD can result from a normal rate of decline after a reduced growth phase (curve C), an early initiation of pulmonary function decline after normal growth (curve B), or an accelerated decline after normal growth (curve D). The rate of decline in pulmonary function can be modified by changing environmental exposures (i.e., quitting smoking), with smoking cessation at an earlier age providing a more beneficial effect than smoking cessation after marked reductions in pulmonary function have already developed. Genetic factors likely contribute to the level of pulmonary function achieved during growth and to the rate of decline in response to smoking and potentially to other environmental factors as well.

PATHOPHYSIOLOGY

Persistent reduction in forced expiratory flow rates is the most typical finding in COPD. Increases in the residual

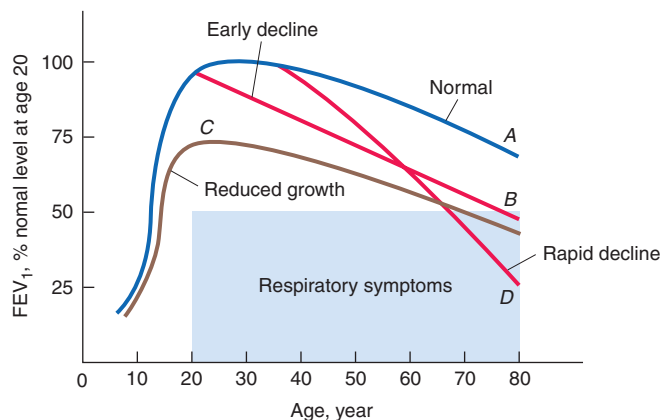


FIGURE 18-2
Hypothetical tracking curves of forced expiratory volume in 1 second (FEV₁) for individuals throughout their life spans. The normal pattern of growth and decline with age is shown by curve A. Significantly reduced FEV₁ (<65% of predicted value at age 20 years) can develop from a normal rate of decline after a reduced pulmonary function growth phase (curve C), early initiation of pulmonary function decline after normal growth (curve B), or accelerated decline after normal growth (curve D). (From B Rijcken: Doctoral dissertation, p 133, University of Groningen, 1991, with permission.)

volume (RV) and the RV/TLC (total lung capacity) ratio, nonuniform distribution of ventilation, and ventilation-perfusion mismatching also occur.

Airflow Obstruction

Airflow limitation, also known as airflow obstruction, is typically determined by spirometry, which involves forced expiratory maneuvers after the subject has inhaled to TLC (see Fig. 5-4). Key phenotypes obtained from spirometry include FEV₁ and the total volume of air exhaled during the entire spirometric maneuver (FVC). Patients with airflow obstruction related to COPD have a chronically reduced FEV₁/FVC ratio. In contrast to asthma, the reduced FEV₁ in COPD seldom shows large responses to inhaled bronchodilators, although improvements up to 15% are common. Asthma patients can also develop chronic (not fully reversible) airflow obstruction. Maximal inspiratory flow can be relatively well preserved in the presence of a markedly reduced FEV₁.

Airflow during forced exhalation is the result of the balance between the elastic recoil of the lungs promoting flow and the resistance of the airways limiting flow. In normal lungs, as well as in lungs affected by COPD, maximal expiratory flow diminishes as the lungs empty because the lung parenchyma provides progressively less elastic recoil and because the cross-sectional area of the airways falls, increasing the resistance to airflow. The decrease in flow coincident with decreased lung volume is readily apparent on the expiratory limb of a flow-volume curve. In the early stages of COPD, the abnormality in airflow is only evident at lung volumes at or below the functional residual capacity (FRC; closer to RV), appearing as a scooped-out lower part of the descending limb of the flow-volume curve. In more advanced disease, the entire curve has decreased expiratory flow compared with normal.

Hyperinflation

Lung volumes are also routinely assessed in pulmonary function testing. In COPD, there is often “air trapping” (increased RV and increased ratio of RV to TLC) and progressive hyperinflation (increased tTLC) late in the disease. Hyperinflation of the thorax during tidal breathing preserves maximum expiratory airflow because as lung volume increases, elastic recoil pressure increases and airways enlarge so that airway resistance decreases.

Hyperinflation helps to compensate for airway obstruction. However, hyperinflation can push the diaphragm into a flattened position with a number of adverse effects. First, by decreasing the zone of apposition between the diaphragm and the abdominal wall, positive abdominal pressure during inspiration is not applied as effectively to the chest wall, hindering rib cage movement and impairing inspiration. Second, because the muscle fibers of the flattened diaphragm are shorter than those of a more normally

182 curved diaphragm, they are less capable of generating inspiratory pressures than normal. Third, the flattened diaphragm (with increased radius of curvature, r) must generate greater tension (t) to develop the transpulmonary pressure (p) required to produce tidal breathing. This follows from Laplace's law, $p = 2t/r$. Also, because the thoracic cage is distended beyond its normal resting volume, during tidal breathing, the inspiratory muscles must do work to overcome the resistance of the thoracic cage to further inflation instead of gaining the normal assistance from the chest wall recoiling outward toward its resting volume.

Gas Exchange

Although there is considerable variability in the relationships between the FEV₁ and other physiologic abnormalities in COPD, certain generalizations may be made. The PaO₂ usually remains near normal until the FEV₁ is decreased to ~50% of predicted, and even much lower FEV₁s can be associated with a normal PaO₂, at least at rest. An elevation of PaCO₂ is not expected until the FEV₁ is <25% of predicted and even then may not occur. Pulmonary hypertension severe enough to cause cor pulmonale and right ventricular failure caused by COPD occurs only in individuals who have marked decreases in FEV₁ (<25% of predicted) together with chronic hypoxemia (PaO₂ <55 mmHg), although earlier in the course, some elevation of pulmonary artery pressure, particularly with exercise, may occur.

Nonuniform ventilation and ventilation-perfusion mismatching are characteristic of COPD, reflecting the heterogeneous nature of the disease process within the airways and lung parenchyma. Nitrogen washout while breathing 100% oxygen is delayed because of regions that are poorly ventilated, and the profile of the nitrogen washout curve is consistent with multiple parenchymal compartments having different washout rates because of regional differences in compliance and airway resistance. Ventilation/perfusion mismatching accounts for essentially all of the reduction in PaO₂ that occurs in COPD; shunting is minimal. This finding explains the effectiveness of modest elevations of inspired oxygen in treating hypoxemia caused by COPD and therefore the need to consider problems other than COPD when hypoxemia is difficult to correct with modest levels of supplemental oxygen in patients with COPD.

PATHOLOGY

Cigarette smoke exposure may affect the large airways, small airways (≤ 2 mm diameter), and alveolar space. Whereas changes in large airways cause cough and sputum, changes in small airways and alveoli are responsible for physiologic alterations. Emphysema and small airway pathology are both present in most persons with COPD,

and their relative contributions to obstruction vary from one person to another.

Large Airway

Cigarette smoking often results in mucous gland enlargement and goblet cell hyperplasia. These changes are proportional to cough and mucus production that define chronic bronchitis, but these abnormalities are not related to airflow limitation. Goblet cells not only increase in number but also in extent through the bronchial tree. Bronchi also undergo squamous metaplasia, which not only predisposes to carcinogenesis but also disrupts mucociliary clearance. Although not as prominent as in asthma, patients may have smooth muscle hypertrophy and bronchial hyperreactivity, leading to airflow limitation. Neutrophil influx has been associated with purulent sputum of upper respiratory tract infections that hamper patients with COPD. Independent of its proteolytic activity, neutrophil elastase is among the most potent secretagogues identified.

Small Airways

The major site of increased resistance in most individuals with COPD is in airways ≤ 2 mm diameter. Characteristic cellular changes include goblet cell metaplasia and replacement of surfactant-secreting Clara cells with mucus-secreting and infiltrating mononuclear inflammatory cells. Smooth muscle hypertrophy may also be present. These abnormalities may cause luminal narrowing by excess mucus, edema, and cellular infiltration. Reduced surfactant may increase surface tension at the air-tissue interface, predisposing to airway narrowing or collapse. Fibrosis in the wall may cause airway narrowing directly or, as in asthma, predispose to hyperreactivity. Respiratory bronchiolitis with mononuclear inflammatory cells collecting in distal airway tissues may cause proteolytic destruction of elastic fibers in the respiratory bronchioles and alveolar ducts where the fibers are concentrated as rings around alveolar entrances.

Because small airway patency is maintained by the surrounding lung parenchyma that provides radial traction on bronchioles at points of attachment to alveolar septa, loss of bronchiolar attachments as a result of extracellular matrix destruction may cause airway distortion and narrowing in COPD. Although the significance of alveolar attachments is not resolved, the concept of decreased alveolar attachments leading to small airway obstruction is appealing because it underscores the mechanistic relationship between loss of elastic recoil and increased resistance to airflow in small airways.

Lung Parenchyma

Emphysema is characterized by destruction of gas-exchanging airspaces (i.e., the respiratory bronchioles,

alveolar ducts, and alveoli). Their walls become perforated and later obliterated with coalescence of small distinct airspaces into abnormal and much larger airspaces. Macrophages accumulate in respiratory bronchioles of essentially all young smokers. Bronchoalveolar lavage fluid from such individuals contains roughly five times as many macrophages as lavage from nonsmokers. In smokers' lavage fluid, macrophages comprise >95% of the total cell count, and neutrophils, nearly absent in nonsmokers' lavage, account for 1–2% of the cells. T lymphocytes, particularly CD8+ cells, are also increased in the alveolar space of smokers.

Emphysema is classified into distinct pathologic types, the most important being centriacinar and panacinar. *Centriacinar emphysema*, the type most frequently associated with cigarette smoking, is characterized by enlarged airspaces found (initially) in association with respiratory bronchioles. Centriacinar emphysema is most prominent in the upper lobes and superior segments of lower lobes and is often quite focal. *Panacinar emphysema* refers to abnormally large airspaces evenly distributed within and across acinar units. Panacinar emphysema is usually observed in patients with α_1 AT deficiency, which has a predilection for the lower lobes. Distinctions between centriacinar and panacinar emphysema are interesting and may ultimately be shown to have different mechanisms of pathogenesis. However, garden-variety smoking-related emphysema is usually mixed, particularly in advanced cases, and these pathologic classifications are not helpful in the care of patients with COPD.

PATHOGENESIS

Airflow limitation, the major physiologic change in COPD, can result from both small airway obstruction and emphysema, as discussed above. Pathologic findings that can contribute to small airway obstruction are described above, but their relative importance is unknown. Fibrosis surrounding the small airways appears to be a significant contributor. Mechanisms leading to collagen accumulation around the airways in the face of increased collagenase activity remain an enigma. Although seemingly counterintuitive, there are several potential mechanisms whereby a proteinase can predispose to fibrosis, including proteolytic activation of transforming growth factor β (TGF- β) and insulin-like growth factor (IGF) binding protein degradation releasing profibrotic IGF. Largely because of the availability of suitable animal models, we know much more about mechanisms involved in emphysema than small airway obstruction.

The pathogenesis of emphysema can be dissected into four interrelated events (Fig. 18-3): (1) Chronic exposure to cigarette smoke may lead to inflammatory cell recruitment within the terminal airspaces of the lung. (2) These inflammatory cells release elastolytic proteinases, which damage the extracellular matrix of the lung. (3) Loss of

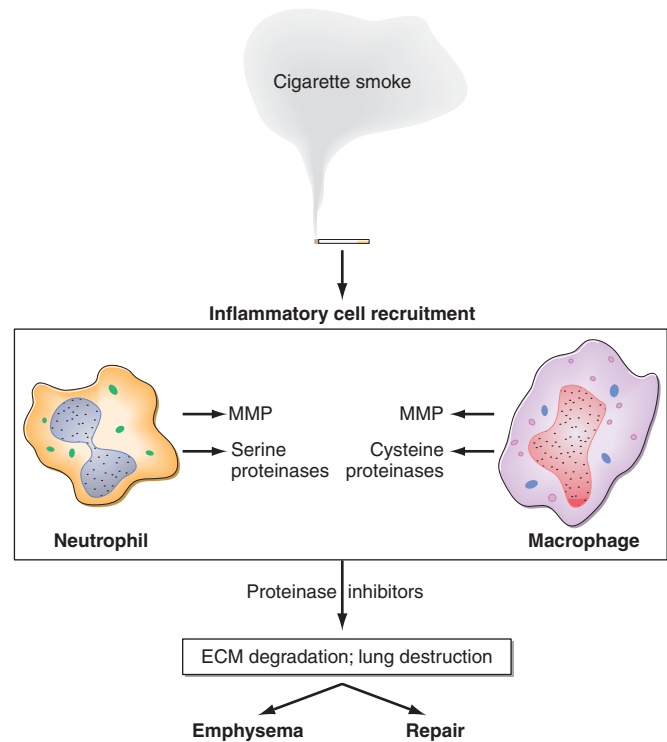


FIGURE 18-3
Pathogenesis of emphysema. Upon long-term exposure to cigarette smoke, inflammatory cells are recruited to the lung; they release proteinases in excess of inhibitors, and if repair is abnormal, this leads to airspace destruction and enlargement or emphysema. ECM, extracellular matrix; MMP, matrix metalloproteinase.

matrix cell attachment leads to apoptosis of structural cells of the lung. (4) Ineffective repair of elastin and perhaps other extracellular matrix components result in airspace enlargement that defines pulmonary emphysema.

The Elastase:Antielastase Hypothesis

Elastin, the principal component of elastic fibers, is a highly stable component of the extracellular matrix that is critical to the integrity of both the small airways and the lung parenchyma. The elastase:antielastase hypothesis proposed in the mid-1960s states that the balance of elastin-degrading enzymes and their inhibitors determines the susceptibility of the lung to destruction, resulting in airspace enlargement. This hypothesis was based on the clinical observation that patients with genetic deficiency in α_1 AT, the inhibitor of the serine proteinase neutrophil elastase, were at increased risk of emphysema and that instillation of elastases, including neutrophil elastase, to experimental animals results in emphysema. To this day, the elastase:antielastase hypothesis is the prevailing mechanism for the development of emphysema. However, a complex network of inflammatory cells and additional proteinases that contribute to emphysema have subsequently been identified.

Macrophages patrol the lower airspace under normal conditions. Upon exposure to oxidants from cigarette smoke, histone deacetylase-2 is inactivated, shifting the balance toward acetylated or loose chromatin, exposing nuclear factor κ B sites and resulting in transcription of matrix metalloproteinase-9 (MMP-9), proinflammatory cytokines interleukin 8 (IL-8), and tumor necrosis factor α (TNF α); this leads to neutrophil recruitment. CD8+ T cells are also recruited in response to cigarette smoke and release interferon inducible protein-10 (IP-10, CXCL-7) that in turn leads to macrophage production of macrophage elastase (MMP-12). MMPs and serine proteinases, most notably neutrophil elastase, work together by degrading the inhibitor of the other, leading to lung destruction. Proteolytic cleavage products of elastin also serve as a macrophage chemokine, fueling this destructive positive feedback loop.

Concomitant cigarette smoke-induced loss of cilia in the airway epithelium predisposes to bacterial infection with neutrophilia. Surprisingly, in end-stage lung disease, long after smoking cessation, an exuberant inflammatory response remains, suggesting that mechanisms of cigarette smoke-induced inflammation that initiate the disease differ from mechanisms that sustain inflammation after smoking cessation.

Collagen turnover in COPD is complex. The three collagenases (MMP-1, MMP-8, and MMP-13) that initiate the cleavage of interstitial collagens are also induced in both inflammatory cells and structural cells in COPD. Although collagen is disrupted as alveolar units are obliterated, overall there is a net increase in collagen content in the COPD lung, with prominent accumulation in the airway submucosa.

Cell Death

Airspace enlargement with loss of alveolar units obviously requires disappearance of both extracellular matrix and cells. Traditional theories suggest that inflammatory cell proteinases degrade lung extracellular matrix as the primary event, with subsequent loss of cell anchoring leading to apoptosis. Animal models have used endothelial and epithelial cell death as a means to generate transient airspace enlargement. Whether apoptosis is a primary or secondary event in COPD remains to be determined.

Ineffective Repair

The ability of the adult lung to repair damaged alveoli appears limited. Whether the process of septation that is responsible for alveogenesis during lung development can be reinitiated is not clear. In animal models, treatment with all-trans retinoic acid has resulted in some repair. Also, lung resection results in compensatory lung growth

in the remaining lung in animal models. In addition to restoring cellularity after injury, it appears difficult for an adult to completely restore an appropriate extracellular matrix, particularly functional elastic fibers.

CLINICAL PRESENTATION

History

The three most common symptoms in COPD are cough, sputum production, and exertional dyspnea. Many patients have such symptoms for months or years before seeking medical attention. Although the development of airflow obstruction is a gradual process, many patients date the onset of their disease to an acute illness or exacerbation. A careful history, however, usually reveals the presence of symptoms before the acute exacerbation. The development of exertional dyspnea, often described as increased effort to breathe, heaviness, air hunger, or gasping, can be insidious. It is best elicited by a careful history focused on typical physical activities and how the patient's ability to perform them has changed. Activities involving significant arm work, particularly at or above shoulder level, are particularly difficult for patients with COPD. Conversely, activities that allow the patient to brace the arms and use accessory muscles of respiration are better tolerated. Examples of such activities include pushing a shopping cart, walking on a treadmill, or pushing a wheelchair. As COPD advances, the principal feature is worsening dyspnea on exertion with increasing intrusion on the ability to perform vocational or avocational activities. In the most advanced stages, patients are breathless doing simple activities of daily living.

Accompanying worsening airflow obstruction is an increased frequency of exacerbations (described later in this chapter). Patients may also develop resting hypoxemia and require institution of supplemental oxygen.

Physical Findings

In the early stages of COPD, patients usually have an entirely normal physical examination. Current smokers may have signs of active smoking, including an odor of smoke or nicotine staining of fingernails. In patients with more severe disease, the physical examination is notable for a prolonged expiratory phase and expiratory wheezing. In addition, signs of hyperinflation include a barrel chest and enlarged lung volumes with poor diaphragmatic excursion as assessed by percussion. Patients with severe airflow obstruction may also exhibit use of accessory muscles of respiration, sitting in the characteristic "tripod" position to facilitate the actions of the sternocleidomastoid, scalene, and intercostal muscles. Patients may develop cyanosis, which is visible in the lips and nail beds.

Although traditional teaching is that patients with predominant emphysema, termed "pink puffers," are thin and noncyanotic at rest and have prominent use of accessory

muscles, and patients with chronic bronchitis are more likely to be heavy and cyanotic (“blue bloaters”), current evidence demonstrates that most patients have elements of both bronchitis and emphysema and that the physical examination does not reliably differentiate the two entities.

Advanced disease may be accompanied by systemic wasting, with significant weight loss, bitemporal wasting, and diffuse loss of subcutaneous adipose tissue. This syndrome has been associated with both inadequate oral intake and elevated levels of inflammatory cytokines (TNF α). Such wasting is an independent poor prognostic factor in COPD. Some patients with advanced disease have paradoxical inward movement of the rib cage with inspiration (Hoover’s sign), the result of alteration of the vector of diaphragmatic contraction on the rib cage as a result of chronic hyperinflation.

Signs of overt right heart failure, termed *cor pulmonale*, are relatively infrequent since the advent of supplemental oxygen therapy.

Clubbing of the digits is not a sign of COPD, and its presence should alert the clinician to initiate an investigation for causes of clubbing. In this population, the development of lung cancer is the most likely explanation for newly developed clubbing.

Laboratory Findings

The hallmark of COPD is airflow obstruction (discussed earlier in chapter). Pulmonary function testing shows airflow obstruction with a reduction in FEV₁ and FEV₁/FVC ratio (Chap. 5). With worsening disease severity, lung volumes may increase, resulting in an increase in \bar{t} TLC, FRC, and RV. In patients with emphysema, the diffusing capacity may be reduced, reflecting the parenchymal destruction characteristic of the disease. The degree of airflow

obstruction is an important prognostic factor in COPD and is the basis for the GOLD disease classification (Table 18-1). More recently, it has been shown that a multifactorial index incorporating airflow obstruction, exercise performance, dyspnea, and body mass index is a better predictor of mortality than pulmonary function alone.

Although arterial blood gases and oximetry are not sensitive (discussed earlier in this chapter), they may demonstrate resting or exertional hypoxemia. Arterial blood gases provide additional information about alveolar ventilation and acid-base status by measuring arterial PCO₂ and pH. The change in pH with PCO₂ is 0.08 units/10 mmHg acutely and 0.03 units/10 mmHg in the chronic state. Knowledge of the arterial pH therefore allows the classification of ventilatory failure, defined as PCO₂ >45 mmHg, into acute or chronic conditions. The arterial blood gas is an important component of the evaluation of patients presenting with symptoms of an exacerbation. An elevated hematocrit suggests the presence of chronic hypoxemia, as does the presence of signs of right ventricular hypertrophy.

Radiographic studies may assist in the classification of the type of COPD. Obvious bullae, paucity of parenchymal markings, or hyperlucency suggest the presence of emphysema. Increased lung volumes and flattening of the diaphragm suggest hyperinflation but do not provide information about chronicity of the changes. CT scanning is the current definitive test for establishing the presence or absence of emphysema in living subjects (Fig. 18-4). From a practical perspective, the CT scan does little to influence therapy of COPD except in individuals considering surgical therapy for their disease (described later in the chapter).

Recent guidelines have suggested testing for α_1 AT deficiency in all subjects with COPD or asthma with chronic airflow obstruction. Measurement of the serum

TABLE 18-1

GOLD CRITERIA FOR COPD SEVERITY

GOLD STAGE	SEVERITY	SYMPTOMS	SPIROMETRY
0	At risk	Chronic cough, sputum production	Normal
I	Mild	With or without chronic cough or sputum production	FEV ₁ /FVC ratio <0.7 and FEV ₁ \geq 80% predicted
IIA	Moderate	With or without chronic cough or sputum production	FEV ₁ /FVC ratio <0.7 and 50% \leq FEV ₁ <80% predicted
III	Severe	With or without chronic cough or sputum production	FEV ₁ /FVC ratio <0.7 and 30% \leq FEV ₁ <50% predicted
IV	Very severe	With or without chronic cough or sputum production	FEV ₁ /FVC ratio <0.7 and FEV ₁ <30% predicted or FEV ₁ <50% predicted with respiratory failure or signs of right heart failure

Note: FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Pulmonary Disease.

Source: From Pauwels et al.



FIGURE 18-4
Chest CT scan of a patient with chronic obstructive pulmonary disease who underwent a left single-lung transplant. Note the reduced parenchymal markings in the right lung (*left side of figure*) compared with the left lung, representing emphysematous destruction of the lung, and mediastinal shift to the left, indicative of hyperinflation.

α_1 AT level is a reasonable initial test. For subjects with low α_1 AT levels, the definitive diagnosis of α_1 AT deficiency requires PI type determination. This is typically performed by isoelectric focusing of serum, which reflects the genotype at the PI locus for the common alleles and many of the rare PI alleles as well. Molecular genotyping of DNA can be performed for the common PI alleles (M, S, and Z).

Treatment:

R_x CHRONIC OBSTRUCTIVE PULMONARY DISEASE

STABLE PHASE COPD Only three interventions—smoking cessation, oxygen therapy in chronically hypoxemic patients, and lung volume reduction surgery in selected patients with emphysema—have been demonstrated to influence the natural history of patients with COPD. There is currently suggestive, but not definitive, evidence that the use of inhaled glucocorticoids may alter mortality (but not lung function). All other current therapies are directed at improving symptoms and decreasing the frequency and severity of exacerbations. The institution of these therapies should involve an assessment of symptoms, potential risks,

costs, and benefits of therapy. This should be followed by an assessment of response to therapy, and a decision should be made whether or not to continue treatment.

PHARMACOTHERAPY

Smoking Cessation It has been shown that middle-aged smokers who were able to successfully stop smoking experienced a significant improvement in the rate of decline in pulmonary function, returning to annual changes similar to that of nonsmoking patients. Thus, all patients with COPD should be strongly urged to quit and educated about the benefits of quitting. An emerging body of evidence demonstrates that combining pharmacotherapy with traditional supportive approaches considerably enhances the chances of successful smoking cessation. There are two principal pharmacologic approaches to the problem: bupropion, originally developed as an antidepressant medication, and nicotine replacement therapy. The latter is available as a gum, transdermal patches, an inhaler, and a nasal spray. Current recommendations from the U.S. Surgeon General are that all adult, nonpregnant smokers considering quitting be offered pharmacotherapy in the absence of any contraindication to treatment.

Bronchodilators In general, bronchodilators are used for symptomatic benefit in patients with COPD. The inhaled route is preferred for medication delivery because the incidence of side effects is lower than that seen with the use of parenteral medication delivery.

Anticholinergic Agents Although regular use of ipratropium bromide does not appear to influence the rate of decline of lung function, it improves symptoms and produces acute improvement in FEV₁. Tiotropium, a long-acting anticholinergic, has been shown to improve symptoms and reduce exacerbations. Side effects are minor, and a trial of inhaled anticholinergics is recommended in symptomatic patients with COPD.

β -Agonists These provide symptomatic benefit. The main side effects are tremor and tachycardia. Long-acting inhaled β -agonists, such as salmeterol, have benefits comparable to ipratropium bromide. Their use is more convenient than short-acting agents. The addition of a β -agonist to inhaled anticholinergic therapy has been demonstrated to provide incremental benefit. A recent report in asthma suggests that patients, particularly African Americans, using a long-acting β -agonist without concomitant inhaled corticosteroids have an increased risk of deaths from respiratory causes. The applicability of these data to patients with COPD is unclear.

Inhaled Glucocorticoids Several trials have failed to find a beneficial effect for the regular use of inhaled glucocorticoids on the rate of decline of lung function, as assessed by FEV₁. Patients studied included those

with mild to severe airflow obstruction and current and ex-smokers. Patients with significant acute response to inhaled β agonists were excluded from these trials. Their use has been associated with increased rates of oropharyngeal candidiasis and an increased rate of loss of bone density. Some analyses suggest that inhaled glucocorticoids reduce exacerbation frequency by ~25%. A more recent meta-analysis suggests that they may also reduce mortality by ~25%. A definitive conclusion regarding the mortality benefits awaits the results of ongoing prospective trials. A trial of inhaled glucocorticoids should be considered in patients with frequent exacerbations, defined as two or more per year, and in patients who demonstrate a significant amount of acute reversibility in response to inhaled bronchodilators.

Oral Glucocorticoids The chronic use of oral glucocorticoids for treatment of COPD is not recommended because of an unfavorable benefit/risk ratio. The chronic use of oral glucocorticoids is associated with significant side effects, including osteoporosis, weight gain, cataracts, glucose intolerance, and increased risk of infection. A recent study demonstrated that patients tapered off chronic low-dose prednisone (~10 mg/d) did not experience any adverse effect on the frequency of exacerbations, health-related quality of life, or lung function. On average, patients lost ~4.5 kg (~10 lb) when steroids were withdrawn.

Theophylline Theophylline produces modest improvements in expiratory flow rates and vital capacity and a slight improvement in arterial oxygen and carbon dioxide levels in patients with moderate to severe COPD. Nausea is a common side effect; tachycardia and tremor have also been reported.

Oxygen Supplemental O_2 is the only pharmacologic therapy demonstrated to decrease mortality in patients with COPD. For patients with resting hypoxemia (resting O_2 saturation <88% or <90% with signs of pulmonary hypertension or right heart failure), the use of O_2 has been demonstrated to have a significant impact on mortality. Patients meeting these criteria should be on continual oxygen supplementation because the mortality benefit is proportional to the number of hours per day oxygen is used. Various delivery systems are available, including portable systems that patients may carry to allow mobility outside the home.

Supplemental O_2 is commonly prescribed for patients with exertional hypoxemia or nocturnal hypoxemia. Although the rationale for supplemental O_2 in these settings is physiologically sound, the benefits of such therapy are not well substantiated.

Other Agents N-acetyl cysteine has been used in patients with COPD for both its mucolytic and antioxidant properties. A prospective trial failed to find any

benefit with respect to decline in lung function or prevention of exacerbations. Specific treatment in the form of intravenous α_1 AT augmentation therapy is available for individuals with severe α_1 AT deficiency. Despite sterilization procedures for these blood-derived products and the absence of reported cases of viral infection from therapy, some physicians recommend hepatitis B vaccination before patients start augmentation therapy. Although biochemical efficacy of α_1 AT augmentation therapy has been shown, a randomized controlled trial of α_1 AT augmentation therapy has never proven the efficacy of augmentation therapy in reducing decline of pulmonary function. Eligibility for α_1 AT augmentation therapy requires a serum α_1 AT level <11 μ M (approximately 50 mg/dL). Typically, Pi^Z individuals will qualify, although other rare types associated with severe deficiency (e.g., null-null) are also eligible. Because only a fraction of individuals with severe α_1 AT deficiency will develop COPD, α_1 AT augmentation therapy is not recommended for severely α_1 AT-deficient persons with normal pulmonary function and a normal chest CT scan.

NONPHARMACOLOGIC THERAPIES

General Medical Care Patients with COPD should receive the influenza vaccine annually. Polyvalent pneumococcal vaccine is also recommended, although proof of efficacy in this patient population is not definitive.

Pulmonary Rehabilitation This refers to a treatment program that incorporates education and cardiovascular conditioning. In COPD, pulmonary rehabilitation has been demonstrated to improve health-related quality of life, dyspnea, and exercise capacity. It has also been shown to reduce rates of hospitalization over a 6- to 12-month period.

Lung Volume Reduction Surgery (LVRS)

Surgery to reduce the volume of lung in patients with emphysema was first introduced with minimal success in the 1950s and was reintroduced in the 1990s. The operation may be performed via either a median sternotomy or a thoracoscopic approach. Patients are excluded if they have significant pleural disease, a pulmonary artery systolic pressure >45 mmHg, extreme deconditioning, congestive heart failure, or other severe comorbid conditions. Recent data demonstrate that patients with an FEV_1 <20% of predicted and either diffusely distributed emphysema on CT scan or DL_{CO} <20% of predicted have an increased mortality after the procedure and thus are not candidates for LVRS.

The National Emphysema Treatment trial demonstrated that LVRS offers both a mortality benefit and a symptomatic benefit in certain patients with emphysema. The anatomic distribution of emphysema and postrehabilitation exercise capacity are important prognostic characteristics. Patients with upper lobe-predominant

emphysema and a low postrehabilitation exercise capacity are most likely to benefit from LVRS.

Lung Transplantation (See also Chap. 24)

COPD is the single leading indication for lung transplantation (see Fig. 18-4). Current recommendations are that candidates for lung transplantation should be younger than 65 years old; have severe disability despite maximal medical therapy; and be free of comorbid conditions such as liver, renal, or cardiac disease. In contrast to LVRS, the anatomic distribution of emphysema and the presence of pulmonary hypertension are not contraindications to lung transplantation. Unresolved issues concerning lung transplantation and COPD include whether single- or double-lung transplant is the preferred procedure.

EXACERBATIONS OF COPD Exacerbations are a prominent feature of the natural history of COPD. Exacerbations are commonly considered to be episodes of increased dyspnea and cough and change in the amount and character of sputum. They may or may not be accompanied by other signs of illness, including fever, myalgias, and sore throat. Self-reported health-related quality of life correlates with frequency of exacerbations more closely than it does with the degree of airflow obstruction. Economic analyses have shown that >70% of COPD-related health care expenditures go to emergency department visits and hospital care; this translates to >\$10 billion annually in the United States. The frequency of exacerbations increases as airflow obstruction increases; patients with moderate to severe airflow obstruction (GOLD stages III and IV; Table 18-1) have one to three episodes per year.

The approach to a patient experiencing an exacerbation includes an assessment of the severity of the patient's illness, both acute and chronic components; an attempt to identify the precipitant of the exacerbation; and the institution of therapy.

Precipitating Causes and Strategies to Reduce Frequency of Exacerbations

A variety of stimuli may result in the final common pathway of airway inflammation and increased symptoms that are characteristic of COPD exacerbations. Bacterial infections play a role in many, but by no means all, episodes. Viral respiratory infections are present in approximately one-third of COPD exacerbations. In a significant minority of instances (20–35%), no specific precipitant can be identified.

Despite the frequent implication of bacterial infection, chronic suppressive, or "rotating," antibiotics are not beneficial in patients with COPD. This is in contrast to their apparent efficacy in patients with significant bronchiectasis. In patients with bronchiectasis caused by cystic fibrosis, suppressive antibiotics have been shown to reduce the frequency of hospital admissions.

The role of anti-inflammatory therapy in reducing exacerbation frequency is less well studied. Chronic oral

glucocorticoids are not recommended for this purpose. Inhaled glucocorticoids did reduce the frequency of exacerbations by 25–30% in some analyses. The use of inhaled glucocorticoids should be considered in patients with frequent exacerbations or those who have an asthmatic component (i.e., significant reversibility on pulmonary function testing or marked symptomatic improvement after the use of inhaled bronchodilators).

Patient Assessment An attempt should be made to establish the severity of the exacerbation as well as the severity of preexisting COPD. The more severe either of these two components, the more likely that the patient will require hospital admission. The history should include quantification of the degree of dyspnea by asking about breathlessness during activities of daily living and typical activities for the patient. The patient should be asked about fever; change in character of sputum; any ill contacts; and associated symptoms such as nausea, vomiting, diarrhea, myalgias, and chills. Inquiring about the frequency and severity of prior exacerbations can provide important information.

The physical examination should incorporate an assessment of the degree of distress of the patient. Specific attention should be focused on tachycardia, tachypnea, use of accessory muscles, signs of perioral or peripheral cyanosis, the ability to speak in complete sentences, and the patient's mental status. The chest examination should establish the presence or absence of focal findings, degree of air movement, presence or absence of wheezing, asymmetry in the chest examination (suggesting large airway obstruction or pneumothorax mimicking an exacerbation), and the presence or absence of paradoxical motion of the abdominal wall.

Patients with severe underlying COPD who are in moderate or severe distress or those with focal findings should have a chest x-ray. Approximately 25% of x-rays in this clinical situation will be abnormal, with the most frequent findings being pneumonia and congestive heart failure. Patients with advanced COPD, those with a history of hypercarbia, those with mental status changes (confusion, sleepiness), or those in significant distress should have an arterial blood gas measurement. The presence of hypercarbia, defined as a $P_{CO_2} >45$ mmHg, has important implications for treatment (discussed below). In contrast to its utility in the management of exacerbations of asthma, measurement of pulmonary function has not been demonstrated to be helpful in the diagnosis or management of exacerbations of COPD.

There are no definitive guidelines concerning the need for inpatient treatment of exacerbations. Patients with respiratory acidosis and hypercarbia, significant hypoxemia, or severe underlying disease or those whose living situation is not conducive to careful observation and the delivery of prescribed treatment should be admitted to the hospital.

ACUTE EXACERBATIONS

Bronchodilators Typically, patients are treated with an inhaled β -agonist, often with the addition of an anticholinergic agent. These may be administered separately or together, and the frequency of administration depends on the severity of the exacerbation. Patients are often treated initially with nebulized therapy because such treatment is often easier to administer in older patients and to those in respiratory distress. It has been shown, however, that conversion to metered-dose inhalers is effective when accompanied by education and training of patients and staff. This approach has significant economic benefits and also allows an easier transition to outpatient care. The addition of methylxanthines (e.g., theophylline) to this regimen can be considered, although convincing proof of its efficacy is lacking. If added, serum levels should be monitored in an attempt to minimize toxicity.

Antibiotics Patients with COPD are frequently colonized with potential respiratory pathogens, and it is often difficult to identify conclusively a specific species of bacteria responsible for a particular clinical event. Bacteria frequently implicated in COPD exacerbations include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. In addition, *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* are found in 5–10% of exacerbations. The choice of antibiotic should be based on local patterns of antibiotic susceptibility of the above pathogens as well as the patient's clinical condition. Most practitioners treat patients with moderate or severe exacerbations with antibiotics, even in the absence of data implicating a specific pathogen.

Glucocorticoids Among patients admitted to the hospital, the use of glucocorticoids has been demonstrated to reduce the length of stay, hasten recovery, and reduce the chance of subsequent exacerbation or relapse for a period of up to 6 months. One study demonstrated that 2 weeks of glucocorticoid therapy produced benefit indistinguishable from 8 weeks of therapy. The GOLD guidelines recommend 30–40 mg of oral prednisolone or its equivalent for 10–14 days. Hyperglycemia, particularly in patients with preexisting diagnosis of diabetes, is the most frequently reported acute complication of glucocorticoid treatment.

Oxygen Supplemental O_2 should be supplied to keep arterial saturations $\geq 90\%$. Hypoxic respiratory drive plays a small role in patients with COPD. Studies have demonstrated that in patients with both acute and chronic hypercarbia, the administration of supplemental O_2 does not reduce minute ventilation. It does, in some patients, result in modest increases in arterial PCO_2 , chiefly by altering ventilation-perfusion relationships within the lung. This should not deter practitioners from providing the oxygen needed to correct hypoxemia.

Mechanical Ventilatory Support The initiation of noninvasive positive pressure ventilation (NIPPV) in patients with respiratory failure, defined as $Paco_2 > 45$ mmHg, results in a significant reduction in mortality, need for intubation, complications of therapy, and hospital length of stay. Contraindications to NIPPV include cardiovascular instability, impaired mental status or inability to cooperate, copious secretions or the inability to clear secretions, craniofacial abnormalities or trauma precluding effective fitting of the mask, extreme obesity, or significant burns.

Invasive (conventional) mechanical ventilation via an endotracheal tube is indicated for patients with severe respiratory distress despite initial therapy, life-threatening hypoxemia, severe hypercapnia or acidosis, markedly impaired mental status, respiratory arrest, hemodynamic instability, or other complications. The goal of mechanical ventilation is to correct the aforementioned conditions. Factors to consider during mechanical ventilatory support include the need to provide sufficient expiratory time in patients with severe airflow obstruction and the presence of auto-PEEP (positive end-expiratory pressure), which can result in patients having to generate significant respiratory effort to trigger a breath during a demand mode of ventilation. The mortality of patients requiring mechanical ventilatory support is 17–30% for that particular hospitalization. For patients > 65 years who are admitted to the intensive care unit for treatment, the mortality doubles over the next year to 60%, regardless of whether mechanical ventilation was required.

FURTHER READINGS

- AMERICAN THORACIC SOCIETY/EUROPEAN RESPIRATORY SOCIETY TASK FORCE: Standards for the diagnosis and management of patients with COPD [Internet]. Version 1.2. New York: American Thoracic Society; 2004 [updated 2005 September 8]. Available from: <http://www-test.thoracic.org/copd/>
- FIGORE MC et al: *Treating Tobacco Use and Dependence*, Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service, June 2000
- ITO K et al: Decreased histone deacetylase activity in chronic obstructive pulmonary disease. *N Engl J Med* 352:1967, 2005
- MANNINO DM, BUIST AS: Global burden of COPD: Risk factors, prevalence, and future trends. *Lancet* 370:765, 2007
- PAUWELS et al: Chronic obstructive pulmonary disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease [updated 2009]. Available from: www.goldcopd.com
- RABE KF et al: Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 176:532, 2007
- et al: Update in chronic obstructive pulmonary disease 2006. *Am J Respir Crit Care Med* 175:1222, 2007
- SIN DD et al: Inhaled corticosteroids and mortality in chronic obstructive pulmonary disease. *Thorax* 60:992, 2005
- WISE RA, TASHKIN DP: Optimizing treatment of chronic obstructive pulmonary disease: An assessment of current therapies. *Am J Med* 120(Suppl):S4, 2007



CHAPTER 19

INTERSTITIAL LUNG DISEASES

Talmadge E. King, Jr.

Pathogenesis	191	Interstitial Lung Disease Associated with	
Respiratory Symptoms and Signs	194	Connective Tissue Disorders	199
Physical Examination	194	Drug-Induced Interstitial Lung Disease	200
Laboratory	194	Eosinophilic Pneumonia	200
Chest Imaging Studies	194	Pulmonary Alveolar Proteinosis	200
Pulmonary Function Testing	195	Pulmonary Lymphangiomyomatosis	200
Cardiopulmonary Exercise Testing	195	Syndromes of Interstitial Lung Disease with	
Fiberoptic Bronchoscopy and Bronchoalveolar Lavage	195	Diffuse Alveolar Hemorrhage	201
Tissue and Cellular Examination	195	Inherited Disorders Associated with	
■ Individual Forms of ILD	197	Interstitial Lung Diseases	201
Idiopathic Pulmonary Fibrosis	197	Interstitial Lung Disease with a Granulomatous	
Nonspecific Interstitial Pneumonia (NSIP)	197	Response in Lung Tissue or Vascular Structures	202
Acute Interstitial Pneumonia (Hamman-Rich Syndrome)	198	Lymphocytic Infiltrative Disorders	202
Cryptogenic Organizing Pneumonia	198	Bronchocentric Granulomatosis	202
Interstitial Lung Disease Associated		Global Considerations	202
with Cigarette Smoking	198	■ Further Readings	202

Patients with interstitial lung diseases (ILDs) come to medical attention mainly because of the onset of progressive exertional dyspnea or a persistent, nonproductive cough. Hemoptysis, wheezing, and chest pain may be present. Often, the identification of interstitial opacities on chest x-ray focuses the diagnostic approach toward one of the ILDs.

ILDs represent a large number of conditions that involve the parenchyma of the lung—the alveoli, the alveolar epithelium, the capillary endothelium, and the spaces between these structures, as well as the perivascular and lymphatic tissues. This heterogeneous group of disorders is classified together because of similar clinical, radiographic, physiologic, or pathologic manifestations. These disorders are often associated with considerable morbidity and mortality, and there is little consensus regarding the best management of most of them.

ILDs have been difficult to classify because >200 known individual diseases are characterized by diffuse parenchymal lung involvement, either as the primary condition or as a significant part of a multiorgan process,

as may occur in the connective tissue diseases (CTDs). One useful approach to classification is to separate the ILDs into two groups based on the major underlying histopathology: (1) those associated with predominant inflammation and fibrosis and (2) those with a predominantly granulomatous reaction in interstitial or vascular areas (**Table 19-1**). Each of these groups can be further subdivided according to whether the cause is known or unknown. For each ILD, there may be an acute phase, and there is usually a chronic one as well. Rarely, some are recurrent, with intervals of subclinical disease.

Sarcoidosis, idiopathic pulmonary fibrosis (IPF), and pulmonary fibrosis associated with CTDs are the most common ILDs of unknown cause. Among the ILDs of known cause, the largest group comprises occupational and environmental exposures, especially the inhalation of inorganic dusts, organic dusts, and various fumes or gases (Chaps. 9 and 10) (**Table 19-2**). A clinical diagnosis is possible for many forms of ILD, especially if an occupational and environmental history is aggressively pursued. For other forms, tissue examination, usually

TABLE 19-1

MAJOR CATEGORIES OF ALVEOLAR AND INTERSTITIAL INFLAMMATORY LUNG DISEASE

LUNG RESPONSE: ALVEOLITIS, INTERSTITIAL INFLAMMATION, AND FIBROSIS

Known Cause	
Asbestos Fumes, gases Drugs (antibiotics, amiodarone, gold) and chemotherapy drugs	Radiation Aspiration pneumonia Residual of adult respiratory distress syndrome
Unknown Cause	
Idiopathic interstitial pneumonias Idiopathic pulmonary fibrosis (usual interstitial pneumonia) Desquamative interstitial pneumonia Respiratory bronchiolitis-associated interstitial lung disease Acute interstitial pneumonia (diffuse alveolar damage) Cryptogenic organizing pneumonia (bronchiolitis obliterans with organizing pneumonia) Nonspecific interstitial pneumonia Connective tissue diseases Systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, systemic sclerosis, Sjögren's syndrome, polymyositis-dermatomyositis Pulmonary hemorrhage syndromes Goodpasture's syndrome, idiopathic pulmonary hemosiderosis, isolated pulmonary capillaritis	Pulmonary alveolar proteinosis Lymphocytic infiltrative disorders (lymphocytic interstitial pneumonitis associated with connective tissue disease) Eosinophilic pneumonias Lymphangioleiomyomatosis Amyloidosis Inherited diseases Tuberous sclerosis, neurofibromatosis, Niemann-Pick disease, Gaucher's disease, Hermansky-Pudlak syndrome Gastrointestinal or liver diseases (Crohn's disease, primary biliary cirrhosis, chronic active hepatitis, ulcerative colitis) Graft-vs.-host disease (bone marrow transplantation, solid organ transplantation)
LUNG RESPONSE: GRANULOMATOUS	
Known Cause	
Hypersensitivity pneumonitis (organic dusts)	Inorganic dusts: beryllium, silica
Unknown Cause	
Sarcoidosis Langerhans' cell granulomatosis (eosinophilic granuloma of the lung) Granulomatous vasculitides Wegener's granulomatosis, allergic granulomatosis of Churg-Strauss	Bronchocentric granulomatosis Lymphomatoid granulomatosis

obtained by thoracoscopic lung biopsy, is critical to confirmation of the diagnosis. High-resolution computed tomography (HRCT) scanning improves diagnostic accuracy as experience with histologic-image correlation is perfected.

PATHOGENESIS

The ILDs are nonmalignant disorders and are not caused by identified infectious agents. The precise pathway(s) leading from injury to fibrosis is not known. Although there are multiple initiating agent(s) of injury, the immunopathogenic responses of lung tissue are limited, and the mechanisms of repair have common features (Fig. 19-1).

As mentioned above, the two major histopathologic patterns are a granulomatous pattern and a pattern in which inflammation and fibrosis predominate.

Granulomatous Lung Disease

This process is characterized by an accumulation of T lymphocytes, macrophages, and epithelioid cells organized into discrete structures (granulomas) in the lung parenchyma. The granulomatous lesions can progress to fibrosis. Many patients with granulomatous lung disease remain free of severe impairment of lung function, or when symptomatic, they improve after treatment. The main differential diagnosis is between sarcoidosis and hypersensitivity pneumonitis (Chap. 9).

ESTIMATED RELATIVE FREQUENCY OF THE INTERSTITIAL LUNG DISEASES

DIAGNOSIS	RELATIVE FREQUENCY, %
Idiopathic interstitial pneumonias	40
Idiopathic pulmonary fibrosis	55
Nonspecific interstitial pneumonia	25
Respiratory bronchiolitis—interstitial lung disease and desquamative interstitial pneumonia	15
Cryptogenic organizing pneumonia	3
Acute interstitial pneumonia	<1
Occupational and environmental	26
Sarcoidosis	10
Connective tissue diseases	9
Drug and radiation	1
Pulmonary hemorrhage syndromes	<1
Other	13

Source: From DB Coultas, R Hubbard, in JP Lynch III (ed): *Lung Biology in Health and Disease*. New York, Marcel Dekker, 2004; and Garantziotis S et al: *J Clin Invest* 114:319, 2004.

Inflammation and Fibrosis

The initial insult is an injury to the epithelial surface causing inflammation in the air spaces and alveolar walls (Fig. 19-2). If the disease becomes chronic, inflammation spreads to adjacent portions of the interstitium and vasculature and eventually causes interstitial fibrosis. Important histopathologic patterns found in the ILDs include usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), respiratory bronchiolitis, organizing pneumonia [bronchiolitis obliterans with organizing pneumonia (BOOP) pattern], diffuse alveolar damage (acute or organizing), desquamative interstitial pneumonia (DIP), and lymphocytic interstitial pneumonia. The development of irreversible scarring (fibrosis) of alveolar walls, airways, or vasculature is the most feared outcome in all of these conditions because it is often progressive and leads to significant derangement of ventilatory function and gas exchange.

History

Duration of Illness

Acute presentation (days to weeks), although unusual, occurs with allergy (drugs, fungi, helminths), acute interstitial pneumonia (AIP), eosinophilic pneumonia, and hypersensitivity pneumonitis. These conditions may be confused with atypical pneumonias because of diffuse alveolar opacities on chest x-ray. **Subacute presentation** (weeks to months) may occur in all ILDs but is seen especially in sarcoidosis, drug-induced ILDs, the alveolar hemorrhage syndromes, cryptogenic organizing pneumonia (COP), and the acute immunologic pneumonia that complicates systemic lupus

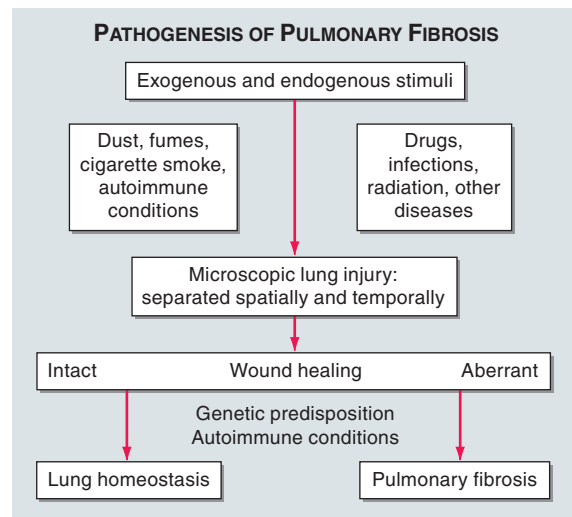


FIGURE 19-1

Proposed mechanism for the pathogenesis of pulmonary fibrosis. The lung is naturally exposed to repetitive injury from a variety of exogenous and endogenous stimuli. Several local and systemic factors (e.g., fibroblasts, circulating fibrocytes, chemokines, growth factors, and clotting factors) contribute to tissue healing and functional recovery. Dysregulation of this intricate network through genetic predisposition, autoimmune conditions, or superimposed diseases can lead to aberrant wound healing with the result of pulmonary fibrosis. Alternatively, excessive injury to the lung may overwhelm even intact reparative mechanisms and lead to pulmonary fibrosis. (From S Garantziotis, et al: *J Clin Invest* 114:319, 2004.)

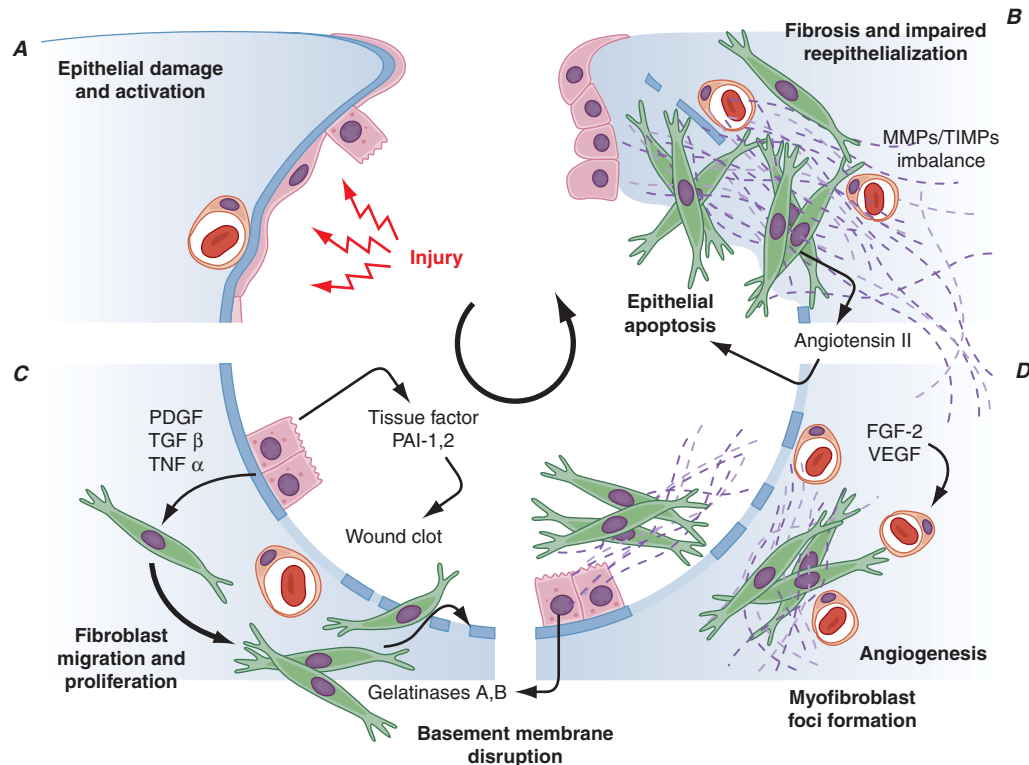
erythematosus (SLE) or polymyositis. In most ILDs the symptoms and signs form a *chronic presentation* (months to years). Examples include IPF, sarcoidosis, pulmonary Langerhans cell histiocytosis (PLCH) (also known as Langerhans cell granulomatosis, eosinophilic granuloma, or histiocytosis X), pneumoconioses, and CTDs. *Episodic presentations* are unusual and include eosinophilic pneumonia, hypersensitivity pneumonitis, COP, vasculitides, pulmonary hemorrhage, and Churg–Strauss syndrome.

Age

Most patients with sarcoidosis, ILD associated with CTD, lymphangiomyomatosis (LAM), PLCH, and inherited forms of ILD (familial IPF, Gaucher’s disease, Hermansky-Pudlak syndrome) present between the ages of 20 and 40 years. Most patients with IPF are older than 50 years.

Gender

LAM and pulmonary involvement in tuberous sclerosis occur exclusively in premenopausal women. Also, ILD in Hermansky-Pudlak syndrome and in the CTDs is more common in women; an exception is ILD in rheumatoid arthritis (RA), which is more common in men. Because of occupational exposures, pneumoconioses also occur more frequently in men.

**FIGURE 19-2**

Cellular bases for the pathogenesis of interstitial lung disease. Multiple microinjuries damage and activate alveolar epithelial cells (**A**), which in turn induce an antifibrinolytic environment in the alveolar spaces, enhancing wound clot formation. Alveolar epithelial cells secrete growth factors and induce migration and proliferation of fibroblasts and differentiation into myfibroblasts (**C**). Subepithelial myfibroblasts and alveolar epithelial cells produce gelatinases that may increase basement membrane disruption and allow fibroblast–myfibroblast migration (**D**). Angiogenic factors induce neovascularization. Both intraalveolar and interstitial myfibroblasts secrete extracellular matrix proteins, mainly collagens. An imbalance between interstitial collagenases and tissue inhibitors of metalloproteinases provokes the progressive

deposit of extracellular matrix (**B**). Signals responsible for myfibroblast apoptosis seem to be absent or delayed in usual interstitial pneumonia, increasing cell survival. Myfibroblasts produce angiotensinogen that as angiotensin II provokes alveolar epithelial cell death, further impairing reepithelialization. FGF-2, fibroblast growth factor 2; MMPs, metalloproteinases; PAI-1, PAI-2, plasminogen activator inhibitor 1, 2; PDGF, platelet-derived growth factor; TGF- β , transforming growth factor β ; TIMPs, tissue inhibitors of metalloproteinases; TNF- α , tumor necrosis factor α ; VEGF, vascular endothelial growth factor. (From M Selman et al: Idiopathic pulmonary fibrosis: Prevailing and evolving hypotheses about its pathogenesis and implications for therapy. *Ann Intern Med* 134:136, 2001; with permission.)

Family History

Family associations (with an autosomal dominant pattern) have been identified in tuberous sclerosis and neurofibromatosis. An autosomal recessive pattern of inheritance occurs in Niemann–Pick disease, Gaucher’s disease, and the Hermansky–Pudlak syndrome. Familial clustering has been increasingly identified in sarcoidosis. Familial lung fibrosis has been associated with mutations in the surfactant protein C gene and is characterized by several patterns of interstitial pneumonia, including NSIP, DIP, and UIP.

Smoking History

Two-thirds to 75% of patients with IPF have a history of smoking. Patients with PLCH, DIP, Goodpasture’s syndrome, respiratory bronchiolitis, and pulmonary alveolar proteinosis (PAP) are almost always current or former smokers.

Occupation and Environmental History

A strict chronologic listing of the patient’s lifelong employment must be sought, including specific duties and known exposures. In hypersensitivity pneumonitis (see Fig. 9–1), respiratory symptoms, fever, chills, and an abnormal chest radiograph are often temporally related to a hobby (e.g., pigeon breeder’s disease) or to the workplace (e.g., farmer’s lung) (Chap. 9). Symptoms may diminish or disappear after the patient leaves the site of exposure for several days; similarly, symptoms may reappear on returning to the exposure site.

Other Important Past History

Parasitic infections may cause pulmonary eosinophilia, so a travel history should be taken in patients with known or suspected ILD. History of risk factors for HIV infection should be elicited from all patients with ILD

194 because several processes may occur at the time of initial presentation or during the clinical course [e.g., HIV infection, BOOP, AIP, lymphocytic interstitial pneumonitis, diffuse alveolar hemorrhage (DAH)].

RESPIRATORY SYMPTOMS AND SIGNS

Dyspnea is a common and prominent complaint in patients with ILD, especially the idiopathic interstitial pneumonias, hypersensitivity pneumonitis, COP, sarcoidosis, eosinophilic pneumonias, and PLCH. Some patients, especially patients with sarcoidosis, silicosis, PLCH, hypersensitivity pneumonitis, lipoid pneumonia, or lymphangitis carcinomatosa, may have extensive parenchymal lung disease on chest x-ray without significant dyspnea, especially early in the course of the illness. Wheezing is an uncommon manifestation of ILD but has been described in patients with chronic eosinophilic pneumonia, Churg-Strauss syndrome, respiratory bronchiolitis, and sarcoidosis. Clinically significant chest pain is uncommon in most ILDs. However, substernal discomfort is common in sarcoidosis. Sudden worsening of dyspnea, especially if associated with acute chest pain, may indicate a spontaneous pneumothorax, which occurs in PLCH, tuberous sclerosis, LAM, and neurofibromatosis. Frank hemoptysis and blood-streaked sputum are rarely presenting manifestations of ILD but can be seen in the DAH syndromes, LAM, tuberous sclerosis, and the granulomatous vasculitides. Fatigue and weight loss are common in all ILDs.

PHYSICAL EXAMINATION

The findings are usually not specific. Most commonly, physical examination reveals tachypnea and bibasilar end-inspiratory dry crackles, which are common in most forms of ILD associated with inflammation but are less likely to be heard in the granulomatous lung diseases. Crackles may be present in the absence of radiographic abnormalities on the chest radiograph. Scattered late inspiratory high-pitched rhonchi—so-called *inspiratory squeaks*—are heard in patients with bronchiolitis. The cardiac examination is usually normal except in the mid or late stages of the disease, when findings of pulmonary hypertension and cor pulmonale may become evident. Cyanosis and clubbing of the digits occur in some patients with advanced disease.

LABORATORY

Antinuclear antibodies and anti-immunoglobulin antibodies (rheumatoid factors) are identified in some patients, even in the absence of a defined CTD. An increased lactate dehydrogenase (LDH) level is a nonspecific finding common to ILDs. Elevation of the serum angiotensin-converting enzyme level is common in sarcoidosis. Serum precipitins confirm exposure when

hypersensitivity pneumonitis is suspected, although they are not diagnostic of the process. Antineutrophil cytoplasmic or anti-basement membrane antibodies are useful if vasculitis is suspected. The electrocardiogram is usually normal unless pulmonary hypertension is present; then it demonstrates right-axis deviation, right ventricular hypertrophy, or right atrial enlargement or hypertrophy. Echocardiography also reveals right ventricular dilatation, hypertrophy, or both in the presence of pulmonary hypertension.

CHEST IMAGING STUDIES

Chest X-ray

ILD may be first suspected based on an abnormal chest radiograph, which most commonly reveals a bibasilar reticular pattern. A nodular or mixed pattern of alveolar filling and increased reticular markings may also be present. A subgroup of ILDs—sarcoidosis, PLCH, chronic hypersensitivity pneumonitis, silicosis, berylliosis, RA (necrobiotic nodular form), ankylosing spondylitis—exhibit nodular opacities with a predilection for the upper lung zones. The chest x-ray correlates poorly with the clinical or histopathologic stage of the disease. The radiographic finding of honeycombing correlates with pathologic findings of small cystic spaces and progressive fibrosis; when present, it portends a poor prognosis. In most cases, the chest radiograph is nonspecific and usually does not allow a specific diagnosis.

Computed Tomography

HRCT is superior to the plain chest x-ray for early detection and confirmation of suspected ILD (Fig. 19-3).



FIGURE 19-3

Idiopathic pulmonary fibrosis. High-resolution CT image shows bibasal, peripheral predominant reticular abnormality with traction bronchiectasis and honeycombing. The lung biopsy showed the typical features of usual interstitial pneumonia.

Also, HRCT allows better assessment of the extent and distribution of disease and is especially useful in the investigation of patients with normal chest radiographs. Coexisting disease (e.g., mediastinal adenopathy, carcinoma, or emphysema) is often best recognized on HRCT scanning. In the appropriate clinical setting, HRCT may be sufficiently characteristic to preclude the need for lung biopsy in patients with IPF, sarcoidosis, hypersensitivity pneumonitis, asbestosis, lymphangitic carcinoma, and PLCH. When a lung biopsy is required, HRCT scanning is useful for determining the most appropriate area from which biopsy samples should be taken.

PULMONARY FUNCTION TESTING

Spirometry and Lung Volumes

Measurement of lung function is important in assessing the extent of pulmonary involvement in patients with ILD. Most forms of ILD produce a restrictive defect with reduced total lung capacity (TLC), functional residual capacity, and residual volume (Chap. 5). Forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) are reduced, but these changes are related to the decreased TLC. The FEV_1/FVC ratio is usually normal or increased. Lung volumes decrease as lung stiffness worsens with disease progression. A few disorders produce interstitial opacities on chest x-ray and obstructive airflow limitation on lung function testing (uncommon in sarcoidosis and hypersensitivity pneumonitis but common in tuberous sclerosis and LAM). Pulmonary function studies have proven to have prognostic value in patients with idiopathic interstitial pneumonias, particularly, IPF or NSIP.

Diffusing Capacity

A reduction in the diffusing capacity of the lung for carbon monoxide (DL_{CO}) is a common but nonspecific finding in most ILDs. This decrease is caused partly by effacement of the alveolar capillary units but, more importantly, to mismatching of ventilation and perfusion (\dot{V}/\dot{Q}). Lung regions with reduced compliance because of either fibrosis or cellular infiltration may be poorly ventilated but may still maintain adequate blood flow, and the ventilation-perfusion mismatch in these regions acts like true venous admixture. The severity of the reduction in DL_{CO} does not correlate with the disease stage.

Arterial Blood Gas

The resting arterial blood gas analysis results may be normal or reveal hypoxemia (secondary to a mismatching of ventilation to perfusion) and respiratory alkalosis. A normal arterial O_2 tension (or saturation by oximetry) at rest does not rule out significant hypoxemia during

exercise or sleep. CO_2 retention is rare and is usually a manifestation of end-stage disease.

CARDIOPULMONARY EXERCISE TESTING

Because hypoxemia at rest is not always present and because severe exercise-induced hypoxemia may go undetected, it is useful to perform exercise testing with measurement of arterial blood gases to detect abnormalities of gas exchange. Arterial oxygen desaturation, a failure to decrease dead space appropriately with exercise (i.e., a high VD/VT ratio; Chap. 5), and an excessive increase in respiratory rate with a lower-than-expected recruitment of tidal volume provide useful information about physiologic abnormalities and extent of disease. Serial assessment of resting and exercise gas exchange is an excellent method for following disease activity and responsiveness to treatment, especially in patients with IPF. Increasingly, the 6-min walk test is used to obtain a global evaluation of submaximal exercise capacity in patients with ILD. The walk distance and level of oxygen desaturation tend to correlate with the patient's baseline lung function.

FIBEROPTIC BRONCHOSCOPY AND BRONCHOALVEOLAR LAVAGE

In selected diseases (e.g., sarcoidosis, hypersensitivity pneumonitis, DAH syndrome, cancer, PAP), cellular analysis of bronchoalveolar lavage (BAL) fluid may be useful in narrowing the differential diagnostic possibilities among various types of ILD (Table 19-3). The role for BAL in defining the stage of disease and assessment of disease progression or response to therapy remains poorly understood, and the usefulness of BAL in clinical assessment and management remains to be established.

TISSUE AND CELLULAR EXAMINATION

Lung biopsy is the most effective method for confirming the diagnosis and assessing disease activity. The findings may identify a more treatable process than originally suspected, particularly chronic hypersensitivity pneumonitis, COP, respiratory bronchiolitis-associated ILD, or sarcoidosis. Biopsy should be obtained before initiation of treatment. A definitive diagnosis avoids confusion and anxiety later in the clinical course if the patient does not respond to therapy or experiences serious side effects from it.

Fiberoptic bronchoscopy with multiple transbronchial lung biopsies (four to eight biopsy samples) is often the initial procedure of choice, especially when sarcoidosis, lymphangitic carcinomatosis, eosinophilic pneumonia, Goodpasture's syndrome, or infection is suspected. If a specific diagnosis is not made by transbronchial biopsy, then surgical lung biopsy by video-assisted thoracic surgery or open thoracotomy is indicated. Adequate-sized

TABLE 19-3

DIAGNOSTIC VALUE OF BRONCHOALVEOLAR LAVAGE IN INTERSTITIAL LUNG DISEASE

CONDITION	BRONCHOALVEOLAR LAVAGE FINDING
Sarcoidosis	Lymphocytosis; CD4:CD8 ratio >3.5 most specific of diagnosis
Hypersensitivity pneumonitis	Marked lymphocytosis (>50%)
Organizing pneumonia	Foamy macrophages; mixed pattern of increased cells characteristic; decreased CD4:CD8 ratio
Eosinophilic lung disease	Eosinophils >25%
Diffuse alveolar bleeding	Hemosiderin-laden macrophages, red blood cells
Diffuse alveolar damage, drug toxicity	Atypical hyperplastic type II pneumocytes
Opportunistic infections	<i>Pneumocystis carinii</i> , fungi, cytomegalovirus-transformed cells
Lymphangitic carcinomatosis, alveolar cell carcinoma, pulmonary lymphoma	Malignant cells
Alveolar proteinosis	Milky effluent, foamy macrophages and lipoproteinaceous intraalveolar material (periodic acid–Schiff stain positive)
Lipoid pneumonia	Fat globules in macrophages
Pulmonary Langerhans' cell histiocytosis	Increased CD1+ Langerhans' cells Electron microscopy demonstrating Birbeck granule in lavaged macrophage (expensive and difficult to perform)
Asbestos-related pulmonary disease	Dust particles, ferruginous bodies
Berylliosis	Positive lymphocyte transformation test to beryllium
Silicosis	Dust particles by polarized light microscopy
Lipoidosis	Accumulation of specific lipopigment in alveolar macrophages

biopsies from multiple sites, usually from two lobes, should be obtained. Relative contraindications to lung biopsy include serious cardiovascular disease, honeycombing and other radiographic evidence of diffuse end-stage disease, severe pulmonary dysfunction, or other major operative risks, especially in the elderly.

Rx Treatment: **INTERSTITIAL LUNG DISEASE**

Although the course of ILD is variable, progression is common and often insidious. All treatable possibilities should be carefully considered. Because therapy does not reverse fibrosis, the major goals of treatment are permanent removal of the offending agent, when known, and early identification and aggressive suppression of the acute and chronic inflammatory process, thereby reducing further lung damage.

Hypoxemia ($\text{PaO}_2 < 55$ mmHg) at rest or with exercise should be managed by supplemental oxygen. If cor pulmonale develops, diuretic therapy and phlebotomy may occasionally be required.

DRUG THERAPY Glucocorticoids are the mainstay of therapy for suppression of the alveolitis present in ILD, but the success rate is low. There have been no

placebo-controlled trials of glucocorticoids in ILD, so there is no direct evidence that steroids improve survival in many of the diseases for which they are commonly used. Glucocorticoid therapy is recommended for symptomatic ILD patients with eosinophilic pneumonias, COP, CTD, sarcoidosis, acute inorganic dust exposures, acute radiation pneumonitis, DAH, and drug-induced ILD. In organic dust disease, glucocorticoids are recommended for both the acute and chronic stages.

The optimal dose and proper length of therapy with glucocorticoids in the treatment of most ILDs are not known. A common starting dose is prednisone, 0.5–1 mg/kg in a once-daily oral dose (based on the patient's lean body weight). This dose is continued for 4–12 weeks, at which time the patient is reevaluated. If the patient is stable or improved, the dose is tapered to 0.25–0.5 mg/kg and is maintained at this level for an additional 4–12 weeks depending on the course. Rapid tapering or a shortened course of glucocorticoid treatment can result in recurrence. If the patient's condition continues to decline while on glucocorticoids, a second agent (see later) is often added, and the prednisone dose is lowered to or maintained at 0.25 mg/kg per day.

Cyclophosphamide and azathioprine (1–2 mg/kg lean body weight per day), with or without glucocorticoids,

have been tried with variable success in IPF, vasculitis, and other ILDs. An objective response usually requires at least 8–12 weeks to occur. In situations in which these drugs have failed or could not be tolerated, other agents, including methotrexate, colchicine, penicillamine, and cyclosporine, have been tried. However, their role in the treatment of ILDs remains to be determined.

Many cases of ILD are chronic and irreversible despite the therapy discussed above, and lung transplantation may then be considered (Chap. 24).

INDIVIDUAL FORMS OF ILD

IDIOPATHIC PULMONARY FIBROSIS

IPF is the most common form of idiopathic interstitial pneumonia. Separating IPF from other forms of lung fibrosis is an important step in the evaluation of all patients presenting with ILD. IPF has a distinctly poor response to therapy and a bad prognosis.

Clinical Manifestations

Exertional dyspnea, a nonproductive cough, and inspiratory crackles with or without digital clubbing may be present on physical examination. The HRCT lung scans typically show patchy, predominantly basilar, subpleural reticular opacities, often associated with traction bronchiectasis and honeycombing (see Fig. 19-3). Atypical findings that should suggest an alternative diagnosis include extensive ground-glass abnormality, nodular opacities, upper or mid-zone predominance, and prominent hilar or mediastinal lymphadenopathy. Pulmonary function tests often reveal a restrictive pattern, a reduced DL_{CO} , and arterial hypoxemia that is exaggerated or elicited by exercise.

Histologic Findings

Confirmation of the presence of the UIP pattern on histologic examination is essential to confirm this diagnosis. Transbronchial biopsies are not helpful in making the diagnosis of UIP, and surgical biopsy is usually required. The histologic hallmark and chief diagnostic criterion of UIP is a heterogeneous appearance at low magnification with alternating areas of normal lung, interstitial inflammation, foci of proliferating fibroblasts, dense collagen fibrosis, and honeycomb changes. These histologic changes affect the peripheral, subpleural parenchyma most severely. The interstitial inflammation is usually patchy and consists of a lymphoplasmacytic infiltrate in the alveolar septa, associated with hyperplasia of type 2 pneumocytes. The fibrotic zones are composed mainly of dense collagen, although scattered foci of proliferating fibroblasts are a consistent finding. The extent of fibroblastic proliferation is predictive of disease progression. Areas of honeycomb

change are composed of cystic fibrotic air spaces that are frequently lined by bronchiolar epithelium and filled with mucin. Smooth muscle hyperplasia is commonly seen in areas of fibrosis and honeycomb change. A fibrotic pattern with some features similar to UIP may be found in the chronic stage of several specific disorders such as pneumoconioses (e.g., asbestosis), radiation injury, certain drug-induced lung diseases (e.g., nitrofurantoin), chronic aspiration, sarcoidosis, chronic hypersensitivity pneumonitis, organized chronic eosinophilic pneumonia, and PLCH. Commonly, other histopathologic features are present in these situations, thus allowing separation of these lesions from the UIP-like pattern. Consequently, the term *UIP* is used for patients in whom the lesion is idiopathic and not associated with another condition.

Patients with IPF may experience acute deterioration secondary to infections, pulmonary embolism, pneumothorax, or heart failure. These patients also commonly suffer an accelerated phase of rapid clinical decline that is associated with a poor prognosis (so-called *acute exacerbations of IPF*). These acute exacerbations are defined by worsening of dyspnea within a few days to 4 weeks; newly developing diffuse radiographic opacities; worsening hypoxemia; and absence of infectious pneumonia, heart failure, and sepsis. The rate of these acute exacerbations ranges from 10–57%, apparently depending on the length of follow-up. During these episodes, the histopathologic pattern of diffuse alveolar damage is often found on the background of UIP.

Rx Treatment: IDIOPATHIC PULMONARY FIBROSIS

No therapy has been found to be effective in the management of patients with acute exacerbations of IPF. Often mechanical ventilation is required but is usually not successful, with a hospital mortality rate of up to three-fourths of the patients. In those who survive, a recurrence of acute exacerbation is common and usually results in death at those times.

Lung transplantation should be considered for patients who experience progressive deterioration despite optimal medical management and who meet the established criteria (Chap. 24).

NONSPECIFIC INTERSTITIAL PNEUMONIA (NSIP)

This condition defines a subgroup of the idiopathic interstitial pneumonias that can be distinguished clinically and pathologically from UIP, DIP, AIP, and idiopathic BOOP. Importantly, many patients with this histopathologic pattern occur in the context of an underlying disorder, such as a connective tissue disease, drug-induced ILD, or chronic hypersensitivity pneumonitis. Idiopathic NSIP is

198 a subacute restrictive process with a presentation similar to IPF but usually at a younger age, most commonly in women who have never smoked. It is often associated with a febrile illness. HRCT shows bilateral, subpleural ground-glass opacities, often associated with lower lobe volume loss (Fig. 19-4). Patchy areas of airspace consolidation and reticular abnormalities may be present, but honeycombing is unusual. The key histopathologic features of NSIP are the uniformity of interstitial involvement across the biopsy section, and this may be predominantly cellular or fibrosing. There is less temporal and spatial heterogeneity than in UIP, and little or no honeycombing is found. The cellular variant is rare. Unlike patients with IPF (UIP), the majority of patients with NSIP have a good prognosis (5-year mortality rate estimated at <15%) with most showing improvement after treatment with glucocorticoids, often used in combination with azathioprine.

ACUTE INTERSTITIAL PNEUMONIA (HAMMAN-RICH SYNDROME)

AIP is a rare, fulminant form of lung injury characterized histologically by diffuse alveolar damage on lung biopsy. Most patients are older than age 40 years. AIP is similar in presentation to the acute respiratory distress syndrome (ARDS) (Chap. 30) and probably corresponds to the subset of cases of idiopathic ARDS. The onset is usually abrupt in a previously healthy individual. A prodromal illness, usually lasting 7–14 days before presentation, is common. Fever, cough, and dyspnea are frequent manifestations at presentation. Diffuse, bilateral,



FIGURE 19-4
Nonspecific interstitial pneumonia. High-resolution CT through the lower lung showing volume loss with extensive ground-glass abnormality, reticular abnormality, and traction bronchiectasis. There is sparing on the lung immediately adjacent to the pleura. Histology showed a combination of inflammation and mild fibrosis.

air-space opacification is present on chest radiography. HRCT scans show bilateral, patchy, symmetric areas of ground-glass attenuation. Bilateral areas of air-space consolidation may also be present. A predominantly subpleural distribution may be seen. The diagnosis of AIP requires the presence of a clinical syndrome of idiopathic ARDS and pathologic confirmation of organizing diffuse alveolar damage. Therefore, lung biopsy is required to confirm the diagnosis. Most patients have moderate to severe hypoxemia and develop respiratory failure. Mechanical ventilation is often required. The mortality rate is high (>60%), with most patients dying within 6 months of presentation. Recurrences have been reported. However, those who recover often have substantial improvement in lung function. The main treatment is supportive. It is not clear that glucocorticoid therapy is effective.

CRYPTOGENIC ORGANIZING PNEUMONIA

Also known as *idiopathic BOOP*, COP is a clinicopathologic syndrome of unknown etiology. The onset is usually in the fifth and sixth decades of life. The presentation may be of a flulike illness with cough, fever, malaise, fatigue, and weight loss. Inspiratory crackles are frequently present on examination. Pulmonary function is usually impaired, with a restrictive defect and arterial hypoxemia being most common. The roentgenographic manifestations are distinctive, revealing bilateral, patchy, or diffuse alveolar opacities in the presence of normal lung volume. Recurrent and migratory pulmonary opacities are common. HRCT shows areas of air-space consolidation, ground-glass opacities, small nodular opacities, and bronchial wall thickening and dilatation. These changes occur more frequently in the periphery of the lung and in the lower lung zone. Lung biopsy shows granulation tissue within small airways, alveolar ducts, and airspaces, with chronic inflammation in the surrounding alveoli. Glucocorticoid therapy induces clinical recovery in two-thirds of patients. A few patients have rapidly progressive courses with fatal outcomes despite glucocorticoids.

Foci of organizing pneumonia (i.e., a “BOOP pattern”) is a nonspecific reaction to lung injury found adjacent to other pathologic processes or as a component of other primary pulmonary disorders (e.g., cryptococcosis, Wegener’s granulomatosis, lymphoma, hypersensitivity pneumonitis, and eosinophilic pneumonia). Consequently, the clinician must carefully reevaluate any patient found to have this histopathologic lesion to rule out these possibilities.

INTERSTITIAL LUNG DISEASE ASSOCIATED WITH CIGARETTE SMOKING

Desquamative Interstitial Pneumonia

DIP is a rare but distinct clinical and pathologic entity found exclusively in cigarette smokers. The histologic

hallmark is the extensive accumulation of macrophages in intraalveolar spaces with minimal interstitial fibrosis. The peak incidence is in the fourth and fifth decades of life. Most patients present with dyspnea and cough. Lung function testing shows a restrictive pattern with reduced DL_{CO} and arterial hypoxemia. The chest x-ray and HRCT scans usually show diffuse hazy opacities. Clinical recognition of DIP is important because the process is associated with a better prognosis (10-year survival rate, ~70%) and a better response to smoking cessation and systemic glucocorticoids than IPF.

Respiratory Bronchiolitis–Associated Interstitial Lung Disease

Respiratory bronchiolitis–associated ILD (RB-ILD) is considered to be a subset of DIP and is characterized by the accumulation of macrophages in peribronchial alveoli. The clinical presentation is similar to DIP. Rales are often heard on chest examination and occur throughout inspiration; sometimes they continue into expiration. The process is seen best on HRCT lung scanning, which shows bronchial wall thickening, centrilobular nodules, ground-glass opacity, and emphysema with air trapping. RB-ILD appears to resolve in most patients after smoking cessation alone.

Pulmonary Langerhans Cell Histiocytosis

Pulmonary Langerhans cell histiocytosis (PLCH) is a rare smoking-related, diffuse lung disease that primarily affects men between the ages of 20 and 40 years. The clinical presentation varies from an asymptomatic state to a rapidly progressive condition. The most common clinical manifestations at presentation are cough, dyspnea, chest pain, weight loss, and fever. Pneumothorax occurs in ~25% of patients. Hemoptysis and diabetes insipidus are rare manifestations. The radiographic features vary with the stage of the disease. The combination of ill-defined or stellate nodules (2–10 mm in diameter), reticular or nodular opacities, bizarre-shaped upper zone cysts, preservation of lung volume, and sparing of the costophrenic angles are characteristics of PLCH. HRCT that reveals a combination of nodules and thin-walled cysts is virtually diagnostic of PLCH. The most frequent pulmonary function abnormality is a markedly reduced DL_{CO}, although varying degrees of restrictive disease, airflow limitation, and diminished exercise capacity may occur. The characteristic histopathologic finding in PLCH is the presence of nodular sclerosing lesions that contain Langerhans' cells accompanied by mixed cellular infiltrates. The nodular lesions are poorly defined and are distributed in a bronchiolocentric fashion with intervening normal lung parenchyma. As the disease progresses, fibrosis progresses to involve adjacent lung tissue, leading to pericardiac air-space enlargement, which accounts for the concomitant cystic changes. Discontinuance of smoking is the key

treatment, resulting in clinical improvement in one-third of patients. Most patients with PLCH experience persistent or progressive disease. Death from respiratory failure occurs in ~10% of patients.

INTERSTITIAL LUNG DISEASE ASSOCIATED WITH CONNECTIVE TISSUE DISORDERS

Clinical findings suggestive of a CTD (musculoskeletal pain, weakness, fatigue, fever, joint pains or swelling, photosensitivity, Raynaud's phenomenon, pleuritis, dry eyes, dry mouth) should be sought in any patient with ILD. The CTDs may be difficult to rule out since the pulmonary manifestations occasionally precede the more typical systemic manifestations by months or years. The most common form of pulmonary involvement is the NSIP histopathologic pattern. However, determining the precise nature of lung involvement in most of the CTDs is difficult because of the high incidence of lung involvement caused by disease-associated complications of esophageal dysfunction (predisposing to aspiration and secondary infections), respiratory muscle weakness (atelectasis and secondary infections), complications of therapy (opportunistic infections), and associated malignancies.

Progressive Systemic Sclerosis

Clinical evidence of ILD is present in about one-half of patients with progressive systemic sclerosis (PSS), and pathologic evidence is present in three-quarters. Pulmonary function tests show a restrictive pattern and impaired diffusing capacity, often before any clinical or radiographic evidence of lung disease appears. Pulmonary vascular disease alone or in association with pulmonary fibrosis, pleuritis, or recurrent aspiration pneumonitis is strikingly resistant to current modes of therapy.

Rheumatoid Arthritis

ILD associated with RA is more common in men. Pulmonary manifestations of RA include pleurisy with or without effusion, ILD in up to 20% of cases, necrobiotic nodules (nonpneumoconiotic intrapulmonary rheumatoid nodules) with or without cavities, Caplan's syndrome (rheumatoid pneumoconiosis), pulmonary hypertension secondary to rheumatoid pulmonary vasculitis, BOOP, and upper airway obstruction caused by cricoarytenoid arthritis.

Systemic Lupus Erythematosus

Lung disease is a common complication in SLE. Pleuritis with or without effusion is the most common pulmonary manifestation. Other lung manifestations include: atelectasis, diaphragmatic dysfunction with loss of lung volumes, pulmonary vascular disease, pulmonary hemorrhage, uremic pulmonary edema, infectious pneumonia, and BOOP. Acute lupus pneumonitis characterized by pulmonary

200 capillaritis leading to alveolar hemorrhage is uncommon. Chronic, progressive ILD is uncommon. It is important to exclude pulmonary infection. Although pleuropulmonary involvement may not be evident clinically, pulmonary function testing, particularly DL_{CO}, reveals abnormalities in many patients with SLE.

Polymyositis and Dermatomyositis

ILD occurs in ~10% of patients with polymyositis and dermatomyositis (PM/DM). Diffuse reticular or nodular opacities with or without an alveolar component occur radiographically, with a predilection for the lung bases. ILD occurs more commonly in the subgroup of patients with an anti-Jo-1 antibody that is directed to histidyl tRNA synthetase. Weakness of respiratory muscles contributing to aspiration pneumonia may be present. A rapidly progressive illness characterized by diffuse alveolar damage may cause respiratory failure.

Sjögren's Syndrome

General dryness and lack of airways secretion cause the major problems of hoarseness, cough, and bronchitis. Lymphocytic interstitial pneumonitis, lymphoma, pseudolymphoma, bronchiolitis, and bronchiolitis obliterans are associated with this condition. Lung biopsy is frequently required to establish a precise pulmonary diagnosis. Glucocorticoids have been used in the management of ILD associated with Sjögren's syndrome with some degree of clinical success.

DRUG-INDUCED INTERSTITIAL LUNG DISEASE

Many classes of drugs have the potential to induce diffuse ILD, which is manifest most commonly as exertional dyspnea and nonproductive cough. A detailed history of the medications taken by the patient, including over-the-counter medications, oily nose drops, or petroleum products (mineral oil), is needed to identify drug-induced disease. In most cases, the pathogenesis is unknown, although a combination of direct toxic effects of the drug (or its metabolite) and indirect inflammatory and immunologic events are likely. The onset of the illness may be abrupt and fulminant, or it may be insidious, extending over weeks to months. The drug may have been taken for several years before a reaction develops (e.g., amiodarone), or the lung disease may occur weeks to years after the drug has been discontinued (e.g., carmustine). The extent and severity of disease are usually dose related. Treatment consists of discontinuation of any possible offending drug and supportive care.

EOSINOPHILIC PNEUMONIA

(See Chap. 9)

PULMONARY ALVEOLAR PROTEINOSIS

Although not strictly an ILD, PAP resembles and is therefore considered with these conditions. It has been proposed that a defect in macrophage function, more specifically an impaired ability to process surfactant, may play a role in the pathogenesis of PAP. This diffuse disease is characterized by the accumulation of an amorphous, periodic acid-Schiff-positive lipoproteinaceous material in the distal air spaces. There is little or no lung inflammation, and the underlying lung architecture is preserved. Mutant mice lacking the gene for granulocyte-macrophage colony-stimulating factor (GM-CSF) have a similar accumulation of surfactant and surfactant apoprotein in the alveolar spaces. Moreover, reconstitution of the respiratory epithelium of GM-CSF knockout mice with the GM-CSF gene completely corrects the alveolar proteinosis. Data from BAL studies in patients suggest that PAP is an autoimmune disease with neutralizing antibody of immunoglobulin G isotype against GM-CSF. These findings suggest that neutralization of GM-CSF bioactivity by the antibody causes dysfunction of alveolar macrophages, which results in reduced surfactant clearance. There are three distinct classes of PAP: acquired (>90% of all cases), congenital, and secondary. *Congenital PAP* is transmitted in an autosomal recessive manner and is caused by homozygosity for a frame shift mutation (121ins2) in the *SP-B* gene, which leads to an unstable *SP-B* mRNA, reduced protein levels, and *secondary disturbances of SP-C processing*. *Secondary PAP* is rare among adults and is caused by lysinuric protein intolerance, acute silicosis and other inhalational syndromes, immunodeficiency disorders, and malignancies (almost exclusively of hematopoietic origin) and hematopoietic disorders.

The typical age of presentation is 30–50 years, and men predominate. The clinical presentation is usually insidious and manifested by progressive exertional dyspnea, fatigue, weight loss, and low-grade fever. A nonproductive cough is common, but occasionally expectoration of “chunky” gelatinous material may occur. Polycythemia, hypergammaglobulinemia, and increased LDH levels are frequent. Markedly elevated serum levels of lung surfactant proteins A and D have been found in patients with PAP. Radiographically, bilateral symmetric alveolar opacities located centrally in the mid and lower lung zones result in a “bat-wing” distribution. HRCT shows a ground-glass opacification and thickened intralobular structures and interlobular septa. Whole-lung lavage(s) through a double-lumen endotracheal tube provides relief to many patients with dyspnea or progressive hypoxemia and may provide long-term benefit.

PULMONARY LYPHANGIOLEIOMYOMATOSIS

Pulmonary LAM is a rare condition that afflicts premenopausal women and should be suspected in young

women with “emphysema,” recurrent pneumothorax, or chylous pleural effusion. It is often misdiagnosed as asthma or chronic obstructive pulmonary disease. Pathologically, LAM is characterized by the proliferation of atypical pulmonary interstitial smooth muscle and cyst formation. The immature-appearing smooth muscle cells react with monoclonal antibody HMB45, which recognizes a 100-kDa glycoprotein (gp100) originally found in human melanoma cells. Whites are affected much more commonly than members of other racial groups. The disease accelerates during pregnancy and abates after oophorectomy. Common complaints at presentation are dyspnea, cough, and chest pain. Hemoptysis may be life threatening. Spontaneous pneumothorax occurs in 50% of patients; it may be bilateral and necessitate pleurodesis. Meningioma and renal angiomyolipomas (hamartomas), characteristic findings in the genetic disorder tuberous sclerosis, are also common in patients with LAM. Chylothorax, chyloperitoneum (chylous ascites), chyluria, and chylopericardium are other complications. Pulmonary function testing usually reveals an obstructive or mixed obstructive-restrictive pattern, and gas exchange is often abnormal. HRCT shows thin-walled cysts surrounded by normal lung without zonal predominance. Progression is common, with a median survival of 8–10 years from diagnosis. Progesterone (10 mg/d) and luteinizing hormone-releasing hormone analogues have been used. Oophorectomy is no longer recommended and estrogen-containing drugs should be discontinued. Lung transplantation offers the only hope for cure despite reports of recurrent disease in the transplanted lung.

SYNDROMES OF INTERSTITIAL LUNG DISEASE WITH DIFFUSE ALVEOLAR HEMORRHAGE

Injury to arterioles, venules, and the alveolar septal (alveolar wall or interstitial) capillaries can result in hemoptysis secondary to disruption of the alveolar-capillary basement membrane. This results in bleeding into the alveolar spaces, which characterizes DAH. Pulmonary capillaritis, characterized by a neutrophilic infiltration of the alveolar septae, may lead to necrosis of these structures, loss of capillary structural integrity, and the pouring of red blood cells into the alveolar space. Fibrinoid necrosis of the interstitium and red blood cells within the interstitial space are sometimes seen. Bland pulmonary hemorrhage (i.e., DAH without inflammation of the alveolar structures) may also occur.

The clinical onset is often abrupt, with cough, fever, and dyspnea. Severe respiratory distress requiring ventilatory support may be evident at initial presentation. Although hemoptysis is expected, it can be absent at the time of presentation in one-third of the cases. For patients without hemoptysis, new alveolar opacities, a decreasing hemoglobin level, and hemorrhagic BAL fluid point to the diagnosis. The chest radiograph is nonspecific and most commonly

shows new patchy or diffuse alveolar opacities. Recurrent episodes of DAH may lead to pulmonary fibrosis, resulting in interstitial opacities on the chest radiograph. An elevated white blood cell count and decreasing hematocrit are frequent. Evidence for impaired renal function caused by focal segmental necrotizing glomerulonephritis, usually with crescent formation, may also be present.

Varying degrees of hypoxemia may occur and are often severe enough to require ventilatory support. The DL_{CO} may be increased, resulting from the increased hemoglobin within the alveoli compartment. Evaluation of either lung or renal tissue by immunofluorescent techniques indicates an absence of immune complexes (pauci-immune) in Wegener's granulomatosis, microscopic polyangiitis pauci-immune glomerulonephritis, and isolated pulmonary capillaritis. A granular pattern is found in the CTDs, particularly SLE, and a characteristic linear deposition is found in Goodpasture's syndrome. Granular deposition of IgA-containing immune complexes is present in Henoch-Schönlein purpura.

The mainstay of therapy for the DAH associated with systemic vasculitis, CTD, Goodpasture's syndrome, and isolated pulmonary capillaritis is IV methylprednisolone, 0.5–2.0 g/d in divided doses for up to 5 days, followed by a gradual tapering and then maintenance on an oral preparation. Prompt initiation of therapy is important, particularly in the face of renal insufficiency, because early initiation of therapy has the best chance of preserving renal function. The decision to start other immunosuppressive therapy (cyclophosphamide or azathioprine) acutely depends on the severity of illness.

Goodpasture's Syndrome

Pulmonary hemorrhage and glomerulonephritis are features in most patients with this disease. Autoantibodies to renal glomerular and lung alveolar basement membranes are present. This syndrome can present and recur as DAH without an associated glomerulonephritis. In such case, circulating anti-basement membrane antibody is often absent, and the only way to establish the diagnosis is by demonstrating linear immunofluorescence in lung tissue. The underlying histology may be bland hemorrhage or DAH associated with capillaritis. Plasmapheresis has been recommended as adjunctive treatment.

INHERITED DISORDERS ASSOCIATED WITH INTERSTITIAL LUNG DISEASES

Pulmonary opacities and respiratory symptoms typical of ILD can develop in related family members and in individuals with several inherited diseases. These include the phakomatoses; tuberous sclerosis and neurofibromatosis; and the lysosomal storage diseases, Niemann-Pick disease and Gaucher's disease. The Hermansky-Pudlak syndrome is an autosomal recessive disorder in which granulomatous colitis and ILD may occur. It is characterized

202 by oculocutaneous albinism; bleeding diathesis secondary to platelet dysfunction; and the accumulation of a chromolipid, lipofuscin material in cells of the reticuloendothelial system. A fibrotic pattern is found on lung biopsy, but the alveolar macrophages may contain cytoplasmic ceroid-like inclusions.

INTERSTITIAL LUNG DISEASE WITH A GRANULOMATOUS RESPONSE IN LUNG TISSUE OR VASCULAR STRUCTURES

Inhalation of organic dusts, which cause hypersensitivity pneumonitis, or of inorganic dust, such as silica, which elicits a granulomatous inflammatory reaction leading to ILD, produces diseases of known etiology (see Table 19-1) that are discussed in Chaps. 9 and 10. Sarcoidosis is prominent among granulomatous diseases of unknown cause in which ILD is an important feature.

Granulomatous Vasculitides

The granulomatous vasculitides are characterized by pulmonary angiitis (i.e., inflammation and necrosis of blood vessels) with associated granuloma formation (i.e., infiltrates of lymphocytes, plasma cells, epithelioid cells, or histiocytes, with or without the presence of multinucleated giant cells, sometimes with tissue necrosis). The lungs are almost always involved, although any organ system may be affected. Wegener's granulomatosis and allergic angiitis and granulomatosis (Churg-Strauss syndrome) primarily affect the lungs but are associated with a systemic vasculitis as well. The granulomatous vasculitides generally limited to the lungs include necrotizing sarcoid granulomatosis and benign lymphocytic angiitis and granulomatosis. Granulomatous infection and pulmonary angiitis due to irritating embolic material (e.g., talc) are important known causes of pulmonary vasculitis.

LYMPHOCYTIC INFILTRATIVE DISORDERS

This group of disorders features lymphocyte and plasma cell infiltration of the lung parenchyma. The disorders either are benign or can behave as low-grade lymphomas. Included are angioimmunoblastic lymphadenopathy with dysproteinemia, a rare lymphoproliferative disorder characterized by diffuse lymphadenopathy, fever, hepatosplenomegaly, and hemolytic anemia, with ILD in some cases.

Lymphocytic Interstitial Pneumonitis

This rare form of ILD occurs in adults, some of whom have an autoimmune disease or dysproteinemia. It has been reported in patients with Sjögren's syndrome and HIV infection.

Lymphomatoid Granulomatosis

This multisystem disorder of unknown etiology is an angiocentric malignant (T cell) lymphoma characterized

by a polymorphic lymphoid infiltrate, an angiitis, and granulomatosis. Although it may affect virtually any organ, it is most frequently characterized by pulmonary, skin, and central nervous system involvement.

BRONCHOCENTRIC GRANULOMATOSIS

Rather than a specific clinical entity, bronchocentric granulomatosis (BG) is a descriptive histologic term that describes an uncommon and nonspecific pathologic response to a variety of airway injuries. Evidence suggests that BG is caused by a hypersensitivity reaction to *Aspergillus* spp. or other fungi in patients with asthma. About half of the patients described have chronic asthma with severe wheezing and peripheral blood eosinophilia. In patients with asthma, BG probably represents one pathologic manifestation of allergic bronchopulmonary aspergillosis or another allergic mycosis. In patients without asthma, BG has been associated with RA and a variety of infections, including tuberculosis, echinococcosis, histoplasmosis, coccidioidomycosis, and nocardiosis. The chest roentgenogram reveals irregularly shaped nodular or mass lesions with ill-defined margins, which are usually unilateral and solitary, with upper lobe predominance. Glucocorticoids are the treatment of choice, often with excellent outcome, although recurrences may occur as therapy is tapered or stopped.

GLOBAL CONSIDERATIONS



Limited epidemiologic data exist describing the prevalence or incidence of ILD in the general population. With a few exceptions (e.g., sarcoidosis, certain occupational and environmental exposures), there appear to be no significant differences in the prevalence or incidence of ILD among various populations. For sarcoidosis, there are important environmental, racial, and genetic differences.

FURTHER READINGS

- AMERICAN THORACIC SOCIETY/EUROPEAN RESPIRATORY SOCIETY: Idiopathic pulmonary fibrosis: Diagnosis and treatment. International consensus statement. *Am J Respir Crit Care Med* 161:646, 2000
- : International multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 165:277, 2002
- COLLARD HR et al: Acute exacerbations of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 176:636, 2007
- EL-ZAMMAR OA, KATZENSTEIN AL: Pathological diagnosis of granulomatous lung disease: A review. *Histopathology* 50:289, 2007
- FREEMER M, KING TE JR: Connective tissue disease, in *Interstitial Lung Diseases*, 4th ed, MI Schwarz, TE King, Jr (eds). Hamilton, Ontario, BC Decker, 2003, pp 535-598
- KINDER BW et al: Idiopathic nonspecific interstitial pneumonia: Lung manifestation of undifferentiated connective tissue disease? *Am J Respir Crit Care Med* 176:691, 2007

KING TE JR: Clinical advances in the diagnosis and therapy of the interstitial lung diseases. *Am J Respir Crit Care Med* 172:268, 2005

MARTINEZ FJ: Idiopathic interstitial pneumonias: Usual interstitial pneumonia versus nonspecific interstitial pneumonia. *Proc Am Thorac Soc* 3:81, 2006

RAGHU G et al: Idiopathic pulmonary fibrosis: Evidence based guidelines for diagnosis and management a joint ATS/ERS/JRS/ALAT statement. *Am J Respir Crit Care Med*, in press, 2010

SELMAN M et al: Idiopathic pulmonary fibrosis: Prevailing and evolving hypotheses about its pathogenesis and implications for therapy. *Ann Intern Med* 134:136, 2001

SEYMOUR JF, PRESNEILL JJ: Pulmonary alveolar proteinosis: Progress in the first 44 years. *Am J Respir Crit Care Med* 166:215, 2002

TRAVIS WD et al: Idiopathic nonspecific interstitial pneumonia: Report of an American Thoracic Society Project. *Am J Respir Crit Care Med* 177:1338, 2008

WALTER N et al: Current perspectives on the treatment of pulmonary fibrosis. *Proc Am Thorac Soc* 3:330, 2006



CHAPTER 20

DEEP VENOUS THROMBOSIS AND PULMONARY THROMBOEMBOLISM

Samuel Z. Goldhaber

Epidemiology	204
Pathophysiology	205
Diagnosis	205
Prevention of Venous Thromboembolism	213
■ Further Readings	214

EPIDEMIOLOGY

A quiet revolution has occurred in the field of venous thromboembolism (VTE), which encompasses deep venous thrombosis (DVT) and pulmonary embolism (PE). VTE is no longer an orphan disease. Its adverse public health impact has been acknowledged in the United States by the National Quality Forum, The Joint Commission, the National Comprehensive Cancer Network, and the Surgeon General's Office. Public service announcements have educated laypersons on the definition and medical consequences of DVT and PE, along with risk factors and warning signs. VTE-related deaths in the United States are estimated at 300,000 annually: 7% diagnosed with VTE and treated, 34% sudden fatal PE, and 59% as undetected PE. Approximately two-thirds of symptomatic VTE events are hospital acquired, and the remainder are community acquired. Residents of skilled nursing facilities are especially vulnerable. The most recent estimates of hospitalized patients at risk for VTE in the United States total 13.4 million patients annually: 5.8 million surgical patients at moderate to high risk and 7.6 million medical patients with comorbidities such as heart failure, cancer, and stroke. These new data provide the rationale for changing the prophylaxis paradigm from voluntary to mandatory compliance with guidelines to prevent VTE among hospitalized patients.

VTE is also a major European health problem, with an estimated 370,000 per year PE-related deaths, when

data in France, Germany, Spain, Italy, Sweden, and the United Kingdom are combined. The estimated direct cost for VTE-associated care in Europe exceeds 3 billion Euros per year.

Although DVT and PE encompass one disease entity, VTE, there are important differences. DVT occurs about three times more often than PE. The major adverse outcome of DVT alone, without PE, is the development of *postphlebotic syndrome*, which occurs in more than half of patients with DVT. Postphlebotic syndrome is a late adverse effect of DVT that is caused by permanent damage to the venous valves of the leg, which become incompetent and permit abnormal exudation of interstitial fluid from the venous system. It may not become clinically manifest until several years after the initial DVT. There is no effective medical therapy for this condition, which impairs quality of life and disables. Most patients describe chronic ankle swelling and calf swelling and aching, especially after prolonged standing. In its most severe form, postphlebotic syndrome causes skin ulceration, especially in the medial malleolus of the leg. PE can be fatal or can cause chronic thromboembolic pulmonary hypertension, with breathlessness at rest or with mild exertion. Patients with PE are more likely to experience recurrent VTE than patients with DVT alone.

Genetic and acquired factors contribute to the likelihood of VTE. The two most common autosomal dominant genetic mutations are the factor V Leiden and the

prothrombin gene mutations. However, only a minority of patients with VTE have identifiable predisposing genetic factors. The majority of patients with predisposing genetic factors will not develop clinical evidence of clotting. Acquired predispositions include long-haul air travel; obesity; cigarette smoking; use of oral contraceptives; pregnancy; postmenopausal hormone replacement; surgery; trauma; and medical conditions such as antiphospholipid antibody syndrome, cancer, systemic arterial hypertension, and chronic obstructive pulmonary disease. Thrombophilia contributes to the risk of venous thrombosis, often because of an inherited risk factor in combination with an acquired predisposition.

PATHOPHYSIOLOGY

Embolization

When venous thrombi dislodge from their site of formation, they embolize to the pulmonary arterial circulation or, paradoxically, to the arterial circulation through a patent foramen ovale or atrial septal defect. About half of patients with pelvic vein thrombosis or proximal leg DVT develop PE, which is usually asymptomatic. Isolated calf vein thrombi pose a much lower risk of PE, but they are the most common source of paradoxical embolism. These tiny thrombi can cross a small patent foramen ovale or atrial septal defect, unlike larger, more proximal leg thrombi. With increased use of chronic indwelling central venous catheters for hyperalimentation and chemotherapy, as well as more frequent insertion of permanent pacemakers and internal cardiac defibrillators, upper extremity venous thrombosis is becoming a more common problem. These thrombi rarely embolize and cause PE.

Physiology

The most common gas exchange abnormalities are hypoxemia (decreased arterial PO_2) and an increased alveolar-arterial O_2 tension gradient, which represents the inefficiency of O_2 transfer across the lungs. Anatomic dead space increases because breathed gas does not enter gas exchange units of the lung. Physiologic dead space increases because ventilation to gas exchange units exceeds venous blood flow through the pulmonary capillaries.

Other pathophysiological abnormalities include:

1. *Increased pulmonary vascular resistance* caused by vascular obstruction or platelet secretion of vasoconstricting neurohumoral agents such as serotonin. Release of vasoactive mediators can produce ventilation-perfusion mismatching at sites remote from the embolus, thereby accounting for a potential discordance between a small PE and a large alveolar-arterial O_2 gradient.
2. *Impaired gas exchange* caused by increased alveolar dead space from vascular obstruction, hypoxemia from

alveolar hypoventilation relative to perfusion in the nonobstructed lung, right-to-left shunting, and impaired carbon monoxide transfer because of loss of gas exchange surface.

3. *Alveolar hyperventilation* caused by reflex stimulation of irritant receptors
4. *Increased airway resistance* caused by constriction of airways distal to the bronchi
5. *Decreased pulmonary compliance* caused by lung edema, lung hemorrhage, or loss of surfactant

Right Ventricular Dysfunction

Progressive right heart failure is the usual cause of death from PE. In the International Cooperative Pulmonary Embolism Registry (ICOPER), the presence of right ventricular (RV) dysfunction on baseline echocardiography of PE patients who presented with a systolic blood pressure >90 mmHg was associated with a doubling of the 3-month mortality rate. As pulmonary vascular resistance increases, RV wall tension increases and causes further RV dilatation and dysfunction. RV contraction continues even after the left ventricle (LV) starts relaxing at end-systole. Consequently, the interventricular septum bulges into and compresses an intrinsically normal LV. Diastolic LV impairment develops, attributable to septal displacement, and results in reduced LV distensibility and impaired LV filling during diastole. Increased RV wall tension also compresses the right coronary artery, diminishes subendocardial perfusion, limits myocardial oxygen supply, and may precipitate myocardial ischemia and RV infarction. Underfilling of the LV may lead to a decrease in LV cardiac output and systemic arterial pressure, thereby provoking myocardial ischemia because of compromised coronary artery perfusion. Eventually, circulatory collapse and death may ensue.

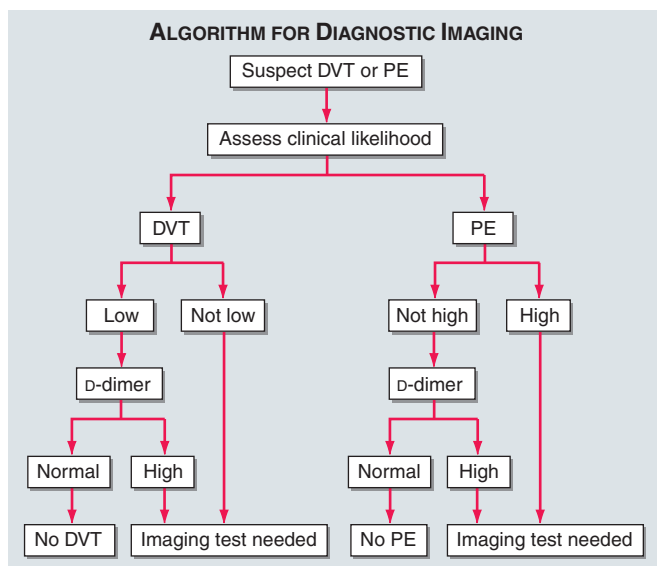
DIAGNOSIS

Clinical Evaluation

The diagnosis is challenging because the symptoms and signs are nonspecific. VTE mimics other illnesses, and PE is known as “the great masquerader.”

For patients who have DVT, the most frequent history is a cramp in the lower calf that persists for several days and that becomes more uncomfortable as time progresses. For patients who have PE, the most frequent history is unexplained breathlessness.

When evaluating patients with possible DVT, the initial task is to decide whether the clinical likelihood for DVT is low. When evaluating patients with possible PE, the initial task is to decide whether the clinical likelihood is high. Patients with a low likelihood of DVT or a non-high (i.e., low or moderate) likelihood of PE can undergo initial diagnostic evaluation with D-dimer testing alone (see later) without obligatory imaging tests (Fig. 20-1).

**FIGURE 20-1**

How to decide whether diagnostic imaging is needed. For assessment of clinical likelihood, see Table 20-1. DVT, deep venous thrombosis; LDH, PE, pulmonary embolism.

Point score methods are useful for estimating the clinical likelihood of DVT and PE (Table 20-1).

Clinical Syndromes

The differential diagnosis is critical because not all leg pain is caused by DVT, and not all dyspnea is caused by PE (Table 20-2). Sudden, severe calf discomfort suggests a ruptured Baker's cyst. Fever and chills usually herald cellulitis rather than DVT, though DVT may be present concomitantly. Physical findings, if present at all, may simply consist of mild palpation discomfort in the lower calf. Massive DVT is much easier to recognize. The patient presents with severe thigh swelling and marked tenderness when the inguinal area and common femoral vein are palpated. In extreme cases, patients will be unable to walk or may require a cane, crutches, or walker.

If the leg is diffusely edematous, DVT is unlikely. Much more common is an acute exacerbation of venous insufficiency caused by postphlebotic syndrome. Upper extremity venous thrombosis may present with asymmetry in the supraclavicular fossa or in the circumference of the upper arms. A prominent superficial venous pattern may be evident on the anterior chest wall.

Patients with *massive PE* present with systemic arterial hypotension and usually have an anatomically widespread thromboembolism. Those with *moderate to large PE* have RV hypokinesis on echocardiography but normal systemic arterial pressure. Patients with *small to moderate PE* have both normal right heart function and normal systemic arterial pressure. They have an excellent prognosis with adequate anticoagulation.

TABLE 20-1

CLINICAL DECISION RULES

Low Clinical Likelihood of Deep Venous Thrombosis if the Point Score Is Zero or Less

CLINICAL VARIABLE	SCORE
Active cancer	1
Paralysis, paresis, or recent cast	1
Bedridden for >3 days; major surgery <12 weeks	1
Tenderness along distribution of deep veins	1
Entire leg swelling	1
Unilateral calf swelling >3 cm	1
Pitting edema	1
Collateral superficial nonvaricose veins	1
Alternative diagnosis at least as likely as DVT	-2

High Clinical Likelihood of Pulmonary Embolism if the Point Score Exceeds 4

CLINICAL VARIABLE	SCORE
Signs and symptoms of DVT	3.0
Alternative diagnosis less likely than PE	3.0
Heart rate >100 bpm	1.5
Immobilization >3 days; surgery within 4 weeks	1.5
Prior PE or DVT	1.5
Hemoptysis	1.0
Cancer	1.0

Note: DVT, deep venous thrombosis; PE, pulmonary embolism.

The presence of *pulmonary infarction* usually indicates a small PE but one that is exquisitely painful because it lodges peripherally, near the innervation of pleural nerves. Pleuritic chest pain is more common with small, peripheral emboli. However, larger, more central PEs can occur concomitantly with peripheral pulmonary infarction.

Nonthrombotic PE may be easily overlooked. Possible etiologies include fat embolism after blunt trauma and

TABLE 20-2

DIFFERENTIAL DIAGNOSIS

DVT
Ruptured Baker's cyst
Cellulitis
Postphlebotic syndrome or venous insufficiency
PE
Pneumonia, asthma, chronic obstructive pulmonary disease
Congestive heart failure
Pericarditis
Pleurisy: "viral syndrome," costochondritis, musculoskeletal discomfort
Rib fracture, pneumothorax
Acute coronary syndrome
Anxiety

Note: DVT, deep venous thrombosis; PE, pulmonary embolism.

long bone fractures, tumor embolism, bone marrow, or air embolism. Cement embolism and bony fragment embolism can occur after total hip or knee replacement. IV drug users may inject themselves with a wide array of substances, such as hair, talc, or cotton. *Amniotic fluid embolism* occurs when fetal membranes leak or tear at the placental margin. Pulmonary edema in this syndrome is probably caused by alveolar capillary leakage.

Dyspnea is the most frequent symptom of PE, and tachypnea is its most frequent sign. Whereas dyspnea, syncope, hypotension, or cyanosis indicates a massive PE, pleuritic pain, cough, or hemoptysis often suggests a small embolism located distally near the pleura. On physical examination, young and previously healthy individuals may appear anxious but otherwise seem deceptively well, even with an anatomically large PE. They may only have dyspnea with moderate exertion. They often lack “classic” signs such as tachycardia, low-grade fever, neck vein distension, or an accentuated pulmonic component of the second heart sound. Sometimes paradoxical bradycardia occurs.

Some patients have occult PE and an overt coexisting illness such as pneumonia or heart failure. In such circumstances, clinical improvement often fails to occur despite standard medical treatment of the concomitant illness. This situation can serve as a clinical clue to the possible coexistence of PE.

Nonimaging Diagnostic Modalities

Nonimaging tests are best used in combination with a clinical likelihood of DVT or PE (Fig. 20-2).

Blood Tests

The quantitative *plasma D-dimer enzyme-linked immunosorbent assay (ELISA)* increases in the presence of DVT or PE because of plasmin’s breakdown of fibrin. Elevation of D-dimer indicates endogenous although often clinically ineffective thrombolysis. The sensitivity of the D-dimer is greater than 80% for DVT (including isolated calf DVT) and greater than 95% for PE. The D-dimer is less sensitive for DVT than PE because the DVT thrombus size is smaller. The D-dimer is a useful “rule out” test. It is normal (<500 ng/mL) in more than 95% of patients without PE. In patients with low clinical suspicion of DVT, it is normal in more than 90% without DVT.

The D-dimer assay is not specific. Levels increase in patients with myocardial infarction, pneumonia, sepsis, cancer, the postoperative state, and during the second or third trimester of pregnancy. Therefore, it rarely has a useful role among hospitalized patients because their D-dimers are frequently elevated because of some systemic illness.

Contrary to classic teaching, *arterial blood gases* lack diagnostic utility for PE, even though both the PO_2 and PCO_2 often decrease. Among patients suspected of PE, neither the room air arterial PO_2 nor calculation of the



FIGURE 20-2

Acute deep venous thrombosis (DVT) on venous ultrasound examination. The vein is not compressible, and thrombus (far left arrow) is visualized directly in the deep venous system. DFV, deep femoral vein (synonymous with profunda femoral vein); SFV, superficial femoral vein (which is a deep vein despite the terminology “superficial”). (From the personal collection of Samuel Z. Goldhaber, MD, with permission.)

alveolar-arterial O_2 gradient can reliably differentiate or triage patients who actually have PE at angiography.

Elevated Cardiac Biomarkers

Serum troponin levels increase in RV microinfarction. Myocardial stretch often results in elevation of brain natriuretic peptide or NT-pro-brain natriuretic peptide. Elevated cardiac biomarkers predict an increase in major complications and mortality from PE.

Electrocardiography

The most cited abnormality, in addition to sinus tachycardia, is the S1Q3T3 sign: an S wave in lead I, Q wave in lead III, and inverted T wave in lead III. This finding is relatively specific but insensitive. Perhaps the most frequent abnormality is T-wave inversion in leads V_1 to V_4 .

Noninvasive Imaging Modalities

Venous Ultrasonography

Ultrasonography of the deep venous system (Table 20-3) relies on loss of vein compressibility as the primary criterion for DVT. When a normal vein is imaged in cross-section, it readily collapses with gentle manual pressure from the ultrasound transducer. This creates the illusion of a “wink.” With acute DVT, the vein loses its compressibility because of passive distension by acute thrombus. The diagnosis of acute DVT is even more secure when thrombus is directly visualized. It appears homogeneous and has low echogenicity (Fig. 20-2). The vein itself often appears mildly dilated, and collateral channels may be absent.

ULTRASONOGRAPHY OF THE DEEP LEG VEINS**Criteria for Establishing the Diagnosis of Acute Deep Venous Thrombosis**

Lack of vein compressibility (the principal criterion)
 Vein does not “wink” when gently compressed in cross-section
 Failure to appose the walls of the vein because of passive distension

Direct Visualization of Thrombus

Homogenous
 Low echogenicity

Abnormal Doppler Flow Dynamics

Normal response: calf compression augments Doppler flow signal and confirms vein patency proximal and distal to Doppler
 Abnormal response: flow blunted rather than augmented with calf compression

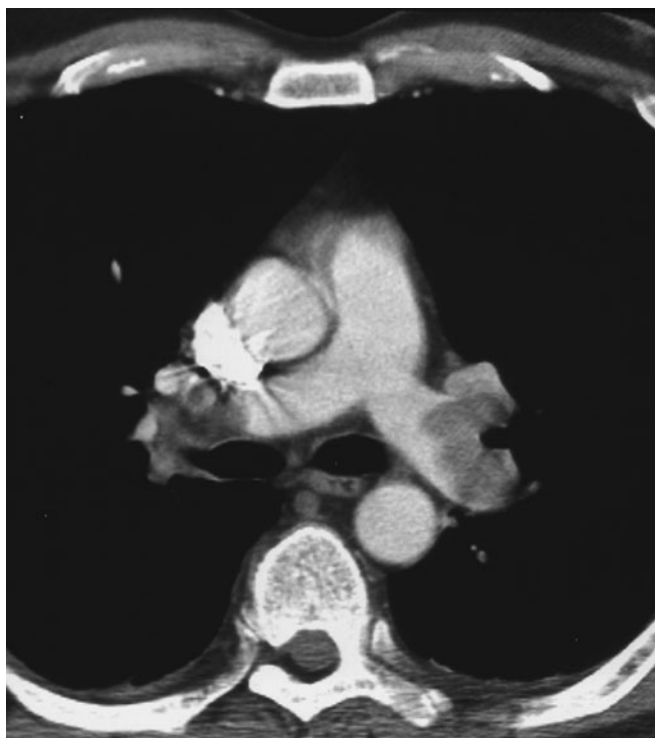
Venous flow dynamics can be examined with Doppler imaging. Normally, manual calf compression causes augmentation of the Doppler flow pattern. Loss of normal respiratory variation is caused by obstructing DVT or by any obstructive process within the pelvis. Because DVT and PE are so closely related and are both treated with anticoagulation (see later), confirmed DVT is usually an adequate surrogate for PE. In contrast, normal venous ultrasonography results do not exclude PE. The majority of patients with PE have no imaging evidence of DVT, probably because the clot has already embolized to the lung or is in the pelvic veins, where ultrasonography is usually inadequate. In patients without DVT, the ultrasound examination may identify other reasons for leg discomfort such as a Baker’s cyst (also known as a popliteal or synovial cyst) or a hematoma. For patients with a technically poor or nondiagnostic venous ultrasonography examination, alternative imaging modalities for DVT, such as CT or MRI, should be considered.

Chest Roentgenography

A normal or near-normal chest x-ray in a dyspneic patient often occurs in PE. Well-established abnormalities include focal oligemia (Westermark’s sign), a peripheral wedged-shaped density above the diaphragm (Hampton’s hump), or an enlarged right descending pulmonary artery (Palla’s sign).

Chest Computed Tomography

CT of the chest with IV contrast is the principal imaging test for the diagnosis of PE (Fig. 20-3). Multidetector-row spiral CT acquires all chest images with ≤ 1 mm resolution during a short breath hold. This generation of CT scanners can image small peripheral emboli. Sixth-order

**FIGURE 20-3**

Large bilateral proximal pulmonary embolism on chest CT after radical prostatectomy.

branches can be visualized with resolution superior to conventional invasive contrast pulmonary angiography. The CT scan also obtains excellent images of the RV and LV and can be used for a risk stratification as well as a diagnostic tool. In patients with PE, RV enlargement on chest CT indicates a fivefold increased likelihood of death within the next 30 days compared with PE patients with normal RV size on chest CT. When imaging is continued below the chest to the knee, pelvic and proximal leg DVT can also be diagnosed by CT scanning. In patients without PE, the lung parenchymal images may establish alternative diagnoses not apparent on chest x-ray that explain the presenting symptoms and signs, such as pneumonia, emphysema, pulmonary fibrosis, pulmonary mass, or aortic pathology. Sometimes asymptomatic early-stage lung cancer is diagnosed incidentally.

Lung Scanning

Lung scanning is now a second-line diagnostic test for PE. It is mostly used for patients who cannot tolerate IV contrast. Small particulate aggregates of albumin labeled with a gamma-emitting radionuclide are injected IV and are trapped in the pulmonary capillary bed. The perfusion scan defect indicates absent or decreased blood flow, possibly caused by PE. Ventilation scans, obtained with radiolabeled inhaled gases such as xenon or krypton, improve the specificity of the perfusion scan. Abnormal ventilation scans indicate abnormal nonventilated lung,

providing possible explanations for perfusion defects other than acute PE, such as asthma or chronic obstructive pulmonary disease. A high probability scan for PE is defined as having two or more segmental perfusion defects in the presence of normal ventilation.

The diagnosis of PE is very unlikely in patients with normal and near-normal scans but is about 90% certain in patients with high-probability scans. Unfortunately, most patients have nondiagnostic scans, and fewer than 50% of patients with angiographically confirmed PE have a high-probability scan. As many as 40% of patients with high clinical suspicion for PE and “low-probability” scans do, in fact, have PE at angiography.

Contrast-Enhanced Magnetic Resonance Imaging

When ultrasonography is equivocal, MR venography is an excellent imaging modality to diagnose DVT. MR uses a gadolinium contrast agent, which, unlike iodinated contrast agents used in venography and CT angiography, is not nephrotoxic. MRI should be considered for suspected DVT or PE patients with renal insufficiency or contrast dye allergy. MR pulmonary angiography detects large proximal PE but is not reliable for smaller segmental and subsegmental PE.

Echocardiography

Echocardiography is *not* a reliable diagnostic imaging tool for acute PE because most patients with PE have normal echocardiograms. However, echocardiography is a very useful diagnostic tool for detecting conditions that might mimic PE, such as acute myocardial infarction, pericardial tamponade, or aortic dissection.

Transthoracic echocardiography rarely images a thrombus directly. The best-known indirect sign of PE on transthoracic echocardiography is McConnell’s sign, which is hypokinesis of the RV free wall with normal motion of the RV apex.

Transesophageal echocardiography should be considered when CT scanning facilities are not available or when a patient has renal failure or severe contrast allergy that precludes administration of contrast despite premedication with high-dose steroids. This imaging modality can directly visualize large proximal PE.

Invasive Diagnostic Modalities

Pulmonary Angiography

Chest CT with contrast (see earlier) has virtually replaced invasive pulmonary angiography as a diagnostic test. Invasive catheter-based diagnostic testing is reserved for patients with technically unsatisfactory chest CTs or for those in whom an interventional procedure such as catheter-directed thrombolysis or embolectomy is planned. A definitive diagnosis of PE depends upon visualization of an intraluminal filling defect in more than one projection. Secondary signs of PE include abrupt occlusion (“cut-off”)

of vessels; segmental oligemia or avascularity; a prolonged arterial phase with slow filling; or tortuous, tapering peripheral vessels.

Contrast Phlebography

Venous ultrasonography has virtually replaced contrast phlebography as the diagnostic test for suspected DVT.

Integrated Diagnostic Approach

An integrated diagnostic approach (see Fig. 20-1) streamlines the workup of suspected DVT and PE (Fig. 20-4).

Rx Treatment: DEEP VEIN THROMBOSIS

PRIMARY THERAPY VERSUS SECONDARY PREVENTION Primary therapy consists of clot dissolution with thrombolysis or removal of PE by

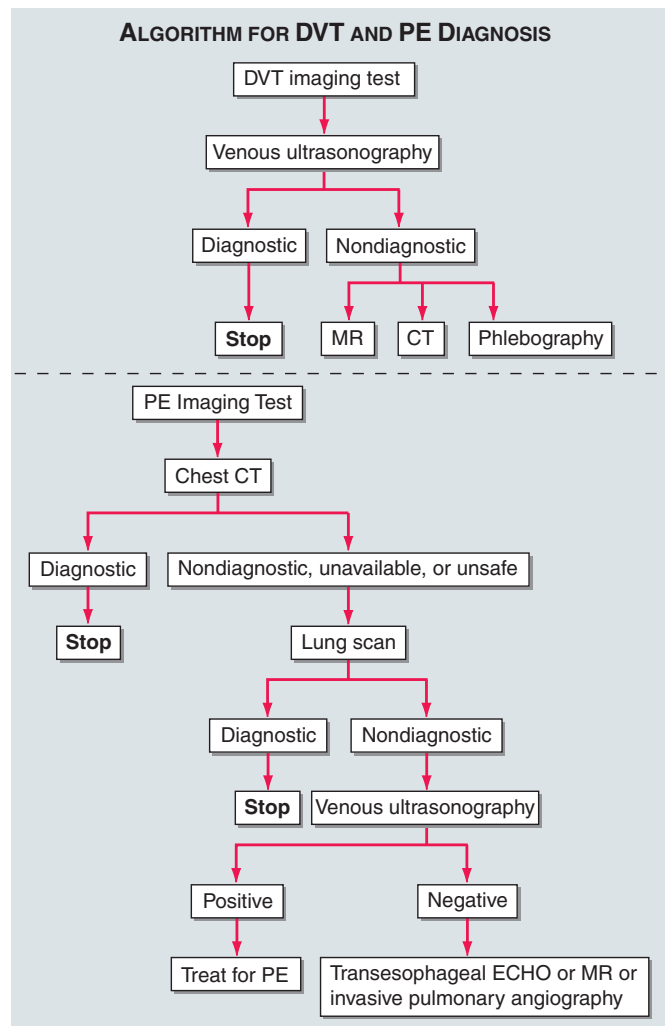


FIGURE 20-4 Imaging tests to diagnose deep venous thrombosis (DVT) and pulmonary embolism (PE). ECHO, echocardiography.

embolectomy. Anticoagulation with heparin and warfarin or placement of an inferior vena caval filter (IVC) constitutes *secondary prevention* of recurrent PE rather than primary therapy.

RISK STRATIFICATION Rapid and accurate risk stratification is critical in determining optimal treatment strategy. The presence of hemodynamic instability, RV dysfunction, or elevation of the troponin level caused by RV microinfarction can identify high-risk patients. Detection of RV hypokinesis on echocardiography is the most widely used approach to risk stratification. However, RV enlargement on chest CT also predicts an increased mortality rate from PE. The combination of RV dysfunction plus elevated biomarkers such as troponin portends an especially ominous prognosis.

Primary therapy should be reserved for patients at high risk of an adverse clinical outcome. When RV function remains normal in a hemodynamically stable patient, a good clinical outcome is highly likely with anticoagulation alone (Fig. 20-5).

MASSIVE PULMONARY EMBOLISM

Anticoagulation Anticoagulation is the foundation for successful treatment of DVT and PE (Table 20-4). Immediately effective anticoagulation is initiated with a parenteral drug: unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or fondaparinux. These parenteral drugs (see later) are continued as a transition or “bridge” to stable, long-term anticoagulation with a vitamin K antagonist (exclusively warfarin in the United States). The first dose of warfarin may be given as soon as several hours after the bridging anticoagulant if LMWH or fondaparinux is used. Otherwise, with UFH a therapeutic activated partial thromboplastin time (aPTT) must first be documented. Warfarin requires 5–7 days to achieve a therapeutic effect. During that period, the parenteral and oral agents are overlapped. After 5–7 days

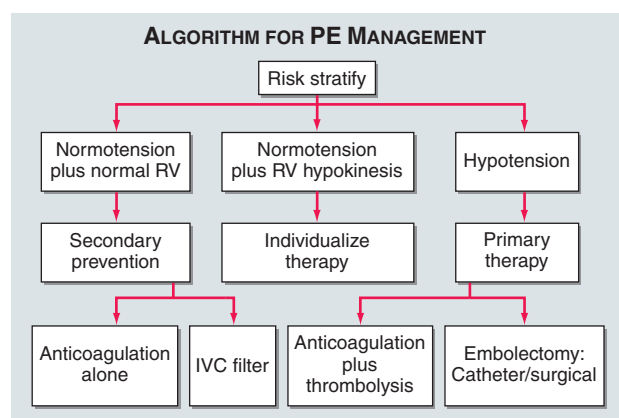


FIGURE 20-5

Acute management of pulmonary thromboembolism (PE). IVC, inferior vena caval; RV, right ventricular.

TABLE 20-4

ANTICOAGULATION OF VENOUS THROMBOEMBOLISM

Immediate Parenteral Anticoagulation

UFH, bolus and continuous infusion, to achieve aPTT two to three times the upper limit of the laboratory normal

or

Enoxaparin 1 mg/kg twice daily with normal renal function

or

Tinzaparin 175 U/kg once daily with normal renal function

or

Weight-based fondaparinux once daily; adjust for impaired renal function

Warfarin Anticoagulation

Usual start dose is 5–10 mg.

Titrate to INR, target 2.0–3.0.

Continue parenteral anticoagulation for a minimum of 5 days and until two sequential INR values, at least 1 day apart, return in the target range.

Note: aPTT, activated partial thromboplastin time; INR, International Normalized Ratio; UFH, unfractionated heparin.

of anticoagulation, residual thrombus begins to become endothelialized in the vein or pulmonary artery. However, anticoagulants do *not* directly dissolve thrombus that already exists.

Unfractionated Heparin UFH anticoagulates by binding to and accelerating the activity of antithrombin III, thus preventing additional thrombus formation and permitting endogenous fibrinolytic mechanisms to lyse clot that has already formed. UFH is dosed to achieve a target aPTT that is two to three times the upper limit of the laboratory normal. This is usually equivalent to an aPTT of 60–80 s. For UFH, a typical IV bolus is 5000–10,000 units followed by a continuous infusion of 1000–1500 units/h. Nomograms based on a patient’s weight may assist in adjusting the dose of heparin. The most popular nomogram uses an initial bolus of 80 units/kg followed by an initial infusion rate of 18 units/kg per hour.

The major advantage of UFH is that it has a short half-life. Its anticoagulant effect abates after several hours. This is especially useful if the patient will undergo an invasive procedure such as surgical embolectomy.

The major disadvantage of UFH is that achieving the target aPTT can be difficult and may require repeated blood sampling and heparin dose adjustment every 4–6 h. Furthermore, by using UFH, patients are at risk of developing heparin-induced thrombocytopenia (HIT).

Low-Molecular-Weight Heparins These fragments of UFH exhibit less binding to plasma proteins

and endothelial cells and consequently have greater bioavailability, a more predictable dose response, and a longer half-life than UFH. No monitoring or dose adjustment is needed unless the patient is markedly obese or has renal insufficiency.

Enoxaparin 1 mg/kg twice daily and *tinzaparin* 175 units/kg once daily have received U.S. Food and Drug Administration (FDA) approval for treatment of patients who present with DVT. The weight-adjusted doses must be adjusted downward in those with renal insufficiency because the kidneys excrete LMWH.

Fondaparinux Fondaparinux, an anti-Xa pentasaccharide, is administered by once-daily subcutaneous injection and has been approved by the FDA to treat patients with DVT and PE. No laboratory monitoring is required. Patients weighing <50 kg receive 5 mg, patients weighing 50–100 kg receive 7.5 mg, and patients weighing >100 kg receive 10 mg. The dose must be adjusted downward for patients with renal dysfunction because the drug is excreted by the kidneys.

Warfarin This vitamin K antagonist prevents carboxylation activation of coagulation factors II, VII, IX, and X. The full effect of warfarin requires at least 5 days, even if the prothrombin time, used for monitoring, becomes elevated more rapidly. If warfarin is initiated as monotherapy during an acute thrombotic illness, a paradoxical exacerbation of hypercoagulability can increase the likelihood of thrombosis rather than prevent it. Overlapping UFH, LMWH, or fondaparinux with warfarin for at least 5 days can counteract the early procoagulant effect of unopposed warfarin.

Dosing In an average-sized adult, warfarin is usually initiated as a dose of 5 mg. Doses of 7.5 or 10 mg can be used in obese or large-framed young patients who are otherwise healthy. Patients who are malnourished or who have received prolonged courses of antibiotics are probably deficient in vitamin K and should receive smaller initial doses of warfarin, such as 2.5 mg. The prothrombin time is standardized with the International Normalized Ratio (INR), which assesses the anticoagulant effect of warfarin. The target INR is usually 2.5, with a range of 2.0–3.0.

The warfarin dose is titrated to achieve the target INR. Proper dosing is difficult because hundreds of drug–drug and drug–food interactions affect warfarin metabolism. Furthermore, variables such as increasing age and comorbidities such as systemic illness, malabsorption, and diarrhea reduce the warfarin-dosing requirement.

No reliable nomogram has been established to predict how individual patients will respond to warfarin. Therefore, dosing is adjusted according to an “educated guess.” Centralized anticoagulation clinics have improved the efficacy and safety of warfarin dosing. Based on a

meta-analysis of trials comparing anticoagulation clinic care versus self-monitoring, patients benefit if they can self-monitor their INR with a home point-of-care fingerstick machine. The subgroup with the best results also learns to self-adjust warfarin doses.

Pharmacogenomics may provide the gateway to rational dosing of warfarin. A recent discovery is that five polymorphisms of the vitamin K receptor gene explain 25% of the variance in warfarin dosing. These polymorphisms can stratify patients into low-, intermediate-, and high-dose warfarin groups. An additional 10% of dosing variance can be explained by allelic variants of the cytochrome P-450 enzyme 2C9. These mutations decrease warfarin dosing because they impair the metabolism of the S-enantiomer of warfarin. In the future, if rapid turnaround of genetic testing becomes possible, warfarin could be dosed according to specific pharmacogenomic profiles.

Complications of Anticoagulants The most important adverse effect of anticoagulation is hemorrhage. For life-threatening or intracranial hemorrhage caused by use of heparin or LMWH, protamine sulfate can be administered. There is no specific antidote for bleeding from fondaparinux.

Major bleeding from warfarin is traditionally managed with cryoprecipitate or fresh-frozen plasma (usually 2–4 units) to achieve rapid hemostasis. Recombinant human coagulation factor VIIa (rFVIIa), which is FDA approved for bleeding in patients with hemophilia, is widely used off label to manage catastrophic bleeding from warfarin. The optimal dose appears to be 40 µg/kg. The greatest risk of this therapy is rebound thromboembolism. For minor bleeding or to manage an excessively high INR in the absence of bleeding, a small 2.5-mg dose of oral vitamin K may be administered.

HIT and osteopenia are far less common with LMWH than with UFH. Thrombosis caused by use of HIT should be managed with a direct thrombin inhibitor—argatroban for patients with renal insufficiency or lepirudin for patients with hepatic failure.

In the setting of percutaneous coronary intervention, bivalirudin should be administered.

The most common nonbleeding side effect of warfarin is alopecia. A rare complication is warfarin-induced skin necrosis, which may be related to warfarin-induced reduction of protein C.

During pregnancy, warfarin should be avoided if possible because of warfarin embryopathy, which is most common with exposure during the sixth through twelfth weeks of gestation. However, women can take warfarin postpartum and breastfeed safely. Warfarin can also be administered safely during the second trimester.

Duration of Hospital Stay Patients with acute DVT who have good family and social support, a permanent

residence, a telephone, and no hearing or language impairment can often be managed as outpatients. They or a family member or a visiting nurse can administer a parenteral anticoagulant. Warfarin dosing can be titrated to the INR and adjusted on an outpatient basis.

Patients with acute PE, who traditionally have required 5 to 7-day hospital stays for IV heparin as a “bridge” to warfarin, can be considered for abbreviated hospitalization if they have an excellent prognosis. The latter are characterized by clinical stability, absence of chest pain or shortness of breath, normal RV size and function, and normal levels of cardiac biomarkers.

Duration of Anticoagulation Patients with PE after surgery or trauma ordinarily have a low rate of recurrence after 3–6 months of anticoagulation. For DVT isolated to an upper extremity or calf that has been provoked by surgery or trauma, 3 months of anticoagulation suffices. For provoked proximal leg DVT or PE, 6 months of anticoagulation is sufficient.

However, among patients with “idiopathic,” unprovoked DVT or PE, the recurrence rate is surprisingly high after cessation of anticoagulation. VTE that occurs during long-haul air travel is considered unprovoked.

Current American College of Chest Physicians (ACCP) guidelines recommend anticoagulation for an indefinite duration with a target INR between 2.0 and 3.0 for patients with idiopathic VTE. However, it is recommended that the intensity of anticoagulation be tailored to the patient’s risk of recurrent VTE versus risk of bleeding. For a patient at high risk of recurrent VTE (e.g., someone with multiple thrombophilic disorders) and a low risk of bleeding (e.g., young age and no comorbidities), I recommend standard-intensity anticoagulation. However, for a patient with a high bleeding risk (e.g., older age and a history of gastrointestinal bleeding), I advise low-intensity anticoagulation (INR, 1.5–2.0) after 6 months.

Several years ago, the presence of genetic mutations such as factor V Leiden or prothrombin gene mutation was thought to markedly increase the risk of recurrent VTE. Now, however, the clinical circumstances in which the DVT or PE occurs rather than underlying thrombophilia are considered much more important in deciding the risk of recurrence and the optimal duration of anticoagulation. However, patients with moderate or high levels of anticardiolipin antibodies probably warrant indefinite duration anticoagulation, even if the initial VTE was provoked by trauma or surgery.

INFERIOR VENA CAVAL FILTERS The two principal indications for insertion of an IVC filter are active bleeding that precludes anticoagulation and recurrent venous thrombosis despite intensive anticoagulation. Prevention of recurrent PE in patients with right heart failure who are not candidates for fibrinolysis

or prophylaxis of extremely high-risk patients are “softer” indications for filter placement. The filter itself may fail by permitting the passage of small- to medium-sized clots. Large thrombi may embolize to the pulmonary arteries via collateral veins that develop. A more common complication is caval thrombosis with marked bilateral leg swelling.

Paradoxically, by providing a nidus for clot formation, filters double the DVT rate over the ensuing 2 years after placement. Therefore, if clinically safe, patients receiving IVC filters should also receive concomitant anticoagulation.

Retrievable filters can now be placed for patients with an anticipated temporary bleeding disorder or for patients at temporary high risk of PE, such as individuals undergoing bariatric surgery with a history of perioperative PE. The filters can be retrieved up to several months after insertion unless a thrombus forms and is trapped within the filter. The retrievable filter becomes permanent if it remains in place or if, for technical reasons such as rapid endothelialization, it cannot be removed.

MAINTAINING ADEQUATE CIRCULATION

For patients with massive PE and hypotension, the most common initial approach is administration of 500–1000 mL of normal saline. However, fluids should be used with extreme caution. Excessive fluid administration exacerbates RV wall stress, causes more profound RV ischemia, and worsens LV compliance and filling by causing further interventricular septal shift toward the LV. Dopamine and dobutamine are first-line inotropic agents for the treatment of PE-related shock. There should be a low threshold to initiate these pressors. However, a “trial and error” approach may be necessary with other agents such as norepinephrine, vasopressin, and phenylephrine.

FIBRINOLYSIS Successful fibrinolytic therapy rapidly reverses right heart failure and leads to a lower rate of death and recurrent PE. Thrombolysis usually (1) dissolves much of the anatomically obstructing pulmonary arterial thrombus; (2) prevents the continued release of serotonin and other neurohumoral factors that exacerbate pulmonary hypertension; and (3) dissolves much of the source of the thrombus in the pelvic or deep leg veins, thereby decreasing the likelihood of recurrent PE.

The preferred fibrinolytic regimen is 100 mg of recombinant tissue plasminogen activator (tPA) administered as a continuous peripheral IV infusion over 2 h. Patients appear to respond to fibrinolysis for up to 14 days after the PE has occurred.

Contraindications to fibrinolysis include intracranial disease, recent surgery, or trauma. The overall major bleeding rate is about 10%, including a 1–3% risk of intracranial hemorrhage. Careful screening of patients for contraindications to fibrinolytic therapy (Chap. 34) is the best way to minimize the bleeding risk.

The only FDA-approved indication for PE fibrinolysis is massive PE. For patients with preserved systolic blood pressure and submassive PE, guidelines recommend individual patient risk assessment of the thrombotic burden versus bleeding risk. I concur with these guidelines. Younger patients with submassive PE but without comorbidities are generally excellent candidates for fibrinolysis. For older patients (age >70 years) with a risk of intracranial hemorrhage, a “watch and wait” approach is suitable, with frequent serial evaluation of RV function by echocardiography; fibrinolysis should be considered in those with deterioration of RV function.

PULMONARY EMBOLECTOMY The risk of intracranial hemorrhage with fibrinolysis has prompted the renaissance of surgical embolectomy for acute PE. At Brigham and Women’s Hospital, 47 patients with massive PE underwent emergency surgery in 53 months, with a 94% survival rate. This high survival rate may be attributed to improved surgical technique, rapid diagnosis and triage, and careful patient selection. A possible alternative to open surgical embolectomy is catheter embolectomy. New-generation catheters are under development.

PULMONARY THROMBOENDARTERECTOMY Chronic thromboembolic pulmonary hypertension is caused by vascular obstruction at the capillary level, not direct thromboembolic occlusion. It used to be considered a rare complication (about one of 500) of acute PE. Now, however, it appears that chronic thromboembolic pulmonary hypertension is a more common development, occurring in approximately 4% of patients who develop acute PE. Therefore, PE patients should be followed to ensure that if they have initial pulmonary hypertension, it abates over time (usually 6 weeks).

Patients severely impaired with dyspnea caused by chronic thromboembolic pulmonary hypertension should be considered for pulmonary thromboendarterectomy, which, if successful, can markedly reduce and at times even cure pulmonary hypertension. The operation requires median sternotomy, cardiopulmonary bypass, deep hypothermia, and periods of hypothermic circulatory arrest. The fibrotic, thromboembolic material is grasped with a forceps and circumferentially dissected from the vessel wall. The mortality rate at experienced centers is approximately 5%. The two most common complications are “pulmonary steal,” in which blood rushes from previously perfused areas to newly revascularized areas of the lung, and reperfusion pulmonary edema.

EMOTIONAL SUPPORT Many patients with VTE appear healthy and fit. However, they may be burdened with fear about the possible genetic implications of DVT or PE. They often feel overwhelmed when advised to

continue lifelong anticoagulation. Many patients in whom anticoagulation is discontinued after 3–6 months of therapy feel vulnerable to a future recurrent VTE. They may be reluctant to discontinue warfarin. Support groups are useful for these patients. Responses to frequently asked questions by these patients have been posted on the website <http://web.mit.edu/karen/www/faq.html>.

PREVENTION OF POSTPHLEBITIC SYNDROME The only therapy to prevent postphlebitic syndrome is daily use of below-knee 30- to 40-mmHg vascular compression stockings. They halve the rate of developing postphlebitic syndrome. These vascular compression stockings should be prescribed as soon as DVT is diagnosed, and the stockings should be fitted carefully to maximize their benefit. When patients are in bed, the stockings do not need to be worn.

PREVENTION OF VENOUS THROMBOEMBOLISM

Prophylaxis is of paramount importance because VTE is difficult to detect and poses an excessive medical and economic burden. Mechanical and pharmacologic measures often succeed in preventing this complication (Table 20-5). Patients at high risk can receive a combination

TABLE 20-5

PREVENTION OF VENOUS THROMBOEMBOLISM

CONDITION	PROPHYLAXIS STRATEGY
High-risk general surgery	Mini-UFH + GCS <i>or</i> LMWH + GCS
Thoracic surgery	Mini-UFH + IPC
Cancer surgery, including gynecologic cancer surgery	LMWH; consider 1 month of prophylaxis
Total hip replacement, total knee replacement, hip fracture surgery	LMWH, fondaparinux (a pentasaccharide) 2.5 mg SC, once daily <i>or</i> (except for total knee replacement) warfarin (target INR, 2.5)
Neurosurgery	GCS + IPC
Neurosurgery for brain tumor	Mini-UFH <i>or</i> LMWH, + IPC, + pre-discharge venous ultrasonography
Benign gynecologic surgery	Mini-UFH + GCS
Medically ill patients	Mini-UFH <i>or</i> LMWH
Anticoagulation contraindicated	GCS + IPC
Long-haul air travel	Consider LMWH for very high-risk patients

Note: Mini-UFH, minidose unfractionated heparin, 5000 U SC twice (less effective) or three times daily (more effective); GCS, graduated compression stockings, usually 10–18 mmHg; IPC, intermittent pneumatic compression devices; LMWH, low-molecular-weight heparin, typically in the United States, enoxaparin, 40 mg once daily, or dalteparin, 2500 or 5000 U once daily; UFH, unfractionated heparin.

214 of mechanical and pharmacologic modalities. Graduated compression stockings and pneumatic compression devices may complement mini-dose UFH (5000 U subcutaneously twice or preferably three times daily), LMWH, a pentasaccharide (fondaparinux 2.5 mg daily), or warfarin administration. Computerized reminder systems can increase the use of preventive measures and at Brigham and Women's Hospital reduced the symptomatic VTE rate by more than 40%. Patients who have undergone total hip replacement, total knee replacement, or cancer surgery benefit from extended pharmacologic prophylaxis for a total of 4–6 weeks.

FURTHER READINGS

- AGENO W et al: Cardiovascular risk factors and venous thromboembolism: A meta-analysis. *Circulation* 117:93, 2008
- BLAIVAS M: Ultrasound in the detection of venous thromboembolism. *Crit Care Med* 35:S224, 2007
- DALEN JE: Should patients with venous thromboembolism be screened for thrombophilia? *Am J Med* 121:458, 2008
- DENNIS M et al: Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): A multicentre, randomised controlled trial. *Lancet* 373:1958, 2009
- DENTALI F et al: Meta-analysis: Anticoagulant prophylaxis to prevent symptomatic venous thromboembolism in hospitalized medical patients. *Ann Intern Med* 146:278, 2007
- FIUMARA K et al: Predictors of major hemorrhage following fibrinolysis for acute pulmonary embolism. *Am J Cardiol* 97:127, 2006
- GEERTS WH et al: Prevention of venous thromboembolism: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 126:338S, 2004
- et al: Prevention of venous thromboembolism: American College of Chest Physicians Evidence-based Clinical Practice Guidelines, 8th edition. *Chest* 133(Suppl):381S, 2008
- GLYNN RJ et al: A randomized trial of rosuvastatin in the prevention of venous thromboembolism. *N Engl J Med* 360:1851, 2009
- HILL J, TREASURE T: Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients having surgery: Summary of NICE guidance. *Br Med J* 334:1053, 2007
- KUCHER N et al: Electronic alerts to prevent venous thromboembolism among hospitalized patients. *N Engl J Med* 352:969, 2005
- et al: Percutaneous catheter thrombectomy device for acute pulmonary embolism: In vitro and in vivo testing. *Radiology* 236:852, 2005
- et al: Prognostic role of echocardiography among patients with acute pulmonary embolism and a systolic arterial pressure of 90 mm Hg or higher. *Arch Intern Med* 165:1777, 2005
- KUCHER N, GOLDBERGER SZ: Management of massive pulmonary embolism. *Circulation* 112:e28, 2005
- LEACCHE M et al: Modern surgical treatment of massive pulmonary embolism: Results in 47 consecutive patients after rapid diagnosis and aggressive surgical approach. *J Thorac Cardiovasc Surg* 129:1018, 2005
- PARK B et al: Recent trends in clinical outcomes and resource utilization for pulmonary embolism in the United States: Findings from the nationwide inpatient sample. *Chest* 136(4):983, 2009
- PIAZZA G, GOLDBERGER SZ: The acutely decompensated right ventricle. *Chest* 128:1836, 2005
- PRANDONI P et al: Residual thrombosis on ultrasonography to guide the duration of anticoagulation in patients with deep venous thrombosis: A randomized trial. *Ann Intern Med* 150:577, 2009
- RIIDKER P et al: Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. *N Engl J Med* 348:1425, 2003
- RIEDER MJ et al: Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. *N Engl J Med* 352:2285, 2005
- SEGAL JB et al: Management of venous thromboembolism: A systematic review for a practice guideline. *Ann Intern Med* 146:211, 2007
- SPENCER FA et al: Venous thromboembolism in the outpatient setting. *Arch Intern Med* 167:1471, 2007
- TODD JL, TAPSON VF: Thrombolytic therapy for acute pulmonary embolism: A critical appraisal. *Chest* 135:1321, 2009
- TORBICKI A et al: Guidelines on the diagnosis and management of acute pulmonary embolism. The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *Eur Heart J* 29:2276, 2008
- VAN BELLE A et al: Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. *JAMA* 295:172, 2006
- et al, WRITING GROUP FOR THE CHRISTOPHER INVESTIGATORS: Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. *JAMA* 295:172, 2006
- WELLS PS et al: Does this patient have deep vein thrombosis? *JAMA* 295:199, 2006
- WRITING GROUP FOR THE CHRISTOPHER INVESTIGATORS: Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. *JAMA* 295:172, 2006



CHAPTER 21

DISORDERS OF THE PLEURA AND MEDIASTINUM

Richard W. Light

■ Disorders of the Pleura	215
Pleural Effusion	215
Effusion Secondary to Viral Infection	217
Pneumothorax	219
■ Disorders of the Mediastinum	219
Mediastinal Masses	219
Acute Mediastinitis	220
Chronic Mediastinitis	220
Pneumomediastinum	220
■ Further Readings	220

DISORDERS OF THE PLEURA

PLEURAL EFFUSION

The pleural space lies between the lung and chest wall and normally contains a very thin layer of fluid, which serves as a coupling system. A pleural effusion is present when there is an excess quantity of fluid in the pleural space.

Etiology

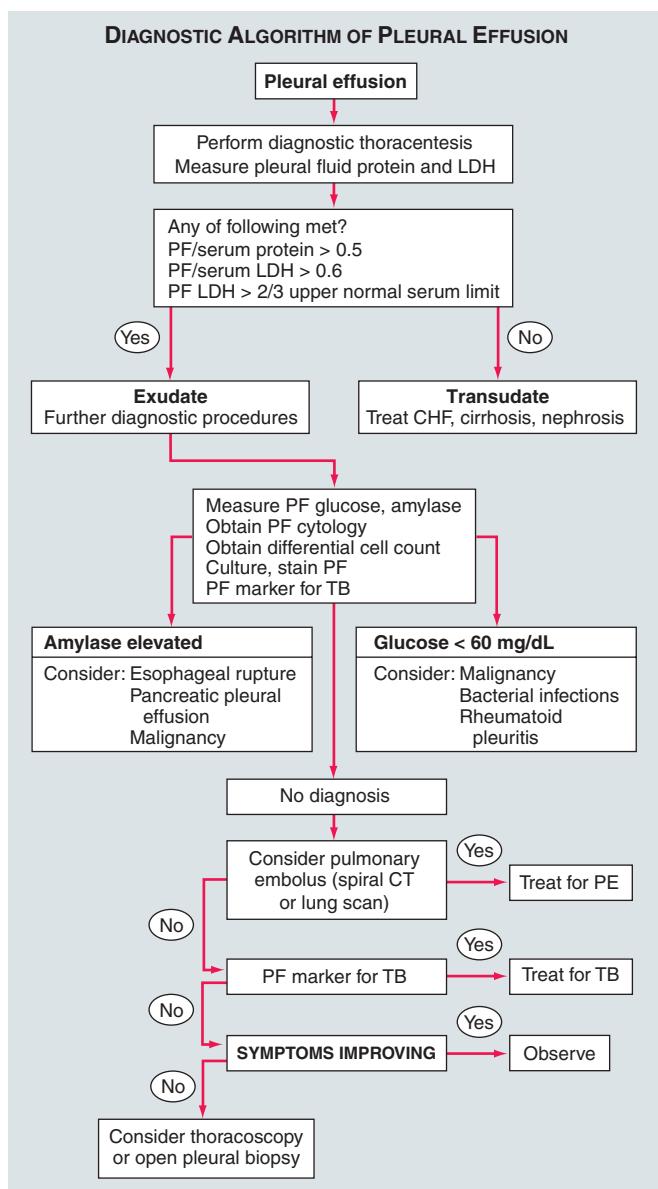
Pleural fluid accumulates when pleural fluid formation exceeds pleural fluid absorption. Normally, fluid enters the pleural space from the capillaries in the parietal pleura and is removed via the lymphatics situated in the parietal pleura. Fluid can also enter the pleural space from the interstitial spaces of the lung via the visceral pleura or from the peritoneal cavity via small holes in the diaphragm. The lymphatics have the capacity to absorb 20 times more fluid than is normally formed. Accordingly, a pleural effusion may develop when there is excess pleural fluid formation (from the interstitial spaces of the lung, the parietal pleura, or the peritoneal

cavity) or when there is decreased fluid removal by the lymphatics.

Diagnostic Approach

When a patient is found to have a pleural effusion, an effort should be made to determine the cause (**Fig. 21-1**). The first step is to determine whether the effusion is a transudate or an exudate. A *transudative pleural effusion* occurs when *systemic factors* that influence the formation and absorption of pleural fluid are altered. The leading causes of transudative pleural effusions in the United States are left ventricular failure and cirrhosis. An *exudative pleural effusion* occurs when *local factors* that influence the formation and absorption of pleural fluid are altered. The leading causes of exudative pleural effusions are bacterial pneumonia, malignancy, viral infection, and pulmonary embolism (PE). The primary reason to make this differentiation is that additional diagnostic procedures are indicated with exudative effusions to define the cause of the local disease.

Transudative and exudative pleural effusions are distinguished by measuring the lactate dehydrogenase (LDH) and protein levels in the pleural fluid. Whereas exudative

**FIGURE 21-1**

Approach to the diagnosis of pleural effusions. CHF, congestive heart failure; CT, computed tomography; LDH, lactate dehydrogenase; PE, pulmonary embolism; PF, pleural fluid; TB, tuberculosis.

pleural effusions meet at least one of the following criteria, transudative pleural effusions meet none:

1. Pleural fluid protein/serum protein >0.5
2. Pleural fluid LDH/serum LDH >0.6
3. Pleural fluid LDH more than two-thirds the normal upper limit for serum

The above criteria misidentify ~25% of transudates as exudates. If one or more of the exudative criteria are met and the patient is clinically thought to have a condition producing a transudative effusion, the difference between the protein levels in the serum and the pleural

fluid should be measured. If this gradient is greater than 31 g/L (3.1 g/dL), the exudative categorization by the above criteria can be ignored because almost all such patients have a transudative pleural effusion.

If a patient has an exudative pleural effusion, the following tests on the pleural fluid should be obtained: description of the fluid, glucose level, differential cell count, microbiologic studies, and cytology.

Effusion Caused by Heart Failure

The most common cause of pleural effusion is left ventricular failure. The effusion occurs because the increased amounts of fluid in the lung interstitial spaces exit in part across the visceral pleura. This overwhelms the capacity of the lymphatics in the parietal pleura to remove fluid. Isolated right-sided pleural effusions are more common than left-sided effusions in heart failure. A diagnostic thoracentesis should be performed if the effusions are not bilateral and comparable in size, if the patient is febrile, or if the patient has pleuritic chest pain, to verify that the patient has a transudative effusion. Otherwise, the patient is best treated with diuretics. If the effusion persists despite diuretic therapy, a diagnostic thoracentesis should be performed. A pleural fluid N-terminal pro-brain natriuretic peptide (NT-proBNP) >1500 pg/mL is virtually diagnostic of an effusion secondary to congestive heart failure.

Hepatic Hydrothorax

Pleural effusions occur in ~5% of patients with cirrhosis and ascites. The predominant mechanism is the direct movement of peritoneal fluid through small openings in the diaphragm into the pleural space. The effusion is usually right sided and frequently is large enough to produce severe dyspnea.

Parapneumonic Effusion

Parapneumonic effusions are associated with bacterial pneumonia, lung abscess, or bronchiectasis and are probably the most common cause of exudative pleural effusion in the United States. *Empyema* refers to a grossly purulent effusion.

Patients with aerobic bacterial pneumonia and pleural effusion present with an acute febrile illness consisting of chest pain, sputum production, and leukocytosis. Patients with anaerobic infections present with a subacute illness with weight loss, a brisk leukocytosis, mild anemia, and a history of some factor that predisposes them to aspiration.

The possibility of a parapneumonic effusion should be considered whenever a patient with a bacterial pneumonia is initially evaluated. The presence of free pleural fluid can be demonstrated with a lateral decubitus radiograph, CT of the chest, or ultrasonography. If the free fluid separates the lung from the chest wall by >10 mm,

a therapeutic thoracentesis should be performed. Factors indicating the likely need for a procedure more invasive than a thoracentesis (in increasing order of importance) include:

1. Loculated pleural fluid
2. Pleural fluid pH <7.20
3. Pleural fluid glucose <3.3 mmol/L (<60 mg/dL)
4. Positive Gram stain or culture of the pleural fluid
5. The presence of gross pus in the pleural space

If the fluid recurs after the initial therapeutic thoracentesis and if any of the above characteristics are present, a repeat thoracentesis should be performed. If the fluid cannot be completely removed with the therapeutic thoracentesis, consideration should be given to inserting a chest tube and instilling a fibrinolytic (e.g., 250,000 U of streptokinase) or performing thoracoscopy with the breakdown of adhesions. Decortication should be considered when the above are ineffective.

Effusion Secondary to Malignancy

Malignant pleural effusions secondary to metastatic disease are the second most common type of exudative pleural effusion. The three tumors that cause ~75% of all malignant pleural effusions are lung carcinoma, breast carcinoma, and lymphoma. Most patients complain of dyspnea, which is frequently out of proportion to the size of the effusion. The pleural fluid is an exudate, and its glucose level may be reduced if the tumor burden in the pleural space is high.

The diagnosis is usually made via cytology of the pleural fluid. If the initial cytologic examination is negative, then thoracoscopy is the best next procedure if malignancy is strongly suspected. At the time of thoracoscopy, a procedure such as pleural abrasion should be performed to effect a pleurodesis. If thoracoscopy is unavailable, then needle biopsy of the pleura should be performed.

Patients with a malignant pleural effusion are treated symptomatically for the most part because the presence of the effusion indicates disseminated disease and most malignancies associated with pleural effusion are not curable with chemotherapy. The only symptom that can be attributed to the effusion itself is dyspnea. If the patient's lifestyle is compromised by dyspnea and if the dyspnea is relieved with a therapeutic thoracentesis, then one of the following procedures should be considered: (1) insertion of a small indwelling catheter or (2) tube thoracostomy with the instillation of a sclerosing agent such as 500 mg of doxycycline.

Mesothelioma

Malignant mesotheliomas are primary tumors that arise from the mesothelial cells that line the pleural cavities;

most are related to asbestos exposure. Patients with mesothelioma present with chest pain and shortness of breath. The chest radiograph reveals a pleural effusion, generalized pleural thickening, and a shrunken hemithorax. Thoracoscopy or open pleural biopsy is usually necessary to establish the diagnosis. Chest pain should be treated with opiates and shortness of breath with oxygen, opiates, or both.

Effusion Secondary to Pulmonary Embolization

The diagnosis most commonly overlooked in the differential diagnosis of a patient with an undiagnosed pleural effusion is PE. Dyspnea is the most common symptom. The pleural fluid is almost always an exudate. The diagnosis is established by spiral CT scan or pulmonary arteriography (Chap. 20). Treatment of a patient with a pleural effusion secondary to PE is the same as for any patient with pulmonary emboli. If the pleural effusion increases in size after anticoagulation, the patient probably has recurrent emboli or another complication such as a hemothorax or a pleural infection.

Tuberculous Pleuritis

(See also Chap. 12) In many parts of the world, the most common cause of an exudative pleural effusion is tuberculosis (TB), but tuberculous effusions are relatively uncommon in the United States. Tuberculous pleural effusions are usually associated with primary TB and are thought to be primarily caused by a hypersensitivity reaction to tuberculous protein in the pleural space. Patients with tuberculous pleuritis present with combinations of fever, weight loss, dyspnea, or pleuritic chest pain. The pleural fluid is an exudate with predominantly small lymphocytes. The diagnosis is established by demonstrating high levels of TB markers in the pleural fluid (adenosine deaminase >40 IU/L; interferon γ >140 pg/mL, or positive polymerase chain reaction for tuberculous DNA). Alternatively, the diagnosis can be established by culture of the pleural fluid, needle biopsy of the pleura, or thoracoscopy. The recommended treatment of patients with pleural and pulmonary TB is identical (Chap. 12).

EFFUSION SECONDARY TO VIRAL INFECTION

Viral infections are probably responsible for a sizable percentage of undiagnosed exudative pleural effusions. In many series, no diagnosis is established for ~20% of exudative effusions, and these effusions resolve spontaneously with no long-term residua. The importance of these effusions is that one should not be too aggressive in trying to establish a diagnosis for the undiagnosed effusion, particularly if the patient is improving clinically.

Pleural effusions are uncommon in patients with AIDS. The most common cause is Kaposi's sarcoma followed by parapneumonic effusion. Other common causes are TB, cryptococcosis, and primary effusion lymphoma. Pleural effusions are very uncommon with *Pneumocystis carinii* infection.

Chylothorax

A chylothorax occurs when the thoracic duct is disrupted and chyle accumulates in the pleural space. The most common cause of chylothorax is trauma, but it may also result from tumors in the mediastinum. Patients with chylothorax present with dyspnea, and a large pleural effusion is present on the chest radiograph. Thoracentesis reveals milky fluid, and biochemical analysis reveals a triglyceride level that exceeds 1.2 mmol/L (110 mg/dL). Patients with chylothorax and no obvious trauma should have a lymphangiogram and a mediastinal CT scan to assess the mediastinum for lymph nodes. The treatment of choice for most chylothoraces is insertion of a chest tube plus the administration of octreotide. If these modalities fail, a pleuroperitoneal shunt should be placed unless the patient has chylous ascites. Patients with chylothoraces should not undergo prolonged tube thoracostomy with chest tube drainage because this will lead to malnutrition and immunologic incompetence.

Hemothorax

When a diagnostic thoracentesis reveals bloody pleural fluid, a hematocrit should be obtained on the pleural fluid. If the hematocrit is more than half of that in the peripheral blood, the patient is considered to have a hemothorax. Most hemothoraces are the result of trauma; other causes include rupture of a blood vessel or tumor. Most patients with hemothorax should be treated with tube thoracostomy, which allows continuous quantification of bleeding. If the bleeding emanates from a laceration of the pleura, apposition of the two pleural surfaces is likely to stop the bleeding. If the pleural hemorrhage exceeds 200 mL/h, consideration should be given to thoracoscopy or thoracotomy.

Miscellaneous Causes of Pleural Effusion

There are many other causes of pleural effusion (Table 21-1). Key features of some of these conditions are as follows: If the pleural fluid amylase level is elevated, the diagnosis of esophageal rupture or pancreatic disease is likely. If the patient is febrile, has predominantly polymorphonuclear cells in the pleural fluid, and has no pulmonary parenchymal abnormalities, an intraabdominal abscess should be considered.

TABLE 21-1

DIFFERENTIAL DIAGNOSES OF PLEURAL EFFUSIONS

Transudative Pleural Effusions

- | | |
|-----------------------------|-----------------------------------|
| 1. Congestive heart failure | 6. Superior vena cava obstruction |
| 2. Cirrhosis | 7. Myxedema |
| 3. Pulmonary embolization | 8. Urinothorax |
| 4. Nephrotic syndrome | |
| 5. Peritoneal dialysis | |

Exudative Pleural Effusions

- | | |
|--------------------------------------|--|
| 1. Neoplastic diseases | 6. Post-coronary artery bypass surgery |
| a. Metastatic disease | 7. Asbestos exposure |
| b. Mesothelioma | 8. Sarcoidosis |
| 2. Infectious diseases | 9. Uremia |
| a. Bacterial infections | 10. Meigs' syndrome |
| b. Tuberculosis | 11. Yellow nail syndrome |
| c. Fungal infections | 12. Drug-induced pleural disease |
| d. Viral infections | a. Nitrofurantoin |
| 3. Pulmonary embolization | b. Dantrolene |
| 4. Gastrointestinal disease | c. Methysergide |
| a. Esophageal perforation | d. Bromocriptine |
| b. Pancreatic disease | e. Procarbazine |
| c. Intraabdominal abscesses | f. Amiodarone |
| d. Diaphragmatic hernia | 13. Trapped lung |
| e. After abdominal surgery | 14. Radiation therapy |
| f. Endoscopic variceal sclerotherapy | 15. Post-cardiac injury syndrome |
| g. After liver transplant | 16. Hemothorax |
| 5. Collagen vascular diseases | 17. Latrogenic injury |
| a. Rheumatoid pleuritis | 18. Ovarian hyperstimulation syndrome |
| b. Systemic lupus erythematosus | 19. Pericardial disease |
| c. Drug-induced lupus | 20. Chylothorax |
| d. Immunoblastic lymphadenopathy | |
| e. Sjögren's syndrome | |
| f. Wegener's granulomatosis | |
| g. Churg-Strauss syndrome | |

The diagnosis of an asbestos pleural effusion is one of exclusion. Benign ovarian tumors can produce ascites and a pleural effusion (Meigs' syndrome), as can ovarian hyperstimulation syndrome. Several drugs can cause pleural effusion; the associated fluid is usually eosinophilic. Pleural effusions commonly occur after coronary artery bypass surgery. Effusions occurring within the first weeks are typically left sided and bloody with large numbers of eosinophils and respond to one or two therapeutic thoracenteses. Effusions occurring after the first few weeks are typically left sided and clear yellow with predominantly small lymphocytes and tend to recur. Other medical manipulations that induce pleural effusions include abdominal surgery; radiation therapy; liver, lung,

or heart transplantation; and intravascular insertion of central lines.

PNEUMOTHORAX

Pneumothorax is the presence of gas in the pleural space. A *spontaneous pneumothorax* is one that occurs without antecedent trauma to the thorax. Whereas a *primary spontaneous pneumothorax* occurs in the absence of underlying lung disease, a *secondary pneumothorax* occurs in its presence. A *traumatic pneumothorax* results from penetrating or nonpenetrating chest injuries. A *tension pneumothorax* is a pneumothorax in which the pressure in the pleural space is positive throughout the respiratory cycle.

Primary Spontaneous Pneumothorax

Primary spontaneous pneumothoraces are usually caused by rupture of apical pleural blebs, small cystic spaces that lie within or immediately under the visceral pleura. Primary spontaneous pneumothoraces occur almost exclusively in smokers, which suggests that these patients have subclinical lung disease. Approximately 50% of patients with an initial primary spontaneous pneumothorax will have a recurrence. The initial recommended treatment for primary spontaneous pneumothorax is simple aspiration. If the lung does not expand with aspiration or if the patient has a recurrent pneumothorax, thoracoscopy with stapling of blebs and pleural abrasion is indicated. Thoracoscopy or thoracotomy with pleural abrasion is almost 100% successful in preventing recurrences.

Secondary Pneumothorax

Most secondary pneumothoraces are caused by chronic obstructive pulmonary disease, but pneumothoraces have been reported with virtually every lung disease. Pneumothorax in patients with lung disease is more life threatening than it is in normal individuals because of the lack of pulmonary reserve in these patients. Nearly all patients with secondary pneumothorax should be treated with tube thoracostomy. Most of them should also be treated with thoracoscopy or thoracotomy with the stapling of blebs and pleural abrasion. If the patient is not a good operative candidate or refuses surgery, then pleurodesis should be attempted by the intrapleural injection of a sclerosing agent such as doxycycline.

Traumatic Pneumothorax

Traumatic pneumothoraces can result from both penetrating and nonpenetrating chest trauma. Traumatic pneumothoraces should be treated with tube thoracostomy unless they are very small. If a hemopneumothorax is present, one chest tube should be placed in the superior part of the hemithorax to evacuate the air, and another should be placed in the inferior part of the hemithorax

to remove the blood. Iatrogenic pneumothorax is a type of traumatic pneumothorax that is becoming more common. The leading causes are transthoracic needle aspiration, thoracentesis, and the insertion of central intravenous catheters. Most can be managed with supplemental oxygen or aspiration, but if these are unsuccessful, a tube thoracostomy should be performed.

Tension Pneumothorax

This condition usually occurs during mechanical ventilation or resuscitative efforts. The positive pleural pressure is life threatening both because ventilation is severely compromised and because the positive pressure is transmitted to the mediastinum, which results in decreased venous return to the heart and reduced cardiac output.

Difficulty in ventilation during resuscitation or high peak inspiratory pressures during mechanical ventilation strongly suggests the diagnosis. The diagnosis is made by physical examination showing an enlarged hemithorax with no breath sounds, hyperresonance to percussion, and shift of the mediastinum to the contralateral side. Tension pneumothorax must be treated as a medical emergency. If the tension in the pleural space is not relieved, the patient is likely to die from inadequate cardiac output or marked hypoxemia. A large-bore needle should be inserted into the pleural space through the second anterior intercostal space. If large amounts of gas escape from the needle after insertion, the diagnosis is confirmed. The needle should be left in place until a thoracostomy tube can be inserted.

DISORDERS OF THE MEDIASTINUM

The mediastinum is the region between the pleural sacs. It is separated into three compartments. The *anterior mediastinum* extends from the sternum anteriorly to the pericardium and brachiocephalic vessels posteriorly. It contains the thymus gland, the anterior mediastinal lymph nodes, and the internal mammary arteries and veins. The *middle mediastinum* lies between the anterior and posterior mediastina and contains the heart; the ascending and transverse arches of the aorta; the venae cavae; the brachiocephalic arteries and veins; the phrenic nerves; the trachea, main bronchi, and their contiguous lymph nodes; and the pulmonary arteries and veins. The *posterior mediastinum* is bounded by the pericardium and trachea anteriorly and the vertebral column posteriorly. It contains the descending thoracic aorta, esophagus, thoracic duct, azygos and hemiazygos veins, and the posterior group of mediastinal lymph nodes.

MEDIASTINAL MASSES

The first step in evaluating a mediastinal mass is to place it in one of the three mediastinal compartments because each has different characteristic lesions. The most common lesions in the anterior mediastinum are thymomas,

220 lymphomas, teratomatous neoplasms, and thyroid masses. The most common masses in the middle mediastinum are vascular masses, lymph node enlargement from metastases or granulomatous disease, and pleuropericardial and bronchogenic cysts. In the posterior mediastinum, neurogenic tumors, meningoceles, meningomyeloceles, gastroenteric cysts, and esophageal diverticula are commonly found.

CT scanning is the most valuable imaging technique for evaluating mediastinal masses and is the only imaging technique that should be done in most instances. Barium studies of the gastrointestinal tract are indicated in many patients with posterior mediastinal lesions because hernias, diverticula, and achalasia are readily diagnosed in this manner. An ^{131}I scan can efficiently establish the diagnosis of intrathoracic goiter.

A definite diagnosis can be obtained with mediastinoscopy or anterior mediastinotomy in many patients with masses in the anterior or middle mediastinal compartments. A diagnosis can be established without thoracotomy via percutaneous fine-needle aspiration biopsy or endoscopic transesophageal or endobronchial ultrasound-guided biopsy of mediastinal masses in most cases. Alternative ways to establish the diagnosis are video-assisted thoracoscopy, mediastinoscopy, or mediastinotomy. In many cases, the diagnosis can be established and the mediastinal mass removed with video-assisted thoracoscopy.

ACUTE MEDIASTINITIS

Most cases of acute mediastinitis either are caused by esophageal perforation or occur after median sternotomy for cardiac surgery. Patients with esophageal rupture are acutely ill with chest pain and dyspnea caused by the mediastinal infection. The esophageal rupture can occur spontaneously or as a complication of esophagoscopy or the insertion of a Blakemore tube. Appropriate treatment is exploration of the mediastinum with primary repair of the esophageal tear and drainage of the pleural space and the mediastinum.

The incidence of mediastinitis after median sternotomy is 0.4–5.0%. Patients most commonly present with wound drainage. Other presentations include sepsis or a widened mediastinum. The diagnosis is usually established with mediastinal needle aspiration. Treatment includes immediate drainage, debridement, and parenteral antibiotic therapy, but the mortality rate still exceeds 20%.

CHRONIC MEDIASTINITIS

The spectrum of chronic mediastinitis ranges from granulomatous inflammation of the lymph nodes in the mediastinum to fibrosing mediastinitis. Most cases are caused by TB or histoplasmosis, but sarcoidosis, silicosis, and other fungal diseases are at times causative. Patients

with granulomatous mediastinitis are usually asymptomatic. Those with fibrosing mediastinitis usually have signs of compression of some mediastinal structure such as the superior vena cava or large airways, phrenic or recurrent laryngeal nerve paralysis, or obstruction of the pulmonary artery or proximal pulmonary veins. Other than antituberculous therapy for tuberculous mediastinitis, no medical or surgical therapy has been demonstrated to be effective for mediastinal fibrosis.

PNEUMOMEDIASTINUM

In this condition, there is gas in the interstices of the mediastinum. The three main causes are (1) alveolar rupture with dissection of air into the mediastinum; (2) perforation or rupture of the esophagus, trachea, or main bronchi; and (3) dissection of air from the neck or the abdomen into the mediastinum. Typically, the patient has severe substernal chest pain with or without radiation into the neck and arms. The physical examination usually reveals subcutaneous emphysema in the suprasternal notch and *Hamman's sign*, which is a crunching or clicking noise synchronous with the heartbeat and best heard in the left lateral decubitus position. The diagnosis is confirmed with the chest radiograph. Usually no treatment is required, but the mediastinal air will be absorbed faster if the patient inspires high concentrations of oxygen. If mediastinal structures are compressed, the compression can be relieved with needle aspiration.

FURTHER READINGS

- GILBERT S et al: Endobronchial ultrasound as a diagnostic tool in patients with mediastinal lymphadenopathy. *Ann Thorac Surg* 88:896, 2009
- LIGHT RW: *Pleural Diseases*, 5th ed. Philadelphia, Lippincott Williams & Wilkins, 2006
- : Pleural effusion. *N Engl J Med* 346:1971, 2002
- PORCEL JM: The use of probrain natriuretic peptide in pleural fluid for the diagnosis of pleural effusions resulting from heart failure. *Curr Opin Pulm Med* 11:329, 2005
- et al: Biomarkers of heart failure in pleural fluid. *Chest* 163:671, 2009
- et al: Biomarkers of infection for the differential diagnosis of pleural effusions. *Eur Respir J* 2009 Jun 18, epub ahead of print
- RAHMAN NM et al: Investigating suspected malignant pleural effusion. *BMJ* 334:206, 2007
- TREMBLAY A et al: Single-center experience with 250 tunneled pleural catheter insertions for malignant pleural effusion. *Chest* 129:362, 2006
- VILMANN P et al: Transesophageal endoscopic ultrasound-guided fine-needle aspiration and endobronchial ultrasound-guided transbronchial needle aspiration biopsy: A combined approach in the evaluation of mediastinal lesions. *Endoscopy* 37:833, 2005
- WARREN WH et al: Identification of clinical factors predicting Pleurx catheter removal in patients treated for malignant pleural effusion. *Eur J Cardiothorac Surg* 33:89, 2008



CHAPTER 22

DISORDERS OF VENTILATION

Eliot A. Phillipson

■ Hypoventilation	221	Obesity-Hypoventilation Syndrome	225
Definition and Etiology	221	■ Hyperventilation and Its Syndromes	225
Physiologic and Clinical Features	221	Definition and Etiology	225
Diagnosis	222	Physiologic and Clinical Features	226
■ Hypoventilation Syndromes	224	Diagnosis	226
Primary Alveolar Hypoventilation	224	■ Further Readings	227
Respiratory Neuromuscular Disorders	224		

HYPOVENTILATION

DEFINITION AND ETIOLOGY

By definition, alveolar hypoventilation exists when arterial PCO_2 (PaCO_2) increases above the normal range of 37–43 mmHg, but in clinically important hypoventilation syndromes, PaCO_2 is generally in the range of 50–80 mmHg. Hypoventilation disorders can be acute or chronic. This chapter deals with chronic hypoventilation syndromes. The acute disorders, which represent life-threatening emergencies, are discussed in Chap. 30.

Chronic hypoventilation can result from numerous disease entities (Table 22-1), but in all cases, the underlying mechanism involves a defect in the metabolic respiratory control system, the respiratory neuromuscular system, or the ventilatory apparatus. Disorders associated with impaired respiratory drive, defects in the respiratory neuromuscular system, some chest wall disorders such as obesity, and upper airway obstruction produce an increase in PaCO_2 , despite normal lungs, because of a reduction in overall minute volume of ventilation and hence in alveolar ventilation. In contrast, most disorders of the chest wall and disorders of the lower airways and lungs may produce an increase in PaCO_2 despite a normal or even increased minute volume of ventilation because of severe ventilation-perfusion mismatching that results in net alveolar hypoventilation.

Several hypoventilation syndromes involve combined disturbances in two elements of the respiratory system. For example, patients with chronic obstructive pulmonary disease may hypoventilate not simply because of impaired ventilatory mechanics but also because of a reduced central respiratory drive, which can be inherent or secondary to a coexisting metabolic alkalosis (related to diuretic and steroid therapy).

PHYSIOLOGIC AND CLINICAL FEATURES

Regardless of cause, the hallmark of all alveolar hypoventilation syndromes is an increase in alveolar PCO_2 (PACO_2) and therefore in PaCO_2 (Fig. 22-1). The resulting respiratory acidosis eventually leads to a compensatory increase in plasma HCO_3^- concentration and a decrease in Cl^- concentration. The increase in PACO_2 produces an obligatory decrease in PAO_2 , resulting in hypoxemia. If severe, the hypoxemia manifests clinically as cyanosis and can stimulate erythropoiesis and induce secondary polycythemia. The combination of chronic hypoxemia and hypercapnia may also induce pulmonary vasoconstriction, leading eventually to pulmonary hypertension, right ventricular hypertrophy, and congestive heart failure. The disturbances in arterial blood gases are typically magnified during sleep because of a further reduction in central respiratory drive. The resulting increased nocturnal hypercapnia may cause cerebral vasodilation leading to morning headache; sleep quality may also be severely

TABLE 22-1

CHRONIC HYPOVENTILATION SYNDROMES

MECHANISM	SITE OF DEFECT	DISORDER
Impaired respiratory drive	Peripheral and central chemoreceptors	Carotid body dysfunction, trauma Prolonged hypoxia Metabolic alkalosis
	Brainstem respiratory neurons	Bulbar poliomyelitis, encephalitis Brainstem infarction, hemorrhage, trauma Brainstem demyelination, degeneration Chronic drug administration Hypothyroidism Primary alveolar hypoventilation syndrome
Defective respiratory neuromuscular system	Spinal cord and peripheral nerves	High cervical trauma Poliomyelitis Motor neuron disease Peripheral neuropathy
	Respiratory muscles	Myasthenia gravis Muscular dystrophy Chronic myopathy
Impaired ventilatory apparatus	Chest wall	Kyphoscoliosis Fibrothorax Thoracoplasty Ankylosing spondylitis Obesity hypoventilation
	Airways and lungs	Laryngeal and tracheal stenosis Obstructive sleep apnea Cystic fibrosis Chronic obstructive pulmonary disease

Source: From EA Phillipson, AS Slutsky, in Murray JF, Nadel JA (eds), *Textbook of Respiratory Medicine*, 3d ed, Philadelphia, Saunders, 2000, with permission.

impaired, resulting in morning fatigue, daytime somnolence, mental confusion, and intellectual impairment. Other clinical features associated with hypoventilation syndromes are related to the specific underlying disease (see Table 22-1).

DIAGNOSIS

Investigation of a patient with chronic hypoventilation involves several laboratory tests that will usually localize the disorder to the metabolic respiratory control system, the neuromuscular system, or the ventilatory apparatus (Fig. 22-2). Defects in the control system impair responses to chemical stimuli, including ventilatory, occlusion pressure, and diaphragmatic electromyographic (EMG) responses. During sleep, hypoventilation is usually more marked, and central apneas and hypopneas are common. However, because the behavioral respiratory control system (which is anatomically distinct from the metabolic control system), the neuromuscular system, and the ventilatory apparatus are intact, such

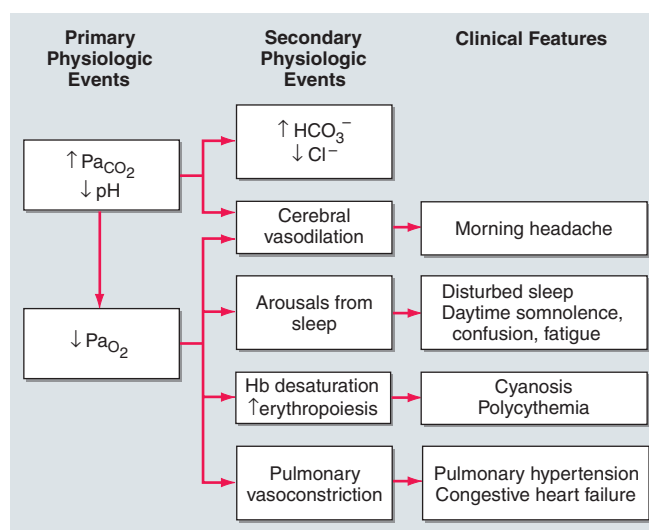


FIGURE 22-1

Physiologic and clinical features of alveolar hypoventilation. Hb, hemoglobin; PaCO₂, arterial PCO₂; PaO₂, arterial PO₂. [Adapted from Phillipson EA, Slutsky AS: in Murray JF, Nadel JA (eds), *Textbook of Respiratory Medicine*, 3d ed, Philadelphia, Saunders, 2000.]

Site of defect	Responses to CO ₂ , hypoxia			Sleep studies	Voluntary hyperventil.	P _{I,max} P _{E,max}	Volume flow rates	Resistance, compliance	(A-a) PO ₂
	Ventil.	P.1	EMGdi						
Metabolic control system (chemoreceptors, brainstem integrating neurons)	↓	↓	↓	↑ Hypoventil, central apneas	N	N	N	N	N
Respiratory neuromuscular system (brainstem motoneurons, spinal cord, respiratory nerves, and muscles)	↓	↓	↓	↑ Hypoventil, central apneas	↓	↓	↓	N	N
Ventilatory apparatus (chest wall, lungs, airways)	↓	N	N	Variable	↓	N	Abnormal	Abnormal	↑

FIGURE 22-2

Pattern of laboratory test results in alveolar hypoventilation syndromes based on the site of defect. Defects in the metabolic control system impair central respiratory drive in response to chemical stimuli (CO₂ or hypoxia); therefore, responses of EMGdi, P.1, and minute volume of ventilation are reduced, and hypoventilation during sleep is aggravated. In contrast, tests of voluntary respiratory control, muscle strength, lung mechanics, and gas exchange [(A-a)PO₂] are normal. Defects in the respiratory neuromuscular system impair muscle strength; therefore, all tests dependent on muscular activity (voluntary or in response to metabolic stimuli) are abnormal, but lung resistance, lung compliance, and

gas exchange are normal. Defects in the ventilatory apparatus usually impair gas exchange. Because resistance and compliance are also impaired, all tests dependent on ventilation (whether voluntary or in response to chemical stimuli) are abnormal; in contrast, tests of muscle activity or strength that do not involve airflow (i.e., P.1, EMGdi, P_{I,max}, P_{E,max}) are normal. (A-a)PO₂, alveolar-arterial PO₂ difference; EMGdi, diaphragmatic EMG; N, normal; P.1, mouth pressure generated after 0.1 s of inspiration against an occluded airway; P_{I,max}, P_{E,max}, maximum inspiratory or expiratory pressure that can be generated against an occluded airway; Ventil, ventilation. (Adapted from Phillipson and Duffin.)

patients can usually hyperventilate voluntarily, generate normal inspiratory and expiratory muscle pressures (P_{I,max}, P_{E,max}, respectively) against an occluded airway, generate normal lung volumes and flow rates on routine spirometry, and have normal respiratory system resistance and compliance and a normal alveolar-arterial PO₂[(A-a)PO₂] difference.

Patients with defects in the respiratory neuromuscular system also have impaired responses to chemical stimuli but in addition are unable to hyperventilate voluntarily or to generate normal static respiratory muscle pressures, lung volumes, and flow rates. However, at least in the early stages of the disease, the resistance and compliance of the respiratory system and the alveolar-arterial oxygen difference are normal.

In contrast to patients with disorders of the respiratory control or neuromuscular systems, patients with disorders of the chest wall, lungs, and airways typically demonstrate abnormalities of respiratory system resistance and compliance and have a widened (A-a)PO₂. Because of the impaired mechanics of breathing, routine spirometric tests are abnormal, as is the ventilatory response to chemical stimuli. However, because the neuromuscular system is intact, tests that are independent of resistance and compliance are usually normal, including tests of respiratory muscle strength and respiratory control that do not involve airflow.

Rx Treatment: HYPOVENTILATION

The management of chronic hypoventilation must be individualized to the patient's particular disorder, circumstances, and needs and should include measures directed toward the underlying disease. Coexistent metabolic alkalosis should be corrected, including elevations of HCO₃⁻ that are inappropriately high for the degree of chronic hypercapnia. Administration of supplemental oxygen is effective in attenuating hypoxemia, polycythemia, and pulmonary hypertension but can aggravate CO₂ retention and the associated neurologic symptoms. For this reason, supplemental oxygen must be prescribed judiciously and the results monitored carefully. Pharmacologic agents that stimulate respiration, such as progesterone and methylxanthines, are of benefit in some patients, but the results are generally disappointing.

Most patients with chronic hypoventilation related to impairment of respiratory drive or neuromuscular disease eventually require mechanical ventilatory assistance for effective management. When hypoventilation is severe, treatment may be required on a 24-h basis, but in most patients, ventilatory assistance only during sleep produces dramatic improvement in clinical features and daytime arterial blood gases. In patients with

reduced respiratory drive but intact respiratory lower motor neurons, phrenic nerves, and respiratory muscles, diaphragmatic pacing through an implanted phrenic electrode can be very effective. However, for patients with defects in the respiratory nerves and muscles, electrophrenic pacing is contraindicated. Such patients can usually be managed effectively with either intermittent negative-pressure ventilation in a cuirass or intermittent positive-pressure ventilation delivered through a tracheostomy or nose mask. For patients who require ventilatory assistance only during sleep, positive-pressure ventilation through a nose mask is the preferred method because it obviates a tracheostomy and avoids the problem of upper airway occlusion that can arise in a negative-pressure ventilator. Hypoventilation related to restrictive disorders of the chest wall (Table 22-1) can also be managed effectively with nocturnal intermittent positive-pressure ventilation through a nose mask or tracheostomy.

HYPOVENTILATION SYNDROMES

PRIMARY ALVEOLAR HYPOVENTILATION

Primary alveolar hypoventilation (PAH) is a disorder of unknown cause characterized by chronic hypercapnia and hypoxemia in the absence of identifiable neuromuscular disease or mechanical ventilatory impairment. The disorder is thought to arise from a defect in the metabolic respiratory control system, but few neuropathologic studies have been reported in such patients. Studies in animals suggest an important role for genetic factors in the pathogenesis of hypoventilation, and familial cases in humans have been described. Isolated PAH is relatively rare, and although it occurs in all age groups, the majority of reported cases in adults have been in men aged 20–50 years. The disorder typically develops insidiously and often first comes to attention when severe respiratory depression occurs after administration of standard doses of sedatives or anesthetics. As the degree of hypoventilation increases, patients typically develop lethargy, fatigue, daytime somnolence, disturbed sleep, and morning headaches; eventually, cyanosis, polycythemia, pulmonary hypertension, and congestive heart failure occur (Fig. 22-1). Despite severe arterial blood gas derangements, dyspnea is uncommon, presumably because of impaired chemoreception and ventilatory drive. If left untreated, PAH is usually progressive over a period of months to years and is ultimately fatal.

The key diagnostic finding in PAH is a chronic respiratory acidosis in the absence of respiratory muscle weakness or impaired ventilatory mechanics (Fig. 22-2). Because patients can hyperventilate voluntarily and reduce PaCO_2 to normal or even hypocapnic levels, hypercapnia

may not be demonstrable in a single arterial blood sample, but the presence of an elevated plasma HCO_3^- level should draw attention to the underlying chronic disturbance. Despite normal ventilatory mechanics and respiratory muscle strength, ventilatory responses to chemical stimuli are reduced or absent (Fig. 22-2), and breath-holding time may be markedly prolonged without any sensation of dyspnea.

Patients with PAH maintain rhythmic respiration when awake, although the level of ventilation is below normal. However, during sleep, when breathing is critically dependent on the metabolic control system, there is typically a further deterioration in ventilation, with frequent episodes of central hypopnea or apnea.

PAH must be distinguished from other central hypoventilation syndromes that are secondary to underlying neurologic disease of the brainstem or chemoreceptors (Table 22-1). This distinction requires a careful neurologic investigation for evidence of brainstem or autonomic disturbances. Unrecognized respiratory neuromuscular disorders, particularly those that produce diaphragmatic weakness, are often misdiagnosed as PAH. However, such disorders can usually be suspected on clinical grounds (see later) and can be confirmed by the finding of reduced voluntary hyperventilation, as well as $\text{P}_{\text{I,max}}$ and $\text{P}_{\text{E,max}}$.

Patients with PAH must be cautioned against the use of sedative medications, which may readily induce acute respiratory failure. Some patients respond favorably to respiratory stimulant medications and to supplemental oxygen. However, the majority eventually require mechanical ventilatory assistance. Excellent long-term benefits can be achieved with diaphragmatic pacing by electrophrenic stimulation or with negative- or positive-pressure mechanical ventilation. The administration of such treatment only during sleep is sufficient in most patients.

RESPIRATORY NEUROMUSCULAR DISORDERS

Several primary disorders of the spinal cord, peripheral respiratory nerves, and respiratory muscles produce a chronic hypoventilation syndrome (Table 22-1). Hypoventilation usually develops gradually over a period of months to years and often first comes to attention when a relatively trivial increase in mechanical ventilatory load (e.g., mild airways obstruction) produces severe respiratory failure. In some of the disorders (e.g., motor neuron disease, myasthenia gravis, and muscular dystrophy), involvement of the respiratory nerves or muscles is usually a later feature of a more widespread disease. In other disorders, respiratory involvement can be an early or even isolated feature, and hence the underlying problem is often not suspected. Included in this category are postpolio syndrome (a form of chronic respiratory insufficiency that develops 20–30 years after recovery from poliomyelitis), myopathy

associated with adult acid maltase deficiency, and idiopathic diaphragmatic paralysis.

Generally, respiratory neuromuscular disorders do not result in chronic hypoventilation unless the patient has significant weakness of the diaphragm. Distinguishing features of bilateral diaphragmatic weakness include orthopnea, paradoxical movement of the abdomen in the supine posture, and paradoxical diaphragmatic movement under fluoroscopy. However, the absence of these features does not exclude diaphragmatic weakness. Important laboratory features are a decrease in forced vital capacity in the supine compared with the upright posture, a rapid deterioration of ventilation during a maximum voluntary ventilation maneuver, and reduced $P_{I_{max}}$ and $P_{E_{max}}$ (Fig. 22-2). More sophisticated investigations reveal reduced or absent transdiaphragmatic pressures, calculated from simultaneous measurement of esophageal and gastric pressures; reduced diaphragmatic EMG responses (recorded from an esophageal electrode) to transcutaneous phrenic nerve stimulation; and marked hypopnea and arterial oxygen desaturation during rapid eye movement sleep, when there is normally a physiologic inhibition of all nondiaphragmatic respiratory muscles and breathing becomes critically dependent on diaphragmatic activity.

The management of patients with chronic alveolar hypoventilation caused by respiratory neuromuscular disease involves treatment of the underlying disorder when feasible and mechanical ventilatory assistance as described for the PAH syndrome. However, electrophrenic diaphragmatic pacing is contraindicated in patients with these disorders, except for those with high cervical spinal cord lesions in whom the phrenic lower motor neurons and nerves are intact.

OBESITY-HYPOVENTILATION SYNDROME

Massive obesity represents a mechanical load to the respiratory system because the added weight on the rib cage and abdomen serves to reduce the compliance of the chest wall. As a result, the functional residual capacity (i.e., end-expiratory lung volume) is reduced, particularly in the recumbent posture. An important consequence of breathing at a low lung volume is that some airways, particularly those in the lung bases, may be closed throughout part or even all of each tidal breath, resulting in underventilation of the lung bases and widening of the $(A-a)PO_2$. Nevertheless, in the majority of obese individuals, central respiratory drive is increased sufficiently to maintain a normal $PaCO_2$. However, a small proportion of obese patients develop chronic hypercapnia, hypoxemia, and eventually polycythemia, pulmonary hypertension, and right-sided heart failure. Studies in mice demonstrate that genetically obese mice lacking circulating leptin also develop chronic hypoventilation that can be reversed by leptin infusions. In

humans with obesity-hypoventilation syndrome, serum leptin levels are elevated, suggesting that leptin resistance may play a role in the pathogenesis of the disorder.

In many patients, obstructive sleep apnea (Chap. 23) is a prominent feature, and even in patients without sleep apnea, sleep-induced hypoventilation is an important element of the disorder and contributes to its progression. Most patients demonstrate a decrease in central respiratory drive, which may be inherent or acquired, and many have mild to moderate degrees of airflow obstruction, usually related to smoking. Based on these considerations, several therapeutic measures can be of considerable benefit, including weight loss, cessation of smoking, elimination of obstructive sleep apnea, and enhancement of respiratory drive by medications such as progesterone.

HYPERVENTILATION AND ITS SYNDROMES

DEFINITION AND ETIOLOGY

Alveolar hyperventilation exists when $PaCO_2$ decreases below the normal range of 37–43 mmHg. *Hyperventilation* is not synonymous with *hyperpnea*, which refers to an increased minute volume of ventilation without reference to $PaCO_2$. Although hyperventilation is frequently associated with dyspnea, patients who are hyperventilating do not necessarily complain of shortness of breath, and conversely, patients with dyspnea need not be hyperventilating.

Numerous disease entities can be associated with alveolar hyperventilation (Table 22-2), but in all cases, the underlying mechanism involves an increase in respiratory drive that is mediated through either the behavioral or the metabolic respiratory control systems (Fig. 22-3). Thus, hypoxemia drives ventilation by stimulating the peripheral chemoreceptors, and several pulmonary disorders and congestive heart failure drive ventilation by stimulating afferent vagal receptors in the lungs and airways. Low cardiac output and hypotension stimulate the peripheral chemoreceptors and inhibit the baroreceptors, both of which increase ventilation. Metabolic acidosis, a potent respiratory stimulant, excites both the peripheral and central chemoreceptors and increases the sensitivity of the peripheral chemoreceptors to coexistent hypoxemia. Hepatic failure can also produce hyperventilation, presumably as a result of metabolic stimuli acting on the peripheral and central chemoreceptors.

Several neurologic and psychological disorders are thought to drive ventilation through the behavioral respiratory control system. Included in this category are psychogenic or anxiety hyperventilation and severe cerebrovascular insufficiency, which may interfere with the inhibitory influence normally exerted by cortical structures on the brainstem respiratory neurons. Rarely, disorders of

HYPERVENTILATION SYNDROMES	
1. Hypoxemia	4. Metabolic disorders
a. High altitude	a. Acidosis (diabetic, renal, lactic)
b. Pulmonary disease	b. Hepatic failure
c. Cardiac shunts	
2. Pulmonary disorders	5. Neurologic and psychogenic disorders
a. Pneumonia	a. Psychogenic or anxiety hyperventilation
b. Interstitial pneumonitis, fibrosis, edema	b. Central nervous system infection, tumors
c. Pulmonary emboli, vascular disease	
d. Bronchial asthma	6. Drug induced
e. Pneumothorax	a. Salicylates
f. Chest wall disorders	b. Methylxanthine derivatives
3. Cardiovascular disorders	c. β -Adrenergic agonists
a. Congestive heart failure	d. Progesterone
b. Hypotension	7. Miscellaneous
	a. Fever, sepsis
	b. Pain
	c. Pregnancy

the midbrain and hypothalamus induce hyperventilation, and it is conceivable that fever and sepsis also cause hyperventilation through effects on these structures. Several drugs cause hyperventilation by stimulating the central or peripheral chemoreceptors or by direct action on the brainstem respiratory neurons. Chronic hyperventilation is a normal feature of pregnancy and results from the effects of progesterone and other hormones acting on the respiratory neurons.

PHYSIOLOGIC AND CLINICAL FEATURES

Because hyperventilation is associated with increased respiratory drive, muscle effort, and minute volume of

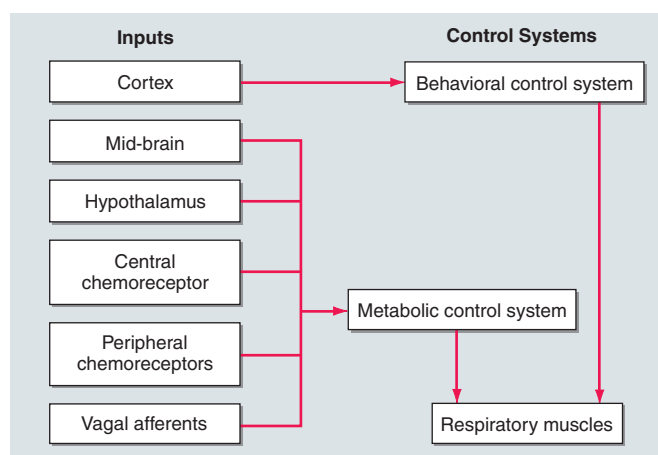


FIGURE 22-3 Schematic diagram of the mechanisms involved in alveolar hyperventilation. [Adapted from Phillipson EA, Slutsky AS: in Murray JF, Nadel JA (eds), *Textbook of Respiratory Medicine*, 3d ed, Philadelphia, Saunders, 2000.]

ventilation, the most frequent symptom associated with hyperventilation is dyspnea. However, there is considerable discrepancy between the degree of hyperventilation, as measured by PaCO_2 , and the degree of associated dyspnea. From a physiologic standpoint, hyperventilation is beneficial in patients who are hypoxemic because the alveolar hypocapnia is associated with an increase in alveolar and arterial PO_2 . Conversely, hyperventilation can also be detrimental. In particular, the alkalemia associated with hypocapnia may produce neurologic symptoms, including dizziness, visual impairment, syncope, and seizure activity (secondary to cerebral vasoconstriction); paresthesia, carpopedal spasm, and tetany (secondary to decreased free serum calcium); and muscle weakness (secondary to hypophosphatemia). It may also be associated with panic attacks, and severe alkalemia can induce cardiac arrhythmias and evidence of myocardial ischemia. Patients with a primary respiratory alkalosis are also prone to periodic breathing and central sleep apnea (Chap. 23).

DIAGNOSIS

In most patients with a hyperventilation syndrome, the cause is readily apparent on the basis of history, physical examination, and knowledge of coexisting medical disorders (see Table 22-2). In patients in whom the cause is not clinically apparent, investigation begins with arterial blood gas analysis, which establishes the presence of alveolar hyperventilation (decreased PaCO_2) and its severity. Equally important is the arterial pH, which generally allows the disorder to be classified as either a primary respiratory alkalosis (elevated pH) or a primary metabolic acidosis (decreased pH). Also of importance is the PaO_2 and calculation of the $(A-a)\text{PO}_2$, because a widened alveolar-arterial oxygen difference suggests a pulmonary disorder as the underlying cause. The finding of a reduced plasma HCO_3^- level establishes the chronic nature of the disorder and points toward an organic cause. Measurements of ventilation and arterial or transcutaneous PCO_2 during sleep are very useful in suspected psychogenic hyperventilation because such patients do not maintain the hyperventilation during sleep.

The disorders that most frequently give rise to unexplained hyperventilation are pulmonary vascular disease (particularly chronic or recurrent thromboembolism) and psychogenic or anxiety hyperventilation. Hyperventilation caused by pulmonary vascular disease is associated with exertional dyspnea, a widened $(A-a)\text{PO}_2$, and maintenance of hyperventilation during exercise. In contrast, patients with psychogenic hyperventilation typically complain of dyspnea at rest, but not during mild exercise, and of the need to sigh frequently. They are also more likely to complain of dizziness, sweating, palpitations, and paresthesia. During mild to moderate exercise, their hyperventilation tends to disappear and $(A-a)\text{PO}_2$ is normal, but heart rate and cardiac output may be increased relative to the metabolic rate.

R_x Treatment: **HYPERVENTILATION**

Mild alveolar hyperventilation is usually of relatively minor clinical consequence and therefore is generally managed by appropriate treatment of the underlying cause. In the few patients in whom alkalemia is thought to be inducing significant cerebral vasoconstriction, paresthesia, tetany, or cardiac disturbances, acute inhalation of a low concentration of CO₂ can be very beneficial. For patients with disabling psychogenic hyperventilation, careful explanation of the basis of their symptoms can be reassuring and is often sufficient. Others have benefited from β-adrenergic antagonists or an exercise program. Specific treatment for anxiety may also be indicated.

FURTHER READINGS

- ANNANE D et al: Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders. *Cochrane Database Sys Rev* 2:CD001941, 2000
- CHUNG F et al: STOP Questionnaire: A tool to screen patients for obstructive sleep apnea. *Anesthesiology* 108:812, 2008
- DOUGLAS IS et al: Acute-on-Chronic respiratory failure, in *Principles of Critical Care*, 3d ed, Hall JB, Schmidt GS and Wood LDH (eds). New York, McGraw-Hill, 2005, pp 549-565
- FANBURG BL, SICILIAN L (eds): Respiratory dysfunction in neuromuscular disease. *Clin Chest Med* 15:607, 1994
- GARDNER WN: The pathophysiology of hyperventilation disorders. *Chest* 109:516, 1996
- LAFFEY JG, KAVANAGH BP: Hypocapnia. *N Engl J Med* 347:43, 2002
- LITTLETON SW, MOKHLESI B: The Pickwickian Syndrome—Obesity Hypoventilation Syndrome. *Clin Chest Med* 30:467, 2009
- O'DONNELL CP et al: Leptin prevents respiratory depression in obesity. *Am J Respir Crit Care Med* 159:1477, 1999
- OLSON AL, ZWILLICH C: The obesity hypoventilation syndrome. *Am J Med* 118:948, 2005
- PHILLIPSON EA, DUFFIN J: Hypoventilation and hyperventilation syndromes, in *Murray and Nadel's Textbook of Respiratory Medicine*, 4th ed, RJ Mason et al (eds). Philadelphia, Saunders, 2005, pp 2069–2091
- PHIPPS PR: Association of serum leptin with hypoventilation in human obesity. *Thorax* 57:75, 2002
- SIMONDS AK: Recent advances in respiratory care for neuromuscular disease. *Chest* 130:1879, 2006
- TANKERSLEY CG et al: Genetic control of differential baseline breathing pattern. *J Appl Physiol* 82:874, 1997



CHAPTER 23

SLEEP APNEA

Neil J. Douglas

■ Obstructive Sleep Apnea	228
Definition	228
Mechanism of Obstruction	228
Epidemiology	229
Clinical Features	229
■ Central Sleep Apnea	232
Clinical Features	232
Investigation	232
■ Further Readings	232

OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea/hypopnea syndrome (OSAHS) is one of the most important medical conditions identified in the past 50 years. It is a major cause of morbidity, a significant cause of mortality throughout the world, and the most common medical cause of daytime sleepiness. Central sleep apnea (CSA) is a less common clinical problem.

DEFINITION

OSAHS may be defined as the coexistence of unexplained excessive daytime sleepiness with at least five obstructed breathing events (apnea or hypopnea) per hour of sleep (**Table 23-1**). This event threshold may need to be refined upward in the elderly. *Apneas* are defined in adults as breathing pauses lasting ≥ 10 s and hypopneas as ≥ 10 s during which there is continued breathing but the ventilation is reduced by at least 50% from the previous baseline during sleep. As a syndrome, OSAHS is the association of a clinical picture with specific abnormalities on testing; asymptomatic individuals with abnormal breathing during sleep should not be labeled as having OSAHS.

MECHANISM OF OBSTRUCTION

Apneas and hypopneas are caused by the airway being sucked closed on inspiration during sleep. This occurs as the upper airway dilating muscles—like all striated muscles—normally relax during sleep. In patients with OSAHS, the dilating muscles can no longer successfully oppose negative pressure within the airway during inspiration. The primary defect is not in the upper airway muscles, which function normally in OSAHS patients when awake. These patients have narrow upper airways already during wakefulness, but when they are awake, their airway-dilating muscles have higher than normal activity, which ensures airway patency. However, when they are asleep, muscle tone decreases, and the airway narrows; snoring may commence before the airway occludes, and apnea results. Apneas and hypopneas terminate when the subject arouses (i.e., awakens briefly) from sleep. This arousal is sometimes too subtle to be seen on the electroencephalogram but may be detected by cardiac acceleration, blood pressure elevation, or sympathetic tone increase. The arousal results in return of upper airway dilating muscle tone, and thus airway patency is resumed.

The factors predisposing to OSAHS by narrowing the pharynx include obesity—around 50% have a body mass index (BMI) >30 kg/m² in Western populations—and

TABLE 23-1

CLINICAL INDICATORS IN THE SLEEPY PATIENT

	OSAHS	NARCOLEPSY	IHS
Age of onset (years)	35–60	10–30	10–30
Cataplexy	No	Yes	No
Night sleep			
Duration	Normal	Normal	Long
Awakenings	Occasional	Frequent	Rare
Snoring	Yes, loud	Occasional	Occasional
Morning drunkenness	Occasional	Occasional	Common
Daytime naps			
Frequency	Usually few	Many	Few
Time of day	Afternoon/ evening	Afternoon/ evening	Morning
Duration	<1 h	<1 h	>1 h

Note: Features suggesting obstructive sleep apnea/hypopnea syndrome (OSAHS), narcolepsy, or idiopathic hypersomnolence (IHS).

shortening of the mandible, maxilla, or both. This change in jaw shape may be subtle and can be familial. Hypothyroidism and acromegaly predispose individuals to OSAHS by narrowing the upper airway with tissue infiltration. Other predisposing factors for OSAHS include male gender and middle age (40–65 years), myotonic dystrophy, Ehlers-Danlos syndrome, and perhaps also smoking.

EPIDEMIOLOGY

Broadly, the frequency of OSAHS is in the range of 1–4% of the middle-aged male population; it is around half as common in women. The syndrome also occurs in childhood, usually associated with tonsil or adenoid enlargement, and in elderly individuals, although the frequency is slightly lower in old age. Irregular breathing during sleep *without* daytime sleepiness is much more common, occurring in perhaps 25% of the middle-aged male population. However, because these individuals are asymptomatic, they do not have OSAHS, and there is no evidence at present that these events are harmful.

CLINICAL FEATURES

Randomized controlled treatment trials have shown that OSAHS causes daytime sleepiness; impaired vigilance, cognitive performance, and driving; depression; disturbed sleep; and hypertension. Daytime sleepiness may range from mild to irresistible, and the sleep attacks can be indistinguishable from those in narcolepsy. The sleepiness may result in an inability to work effectively and may damage interpersonal relationships and prevent socializing. The somnolence is dangerous when driving, with a three- to sixfold risk in accidents on the road or when

operating machinery. Experiments with normal subjects repeatedly aroused from sleep indicate that the sleepiness results, at least in part, from the repetitive sleep disruption associated with the breathing abnormality. The possible contribution from the recurrent hypoxemia requires further evaluation.

Other symptoms include difficulty concentrating, unrefreshing nocturnal sleep, nocturnal choking, nocturia, and decreased libido. Partners report nightly loud snoring in all postures, which may be punctuated by the silence of apneas. Partners often give a markedly different assessment of the extent of sleepiness.

Cardiovascular and Cerebrovascular Events

OSAHS increases 24-h mean blood pressure. The increase is greater in those with recurrent nocturnal hypoxemia, is at least 4–5 mmHg, and may be as great as 10 mmHg in those with >20% arterial oxygen desaturations per hour of sleep. This increase probably results from a combination of surges in blood pressure accompanying each arousal from sleep that end each apnea or hypopnea and from the associated 24-h increases in sympathetic tone.

Epidemiologic data in normal populations indicate that this increase in blood pressure would increase the risk of myocardial infarction by around 20% and stroke by about 40%. Although there have been no long-term randomized controlled trials (RCTs) to indicate whether this is true in OSAHS patients—and such studies would not be ethically defensible—observational studies suggest an increase in the risk of myocardial infarction and stroke in individuals with untreated OSAHS. Furthermore, epidemiologic studies suggest, but do not prove, increased vascular risk in normal subjects with increased apneas and hypopneas during sleep. Patients with recent stroke have a high frequency of apneas and hypopneas during sleep. These seem largely to be a consequence, not a cause, of the stroke and to decline over the weeks after the vascular event. There is no evidence that treating the apneas and hypopneas improves stroke outcome.

There has been debate for decades whether OSAHS is an adult form of sudden infant death syndrome. Although earlier studies showed no increase in sudden nocturnal deaths in OSAHS, a recent large study reported excess nocturnal deaths in subjects previously shown to have apneas and hypopneas during sleep.

Diabetes Mellitus

The association of OSAHS with diabetes mellitus is not just because obesity is common in both conditions. Recent data suggest that increased apneas and hypopneas during sleep are associated with insulin resistance independent of obesity. In addition, uncontrolled trials suggest that OSAHS can aggravate diabetes and that treatment of

Liver

Hepatic dysfunction has also been associated with irregular breathing during sleep. Non-alcohol-drinking subjects with apneas and hypopneas during sleep were found to have increased liver enzymes and more steatosis and fibrosis on liver biopsy independent of body weight.

Anesthetic Risk

Patients with OSAHS are at increased risk perioperatively because their upper airway may obstruct during the recovery period or as a consequence of sedation. Patients whose anesthesiologists have difficulty intubating are much more likely to have irregular breathing during sleep. Anesthesiologists should thus take sleep histories on patients preoperatively and take the appropriate precautions with those who might have OSAHS. This should include referring patients suspected of having OSAHS for investigation, and some elective operations may need to be postponed until the OSAHS is treated.

Differential Diagnosis

Causes of sleepiness that may need to be distinguished include (see Table 23-1):

- *Insufficient sleep:* This can usually be diagnosed by history.
- *Shift work:* This is a major cause of sleepiness, especially in those older than age 40 years old on either rotating shift or night shift work patterns.
- *Psychological/psychiatric causes:* Depression is a major cause of sleepiness.
- *Drugs:* Both stimulant and sedative drugs can produce sleepiness.
- *Narcolepsy:* Around 50 times less common than OSAHS, narcolepsy is usually evident from childhood or the teenage years and is associated with cataplexy.
- *Idiopathic hypersomnolence:* This is an ill-defined condition typified by long sleep duration and sleepiness.
- *Phase alteration syndromes:* Both the phase delay and the less common phase advancement syndromes are characterized by sleepiness at the characteristic time of day.

Who to Refer for Diagnosis

Anyone whose troublesome sleepiness is not readily explained and rectified by considering the above differential diagnosis should be referred to a sleep specialist. The guideline I use for patients with troublesome sleepiness includes those with an Epworth Sleepiness Score >11 (Table 23-2) and those for whom sleepiness during work or driving poses problems. However, the Epworth Score

TABLE 23-2

EPWORTH SLEEPINESS SCORE

How often are you likely to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the *most appropriate number* for each situation:

0 = would never doze
 1 = slight chance of dozing
 2 = moderate chance of dozing
 3 = high chance of dozing

Sitting and reading
Watching TV
Sitting, inactive in a public place (e.g., a theater or a meeting)
As a passenger in a car for 1 h without a break
Lying down to rest in the afternoon when circumstances permit
Sitting and talking to someone
Sitting quietly after lunch without alcohol
In a car while stopped for a few minutes in traffic
TOTAL

Source: From Johns MW: A new method for measuring daytime sleepiness: The Epworth sleepiness scale. *Sleep* 14:540, 1991.

is not a perfect measure for detecting troublesome sleepiness because many whose life is troubled by frequently fighting sleepiness but who never doze will correctly score themselves as having a low Epworth Score. The patient and his or her partner often give divergent scores for the patient’s sleepiness, and in such cases, the higher of the two scores should be used.

Diagnosis

OSAHS is a condition requiring lifelong treatment, and the diagnosis needs to be made or excluded with certainty, when possible, by a specialist. This hinges on obtaining a good sleep history from the patient and partner, including asking both to complete sleep questionnaires, including the Epworth Sleepiness Score (see Table 23-2). Physical examination must include assessment of obesity; jaw structure; the upper airway; blood pressure; and possible predisposing causes, including hypothyroidism and acromegaly (see earlier).

In those with appropriate clinical features, the diagnostic test must demonstrate recurrent breathing pauses during sleep. This may be a full polysomnographic examination with recording of multiple respiratory and neurophysiologic signals during sleep. Increasingly, and especially outside the United States, most diagnostic tests are “limited studies”—recording respiratory and oxygenation patterns overnight without neurophysiologic

recording. Such approaches in expert hands produce good patient outcomes and are cost effective. It is sensible to use such limited sleep studies as the first-line diagnostic test and then allow positively diagnosed patients to proceed to treatment. However, a reasonable approach at present is for patients with troublesome sleepiness but negative limited studies to then have polysomnography to exclude or confirm OSAHS.

Rx Treatment: **OBSTRUCTIVE SLEEP APNEA**

WHOM TO TREAT Evidence obtained from robust RCTs suggests that treatment improves symptoms, sleepiness, driving, cognition, mood, quality of life, and blood pressure in patients who have Epworth scores of >11, troublesome sleepiness while driving or working, and >15 apneas + hypopneas per hour of sleep. For those with similar degrees of sleepiness and 5–15 events per hour of sleep, RCTs indicate improvements in symptoms, including subjective sleepiness, with less strong evidence indicating gains in cognition and quality of life. There is no evidence of blood pressure improvements in this group, nor is there is evidence that treating nonsleepy subjects improves their symptoms, function, or blood pressure. Thus, treatment cannot be advocated for this large group.

HOW TO TREAT All patients diagnosed with OSAHS should have the condition and its significance explained to them and to their partner. This should be accompanied by provision of written or Web-based information and a discussion of the implications of the local regulations for driving. Rectifiable predispositions should be discussed; this often includes weight loss and sometimes reduction of alcohol consumption to reduce caloric intake and because alcohol acutely decreases upper airway dilating muscle tone, thus predisposing patients to obstructed breathing. Sedative drugs, which also affect airway tone, should be carefully withdrawn.

Continuous Positive Airway Pressure Continuous positive airway pressure (CPAP) therapy works by blowing the airway open during sleep, usually with pressures of 5–20 cmHg. CPAP has been shown in randomized placebo-controlled trials to improve breathing during sleep, sleep quality, sleepiness, blood pressure, vigilance, cognition, and driving ability, as well as mood and quality of life in patients with OSAHS. However, this is obtrusive therapy, and care must be taken to explain the need for the treatment to the patient and his or her partner and to support all patients on CPAP intensively, providing access to telephone support and regular follow-up. Initiation should include finding the most comfortable mask from the ranges of several manufacturers and trying the system for at least 30 min during

the day to prepare for the overnight trial. An overnight monitored trial of CPAP is used to identify the pressure required to keep the patient's airway patent. The development of pressure-varying CPAP machines may make the in-laboratory CPAP night trial unnecessary, but treatment must be initiated in a supportive environment. Thereafter, patients can be treated with fixed-pressure CPAP machines set at the determined pressure or by a self-adjusting, intelligent CPAP device. The main side effect of CPAP is airway drying, which can be countered using an integral heated humidifier. CPAP use, like that of all therapies, is imperfect, but around 94% of patients with severe OSAHS are still using their therapy after 5 years on objective monitoring.

Mandibular Repositioning Splint Also called oral devices, mandibular repositioning splints (MRSs) work by holding the lower jaw and the tongue forward, thereby widening the pharyngeal airway. MRSs have been shown in RCTs to improve OSAHS patients' breathing during sleep, daytime somnolence, and blood pressure. Because many devices of differing design with unknown relative efficacy are available, these results cannot be generalized to all MRSs. Self-reports of the long-term use of devices suggest high dropout rates.

Surgery Four forms of surgery have a role in OSAHS, although it must always be remembered that these patients have an increased perioperative risk. Bariatric surgery can be curative in morbidly obese patients. Tonsillectomy can be highly effective in children but rarely in adults. Tracheostomy is curative but rarely used because of the associated morbidity; nevertheless, it should not be overlooked in extremely advanced cases. Jaw advancement surgery—particularly maxillo-mandibular osteotomy—is effective in those with retrognathia (posterior displacement of the mandible) and should be particularly considered in young and thin patients. There is no robust evidence that pharyngeal surgery, including uvulopalatopharyngoplasty (whether by scalpel, laser, or thermal techniques) helps OSAHS.

Drugs Unfortunately, no drugs are clinically useful in the prevention or reduction of apneas and hypopneas. A marginal improvement in sleepiness in patients who remain sleepy despite CPAP can be produced by modafinil, but the clinical value is debatable and the financial cost significant.

CHOICE OF TREATMENT CPAP and MRS are the two most widely used and best evidence-based therapies. Direct comparisons in RCTs indicate better outcomes with CPAP in terms of apneas and hypopneas, nocturnal oxygenation, symptoms, quality of life, mood, and vigilance. Adherence to CPAP is generally better than to an MRS, and evidence suggests that CPAP improves driving; there are no such data on MRSs. Thus,

CPAP is the current treatment of choice. However, MRSs are evidence-based second-line therapy in those who fail CPAP. In younger, thinner patients, maxillo-mandibular advancement should be considered.

HEALTH RESOURCES Untreated OSAHS patients are heavy users of health care and dangerous drivers; they also work beneath their potential. Treatment of OSAHS with CPAP is cost-effective in terms of reducing health care costs of associated illness and associated accidents.

CENTRAL SLEEP APNEA

CSAs are respiratory pauses caused by lack of respiratory effort. These occur occasionally in normal subjects, particularly at sleep onset and in REM sleep, and are transiently increased after ascent to altitude. Recurrent CSA is most commonly found in the presence of cardiac failure or neurologic disease, especially stroke. Spontaneous central sleep syndrome is rare and can be classified on the basis of the arterial PCO_2 .

Hypercapnic CSA occurs in conjunction with diminished ventilatory drive in Ondine's curse (central alveolar hypoventilation). Patients with normocapnic spontaneous CSA have a normal or low arterial PCO_2 when awake, with brisk ventilatory responses to hypercapnia. This combination results in unstable ventilatory control, with subjects breathing close to or below their apneic threshold for PCO_2 during sleep; this apneic tendency is compounded by cycles of arousal-induced hyperventilation, inducing further hypocapnia.

CLINICAL FEATURES

Patients may present with sleep maintenance insomnia, which is relatively unusual in those with OSAHS. Day-time sleepiness may occur.

INVESTIGATION

Many apneas previously labeled central because of absent thoracoabdominal movement are actually obstructive; identification of movement is particularly difficult in very obese patients. CSA can only be identified with certainty if either esophageal pressure or respiratory muscle electromyography is recorded and shown to be absent during the events.

Rx Treatment: CENTRAL SLEEP APNEA

Patients with underlying cardiac failure should have their failure treated appropriately. CPAP may improve outcome but is difficult to initiate and has not been shown to improve survival. Patients with spontaneous normocapnic CSA may be successfully treated with acetazolamide. In a minority of patients, CPAP is effective, perhaps because in some patients with OSAHS, pharyngeal collapse initiates reflex inhibition of respiration, and these episodes are prevented by CPAP. Oxygen and nocturnal nasal positive-pressure ventilation may also be tried.

FURTHER READINGS

- BRADLEY TD et al: Obstructive sleep apnoea and its cardiovascular consequences. *Lancet* 373:82, 2009
- DOUGLAS NJ: *Clinicians' Guide to Sleep Medicine*. London, Arnold, 2002
- : Home diagnosis of the obstructive sleep apnoea/hypopnoea syndrome. *Sleep Med Rev* 7:53, 2003
- ECKERT DJ et al: Central sleep apnea: Pathophysiology and treatment. *Chest* 131:595, 2007
- ENGLEMAN HM et al: Randomized crossover trial of two treatments for sleep apnea/hypopnea syndrome: Continuous positive airway pressure and mandibular repositioning splint. *Am J Respir Crit Care Med* 165:855, 2002
- MARIN JM et al: Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: An observational study. *Lancet* 365:1046, 2005
- PACK AL et al: Risk factors for excessive sleepiness in older adults. *Ann Neurol* 59:893, 2006
- SOMERS VK et al: Sleep apnea and vascular disease. *Circulation* 118:1080, 2008
- SUNDARAM S et al: Surgery for obstructive sleep apnoea. *Cochrane Database Syst Rev* 2005, CD001004
- WHITELAW WA et al: Clinical usefulness of home oximetry compared with polysomnography for assessment of sleep apnea. *Am J Respir Crit Care Med* 171:188, 2005
- YAGGI HK et al: Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med* 353:2034, 2005
- YOUNG T et al: Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. *Sleep* 31:1071, 2008



CHAPTER 24

LUNG TRANSPLANTATION

Elbert P. Trulock

Indications	233
Recipient Selection	233
Waiting List and Organ Allocation	234
Transplant Procedure	234
Posttransplantation Management	235
Outcomes	235
■ Further Readings	238

Lung transplantation is a therapeutic consideration for patients with most nonmalignant end-stage lung diseases. After an initial period of rapid growth from 1990 through 1995, activity has increased slowly to ~1700 transplants per year worldwide. The demand for transplantation exceeds the supply of donor organs, and the waiting time is often lengthy. Recognizing the window of opportunity for transplantation in the clinical course of various lung diseases is crucial because deaths while awaiting transplantation are not unusual. In appropriately selected recipients, transplantation prolongs survival and improves quality of life, but it is also associated with significant morbidity and mortality.

INDICATIONS

The indications for lung transplantation span the gamut of lung diseases (Table 24-1). The distribution reflects the prevalence and natural history of the diseases, and the most common indications are chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), cystic fibrosis (CF), α_1 -antitrypsin deficiency emphysema, and primary pulmonary hypertension (PPH). Others indications given in Table 24-1 comprise many less prevalent lung diseases.

RECIPIENT SELECTION

Transplantation should be considered when other therapeutic options have been exhausted and when the patient's

prognosis will be improved by the procedure. Survival rates after transplantation can be compared with predictive indices for the underlying disease, but each patient's clinical course must be integrated into the assessment, too. In any case, projected survival after transplantation should exceed life expectancy without the procedure. Quality of life is the primary motive for transplantation for many patients, and the prospect of an improved quality-adjusted survival is often attractive, even if the survival advantage itself might be marginal.

Disease-specific guidelines for referring patients for transplantation are summarized in Table 24-2, and these are intended to identify patients who may benefit from transplantation. Candidates for lung transplantation are thoroughly screened for any comorbidity that might adversely affect the outcome. Suitable candidates should have clinically and physiologically severe lung disease, but otherwise they must be in reasonably good health. The upper age limit is ~65 years at most centers.

Typical exclusions include HIV infection, chronic hepatitis B antigenemia or chronic active hepatitis C infection, uncured malignancy, active cigarette smoking, drug or alcohol dependency or abuse, uncontrolled or untreatable pulmonary or extrapulmonary infection, irreversible physical deconditioning, chronic noncompliance with medical care, and significant disease of any vital organ other than the lungs. Other problems that might increase the risk of complications or might be aggravated by the posttransplantation medical regimen constitute

INDICATIONS FOR ADULT LUNG TRANSPLANTATION (1995–2004)

DIAGNOSIS	SINGLE LUNG TRANSPLANTATION (n = 6731)		BILATERAL LUNG TRANSPLANTATION (n = 6276)		TOTAL (n = 13,007)	
Chronic obstructive pulmonary disease	3,541	52.6%	1,462	23.3%	5,003	38.5%
Idiopathic pulmonary fibrosis	1,618	24.0%	639	10.0%	2,257	17.4%
Cystic fibrosis	151	2.2%	2,002	31.9%	2,153	16.6%
α_1 -Antitrypsin deficiency emphysema	554	8.2%	571	9.1%	1,125	8.6%
Primary pulmonary hypertension	79	1.2%	436	6.9%	515	4.0%
Sarcoidosis	157	2.3%	166	2.6%	323	2.5%
Bronchiectasis	45	0.7%	309	4.9%	354	2.7%
Eisenmenger's syndrome	13	0.2%	118	1.9%	131	1.0%
Lymphoangiomyomatosis	55	0.8%	83	1.3%	138	1.0%
Retransplantation	129	1.9%	104	1.7%	233	1.8%
Others	389	5.8%	386	6.2%	775	6.0%

Source: Adapted from Trulock et al.

relative contraindications. Some typical issues are ventilator-dependent respiratory failure, previous thoracic surgical procedures, osteoporosis, systemic hypertension, diabetes mellitus, obesity or cachexia, and psychosocial problems. Chronic infection with antibiotic-resistant *Pseudomonas* spp., some *Burkholderia* spp., *Aspergillus* spp., or nontuberculous mycobacteria is a unique concern in some patients with CF or other diseases that have a component of bronchiectasis or chronic bronchitis. The potential impact of these and many other factors has to be judged in clinical context to determine an individual candidate's suitability for transplantation.

WAITING LIST AND ORGAN ALLOCATION

Organ allocation policies are influenced by ethical, medical, geographical, and political factors, and systems vary from country to country. Regardless of the system, potential recipients are placed on a waiting list and must be matched for blood group compatibility and, with some latitude, for lung size with an acceptable donor. In the United States, a priority algorithm for allocating donor lungs was implemented in May 2005. Priority is determined by a lung allocation score that weighs both the patient's risk of death on the waiting list and the likelihood of survival after transplantation. Both the type and the severity of lung disease affect the allocation score; relevant parameters must be updated periodically but can be submitted whenever the patient's condition changes. However, this priority system does not diminish the importance of timely referral.

The impact of the priority allocation scheme on key outcome measures has not been analyzed yet; however, this information will be forthcoming and may lead to further refinement of the allocation system. Under the previous seniority system, the median time to transplantation was

1104 days for patients who initially registered on the national waiting list in 1998. Approximately 10% of the patients on the waiting list died before transplantation, but the death rate while waiting was much higher for patients with IPF, PPH, or CF than for those with COPD or α_1 -antitrypsin deficiency emphysema.

TRANSPLANT PROCEDURE

Bilateral transplantation is mandatory for patients with bronchiectasis because the risk of spillover infection from a remaining native lung precludes single lung transplantation. Heart–lung transplantation is obligatory for those with Eisenmenger's syndrome with complex anomalies that cannot be readily repaired in conjunction with lung transplantation and for concomitant end-stage lung and heart disease. However, cardiac replacement is not necessary for those with cor pulmonale because right ventricular function will recover when pulmonary vascular afterload is normalized by lung transplantation.

Either bilateral or single lung transplantation is an acceptable alternative for patients with other diseases unless there is a special consideration. Bilateral transplantation provides more reserve lung function as a buffer against complications, and it has been increasingly used for many indications. In recipients with COPD and α_1 -antitrypsin deficiency emphysema, survival has been significantly better after bilateral transplantation, but there has not been a significant difference in survival between the two procedures for other diseases.

Living donor lobar transplantation has a limited role in adult lung transplantation. It has been performed predominantly in teenagers and young adults with CF. A right lower lobe is obtained from one living donor and a left lower lobe from another, and these lobes are implanted to replace the right and left lungs, respectively, in the

TABLE 24-2

DISEASE-SPECIFIC GUIDELINES FOR SELECTING CANDIDATES FOR LUNG TRANSPLANTATION

COPD and α_1 -antitrypsin deficiency emphysema
 $FEV_1 < 25\%$ of predicted normal value
 (post-bronchodilator)
 $Paco_2 \geq 55$ mmHg
 Pulmonary arterial hypertension (mean pulmonary artery pressure >25 mmHg)

Cystic fibrosis/bronchiectasis
 $FEV_1 < 30\%$ of predicted normal value
 $Paco_2 > 50$ mmHg
 $PaO_2 < 50$ mmHg (on room air)
 Pulmonary arterial hypertension
 Adverse clinical course in spite of optimal medical management
 Increasing hospitalizations
 Recurrent, massive hemoptysis
 Rapidly declining FEV_1

Idiopathic pulmonary fibrosis
 VC or $TLC < 60\%$ – 70% of predicted normal value
 $DLCO < 50\%$ – 60% of predicted normal value
 Pulmonary arterial hypertension
 Hypoxemia ($PaO_2 < 60$ mmHg or $SpO_2 < 90\%$) at rest or with activity (on room air)
 Progressive disease despite drug therapy

Primary pulmonary hypertension
 NYHA functional class III or IV despite optimal drug therapy
 Unfavorable hemodynamic profile
 Right atrial pressure >15 mmHg
 Mean pulmonary artery pressure >55 mmHg
 Cardiac index < 2 (L/min)/ m^2

Note: COPD, chronic obstructive pulmonary disease; $DLCO$, diffusing capacity for carbon monoxide; FEV_1 , forced expiratory volume in 1 second; NYHA, New York Heart Association; PaO_2 , partial pressure of oxygen in arterial blood; $Paco_2$, partial pressure of oxygen carbon dioxide in arterial blood; SpO_2 , oxygen saturation by pulse oximetry; TLC , total lung capacity; VC , vital capacity. VC , vital capacity; TLC , total lung capacity; FEV_1 , forced expiratory volume in 1 s; $DLCO$, diffusing capacity for carbon monoxide; PaO_2 and $Paco_2$, partial pressure of oxygen and carbon dioxide, respectively, in arterial blood; SpO_2 , oxygen saturation by pulse oximetry.

Source: Modified from International Guidelines for the Selection of Lung Transplant Candidates: Am J Respir Crit Care Med 158:335, 1998.

recipient. Because a lobe must replace a whole lung, donor–recipient size considerations are crucial. The results have been comparable to those with transplantation from cadaveric donors. The usual morbidities associated with a lobectomy have been encountered in the donors, but no death has yet been reported. Because of ethical concerns, this approach is usually restricted to patients who are unlikely to survive the wait for a cadaveric donor.

POSTTRANSPLANTATION MANAGEMENT

Induction therapy with an antilymphocyte globulin or an interleukin 2 receptor antagonist is used by some centers,

and a three-drug maintenance immunosuppressive regimen that includes a calcineurin inhibitor (cyclosporine or tacrolimus), a purine synthesis antagonist (azathioprine or mycophenolate mofetil), and prednisone is customary. Subsequently, other drugs such as sirolimus may be substituted in the maintenance regimen for various reasons. Prophylaxis for *Pneumocystis jiroveci* pneumonia is standard, and prophylaxis against cytomegalovirus (CMV) infection is prescribed in many protocols. The dose of cyclosporine or tacrolimus is adjusted by blood-level monitoring. Both are metabolized by the hepatic cytochrome P450 system, and interactions with medications that affect this pathway can significantly alter the clearance and blood levels of these key immunosuppressants.

Routine management is designed to monitor the allograft, regulate immunosuppressive therapy, and detect problems or complications expeditiously. The techniques include periodic contact with a transplant nurse coordinator, appointments with a physician, chest radiographs, blood tests, spirometry, and bronchoscopy. Lung function rapidly improves and then stabilizes by 3 to 6 months after transplantation. Subsequently, the coefficient of variation in spirometric measurements is small, and a sustained decline of 10% to 15% or more signals a potentially significant problem.

OUTCOMES

Survival

Major registries publish survival (Table 24-3) and other outcomes annually, and these reports are accessible via the Internet (<http://www.isHLT.org>; <http://www.ustransplant.org>).

The main sources of perioperative mortality include technical complications of the operation, primary graft dysfunction, and infections. Acute rejection and CMV infection are common problems in the first year, but neither is usually fatal. Beyond the first year, chronic rejection and non-CMV infections cause the majority of deaths.

Function

Regardless of the disease, successful transplantation impressively restores cardiopulmonary function. After bilateral transplantation, standard pulmonary function test results are typically normal; after single lung transplantation, the remaining diseased lung typically contributes a mild abnormality. Formal exercise testing usually demonstrates some impairment in maximum work rate and maximum oxygen uptake, but few recipients report any limitation to activity.

Quality of Life

Both overall and health-related quality of life are enhanced. With multidimensional profiles, improvements extend

TABLE 24-3

RECIPIENT SURVIVAL, BY PRETRANSPLANTATION DIAGNOSIS (1994–2003)

DIAGNOSIS	n	SURVIVAL RATE, %				
		3 MONTHS	1 YEAR	3 YEARS	5 YEARS	10 YEARS
Chronic obstructive pulmonary disease	4888	90	81	63	48	19
α_1 -Antitrypsin deficiency emphysema	1127	86	76	60	51	31
Cystic fibrosis	1934	88	81	65	54	32
Idiopathic pulmonary fibrosis	2058	81	69	54	42	15
Primary pulmonary hypertension	553	73	65	56	46	26

Source: Data from Trulock et al.

across most domains and are sustained longitudinally unless chronic rejection or some other complication develops. Other problems that detract from quality of life include renal dysfunction and drug side effects.

Cost

The cost of transplantation depends on the health care system, other health care policies, and economic factors that vary from country to country. In the 1990s, transplant hospitalization costs in the range of \$160,000 were reported from two centers in the United States. At one of these centers, the average charge for posttransplantation care was ~\$132,000 in the first year and \$54,000 in subsequent years. The distribution of costs after lung transplantation was estimated by a center in the United Kingdom as 57% for routine care, including medications, clinic appointments, and tests; 17% for rejection episodes; and 26% for infectious complications.

Complications

Lung transplantation can be complicated by a variety of problems. Aside from those that are unique to transplantation, side effects and toxicities of the immunosuppressive medications can cause new medical problems or aggravate preexisting conditions (Table 24-4).

Graft Dysfunction

Primary graft dysfunction is an acute lung injury that is a manifestation of insults that are inherent in the transplantation process, and it has been referred to as *reperfusion edema*, *reimplantation response*, and *ischemia-reperfusion injury*. The principal clinical features are diffuse pulmonary infiltrates and hypoxemia within 72 h of transplantation, but the severity is variable. Pulmonary venous obstruction and hyperacute rejection can produce a similar pattern, and cardiogenic pulmonary edema and pneumonia must also be excluded. The treatment is

the conventional, supportive paradigm for acute lung injury, but inhaled nitric oxide and extracorporeal membrane oxygenation have been used successfully in severe cases. Most recipients recover, but severe primary graft dysfunction is a leading cause of early morbidity and mortality.

Airway Complications

The bronchial blood supply to the donor lung is disrupted, and bronchial revascularization is not widely practiced. Consequently, when the lung is implanted in the recipient, the bronchus is dependent on retrograde bronchial blood flow through the pulmonary circulation and is vulnerable to ischemia.

The prevalence of major airway complications—dehiscence, stenosis, and bronchomalacia—has ranged from 4–20%, but the associated mortality has been very low. Bronchoscopic debridement or dilatation is sufficient in many cases, but stent placement is often necessary if a stricture or bronchomalacia evolves.

Acute Rejection

This is an immunologic response to alloantigen recognition, and it is characterized by arteriolar and bronchiolar lymphocytic inflammation. With current immunosuppressive regimens, ~50% recipients have at least one episode of acute rejection in the first year. Acute rejection can be clinically silent, or it can be manifested by nonspecific symptoms or signs that may include cough, low-grade fever, dyspnea, hypoxemia, inspiratory crackles, interstitial infiltrates, and declining lung function; however, the clinical impression is not reliable. The diagnosis should be confirmed by transbronchial biopsy, and a standardized pathologic classification scheme for rejection is used to grade the biopsies. Treatment usually includes a short course of high-dose steroid therapy and adjustment of the maintenance immunosuppressive

TABLE 24-4

MAJOR POTENTIAL COMPLICATIONS OF LUNG TRANSPLANTATION AND POSTTRANSPLANTATION IMMUNOSUPPRESSION

CATEGORY	COMPLICATION
Allograft	Acute graft dysfunction; anastomotic dehiscence or stenosis; ischemic airway injury with bronchostenosis or bronchomalacia; rejection; infections
Thoracic	Phrenic nerve injury (diaphragmatic dysfunction; recurrent laryngeal nerve injury) vocal cord dysfunction; cervical ganglia injury (Horner's syndrome); chylothorax; pneumothorax; pleural effusion
Cardiovascular	Air embolism; postoperative pericarditis; venous thromboembolism; supraventricular dysrhythmias; systemic hypertension
Gastrointestinal	Esophagitis (especially <i>Candida</i> spp. or CMV); gastroparesis; gastroesophageal reflux; <i>Clostridium difficile</i> toxin diarrhea or pseudomembranous colitis
Hepatobiliary	Hepatitis (especially CMV or drug induced)
Renal	Calcineurin inhibitor nephropathy; hemolytic-uremic syndrome (thrombotic microangiopathy)
Neurologic	Tremors; seizures; reversible posterior leukoencephalopathy; headaches
Musculoskeletal	Steroid myopathy; rhabdomyolysis (cyclosporine + HMG-CoA reductase inhibitor treatment); osteoporosis; avascular necrosis
Metabolic	Obesity; diabetes mellitus; hyperlipidemia; idiopathic hyperammonemia
Hematologic	Anemia; leukopenia; thrombocytopenia; thrombotic microangiopathy
Oncologic	Lymphoproliferative disease and lymphoma; skin cancers; other malignancies

Note: CMV, cytomegalovirus; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-CoA.

regimen, but more intensive therapy may be necessary for persistent or recurrent episodes.

Chronic Rejection

This complication is the main impediment to better medium-term survival rates, and it is the source of substantial morbidity because of its impact on lung function and quality of life. The pathogenesis is still a conundrum, but both alloimmune inflammatory and nonalloimmune fibroproliferative mechanisms are probably important.

Clinically, chronic rejection is a form of graft dysfunction that is synonymous with bronchiolitis obliterans syndrome (BOS). BOS is characterized physiologically by airflow limitation and pathologically by bronchiolitis obliterans. Transbronchial biopsies are relatively insensitive for detecting bronchiolitis obliterans, and the diagnosis of BOS is usually based on a sustained decrement ($\geq 20\%$) in the forced expiratory volume in 1 second (FEV_1). A smaller decline in FEV_1 ($\geq 10\%$) or a decrease in the forced expiratory flow (FEF)_{25–75%} may presage BOS.

The prevalence of BOS approaches 50% by 5 years after transplantation. Both antecedent acute rejection and lymphocytic bronchiolitis are risk factors for subsequent BOS, and CMV pneumonitis has been implicated inconsistently. Patients with BOS are usually treated with augmented immunosuppression. Although immunosuppressive therapy may stabilize lung function, the overall results of

treatment have been disappointing, probably because the fibroproliferative process is already well established. Retransplantation may be an option in ambulatory recipients without other complications, but in many cases, the risk is prohibitive.

Infection

The lung allograft is especially susceptible to infection, and infection has been one of the leading causes of death. In addition to a blunted immune response from immunosuppressive drugs, other normal defenses are breached—the cough reflex is diminished, and mucociliary clearance is impaired in the transplanted lung. The spectrum of infections includes both opportunistic and nonopportunistic pathogens.

Bacterial bronchitis and pneumonia can occur at any time but are almost universal in the postoperative period. Later, episodes of bronchitis are quite common, especially in recipients with BOS, and *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus* is often the culprit.

CMV is the most frequent viral infection. Although gastroenteritis, colitis, and hepatitis can occur, CMV viremia and CMV pneumonia are the main illnesses. Most episodes occur in the first 6 months, and treatment with ganciclovir is effective unless resistance develops with repeated exposure. Other community-acquired viruses, such as influenza, parainfluenza, and respiratory syncytial virus, also contribute to respiratory complications. *Aspergillus* spp. has been the most problematic fungal infection.

Other potential complications are summarized in Table 24-4, and many of these are related to side effects or toxicities of the immunosuppressive drugs. The management of patients with most of these general medical problems is guided by standard practices for the condition, but the complex milieu of transplantation dictates close collaboration and good communication among health care providers.

ACKNOWLEDGMENT

Dr. G. Alexander Patterson and Dr. Joel D. Cooper were co-authors of this chapter in the 16th edition of Harrison's Principles of Internal Medicine. Some of the materials have been carried over into this edition.

FURTHER READINGS

- BOASQUEVISCUCQ CH et al: Surgical therapies for lung disease: Transplant and lung reduction. *Proc Am Thorac Soc* 6(1), 2009
- ESTENNE M et al: Bronchiolitis obliterans syndrome 2001: An update of the diagnostic criteria. *J Heart Lung Transplant* 21:297, 2002
- KOTLOFF RM, AHYA VN: Medical complications of lung transplantation. *Eur Respir J* 23:334; 2004
- LANDE JD et al: Novel insights into lung transplant rejection by microarray analysis. *Proc Am Thorac Soc* 4:44, 2007
- ORENS JB et al: International guidelines for the selection of lung transplant candidates: 2006 update—A consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 25:745, 2006
- TRULOCK EP et al: Registry of the International Society for Heart and Lung Transplantation: Twenty-second official adult lung and heart-lung transplant report—2005. *J Heart Lung Transplant* 24:956, 2005



CHAPTER 25

INFECTIONS IN LUNG TRANSPLANT RECIPIENTS

Robert Finberg ■ Joyce Fingerroth

Pretransplantation Evaluation	239
■ Infections in Lung Transplant Recipients	240
Miscellaneous Infections in Lung Transplantation	241
■ Vaccination of Transplant Recipients	242
■ Further Readings	243

The evaluation of infections in transplant recipients involves consideration of both the donor and the recipient of the transplanted organ. Infections after transplantation are complicated by the use of drugs that are necessary to enhance the likelihood of survival of the transplanted organ but that also cause the host to be immunocompromised. Thus, what might have been a latent or asymptomatic infection in an immunocompetent donor or in the recipient before therapy can become a life-threatening problem when the recipient becomes immunosuppressed.

PRETRANSPLANTATION EVALUATION

A variety of organisms have been transmitted by organ transplantation. Careful attention to the sterility of the medium used to process the organ combined with meticulous microbiologic evaluation reduces rates of transmission of bacteria that may be present or grow in the organ culture medium. From 2% to >20% of donor kidneys are estimated to be contaminated with bacteria—in most cases, with the organisms that colonize the skin or grow in the tissue culture medium used to bathe the donor kidney while it awaits implantation. The reported rate of bacterial contamination of transplanted stem cells (bone marrow, peripheral blood, cord blood) is as high as 17% but is most commonly ~1%. The use of enrichment columns and monoclonal-antibody depletion procedures results in a higher incidence of contamination.

In one series of patients receiving contaminated products, 14% had fever or bacteremia, but none died. Results of cultures performed at the time of cryopreservation and at the time of thawing were helpful in guiding therapy for the recipient.

In many transplantation centers, transmission of infections that may be latent or clinically inapparent in the donor organ has resulted in the development of specific donor-screening protocols. In addition to ordering serologic studies focused on viruses such as herpes-group viruses [herpes simplex virus types 1 and 2 (HSV-1, HSV-2), varicella-zoster virus (VZV), cytomegalovirus (CMV), human herpesvirus (HHV) type 6, Epstein-Barr virus (EBV), and Kaposi's sarcoma-associated herpesvirus (KSHV)] as well as hepatitis B and C viruses, human immunodeficiency virus (HIV), human T cell lymphotropic virus type I, and West Nile virus, donors should be screened for parasites such as *Toxoplasma gondii* and *Trypanosoma cruzi* (the latter particularly in Latin America). Clinicians caring for prospective organ donors should also consider assessing stool for parasites, should examine chest radiographs for evidence of granulomatous disease, and should perform purified protein derivative (PPD) skin testing or obtain blood for immune cell-based assays that detect active or latent *Mycobacterium tuberculosis* infection. An investigation of the donor's dietary habits (e.g., consumption of raw meat or fish or of unpasteurized dairy products), occupations or avocations (e.g., gardening or spelunking), and travel

240 history (e.g., travel to areas with endemic fungi) is also mandatory. It is expected that the recipient will have been likewise assessed. Because of immune dysfunction resulting from chemotherapy or underlying chronic disease, however, direct testing of the recipient may prove less reliable. This chapter considers aspects of infection unique to various transplantation settings.

INFECTIONS IN LUNG TRANSPLANT RECIPIENTS

Morbidity and mortality among lung transplant (LT) recipients are reduced by the use of effective antibiotics. The organisms that cause acute infections in LT recipients are different from those that infect hematopoietic stem cell transplantation (HSCT) recipients because LT recipients do not go through a period of neutropenia. Because the transplantation procedure involves major surgery, however, LT recipients are subject to infections at anastomotic sites and to wound infections. Compared with HSCT recipients, LT patients are immunosuppressed for longer periods (often permanently). Thus, they are susceptible to many of the same organisms as patients with chronically impaired T cell immunity.

During the early period (<1 month after transplantation), infections are most commonly caused by extracellular bacteria (staphylococci, streptococci, enterococci, *E. coli*, other gram-negative organisms), which often originate in surgical wound or anastomotic sites. The type of transplant largely determines the spectrum of infection.

In subsequent weeks, the consequences of the administration of agents that suppress cell-mediated immunity become apparent, and acquisition or reactivation of viruses and parasites (from the recipient or from the transplanted organ) can occur. CMV infection is often a problem, particularly in the first 6 months after transplantation, and may present as severe systemic disease or as infection of the transplanted organ. HHV-6 reactivation (assessed by plasma polymerase chain reaction) occurs within the first 2–4 weeks after transplantation and may be associated with fever, leukopenia, and possibly encephalitis. Data suggest that replication of HHV-6 and HHV-7 may exacerbate CMV-induced disease. CMV is associated not only with generalized immunosuppression but also with organ-specific, rejection-related syndromes, including glomerulopathy in kidney transplant recipients, bronchiolitis obliterans in LT recipients, vasculopathy in heart transplant recipients, and the vanishing bile duct syndrome in liver transplant recipients. A complex interplay between increased CMV replication and enhanced graft rejection is well established: increasing immunosuppression leads to increased CMV replication, which is associated with graft rejection. For this reason, considerable attention has been focused on the diagnosis, prophylaxis, and treatment of CMV infection in LT recipients. Early transmission of

West Nile virus to transplant recipients from an organ donor has been reported; however, the risk of West Nile acquisition has been reduced by implementation of screening procedures.

Beyond 6 months after transplantation, infections characteristic of patients with defects in cell-mediated immunity—e.g., infections with *Listeria*, *Nocardia*, and *Rhodococcus* spp.; various fungi; and other intracellular pathogens—may be a problem. International patients and global travelers may experience reactivation of dormant infections with trypanosomes; *Leishmania*, *Plasmodium*, and *Strongyloides* spp.; and other parasites. Elimination of these late infections is not possible until the patient develops specific tolerance to the transplanted organ in the absence of drugs that lead to generalized immunosuppression. Meanwhile, vigilance, prophylaxis or preemptive therapy (when indicated), and rapid diagnosis and treatment of infections can be lifesaving in LT recipients, who, unlike most HSCT recipients, continue to be immunosuppressed.

LT recipients are susceptible to EBV-LPD from as early as 2 months to many years after transplantation. The prevalence of this complication is increased by potent and prolonged use of T cell-suppressive drugs. In some cases, decreasing the degree of immunosuppression may reverse the condition. Among LT patients, those with heart and lung transplants—who receive the most intensive immunosuppressive regimens—are most likely to develop EBV-LPD, particularly in the lungs. Although the disease usually originates in recipient B cells, several cases of donor origin, particularly in the transplanted organ, have been noted. High organ-specific content of B lymphoid tissues (e.g., bronchial-associated lymphoid tissue in the lung), anatomic factors (e.g., lack of access of host T cells to the transplanted organ because of disturbed lymphatics), and differences in major histocompatibility loci between the host T cells and the organ (e.g., lack of cell migration or lack of effective T cell/macrophage cooperation) may result in defective elimination of EBV-infected B cells. LT recipients are also highly susceptible to the development of Kaposi's sarcoma and less frequently to the B cell proliferative disorders associated with KSHV, such as primary effusion lymphoma and multicentric Castleman's disease. Kaposi's sarcoma is much more common (550–1000 times more common than in the general population), can develop very rapidly after transplantation, and can also occur in the allograft. However, because the seroprevalence of KSHV is very low in Western countries, Kaposi's sarcoma is not often observed.

Early Infections

It is not surprising that LT recipients are predisposed to the development of pneumonia. The combination of ischemia and the resulting mucosal damage, together with accompanying denervation and lack of lymphatic drainage, probably contributes to the high rate of pneumonia

(66% in one series). The prophylactic use of high doses of broad-spectrum antibiotics for the first 3–4 days after surgery may decrease the incidence of pneumonia. Gram-negative pathogens (Enterobacteriaceae and *Pseudomonas* spp.) are troublesome in the first 2 weeks after surgery (the period of maximal vulnerability). Pneumonia can also be caused by *Candida* spp. (possibly as a result of colonization of the donor lung), *Aspergillus* spp., and *Cryptococcus* spp.

Mediastinitis may occur at an even higher rate among LT recipients than among heart transplant recipients and most commonly develops within 2 weeks of surgery. In the absence of prophylaxis, pneumonitis caused by CMV (which may be transmitted as a consequence of transplantation) usually presents between 2 weeks and 3 months after surgery, with primary disease occurring later than reactivation disease.

Middle-Period Infections

The incidence of CMV infection, either reactivated or primary, is 75–100% if either the donor or the recipient is seropositive for CMV. CMV-induced disease appears to be most severe in recipients of lung and heart–lung transplants. Whether this severity relates to the mismatch in lung antigen-presenting and host immune cells or is attributable to other (nonimmunologic) factors is not known. More than half of LT recipients with symptomatic CMV disease have pneumonia. Difficulty in distinguishing the radiographic picture of CMV infection from other infections and organ rejection further complicates therapy. CMV can also cause bronchiolitis obliterans in LTs. The development of pneumonitis related to HSV has led to the prophylactic use of acyclovir. Such prophylaxis may also decrease rates of CMV disease, but ganciclovir is more active against CMV and is also active against HSV. The prophylaxis of CMV infection with IV ganciclovir—or increasingly with valganciclovir, the oral alternative—is recommended for LT recipients. Antiviral alternatives are discussed in the earlier section on HSCT. Although the overall incidence of serious disease is decreased during prophylaxis, late disease may occur when prophylaxis is stopped, a pattern observed increasingly in recent years. With recovery from peritransplantation complications and, in many cases, a decrease in immunosuppression, the recipient is often better equipped to combat late infection.

Late Infections

The incidence of *Pneumocystis* infection (which may present with a paucity of findings) is high among lung and heart–lung transplant recipients. Some form of prophylaxis for *Pneumocystis* pneumonia is indicated in all organ transplant situations. Prophylaxis with trimethoprim–sulfamethoxazole for 12 months after transplantation may

be sufficient to prevent *Pneumocystis* disease in patients whose degree of immunosuppression is not increased.

As in other transplant recipients, infection with EBV may cause either a mononucleosis-like syndrome or EBV-LPD. The tendency of the B cell blasts to present in the lung appears to be greater after lung transplantation than after the transplantation of other organs. Reduction of immunosuppression and switching of regimens, as discussed in earlier sections, causes remission in some cases, but airway compression can be fatal, and more rapid intervention may therefore become necessary. The approach to EBV-LPD is similar to that described in other sections.

MISCELLANEOUS INFECTIONS IN LUNG TRANSPLANTATION

Indwelling Intravenous Catheter Infections

The prolonged use of indwelling IV catheters for administration of medications, blood products, and nutrition is common in diverse transplantation settings and poses a risk of local and bloodstream infections. Significant insertion-site infection is most commonly caused by *Staphylococcus aureus*. Bloodstream infection most frequently develops within a week of catheter placement or in patients who become neutropenic. Coagulase-negative staphylococci are the most common isolates from the blood.

Tuberculosis

The incidence of tuberculosis occurring within the first 12 months after solid organ transplantation (SOT) is greater than that observed after HSCT (0.23–0.79%) and ranges broadly worldwide (1.2–15%), reflecting the prevalences of tuberculosis in local populations. Lesions suggesting prior tuberculosis on chest x-ray, older age, diabetes, chronic liver disease, graft-versus-host disease (GVHD), and intense immunosuppression are predictive of tuberculosis reactivation and development of disseminated disease in a host with latent disease. Tuberculosis has rarely been transmitted from the donor organ. In contrast to the low mortality rate among HSCT recipients, mortality rates among SOT patients are reported to be as high as 30%. Vigilance is indicated because the presentation of disease is often extrapulmonary (gastrointestinal, genitourinary, central nervous, endocrine, musculoskeletal, laryngeal) and atypical, sometimes manifesting as a fever of unknown origin. A careful history and a direct evaluation of both the recipient and the donor prior to transplantation are optimal. Skin testing of the recipient with purified protein derivative may be unreliable because of chronic disease and/or immunosuppression, but newer cell-based assays that measure interferon and/or cytokine production may prove more sensitive in the future.

Isoniazid toxicity has not been a significant problem except in the setting of liver transplantation. Therefore, appropriate prophylaxis should proceed. An assessment of

242 the need to treat latent disease should include careful consideration of the possibility of a false-negative test result. Pending final confirmation of suspected tuberculosis, aggressive multidrug treatment in accordance with the guidelines of the Centers for Disease Control and Prevention (CDC), Infectious Diseases Society of America, and American Thoracic Society is indicated because of the high mortality rates among these patients. Altered drug metabolism (e.g., upon co-administration of rifampin and certain immunosuppressive agents) can be managed with careful monitoring of drug levels and appropriate dose adjustment. Close follow-up of hepatic enzymes is warranted, particularly during treatment with isoniazid, pyrazinamide, or rifampin. Drug-resistant tuberculosis is especially problematic in these individuals.

Virus-Associated Malignancies

In addition to malignancy associated with gammaherpesvirus infection (EBV, KSHV) and simple warts (HPV), other tumors that are virus associated or suspected of being virus associated are more likely to develop in transplant recipients, particularly those who require long-term immunosuppression, than in the general population. The interval to tumor development is usually >1 year. Transplant recipients develop nonmelanoma skin or lip cancers that, in contrast to de novo skin cancers, have a high ratio of squamous cells to basal cells. HPV may play a major role in these lesions. Cervical and vulvar carcinomas, quite clearly associated with HPV, develop with increased frequency in female transplant recipients. Among renal transplant recipients, rates of melanoma are modestly increased, and rates of cancers of the kidney and bladder are increased.

VACCINATION OF TRANSPLANT RECIPIENTS

In addition to receiving antibiotic prophylaxis, transplant recipients should be vaccinated against likely pathogens (Table 25-1). In the case of HSCT recipients, optimal responses cannot be achieved until after immune reconstitution despite previous immunization of both donor and recipient. Recipients of allogeneic HSCTs must be reimmunized if they are to be protected against pathogens. The situation is less clear-cut in the case of autologous transplantation. T and B cells in the peripheral blood may reconstitute the immune response if they are transferred in adequate numbers. However, cancer patients (particularly those with Hodgkin's disease, in whom vaccination has been extensively studied) who are undergoing chemotherapy do not respond normally to immunization, and titers of antibodies to infectious agents decrease more rapidly than in healthy individuals. Therefore, even immunosuppressed patients who have

TABLE 25-1

VACCINATION FOR HEMATOPOIETIC STEM CELL TRANSPLANT OR SOLID ORGAN TRANSPLANT RECIPIENTS^a

VACCINE	TYPE OF TRANSPLANTATION
<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Neisseria meningitidis</i>	Immunize before transplantation and every 5 years for Pneumovax (others not established) See CDC recommendations
Seasonal influenza	Vaccinate in the fall Vaccinate close contacts
Poliomyelitis	Administer inactivated vaccine
Measles/ mumps/rubella	Immunize before transplantation with attenuated vaccine
Tetanus, diphtheria	Immunize before transplantation; give boosters at 10 years or as required; primary series not required
Hepatitis A and B	Immunize before transplantation as appropriate
Human papillomavirus	Recommendations pending

^aImmunizations should be given before transplantation whenever possible.

Note: CDC, Centers for Disease Control and Prevention.

not had HSCTs may need booster vaccine injections. If memory cells are specifically eliminated as part of a stem cell “cleanup” procedure, it will be necessary to reimmunize the recipient with a new primary series. Optimal times for immunizations of different transplant populations are being evaluated. Yearly immunization of household and other contacts (including health care personnel) against influenza benefits the patient by preventing local spread.

In the absence of compelling data as to optimal timing, it is reasonable to administer the pneumococcal and *Haemophilus influenzae* type b conjugate vaccines to both autologous and allogeneic HSCT recipients beginning 12 months after transplantation. A series that includes both the seven-valent pneumococcal conjugate vaccine and the 23-valent Pneumovax is now recommended (following CDC guidelines). The pneumococcal and *H. influenzae* type b vaccines are particularly important for patients who have undergone splenectomy. In addition, diphtheria, tetanus, acellular pertussis, and inactivated polio vaccines can all be given at these same intervals (12 months and, as required, 24 months after transplantation). *Neisseria meningitidis* polysaccharide (a new conjugate vaccine) is now available and will probably be recommended in the future. Some authorities recommend a new primary series for tetanus/diphtheria/pertussis and inactivated polio vaccine beginning 12 months after

transplantation. Because of the risk of spread, household contacts of HSCT recipients (or of patients immunosuppressed as a result of chemotherapy) should receive only inactivated polio vaccine. Live-virus measles/mumps/rubella vaccine can be given to autologous HSCT recipients 24 months after transplantation and to most allogeneic HSCT recipients at the same point if they are not receiving maintenance therapy with immunosuppressive drugs and do not have ongoing GVHD. The risk of spread from a household contact is lower for measles/mumps/rubella (MMR) vaccine than for polio vaccine. Neither patients nor their household contacts should be vaccinated with vaccinia unless they have been exposed to the smallpox virus. Among patients who have active GVHD or are taking high maintenance doses of glucocorticoids, it may be prudent to avoid all live-virus vaccines. Vaccination to prevent hepatitis B and hepatitis A also seems advisable.

In the case of SOT recipients, administration of all the usual vaccines and of the indicated booster doses should be completed before immunosuppression, if possible, to maximize responses. For patients taking immunosuppressive agents, the administration of pneumococcal vaccine should be repeated every 5 years. No data are available for the meningococcal vaccine, but it is probably reasonable to administer it along with the pneumococcal vaccine. *H. influenzae* conjugate vaccine is safe and should be efficacious in this population; therefore, its administration before transplantation is recommended. Booster doses of this vaccine are not recommended for adults. SOT recipients who continue to receive immunosuppressive drugs should not receive live-virus vaccines. A person in this group who is exposed to measles should be given immune globulin. Similarly, an immunocompromised patient who is seronegative for varicella and who comes into contact with a person who has chickenpox should be given varicella-zoster immune globulin as soon as possible (and certainly within 96 h) or, if this is not possible, should be started immediately on a 10- to 14-day course of acyclovir therapy. Upon discontinuation of treatment, clinical disease may still occur in a small number of patients; thus, vigilance is indicated. Rapid retreatment should limit the symptoms of disease. Household contacts of transplant recipients can receive live attenuated VZV

vaccine, but vaccinees should avoid direct contact with the patient if a rash develops. Virus-like particle (VLP) vaccines (not live attenuated) have recently been licensed for the prevention of infection with several HPV serotypes most commonly implicated in cervical and anal carcinomas and in anogenital and laryngeal warts. For example, the tetravalent vaccine contains HPV serotypes 6, 11, 16, and 18. At present, no information is available about the safety, immunogenicity, or efficacy of this vaccine in transplant recipients.



Immunocompromised patients who travel may benefit from some but not all vaccines. In general, these patients should receive any killed or inactivated vaccine preparation appropriate to the area they are visiting; this recommendation includes the vaccines for Japanese encephalitis, hepatitis A and B, poliomyelitis, meningococcal infection, and typhoid. The live typhoid vaccines are not recommended for use in most immunocompromised patients, but inactivated or purified polysaccharide typhoid vaccine can be used. Live yellow fever vaccine should not be administered. On the other hand, primary immunization or boosting with the purified-protein hepatitis B vaccine is indicated if patients are likely to be exposed. Patients who will reside for >6 months in areas where hepatitis B is common (Africa, Southeast Asia, the Middle East, Eastern Europe, parts of South America, and the Caribbean) should receive hepatitis B vaccine. Inactivated hepatitis A vaccine should also be used in the appropriate setting. A combined vaccine is now available that provides dual protection against hepatitis A and hepatitis B. If hepatitis A vaccine is not administered, travelers should consider receiving passive protection with immune globulin (the dose depending on the duration of travel in the high-risk area).

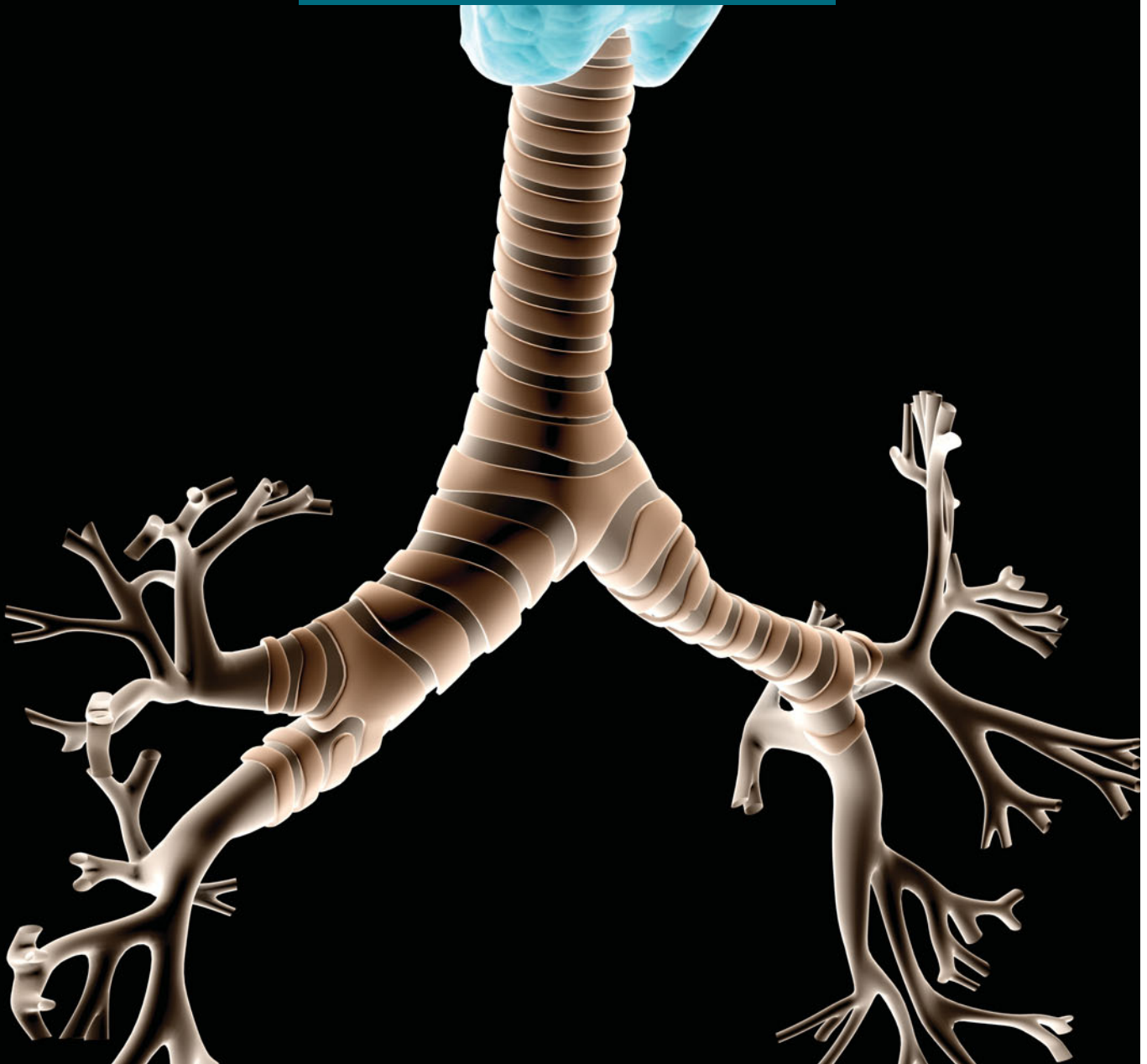
FURTHER READINGS

- CORNELY OA et al: Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med* 356:348, 2007
- KOTTON CN et al: Prevention of infection in adult travelers after solid organ transplantation. *Am J Transplant* 5:8, 2004
- MUNOZ P et al: *Mycobacterium tuberculosis* infection in recipients of solid organ transplants. *Clin Infect Dis* 40:581, 2005

This page intentionally left blank

SECTION III

GENERAL APPROACH TO THE CRITICALLY ILL PATIENT





CHAPTER 26

PRINCIPLES OF CRITICAL CARE MEDICINE

John P. Kress ■ Jesse B. Hall

Assessment of Severity of Illness	246	■ Multiorgan System Failure	252
APACHE II Scoring System	247	■ Monitoring in the Intensive Care Unit	252
The SAPS and MPM Scoring Systems	247	Pulse Oximetry	252
■ Shock	247	Circulatory Status	253
Initial Evaluation	247	■ Prevention of Complications of Critical Illness	254
Mechanical Ventilatory Support	249	■ Neurologic Dysfunction in Critically Ill Patients	255
■ Respiratory Failure	250	■ Withholding and Withdrawing Care	256
■ Care of the Mechanically Ventilated Patient	251	■ Further Readings	256

The care of critically ill patients requires a thorough understanding of pathophysiology and is centered initially around resuscitation of patients at the extremes of physiologic deterioration. This resuscitation is often fast paced and may occur in the early stages without a detailed awareness of the patient's chronic medical problems. While physiologic stabilization is taking place, intensivists attempt to gather important background medical information to supplement the real-time assessment of the patient's current physiologic conditions. Numerous tools are available to assist intensivists in the accurate assessment of pathophysiology and to support incipient organ failures, thus offering a window of opportunity for diagnosing and treating underlying disease(s) in a stabilized patient. Indeed, the use of invasive interventions such as mechanical ventilation and renal replacement therapy as well as diagnostic tools such as central venous catheters are commonplace in the intensive care unit (ICU). An appreciation of the risks and benefits of such aggressive and often invasive interventions is vital to ensure optimal patient outcomes. Intensivists must also recognize when a patient's chance for recovery is remote or impossible and work to counsel and comfort dying patients and their significant others. Critical care physicians must often redirect the goals of care from resuscitation and cure to comfort when the resolution of an underlying illness is not possible.

ASSESSMENT OF SEVERITY OF ILLNESS

Categorization of a patient's illness into grades of severity occurs frequently in the ICU. Numerous severity-of-illness scoring systems have been developed and validated over the past two decades. Although these scoring systems have been validated as tools to accurately assess populations of critically ill patients, their utility in predicting individual patient outcomes is not clear.

Severity-of-illness scoring systems are important for defining populations of critically ill patients. This allows effective comparison of groups of patients enrolled in clinical trials. To be assured that a purported benefit of a therapy is real, investigators must be assured that different groups involved in a clinical trial have similar illness severities. Severity-of-illness scores are also useful in guiding hospital administrative policies. Allocation of resources, such as nursing and ancillary care, can be directed by such scoring systems. Severity-of-illness scoring systems can also assist in the assessment of quality of ICU care over time. Scoring system validations are based on the premise that increasing age, the presence of chronic medical illnesses, and increasingly severe derangements from normal physiology are each associated with increased mortality. All currently existing severity-of-illness scoring systems are derived from patients who have been already admitted to the ICU. There are no established scoring systems available that allege to direct clinicians' decision-making

processes regarding what constitute criteria for admission to an ICU.

Currently, the most commonly used scoring systems are the APACHE (Acute Physiology and Chronic Health Evaluation) system, the MPM (Mortality Probability Model), and the SAPS (Simplified Acute Physiology Score) system. These were all designed to predict outcomes in critical illness and use severity-of-illness scoring systems with common variables. These include age; vital signs; assessments of respiratory, renal, and neurologic function; and an evaluation of chronic medical illnesses.

APACHE II SCORING SYSTEM

The APACHE II system is the most commonly used severity-of-illness scoring system in North America. Age, type of ICU admission (after elective surgery vs. nonsurgical or after emergency surgery), a chronic health problem score, and 12 physiologic variables (the most severely abnormal of each in the first 24 h of ICU admission) are used to derive a score. The predicted hospital mortality is derived from a formula that takes into account the APACHE II score; the need for emergency surgery; and a weighted, disease-specific diagnostic category (Table 26-1). The relationship between the APACHE II score and mortality is illustrated in Fig. 26-1. More recently, the APACHE III scoring system has been released. This scoring system is similar to APACHE II in that it is based on age, physiologic abnormalities, and chronic medical comorbidities. The database from which this score was derived is larger.

THE SAPS AND MPM SCORING SYSTEMS

The SAPS II score, used more frequently in Europe, was derived in a manner similar to the APACHE scores. This score is not disease specific but rather incorporates three underlying disease variables (AIDS, metastatic cancer, and hematologic malignancy). The MPM can be used to calculate a direct probability of death in patients admitted to the ICU.

Severity-of-illness scoring systems suffer from the problem of inability to predict survival in individual patients. Accordingly, the use of these scoring systems to direct therapy and clinical decision making cannot be recommended at present. Rather, these tools should be used as important data to complement clinical bedside decision-making processes.

SHOCK

(See also Chap. 28)

INITIAL EVALUATION

Shock is a common condition necessitating admission to the ICU or occurring in the course of critical care.

Shock is defined by the presence of multisystem end-organ hypoperfusion. Clinical indicators include reduced mean arterial pressure (MAP), tachycardia, tachypnea, cool skin and extremities, acute altered mental status, and oliguria. Hypotension is usually, although not always, present. The end result of multiorgan hypoperfusion is tissue hypoxia, often clinically manifested by lactic acidosis. Because the MAP is the product of cardiac output (CO) and systemic vascular resistance (SVR), reductions in blood pressure can be caused by decreased CO, decreased SVR, or both. Accordingly, the initial evaluation of a hypotensive patient should evaluate the adequacy of the CO. This should be part of the earliest assessment of the patient by the clinician at the bedside when shock is contemplated (Fig. 26-2). Clinical evidence of *diminished* CO includes a narrow pulse pressure—a marker that correlates with stroke volume—and cool extremities with delayed capillary refill. Signs of *increased* CO include a widened pulse pressure (particularly with a reduced diastolic pressure), warm extremities with bounding pulses, and rapid capillary refill. If a hypotensive patient has clinical signs of increased CO, one can infer that the reduced blood pressure is a result of decreased SVR.

In hypotensive patients with clinical signs of a reduced CO, an assessment of intravascular and cardiac volume status is appropriate. A hypotensive patient with decreased intravascular and cardiac volume status may have a history suggesting hemorrhage or other volume losses (e.g., vomiting, diarrhea, polyuria). Whereas the jugular venous pressure (JVP) is often reduced in such a patient, the change in pulse pressure as a function of respiration is increased. A hypotensive patient with increased intravascular volume status and cardiac dysfunction may have S₃ or S₄ gallops (or both) on cardiac examination, increased JVP, extremity edema, and crackles on lung auscultation. The chest x-ray may show cardiomegaly, widening of the vascular pedicle, Kerley B lines, and pulmonary edema. Chest pain and electrocardiographic changes consistent with ischemia may also be noted (Chap. 31).

In hypotensive patients with clinical evidence of increased CO, a search for causes of decreased SVR is appropriate. The most common cause of high cardiac output hypotension is sepsis (Chap. 29). Other causes of high CO hypotension include liver failure, severe pancreatitis, burns and other trauma that elicit the systemic inflammatory response syndrome (SIRS), anaphylaxis, thyrotoxicosis, and peripheral arteriovenous shunts.

In summary, the three most common categories of shock are hypovolemic, cardiogenic, and high CO with decreased SVR (high-output hypotension). Certainly, these categories may overlap and occur simultaneously (e.g., hypovolemic and septic shock, septic and cardiogenic shock).

The initial assessment of a patient in shock as outlined above should take only a few minutes. It is important

CALCULATION OF ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION II (APACHE II)^a

Acute Physiology Score									
SCORE	4	3	2	1	0	1	2	3	4
Rectal temperature, °C	≥41	39.0–40.9		38.5–38.9	36.0–38.4	34.0–35.9	32.0–33.9	30.0–31.9	≤29.9
Mean blood pressure, mmHg	≥160	130–159	110–129		70–109		50–69		≤49
Heart rate, bpm	≥180	140–179	110–139		70–109		55–69	40–54	≤39
Respiratory rate, bpm	≥50	35–49		25–34	12–24	10–11	6–9		≤5
Arterial pH	≥7.70	7.60–7.69		7.50–7.59	7.33–7.49		7.25–7.32	7.15–7.24	<7.15
Oxygenation									
If FiO ₂ > 0.5, use (A - a) Do ₂	≥500	350–499	200–349		<200				
If FiO ₂ ≤ 0.5, use Pao ₂					>70	61–70		55–60	<55
Serum sodium, meq/L	≥180	160–179	155–159	150–154	130–149		120–129	111–119	≤110
Serum potassium, meq/L	≥7.0	6.0–6.9		5.5–5.9	3.5–5.4	3.0–3.4	2.5–2.9		<2.5
Serum creatinine, mg/dL	≥3.5	2.0–3.4	1.5–1.9		0.6–1.4		<0.6		
Hematocrit	≥60		50–59.9	46–49.9	30–45.9		20–29.9		<20
WBC count, 10 ³ /mL	≥40		20–39.9	15–19.9	3–14.9		1–2.9		<1
Glasgow Coma Score^{b,c}									
EYE OPENING	VERBAL (NONINTUBATED)			VERBAL (INTUBATED)			MOTOR ACTIVITY		
4—Spontaneous	5—Oriented and talks			5—Seems able to talk			6—Verbal command		
3—Verbal stimuli	4—Disoriented and talks			3—Questionable ability to talk			5—Localizes to pain		
2—Painful stimuli	3—Inappropriate words			1—Generally unresponsive			4—Withdraws to pain		
1—No response	2—Incomprehensible sounds						3—Decorticate		
	1—No response						2—Decerebrate		
							1—No response		
Points Assigned to Age and Chronic Disease as Part of the APACHE II Score									
AGE, YEARS	SCORE								
<45	0								
45–54	2								
55–64	3								
65–74	5								
≥75	6								
CHRONIC HEALTH (HISTORY OF CHRONIC CONDITIONS)^d					SCORE				
None					0				
If patient is admitted after elective surgery					2				
If patient is admitted after emergency surgery or for reason other than after elective surgery					5				

^aThe APACHE II score is the sum of the acute physiology score (vital signs, oxygenation, laboratory values), Glasgow Coma Score (GCS), age, and chronic health points. The worst values during first 24 h in the ICU should be used.

^bGCS = eye-opening score + verbal (intubated or nonintubated) score + motor score.

^cFor the GCS component of acute physiology score, subtract GCS from 15 to obtain the points assigned.

^dChronic health conditions include liver, cirrhosis with portal hypertension or encephalopathy; cardiovascular, class IV angina (at rest or with minimal self-care activities); pulmonary, chronic hypoxemia or hypercapnia, polycythemia, ventilator dependent; kidney, chronic peritoneal or hemodialysis; immune, immunocompromised host.

Note: (A - a) Do₂, alveolar-arterial oxygen difference; WBC, white blood (cell) count.

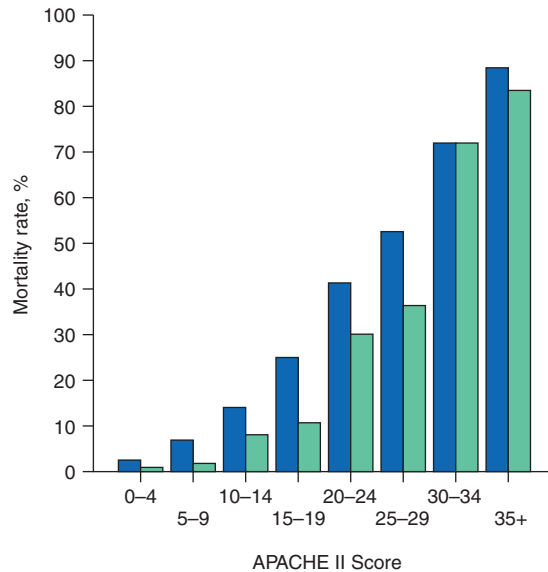


FIGURE 26-1
APACHE (Acute Physiology and Chronic Health Evaluation) II survival curve. Blue, nonoperative; green, postoperative.

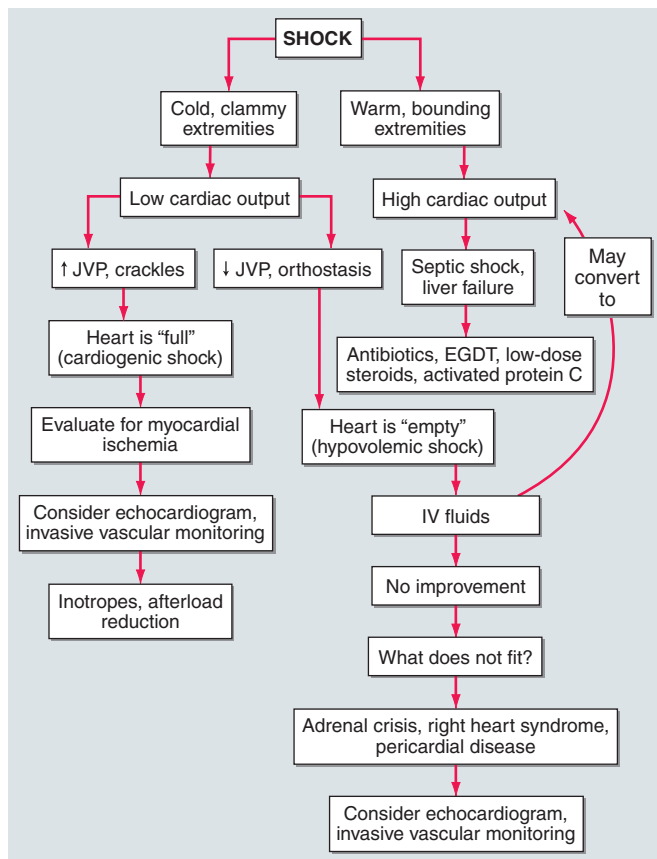


FIGURE 26-2
Approach to a patient in shock. EGDT, early goal-directed therapy; JVP, jugular venous pressure.

that aggressive, early resuscitation be instituted based on the initial assessment, particularly because early resuscitation of patients with septic and cardiogenic shock may improve their survival (see later). If the initial bedside assessment yields equivocal or confounding data, more objective assessments such as echocardiography or invasive vascular monitoring may be useful. The goal of early resuscitation is to reestablish adequate tissue perfusion to prevent or minimize end-organ injury.

MECHANICAL VENTILATORY SUPPORT

(See also Chap. 27) During the initial resuscitation of patients in shock, principles of advanced cardiac life support should be followed. Because patients in shock may be obtunded and unable to protect the airway, an early assessment of the patient's airway is mandatory during resuscitation from shock. Early intubation and mechanical ventilation are often required. Reasons for institution of endotracheal intubation and mechanical ventilation include acute hypoxemic respiratory failure as well as ventilatory failure, which frequently accompany shock. Acute hypoxemic respiratory failure may occur in patients with cardiogenic shock and pulmonary edema (Chap. 31) as well as in those in septic shock with pneumonia or acute respiratory distress syndrome (ARDS) (Chap. 29). Ventilatory failure often occurs as a result of an increased load on the respiratory system. This load may present in the form of acute metabolic acidosis (often lactic acidosis) or decreased compliance of the lungs ("stiff" lungs) as a result of pulmonary edema. Inadequate perfusion to respiratory muscles in the setting of shock may be another reason for early intubation and mechanical ventilation. Normally, the respiratory muscles receive a very small percentage of the CO. However, in patients who are in shock with respiratory distress for the reasons listed above, the percentage of CO dedicated to respiratory muscles may increase 10-fold or more. Lactic acid production from inefficient respiratory muscle activity presents an additional ventilatory load.

Mechanical ventilation may relieve the patient of the work of breathing and allow redistribution of a limited CO to other vital organs, often with an improvement in lactic acidosis. Patients demonstrate signs of respiratory muscle fatigue with a number of clinical signs, including an inability to speak full sentences, accessory respiratory muscle use, paradoxical abdominal muscle activity, extreme tachypnea (>40 breaths/min), and decreasing respiratory rate despite an increasing drive to breathe. When patients with shock are treated with mechanical ventilation, a major goal of ventilator settings is to assume all or the majority of work of breathing, facilitating a state of minimal respiratory muscle work. With the institution of mechanical ventilation for shock, further worsening of MAP is frequently seen. The reasons for this include impedance of venous

250 return with positive-pressure ventilation, reduced endogenous catecholamine secretion after the stress associated with respiratory failure is abated, and drugs used to facilitate endotracheal intubation (e.g., barbiturates, benzodiazepines, opiates), all of which may result in hypotension. Accordingly, hypotension should be anticipated after endotracheal intubation and positive-pressure ventilation. Many of these patients have a component of hypovolemia, which may respond to IV volume administration. Figure 26-2 summarizes the diagnosis and treatment of patients with different types of shock.

For further discussion of individual forms of shock, see Chaps. 28, 29, and 31.

RESPIRATORY FAILURE

Respiratory failure is one of the most common reasons patients are admitted to the ICU. In some ICU settings, $\geq 75\%$ of patients require mechanical ventilation during their ICU stay. Respiratory failure can be categorized mechanistically, based on pathophysiologic derangements in respiratory function. Accordingly, four different types of respiratory failure can be described based on these pathophysiologic derangements.

Type I, or Acute Hypoxemic, Respiratory Failure

This occurs when alveolar flooding and subsequent intrapulmonary shunt physiology occurs. Alveolar flooding may be a consequence of pulmonary edema, pneumonia, or alveolar hemorrhage. Pulmonary edema can be further categorized as occurring because of elevated intravascular pressures seen in heart failure and intravascular volume overload or because of acute lung injury (“low-pressure pulmonary edema”; Chap. 31). ARDS (Chap. 30) represents an extreme degree of lung injury. This syndrome is defined by diffuse bilateral airspace edema seen by chest radiography, the absence of left atrial hypertension, and profound shunt physiology (Fig. 30-2) in a clinical setting in which this syndrome is known to occur. This includes sepsis, gastric aspiration, pneumonia, near drowning, multiple blood transfusions, and pancreatitis. The mortality rate of patients with ARDS was traditionally very high (50–70%), although recent changes in ventilator management strategy have led to reports of mortality in the low 30% range (see later).

For many years, physicians have suspected that mechanical ventilation of patients with acute lung injury and ARDS may propagate lung injury. Cyclical collapse and reopening of alveoli may be partly responsible for this. As seen in Fig. 26-3, the pressure-volume relationship of the lung in ARDS is not linear. Alveoli may collapse at very low lung volumes. Animal studies have suggested that stretching and overdistention of injured alveoli during mechanical ventilation can further injure the lung.

Concern over this alveolar overdistention, termed *ventilator-induced “volutrauma,”* led to a multicenter, randomized, prospective trial comparing traditional ventilator strategies for acute lung injury and ARDS (large tidal volume, 12 mL/kg ideal body weight) with a low tidal volume (6 mL/kg ideal body weight). This study showed a dramatic reduction in mortality in the low tidal volume group (large tidal volume, 39.8% mortality versus low tidal volume, 31% mortality) and confirmed that ventilator management could impact outcomes in these patients. In addition, a “fluid conservative” management strategy [maintaining a relatively low central venous pressure (CVP)] or pulmonary capillary wedge pressure (PCWP) is associated with the need for fewer days of mechanical ventilation compared with a “fluid liberal” management strategy (maintaining a relatively high CVP or PCWP) in acute lung injury and ARDS.

Type II Respiratory Failure

This type of respiratory failure occurs as a result of alveolar hypoventilation and results in the inability to eliminate carbon dioxide effectively. Mechanisms by which this occurs are categorized by impaired central nervous system (CNS) drive to breathe, impaired strength with failure of neuromuscular function in the respiratory system, and increased load(s) on the respiratory system. Reasons for diminished CNS drive to breathe include drug overdose, brainstem injury, sleep-disordered breathing, and hypothyroidism. Reduced strength can be caused by impaired neuromuscular transmission (e.g., myasthenia gravis, Guillain-Barré syndrome, amyotrophic lateral sclerosis, phrenic nerve injury) or respiratory muscle weakness (e.g., myopathy, electrolyte derangements, fatigue).

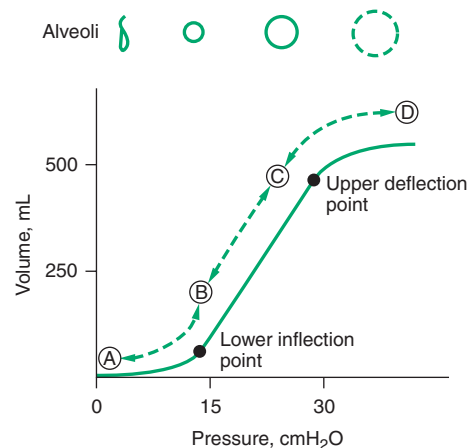


FIGURE 26-3 Pressure-volume relationship of the lungs of a patient with acute respiratory distress syndrome. At the lower inflection point, collapsed alveoli begin to open, and the lung compliance changes. At the upper deflection point, alveoli become overdistended. The shape and size of alveoli are illustrated at the top of the figure.

The overall load on the respiratory system can be classified into increased resistive loads (e.g., bronchospasm), loads caused by reduced lung compliance [e.g., alveolar edema, atelectasis, intrinsic positive end-expiratory pressure (auto-PEEP); see later in this chapter], loads caused by reduced chest wall compliance (e.g., pneumothorax, pleural effusion, abdominal distension), and loads caused by increased minute ventilation requirements (e.g., pulmonary embolus with increased dead space fraction, sepsis).

The mainstays of therapy for type II respiratory failure are treatments directed at reversing the underlying cause(s) of ventilatory failure. Noninvasive positive-pressure ventilation using a mechanical ventilator with a tight-fitting face or nasal mask that avoids endotracheal intubation can often stabilize these patients. This approach has been shown to be beneficial in treating patients with exacerbations of chronic obstructive pulmonary disease (COPD). Noninvasive ventilation has been tested less extensively in other types of type II respiratory failure but may be attempted nonetheless in the absence of contraindications (hemodynamic instability, inability to protect the airway, respiratory arrest).

Type III Respiratory Failure

This form of respiratory failure occurs as a result of lung atelectasis. Because atelectasis occurs so commonly in the perioperative period, this is also called *perioperative respiratory failure*. After general anesthesia, decreases in functional residual capacity lead to collapse of dependent lung units. Such atelectasis can be treated by frequent changes in position, chest physiotherapy, upright positioning, and aggressive control of incisional or abdominal pain. Noninvasive positive-pressure ventilation may also be used to reverse regional atelectasis.

Type IV Respiratory Failure

This form occurs because of hypoperfusion of respiratory muscles in patients in shock. Normally, respiratory muscles consume <5% of the total CO and O₂ delivery. Patients in shock often suffer respiratory distress because of pulmonary edema (e.g., patients in cardiogenic shock), lactic acidosis, and anemia. In this setting, ≤40% of the CO may be distributed to the respiratory muscles. Intubation and mechanical ventilation can allow redistribution of the CO away from the respiratory muscles and back to vital organs while the shock is treated.

CARE OF THE MECHANICALLY VENTILATED PATIENT

(See also Chap. 27) Although a thorough understanding of the pathophysiology of respiratory failure is essential to optimize patient care, recognition of a patient's readiness to be liberated from mechanical ventilation is similarly important. Several studies have shown that subjecting

patients to daily spontaneous breathing trials can identify those ready for extubation. Accordingly, all intubated, mechanically ventilated patients should undergo a daily screening of respiratory function. If oxygenation is stable (i.e., $PAO_2/FIO_2 > 200$ and $PEEP \leq 5$ cmH₂O), cough and airway reflexes are intact, and no vasopressor agents or sedatives are being administered, the patient has passed the screening test and should undergo a spontaneous breathing trial. This trial consists of a period of breathing through the endotracheal tube without ventilator support [both continuous positive airway pressure (CPAP)] of 5 cmH₂O and an open T-piece breathing system can be used) for 30–120 min. The spontaneous breathing trial is declared a failure and stopped if *any* of the following occur: (1) respiratory rate >35/min for >5 min, (2) O₂ saturation < 90%, (3) heart rate >140/min or a 20% increase or decrease from baseline, (4) systolic blood pressure < 90 mmHg or >180 mmHg, or (5) increased anxiety or diaphoresis. If, at the end of the spontaneous breathing trial, the ratio of the respiratory rate and tidal volume in liters (f/V_T) is <105, the patient can be extubated. Such protocol-driven approaches to patient care can have an important impact on the duration of mechanical ventilation and length of stay in the ICU. Despite such a careful approach to liberation from mechanical ventilation, up to 10% of patients develop respiratory distress after extubation and may require resumption of mechanical ventilation. Many of these patients require re-intubation. A recent study suggested that the use of noninvasive ventilation in patients who fail extubation may be associated with worse outcomes compared with immediate re-intubation.

Mechanically ventilated patients frequently require sedatives and analgesics. Most patients undergoing mechanical ventilation experience pain, which can be elicited by the presence of the endotracheal tube and endotracheal suctioning. Accordingly, early and aggressive attention to pain control is extremely important. Opiates are the mainstay of therapy for pain control in mechanically ventilated patients. After assuring adequate pain control, additional indications for sedation for mechanically ventilated patients include anxiety; treatment of subjective dyspnea; psychosis; facilitation of nursing care; reduction of autonomic hyperactivity, which may precipitate myocardial ischemia; and reducing total O₂ consumption ($\dot{V}O_2$).

Neuromuscular blocking agents are occasionally needed to facilitate mechanical ventilation in patients with profound dyssynchrony with the ventilator despite optimal sedation. The use of neuromuscular blocking agents may result in prolonged weakness—a myopathy known as the *postparalytic syndrome*. As such, these agents are typically used as a last resort, when aggressive sedation fails to achieve patient–ventilator synchrony. Because neuromuscular blocking agents result in pharmacologic paralysis without altering mental status, sedative-induced amnesia is mandatory when these agents are administered.

252 Amnesia can be reliably achieved with benzodiazepines such as lorazepam or midazolam, as well as the IV anesthetic agent propofol. Outside of the setting of pharmacologic paralysis, few data support the idea that amnesia is mandatory in all patients who require intubation and mechanical ventilation. Because many of these patients are critically ill with impaired hepatic and renal function, sedatives and opiates may accumulate in them when given for prolonged periods of time. A protocol-driven approach to sedation of mechanically ventilated patients with daily interruption of sedative infusions has been shown to prevent excessive drug accumulation and shorten the durations of mechanical ventilation and length of stay in the ICU.

MULTIORGAN SYSTEM FAILURE

The syndrome of multiorgan system failure is a common problem associated with critical illness. This syndrome is defined by the simultaneous presence of physiologic dysfunction or failure of two or more organs. Typically, this occurs in the setting of severe sepsis, shock of any kind, severe inflammatory conditions such as pancreatitis, and trauma. That multiorgan system failure occurs commonly in the ICU is a testament to our current ability to stabilize and support single organ failure. The ability to support single organ failure aggressively (e.g., with mechanical ventilation for respiratory failure, renal replacement therapy for acute renal failure) has greatly impacted early mortality in critical illness. As such, it is uncommon for critically ill patients to die in the initial stages of resuscitation. Instead, many patients succumb to critical illness later in the ICU stay after the initial presenting problem has been stabilized.

Although there is debate regarding specific definitions of organ failure, several general principles governing the syndrome of multiorgan system failure apply. First, organ failure, no matter how defined, must persist beyond 24 h. Second, the mortality risk increases as patients accrue additional organ failures. Third, prognosis is worsened by increased duration of organ failure. These observations remain true across various critical care settings (e.g., medical versus surgical). SIRS is a common basis for multiorgan system failure. Although infection is a common cause of SIRS, “sterile” triggers such as pancreatitis, trauma, and burns are often invoked to explain multiorgan system failure.

MONITORING IN THE INTENSIVE CARE UNIT

Because respiratory failure occurs commonly in critically ill patients, monitoring of the respiratory and cardiovascular systems is undertaken frequently in the ICU. Evaluation of respiratory gas exchange is routine in critical

illness. The “gold standard” remains arterial blood gas analysis (ABG), in which pH, partial pressures of O₂ and CO₂, and O₂ saturation are measured directly. With ABG, the two main functions of the lung—oxygenation of arterial blood and elimination of CO₂—can be directly assessed. Importantly, the blood pH, which has a profound effect on the drive to breathe, can be assessed only by sampling of arterial blood. Although sampling of arterial blood is generally safe, it may be painful and cannot provide continuous information for clinicians routinely. Given these limitations, noninvasive monitoring of respiratory function is often used in the critical care setting.

PULSE OXIMETRY

This is the most commonly used noninvasive monitor of respiratory function. This technique takes advantage of differences in the absorptive properties of oxygenated and deoxygenated hemoglobin. At wavelengths of 660 nm, oxyhemoglobin reflects light more effectively than deoxyhemoglobin; the reverse is true in the infrared spectrum (940 nm). A pulse oximeter passes both wavelengths of light through a perfused digit such as a finger, and the relative intensity of light transmission at these two wavelengths is recorded. This allows the derivation of the relative percent of oxyhemoglobin. Because arterial pulsations produce phasic changes in the intensity of transmitted light, the pulse oximeter is designed to detect only light of alternating intensity. This allows distinction of arterial and venous blood O₂ saturations.

Respiratory System Mechanics

These can be measured in patients during mechanical ventilation (Chap. 27). When volume-controlled modes of mechanical ventilation are used, accompanying airway pressures can be easily measured. The peak airway pressure is determined by two variables—the airways resistance and respiratory system compliance. At the end of inspiration, inspiratory flow can be stopped transiently. This end-inspiratory pause (*plateau pressure*) is a static measurement, impacted only by respiratory system compliance, not airways resistance. Therefore, during volume-controlled ventilation, the difference between the peak (airways resistance + respiratory system compliance) and plateau (respiratory system compliance only) airway pressures provides a quantitative assessment of airways resistance. Accordingly, during volume-controlled ventilation, patients with increases in airways resistance typically have increased peak airway pressures as well as abnormally high gradients between peak and plateau airway pressures (typically >15 cmH₂O). The compliance of the respiratory system is defined by the change in pressure of the respiratory system per unit change in volume.

The respiratory system can be divided further into two components—the lungs and the chest wall. Normally, the

respiratory system compliance is ~ 100 mL/cmH₂O. Pathophysiologic processes such as pleural effusions, pneumothorax, or increased abdominal girth from ascites or obesity all reduce chest wall compliance. Lung compliance may be reduced by pneumonia, pulmonary edema from any cause, or auto-PEEP. Accordingly, patients with abnormalities in compliance of the respiratory system (lungs or chest wall) typically have elevated peak *and* plateau airway pressures but a normal gradient between peak and plateau airway pressures. Auto-PEEP occurs when there is insufficient time for emptying of alveoli before the next inspiratory cycle. Because the alveoli have not decompressed completely, alveolar pressure remains positive at end-exhalation (functional residual capacity). This phenomenon occurs most commonly because of critical narrowing of distal airways in disease processes such as asthma and COPD. Auto-PEEP with resulting alveolar overdistention may result in diminished lung compliance, reflected by abnormally increased plateau airway pressures. Modern mechanical ventilators allow breath-to-breath display of pressure and flow, which may allow detection of problems such as patient-ventilator dyssynchrony, airflow obstruction, and auto-PEEP (Fig. 26-4).

CIRCULATORY STATUS

Monitors to characterize the circulation status of critically ill patients are used commonly in the ICU. One of

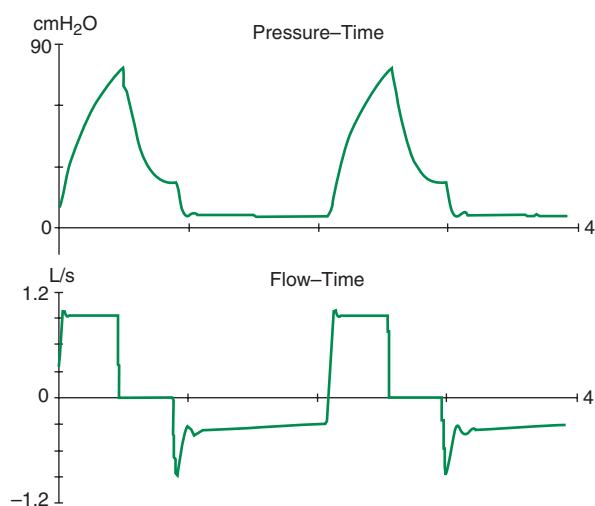


FIGURE 26-4

Increased airway resistance with auto-PEEP (alveolar edema, atelectasis, intrinsic positive end-expiratory pressure). The top waveform (airway pressure versus time) shows a large difference between the peak airway pressure (80 cmH₂O) and the plateau airway pressure (20 cmH₂O). The bottom waveform (flow versus time) demonstrates airflow throughout expiration (reflected by the flow tracing on the negative portion of the abscissa) that persists up to the next inspiratory effort.

the most frequently used is the pulmonary artery catheter, also known as the right heart catheter or Swan-Ganz catheter. This catheter was originally designed as a tool to guide therapy in patients with acute myocardial infarction but is currently used in the ICU for evaluation and treatment of a variety of other conditions such as ARDS, septic shock, congestive heart failure, and acute renal failure. This device has never been validated as a tool associated with reduction in morbidity and mortality. Indeed, despite numerous prospective studies, there has been no report of mortality or morbidity benefit associated with the use of the pulmonary artery catheter in any setting.

Pulmonary artery catheters are invasive monitors and may be associated with a number of complications. Because the catheter is inserted via a central vein, all of the complications associated with central venous catheterization are present. These include central venous catheter-related infections, pneumothorax, arterial puncture with or without cannulation, bleeding, air embolism, venous thrombosis, and catheter embolism. The insertion of the pulmonary artery catheter also carries a number of risks, including dysrhythmias, heart block, cardiac perforation, and balloon fragmentation. After the catheter is placed, pulmonary infarction, pulmonary artery rupture, and pulmonic valve insufficiency may occur. Fortunately, most of these complications are quite rare. Indeed, misinterpretation of data derived from central venous and pulmonary artery catheters may be the most common “complication” seen with these monitors. Pressure measurements in various cardiac chambers require careful zeroing of the pressure transducer relative to atmospheric pressure. In addition, the transducer must also be at the same level as the cardiac chamber whose pressure is being measured. If the transducer is either higher or lower by several centimeters, the value recorded may be quite inaccurate.

Atrial pressure measurements should be made at end-expiration when there is no movement of air in or out of the thorax. It is during this period, with the lungs at functional residual capacity (cessation of gas flow), that gas flow in or out of the chest cannot complicate measurements of the atrial pressure. Many critically ill patients with respiratory distress may never come to a point where airflow in and out of the thorax ceases, instead breathing with continuous inspiratory and expiratory movements. In such patients, atrial pressure may be difficult to measure accurately. Failure to recognize this limitation may lead to reliance on inaccurate data obtained from the central venous or pulmonary artery catheter. Indeed, studies have shown that many clinicians are unable to accurately obtain and interpret data from such catheters. Accordingly, it appears that the routine use of pulmonary artery catheterization is not indicated as a monitor to characterize the circulatory status in most critically ill patients.

254 Oxygen delivery (Q_{O_2}) is a function of CO and the content of O_2 in the arterial blood (Ca_{O_2}). The Ca_{O_2} is determined by the hemoglobin concentration, the arterial hemoglobin saturation, and dissolved O_2 not bound to hemoglobin. For normal adults:

$$\begin{aligned} Q_{O_2} &= 50 \text{ dL/min} \times (1.39 \times 15 \text{ g/dL} \\ &\quad [\text{hemoglobin concentration}] \times 1.0 \\ &\quad [\text{hemoglobin \% saturation}] + 0.0031 \\ &\quad \times 100 [\text{Pa}_{O_2}]) \\ &= 50 \text{ dL/min (CO)} \times 21.16 \text{ mL } O_2/\text{dL} \\ &\quad \text{blood (Ca}_{O_2}) \\ &= 1058 \text{ mL } O_2/\text{min} \end{aligned}$$

It is apparent that the vast majority of O_2 delivered to tissues is bound to hemoglobin and that the dissolved O_2 (Pa_{O_2}) contributes very little to O_2 content in arterial blood or O_2 delivery. Normally, the content of O_2 in mixed venous blood ($C\bar{v}O_2$) is 15.95 mL O_2 /dL blood because the mixed venous blood is 75% saturated. Therefore, the normal tissue extraction ratio for O_2 is $Ca_{O_2} - C\bar{v}O_2/Ca_{O_2}$ ($21.16 - 15.95/21.16$) or ~25%. A pulmonary artery catheter allows measurements of O_2 delivery and O_2 extraction ratio.

The mixed venous O_2 saturation allows assessment of global tissue perfusion. A reduced mixed venous O_2 saturation may be caused by inadequate cardiac output, reduced hemoglobin concentration, or reduced arterial O_2 saturation. An abnormally high O_2 consumption (VO_2) may also lead to a reduced mixed venous O_2 saturation if O_2 delivery is not concomitantly increased. Abnormally increased VO_2 by peripheral tissues may be caused by a multitude of problems such as fever, agitation, shivering, or thyrotoxicosis.

PREVENTION OF COMPLICATIONS OF CRITICAL ILLNESS

Sepsis in the Critical Care Unit

(See also Chap. 29) Sepsis is a significant problem in the care of critically ill patients. It is the leading cause of death in noncoronary ICUs in the United States. Current estimates suggest that >750,000 patients are affected with this condition each year, and these numbers are expected to increase as the population continues to age and a greater percentage of persons vulnerable to infection seek medical care.

Many therapeutic interventions in the ICU are invasive and predispose patients to infectious complications. These interventions include endotracheal intubation, indwelling vascular catheters, nasally placed enteral feeding tubes, transurethral bladder catheters, and other catheters placed into sterile body cavities (e.g., tube thoracostomy, percutaneous intraabdominal drainage catheters). The longer such devices remain in place, the more prone to infections these

patients become. For example, ventilator-associated pneumonia correlates strongly with the duration of intubation and mechanical ventilation. Therefore, an important aspect of preventive care is the timely removal of invasive devices as soon as they are no longer needed. Multidrug-resistant organisms are common in the ICU.

An important aspect of critical care is infection control in the ICU. Simple measures such as frequent hand-washing are effective but underused strategies. Protective isolation of patients with colonization or infection by drug-resistant organisms is another frequently used strategy in the critical care setting. Antibiotic-coated vascular catheters or endotracheal tubes with specialized suction ports above the cuff to decrease pooling and aspiration of oral secretions are other strategies that may be used, with varying degrees of effectiveness reported. Surveillance programs monitoring adherence to infection control practices such as those described here may reduce the incidence of nosocomial infections.

Deep Venous Thromboses

All ICU patients are at high risk for this complication given their predilection toward immobility. Therefore, all ICU patients should receive some form of prophylaxis against deep venous thrombosis (DVT). The most commonly used forms of prophylaxis are subcutaneous low-dose heparin injections and sequential compression devices for the lower extremities. Observational studies report an alarming incidence of the occurrence of DVTs despite the use of these standard prophylactic regimens. Heparin prophylaxis may result in heparin-induced thrombocytopenia (HIT), another relatively common nosocomial complication in critically ill patients.

Low-molecular-weight heparins such as enoxaparin are more effective than unfractionated heparin for DVT prophylaxis in high-risk patients, such as those undergoing orthopedic surgery, and they have a lower incidence of HIT. Fondaparinux, a selective factor Xa inhibitor, is even more effective than enoxaparin in high-risk orthopedic patients.

Stress Ulcers

Prophylaxis against stress ulcers is frequently administered in most ICUs. Typically, histamine-2 antagonists are administered. Currently available data suggest that high-risk patients, such as those with coagulopathy, shock, or respiratory failure requiring mechanical ventilation, benefit from such prophylactic treatment.

Nutrition and Glycemic Control

These are important issues in critically ill patients that may be associated with respiratory failure, impaired wound healing, and dysfunctional immune response. Early enteral

feeding is reasonable, but no data are available to suggest that this improves patient outcome per se. Certainly, enteral feeding, if possible, is preferred over parenteral nutrition, which is associated with numerous complications, including hyperglycemia, fatty liver, cholestasis, and sepsis. In addition, enteral feeding may prevent bacterial translocation across the gut mucosa.

Intensive insulin therapy to normalize glucose levels is associated with improved survival in surgical ICU patients.

Intensive Care Unit–Acquired Weakness

Weakness occurs frequently in patients who survive critical illness. It is particularly common in those with SIRS and sepsis. Neuropathies and myopathies both have been described, most commonly after ~1 week in the ICU. The mechanisms behind ICU-acquired weakness syndromes are poorly understood. Intensive insulin therapy may reduce polyneuropathy of critical illness. Apart from this, no preventative measures against this complication of critical illness have been described.

Anemia

Anemia is a common problem in critically ill patients. Studies have shown that the vast majority of ICU patients are anemic. Furthermore, most have anemia of chronic inflammation. Phlebotomy contributes significantly to anemia in ICU patients. Studies have demonstrated that erythropoietin levels are inappropriately reduced in most ICU patients and that exogenous erythropoietin administration may reduce transfusion requirements in the ICU. The hemoglobin level that merits transfusion in critically ill patients has been a long-standing area of controversy. A large, multicenter study involving patients in many different ICU settings challenged the conventional notion that a hemoglobin level of 100 g/L (10 g/dL) is needed in critically ill patients. Red blood cell transfusion is associated with impairment of immune function and increased risk of infections, as well as acute lung injury and volume overload—all of which may explain the findings in this study. A conservative transfusion strategy should be the rule in managing critically ill patients who are not actively hemorrhaging.

Acute Renal Failure

(See also Chap. 37) This occurs in a significant percentage of critically ill patients. The most common underlying cause is acute tubular necrosis, usually precipitated by hypoperfusion or nephrotoxic agents. Currently, no pharmacologic agents are available for prevention of renal injury in critical illness. A recent study showed convincingly that low-dose dopamine is *not* effective in protecting the kidneys from acute injury.

Neurologic dysfunction is common in critically ill patients.

Delirium

(See also Chap. 35) This state is defined by (1) an acute onset of changes or fluctuations in the course of mental status, (2) inattention, (3) disorganized thinking, and (4) an altered level of consciousness (i.e., other than alert). Delirium has been reported to occur in >80% of a cohort of patients admitted to the ICU. A rapid test—the Confusion Assessment Method (CAM)—to assess critically ill patients for delirium is available and has been validated. This assessment asks patients to answer simple questions and perform simple tasks and can be completed by the bedside nurse in ~2 min. The differential diagnosis of delirium in ICU patients is broad and includes infectious etiologies (including sepsis), medications (particularly sedatives and analgesics), drug withdrawal, metabolic and electrolyte derangements, intracranial pathology (e.g., stroke, intracranial hemorrhage), seizures, hypoxia, hypertensive crisis, shock, and vitamin deficiencies (particularly thiamine).

Anoxic Cerebral Injury

(See also Chap. 36) This condition is common after cardiac arrest and often results in severe and permanent brain injury in patients whose cardiac arrest is resuscitated. Active cooling of patients after cardiac arrest has been shown to improve neurologic outcomes. As such, patients who present to the ICU after circulatory arrest from ventricular fibrillation or pulseless ventricular tachycardia should be actively cooled with cooling blankets and ice packs, if necessary, to achieve a core body temperature of 32–34°C.

Stroke

Stroke is a common cause of neurologic critical illness. Hypertension must be managed carefully because abrupt reductions in blood pressure may be associated with further brain ischemia and injury. Acute ischemic stroke treated with tissue plasminogen activator (tPA) shows improved neurologic outcome when treatment is given within 3 h of onset of symptoms. Mortality is not improved when tPA is compared with placebo despite improved neurologic outcome. Cerebral hemorrhage is significantly higher in patients given tPA. A treatment benefit is not seen when tPA therapy is given beyond 3 h. Heparin has not been shown to demonstrate improved outcomes convincingly in patients with acute ischemic stroke.

Subarachnoid hemorrhage may occur secondary to aneurysm rupture and is often complicated by cerebral vasospasm, rebleeding, and hydrocephalus. Vasospasm can be detected by either transcranial Doppler assessment or cerebral angiography; it is typically treated with the calcium channel blocker nimodipine; aggressive IV fluid administration; and therapy aimed at increasing the blood pressure, typically with vasoactive drugs such as phenylephrine. The IV fluids and vasoactive drugs (hypertensive hypervolemic therapy) are used to overcome the cerebral vasospasm. Early surgical clipping of aneurysms is advocated by most authorities to prevent complications related to rebleeding. Hydrocephalus, typically heralded by a decreased level of consciousness, may require ventriculostomy drainage.

Status Epilepticus

Recurrent or relentless seizure activity is a medical emergency. Cessation of seizure activity is required to prevent irreversible neurologic injury. Lorazepam is the most effective benzodiazepine for treating status epilepticus and is the treatment of choice for controlling seizures acutely. Phenytoin or fosphenytoin should be given concomitantly because lorazepam has a short half-life. Other drugs such as gabapentin, carbamazepine, and phenobarbital should be reserved for patients with contraindications to phenytoin (e.g., allergy or pregnancy) or ongoing seizures despite use of phenytoin.

Brain Death

(See also Chap. 36) Although critically ill patients usually die from irreversible cessation of circulatory and respiratory function, a diagnosis of death may also be established by irreversible cessation of all functions of the entire brain, including the brainstem, even if circulatory and respiratory function remains intact by artificial life support. Patients must demonstrate absence of cerebral function (unresponsive to all external stimuli) and brainstem functions [e.g., nonreactive pupils, absent ocular movement to head turning or ice water irrigation of ear canals, positive apnea test (no drive to breathe)]. Absence of brain function must have an established cause and be permanent without possibility of recovery (e.g., must confirm the absence of sedative effect, hypothermia, hypoxemia, neuromuscular paralysis, or severe hypotension). If there is uncertainty about the cause of coma, studies of cerebral blood flow and electroencephalography should be performed.

WITHHOLDING AND WITHDRAWING CARE

The withholding and withdrawing of care occurs commonly in the ICU setting. The Task Force on Ethics of

the Society of Critical Care Medicine reported that it is ethically sound to withhold or withdraw care if a patient or surrogate makes such a request or if the goals of therapy are not achievable according to the physician. Because all medical treatments are justified by their expected benefits, the loss of such an expectation justifies the act of withdrawing or withholding such a treatment. As such, the act of withdrawing care is fundamentally similar to the act of withholding care. An underlying stipulation derived from this Task Force report is that the informed patient should have his or her wishes respected with regard to life-sustaining therapy. Implicit in this stipulation is the need to ensure that patients are thoroughly and accurately informed regarding the plausibility and expected results of various therapies.

The act of informing patients, surrogate decision makers, or both is the responsibility of the physician and other health care providers. In the event that a patient or surrogate desires therapy deemed futile by the treating physician, the latter is not obligated ethically to provide such treatment. Rather, arrangements may be made to transfer the patient's care to another care provider. Critical care providers should meet regularly with patients, surrogates, or both to discuss prognosis when the withholding or withdrawal of care is being considered. After a consensus among caregivers has been reached regarding withholding or withdrawal of care, this should be relayed to the patient, surrogate decision maker, or both. If a decision to withhold or withdraw life-sustaining care for a patient has been reached, aggressive attention to analgesia and anxiolysis is needed. Opiates and benzodiazepines are typically used to achieve these goals.

FURTHER READINGS

- ABRAHAM E et al: Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. *N Engl J Med* 353:1332, 2005
- COOK DJ et al: Deep venous thrombosis in medical-surgical critically ill patients: Prevalence, incidence, and risk factors. *Crit Care Med* 33:1565, 2005
- ESTEBAN A et al: Noninvasive positive-pressure ventilation for respiratory failure after extubation. *N Engl J Med* 350:2452, 2004
- GIRARD T et al: Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): A randomised controlled trial. *Lancet* 371:126, 2008
- PRONOVOST P et al: An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med* 355:2725, 2006
- SCHWEICKERT WD et al: Early physical and occupational therapy in mechanically ventilated, critically ill patients: A randomized controlled trial. *Lancet* 373:1874, 2009
- SHAH MR et al: Impact of the pulmonary artery catheter in critically ill patients: Meta-analysis of randomized clinical trials. *JAMA* 294:1664, 2005
- TASK FORCE ON ETHICS OF THE SOCIETY OF CRITICAL CARE MEDICINE: Consensus report on the ethics of forgoing life-sustaining treatments in the critically ill. *Crit Care Med* 18:1424, 1990

THE ACUTE RESPIRATORY DISTRESS SYNDROME NETWORK: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 342:1301, 2000

THE HYPOTHERMIA AFTER CARDIAC ARREST STUDY GROUP: Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 346:549, 2002

THE NATIONAL HEART, LUNG, AND BLOOD INSTITUTE ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS) CLINICAL TRIALS

NETWORK: Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 354:2564, 2006

THE NICE-SUGAR STUDY INVESTIGATORS: Intensive versus glucose control in critically ill patients. *N Engl J Med* 360:1283, 2009

VAN DEN BERGHE G et al: Intensive insulin therapy in the medical ICU. *N Engl J Med* 354:449, 2006



CHAPTER 27

MECHANICAL VENTILATORY SUPPORT

Edward P. Ingenito

Indications for Mechanical Ventilation	258
Physiology of Mechanical Ventilation	259
Establishing and Maintaining an Airway	259
Ventilator Operation	259
■ Ventilator Management Principles	263
■ General Support During Ventilation	263
Complications of Mechanical Ventilation	264
Weaning from Mechanical Ventilation	264
■ Further Readings	265

Ventilators are special pumps that can support the ventilatory function of the respiratory system and improve oxygenation through application of high oxygen content gas and positive pressure (Chap. 26).

INDICATIONS FOR MECHANICAL VENTILATION

The primary indication for initiation of mechanical ventilation is respiratory failure, of which there are two basic types.

1. *Hypoxemic respiratory failure* most commonly results from conditions such as pneumonia, pulmonary edema, pulmonary hemorrhage, and respiratory distress syndrome that cause ventilation-perfusion (\dot{V}/\dot{Q}) mismatch and shunt. Hypoxemic respiratory failure is present when arterial O_2 saturation (SaO_2) $<90\%$ occurs despite an inspired O_2 fraction (FiO_2) >0.6 . The goal of ventilator treatment in this setting is to provide adequate SaO_2 through a combination of supplemental O_2 and specific patterns of ventilation that improve \dot{V}/\dot{Q} matching and reduce intrapulmonary shunt.
2. *Hypercarbic respiratory failure* results from conditions that decrease minute ventilation or increase physiologic dead space such that alveolar ventilation is inadequate

to meet metabolic demands. Clinical conditions associated with hypercarbic respiratory failure include neuromuscular diseases, such as myasthenia gravis, ascending polyradiculopathy, and myopathies, and diseases that cause respiratory muscle fatigue due to increased workload, such as asthma, chronic obstructive pulmonary disease, and restrictive lung disease. *Acute* hypercarbic respiratory failure is characterized by arterial P_{CO_2} values >50 mmHg and an arterial pH <7.30 .

Mechanical ventilation generally should be instituted in acute hypercarbic respiratory failure. In contrast, initiation of ventilator support when components of both acute and chronic hypercarbic respiratory failure are present depends on blood gas parameters and clinical evaluation. If a patient is not in respiratory distress and is not mentally impaired by CO_2 accumulation, it is not mandatory to initiate mechanical ventilation while other forms of treatment are being administered. The goal of ventilator treatment in patients with hypercarbic respiratory failure is to normalize arterial pH through changes in CO_2 tensions. In patients with severe obstructive or restrictive lung disease, potentially injurious elevation in airway pressures may limit tidal volumes such that normalization of pH is not possible, a situation known as *permissive hypercapnia*. This strategy generally requires

sufficient sedation to prevent tachypnea and dyssynchrony between patient and ventilator.

Accepted therapeutic applications of mechanical ventilation include controlled hyperventilation to reduce cerebral blood flow in patients with increased intracranial pressure (ICP) or to improve pulmonary hemodynamics in patients with postoperative pulmonary hypertension. Mechanical ventilation has also been used to reduce the work of breathing and decrease cardiac preload and afterload in patients with congestive heart failure or myocardial ischemia. Ventilator support is also frequently used in conjunction with endotracheal intubation to prevent aspiration of gastric contents in otherwise unstable patients during gastric lavage for suspected drug overdose or during upper gastrointestinal endoscopy. In critically ill patients, intubation and mechanical ventilation are indicated before essential diagnostic or therapeutic studies if it appears that respiratory failure may occur during these maneuvers.

PHYSIOLOGY OF MECHANICAL VENTILATION

Mechanical ventilators provide warmed and humidified gas to the airway in conformance with various specific volume, pressure, and time patterns. The ventilator serves as the energy source for inspiration, replacing the muscles of the diaphragm and chest wall. Expiration is passive, driven by the recoil of the lungs and chest wall; at the completion of inspiration, internal ventilator circuitry vents the airway to atmospheric pressure or a specified level of positive end-expiratory pressure (PEEP).

PEEP helps maintain the patency of the alveoli and small airways in the presence of destabilizing factors, improving matching of ventilation and perfusion by reversing atelectasis. PEEP levels between 0 and 10 cmH₂O are generally safe and effective; higher levels can be used with caution in the management of significant refractory hypoxemia unresponsive to increments in FIO₂ up to 0.6 but increase the risk of barotrauma and hypotension.

Positive-pressure ventilation affects the cardiovascular system through transmission of intrathoracic pressures to the heart and great vessels. Initiation of positive-pressure ventilation decreases both preload and afterload; discontinuation increases both. The potential clinical impact of these effects should be considered when modifying ventilator support in hemodynamically tenuous patients.

ESTABLISHING AND MAINTAINING AN AIRWAY

A cuffed endotracheal tube is often inserted to allow positive-pressure ventilators to deliver conditioned gas to the lungs at pressures above atmospheric pressure. If neuromuscular paralysis is used during intubation, the

use of agents whose mechanism of action includes depolarization at the neuromuscular junction, such as succinylcholine chloride, should be avoided in patients with renal failure, tumor lysis syndrome, crush injuries, medical conditions associated with elevated serum potassium levels, and muscular dystrophy syndromes. Opiates and benzodiazepines can have a deleterious effect on hemodynamics in patients with depressed cardiac function or low systemic vascular resistance. Morphine can promote histamine release from tissue mast cells and may worsen bronchospasm in patients with asthma; fentanyl, sufentanil, and alfentanil are acceptable alternatives. Ketamine may increase systemic arterial pressure as well as ICP and has been associated with hallucinatory responses; it should be used with caution in patients with hypertensive crisis, increased ICP, or a history of psychiatric disorders. Newer agents such as etomidate and propofol have also been used for both induction and maintenance of anesthesia in ventilated patients. They are shorter acting, and etomidate has fewer adverse hemodynamic effects, but both agents are significantly more expensive than older agents.

Although definitive guidelines for performing a tracheostomy in ventilated patients have not been established, in current clinical practice, patients who are likely to require ventilator therapy for >3 weeks should be considered for this procedure. Although it does not clearly reduce the incidence of laryngeal injury or tracheal stenosis, tracheostomy has been associated with improved patient comfort and enhanced ability to partake in rehabilitation-oriented activities.

VENTILATOR OPERATION

Terminology

Mode refers to the manner in which ventilator breaths are triggered, cycled, and limited; commonly used modes of mechanical ventilation are given in [Table 27-1](#). The *trigger*, either an inspiratory effort or a time-based signal, defines what the ventilator senses to initiate an assisted breath. *Cycle* refers to the factors that determine the end of inspiration. For example, in volume-cycled ventilation, inspiration ends when a specific tidal volume is delivered. Other types of cycling include pressure cycling, time cycling, and flow cycling. *Limiting factors* are operator-specified values, such as airway pressure, that are monitored by transducers internal to the ventilator circuit throughout the respiratory cycle; if the specified values are exceeded, inspiratory flow is terminated, and the ventilator circuit is vented to atmospheric pressure or the specified PEEP.

Assist Control Mode Ventilation

An inspiratory cycle is initiated either by the patient's inspiratory effort or, if none is detected within a specified

TABLE 27-1

CLINICAL CHARACTERISTICS OF COMMONLY USED MODES OF MECHANICAL VENTILATION

VENTILATOR MODE	INDEPENDENT VARIABLES (SET BY USER)	DEPENDENT VARIABLES (MONITORED BY USER)	TRIGGER/CYCLE LIMIT	ADVANTAGES	DISADVANTAGES	INITIAL SETTINGS
ACMV ^a	FiO ₂ Tidal volume Ventilator rate Level of PEEP Inspiratory flow pattern Peak inspiratory flow Pressure limit	Peak airway pressure, PaO ₂ , PaCO ₂ Mean airway pressure I/E ratio	Patient/timer Pressure limit	Timer backup Patient-ventilator synchrony Patient controls minute ventilation	Not useful for weaning Potential for dangerous respiratory alkalosis	FiO ₂ = 1.0 ^b V _t = 10–15 mL/kg ^a f = 12–15/min PEEP = 0–5 cmH ₂ O Inspiratory flow = 60 L/min
SIMV ^a	Same as for ACMV	Same as for ACMV	Same as for ACMV	Timer backup useful for weaning	Potential dyssynchrony	Same as for ACMV ^a
CPAP	FiO ₂ Level of CPAP	Tidal volume Rate, flow pattern Airway pressure PaO ₂ , PaCO ₂ , I/E ratio	No trigger Pressure limit	Allows assessment of spontaneous function Helps prevent atelectasis	No backup	FiO ₂ = 0.5–1.0 ^b CPAP = 5–15 cmH ₂ O
PCV ^a	FiO ₂ Inspiratory pressure level Ventilator rate Level of PEEP Pressure limit I/E ratio	Tidal volume Flow rate, pattern Minute ventilation PaO ₂ , PaCO ₂	Timer/patient Timer/pressure limit	System pressures regulated Useful for barotrauma treatment Timer backup	Requires heavy sedation Not useful for weaning	FiO ₂ = 1.0 ^b PC = 20–40 cmH ₂ O ^a PEEP = 5–10 cmH ₂ O f = 12–15/min I/E = 0.7/1–4/1
PSV	FiO ₂ Inspiratory pressure level PEEP Pressure limit	Same as for PCV + I/E ratio	Inspiratory flow Pressure limit	Assures synchrony Good for weaning	No timer backup	FiO ₂ = 0.5–1.0 ^b PS = 10–30 cmH ₂ O 5 cmH ₂ O usually the level used PEEP = 0–5 cmH ₂ O

^aOpen lung ventilation (OLV) involves the use of any of these specific modes with tidal volumes (or applied pressures) to achieve 5–6 mL/kg and positive end-expiratory pressures (PEEPs) achieve maximal alveolar recruitment.

^bFiO₂ is usually set to 1.0 initially unless there is a specific clinical indication to minimize FiO₂ (inspired O₂), such as history of chemotherapy with bleomycin. After adequate oxygenation is documented by blood gas analysis, FiO₂ should be decreased in decrements of 0.1 to 0.2 as tolerated, until the lowest FiO₂ required for an SaO₂ >90% is achieved.

Note: ACMV, assist control mode ventilation; CPAP, continuous positive airway pressure; f, frequency; I/E, inspiration/expiration; PCV, pressure-control ventilation; PSV, pressure-support ventilation; SIMV, synchronized intermittent mandatory ventilation; V_t, tidal ventilation.

time window, by a timer signal within the ventilator. Every breath delivered, whether patient or timer triggered, consists of the operator-specified tidal volume. The ventilatory rate is determined either by the patient or by the operator-specified backup rate, whichever is of higher frequency (Fig. 27-1A). Assist control mode ventilation (ACMV) is commonly used for initiation of mechanical ventilation because it ensures a backup minute ventilation in the absence of an intact respiratory drive and allows for synchronization of the ventilator cycle with the patient's inspiratory effort.

Problems can arise when ACMV is used in patients with tachypnea because of nonrespiratory or nonmetabolic factors such as anxiety, pain, or airway irritation. Respiratory alkalemia may develop and trigger myoclonus or seizures. Dynamic hyperinflation (so-called *auto-PEEP*) may occur if the patient's respiratory mechanics are such that inadequate time is available for complete exhalation between inspiratory cycles. Auto-PEEP can limit venous return, decrease cardiac output, and increase airway pressures, predisposing patients to barotrauma. ACMV is not effective for weaning patients from mechanical ventilation because it provides full ventilator assistance on each breath.

Synchronized Intermittent Mandatory Ventilation

The major difference between synchronized intermittent mandatory ventilation (SIMV) and ACMV is that in the former the patient is allowed to breathe spontaneously (i.e., without ventilator assist) between delivered ventilator breaths. However, mandatory breaths are delivered in synchrony with the patient's inspiratory efforts at a frequency determined by the operator. If the patient fails to initiate a breath, the ventilator delivers a fixed-*tidal-volume* breath and resets the internal timer for the next inspiratory cycle (Fig. 27-1B). SIMV differs from ACMV in that only the preset number of breaths is ventilator assisted.

SIMV allows patients with an intact respiratory drive to exercise inspiratory muscles between assisted breaths, making it useful for both supporting and weaning intubated patients. SIMV may be difficult to use in patients with tachypnea because they may attempt to exhale during the ventilator-programmed inspiratory cycle. When this occurs, the airway pressure may exceed the inspiratory pressure limit, the ventilator-assisted breath will be aborted, and minute volume may decrease below that programmed by the operator. In this setting, if the tachypnea is in response to respiratory or metabolic acidosis, a change to ACMV will increase minute ventilation and help normalize pH while the underlying process is further evaluated and treated.

Continuous Positive Airway Pressure

This is not a true support mode of ventilation, inasmuch as all ventilation occurs through the patient's spontaneous efforts. The ventilator provides fresh gas to the breathing

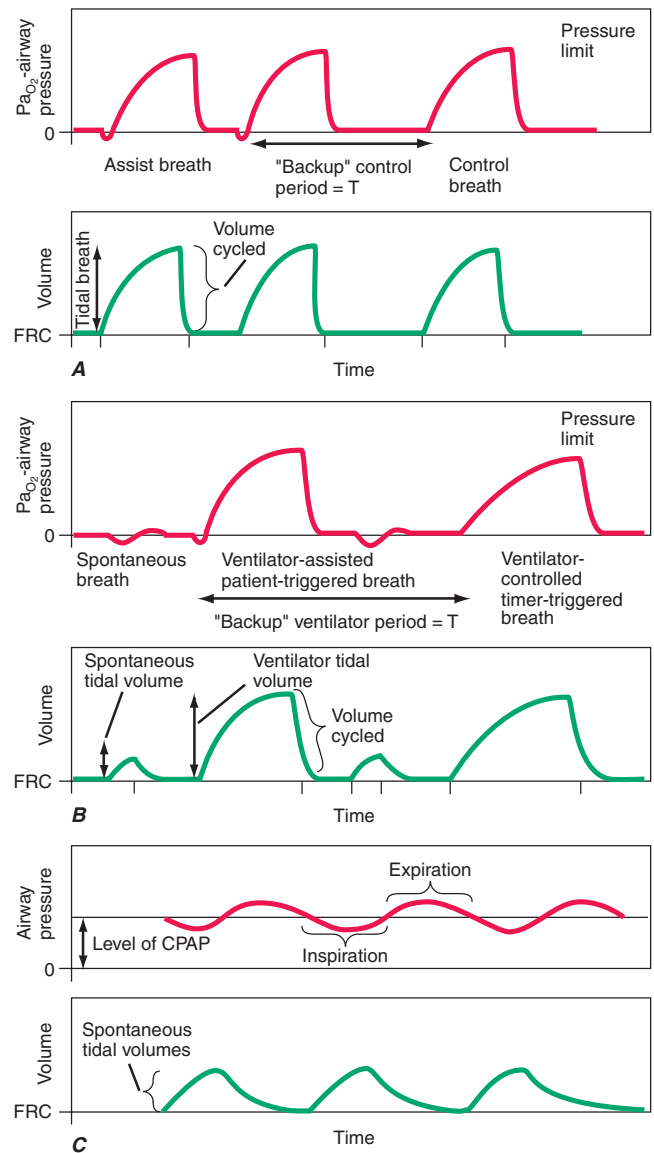


FIGURE 27-1

Airway pressure and lung volume versus time profiles. A. During assist control mode ventilation (ACMV). Assisted breaths are triggered by the patient's effort. Controlled breaths are triggered by the ventilator timer. Every breath, whether triggered by the patient or by the timer, is a complete volume-cycled breath, with airway pressure as a dependent variable. The pressure limit is set above the peak inspiratory pressure. **B.** During synchronized intermittent mandatory ventilation (SIMV). Spontaneous breaths occur between patient-triggered assisted breaths and timer-triggered breaths. The tidal volume of the spontaneous breaths is determined by the patient's effort and lung impedance. Assisted and controlled breaths are volume cycled. **C.** During continuous positive airway pressure (CPAP). Breathing is spontaneous, and no ventilator assist is provided. The spontaneous profile is superimposed on an elevated mean airway pressure that the user specifies. FRC, functional residual capacity.

262 circuit with each inspiration and charges the circuit to a constant, operator-specified pressure that can range from 0 to 20 cmH₂O (Fig. 27-1C). Continuous positive airway pressure (CPAP) is used to assess the extubation potential in patients who have been effectively weaned and require little ventilator support and in patients with intact respiratory system function who require an endotracheal tube for airway

Pressure-Control Ventilation

Pressure-control ventilation (PCV) is time triggered, time cycled, and pressure limited. During the inspiratory phase, a specified pressure is imposed at the airway opening throughout inspiration (Fig. 27-2A). Because inspiratory airway pressure is specified by the operator, tidal volume and inspiratory flow rate are dependent rather than independent variables and are not user specified. PCV is the preferred mode of ventilation for patients in whom it is desirable to regulate peak airway pressures, such as those with preexisting barotrauma or postoperative thoracic surgical patients, in whom the shear forces across a fresh suture line should be limited. When PCV is used, minute ventilation and tidal volume must be monitored; minute ventilation is altered through changes in rate or in the pressure-control value, which changes tidal volume.

PCV with the use of a prolonged inspiratory time has been applied to patients with severe hypoxemic respiratory failure. This approach, called inverse inspiratory-to-expiratory ratio ventilation (IRV), increases mean distending pressures without increasing peak airway pressures. It is thought to work in conjunction with PEEP to open collapsed alveoli and improve oxygenation, although no conclusive data are available to show that IRV improves outcomes in clinical trials.

Pressure-Support Ventilation

This form of ventilation is patient triggered, flow cycled, and pressure limited; it is specifically designed for use in the weaning process. During pressure-support ventilation (PSV), the inspiration is terminated when inspiratory airflow decreases below a certain level; in most ventilators, this flow rate cannot be adjusted by the operator. When PSV is used, patients receive ventilator assist only when the ventilator detects an inspiratory effort (Fig. 27-2B). PSV can also be used in combination with SIMV to ensure volume-cycled backup for patients whose respiratory drive is depressed.

PSV is well tolerated by most patients who are being weaned; PSV parameters can be set to provide full or nearly full ventilatory support and can be withdrawn slowly over a period of days in a systematic fashion to gradually load the respiratory muscles.

Noninvasive Ventilation

Noninvasive ventilator support through a tight-fitting face mask or nasal mask, traditionally used for treatment

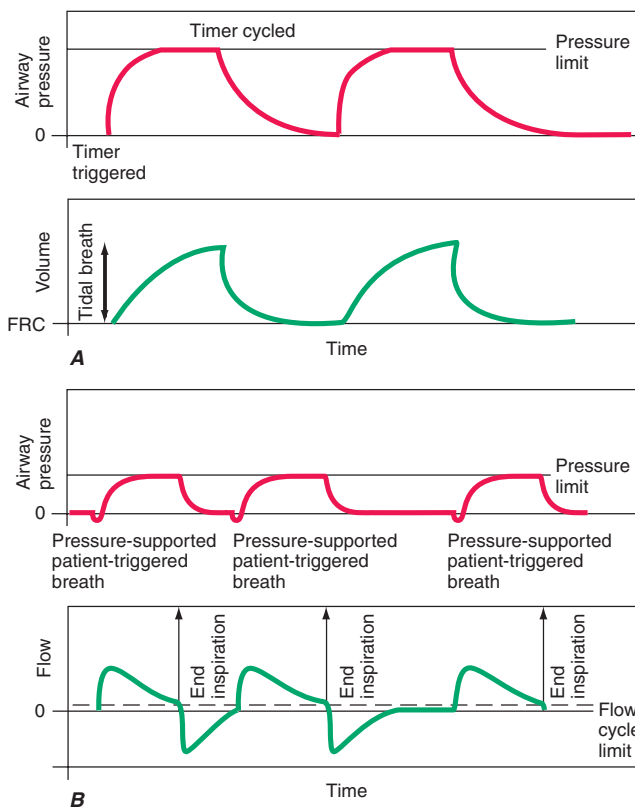


FIGURE 27-2

Pressure-control ventilation (PCV). **A.** Airway pressure and lung volume versus time profiles during PCV. All breaths are timer triggered, timer cycled, and pressure limited. Peak airway pressure is set by the operator, and tidal volume is a dependent variable. The profiles shown here display the pressure limit as slightly higher than pressure-control level. This need not be the case, but it is appropriate to set the pressure limit only slightly above the pressure-control level when using this mode of ventilation for management of the patient with barotrauma. **B.** Airway pressure and airway flow versus time profiles during pressure-support ventilation (PSV). All breaths are patient triggered and flow cycled. Inspiration is cycled off when the inspiratory flow decreases below a predetermined threshold internally set in the ventilator circuit. In the example shown, the pressure limit is slightly greater than the pressure-support level. Because each can be set independently, this need not be the case. FRC, functional residual capacity.

of sleep apnea, has recently been used as primary ventilator support in patients with impending respiratory failure. Noninvasive ventilation (NIV) is most frequently used using PSV or bilevel positive airway pressure ventilation, inasmuch as both of these modes are well tolerated by conscious patients and optimize patient-ventilator synchrony. NIV has met with varying degrees of success when applied to patients with acute or chronic respiratory failure. The major limitation to its widespread application has been patient intolerance because the tight-fitting mask required for NIV can cause both physical and emotional discomfort.

Nonconventional Ventilation Strategies

Several nonconventional ventilator strategies have been evaluated for their ability to improve oxygenation and reduce mortality in patients with advanced hypoxemic respiratory failure. These include high-frequency oscillatory ventilation (HFOV), extracorporeal membrane oxygenation (ECMO), and partial liquid ventilation using perfluorocarbons. Although case reports and small uncontrolled cohort studies have shown benefit, randomized controlled trials have failed to demonstrate consistent improvements in outcome with any of these strategies. Currently, these approaches should be considered as “salvage” techniques and considered for patients with hypoxemia refractory to conventional therapy.

Interventions Used with Ventilator Support

Open Lung Ventilation

Open lung ventilation (OLV) is not a distinct mode of ventilation but rather a strategy for applying either volume-cycled or PCV to patients with severe hypoxemic respiratory failure. In OLV, the primary objectives of ventilator support are maintenance of adequate oxygenation and avoidance of cyclic opening and closing of alveolar units by selecting a tidal volume and level of PEEP that allow the majority of units to remain inflated during tidal ventilation. Achievement of eucapnia and normal blood pH are of lower priority, and permissive hypercapnia is accepted. Current data suggest that a small tidal volume (i.e., 6 mL/kg) provides adequate ventilatory support with a lower incidence of adverse effects than more conventional tidal volumes of 10–15 mL/kg. Hypercapnia and consequent respiratory acidosis tend to be well tolerated physiologically, except in patients with significant hemodynamic compromise, ventricular dysfunction, cardiac dysrhythmias, or increased ICP. OLV has been used most extensively in the management of patients with hypoxemic respiratory failure caused by acute lung injury (ALI). Several randomized clinical trials of OLV have been performed and suggest that this strategy reduces mortality and improves gas exchange in patients with ALI.

Prone Positioning during Mechanical Ventilation

Patients with acute respiratory distress syndrome (ARDS) experience hypoxemia as a result of intrapulmonary shunting caused by regional atelectasis (Chap. 30). Collapse occurs most extensively in dependent regions of the lung. Prone positioning increases transdiaphragmatic pressures in these regions by altering their position relative to the hydrostatic pressures generated by abdominal contents. Thus, prone positioning increases distending pressures in these areas without the need to apply additional airway pressures that can overdistend less damaged areas of lung and potentially cause additional lung damage. Although conceptually appealing and simple to implement, a randomized trial in patients with ALI failed to demonstrate a

survival advantage with prone positioning despite demonstration of transient physiologic benefit.

Nitric Oxide Administration

Nitric oxide (NO) gas has bronchodilator and pulmonary vasodilator effects when delivered through the airways and has been shown to improve arterial oxygenation in many patients with advanced hypoxemic respiratory failure. Although physiologic benefits have been demonstrated in small cohort studies, randomized controlled trials have failed to confirm that therapeutic administration of NO reduces mortality in patients with advanced hypoxemic respiratory failure.

VENTILATOR MANAGEMENT PRINCIPLES

Most patients who are started on ventilator support receive ACMV or SIMV because these modes ensure user-specified backup minute ventilation. After the intubated patient has been stabilized with respect to oxygenation, definitive therapy for the underlying process responsible for respiratory failure is initiated. Subsequent modifications in ventilator therapy must be provided in parallel with changes in the patient's clinical status. As improvement in respiratory function is noted, the first priorities are to reduce PEEP and supplemental O₂. After a patient can achieve adequate arterial saturation with an FiO₂ ≤ 0.5 and 5 cmH₂O PEEP, attempts should be made to reduce the level of mechanical ventilatory support. Patients previously on full ventilator support should be switched to a mode that allows for weaning, such as SIMV, PSV, or SIMV combined with PSV. Ventilator therapy can then be gradually removed, as outlined in the section on weaning. Patients whose condition continues to deteriorate after ventilator support is initiated may require increased O₂, PEEP, and alternative modes of ventilation such as IRV or OLV.

GENERAL SUPPORT DURING VENTILATION

Patients started on mechanical ventilation usually require sedation and analgesia to maintain an acceptable level of comfort. Often, this consists of a combination of a benzodiazepine and opiate administered intravenously. Medications commonly used for this purpose include lorazepam, midazolam, diazepam, morphine, and fentanyl.

Immobilized patients in the intensive care unit on mechanical ventilator support are at increased risk for deep venous thrombosis and decubitus ulcers. To prevent venous thrombosis, prophylaxis in the form of subcutaneous heparin, pneumatic compression boots, or both is frequently prescribed. Fractionated low-molecular-weight heparin appears to be equally effective for this purpose.

264 To help prevent decubitus ulcers, frequent changes in body position and use of soft mattress overlays and air mattresses are used.

Prophylaxis against diffuse gastrointestinal mucosal injury is indicated for patients who have had a neurologic insult or those with severe respiratory failure in association with ARDS. Histamine receptor antagonists (H₂-receptor antagonists), antacids, and cytoprotective agents such as carafate have all been used for this purpose and appear to be effective. Recent data suggest that carafate use may be associated with a reduction in the incidence of nosocomial pneumonias because it does not affect stomach pH and is less likely to permit colonization of the gastrointestinal tract by pathogenic organisms.

Nutrition support by enteral feeding through either a nasogastric or an orogastric tube should be maintained in all intubated patients whenever possible. In patients with a normal baseline nutritional state, support should be initiated within 7 days. In malnourished patients, nutrition support should be initiated within 72 h. Delayed gastric emptying is common in critically ill patients on sedative medications but often responds to promotility agents such as metoclopramide. Parenteral nutrition is an alternative to enteral nutrition in patients with severe gastrointestinal pathology.

COMPLICATIONS OF MECHANICAL VENTILATION

Endotracheal intubation and positive-pressure mechanical ventilation have direct and indirect effects on the lung and upper airways, the cardiovascular system, and the gastrointestinal system. Pulmonary complications include barotrauma, nosocomial pneumonia, oxygen toxicity, tracheal stenosis, and deconditioning of respiratory muscles. *Barotrauma*, which occurs when high pressures (i.e., >50 cmH₂O) overdistend and disrupt lung tissue, is clinically manifest by interstitial emphysema, pneumomediastinum, subcutaneous emphysema, or pneumothorax. Although the first three conditions may resolve spontaneously through the reduction of airway pressures, clinically significant pneumothorax requires tube thoracostomy.

Patients intubated for >72 h are at high risk for ventilator-associated pneumonia (VAP) as a result of aspiration from the upper airways through small leaks around the endotracheal tube cuff; the most common organisms responsible for this condition are *Pseudomonas aeruginosa*, enteric gram-negative rods, and *Staphylococcus aureus*. The diagnosis of VAP requires “protected brush” bronchoscopic sampling of airway secretions coupled with quantitative microbiologic techniques because this approach avoids sample contamination with bacteria that colonize the upper airways. Because this condition is associated with high mortality rate, early initiation of empirical antibiotics directed against likely pathogens is recommended.

Hypotension resulting from elevated intrathoracic pressures with decreased venous return is almost always responsive to intravascular volume repletion. In patients judged to have hypotension or respiratory failure on the basis of alveolar edema, hemodynamic monitoring with a pulmonary arterial catheter may be of value in optimizing O₂ delivery via manipulation of intravascular volume and FIO₂ and PEEP levels.

Gastrointestinal effects of positive-pressure ventilation include *stress ulceration* and *mild to moderate cholestasis*. It is common practice to provide prophylaxis with H₂-receptor antagonists or sucralfate for stress-related ulcers. Mild cholestasis [i.e., total bilirubin values ≤68 μmol/L (≤4.0 mg/dL)] attributable to the effects of increased intrathoracic pressures on portal vein pressures is common and generally self-limited. Cholestasis of a more severe degree should not be attributed to a positive-pressure ventilation response and is more likely caused by a primary hepatic process.

WEANING FROM MECHANICAL VENTILATION

Removal of mechanical ventilator support requires that a number of criteria be met. Upper airway function must be intact for a patient to remain extubated but is difficult to assess in the intubated patient. Therefore, if a patient can breathe on his or her own through an endotracheal tube but develops stridor or recurrent aspiration when the tube is removed, upper airway dysfunction or an abnormal swallowing mechanism should be suspected and evaluated. Respiratory drive and chest wall function are assessed by observation of respiratory rate, tidal volume, inspiratory pressure, and vital capacity. The weaning index, defined as the ratio of breathing frequency to tidal volume (breaths per minute per liter), is both sensitive and specific for predicting the likelihood of successful extubation. When this ratio is <105 with the patient breathing without mechanical assistance through an endotracheal tube, successful extubation is likely. Alveolar ventilation is deemed adequate when elimination of CO₂ is sufficient to maintain arterial pH in the range of 7.35–7.40, and an SaO₂ >90% can be achieved with an FIO₂ <0.5 and a PEEP ≤5 cmH₂O. Although many patients may not meet all criteria for weaning, the likelihood of successful extubation increases as more criteria are met.

Many approaches to weaning patients from ventilator support have been advocated. Whereas T-piece and CPAP weaning are best tolerated by patients who have undergone mechanical ventilation for brief periods and require little respiratory muscle reconditioning, SIMV and PSV are best for patients intubated for extended periods likely to require gradual respiratory muscle reconditioning.

T-piece and CPAP weaning involve brief spontaneous breathing trials with supplemental O₂. These trials

are usually initiated for 5 min/h followed by a 1-h interval of rest. Trials are increased in 5- to 10-min/h increments until the patient can remain ventilator independent for periods of several hours. Extubation can then be attempted.

Weaning by means of SIMV involves gradually tapering the mandatory backup rate in increments of 2–4 breaths/min while blood gas parameters and respiratory rates are monitored. Rates of >25 breaths/min on withdrawal of mandatory ventilator breaths generally indicate respiratory muscle fatigue and the need to combine periods of exercise with rest. Exercise periods are gradually increased until a patient remains stable on SIMV at ≤ 4 breaths/min. A CPAP or T-piece trial can then be attempted before extubation.

PSV, as described in detail above, is used primarily for weaning from mechanical ventilation. PSV is usually initiated at a level adequate for full ventilator support (PSV_{max} ; i.e., PSV is set slightly below the peak inspiratory pressures required by the patient during volume-cycled ventilation). The level of pressure support is then gradually withdrawn in increments of 3–5 cmH₂O until a level is reached at which the respiratory rate increases to 25 breaths/min. At this point, intermittent periods of higher-pressure support are alternated with periods of lower-pressure support to provide muscle reconditioning while avoiding diaphragmatic fatigue. Gradual withdrawal of PSV continues until the level of support is just adequate to overcome the resistance of the endotracheal

tube (~5–10 cmH₂O). Support can be discontinued and the patient extubated.

FURTHER READINGS

- BOLES JM et al: Weaning from mechanical ventilation. *Eur Respir J* 29:1033, 2007
- BROWER RG et al: Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 351(4):327, 2004
- ESTEBAN A et al: Non-invasive ventilation for respiratory failure after extubation. *N Engl J Med* 350:2452, 2004
- FAN E et al: Ventilatory management of acute lung injury and acute respiratory distress syndrome. *JAMA* 294(22):2889, 2005
- MACINTYRE NR: Current issues in mechanical ventilation for respiratory failure. *Chest* 128(Suppl 2):561S, 2005
- (Ed.) *Controversies in mechanical ventilation*. *Clin Chest Med* 29(2), 2008
- MERCAT A, et al: for the Expiratory Pressure Study Group. Positive and end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 299: 646, 2008
- MICHAEL JR et al: Inhaled nitric oxide versus conventional therapy. *Am J Respir Crit Care Med* 157(5):1372, 1998
- PARK JE, GRIFFITHS MJ: Recent advances in mechanical ventilation. *Clin Med* 5:441, 2005
- SCALISE PJ, VOTTO JJ: Weaning from long term mechanical ventilation. *Chron Respir Dis* 2:99, 2005
- THE ACUTE RESPIRATORY DISTRESS SYNDROME NETWORK: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 342:1301, 2000



CHAPTER 28

APPROACH TO THE PATIENT WITH SHOCK

Ronald V. Maier

■ Pathogenesis and Organ Response	266	Traumatic Shock	274
Microcirculation	266	Cardiogenic Shock	274
Cellular Responses	268	Compressive Cardiogenic Shock	274
Neuroendocrine Response	268	Septic Shock	275
Cardiovascular Response	268	Neurogenic Shock	275
Pulmonary Response	269	Hypoadrenal Shock	275
Renal Response	269	■ Adjunctive Therapies	275
Metabolic Derangements	269	Positioning	275
Inflammatory Responses	269	Pneumatic Antishock Garment	276
■ Specific Forms of Shock	271	Rewarming	276
Hypovolemic Shock	271	■ Further Readings	276

Shock is the clinical syndrome that results from inadequate tissue perfusion. Irrespective of cause, the hypoperfusion-induced imbalance between the delivery of and requirements for oxygen and substrate leads to cellular dysfunction. The cellular injury created by the inadequate delivery of oxygen and substrates also induces the production and release of inflammatory mediators that further compromise perfusion through functional and structural changes within the microvasculature. This leads to a vicious circle in which impaired perfusion is responsible for cellular injury, which causes maldistribution of blood flow, further compromising cellular perfusion; the latter causes multiple organ failure and, if the process is not interrupted, leads to death. The clinical manifestations of shock are the result, in part, of autonomic neuroendocrine responses to hypoperfusion as well as the breakdown in organ function induced by severe cellular dysfunction (Fig. 28-1).

When very severe or persistent, inadequate oxygen delivery leads to irreversible cell injury; thus, only rapid restoration of oxygen delivery can reverse the progression of the shock state. The fundamental approach to management, therefore, is to recognize overt and impending shock in a timely fashion and to intervene emergently to restore perfusion. This often requires the

expansion or reexpansion of intravascular blood volume. Control of any inciting pathologic process (e.g., continued hemorrhage, impairment of cardiac function, or infection) must occur simultaneously.

Clinical shock is usually accompanied by hypotension—i.e., a mean arterial pressure <60 mmHg in previously normotensive persons. Multiple classification schemes have been developed in an attempt to synthesize the seemingly dissimilar processes leading to shock. Strict adherence to a classification scheme may be difficult from a clinical standpoint because of the frequent combination of two or more causes of shock in any individual patient, but the classification shown in Table 28-1 provides a useful reference point from which to discuss and further delineate the underlying processes.

PATHOGENESIS AND ORGAN RESPONSE

MICROCIRCULATION

Normally, when cardiac output decreases, systemic vascular resistance (SVR) increases to maintain a level of systemic pressure that is adequate for perfusion of the heart and brain at the expense of other tissues such as

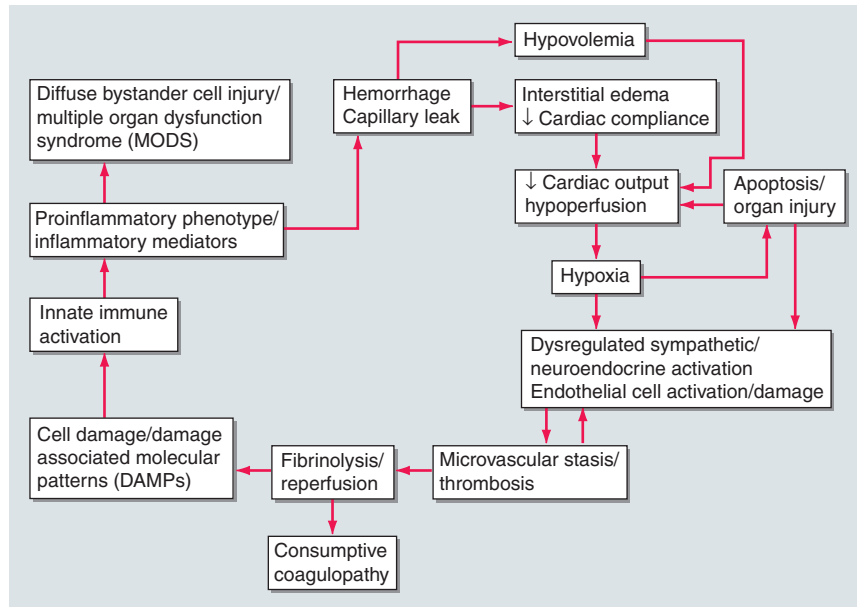


FIGURE 28-1
Shock-induced vicious cycle.

muscle, skin, and especially the gastrointestinal tract. SVR is determined primarily by the luminal diameter of arterioles. The metabolic rates of the heart and brain are high, and their stores of energy substrate are low. These organs are critically dependent on a continuous supply of oxygen and nutrients, and neither tolerates severe ischemia for more than brief periods. Autoregulation (i.e., the maintenance of blood flow over a wide range of perfusion pressures) is critical in sustaining cerebral and coronary perfusion despite significant hypotension. However, when mean arterial pressure decreases to ≤ 60 mmHg, flow to these organs decreases, and their function deteriorates.

Arteriolar vascular smooth muscle has both α - and β -adrenergic receptors. The α_1 receptors mediate vasoconstriction, and the β_2 receptors mediate vasodilation. Efferent sympathetic fibers release norepinephrine, which acts primarily on α_1 receptors in one of the most fundamental compensatory responses to reduced perfusion pressure. Other constrictor substances that are increased in most forms of shock include angiotensin II, vasopressin, endothelin 1, and thromboxane A_2 . Both norepinephrine and epinephrine are released by the adrenal medulla, and

the concentrations of these catecholamines in the bloodstream increase. Circulating vasodilators in shock include prostacyclin [prostaglandin (PG) I_2]; nitric oxide (NO); and, importantly, products of local metabolism such as adenosine that match flow to the tissue's metabolic needs. The balance between these various vasoconstrictor and vasodilator influences acting on the microcirculation determines local perfusion.

Transport to cells depends on microcirculatory flow; capillary permeability; the diffusion of oxygen, carbon dioxide, nutrients, and products of metabolism through the interstitium; and the exchange of these products across cell membranes. Impairment of the microcirculation, which is central to the pathophysiologic responses in the late stages of all forms of shock, results in the derangement of cellular metabolism, which is ultimately responsible for organ failure.

The endogenous response to mild or moderate hypovolemia is an attempt at restitution of intravascular volume through alterations in hydrostatic pressure and osmolarity. Constriction of arterioles leads to reductions in both the capillary hydrostatic pressure and the number of capillary beds perfused, thereby limiting the capillary surface area across which filtration occurs. When filtration is reduced while intravascular oncotic pressure remains constant or increases, there is net reabsorption of fluid into the vascular bed, in accord with Starling's law of capillary–interstitial liquid exchange. Metabolic changes (including hyperglycemia and elevations in the products of glycolysis, lipolysis, and proteolysis) increase extracellular osmolarity, leading to an osmotic gradient between cells and interstitium that increases interstitial and intravascular volume at the expense of intracellular volume.

TABLE 28-1

CLASSIFICATION OF SHOCK	
Hypovolemic	Septic
Traumatic	Hyperdynamic
Cardiogenic	Hypodynamic
Intrinsic	Neurogenic
Compressive	Hypoadrenal

Interstitial transport of nutrients is impaired in shock, leading to a decline of intracellular high-energy phosphate stores. Mitochondrial dysfunction and uncoupling of oxidative phosphorylation are the most likely causes for decreased amounts of adenosine triphosphate (ATP). As a consequence, there is an accumulation of hydrogen ions, lactate, and other products of anaerobic metabolism. As shock progresses, these vasodilator metabolites override vasomotor tone, causing further hypotension and hypoperfusion. Dysfunction of cell membranes is thought to represent a common end-stage pathophysiologic pathway in the various forms of shock. Normal cellular transmembrane potential decreases, and there is an associated increase in intracellular sodium and water, leading to cell swelling, which interferes further with microvascular perfusion. In a preterminal event, homeostasis of calcium via membrane channels is lost with flooding of calcium intracellularly and a concomitant extracellular hypocalcemia. There is also increasing evidence for a widespread but selective apoptotic loss of cells, contributing to organ and immune failure.

NEUROENDOCRINE RESPONSE

Hypovolemia, hypotension, and hypoxia are sensed by baroreceptors and chemoreceptors, which contribute to an autonomic response that attempts to restore blood volume, maintain central perfusion, and mobilize metabolic substrates. Hypotension disinhibits the vasomotor center, resulting in increased adrenergic output and reduced vagal activity. Release of norepinephrine from adrenergic neurons induces peripheral and splanchnic vasoconstriction, a major contributor to the maintenance of central organ perfusion, and reduced vagal activity increases the heart rate and cardiac output. Vagal tone is also recognized to downregulate the innate immunity inflammatory response. The effects of circulating epinephrine released by the adrenal medulla in shock are largely metabolic, causing increased glycogenolysis and gluconeogenesis and reduced pancreatic insulin release. Epinephrine also inhibits production and release of inflammatory mediators through stimulation of β -adrenergic receptors on innate immune cells.

Severe pain and other severe stress cause the hypothalamic release of adrenocorticotrophic hormone (ACTH). This stimulates cortisol secretion, which contributes to decreased peripheral uptake of glucose and amino acids, enhances lipolysis, and increases gluconeogenesis. Increased pancreatic secretion of glucagon during stress accelerates hepatic gluconeogenesis and further elevates blood glucose concentration. These hormonal actions act synergistically to increase blood glucose in the maintenance of blood volume. Many critically ill patients have recently been shown to exhibit low plasma cortisol levels

and an impaired response to ACTH stimulation. Low levels of cortisol in response to stimulation are linked to a decrease in survival. The importance of the cortisol response to stress is illustrated by the profound circulatory collapse that occurs in patients with adrenal cortical insufficiency.

Renin release is increased in response to adrenergic discharge and reduced perfusion of the juxtaglomerular apparatus in the kidney. Renin induces the formation of angiotensin I, which is then converted to angiotensin II, an extremely potent vasoconstrictor and stimulator of aldosterone release by the adrenal cortex and of vasopressin by the posterior pituitary. Aldosterone contributes to the maintenance of intravascular volume by enhancing renal tubular reabsorption of sodium, resulting in the excretion of low-volume, concentrated, sodium-free urine. Vasopressin has a direct action on vascular smooth muscle, contributing to vasoconstriction, and acts on the distal renal tubules to enhance water reabsorption.

CARDIOVASCULAR RESPONSE

Three variables—ventricular filling (preload), the resistance to ventricular ejection (afterload), and myocardial contractility—are paramount in controlling stroke volume. Cardiac output, the major determinant of tissue perfusion, is the product of stroke volume and heart rate. Hypovolemia leads to decreased ventricular preload, which in turn reduces the stroke volume. An increase in heart rate is a useful but limited compensatory mechanism to maintain cardiac output. A shock-induced reduction in myocardial compliance is frequent, reducing ventricular end-diastolic volume and hence stroke volume at any given ventricular filling pressure. Restoration of intravascular volume may return stroke volume to normal but only at elevated filling pressures. Increased filling pressures also stimulate release of brain natriuretic peptide (BNP) to secrete sodium and volume to relieve the pressure on the heart. Levels of BNP correlate with outcome after severe stress. In addition, sepsis, ischemia, myocardial infarction, severe tissue trauma, hypothermia, general anesthesia, prolonged hypotension, and acidemia may all impair myocardial contractility and reduce the stroke volume at any given ventricular end-diastolic volume. The resistance to ventricular ejection is significantly influenced by the SVR, which is elevated in most forms of shock. However, resistance is depressed in the early hyperdynamic stage of septic shock (Chap. 29), thereby initially allowing the cardiac output to be maintained or elevated.

The venous system contains nearly two-thirds of the total circulating blood volume, most in the small veins, and serves as a dynamic reservoir for autoinfusion of blood. Active venoconstriction as a consequence of α -adrenergic activity is an important compensatory mechanism for the maintenance of venous return and therefore

of ventricular filling during shock. On the other hand, venous dilatation, as occurs in neurogenic shock, reduces ventricular filling and hence stroke volume and cardiac output (see later).

PULMONARY RESPONSE

The response of the pulmonary vascular bed to shock parallels that of the systemic vascular bed, and the relative increase in pulmonary vascular resistance (PVR), particularly in septic shock, may exceed that of the SVR. Shock-induced tachypnea reduces tidal volume and increases both dead space and minute ventilation. Relative hypoxia and the subsequent tachypnea induce a respiratory alkalosis. Recumbency and involuntary restriction of ventilation secondary to pain reduce functional residual capacity and may lead to atelectasis. Shock is recognized as a major cause of acute lung injury and subsequent acute respiratory distress syndrome (ARDS; Chap. 30). These disorders are characterized by noncardiogenic pulmonary edema secondary to diffuse pulmonary capillary endothelial and alveolar epithelial injury, hypoxemia, and bilateral diffuse pulmonary infiltrates. Hypoxemia results from perfusion of underventilated and nonventilated alveoli. Loss of surfactant and lung volume in combination with increased interstitial and alveolar edema reduces lung compliance. The work of breathing and the oxygen requirements of respiratory muscles increase.

RENAL RESPONSE

Acute renal failure (Chap. 37), a serious complication of shock and hypoperfusion, occurs less frequently than heretofore because of early aggressive volume repletion. Acute tubular necrosis is now more frequently seen as a result of the interactions of shock, sepsis, the administration of nephrotoxic agents (e.g., aminoglycosides and angiographic contrast media), and rhabdomyolysis; the latter may be particularly severe in skeletal muscle trauma. The physiologic response of the kidney to hypoperfusion is to conserve salt and water. In addition to decreased renal blood flow, increased afferent arteriolar resistance accounts for diminished glomerular filtration rate, which together with increased aldosterone and vasopressin is responsible for reduced urine formation. Toxic injury causes necrosis of tubular epithelium and tubular obstruction by cellular debris with back-leak of filtrate. The depletion of renal ATP stores that occurs with prolonged renal hypoperfusion contributes to subsequent impairment of renal function.

METABOLIC DERANGEMENTS

During shock, there is disruption of the normal cycles of carbohydrate, lipid, and protein metabolism. Through

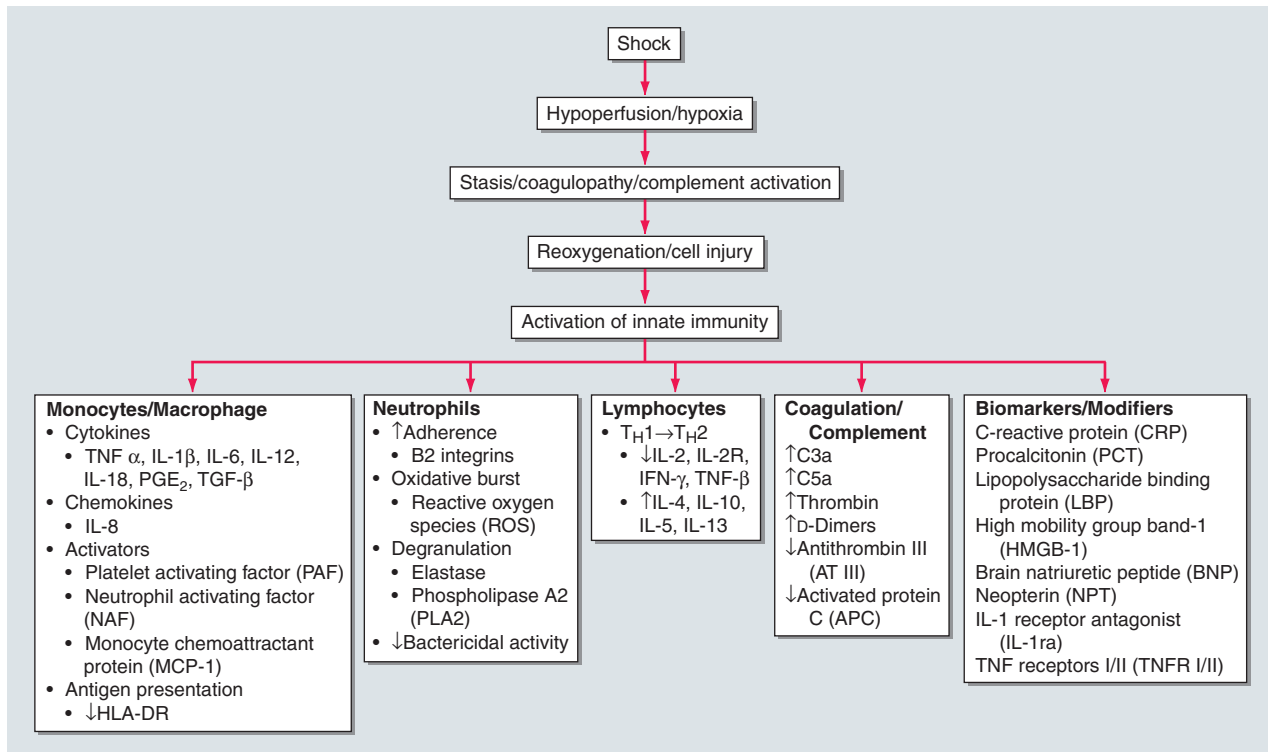
the citric acid cycle, alanine in conjunction with lactate (which is converted from pyruvate in the periphery in the presence of oxygen deprivation) enhances the hepatic production of glucose. With reduced availability of oxygen, the breakdown of glucose to pyruvate and ultimately lactate represents an inefficient cycling of substrate with minimal net energy production. An elevated plasma lactate/pyruvate ratio is consistent with anaerobic metabolism and reflects inadequate tissue perfusion. Decreased clearance of exogenous triglycerides coupled with increased hepatic lipogenesis causes a significant increase in serum triglyceride concentrations. There is increased protein catabolism; a negative nitrogen balance; and, if the process is prolonged, severe muscle wasting.

INFLAMMATORY RESPONSES

Activation of an extensive network of proinflammatory mediator systems plays a significant role in the progression of shock and contributes importantly to the development of organ injury and failure (Fig. 28-2). In patients who survive the acute insult, there is a delayed endogenous counterregulatory response to “turn off” the excessive proinflammatory response. If balance is restored, the patient does well. If the immunosuppressive response is excessive, the patient is highly susceptible to secondary nosocomial infections, which can then drive the inflammatory response and lead to delayed multiple organ failure.

Multiple humoral mediators are activated during shock and tissue injury. The complement cascade, activated through both the classic and alternate pathways, generates the anaphylatoxins C3a and C5a. Direct complement fixation to injured tissues can progress to the C5–C9 attack complex, causing further cell damage. Activation of the coagulation cascade (Chap. 41) causes microvascular thrombosis, with subsequent fibrinolysis leading to repeated episodes of ischemia and reperfusion. Components of the coagulation system, such as thrombin, are potent proinflammatory mediators that cause expression of adhesion molecules on endothelial cells and activation of neutrophils, leading to microvascular injury. Coagulation also activates the kallikrein–kininogen cascade, contributing to hypotension.

Eicosanoids are vasoactive and immunomodulatory products of arachidonic acid metabolism that include cyclooxygenase-derived PGs and thromboxane A₂ as well as lipoxygenase-derived leukotrienes and lipoxins. Thromboxane A₂ is a potent vasoconstrictor that contributes to the pulmonary hypertension and acute tubular necrosis of shock. PGI₂ and PGE₂ are potent vasodilators that enhance capillary permeability and edema formation. The cysteinyl leukotrienes LTC₄ and LTD₄ are pivotal mediators of the vascular sequelae of anaphylaxis as well as of shock states resulting from sepsis or tissue injury.

**FIGURE 28-2**

A schematic of the host immunoinflammatory response to shock. IL, interleukin; PGE₂, prostaglandin E₂; TGF- β , transforming growth factor β ; TNF α , tumor necrosis factor α .

LTB₄ is a potent neutrophil chemoattractant and secretagogue that stimulates the formation of reactive oxygen species. Platelet-activating factor, an ether-linked, arachidonyl-containing phospholipid mediator, causes pulmonary vasoconstriction, bronchoconstriction, systemic vasodilation, increased capillary permeability, and the priming of macrophages and neutrophils to produce enhanced levels of inflammatory mediators.

Tumor necrosis factor α (TNF α), produced by activated macrophages, reproduces many components of the shock state, including hypotension, lactic acidosis, and respiratory failure. Interleukin 1 β (IL-1 β), produced by tissue-fixed macrophages, is critical to the inflammatory response. Both are significantly elevated immediately after trauma and shock. IL-6, also produced predominantly by the macrophage, has a slightly delayed peak response but is the best predictor of prolonged recovery and development of multiple organ failure after shock. Chemokines such as IL-8 are potent neutrophil chemoattractants and activators that upregulate adhesion molecules on the neutrophil to enhance aggregation, adherence, and damage to the vascular endothelium. Although the endothelium normally produces NO, the inflammatory response stimulates the inducible isoform of NO synthase (iNOS), which is overexpressed and produces toxic nitrosyl- and oxygen-derived free radicals that contribute to the hyperdynamic cardiovascular response in sepsis.

Multiple inflammatory cells, including neutrophils, macrophages, and platelets, are major contributors to inflammation-induced injury. Margination of activated neutrophils in the microcirculation is a common pathologic finding in shock, causing secondary injury because of the release of toxic oxygen radicals, lipases, and proteases. Tissue-fixed macrophages produce virtually all major components of the inflammatory response and orchestrate the progression and duration of the inflammatory response. A major source of activation of the monocyte/macrophage is through the highly conserved membrane Toll-like receptors (TLRs), which recognize damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) released after tissue injury and by pathogenic microbial organisms, respectively. TLRs also appear important for the chronic inflammation seen in Crohn's disease, ulcerative colitis, and transplant rejection.

Approach to the Patient: SHOCK

MONITORING Patients in shock require care in an intensive care unit (ICU). Careful and continuous assessment of the physiologic status is necessary. Arterial pressure through an indwelling line, pulse, and

respiratory rate should be monitored continuously; a Foley catheter should be inserted to follow urine flow; and mental status should be assessed frequently. Sedated patients should be allowed to awaken (“drug holiday”) daily to assess their neurologic status and to shorten the duration of ventilator support.

There is ongoing debate as to the indications for using the flow-directed pulmonary artery catheter (PAC; Swan-Ganz catheter). Most patients in the ICU can be safely managed without the use of a PAC. However, in patients with significant ongoing blood loss, fluid shifts, and underlying cardiac dysfunction, a PAC may be useful. The PAC is placed percutaneously via the subclavian or jugular vein through the central venous circulation and right heart into the pulmonary artery. There are ports both proximal in the right atrium and distal in the pulmonary artery to provide access for infusions and for cardiac output measurements. Right atrial and pulmonary artery pressures are measured, and the pulmonary capillary wedge pressure (PCWP) serves as an approximation of the left atrial pressure. Normal hemodynamic parameters are shown in [Table 28-2](#).

Cardiac output is determined by the thermodilution technique, and high-resolution thermistors can also be used to determine right ventricular end-diastolic volume to monitor further the response of the right heart to fluid resuscitation. A PAC with an oximeter port offers the additional advantage of online monitoring of the mixed venous oxygen saturation, an important index of tissue perfusion. SVR and PVR are calculated as the ratio of the pressure decrease across these vascular beds to the cardiac output. Determinations of oxygen content in arterial and venous blood, together with cardiac output and hemoglobin concentration, allow calculation of oxygen delivery, oxygen consumption, and oxygen-extraction ratio ([Table 28-3](#)). The hemodynamic patterns associated with the various forms of shock are shown in [Table 28-4](#).

In resuscitation from shock, it is critical to restore tissue perfusion and optimize oxygen delivery, hemodynamics, and cardiac function rapidly. A reasonable goal of therapy is to achieve normal mixed venous oxygen saturation and arteriovenous oxygen-extraction ratio. To enhance oxygen delivery, red cell mass, arterial oxygen saturation, and cardiac output may be augmented singly or simultaneously. An increase in oxygen delivery not accompanied by an increase in oxygen consumption implies that oxygen availability is adequate and that oxygen consumption is not flow dependent. Conversely, an elevation of oxygen consumption with increased cardiac output implies that the oxygen supply was inadequate. A reduction in SVR accompanying an increase in cardiac output indicates that compensatory vasoconstriction is reversing because of improved tissue perfusion. The determination of stepwise expansion of blood volume on cardiac performance allows identification of the optimum preload (Starling’s law). An algorithm for the resuscitation of patients in shock is shown in [Fig. 28-3](#).

SPECIFIC FORMS OF SHOCK

HYPOVOLEMIC SHOCK

This most common form of shock results either from the loss of red blood cell mass and plasma from hemorrhage or from the loss of plasma volume alone arising from extravascular fluid sequestration or gastrointestinal, urinary, and insensible losses. The signs and symptoms of nonhemorrhagic hypovolemic shock are the same as those of hemorrhagic shock, although they may have a more insidious onset. The normal physiologic response to hypovolemia is to maintain perfusion of the brain and heart while restoring an effective circulating blood volume. There is an increase in sympathetic activity, hyperventilation, collapse of venous capacitance vessels, release

TABLE 28-2

NORMAL HEMODYNAMIC PARAMETERS

PARAMETER	CALCULATION	NORMAL VALUES
Cardiac output (CO)	$SV \times HR$	4–8 L/min
Cardiac index (CI)	CO/BSA	2.6–4.2 (L/min)/m ²
Stroke volume (SV)	CO/HR	50–100 mL/beat
Systemic vascular resistance (SVR)	$[(MAP - RAP)/CO] \times 80$	700–1600 dynes · s/cm ⁵
Pulmonary vascular resistance (PVR)	$[(PAP_m - PCWP)/CO] \times 80$	20–130 dynes · s/cm ⁵
Left ventricular stroke work (LVSW)	$SV(MAP - PCWP) \times 0.0136$	60–80 g-m/beat
Right ventricular stroke work (RVSW)	$SV(PAP_m - RAP)$	10–15 g-m/beat

Note: BSA, body surface area; HR, heart rate; MAP, mean arterial pressure; PAP_m, pulmonary artery pressure—mean; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure.

TABLE 28-3

OXYGEN TRANSPORT CALCULATIONS

PARAMETER	CALCULATION	NORMAL VALUES
Oxygen-carrying capacity of hemoglobin		1.39 mL/g
Plasma O ₂ concentration		PO ₂ × 0.0031
Arterial O ₂ concentration (CaO ₂)	1.39 SaO ₂ + 0.0031 PaO ₂	20 vol%
Venous O ₂ concentration (CvO ₂)	1.39 SvO ₂ + 0.0031 PvO ₂	15.5 vol%
Arteriovenous O ₂ difference (CaO ₂ – CvO ₂)	1.39 (SaO ₂ – SvO ₂) + 0.0031 (PaO ₂ – PvO ₂)	3.5 vol%
Oxygen delivery (D _{O₂})	CaO ₂ × CO (L/min) × 10 (dL/L) 1.39 SaO ₂ × CO × 10	800–1600 mL/min
Oxygen uptake (V _{O₂})	(CaO ₂ – CvO ₂) × CO × 10 1.39 (SaO ₂ – SvO ₂) × CO × 10	150–400 mL/min
Oxygen delivery index (D _{O₂} I)	D _{O₂} /BSA	520–720 (mL/min)/m ²
Oxygen uptake index (V _{O₂} I)	V _{O₂} /BSA	115–165 (mL/min)/m ²
Oxygen extraction ratio (O ₂ ER)	[1 – (V _{O₂} /D _{O₂})] × 100	22–32%

Note: BSA, body surface area; CO, cardiac output; PaO₂, partial pressure of O₂ in arterial blood; PO₂, partial pressure of oxygen; PvO₂, partial pressure of O₂ in venous blood; SaO₂, saturation of hemoglobin with O₂ in arterial blood; SvO₂, saturation of hemoglobin with O₂ in venous blood.

of stress hormones, and an attempt to limit the loss of intravascular volume through the recruitment of interstitial and intracellular fluid and reduction of urine output.

Mild hypovolemia ($\leq 20\%$ of the blood volume) generates mild tachycardia but relatively few external signs, especially in a supine, resting young patient (Table 28-5). With moderate hypovolemia ($\sim 20\text{--}40\%$ of the blood volume), the patient becomes increasingly anxious and tachycardic; although normal blood pressure may be maintained in the supine position, there may be significant postural hypotension and tachycardia. If hypovolemia is severe ($\geq 40\%$ of the blood volume), the classic signs of shock appear; the blood pressure declines and becomes unstable even in the supine position, and the patient develops marked tachycardia, oliguria, and agitation or confusion. Perfusion of the central nervous system is well maintained until shock becomes severe. Hence, mental obtundation is an ominous clinical sign. The transition from mild to severe hypovolemic shock

can be insidious or extremely rapid. If severe shock is not reversed rapidly, especially in elderly patients and those with comorbid illnesses, death is imminent. A very narrow time frame separates the derangements found in severe shock that can be reversed with aggressive resuscitation from those of progressive decompensation and irreversible cell injury.

Diagnosis

Hypovolemic shock is readily diagnosed when there are signs of hemodynamic instability and the source of volume loss is obvious. The diagnosis is more difficult when the source of blood loss is occult, as into the gastrointestinal tract, or when plasma volume alone is depleted. After acute hemorrhage, hemoglobin and hematocrit values do not change until compensatory fluid shifts have occurred or exogenous fluid is administered. Thus, an initial normal hematocrit does not disprove the

TABLE 28-4

PHYSIOLOGIC CHARACTERISTICS OF THE VARIOUS FORMS OF SHOCK

TYPE OF SHOCK	CVP AND PCWP	CARDIAC OUTPUT	SYSTEMIC VASCULAR RESISTANCE	VENOUS O ₂ SATURATION
Hypovolemic	↓	↓	↑	↓
Cardiogenic	↑	↓	↑	↓
Septic				
Hyperdynamic	↓↑	↑	↓	↑
Hypodynamic	↓↑	↓	↑	↑↓
Traumatic	↓	↓↑	↑↓	↓
Neurogenic	↓	↓	↓	↓
Hypoadrenal	↓↑	↓	=↓	↓

Note: CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure.

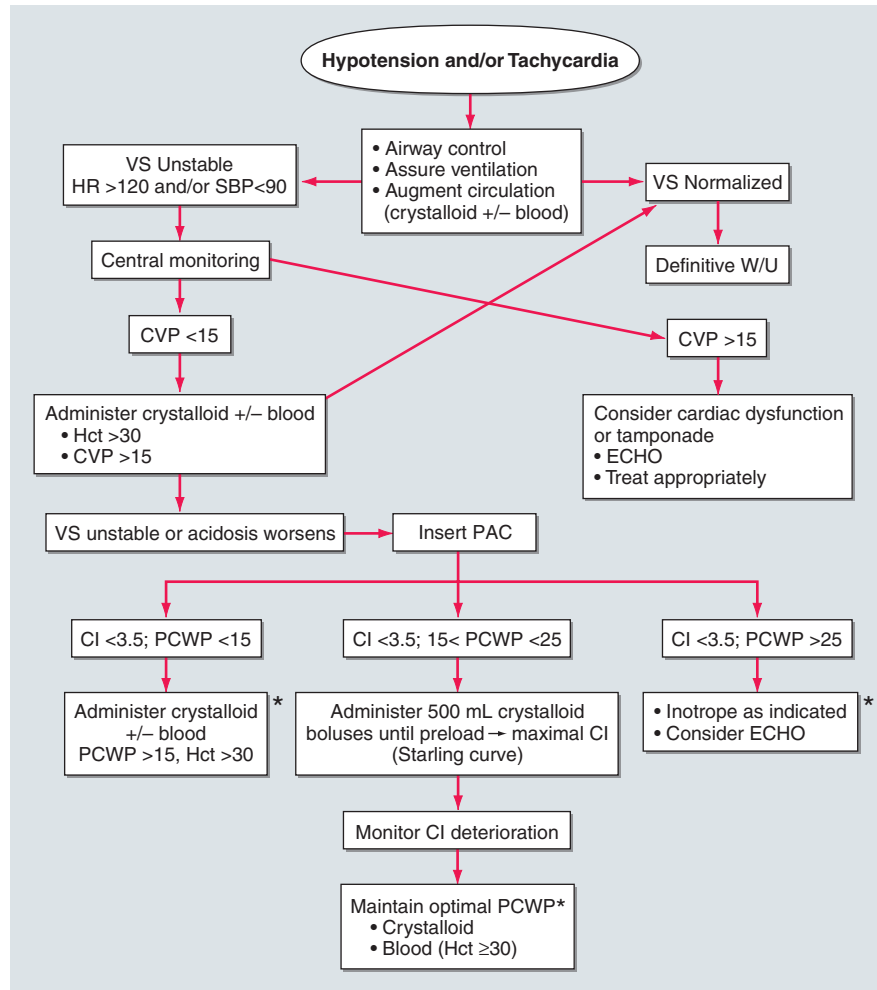


FIGURE 28-3
An algorithm for the resuscitation of the patient in shock.

*Monitor saturation of hemoglobin with O₂ in venous blood (Svo₂), systemic vascular resistance index (SVRI), and right-ventricular end-diastolic volume index (RVEDVI) as additional markers of correction for perfusion and hypovolemia. Consider

age-adjusted cardiac index (CI); CI is shown in (L/min) per m². CVP, central venous pressure; ECHO, echocardiogram; Hct, hematocrit; HR, heart rate; PAC, pulmonary artery catheter; PCWP, pulmonary capillary wedge pressure in mmHg; SBP, systolic blood pressure; VS, vital signs; W/U, workup.

presence of significant blood loss. Plasma losses cause hemoconcentration, and free water loss leads to hypernatremia. These findings should suggest the presence of hypovolemia.

TABLE 28-5
HYPOVOLEMIC SHOCK

MILD (<20% BLOOD VOLUME)	MODERATE (20–40% BLOOD VOLUME)	SEVERE (>40% BLOOD VOLUME)
Cool extremities Increased capillary refill time Diaphoresis Collapsed veins Anxiety	Same, plus: Tachycardia Tachypnea Oliguria Postural changes	Same, plus: Hemodynamic instability Marked tachycardia Hypotension Mental status deterioration (coma)

It is essential to distinguish between hypovolemic and cardiogenic shock (Chap. 31) because definitive therapy differs significantly. Both forms are associated with a reduced cardiac output and a compensatory sympathetic mediated response characterized by tachycardia and elevated SVR. However, the findings in cardiogenic shock of jugular venous distention, rales, and an S₃ gallop distinguish it from hypovolemic shock and signify that ongoing volume expansion is undesirable.

Rx Treatment:
HYPOVOLEMIC SHOCK

Initial resuscitation requires rapid reexpansion of the circulating intravascular blood volume along with interventions to control ongoing losses. In accordance with Starling's law, stroke volume and cardiac output increase

with the increase in preload. After resuscitation, the compliance of the ventricles may remain reduced because of increased interstitial fluid in the myocardium. Therefore, elevated filling pressures are required to maintain adequate ventricular performance.

Volume resuscitation is initiated with the rapid infusion of isotonic saline (although care must be taken to avoid hyperchloremic acidosis from loss of bicarbonate buffering capacity and replacement with excess chloride) or a balanced salt solution such as Ringer's lactate through large-bore IV lines. No distinct benefit from the use of colloid has been demonstrated, and in trauma patients, it is associated with a higher mortality, particularly in patients with traumatic brain injury. The infusion of 2–3 L of salt solution over 20–30 min should restore normal hemodynamic parameters. Continued hemodynamic instability implies that shock has not been reversed or that there are significant ongoing blood or volume losses. Continuing blood loss, with hemoglobin concentrations declining to ≤ 100 g/L (10 g/dL), should initiate blood transfusion, preferably as fully cross-matched blood. In extreme emergencies, type-specific or O-negative packed red cells may be transfused. In the presence of severe or prolonged hypovolemia, inotropic support with dopamine, vasopressin, or dobutamine may be required to maintain adequate ventricular performance *after* the blood volume has been restored. Infusion of norepinephrine to increase arterial pressure by increasing peripheral resistance is inappropriate, other than as a temporizing measure in severe shock while blood volume is reexpanded. After hemorrhage has been controlled and the patient has stabilized, blood transfusions should not be continued unless the hemoglobin is < 7 g/dL. Studies have demonstrated an increased survival in patients treated with this restrictive blood transfusion protocol.

Successful resuscitation also requires support of respiratory function. Supplemental oxygen should be provided, and endotracheal intubation may be necessary to maintain arterial oxygenation. After resuscitation from isolated hemorrhagic shock, end-organ damage is frequently less than after septic or traumatic shock. This may be because of the absence of the massive activation of inflammatory mediator response systems and the consequent nonspecific organ injury seen in the latter conditions.

TRAUMATIC SHOCK

Shock after trauma is, in large measure, due to hypovolemia. However, even when hemorrhage has been controlled, patients can continue to have a loss of plasma volume into the interstitium of injured tissues. These fluid losses are compounded by injury-induced inflammatory responses, which contribute to the secondary

microcirculatory injury. Recent evidence demonstrates release of mediators induced by DAMPs from injured tissue that are recognized by the highly conserved membrane receptors of the TLR family (see Inflammatory Responses earlier in the chapter). These receptors on the cells of the innate immune system, particularly the circulating monocyte, tissue-fixed macrophage, and dendritic cell, are potent activators of an excessive proinflammatory phenotype in response to cellular injury. This causes secondary tissue injury and maldistribution of blood flow, intensifying tissue ischemia and leading to multiple organ system failure. In addition, direct trauma to the heart, chest, or head can also contribute to the shock. For example, pericardial tamponade or tension pneumothorax impairs ventricular filling, and myocardial contusion depresses myocardial contractility.

Rx Treatment: TRAUMATIC SHOCK

An inability of the patient to maintain a systolic blood pressure ≥ 90 mmHg after trauma-induced hypovolemia is associated with a mortality rate of $\sim 50\%$. To prevent decompensation of homeostatic mechanisms, therapy must be promptly administered.

The initial management of the seriously injured patient requires attention to the “ABCs” of resuscitation: assurance of an *airway* (A), adequate ventilation (*breathing*, B), and establishment of an adequate blood volume to support the *circulation* (C). Control of ongoing hemorrhage requires immediate attention. Early stabilization of fractures, debridement of devitalized or contaminated tissues, and evacuation of hematomata all reduce the subsequent inflammatory response to the initial insult and minimize subsequent diffuse organ injury. Supplementation of depleted endogenous antioxidants also reduces subsequent organ failure and mortality.

CARDIOGENIC SHOCK

See Chap. 31.

COMPRESSIVE CARDIOGENIC SHOCK

With compression, the heart and surrounding structures are less compliant, and thus normal filling pressures generate inadequate diastolic filling. Blood or fluid within the poorly distensible pericardial sac may cause tamponade. Any cause of increased intrathoracic pressure, such as tension pneumothorax, herniation of abdominal viscera through a diaphragmatic hernia, or excessive positive pressure ventilation to support pulmonary function, can also cause compressive cardiogenic shock while simultaneously impeding venous return. Although initially responsive to

increased filling pressures produced by volume expansion, as compression increases, cardiogenic shock recurs. The window of opportunity gained by volume loading may be very brief until irreversible shock recurs. Diagnosis and intervention must occur urgently.

The diagnosis of compressive cardiogenic shock is most frequently based on clinical findings, the chest radiograph, and an echocardiogram. The diagnosis of compressive cardiac shock may be more difficult to establish in the setting of trauma when hypovolemia and cardiac compression are present simultaneously. The classic findings of pericardial tamponade include the triad of hypotension, neck vein distention, and muffled heart sounds. Pulsus paradoxus (i.e., an inspiratory reduction in systolic pressure >10 mmHg) may also be noted. The diagnosis is confirmed by echocardiography, and treatment consists of immediate pericardiocentesis. A tension pneumothorax produces ipsilateral decreased breath sounds, tracheal deviation away from the affected thorax, and jugular venous distention. Radiographic findings include increased intrathoracic volume, depression of the diaphragm of the affected hemithorax, and shifting of the mediastinum to the contralateral side. Chest decompression must be carried out immediately. Release of air and restoration of normal cardiovascular dynamics are both diagnostic and therapeutic.

SEPTIC SHOCK

See Chap. 29.

NEUROGENIC SHOCK

Interruption of sympathetic vasomotor input after a high cervical spinal cord injury, inadvertent cephalad migration of spinal anesthesia, or devastating head injury may result in neurogenic shock. In addition to arteriolar dilatation, venodilation causes pooling in the venous system, which decreases venous return and cardiac output. The extremities are often warm, in contrast to the usual vasoconstriction-induced coolness in hypovolemic or cardiogenic shock. Treatment involves a simultaneous approach to the relative hypovolemia and to the loss of vasomotor tone. Excessive volumes of fluid may be required to restore normal hemodynamics if given alone. After hemorrhage has been ruled out, norepinephrine or a pure α -adrenergic agent (phenylephrine) may be necessary to augment vascular resistance and maintain an adequate mean arterial pressure.

HYPOADRENAL SHOCK

The normal host response to the stress of illness, operation, or trauma requires that the adrenal glands hypersecrete cortisol in excess of that normally required. Hypoadrenal shock occurs in settings in which unrecognized adrenal

insufficiency complicates the host response to the stress induced by acute illness or major surgery. Adrenocortical insufficiency may occur as a consequence of the chronic administration of high doses of exogenous glucocorticoids. In addition, recent studies have shown that critical illness, including trauma and sepsis, may also induce a relative hypoadrenal state. Other, less common causes include adrenal insufficiency secondary to idiopathic atrophy, tuberculosis, metastatic disease, bilateral hemorrhage, and amyloidosis. The shock produced by adrenal insufficiency is characterized by loss of homeostasis with reductions in SVR, hypovolemia, and reduced cardiac output. The diagnosis of adrenal insufficiency may be established by means of an ACTH stimulation test.

R_x Treatment: **HYPOADRENAL SHOCK**

In a persistently hemodynamically unstable patient, 4 mg of dexamethasone sodium phosphate should be given IV. This agent is preferred if empiric therapy is required because, unlike hydrocortisone, it does not interfere with the ACTH stimulation test. If the diagnosis of absolute or relative adrenal insufficiency is established as shown by nonresponse to corticotropin stimulation (cortisol ≤ 9 $\mu\text{g}/\text{dL}$ change poststimulation), the patient has a reduced risk of death if treated with hydrocortisone (100 mg every 6–8 h) and tapered as the patient achieves hemodynamic stability. Simultaneous volume resuscitation and pressor support are required. The need for simultaneous mineralocoid is unclear.

ADJUNCTIVE THERAPIES

The sympathomimetic amines dobutamine, dopamine, and norepinephrine are widely used in the treatment of all forms of shock. Dobutamine is inotropic with simultaneous afterload reduction, thus minimizing cardiac oxygen consumption increases as cardiac output increases. Dopamine is an inotropic and chronotropic agent that also supports vascular resistance in those whose blood pressure will not tolerate peripheral vascular dilatation. Norepinephrine primarily supports blood pressure through vasoconstriction and increases myocardial oxygen consumption while placing marginally perfused tissues, such as the extremities and splanchnic organs, at risk for necrosis, but it is also inotropic without chronotropy. Arginine-vasopressin (antidiuretic hormone) is also being used increasingly and may better protect vital organ blood flow and prevent pathologic vasodilation.

POSITIONING

Positioning of the patient may be a valuable adjunct in the initial treatment of hypovolemic shock. Elevating

276 the foot of the bed (i.e., placing it on “shock blocks”) and assumption of the Trendelenburg position without flexion at the knees are effective but may increase work of breathing and risk for aspiration. Simply elevating both legs may be the optimal approach.

PNEUMATIC ANTISHOCK GARMENT

The pneumatic antishock garment (PASG) and the military antishock trousers (MAST) are inflatable external compression devices that can be wrapped around the legs and abdomen and have been widely used in the prehospital setting as a means of providing temporary support of central hemodynamics in shock. However, they cause a significant increase in SVR and blood pressure by arterial compression without causing a significant change in cardiac output or tissue perfusion. The most appropriate use appears to be as a means to tamponade and to prevent ongoing bleeding and augment hemostasis. Inflation of the suit provides splinting of fractures of the pelvis and lower extremities and helps to arrest hemorrhage.

REWARMING

Hypothermia is a potential adverse consequence of massive volume resuscitation. The infusion of large volumes of refrigerated blood products and room-temperature crystalloid solutions can rapidly decrease core temperatures if fluid is not run through warming devices. Hypothermia may depress cardiac contractility and thereby further impair cardiac output and oxygen delivery. Hypothermia, particularly temperatures $<35^{\circ}\text{C}$, directly impairs the coagulation pathway, sometimes causing significant coagulopathy. Rapid rewarming to $>35^{\circ}\text{C}$ significantly decreases the requirement for blood products and produces an improvement in cardiac function. The most effective method for rewarming is endovascular countercurrent warmers through femoral vein cannulation. This process does not require a pump and can rewarm from $30\text{--}35^{\circ}\text{C}$ in <30 min.

FURTHER READINGS

ANNANE D et al: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 288:862, 2002

ANZICS CLINICAL TRIALS GROUP: Low-dose dopamine in patients with early renal dysfunction: A placebo-controlled randomized trial. *Lancet* 356:2139, 2000

ARDS CLINICAL TRIALS NETWORK: Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. *N Engl J Med* 354:2213, 2006

CHEN P: Vasopressin: New uses in critical care. *Am J Med Sci* 324:146, 2002

EGI M et al: Selecting a vasopressor drug for vasoplegic shock after adult cardiac surgery; a systematic literature review. *Ann Thor Surg* 83:715, 2007

ENGLEHART MS et al: Measurement of acid-base resuscitation endpoints: lactate, base deficit, bicarbonate or what? *Curr Opin Crit Care* 12:569, 2006

FINFER S et al: A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 350:2247, 2004

GONZALES EA et al: Fresh frozen plasma should be given earlier to patients receiving massive transfusion. *J Trauma* 62:112, 2007

HEBERT PC et al: Clinical consequence of anemia and red cell transfusion in the critically ill. *Crit Care Clin* 20:225, 2004

JABRE P et al: Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: A multicentre randomised controlled trial. *Lancet* 374:293, 2009

JONES AE et al: Goal-directed hemodynamic optimization in the post-cardiac arrest syndrome: A systematic review. *Resuscitation* 77:26, 2008

MATSUDA N et al: Systemic inflammatory response syndrome (SIRS): Molecular pathophysiology and gene therapy. *J Pharmacol Sci* 101:189, 2006

MOORE FA et al: The next generation in shock resuscitation. *Lancet* 363:1988, 2004

OSUCHOWSKI MF et al: Circulating cytokine/inhibitor profiles reshape the understanding of SIRS/CARS continuum in sepsis and predict mortality. *J Immunol* 177:1967, 2006

RIVERS EP et al: The influence of early hemodynamic optimization on biomarker patterns of severe sepsis and septic shock. *Crit Care Med* 35:2016, 2007

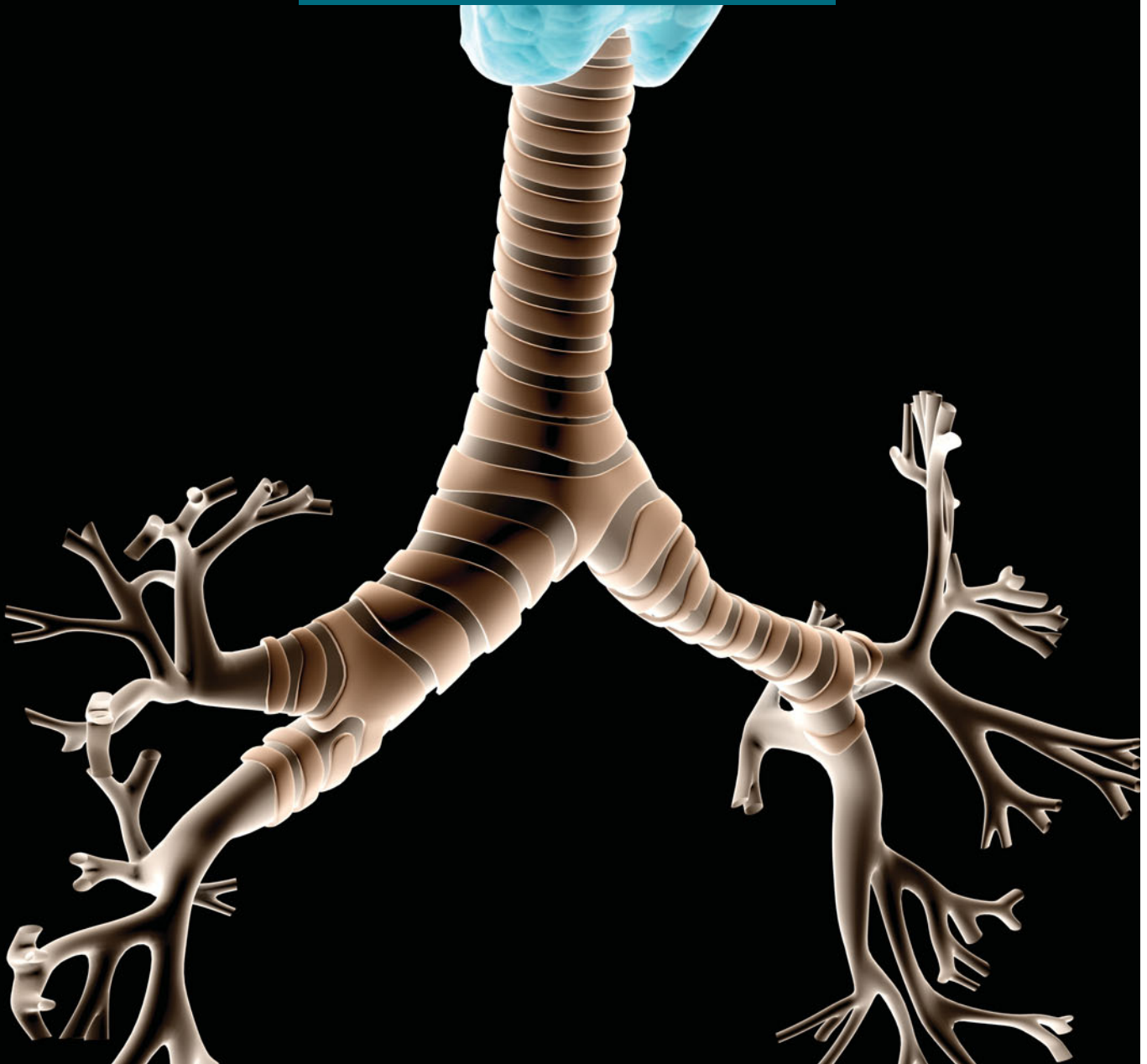
ROMICS L Jr et al: The emerging role of toll-like receptor pathways in surgical diseases. *Arch Surg* 141:595, 2006

SPRUNG CL et al: Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 358:111, 2008

THE SAFE STUDY INVESTIGATORS: Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *N Engl J Med* 357:874, 2007

SECTION IV

COMMON CRITICAL ILLNESSES AND SYNDROMES





CHAPTER 29

SEVERE SEPSIS AND SEPTIC SHOCK

Robert S. Munford

Definitions	278
Etiology	278
Epidemiology	278
Pathophysiology	280
Clinical Manifestations	283
Major Complications	283
Laboratory Findings	284
Diagnosis	284
Prognosis	288
Prevention	289
■ Further Readings	289

DEFINITIONS

(Table 29-1) Animals mount both local and systemic responses to microbes that traverse epithelial barriers and invade underlying tissues. Fever or hypothermia, leukocytosis or leukopenia, tachypnea, and tachycardia are the cardinal signs of the systemic response often called the *systemic inflammatory response syndrome* (SIRS). SIRS may have an infectious or a noninfectious etiology. If infection is suspected or proven, a patient with SIRS is said to have *sepsis*. When sepsis is associated with dysfunction of organs distant from the site of infection, the patient has *severe sepsis*. Severe sepsis may be accompanied by hypotension or evidence of hypoperfusion. When hypotension cannot be corrected by infusing fluids, the diagnosis is *septic shock*. These definitions were proposed by consensus conference committees in 1992 and 2001 and are now widely used; there is evidence that the different stages form a continuum. As sepsis progresses to septic shock, the risk of dying increases substantially. Whereas sepsis is usually reversible, patients with septic shock often succumb despite aggressive therapy.

ETIOLOGY

Severe sepsis can be a response to any class of microorganism. Microbial invasion of the bloodstream is not

essential for the development of severe sepsis because local inflammation can also elicit distant organ dysfunction and hypotension. In fact, blood cultures yield bacteria or fungi in only ~20–40% of cases of severe sepsis and 40–70% of cases of septic shock. Individual gram-negative or gram-positive bacteria account for ~70% of these isolates; the remainder are fungi or a mixture of microorganisms (Table 29-2). In patients whose blood cultures are negative, the etiologic agent is often established by culture or microscopic examination of infected material from a local site. In some case series, a majority of patients with a clinical picture of severe sepsis or septic shock have had negative microbiologic data.

EPIDEMIOLOGY

The septic response is a contributing factor in >200,000 deaths per year in the United States. The incidence of severe sepsis and septic shock has increased over the past 20 years, and the annual number of cases is now >700,000 (~three per 1000 population). Approximately two-thirds of the cases occur in patients with significant underlying illness. Sepsis-related incidence and mortality rates increase with age and preexisting comorbidity. The rising incidence of severe sepsis in the United States is attributable to the aging of the population, the increasing

TABLE 29-1

DEFINITIONS USED TO DESCRIBE THE CONDITION OF PATIENTS WITH SEPSIS

TERM	DEFINITION
Bacteremia	Presence of bacteria in blood, as evidenced by positive blood cultures
Septicemia	Presence of microbes or their toxins in blood
Systemic inflammatory response syndrome (SIRS)	Two or more of the following conditions: (1) fever (oral temperature $>38^{\circ}\text{C}$) or hypothermia ($<36^{\circ}\text{C}$); (2) tachypnea (>24 breaths/min); (3) tachycardia (heart rate >90 bpm); (4) leukocytosis ($>12,000/\mu\text{L}$), leukopenia ($<4,000/\mu\text{L}$) or $>10\%$ bands; may have a noninfectious cause
Sepsis	SIRS that has a proven or suspected microbial etiology
Severe sepsis (similar to “sepsis syndrome”)	Sepsis with one or more signs of organ dysfunction—for example: <ol style="list-style-type: none"> <i>Cardiovascular</i>: Arterial systolic blood pressure ≤ 90 mmHg or mean arterial pressure ≤ 70 mmHg that responds to administration of IV fluid <i>Renal</i>: Urine output <0.5 mL/kg per hour for 1 h despite adequate fluid resuscitation <i>Respiratory</i>: $\text{PaO}_2/\text{FiO}_2 \leq 250$ or, if the lung is the only dysfunctional organ, ≤ 200 <i>Hematologic</i>: Platelet count $<80,000/\mu\text{L}$ or 50% decrease in platelet count from highest value recorded over the previous 3 days <i>Unexplained metabolic acidosis</i>: A pH ≤ 7.30 or a base deficit ≥ 5.0 mEq/L and a plasma lactate level >1.5 times the upper limit of normal for the reporting laboratory <i>Adequate fluid resuscitation</i>: Pulmonary artery wedge pressure ≥ 12 mmHg or central venous pressure ≥ 8 mmHg
Septic shock	Sepsis with hypotension (arterial blood pressure <90 mmHg systolic or 40 mmHg less than patient’s normal blood pressure) for at least 1 h despite adequate fluid resuscitation or Need for vasopressors to maintain systolic blood pressure ≥ 90 mmHg or mean arterial pressure ≥ 70 mmHg
Refractory septic shock	Septic shock that lasts for >1 h and does not respond to fluid or pressor administration
Multiple-organ dysfunction syndrome (MODS)	Dysfunction of more than one organ, requiring intervention to maintain homeostasis

Source: Adapted from the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee and Bernard et al. Crit Care Med, with permission.

TABLE 29-2

MICROORGANISMS INVOLVED IN EPISODES OF SEVERE SEPSIS AT EIGHT ACADEMIC MEDICAL CENTERS

MICROORGANISMS	EPISODES WITH BLOODSTREAM INFECTION, % (n = 436)	EPISODES WITH DOCUMENTED INFECTION BUT NO BLOODSTREAM INFECTION, % (n = 430)	TOTAL EPISODES, % (n = 866)
Gram-negative bacteria ^a	35	44	40
Gram-positive bacteria ^b	40	24	31
Fungi	7	5	6
Polymicrobial	11	21	16
Classic pathogens ^c	<5	<5	<5

^aEnterobacteriaceae, pseudomonads, *Haemophilus* spp., other gram-negative bacteria.

^b*Staphylococcus aureus*, coagulase-negative staphylococci, enterococci, *Streptococcus pneumoniae*, other streptococci, other gram-positive bacteria.

^cSuch as *Neisseria meningitidis*, *S. pneumoniae*, *H. influenzae*, and *Streptococcus pyogenes*.

Source: Adapted from Sands et al.

280 longevity of patients with chronic diseases, and the relatively high frequency with which sepsis develops in patients with AIDS. The widespread use of antimicrobial agents, immunosuppressive drugs, indwelling catheters and mechanical devices, and mechanical ventilation also plays a role.



Invasive bacterial infections are prominent causes of death around the world, particularly among young children. In sub-Saharan Africa, for example, careful screening for positive blood cultures found that community-acquired bacteremia accounted for at least one-fourth of deaths of children >1 year of age. Nontyphoidal *Salmonella* spp., *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Escherichia coli* were the most commonly isolated bacteria. Children with bacteremia often had HIV infection or were severely malnourished.

PATHOPHYSIOLOGY

Most cases of severe sepsis are triggered by bacteria or fungi that do not ordinarily cause systemic disease in immunocompetent hosts (Table 29-2). These microbes probably exploit deficiencies in innate host defenses (e.g., phagocytes, complement, and natural antibodies) to survive within the body. Microbial pathogens, in contrast, are able to circumvent innate defenses by elaborating toxins or other virulence factors. In both cases, the body can fail to kill the invaders despite mounting a vigorous inflammatory reaction that can result in severe sepsis. The septic response may also be induced by microbial exotoxins that act as superantigens (e.g., toxic shock syndrome toxin 1).

Host Mechanisms for Sensing Microbes

Animals have exquisitely sensitive mechanisms for recognizing and responding to conserved microbial molecules. Recognition of the lipid A moiety of lipopolysaccharide (LPS, also called *endotoxin*) is the best-studied example. A host protein (LPS-binding protein, or LBP) binds lipid A and transfers the LPS to CD14 on the surfaces of monocytes, macrophages, and neutrophils. LPS then is passed to MD-2, which interacts with Toll-like receptor 4 (TLR-4) to form a molecular complex that transduces the LPS recognition signal to the interior of the cell. This signal rapidly triggers the production and release of mediators, such as tumor necrosis factor (TNF; see later), that amplifies the LPS signal and transmit it to other cells and tissues. Bacterial peptidoglycan and lipoteichoic acids elicit responses in animals that are generally similar to those induced by LPS; although these molecules also bind CD14, they interact with different TLRs. Having numerous TLR-based receptor complexes (10 different TLRs have been identified so far in humans) allows animals to recognize many conserved microbial molecules. The ability of some of the TLRs to serve as receptors for

host ligands (e.g., hyaluronans, heparan sulfate, saturated fatty acids) raises the possibility that these molecules play a role in producing noninfectious sepsis-like states. Other host pattern-recognition proteins that are important for sensing microbial invasion and initiating host inflammation include the intracellular NOD1 and NOD2 proteins, which recognize discrete fragments of bacterial peptidoglycan; complement (principally the alternative pathway); mannose-binding lectin; and C-reactive protein.

The ability to recognize certain microbial molecules may influence both the potency of the host defense and the pathogenesis of severe sepsis. For example, MD-2-TLR4 best senses LPS that has a hexaacyl lipid A moiety (i.e., one with six fatty acyl chains). Most of the commensal aerobic and facultatively anaerobic gram-negative bacteria that trigger severe sepsis and shock (including *E. coli*, *Klebsiella* spp., and *Enterobacter* spp.) make this lipid A structure. When they invade human hosts, often through breaks in an epithelial barrier, infection is typically localized to the subepithelial tissue. Bacteremia, if it occurs, is intermittent and low grade because these bacteria are efficiently cleared from the bloodstream by TLR4-expressing Kupffer cells and splenic macrophages. These mucosal commensals seem to induce severe sepsis most often by triggering severe local tissue inflammation rather than by circulating within the bloodstream. In contrast, gram-negative bacteria that do not make hexaacyl lipid A (*Yersinia pestis*, *Francisella tularensis*, *Vibrio vulnificus*, *Pseudomonas aeruginosa*, and *Burkholderia pseudomallei*, among others) are poorly recognized by MD-2-TLR4. These bacteria usually enter the body via nonmucosal routes (e.g., as a result of bites, cuts, or inhalation) and initially induce relatively little inflammation. When they do trigger severe sepsis, it is often in the setting of massive bacterial growth throughout the body. Engineering a virulent strain of *Y. pestis* to produce hexaacyl lipid A has rendered it avirulent in mice; this result attests to the importance of TLR4-based bacterial recognition in host defense. For most gram-negative bacteria, the pathogenesis of sepsis thus depends, at least in part, on whether the bacterium's LPS is sensed by the host receptor MD-2-TLR4.

Local and Systemic Host Responses to Invading Microbes

Recognition of microbial molecules by tissue phagocytes triggers the production or release of numerous host molecules (cytokines, chemokines, prostanooids, leukotrienes, and others) that increase blood flow to the infected tissue, enhance the permeability of local blood vessels, recruit neutrophils to the site of infection, and elicit pain. These phenomena are familiar elements of local inflammation, the body's frontline innate immune mechanism for eliminating microbial invaders. Systemic responses are activated by neural or humoral communication with the

hypothalamus and brainstem; these responses enhance local defenses by increasing blood flow to the infected area, augmenting the number of circulating neutrophils and elevating blood levels of numerous molecules (e.g., the microbial recognition proteins discussed above) that have anti-infective functions.

■ Cytokines and Other Mediators

Cytokines can exert endocrine, paracrine, and autocrine effects. TNF α stimulates leukocytes and vascular endothelial cells to release other cytokines (as well as additional TNF α), express cell-surface molecules that enhance neutrophil–endothelial adhesion at sites of infection, and increase prostaglandin and leukotriene production. Whereas blood levels of TNF α are not elevated in individuals with localized infections, they increase in most patients with severe sepsis or septic shock. Moreover, IV infusion of TNF α can elicit the characteristic abnormalities of SIRS. In animals, larger doses of TNF α induce shock, disseminated intravascular coagulation (DIC), and death.

Although TNF α is a central mediator, it is only one of many proinflammatory molecules that contribute to innate host defense. Chemokines, most prominently interleukin (IL) 8, attract circulating neutrophils to the infection site. IL-1 β exhibits many of the same activities as TNF α . TNF α , IL-1 β , interferon (IFN) γ , IL-12, and other cytokines probably interact synergistically with one another and with additional mediators. High-mobility group B-1, a transcription factor, can also be released from cells and interact with microbial products to induce host responses late in the course of the septic response.

■ Coagulation Factors

Intravascular thrombosis, a hallmark of the local inflammatory response, may help wall off invading microbes and prevent infection and inflammation from spreading to other tissues. Intravascular fibrin deposition, thrombosis, and DIC can also be important features of the systemic response. IL-6 and other mediators promote intravascular coagulation initially by inducing blood monocytes and vascular endothelial cells to express tissue factor. When tissue factor is expressed on cell surfaces, it binds to factor VIIa to form an active complex that can convert factors X and IX to their enzymatically active forms. The result is activation of both extrinsic and intrinsic clotting pathways, culminating in the generation of fibrin. Clotting is also favored by impaired function of the protein C–protein S inhibitory pathway and depletion of antithrombin and protein C, and fibrinolysis is prevented by increased plasma levels of plasminogen activator inhibitor 1. Thus, there may be a striking propensity toward intravascular fibrin deposition, thrombosis, and bleeding; this propensity has been most apparent in patients with intravascular endothelial infections such as meningococemia. Contact-system activation occurs

during sepsis but contributes more to the development of hypotension than to DIC.

■ Control Mechanisms

Elaborate control mechanisms operate within both local sites of inflammation and the systemic circulation.

■ Local Control Mechanisms

Host recognition of invading microbes within subepithelial tissues typically ignites immune responses that rapidly kill the invader and then subside to allow tissue recovery. The anti-inflammatory forces that put out the fire and clean up the battleground include molecules that neutralize or inactivate microbial signals. Among these molecules are LPS; intracellular factors (e.g., suppressor of cytokine signaling 3) that diminish the production of proinflammatory mediators by neutrophils and macrophages; anti-inflammatory cytokines (IL-10, IL-4); and molecules derived from essential polyunsaturated fatty acids (lipoxins, resolvins, and protectins) that promote tissue restoration.

■ Systemic Control Mechanisms

The signaling apparatus that links microbial recognition to cellular responses in tissues is less active in the blood. For example, whereas LBP plays a role in recognizing the presence of LPS, in plasma, it also prevents LPS signaling by transferring LPS molecules into plasma lipoprotein particles, which sequester the lipid A moiety so that it cannot interact with cells. At the high concentrations found in blood, LBP also inhibits monocyte responses to LPS, and the soluble (circulating) form of CD14 strips off LPS that has bound to monocyte surfaces.

Systemic responses to infection also diminish cellular responses to microbial molecules. Circulating levels of anti-inflammatory cytokines (e.g., IL-6 and IL-10) increase even in patients with mild infections. Glucocorticoids inhibit cytokine synthesis by monocytes *in vitro*; the increase in blood cortisol levels early in the systemic response presumably plays a similarly inhibitory role. Epinephrine inhibits the TNF- α response to endotoxin infusion in humans while augmenting and accelerating the release of IL-10; prostaglandin E₂ has a similar “reprogramming” effect on the responses of circulating monocytes to LPS and other bacterial agonists. Cortisol, epinephrine, IL-10, and C-reactive protein reduce the ability of neutrophils to attach to vascular endothelium, favoring their demargination and thus contributing to leukocytosis while preventing neutrophil–endothelial adhesion in uninflamed organs. The available evidence thus suggests that the body’s systemic responses to injury and infection normally prevent inflammation within organs distant from a site of infection.

The acute-phase response increases the blood concentrations of numerous molecules that have anti-inflammatory actions. Blood levels of IL-1 receptor antagonist

282 (IL-1Ra) often greatly exceed those of circulating IL-1 β , for example, and this excess may result in inhibition of the binding of IL-1 β to its receptors. High levels of soluble TNF receptors neutralize TNF α that enters the circulation. Other acute-phase proteins are protease inhibitors; these may neutralize proteases released from neutrophils and other inflammatory cells.

Organ Dysfunction and Shock

As the body's responses to infection intensify, the mixture of circulating cytokines and other molecules becomes very complex: elevated blood levels of more than 50 molecules have been found in patients with septic shock. Although high concentrations of both pro- and anti-inflammatory molecules are found, the net mediator balance in the plasma of these extremely sick patients may actually be anti-inflammatory. For example, blood leukocytes from patients with severe sepsis are often hyporesponsive to agonists such as LPS. In patients with severe sepsis, the persistence of leukocyte hyporesponsiveness has been associated with an increased risk of dying. Apoptotic death of B cells, follicular dendritic cells, and CD4+ T lymphocytes also may contribute significantly to the immunosuppressive state.

Endothelial Injury

Most investigators have favored widespread vascular endothelial injury as the major mechanism for multiorgan dysfunction. In keeping with this idea, one study found high numbers of vascular endothelial cells in the peripheral blood of septic patients. Leukocyte-derived mediators and platelet-leukocyte-fibrin thrombi may contribute to vascular injury, but the vascular endothelium also seems to play an active role. Stimuli such as TNF α induce vascular endothelial cells to produce and release cytokines, procoagulant molecules, platelet-activating factor (PAF), nitric oxide, and other mediators. In addition, regulated cell-adhesion molecules promote the adherence of neutrophils to endothelial cells. Although these responses can attract phagocytes to infected sites and activate their antimicrobial arsenals, endothelial cell activation can also promote increased vascular permeability, microvascular thrombosis, DIC, and hypotension.

Tissue oxygenation may decrease as the number of functional capillaries is reduced by luminal obstruction caused by swollen endothelial cells, decreased deformability of circulating erythrocytes, leukocyte-platelet-fibrin thrombi, or compression by edema fluid. On the other hand, studies using orthogonal polarization spectral imaging of the microcirculation in the tongue found that sepsis-associated derangements in capillary flow could be reversed by applying acetylcholine to the surface of the tongue or giving IV nitroprusside; these observations suggest a neuroendocrine basis for the loss of capillary filling. Oxygen utilization by tissues may also be impaired by a

state of "hibernation" in which adenosine triphosphate (ATP) production is diminished as oxidative phosphorylation decreases because of mitochondrial dysfunction; nitric oxide or its metabolites may be responsible for inducing this response.

Remarkably, poorly functioning "septic" organs usually appear normal at autopsy. There is typically very little necrosis or thrombosis, and apoptosis is largely confined to lymphoid organs and the gastrointestinal tract. Moreover, organ function usually returns to normal if patients recover. These points suggest that organ dysfunction during severe sepsis has a basis that is principally biochemical, not anatomic.

Septic Shock

The hallmark of septic shock is a decrease in peripheral vascular resistance that occurs despite increased levels of vasopressor catecholamines. Before this vasodilatory phase, many patients experience a period during which oxygen delivery to tissues is compromised by myocardial depression, hypovolemia, and other factors. During this "hypodynamic" period, the blood lactate concentration is elevated, and central venous oxygen saturation is low. Fluid administration is usually followed by the hyperdynamic, vasodilatory phase during which cardiac output is normal (or even high) and oxygen consumption is independent of oxygen delivery. The blood lactate level may be normal or increased, and normalization of the central venous oxygen saturation (SvO₂) may reflect either improved oxygen delivery or left-to-right shunting.

Prominent hypotensive molecules include nitric oxide, β -endorphin, bradykinin, PAF, and prostacyclin. Agents that inhibit the synthesis or action of each of these mediators can prevent or reverse endotoxic shock in animals. However, in clinical trials, neither a PAF receptor antagonist nor a bradykinin antagonist improved survival rates among patients with septic shock, and a nitric oxide synthetase inhibitor, L-N^G-methylarginine HCl, actually increased the mortality rate.

Severe Sepsis: A Single Pathogenesis?

In some cases, circulating bacteria and their products almost certainly elicit multiorgan dysfunction and hypotension by directly stimulating inflammatory responses within the vasculature. In patients with fulminant meningococemia, for example, mortality rates have correlated well with blood endotoxin levels and with the occurrence of DIC. In most patients with nosocomial infections, in contrast, circulating bacteria or bacterial molecules may reflect uncontrolled infection at a local tissue site and have little or no direct impact on distant organs; in these patients, inflammatory mediators or neural signals arising from the local site seem to be the key triggers for severe sepsis and septic shock. In a large series of patients with positive blood cultures, the risk of developing severe

sepsis was strongly related to the site of primary infection: bacteremia arising from a pulmonary or abdominal source was eightfold more likely to be associated with severe sepsis than was bacteremic urinary tract infection, even after the investigators controlled for age, the kind of bacteria isolated from the blood, and other factors. A third pathogenesis may be represented by severe sepsis caused by superantigen-producing *Staphylococcus aureus* or *Streptococcus pyogenes*, because the T cell activation induced by these toxins produces a cytokine profile that differs substantially from that elicited by gram-negative bacterial infection.

In summary, the pathogenesis of severe sepsis may differ according to the infecting microbe, the ability of the host's innate defense mechanisms to sense it, the site of the primary infection, the presence or absence of immune defects, and the prior physiologic status of the host. Genetic factors may also be important. For example, studies in different ethnic groups have identified associations between allelic polymorphisms in TLR4, caspase 12L, TNF α , and IFN- γ genes and the risk of developing severe sepsis. Further studies in this area are needed.

CLINICAL MANIFESTATIONS

The manifestations of the septic response are usually superimposed on the symptoms and signs of the patient's underlying illness and primary infection. The rate at which signs and symptoms develop may differ from patient to patient, and there are striking individual variations in presentation. For example, some patients with sepsis are normo- or hypothermic; the absence of fever is most common in neonates, elderly patients, and persons with uremia or alcoholism.

Hyperventilation is often an early sign of the septic response. Disorientation, confusion, and other manifestations of encephalopathy may also develop early on, particularly in elderly patients and in individuals with preexisting neurologic impairment. Focal neurologic signs are uncommon, although preexisting focal deficits may become more prominent.

Hypotension and DIC predispose to acrocyanosis and ischemic necrosis of peripheral tissues, most commonly the digits. Cellulitis, pustules, bullae, or hemorrhagic lesions may develop when hematogenous bacteria or fungi seed the skin or underlying soft tissue. Bacterial toxins may also be distributed hematogenously and elicit diffuse cutaneous reactions. On occasion, skin lesions may suggest specific pathogens. When sepsis is accompanied by cutaneous petechiae or purpura, infection with *Neisseria meningitidis* (or, less commonly, *H. influenzae*) should be suspected; in a patient who has been bitten by a tick while in an endemic area, petechial lesions also suggest Rocky Mountain spotted fever. A cutaneous lesion seen almost exclusively in neutropenic patients is ecthyma gangrenosum, usually caused by *P. aeruginosa*. It is a bullous lesion surrounded by edema that undergoes central

hemorrhage and necrosis. Histopathologic examination shows bacteria in and around the wall of a small vessel, with little or no neutrophilic response. Hemorrhagic or bullous lesions in a septic patient who has recently eaten raw oysters suggest *V. vulnificus* bacteremia, but such lesions in a patient who has recently suffered a dog bite may indicate bloodstream infection caused by *Capnocytophaga canimorsus* or *Capnocytophaga cynodegmi*. Generalized erythroderma in a septic patient suggests the toxic shock syndrome caused by *S. aureus* or *S. pyogenes*.

Gastrointestinal manifestations such as nausea, vomiting, diarrhea, and ileus may suggest acute gastroenteritis. Stress ulceration can lead to upper gastrointestinal bleeding. Cholestatic jaundice, with elevated levels of serum bilirubin (mostly conjugated) and alkaline phosphatase, may precede other signs of sepsis. Hepatocellular or canalicular dysfunction appears to underlie most cases, and the results of hepatic function tests return to normal with resolution of the infection. Prolonged or severe hypotension may induce acute hepatic injury or ischemic bowel necrosis.

Many tissues may be unable to extract oxygen normally from the blood, so anaerobic metabolism occurs despite near-normal mixed venous oxygen saturation. Blood lactate levels increase early because of increased glycolysis as well as impaired clearance of the resulting lactate and pyruvate by the liver and kidneys. The blood glucose concentration often increases, particularly in patients with diabetes, although impaired gluconeogenesis and excessive insulin release occasionally produce hypoglycemia. The cytokine-driven acute-phase response inhibits the synthesis of transthyretin while enhancing the production of C-reactive protein, fibrinogen, and complement components. Protein catabolism is often markedly accelerated. Serum albumin levels decline as a result of decreased hepatic synthesis and the movement of albumin into interstitial spaces, which is promoted by arterial vasodilation.

MAJOR COMPLICATIONS

Cardiopulmonary Complications

Ventilation-perfusion mismatching produces a decrease in arterial PO_2 early in the course. Increasing alveolar capillary permeability results in an increased pulmonary water content, which decreases pulmonary compliance and interferes with oxygen exchange. Progressive diffuse pulmonary infiltrates and arterial hypoxemia (PaO_2/FiO_2 , <200) indicate the development of the acute respiratory distress syndrome (ARDS). ARDS develops in ~50% of patients with severe sepsis or septic shock. Respiratory muscle fatigue can exacerbate hypoxemia and hypercapnia. An elevated pulmonary capillary wedge pressure (PCWP; >18 mmHg) suggests fluid volume overload or cardiac failure rather than ARDS. Pneumonia caused by viruses or by *Pneumocystis* spp. Infection may be clinically indistinguishable from ARDS.

284 Sepsis-induced hypotension (see Septic Shock earlier in the chapter) usually results initially from a generalized maldistribution of blood flow and blood volume and from hypovolemia that is caused at least partly by diffuse capillary leakage of intravascular fluid. Other factors that may decrease effective intravascular volume include dehydration from antecedent disease or insensible fluid losses, vomiting or diarrhea, and polyuria. During early septic shock, systemic vascular resistance (SVR) is usually elevated, and cardiac output may be low. After fluid repletion, in contrast, cardiac output typically increases, and SVR decreases. Indeed, normal or increased cardiac output and decreased SVR distinguish septic shock from cardiogenic, extracardiac obstructive, and hypovolemic shock; other processes that can produce this combination include anaphylaxis, beriberi, cirrhosis, and overdoses of nitroprusside or narcotics.

Depression of myocardial function, manifested as increased end-diastolic and systolic ventricular volumes with a decreased ejection fraction, develops within 24 h in most patients with severe sepsis. Cardiac output is maintained despite the low ejection fraction because ventricular dilatation permits a normal stroke volume. In survivors, myocardial function returns to normal over several days. Although myocardial dysfunction may contribute to hypotension, refractory hypotension is usually caused by a low SVR, and death results from refractory shock or the failure of multiple organs rather than from cardiac dysfunction per se.

Renal Complications

Oliguria, azotemia, proteinuria, and nonspecific urinary casts are frequently found. Many patients are inappropriately polyuric; hyperglycemia may exacerbate this tendency. Most renal failure is caused by acute tubular necrosis induced by hypotension or capillary injury, although some patients also have glomerulonephritis, renal cortical necrosis, or interstitial nephritis. Drug-induced renal damage may complicate therapy, particularly when hypotensive patients are given aminoglycoside antibiotics.

Coagulopathy

Although thrombocytopenia occurs in 10–30% of patients, the underlying mechanisms are not understood. Platelet counts are usually very low ($<50,000/\mu\text{L}$) in patients with DIC; these low counts may reflect diffuse endothelial injury or microvascular thrombosis.

Neurologic Complications

When the septic illness lasts for weeks or months, “critical illness polyneuropathy” may prevent weaning from ventilatory support and produce distal motor weakness. Electrophysiologic studies are diagnostic. Guillain-Barré

syndrome, metabolic disturbances, and toxin activity must be ruled out.

LABORATORY FINDINGS

Abnormalities that occur early in the septic response may include leukocytosis with a left shift, thrombocytopenia, hyperbilirubinemia, and proteinuria. Leukopenia may develop. The neutrophils may contain toxic granulations, Döhle bodies, or cytoplasmic vacuoles. As the septic response becomes more severe, thrombocytopenia worsens (often with prolongation of the thrombin time, decreased fibrinogen, and the presence of D-dimers, suggesting DIC), azotemia and hyperbilirubinemia become more prominent, and levels of aminotransferases increase. Active hemolysis suggests clostridial bacteremia, malaria, a drug reaction, or DIC; in the case of DIC, microangiopathic changes may be seen on a blood smear.

During early sepsis, hyperventilation induces respiratory alkalosis. With respiratory muscle fatigue and the accumulation of lactate, metabolic acidosis (with increased anion gap) typically supervenes. Evaluation of arterial blood gases reveals hypoxemia, which is initially correctable with supplemental oxygen but whose later refractoriness to 100% oxygen inhalation indicates right-to-left shunting. The chest radiograph may be normal or may show evidence of underlying pneumonia, volume overload, or the diffuse infiltrates of ARDS. The electrocardiogram may show only sinus tachycardia or nonspecific ST–T-wave abnormalities.

Most diabetic patients with sepsis develop hyperglycemia. Severe infection may precipitate diabetic ketoacidosis, which may exacerbate hypotension. Hypoglycemia occurs rarely. The serum albumin level, which is initially within the normal range, declines as sepsis continues. Hypocalcemia is rare.

DIAGNOSIS

There is no specific diagnostic test for the septic response. Diagnostically sensitive findings in a patient with suspected or proven infection include fever or hypothermia, tachypnea, tachycardia, and leukocytosis or leukopenia (Table 29-1); acutely altered mental status, thrombocytopenia, an elevated blood lactate level, or hypotension also should suggest the diagnosis. The septic response can be quite variable, however. In one study, 36% of patients with severe sepsis had a normal temperature, 40% had a normal respiratory rate, 10% had a normal pulse rate, and 33% had a normal white blood cell count. Moreover, the systemic responses of uninfected patients with other conditions may be similar to those characteristic of sepsis. Noninfectious causes of SIRS (see Table 29-1) include pancreatitis, burns, trauma, adrenal insufficiency, pulmonary embolism, dissecting or ruptured aortic aneurysm, myocardial infarction, occult

hemorrhage, cardiac tamponade, post–cardiopulmonary bypass syndrome, anaphylaxis, and drug overdose.

Definitive etiologic diagnosis requires isolation of the microorganism from blood or a local site of infection. At least two blood samples (10 mL each) should be obtained (from different venipuncture sites) for culture. Because gram-negative bacteremia is typically low grade (<10 organisms/mL of blood), prolonged incubation of cultures may be necessary; *S. aureus* grows more readily and is detectable in blood cultures within 48 h in most instances. In many cases, blood cultures are negative; this result can reflect prior antibiotic administration, the presence of slow-growing or fastidious organisms, or the absence of microbial invasion of the bloodstream. In these cases, Gram's staining and culture of material from the primary site of infection or of infected cutaneous lesions may help establish the microbial etiology. The skin and mucosae should be examined carefully and repeatedly for lesions that might yield diagnostic information. With overwhelming bacteremia (e.g., pneumococcal sepsis in splenectomized individuals, fulminant meningococemia, or infection with *V. vulnificus*, *B. pseudomallei*, or *Y. pestis*), microorganisms are sometimes visible on buffy coat smears of peripheral blood.

Rx Treatment: **SEVERE SEPSIS AND SEPTIC SHOCK**

Patients in whom sepsis is suspected must be managed expeditiously. This task is best accomplished by personnel who are experienced in the care of critically ill patients. Successful management requires urgent measures to treat the infection, provide hemodynamic and respiratory support, and eliminate the offending microorganism. Most emergency centers now aim to initiate these measures within 1 h of the patient's presentation with severe sepsis or shock. Rapid assessment and diagnosis are therefore essential.

ANTIMICROBIAL AGENTS Antimicrobial chemotherapy should be initiated as soon as samples of blood and other relevant sites have been cultured. A large retrospective review of patients who developed septic shock found that the interval between the onset of hypotension and the administration of appropriate antimicrobial chemotherapy was the major determinant of outcome; a delay of as little as 1 h was associated with lower survival rates.

It is important, pending culture results, to initiate empirical antimicrobial therapy that is effective against both gram-positive and gram-negative bacteria (Table 29-3). Maximal recommended doses of antimicrobial drugs should be given intravenously, with adjustment for impaired renal function when necessary.

Available information about patterns of antimicrobial susceptibility among bacterial isolates from the community, the hospital, and the patient should be taken into account. When culture results become available, the regimen can often be simplified because a single antimicrobial agent is usually adequate for the treatment of a known pathogen. Meta-analyses have concluded that, with one exception, combination antimicrobial therapy is not superior to monotherapy for treating gram-negative bacteremia; the exception is that aminoglycoside monotherapy for *P. aeruginosa* bacteremia is less effective than the combination of an aminoglycoside with an antipseudomonal β -lactam agent. Most patients require antimicrobial therapy for at least 1 week; the duration of treatment is typically influenced by factors such as the site of tissue infection, the adequacy of surgical drainage, the patient's underlying disease, and the antimicrobial susceptibility of the bacterial isolate(s).

REMOVAL OF THE SOURCE OF INFECTION

Removal or drainage of a focal source of infection is essential. Sites of occult infection should be sought carefully. Indwelling IV catheters should be removed and the tip rolled over a blood agar plate for quantitative culture; after antibiotic therapy has been initiated, a new catheter should be inserted at a different site. Foley and drainage catheters should be replaced. The possibility of paranasal sinusitis (often caused by gram-negative bacteria) should be considered if the patient has undergone nasal intubation. In patients with abnormalities on chest radiographs, CT of the chest may identify unsuspected parenchymal, mediastinal, or pleural disease. In neutropenic patients, cutaneous sites of tenderness and erythema, particularly in the perianal region, must be carefully sought. In patients with sacral or ischial decubitus ulcers, it is important to exclude pelvic or other soft tissue pus collections with CT or MRI. In patients with severe sepsis arising from the urinary tract, sonography or CT should be used to rule out ureteral obstruction, perinephric abscess, and renal abscess.

HEMODYNAMIC, RESPIRATORY, AND METABOLIC SUPPORT

The primary goals are to restore adequate oxygen and substrate delivery to the tissues as quickly as possible and to improve tissue oxygen utilization and cellular metabolism. Adequate organ perfusion is thus essential. The initial management of hypotension should include the administration of IV fluids, typically beginning with 1–2 L of normal saline over 1–2 h. To avoid pulmonary edema, the PCWP should be maintained at 12–16 mmHg or the central venous pressure at 8–12 cm H₂O. The urine output rate should be kept at >0.5 mL/kg per hour by continuing fluid administration; a diuretic such as furosemide may be used if needed. In about one-third of patients, hypotension and organ

INITIAL ANTIMICROBIAL THERAPY FOR SEVERE SEPSIS WITH NO OBVIOUS SOURCE IN ADULTS WITH NORMAL RENAL FUNCTION

CLINICAL CONDITION	ANTIMICROBIAL REGIMENS (IV THERAPY)
Immunocompetent adult	The many acceptable regimens include (1) ceftriaxone (2 g q24h) or ticarcillin–clavulanate (3.1 g q4–6h) or piperacillin–tazobactam (3.375 g q4–6h); (2) imipenem–cilastatin (0.5 g q6h) or meropenem (1 g q8h) or cefepime (2 g q12h). Gentamicin or tobramycin (5–7 mg/kg q24h) may be added to either regimen. If the patient is allergic to β -lactam agents, use ciprofloxacin (400 mg q12h) or levofloxacin (500–750 mg q12h) plus clindamycin (600 mg q8h). If the institution or the community has a high prevalence of MRSA isolates, add vancomycin (15 mg/kg q12h) to each of the above regimens.
Neutropenia (<500 neutrophils/mL)	Regimens include (1) imipenem–cilastatin (0.5 g q6h) or meropenem (1 g q8h) or cefepime (2 g q8h); (2) ticarcillin–clavulanate (3.1 g q4h) or piperacillin–tazobactam (3.375 g q4h) plus tobramycin (5–7 mg/kg q24h). Vancomycin (15 mg/kg q12h) should be added if the patient has an infected vascular catheter, if staphylococci are suspected, if the patient has received quinolone prophylaxis, if the patient has received intensive chemotherapy that produces mucosal damage, if the institution has a high incidence of MRSA infections, or if there is a high prevalence of MRSA isolates in the community.
Splenectomy	Cefotaxime (2 g q6–8h) or ceftriaxone (2 g q12h) should be used. If the local prevalence of cephalosporin-resistant pneumococci is high, add vancomycin. If the patient is allergic to β -lactam drugs, vancomycin (15 mg/kg q12h) plus ciprofloxacin (400 mg q12h) or levofloxacin (750 mg q12h) or aztreonam (2 g q8h) should be used.
IV drug user	Nafcillin or oxacillin (2 g q8h) plus gentamicin (5–7 mg/kg q24h). If the local prevalence of MRSA is high or if the patient is allergic to β -lactam drugs, vancomycin (15 mg/kg q12h) with gentamicin should be used.
AIDS	Cefepime (2 g q8h), ticarcillin–clavulanate (3.1 g q4h), or piperacillin–tazobactam (3.375 g q4h) plus tobramycin (5–7 mg/kg q24h) should be used. If the patient is allergic to β -lactam drugs, ciprofloxacin (400 mg q12h) or levofloxacin (750 mg q12h) plus vancomycin (15 mg/kg q12h) plus tobramycin should be used.

Note: MRSA, methicillin-resistant *Staphylococcus aureus*.

Source: Adapted in part from Hughes WT et al: Clin Infect Dis 25:551, 1997.

hypoperfusion respond to fluid resuscitation; a reasonable goal is to maintain a mean arterial blood pressure of >65 mmHg (systolic pressure >90 mmHg) and a cardiac index of ≥ 4 L/min per m^2 . If these guidelines cannot be met by volume infusion, vasopressor therapy is indicated. Circulatory adequacy is also assessed by clinical parameters (mentation, urine output, skin perfusion) and, when possible, by measurements of oxygen delivery and consumption.

A study of “early goal-directed therapy” (EGDT) found that prompt resuscitation based on maintenance of the SvO_2 at >70% was associated with significantly improved survival of patients who were admitted to an emergency department with severe sepsis. The treatment algorithm included rapid administration of fluids, antibiotics, and vasopressor support; erythrocyte transfusion (to maintain the hematocrit >30%); and administration of dobutamine if fluids, erythrocytes, and pressors did not result in an SvO_2 of >70%. The extent to which the different components of the EGDT algorithm contribute to the overall effect has not been examined in controlled trials. In particular,

neither the use of SvO_2 to manage therapy nor the need for continuous SvO_2 monitoring with a pulmonary artery catheter has been formally confirmed. A multicenter study sponsored by the National Institutes of Health of the efficacy of the EGDT approach is in progress.

In patients with septic shock, plasma vasopressin levels increase transiently but then decrease dramatically. Studies have found that vasopressin infusion can reverse septic shock in some patients, reducing or eliminating the need for catecholamine pressors. An adequately powered and randomized trial of vasopressin infusion has not been performed. Vasopressin is a potent vasoconstrictor that may be most useful in patients who have vasodilatory shock and relative resistance to other pressor hormones.

Adrenal insufficiency is very likely when the plasma cortisol level is <15 μ g/dL in a patient with severe sepsis. Generally accepted criteria for *partial* adrenal insufficiency have not been devised; major problems have been the inability to increase cortisol levels in extremely stressed individuals above high baseline values in

response to cosyntropin (α^{1-24} -ACTH) and the high frequency of hypoalbuminemia, which decreases total but not free (active) plasma cortisol levels. Adrenal insufficiency should be strongly considered in septic patients with refractory hypotension; fulminant meningococcal bacteremia; disseminated tuberculosis; AIDS; or prior use of glucocorticoids, megestrol, etomidate, or ketoconazole. Hydrocortisone (50 mg IV every 6 h) may be given as a trial therapeutic intervention. If clinical improvement occurs over 24–48 h, most experts would continue hydrocortisone therapy, tapering and discontinuing it after 5–7 days. Improved recommendations regarding hydrocortisone therapy may come from the European CORTICUS trial.

Ventilator therapy is indicated for progressive hypoxemia, hypercapnia, neurologic deterioration, or respiratory muscle failure. Sustained tachypnea (respiratory rate, >30 breaths/min) is frequently a harbinger of impending respiratory collapse; mechanical ventilation is often initiated to ensure adequate oxygenation, divert blood from the muscles of respiration, prevent aspiration of oropharyngeal contents, and reduce the cardiac afterload. The results of recent studies favor the use of low tidal volumes (6 mL/kg of ideal body weight or as low as 4 mL/kg if the plateau pressure >30 cmH₂O). Patients undergoing mechanical ventilation require careful sedation with daily interruptions; elevation of the head of the bed helps to prevent nosocomial pneumonia. Stress ulcer prophylaxis with a histamine H₂-receptor antagonist may decrease the risk of gastrointestinal hemorrhage in ventilated patients.

The use of erythrocyte transfusion continues to be debated. In the study of EGDT, packed erythrocytes were given to raise the hematocrit to 30% if the patient's SvO₂ was <70%. The extent to which this intervention contributed to the improvement reported in patients who received the EGDT regimen is uncertain.

Bicarbonate is sometimes administered for severe metabolic acidosis (arterial pH <7.2), but there is little evidence that it improves either hemodynamics or the response to vasopressor hormones. DIC, if complicated by major bleeding, should be treated with transfusion of fresh-frozen plasma and platelets. Successful treatment of the underlying infection is essential to reverse both acidosis and DIC. Patients who are hypercatabolic and have acute renal failure may benefit greatly from hemodialysis or hemofiltration.

GENERAL SUPPORT In patients with prolonged severe sepsis (i.e., that lasting more than 2 or 3 days), nutritional supplementation may reduce the impact of protein hypercatabolism; the available evidence, which is not strong, favors the enteral delivery route. Prophylactic heparinization to prevent deep venous thrombosis is

indicated for patients who do not have active bleeding or coagulopathy. Recovery is also assisted by preventing skin breakdown, nosocomial infections, and stress ulcers.

Investigators in Belgium reported in 2001 that maintaining blood glucose levels in the normal range (80–110 mg/dL) greatly improved survival rates among patients who had just undergone major surgery and had received IV glucose feeding for the previous 24 h. The same group then studied intensive glucose control in critically ill medical patients and found a survival benefit only for patients who remained in the intensive care unit (ICU) for ≥ 3 days. Hypoglycemia was much more common in the intensive-insulin group. Until more experience with intensive glucose control is reported, it seems reasonable to maintain glucose levels of <150 mg/dL during the first 3 days of severe sepsis and then to target the normoglycemic range if the patient remains in the ICU for a longer period. Frequent monitoring of blood glucose levels is indicated to avoid hypoglycemia during intensive insulin therapy.

OTHER MEASURES Despite aggressive management, many patients with severe sepsis or septic shock die. Numerous interventions have been tested for their ability to improve survival in patients with severe sepsis. The list includes endotoxin-neutralizing proteins; inhibitors of cyclooxygenase or nitric oxide synthase; anticoagulants; polyclonal immunoglobulins; glucocorticoids; and antagonists to TNF α , IL-1, PAF, and bradykinin. Unfortunately, none of these agents has improved rates of survival among patients with severe sepsis or septic shock in more than one large, randomized, placebo-controlled clinical trial. This lack of reproducibility has had many contributing factors, including (1) heterogeneity in the patient populations studied and the inciting microbes and (2) the nature of the “standard” therapy also used. A dramatic example of this problem was seen in a trial of tissue factor pathway inhibitor (Fig. 29-1). Whereas the drug appeared to improve survival rates after 722 patients had been studied ($p = .006$), it did not do so in the next 1032 patients, and the overall result was negative. This inconsistency, even within a carefully selected patient population, argues strongly that a sepsis intervention should show significant survival benefit in more than one placebo-controlled clinical trial before it is accepted as part of routine clinical practice.

Recombinant activated protein C (aPC) was the first drug to be approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with severe sepsis or septic shock. In a single randomized controlled trial in which drug or placebo was given within 24 h of the patient's first sepsis-related organ dysfunction, 28-day mortality was significantly lower among recipients of aPC than among patients who received placebo

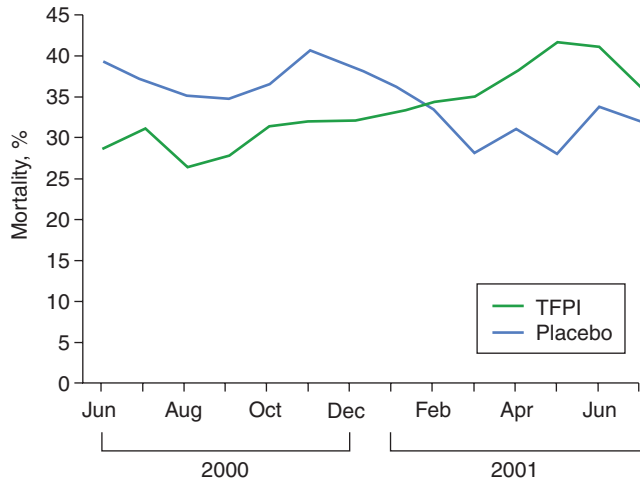


FIGURE 29-1

Mortality rates among patients who received tissue factor pathway inhibitor (TFPI) or placebo, shown as the running average over the course of the clinical trial. The drug seemed highly efficacious at the interim analysis in December 2000, but this trend reversed later in the trial. Demonstrating that therapeutic agents for sepsis have consistent, reproducible efficacy has been extremely difficult, even within well-defined patient populations. (Reprinted with permission from Abraham et al.)

(24.7% versus 30.8%; $p < .005$). In addition, aPC recipients were more likely than placebo recipients to have severe bleeding (3.5% versus 2%). Survival improved only for patients who had an APACHE (Acute Physiology and Chronic Health Evaluation) II score of ≥ 25 during the 24 hours before initiation of aPC infusion. Midtrial changes in the protocol and drug were followed by improvement in the apparent efficacy of aPC. The FDA approved aPC for use in adults (>18 years of age) who meet the APACHE II criterion and have a low risk of hemorrhage-related side effects.

aPC is administered as a constant IV infusion of 24 $\mu\text{g}/\text{kg}$ per hour for 96 h. Each patient's clotting parameters must be monitored carefully. aPC should not be given to patients who have platelet counts of $<30,000/\mu\text{L}$ or to patients who have dysfunction of one organ system and have had surgery during the previous 30 days. Treatment with aPC should not be started >24 h after the onset of severe sepsis, nor should it be used in the patient subsets (e.g., patients with pancreatitis or AIDS) that were excluded from the clinical trial.

Although the theoretical rationale for treating septic patients with anticoagulants is strong and studies have found that aPC may have antiinflammatory and antiapoptotic properties in vitro, two additional randomized, placebo-controlled trials of aPC were stopped when interim analyses showed lack of efficacy. One trial

was in children, and the other was in adults with APACHE II scores of ≤ 25 . aPC has not been tested again in the patient population for which it was approved by the FDA (i.e., adults with high APACHE II scores).

Some experts have advocated "bundling" of multiple therapeutic maneuvers into a unified, algorithmic approach to management that would become the standard of care for patients with severe sepsis. The proposed *resuscitation* (6-h) bundle incorporates most of the elements discussed above for acute (EGDT) resuscitation. The *management* (24-h) bundle includes three measures of uncertain or marginal benefit: tight control of blood glucose, administration of low-dose hydrocortisone, and treatment with aPC. Bundling of therapies obscures the efficacy and toxicity of the individual interventions and allows little room for individualizing therapy. The use of bundling in an industry-sponsored marketing program for aPC (the Surviving Sepsis Campaign) has also been criticized.

A careful retrospective analysis found that the apparent efficacy of all sepsis therapeutics studied to date has been greatest among the patients at greatest risk of dying before treatment; conversely, use of many of these drugs has been associated with increased mortality rates among patients who are less ill. The authors proposed that whereas neutralizing one of many different mediators may help patients who are very sick, disrupting the mediator balance may be harmful to those whose adaptive defense mechanisms are still working. This analysis suggests that if more aggressive early resuscitation improves survival rates among sicker patients, it should become more difficult to show additional benefit from other therapies; that is, if early resuscitation improves patients' status, moving them into a "less severe illness" category, the addition of another agent is less likely to be beneficial.

PROGNOSIS

Approximately 20–35% of patients with severe sepsis and 40–60% of patients with septic shock die within 30 days. Others die within the ensuing 6 months. Late deaths often result from poorly controlled infection, immunosuppression, complications of intensive care, failure of multiple organs, or the patient's underlying disease.

Prognostic stratification systems such as APACHE II indicate that factoring in the patient's age, underlying condition, and various physiologic variables can yield estimates of the risk of dying of severe sepsis. Of the individual covariates, the severity of underlying disease most strongly influences the risk of dying. Septic shock is also a strong predictor of short- and long-term mortality. Case-fatality rates are similar for culture-positive and culture-negative severe sepsis.

PREVENTION

Prevention offers the best opportunity to reduce morbidity and mortality. In developed countries, most episodes of severe sepsis and septic shock are complications of nosocomial infections. These cases might be prevented by reducing the number of invasive procedures undertaken, limiting the use (and duration of use) of indwelling vascular and bladder catheters, reducing the incidence and duration of profound neutropenia (<500 neutrophils/ μL), and more aggressively treating localized nosocomial infections. Indiscriminate use of antimicrobial agents and glucocorticoids should be avoided, and optimal infection-control measures should be used. Several studies point to associations between allelic polymorphisms in specific genes and risk of severe sepsis; if these associations prove to be broadly applicable, such polymorphisms can be used prospectively to identify high-risk patients and to target preventive or therapeutic measures to them. Studies indicate that 50–70% of patients who develop nosocomial severe sepsis or septic shock have experienced a less severe stage of the septic response (e.g., SIRS, sepsis) on at least one previous day in the hospital. Research is needed to develop adjunctive agents that can damp the septic response before organ dysfunction or hypotension occurs.

FURTHER READINGS

- ABRAHAM E et al: Efficacy and safety of tifacogin (recombinant tissue factor pathway inhibitor) in severe sepsis: A randomized controlled trial. *JAMA* 290:238, 2003
- ARAFAH BM: Hypothalamic pituitary adrenal function during critical illness: Limitations of current assessment methods. *J Clin Endocrinol Metab* 91:3725, 2006
- BERKLEY JA et al: Bacteremia among children admitted to a rural hospital in Kenya. *N Engl J Med* 352:39, 2005
- EICHACKER P et al: Risk and the efficacy of anti-inflammatory agents: Retrospective and confirmatory studies of sepsis. *Am J Respir Crit Care Med* 166:1197, 2002
- HARBATH S et al: Does antibiotic selection impact patient outcome? *Clin Infect Dis* 44:87, 2007
- HOTCHKISS RS, NICHOLSON DW: Apoptosis and caspases regulate death and inflammation in sepsis. *Nat Rev Immunol* 6:813, 2006
- KUMAR A et al: Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 34:1589, 2006
- MUNFORD RS: Severe sepsis and septic shock: The role of gram-negative bacteremia. *Annu Rev Pathol Mech Dis* 1:467, 2006
- OTERO RM et al: Early goal-directed therapy in severe sepsis and septic shock revisited: Concepts, controversies, and contemporary findings. *Chest* 130:1579, 2006
- RUSSELL JA: Management of sepsis. *N Engl J Med* 355:1699, 2006
- SANDS KE et al: Epidemiology of sepsis syndrome in 8 academic medical centers. *JAMA* 278:234, 1997
- TURGEON AF et al: Meta-analysis: Intravenous immunoglobulin in critically ill adult patients with sepsis. *Ann Intern Med* 146:193, 2007



CHAPTER 30

ACUTE RESPIRATORY DISTRESS SYNDROME

Bruce D. Levy ■ Steven D. Shapiro

Etiology	290
Clinical Course and Pathophysiology	290
Prognosis	295
■ Further Readings	296

Acute respiratory distress syndrome (ARDS) is a clinical syndrome of severe dyspnea of rapid onset, hypoxemia, and diffuse pulmonary infiltrates leading to respiratory failure. ARDS is caused by diffuse lung injury from many underlying medical and surgical disorders. The lung injury may be direct, as occurs in toxic inhalation, or indirect, as occurs in sepsis (**Table 30-1**). The clinical features of ARDS are listed in **Table 30-2**. Acute lung injury (ALI) is a less severe disorder but has the potential to evolve into ARDS (**Table 30-2**). The arterial (a) P_{O_2} (in mmHg)/ F_{IO_2} (inspiratory O_2 fraction) <200 mmHg is characteristic of ARDS, and a P_{aO_2}/F_{IO_2} between 200 and 300 identifies patients with ALI who are likely to benefit from aggressive therapy.

The annual incidences of ALI and ARDS are estimated to be up to 80 in 100,000 and 60 in 100,000, respectively. Approximately 10% of all intensive care unit (ICU) admissions experience acute respiratory failure, with ~20% of these patients meeting criteria for ALI or ARDS.

ETIOLOGY

Although many medical and surgical illnesses have been associated with the development of ALI and ARDS, most cases (>80%) are caused by a relatively small number of clinical disorders, namely, severe sepsis syndrome or bacterial pneumonia (~40–50%), trauma, multiple transfusions, aspiration of gastric contents, and drug overdose. Among patients with trauma, pulmonary contusion, multiple bone fractures, and chest wall trauma or flail chest are the

most frequently reported surgical conditions in ARDS; head trauma, near-drowning, toxic inhalation, and burns are rare causes. The risks of developing ARDS are increased in patients who have more than one predisposing medical or surgical condition; e.g., the risk for ARDS increases from 25% in patients with severe trauma to 56% in patients with trauma and sepsis.

Several other clinical variables have been associated with the development of ARDS. These include older age, chronic alcohol abuse, metabolic acidosis, and severity of critical illness. Trauma patients with an acute physiology and chronic health evaluation [Acute Physiology and Chronic Health Evaluation (APACHE)] II scores ≥ 16 (Chap. 26) have a 2.5-fold increase in the risk of developing ARDS, and those with scores >20 have an incidence of ARDS that is more than threefold greater than those with APACHE II scores ≤ 9 .

CLINICAL COURSE AND PATHOPHYSIOLOGY

The natural history of ARDS is marked by three phases—exudative, proliferative, and fibrotic—each with characteristic clinical and pathologic features (**Fig. 30-1**).

Exudative Phase

(**Fig. 30-2**) In this phase, alveolar capillary endothelial cells and type I pneumocytes (alveolar epithelial cells) are injured, leading to the loss of the normally tight alveolar barrier to fluid and macromolecules. Edema fluid that is

TABLE 30-1

CLINICAL DISORDERS COMMONLY ASSOCIATED WITH ACUTE RESPIRATORY DISTRESS SYNDROME	
DIRECT LUNG INJURY	INDIRECT LUNG INJURY
Pneumonia	Sepsis
Aspiration of gastric contents	Severe trauma
Pulmonary contusion	Multiple bone fractures
Near-drowning	Flail chest
Toxic inhalation injury	Head trauma
	Burns
	Multiple transfusions
	Drug overdose
	Pancreatitis
	Post-cardiopulmonary bypass

rich in protein accumulates in the interstitial and alveolar spaces. Significant concentrations of cytokines (e.g., interleukin 1, interleukin 8, and tumor necrosis factor α) and lipid mediators (e.g., leukotriene B₄) are present in the lung in this acute phase. In response to proinflammatory mediators, leukocytes (especially neutrophils) traffic into the pulmonary interstitium and alveoli. In addition, condensed plasma proteins aggregate in the air spaces with cellular debris and dysfunctional pulmonary surfactant to form hyaline membrane whorls. Pulmonary vascular injury also occurs early in ARDS, with vascular obliteration by microthrombi and fibrocellular proliferation (Fig. 30-3).

Alveolar edema predominantly involves dependent portions of the lung, leading to diminished aeration and atelectasis. Collapse of large sections of dependent lung markedly decreases lung compliance. Consequently, intrapulmonary shunting and hypoxemia develop, and the work of breathing increases, leading to dyspnea. The pathophysiologic alterations in alveolar spaces are

TABLE 30-2

OXYGENATION	ONSET	CHEST RADIOGRAPH	ABSENCE OF LEFT ATRIAL HYPERTENSION
ALI: Pao ₂ /Fio ₂ ≤ 300 mmHg	Acute	Bilateral alveolar or interstitial infiltrates	PCWP ≤ 18 mmHg
ARDS: Pao ₂ /Fio ₂ ≤ 200 mmHg			or no clinical evidence of increased left atrial pressure

Note: ALI, acute lung injury; ARDS, acute respiratory distress syndrome; Fio₂, inspired O₂ percentage; Pao₂, arterial partial pressure of O₂; PCWP, pulmonary capillary wedge pressure.

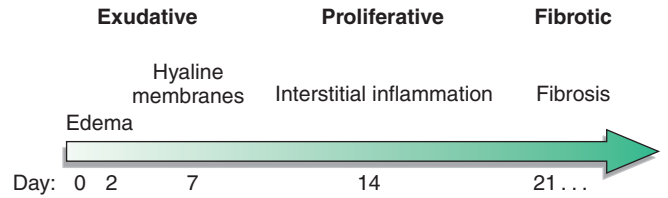


FIGURE 30-1

Diagram illustrating the time course for the development and resolution of acute respiratory distress syndrome. The exudative phase is notable for early alveolar edema and neutrophil-rich leukocytic infiltration of the lungs with subsequent formation of hyaline membranes from diffuse alveolar damage. Within 7 days, a proliferative phase ensues with prominent interstitial inflammation and early fibrotic changes. Approximately 3 weeks after the initial pulmonary injury, most patients recover. However, some patients enter the fibrotic phase, with substantial fibrosis and bullae formation.

exacerbated by microvascular occlusion, which leads to reductions in pulmonary arterial blood flow to ventilated portions of the lung, increasing the dead space, and pulmonary hypertension. Thus, in addition to severe hypoxemia, hypercapnia secondary to an increase in pulmonary dead space is also prominent in early ARDS.

The exudative phase encompasses the first 7 days of illness after exposure to a precipitating ARDS risk factor, with the patient experiencing the onset of respiratory symptoms. Although usually present within 12–36 h after the initial insult, symptoms can be delayed by 5–7 days. Dyspnea develops with a sensation of rapid



FIGURE 30-2

A representative anteroposterior (AP) chest x-ray in the exudative phase of acute respiratory distress syndrome that shows diffuse interstitial and alveolar infiltrates, which can be difficult to distinguish from left ventricular failure.

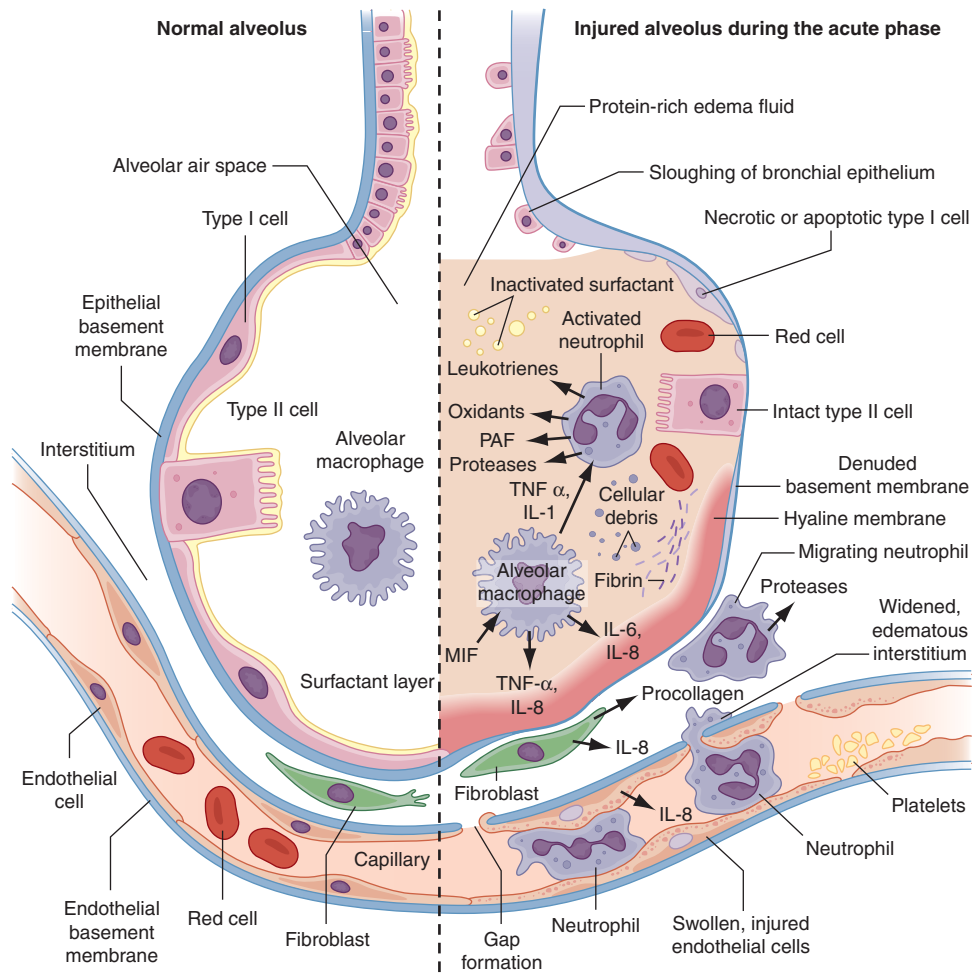


FIGURE 30-3

The normal alveolus (*left-hand side*) and the injured alveolus in the acute phase of acute lung injury and acute respiratory distress syndrome (*right-hand side*). In the acute phase of the syndrome (*right-hand side*), there is sloughing of both the bronchial and alveolar epithelial cells, with the formation of protein-rich hyaline membranes on the denuded basement membrane. Neutrophils are shown adhering to the injured capillary endothelium and marginating through the interstitium into the air space, which is filled with protein-rich edema fluid. In the air space, an alveolar macrophage is secreting cytokines, interleukin 1, 6, 8, and 10 (IL-1, IL-6, IL-8, and IL-10) and tumor necrosis factor α (TNF α), which act locally to stimulate

chemotaxis and activate neutrophils. Macrophages also secrete other cytokines, including IL-1, IL-6, and IL-10. IL-1 can also stimulate the production of extracellular matrix by fibroblasts. Neutrophils can release oxidants, proteases, leukotrienes, and other proinflammatory molecules, such as platelet-activating factor (PAF). A number of anti-inflammatory mediators are also present in the alveolar milieu, including IL-1-receptor antagonist, soluble TNF receptor, autoantibodies against IL-8, and cytokines such as IL-10 and IL-11 (not shown). The influx of protein-rich edema fluid into the alveolus has led to the inactivation of surfactant. MIF, macrophage inhibitory factor. (From Ware and Matthay, with permission.)

shallow breathing and an inability to get enough air. Tachypnea and increased work of breathing frequently result in respiratory fatigue and ultimately in respiratory failure. Laboratory values are generally nonspecific and primarily indicative of underlying clinical disorders. The chest radiograph usually reveals alveolar and interstitial opacities involving at least three-quarters of the lung fields (Fig. 30-2). Although characteristic of ARDS or ALI, these radiographic findings are not specific and can be indistinguishable from cardiogenic pulmonary edema

(Chap. 31). Unlike the latter, however, the chest x-ray in ARDS rarely shows cardiomegaly, pleural effusions, or pulmonary vascular redistribution. Chest CT scanning in patients with ARDS reveals extensive heterogeneity of lung involvement (Fig. 30-4).

Because the early features of ARDS and ALI are nonspecific, alternative diagnoses must be considered. In the differential diagnosis of ARDS, the most common disorders are cardiogenic pulmonary edema, diffuse pneumonia, and alveolar hemorrhage. Less frequent diagnoses to

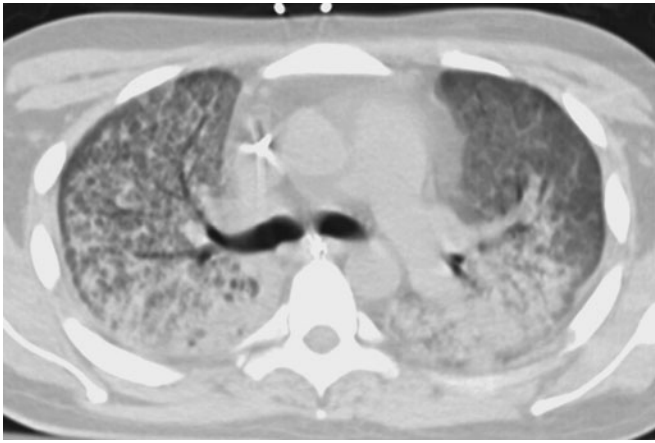


FIGURE 30-4

A representative computed tomographic scan of the chest during the exudative phase of acute respiratory distress syndrome in which *dependent* alveolar edema and atelectasis predominate.

consider include acute interstitial lung diseases [e.g., acute interstitial pneumonitis (Chap. 19)], acute immunologic injury [e.g., hypersensitivity pneumonitis (Chap. 9)], toxin injury (e.g., radiation pneumonitis), and neurogenic pulmonary edema.

Proliferative Phase

This phase of ARDS usually lasts from day 7 to day 21. Most patients recover rapidly and are liberated from mechanical ventilation during this phase. Despite this improvement, many still experience dyspnea, tachypnea, and hypoxemia. Some patients develop progressive lung injury and early changes of pulmonary fibrosis during the proliferative phase. Histologically, the first signs of resolution are often evident in this phase with the initiation of lung repair, organization of alveolar exudates, and a shift from a neutrophil to a lymphocyte-predominant pulmonary infiltrate. As part of the reparative process, there is a proliferation of type II pneumocytes along alveolar basement membranes. These specialized epithelial cells synthesize new pulmonary surfactant and differentiate into type I pneumocytes. The presence of alveolar type III procollagen peptide, a marker of pulmonary fibrosis, is associated with a protracted clinical course and increased mortality from ARDS.

Fibrotic Phase

Although many patients with ARDS recover lung function 3–4 weeks after the initial pulmonary injury, some enter a fibrotic phase that may require long-term support on mechanical ventilators, supplemental oxygen, or both. Histologically, the alveolar edema and inflammatory exudates of the earlier phases are now converted to

extensive alveolar duct and interstitial fibrosis. Acinar architecture is markedly disrupted, leading to emphysema-like changes with large bullae. Intimal fibroproliferation in the pulmonary microcirculation leads to progressive vascular occlusion and pulmonary hypertension. The physiologic consequences include an increased risk of pneumothorax, reductions in lung compliance, and increased pulmonary dead space. Patients in this late phase experience a substantial burden of excess morbidity. Lung biopsy evidence for pulmonary fibrosis in any phase of ARDS is associated with increased mortality.

R_x Treatment: ACUTE RESPIRATORY DISTRESS

GENERAL PRINCIPLES Recent reductions in ARDS and ALI mortality are largely the result of general advances in the care of critically ill patients (Chap. 26). Thus, caring for these patients requires close attention to (1) the recognition and treatment of the underlying medical and surgical disorders (e.g., sepsis, aspiration, trauma); (2) minimizing procedures and their complications; (3) prophylaxis against venous thromboembolism, gastrointestinal bleeding, and central venous catheter infections; (4) the prompt recognition of nosocomial infections; and (5) provision of adequate nutrition.

MANAGEMENT OF MECHANICAL VENTILATION (See also Chap. 27) Patients meeting clinical criteria for ARDS frequently fatigue from increased work of breathing and progressive hypoxemia, requiring mechanical ventilation for support.

Ventilator-Induced Lung Injury Despite its life-saving potential, mechanical ventilation can aggravate lung injury. Experimental models have demonstrated that ventilator-induced lung injury appears to require two processes: repeated alveolar overdistention and recurrent alveolar collapse. Clearly evident by chest CT (Fig. 30-4), ARDS is a heterogeneous disorder, principally involving dependent portions of the lung with relative sparing of other regions. Because of their differing compliance, attempts to fully inflate the consolidated lung may lead to overdistention and injury to the more “normal” areas of lung. Ventilator-induced injury can be demonstrated in experimental models of ALI, with high tidal volume ventilation resulting in additional, synergistic alveolar damage. These findings led to the hypothesis that ventilating patients who have ALI or ARDS with lower tidal volumes would protect against ventilator-induced lung injury and improve clinical outcomes.

A large-scale, randomized controlled trial sponsored by the National Institutes of Health and conducted by the ARDS Network compared low tidal volume (6 mL/kg predicted body weight) ventilation with conventional

tidal volume (12 mL/kg predicted body weight) ventilation. Mortality was significantly lower in the low tidal volume patients (31%) compared with the conventional tidal volume patients (40%). This improvement in survival represents the most substantial benefit in ARDS mortality demonstrated for *any* therapeutic intervention in ARDS to date.

Prevention of Alveolar Collapse In patients with ARDS, the presence of alveolar and interstitial fluid and the loss of surfactant can lead to a marked reduction of lung compliance. Without an increase in end-expiratory pressure, significant alveolar collapse can occur at end-expiration, impairing oxygenation. In most clinical settings, positive end-expiratory pressure (PEEP) is empirically set to minimize F_{IO_2} and maximize P_{aO_2} . On most modern mechanical ventilators, it is possible to construct a static pressure–volume curve for the respiratory system. The lower inflection point on the curve represents alveolar opening (or “recruitment”). The pressure at this point, usually 12–15 mmHg in ARDS, is a theoretical “optimal PEEP” for alveolar recruitment. Titration of the PEEP to the lower inflection point on the static pressure–volume curve has been hypothesized to keep the lung open, improving oxygenation and protecting against lung injury. ARDS Network investigators compared low-to-high PEEP (8.3–13.2 cmH₂O) in more than 500 patients with ARDS ventilated at low tidal volumes [6 mL/kg patient body weight (PBW)]. No significant differences in mortality, ventilator-free days, or ICU stay were observed. Until more data become available on the clinical utility of high PEEP, it is advisable to set PEEP to minimize F_{IO_2} and optimize P_{aO_2} (Chap. 27).

Oxygenation can also be improved by increasing mean airway pressure with “inverse ratio ventilation.” In this technique, the inspiratory (*I*) time is lengthened so that it is longer than the expiratory (*E*) time (*I*:*E* >1:1). With diminished time to exhale, dynamic hyperinflation leads to increased end-expiratory pressure, similar to ventilator-prescribed PEEP. This mode of ventilation has the advantage of improving oxygenation with lower peak pressures than conventional ventilation. Although inverse ratio ventilation can improve oxygenation and help reduce F_{IO_2} to ≤ 0.60 to avoid possible oxygen toxicity, no mortality benefit in patients with ARDS has been demonstrated.

In several randomized trials, mechanical ventilation in the prone position improved arterial oxygenation, but its effect on survival and other important clinical outcomes remains uncertain. Moreover, unless the critical care team is experienced in “proning,” repositioning critically ill patients can be hazardous, leading to accidental endotracheal extubation, loss of central venous catheters, and orthopedic injury. Until validation of its efficacy, prone-position ventilation

should be reserved for only the most critically ill ARDS patients.

Other Strategies in Mechanical Ventilation

Several additional mechanical ventilation strategies that use specialized equipment have been tested in ARDS patients, most with mixed or disappointing results in adults. These include high-frequency ventilation [HFV, i.e., ventilating at extremely high respiratory rates (5–20 cycles/sec) and low tidal volumes (1–2 mL/kg)]. Also, lung-replacement therapy with extracorporeal membrane oxygenation (ECMO), which provides a clear survival benefit in neonatal respiratory distress syndrome, has yet to have proven survival benefit in adults with ARDS. Ongoing research on partial liquid ventilation (PLV) with perfluorocarbon, an inert, high-density liquid that easily solubilizes oxygen and carbon dioxide, has revealed promising preliminary data on pulmonary function in patients with ARDS but without survival benefit.

Data in support of the efficacy of “adjunctive” ventilator therapies (e.g., high PEEP, inverse ratio ventilation, prone positioning, HFV, ECMO, and PLV) remain incomplete, so these modalities are not routinely used.

FLUID MANAGEMENT

(See also Chap. 26) Increased pulmonary vascular permeability leading to interstitial and alveolar edema rich in protein is a central feature of ARDS. In addition, impaired vascular integrity augments the normal increase in extravascular lung water that occurs with increasing left atrial pressure. Maintaining a normal or low left atrial filling pressure minimizes pulmonary edema and prevents further decrements in arterial oxygenation and lung compliance, improves pulmonary mechanics, shortens ICU stay and the duration of mechanical ventilation, and is associated with a lower mortality. Thus, aggressive attempts to reduce left atrial filling pressures with fluid restriction and diuretics should be an important aspect of ARDS management, limited only by hypotension and hypoperfusion of critical organs, such as the kidneys.

GLUCOCORTICOIDS Inflammatory mediators and leukocytes are abundant in the lungs of patients with ARDS. Many attempts have been made to treat patients with both early and late ARDS with glucocorticoids to reduce this potentially deleterious pulmonary inflammation. Few studies have shown any benefit. Current evidence does *not* support the use of glucocorticoids in the care of ARDS patients. However, the ARDS Network is currently conducting a large-scale study of glucocorticoids in the late phase of ARDS.

OTHER THERAPIES Clinical trials of surfactant replacement therapy have proved disappointing.

Similarly, although several randomized clinical trials of inhaled nitric oxide (NO) in ARDS have demonstrated improved oxygenation, no significant improvement in survival or decrements in time on mechanical ventilation has been observed. Therefore, the use of NO is *not* currently recommended for patients with ARDS.

RECOMMENDATIONS Many clinical trials have been undertaken to improve the outcome of patients with ARDS; most have been unsuccessful in modifying the natural history. The large number and uncertain clinical efficacy of ARDS therapies can make it difficult for clinicians to select a rational treatment plan, and these patients' critical illness can tempt physicians to try unproven and potentially harmful therapies. Although results of large clinical trials must be judiciously administered to *individual* patients, evidence-based recommendations are summarized in **Table 30-3**, and an algorithm for the initial therapeutic goals and limits in ARDS management is provided in **Figure 30-5**.

PROGNOSIS

Mortality

Recent mortality estimates for patients with ARDS range from 41–65%. There is substantial variability, but a trend toward improved ARDS outcomes appears evident. Of

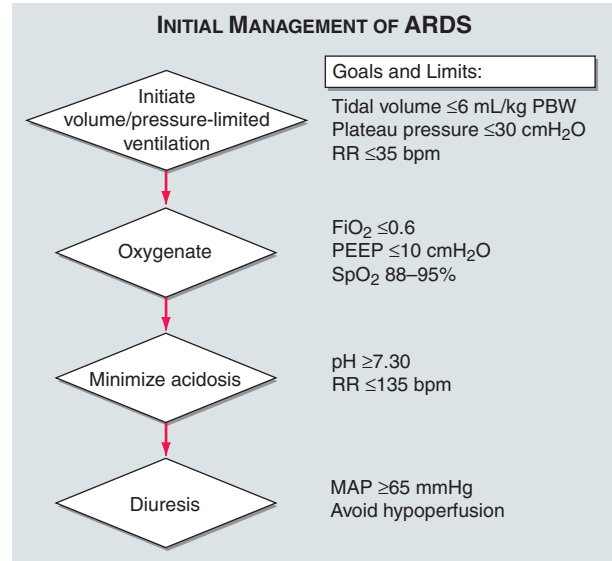


FIGURE 30-5 Algorithm for the initial management of acute respiratory distress syndrome (ARDS). Clinical trials have provided evidence-based therapeutic goals for a stepwise approach to the early mechanical ventilation, oxygenation, correction of acidosis, and diuresis of critically ill patients with ARDS. FiO₂, inspiratory O₂ fraction; MAP, mean arterial pressure; PBW, patient body weight; PEEP, positive end-expiratory pressure; RR, respiratory rate.

TABLE 30-3
EVIDENCE-BASED RECOMMENDATIONS FOR ACUTE RESPIRATORY DISTRESS SYNDROME THERAPIES

TREATMENT	RECOMMENDATION ^a
Mechanical ventilation:	
Low tidal volume	A
High-PEEP or “open-lung”	C
Prone position	C
Recruitment maneuvers	C
High-frequency ventilation and ECMO	D
Minimize left atrial filling pressures	B
Glucocorticoids	C
Surfactant replacement, inhaled nitric oxide, and other anti-inflammatory therapy (e.g., ketoconazole, PGE ₁ , NSAIDs)	D

^a**A**, recommended therapy based on strong clinical evidence from randomized clinical trials; **B**, recommended therapy based on supportive but limited clinical data; **C**, indeterminate evidence: recommended only as alternative therapy; **D**, not recommended based on clinical evidence against efficacy of therapy.

Note: ECMO, extracorporeal membrane oxygenation; NSAID, nonsteroidal anti-inflammatory drug; PEEP, positive end-expiratory pressure; PGE₁, prostaglandin E₁.

interest, mortality in those with ARDS is largely attributable to nonpulmonary causes, with sepsis and nonpulmonary organ failure accounting for >80% of deaths. Thus, improvement in survival is likely secondary to advances in the care of patients with sepsis or infection and those with multiple organ failure (Chap. 26).

Several risk factors for mortality to help estimate prognosis have been identified. Similar to the risk factors for developing ARDS, the major risk factors for ARDS mortality are also nonpulmonary. Advanced age is an important risk factor. Patients >75 years have a substantially increased mortality (~60%) compared with those <45 years of age (~20%). Also, patients >60 years of age who have ARDS and sepsis have a threefold higher mortality compared with those <60 years of age. Preexisting organ dysfunction from chronic medical illness is an important additional risk factor for increased mortality. In particular, chronic liver disease, cirrhosis, chronic alcohol abuse, chronic immunosuppression, sepsis, chronic renal disease, any nonpulmonary organ failure, and increased APACHE II scores (Chap. 26) have also been linked to increased ARDS mortality. Several factors related to the presenting clinical disorders also increase risk for ARDS mortality. Patients with ARDS from direct lung injury (including pneumonia, pulmonary contusion, and aspiration; Table 30-1) have nearly twice the mortality of those with indirect causes of lung injury, while surgical and trauma patients with ARDS, especially those

296 without direct lung injury, have a better survival rate than other ARDS patients.

Surprisingly, there is little value in predicting ARDS mortality from the extent of hypoxemia and any of the following measures of the severity of lung injury: the level of PEEP used in mechanical ventilation, the respiratory compliance, the extent of alveolar infiltrates on chest radiography, and the lung injury score (a composite of all these variables). However, recent data indicate that an early (within 24 h of presentation) elevation in dead space may predict increased mortality from ARDS.

Functional Recovery in Acute Respiratory Distress Syndrome Survivors

Although it is common for patients with ARDS to experience prolonged respiratory failure and remain dependent on mechanical ventilation for survival, it is a testament to the resolving powers of the lung that the majority of patients recover nearly normal lung function. Patients usually recover their maximum lung function within 6 months. One year after endotracheal extubation, more than one-third of ARDS survivors have normal spirometry values and diffusion capacity. Most of the remaining patients have only mild abnormalities in their pulmonary function. Unlike the risk for mortality, recovery of lung function is strongly associated with the extent of lung injury in early ARDS. Low static respiratory compliance,

high levels of required PEEP, longer durations of mechanical ventilation, and high lung injury scores are all associated with worse recovery of pulmonary function. When caring for ARDS survivors, it is important to be aware of the potential for a substantial burden of emotional and respiratory symptoms. There are significant rates of depression and posttraumatic stress disorder in ARDS survivors.

FURTHER READINGS

- ARDS FOUNDATION: Available at <http://www.ardsusa.org>
- ARDS NETWORK CLINICAL TRIALS INFORMATION: Available at <http://www.ardsnet.org>
- ARDS SUPPORT CENTER FOR PATIENT-ORIENTED EDUCATION: Available at <http://www.ards.org>
- BROWER RG et al: Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 351:327, 2004
- FAN EDM et al: Ventilatory management of acute lung injury and acute respiratory distress syndrome. *JAMA* 294:2889, 2005
- GUERIN CS et al: Effects of systemic prone positioning in hypoxemic acute respiratory failure: A randomized controlled trial. *JAMA* 292:2379, 2004
- RUBENFIELD GD et al: Incidence and outcomes of acute lung injury. *N Engl J Med* 353:1685, 2005
- TOMASHEFSKI JF JR.: Pulmonary pathology of acute respiratory distress syndrome. *Clin Chest Med* 21:435, 2000
- WARE LB, MATTHAY MA: The acute respiratory distress syndrome. *N Engl J Med* 342:1334, 2000
- WHEELER AP, BERNARD GR: Acute lung injury and the acute respiratory distress syndrome: A clinical review. *Lancet* 369:1553, 2007



CHAPTER 31

CARDIOGENIC SHOCK AND PULMONARY EDEMA

Judith S. Hochman ■ David H. Ingbar

■ Cardiogenic Shock	297
Shock Secondary to Right Ventricular Infarction	302
Mitral Regurgitation	302
Ventricular Septal Rupture	302
Free Wall Rupture	302
Acute Fulminant Myocarditis	303
■ Pulmonary Edema	303
■ Further Readings	305

Cardiogenic shock (CS) and pulmonary edema are life-threatening conditions that should be treated as medical emergencies. The most common etiology for both is severe left ventricular (LV) dysfunction, leading to pulmonary congestion, systemic hypoperfusion, or both (**Fig. 31-1**).

The pathophysiology of pulmonary edema and shock are discussed in Chaps. 2 and 28, respectively.

CARDIOGENIC SHOCK

CS is characterized by systemic hypoperfusion caused by severe depression of the cardiac index [<2.2 (L/min)/m²] and sustained systolic arterial hypotension (<90 mmHg) despite an elevated filling pressure [pulmonary capillary wedge pressure (PCWP) >18 mmHg]. It is associated with in-hospital mortality rates $>50\%$. The major causes of CS are listed in **Table 31-1**. Circulatory failure based on cardiac dysfunction may be caused by primary myocardial failure, most commonly secondary to acute myocardial infarction (MI) (Chap. 34) and less frequently by cardiomyopathy or myocarditis or cardiac tamponade.

Incidence

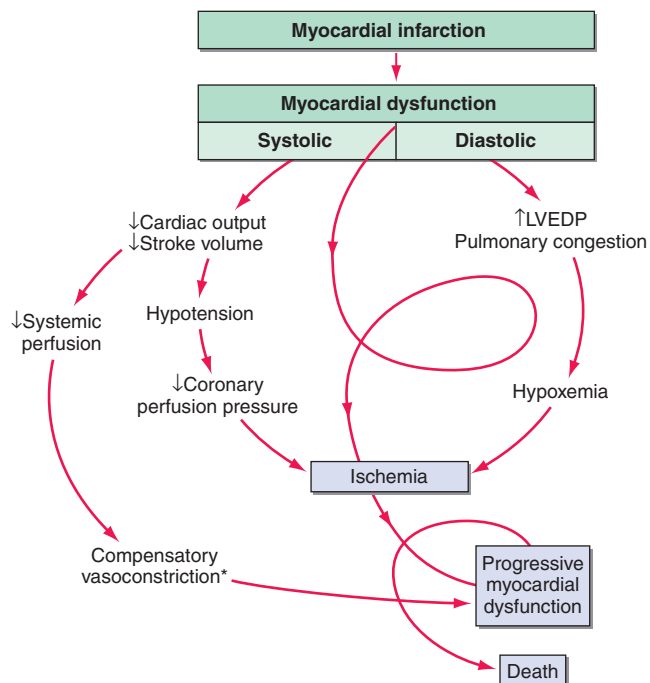
CS is the leading cause of death of patients hospitalized with MI. Early reperfusion therapy for acute MI decreases the incidence of CS. The rate of CS complicating acute

MI decreased from 20% in the 1960s but has plateaued at $\sim 8\%$ for >20 years. Shock is typically associated with ST elevation MI (STEMI) and is less common with non-ST elevation MI (Chap. 34).

LV failure accounts for $\sim 80\%$ of the cases of CS complicating acute MI. Acute severe mitral regurgitation (MR), ventricular septal rupture (VSR), predominant right ventricular (RV) failure, and free wall rupture or tamponade account for the remainder.

Pathophysiology

CS is characterized by a vicious circle in which depression of myocardial contractility, usually caused by ischemia, results in reduced cardiac output and arterial pressure (BP), which result in hypoperfusion of the myocardium and further ischemia and depression of the cardiac output (**Fig. 31-1**). Systolic myocardial dysfunction reduces stroke volume and, together with diastolic dysfunction, leads to elevated LV end-diastolic pressure and PCWP as well as to pulmonary congestion. Reduced coronary perfusion leads to worsening ischemia and progressive myocardial dysfunction and a rapid downward spiral, which, if uninterrupted, is often fatal. A systemic inflammatory response syndrome may accompany large infarctions and shock. Inflammatory cytokines, inducible nitric oxide synthase, and excess nitric oxide and peroxynitrite may contribute

**FIGURE 31-1**

Pathophysiology of cardiogenic shock. Systolic and diastolic myocardial dysfunction result in a reduction in cardiac output and often pulmonary congestion. Systemic and coronary hypoperfusion occur, resulting in progressive ischemia. Although a number of compensatory mechanisms are activated in an attempt to support the circulation, these compensatory mechanisms may become maladaptive and produce a worsening of hemodynamics. *Release of inflammatory cytokines after myocardial infarction may lead to inducible nitrous oxide expression, excess NO, and inappropriate vasodilation. This causes further reduction in systemic and coronary perfusion. A vicious spiral of progressive myocardial dysfunction occurs that ultimately results in death if it is not interrupted. LVEDP, left ventricular end-diastolic pressure. (From Hollenberg SM et al: *Cardiogenic shock*. *Ann Intern Med* 131:47, 1999.)

to the genesis of CS as they do to other forms of shock (Chap. 28). Lactic acidosis from poor tissue perfusion and hypoxemia from pulmonary edema may result from pump failure and then contribute to the vicious circle by worsening myocardial ischemia and hypotension. Severe acidosis (pH <7.25) reduces the efficacy of endogenous and exogenously administered catecholamines. Refractory sustained ventricular or atrial tachyarrhythmias can cause or exacerbate CS.

Autopsy specimens often reflect the stuttering course and piecemeal necrosis of the LV, showing varying stages of infarction. Reinfarction is apparent as new areas of necrosis contiguous with or remote from a slightly older infarct. Infarctions that extend through the full myocardial thickness and result in rupture of the interventricular septum, papillary muscle, or ventricular free wall may result in shock (Chap. 34).

TABLE 31-1**CAUSES OF CARDIOGENIC SHOCK (CS)^a AND CARDIOGENIC PULMONARY EDEMA****Causes of Cardiogenic Shock or Pulmonary Edema**

- Acute myocardial infarction or ischemia
- LV failure
- VSR
- Papillary muscle or chordal rupture—severe MR
- Ventricular free wall rupture with subacute tamponade
- Other conditions complicating large MIs
- Hemorrhage
- Infection
- Excess negative inotropic or vasodilator medications
- Prior valvular heart disease
- Hyperglycemia or ketoacidosis
- Post-cardiac arrest
- Post-cardiotomy
- Refractory sustained tachyarrhythmias
- Acute fulminant myocarditis
- End-stage cardiomyopathy
- Left ventricular apical ballooning
- Takotsubo cardiomyopathy
- Hypertrophic cardiomyopathy with severe outflow obstruction
- Aortic dissection with aortic insufficiency or tamponade
- Pulmonary embolus
- Severe valvular heart disease
 - Critical aortic or mitral stenosis
 - Acute severe aortic or MR
- Toxic-metabolic
 - β-Blocker or calcium channel antagonist overdose

Other Etiologies of Cardiogenic Shock^b

RV failure caused by:

- Acute MI
- Acute coronary pulmonale
- Refractory sustained bradyarrhythmias
- Pericardial tamponade
- Toxic or metabolic
- Severe acidosis, severe hypoxemia

^aThe etiologies of cardiogenic shock are listed. Most of these can cause pulmonary edema instead of shock or pulmonary edema with CS.

^bThese cause CS but not pulmonary edema.

Note: LV, left ventricular; MR, mitral regurgitation; RV, right ventricular; VSR, ventricular septal rupture.

Patient Profile

In patients with acute MI, older age, female gender, prior MI, diabetes, and anterior MI location are all associated with increased risk of CS. Shock associated with a first inferior MI should prompt a search for a mechanical cause. Reinfarction soon after MI increases the risk of CS. Two-thirds of patients with CS have flow-limiting stenoses in all three major coronary arteries, and 20% have left main coronary artery stenosis. CS may rarely occur in the absence of significant stenosis, as seen in LV apical ballooning or Takotsubo cardiomyopathy, often in response to sudden severe emotional stress.

Timing

Shock is present on admission in only 25% of patients who develop CS complicating MI; 25% develop it rapidly thereafter within 6 h of MI onset. Another 25% develop shock later on the first day. Subsequent onset of CS may be caused by reinfarction, marked infarct expansion, or a mechanical complication.

Diagnosis

Because of the unstable condition of these patients, supportive therapy must be initiated simultaneously with diagnostic evaluation (Fig. 31-2). A focused history

and physical examination should be performed, blood specimens sent to the laboratory, and an electrocardiogram (ECG) and chest x-ray obtained. Echocardiography is an invaluable diagnostic tool in patients suspected of having CS.

Clinical Findings

Most patients have continuing chest pain and dyspnea and appear pale, apprehensive, and diaphoretic. Mentation may be altered, with somnolence, confusion, and agitation. The pulse is typically weak and rapid, often in the range of 90–110 bpm, or severe bradycardia caused by high-grade heart block may be present. Systolic BP is reduced (<90 mmHg) with a narrow pulse pressure

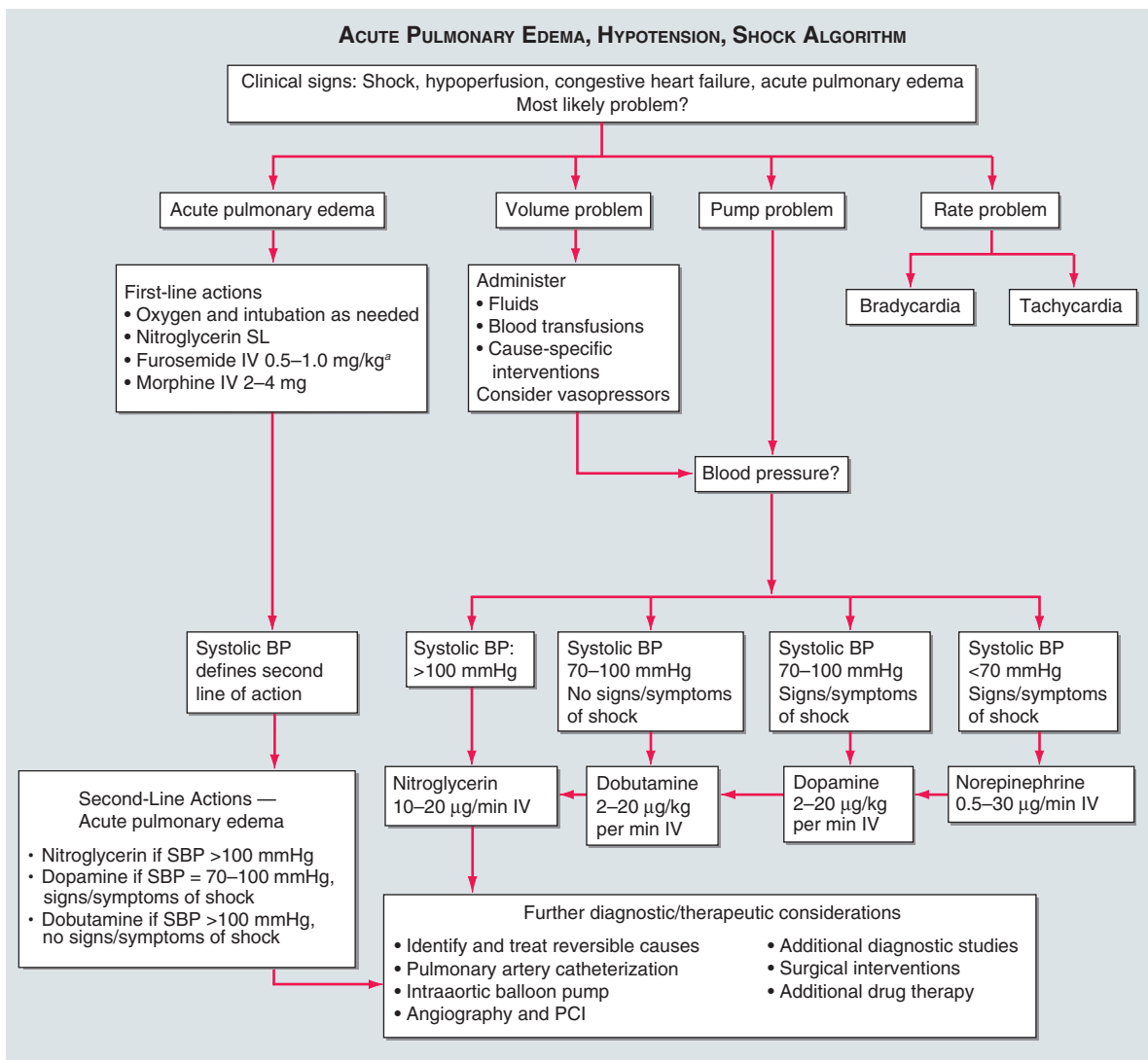


FIGURE 31-2

Emergency management of patients with cardiogenic shock, acute pulmonary edema, or both is outlined. ^aFurosemide: <0.5 mg/kg for new-onset acute pulmonary edema without hypervolemia; 1 mg/kg for acute on chronic volume overload, renal insufficiency. ACE, angiotensin-converting enzyme; BP, blood pressure; MI, myocardial infarction; PCI,

percutaneous coronary intervention; SBP, systolic blood pressure; SL, sublingual. [From Fields J et al (eds): *Handbook of Emergency Cardiovascular Care for Healthcare Providers*. Copyright 2006, American Heart Association, Inc. Reprinted with permission.]

300 (<30 mmHg), but occasionally, BP may be maintained by very high systemic vascular resistance. Tachypnea, Cheyne-Stokes respirations, and jugular venous distention may be present. The precordium is typically quiet, with a weak apical pulse. S1 is usually soft, and an S3 gallop may be audible. Acute, severe MR and VSR are usually associated with characteristic systolic murmurs (Chap. 34). Rales are audible in most patients with LV failure causing CS. Oliguria (urine output <30 mL/h) is common.

Laboratory Findings

The white blood cell count is typically elevated with a left shift. In the absence of prior renal insufficiency, renal function is initially normal, but blood urea nitrogen and creatinine increase progressively. Hepatic transaminases may be markedly elevated because of liver hypoperfusion. Poor tissue perfusion may result in an anion gap acidosis and elevation of lactic acid level. Before support with supplemental O₂, arterial blood gases usually demonstrate hypoxemia and metabolic acidosis, which may be compensated by respiratory alkalosis. Cardiac markers, creatine phosphokinase and its MB fraction, are markedly elevated, as are troponins I and T.

Electrocardiography

In CS caused by acute MI with LV failure, Q waves or >2-mm ST elevation in multiple leads or left bundle branch block are usually present. More than 50% of all infarcts associated with shock are anterior. Global ischemia caused by severe left main stenosis is usually accompanied by severe (e.g., >3 mm) ST depressions in multiple leads.

Chest Radiography

The chest x-ray typically shows pulmonary vascular congestion and often pulmonary edema, but these findings may be absent in up to one-third of patients. The heart size is usually normal when CS results from a first MI but is enlarged when it occurs in a patient with a previous MI.

Echocardiography

A two-dimensional echocardiogram with color-flow Doppler should be obtained promptly in patients with suspected CS to help define its etiology. Doppler mapping demonstrates a left-to-right shunt in patients with VSR and the severity of MR when the latter is present. Proximal aortic dissection with aortic regurgitation or tamponade may be visualized or evidence for pulmonary embolism obtained (Chap. 20).

Pulmonary Artery Catheterization

There is controversy regarding the use of pulmonary artery (Swan-Ganz) catheters in patients with established or suspected CS (Chap 26). However, their use is generally recommended for measurement of filling pressures

and cardiac output to confirm the diagnosis and optimize use of IV fluids, inotropic agents, and vasopressors (Table 31-2). Blood samples for O₂ saturation measurement should be obtained from the right atrium, right ventricle, and pulmonary artery to rule out a left-to-right shunt. Mixed venous O₂ saturations are low and arterial-venous O₂ differences are elevated, reflecting low cardiac index and high fractional O₂ extraction. The PCWP is elevated. However, use of sympathomimetic amines may return these measurements and the systemic BP toward normal. Systemic vascular resistance may be low, normal, or elevated in patients with CS. Equalization of right- and left-sided filling pressures (right atrial and PCWP) suggests cardiac tamponade as the cause of CS.

Left Heart Catheterization and Coronary Angiography

Measurement of LV pressure, the definition of the coronary anatomy, and left ventriculography provide useful information and are indicated in most patients with CS complicating MI. Because of the procedural risk in this critically ill population, cardiac catheterization should be performed when there is a plan and capability for immediate coronary intervention (see later) or when a definitive diagnosis has not been made by other tests.

Rx Treatment: ACUTE MYOCARDIAL INFARCTION

GENERAL MEASURES (Fig. 31-2) In addition to the usual treatment of acute MI (Chap. 34), initial therapy is aimed at maintaining adequate systemic and coronary perfusion by increasing the systemic BP with vasopressors and adjusting the volume status to a level that ensures optimum LV filling pressure. There is interpatient variability, but the values that are generally associated with adequate perfusion are systolic BP of ~90 mmHg or mean BP >60 mmHg and PCWP of ~20 mmHg. Hypoxemia and acidosis must be corrected; most patients require ventilatory support with either endotracheal intubation or bilevel positive airway pressure (Bi-PAP) to correct these abnormalities and reduce the work of breathing (see Pulmonary Edema later). Negative inotropic agents should be discontinued and the doses of renally cleared medications adjusted. Hyperglycemia should be corrected with continuous infusion of insulin. Bradyarrhythmias may require transvenous pacing. Recurrent ventricular tachycardia or rapid atrial fibrillation may require immediate treatment.

VASOPRESSORS Various IV drugs may be used to augment BP and cardiac output in patients with CS. All have important disadvantages, and none has been shown to change the outcome in patients with established shock. *Norepinephrine* is a potent vasoconstrictor

TABLE 31-2

HEMODYNAMIC PATTERNS^a

	RA, mmHg	RVS, mmHg	RVD, mmHg	PAS, mmHg	PAD, mmHg	PCW, mmHg	CI, (L/min)/m ²	SVR, (dyn · s)/cm ⁵
Normal values	<6	<25	0–12	<25	0–12	<6–12	2.5	(800–1600)
MI without pulmonary edema ^b	—	—	—	—	—	13 (5–18)	2.7 (2.2–4.3)	—
Pulmonary edema	↔↑	↔↑	↔↑	↑	↑	↑	↔↓	↑
Cardiogenic shock								
LV failure	↔↑	↔↑	↔↑	↔↑	↑	↑	↓	↔↑
RV failure ^c	↑	↓↔↑ ^d	↑	↓↔↑ ^d	↔↓↑ ^d	↓↔↑ ^d	↓	↑
Cardiac tamponade	↑	↔↑	↑	↔↑	↔↑	↔↑	↓	↑
Acute mitral regurgitation	↔↑	↑	↔↑	↑	↑	↑	↔↓	↔↑
Ventricular septal rupture	↑	↔↑	↑	↔↑	↔↑	↔↑	↑PBF ↓SBF	↔↑
Hypovolemic shock	↓	↔↓	↔↓	↓	↓	↓	↓	↑
Septic shock	↓	↔↓	↔↓	↓	↓	↓	↑	↓

^aThere is significant patient-to-patient variation. Pressure may be normalized if cardiac output is low.

^bForrester et al. classified nonreperused MI patients into four hemodynamic subsets. (From Forrester JS et al: *N Engl J Med* 295:1356, 1976.) Pulmonary capillary wedge (PCWP) and cardiac index (CI) in clinically stable subset 1 patients are shown. Values in parentheses represent range.

^c“Isolated” or predominant right ventricular (RV) failure.

^dPCW and PA pressures may rise in RV failure after volume loading due to RV dilatation, right-to-left shift of the interventricular septum, resulting in impaired left ventricular (LV) filling. When biventricular failure is present, the patterns are similar to those shown for LV failure.

Note: MI, myocardial infarction; PAS/D, pulmonary artery systolic/diastolic; P/SBF, pulmonary/systemic blood flow; RA, right atrium; RVS/D, right ventricular systolic/diastolic; SVR, systemic vascular resistance.

Source: Table prepared with the assistance of Krishnan Ramanathan, MD.

and inotropic stimulant that increases myocardial O₂ consumption; it should be reserved for patients with CS and refractory hypotension, particularly those without elevated systemic vascular resistance. It should be started at a dose of 2–4 µg/min and titrated upward as necessary. If systemic perfusion or systolic pressure cannot be maintained at >90 mmHg with a dose of 15 µg/min, it is unlikely that a further increase will be beneficial.

Dopamine is useful in many patients; at low doses (≤2 µg/kg per min), it dilates the renal vascular bed; at moderate doses (2–10 µg/kg per min), it has positive chronotropic and inotropic effects as a consequence of β-adrenergic receptor stimulation. At higher doses, a vasoconstrictor effect results from α-receptor stimulation. It is started at an infusion rate of 2–5 µg/kg per min, and the dose is increased every 2–5 min to a maximum of 20–50 µg/kg per min. **Dobutamine** is a synthetic sympathomimetic amine with positive inotropic action and minimal positive chronotropic activity at low doses (2.5 µg/kg per min) but moderate chronotropic activity at higher doses. Although the usual dose is up to 10 µg/kg per min, its vasodilating activity precludes its use when a vasoconstrictor effect is required.

AORTIC COUNTERPULSATION In CS, mechanical assistance with an intraaortic balloon pump (IABP) system capable of augmenting both arterial diastolic

pressure and cardiac output is helpful in rapidly stabilizing patients. A sausage-shaped balloon is introduced percutaneously into the aorta via the femoral artery; the balloon is automatically inflated during early diastole, augmenting coronary blood flow. The balloon collapses in early systole, reducing the afterload against which the LV ejects. IABP improves hemodynamic status temporarily in most patients. In contrast to vasopressors and inotropic agents, myocardial O₂ consumption is reduced, ameliorating ischemia. IABP is useful as a stabilizing measure in patients with CS before and during cardiac catheterization and percutaneous coronary intervention (PCI) or before urgent surgery. IABP is contraindicated if aortic regurgitation is present or aortic dissection is suspected. Ventricular assist devices may be considered for eligible young patients with refractory shock as a bridge to cardiac transplantation.

REPERFUSION-REVASCULARIZATION The rapid establishment of blood flow in the infarct-related artery is essential in the management of patients with CS and forms the centerpiece of management. The randomized SHOCK (SHould we emergently revascularize Occluded coronaries for Cardiogenic shock?) trial demonstrated 132 lives saved per 1000 patients treated with early revascularization with PCI or coronary artery bypass graft (CABG) surgery compared with initial

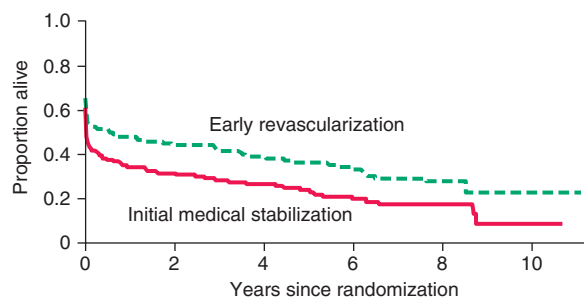


FIGURE 31-3

Early revascularization (percutaneous coronary intervention or coronary artery bypass graft) for cardiogenic shock complicating acute myocardial infarction resulted in substantially improved 1-year and long-term survival compared with initial mechanical stabilization, including intraaortic balloon pump and fibrinolytic agents followed by selective delayed revascularization in the SHOCK (SHould we emergently revascularize Occluded coronaries for Cardiogenic shock?) trial. (From Hochman JS et al: *Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction*. *JAMA* 295:2511–2515, 2006; reprinted with permission from JAMA.)

medical therapy, including IABP with fibrinolytics followed by delayed revascularization (Fig. 31-3). The benefit is seen across the risk strata and is sustained up to 11 years post-MI. Early revascularization with PCI or CABG is a class I recommendation for patients age <75 years of age with ST elevation or left bundle branch block MI who develop CS within 36 h of MI and who can be revascularized within 18 h of development of CS. When mechanical revascularization is not possible, IABP and fibrinolytic therapy are recommended. Older patients who are suitable candidates for aggressive care should also be offered early revascularization.

Prognosis

Within this high-risk condition, there is a wide range of expected death rates based on age, the severity of hemodynamic abnormalities, the severity of the clinical manifestations of hypoperfusion, and the performance of early revascularization. Independent risk factors are advanced age; depressed cardiac index, ejection fraction, and BP; more extensive coronary artery disease; and renal insufficiency.

SHOCK SECONDARY TO RIGHT VENTRICULAR INFARCTION

Although transient hypotension is common in patients with RV infarction and inferior MI (Chap. 34), persistent

CS caused by RV failure accounts for only 3% of CS complicating MI. The salient features of RV shock are absence of pulmonary congestion, high right atrial pressure (which may be seen only after volume loading), RV dilatation and dysfunction, only mildly or moderately depressed LV function, and predominance of single-vessel proximal right coronary artery occlusion. Management includes IV fluid administration to optimize right atrial pressure (10–15 mmHg); avoidance of excess fluids, which cause a shift of the interventricular septum into the LV; sympathomimetic amines; IABP; and the early reestablishment of infarct–artery flow.

MITRAL REGURGITATION

(See also Chap. 34) Acute severe MR caused by papillary muscle dysfunction or rupture may complicate MI and result in CS, pulmonary edema, or both. This complication most often occurs on the first day, with a second peak several days later. The diagnosis is confirmed by echo-Doppler. Rapid stabilization with IABP is recommended, with administration of dobutamine as needed to increase cardiac output. Reducing the load against which the LV pumps (afterload) reduces the volume of regurgitant flow of blood into the left atrium. Mitral valve surgery is the definitive therapy and should be performed early in the course in suitable candidates.

VENTRICULAR SEPTAL RUPTURE

(See also Chap. 34) Echo-Doppler demonstrates shunting of blood from the left to the right ventricle and may visualize the opening in the interventricular septum. Timing and management are similar to that for MR with IABP support and surgical correction for suitable candidates.

FREE WALL RUPTURE

Myocardial rupture is a dramatic complication of STEMI that is most likely to occur during the first week after the onset of symptoms; its frequency increases with the age of the patient. First infarction, a history of hypertension, no history of angina pectoris, and a relatively large Q-wave infarct are associated with a higher incidence of cardiac rupture. The clinical presentation typically is a sudden loss of pulse, blood pressure, and consciousness but sinus rhythm on ECG (pulseless electrical activity). The myocardium continues to contract, but forward flow is not maintained as blood escapes into the pericardium. Cardiac tamponade ensues, and closed-chest massage is ineffective. This condition is almost universally fatal, although dramatic cases of urgent pericardiocentesis followed by successful surgical repair have been reported. Free wall rupture may also result in subacute tamponade when the pericardium temporarily seals the rupture sites. Definitive surgical repair is required.

ACUTE FULMINANT MYOCARDITIS

Myocarditis can mimic acute MI with ST deviation or bundle branch block on the ECG and marked elevation of cardiac markers. Acute myocarditis causes CS in ~15% of cases. These patients are typically younger than those with CS caused by acute MI and often do not have typical ischemic chest pain. Echocardiography usually shows global LV dysfunction. Initial management is the same as for CS complicating acute MI (see Fig. 31-2) but of course does not involve coronary revascularization.

PULMONARY EDEMA

The etiologies and pathophysiology of pulmonary edema are discussed in Chap. 2.

Diagnosis

Acute pulmonary edema usually presents with the rapid onset of dyspnea at rest, tachypnea, tachycardia, and severe hypoxemia. Rales and wheezing caused by airway compression from peribronchial cuffing may be audible. Hypertension is usually present because of release of endogenous catecholamines.

It is often difficult to distinguish between cardiogenic and noncardiogenic causes of acute pulmonary edema. *Echocardiography* may identify systolic and diastolic ventricular dysfunction and valvular lesions. Pulmonary edema associated with electrocardiographic ST elevation and evolving Q waves is usually diagnostic of acute MI and should prompt immediate institution of MI protocols and coronary artery reperfusion therapy (Chap. 34). Brain natriuretic peptide levels, when substantially elevated, support heart failure as the cause of acute dyspnea with pulmonary edema.

The use of a *Swan-Ganz catheter* permits measurement of PCWP and helps differentiate between high pressure (cardiogenic) and normal pressure (noncardiogenic) causes of pulmonary edema. Pulmonary artery catheterization is indicated when the cause of the pulmonary edema is uncertain, when it is refractory to therapy, or when it is accompanied by hypotension. Data derived from use of a catheter often alter the treatment plan, but an impact on mortality has not been demonstrated.

Rx Treatment: PULMONARY EDEMA

The treatment of patients with pulmonary edema depends on the specific cause. Given the acute, life-threatening nature of the condition, a number of measures must be applied immediately to support the circulation, gas exchange, and lung mechanics. In addition,

conditions that frequently complicate pulmonary edema, such as infection, acidemia, anemia, and renal failure, must be corrected.

SUPPORT OF OXYGENATION AND VENTILATION Patients with acute cardiogenic pulmonary edema generally have an identifiable cause of acute LV failure such as arrhythmia, ischemia or infarction, or myocardial decompensation that can be rapidly treated, with improvement in gas exchange. In contrast, noncardiogenic edema usually resolves much less quickly, and most patients require mechanical ventilation.

Oxygen Therapy Support of oxygenation is essential to ensure adequate O₂ delivery to peripheral tissues, including the heart.

Positive-Pressure Ventilation Pulmonary edema increases the work of breathing and the O₂ requirements of this work and may pose a significant physiologic stress on the heart. For patients with inadequate oxygenation or ventilation despite supplemental O₂, assisted ventilation by face or nasal mask or by endotracheal intubation should be initiated. Continuous or Bi-PAP (Chap. 27) can rest the respiratory muscles, improve oxygenation and cardiac function, and reduce the need for intubation. In refractory cases, mechanical ventilation can relieve the work of breathing more completely than noninvasive ventilation. Mechanical ventilation with positive end-expiratory pressure can have multiple beneficial effects on pulmonary edema: (1) it can decrease both preload and afterload, thereby improving cardiac function; (2) it can redistribute lung water from the intraalveolar to the extraalveolar space, where the fluid does not interfere as much with gas exchange; and (3) it can increase lung volume to avoid atelectasis.

REDUCTION OF PRELOAD In most forms of pulmonary edema, the quantity of extravascular lung water is related to both the PCWP and the intravascular volume status.

Diuretics The “loop diuretics” furosemide, bumetanide, and torsemide are effective in most forms of pulmonary edema, even in the presence of hypoalbuminemia, hyponatremia, or hypochloremia. Furosemide is also a venodilator that can reduce preload rapidly before any diuresis and is the diuretic of choice. The initial dose of furosemide should be ≤0.5 mg/kg, but a higher dose (1 mg/kg) is required in patients with renal insufficiency, chronic diuretic use, or hypervolemia or after failure of a lower dose.

Nitrates Nitroglycerin and isosorbide dinitrate act predominantly as venodilators, with coronary vasodilating properties as well. They are rapid in onset and effective when administered by a variety of routes. Sublingual nitroglycerin (0.4 mg × 3 every 5 min) is first-line therapy for patients with acute cardiogenic pulmonary edema.

If pulmonary edema persists in the absence of hypotension, sublingual may be followed by IV nitroglycerin, commencing at 5–10 µg/min. IV nitroprusside (0.1–5 µg/kg/per min) is a potent venous and arterial vasodilator. It is useful for patients with pulmonary edema and hypertension but is not recommended in states of reduced coronary artery perfusion. It requires close monitoring and titration, including the use of an arterial catheter for continuous BP measurement in the intensive care unit.

Morphine Given in 2- to 4-mg IV boluses, morphine is a transient venodilator that reduces preload while relieving dyspnea and anxiety. These effects can diminish stress, catecholamine levels, tachycardia, and ventricular afterload in patients with pulmonary edema and systemic hypertension.

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors reduce both afterload and preload and are recommended in patients with hypertension. A low dose of a short-acting agent may be initiated and followed by increasing oral doses. In acute MI with heart failure, ACE inhibitors reduce short- and long-term mortality.

Other Preload-Reducing Agents IV recombinant brain natriuretic peptide (nesiritide) is a potent vasodilator with diuretic properties and is effective in the treatment of patients with cardiogenic pulmonary edema. It should be reserved for refractory patients and is not recommended in the setting of ischemia or MI.

Physical Methods Reduction of venous return reduces preload. Patients without hypotension should be maintained in the sitting position with the legs dangling along the side of the bed.

Inotropic and Inodilator Drugs The sympathomimetic amines dopamine and dobutamine (see earlier) are potent inotropic agents. The bipyridine phosphodiesterase-3 inhibitors (inodilators), such as milrinone (50 µg/kg followed by 0.25–0.75 µg/kg per min), stimulate myocardial contractility while promoting peripheral and pulmonary vasodilation. Such agents are indicated in patients with cardiogenic pulmonary edema and severe LV dysfunction.

Digitalis Glycosides Once a mainstay of treatment because of their positive inotropic action, digitalis glycosides are rarely used at present. However, they may be useful for control of the ventricular rate in patients with rapid atrial fibrillation or flutter and LV dysfunction because they do not have the negative inotropic effects of other drugs that inhibit atrioventricular (AV) nodal conduction.

Intraaortic Counterpulsation IABP may help to relieve cardiogenic pulmonary edema. It is indicated as a stabilizing measure when acute severe MR or VSR

causes refractory pulmonary edema, especially in preparation for surgical repair. IABP or LV-assist devices are useful as bridging therapy to cardiac transplantation in patients with refractory pulmonary edema secondary to myocarditis or cardiomyopathy.

Treatment of Tachyarrhythmias and Atrial-Ventricular Resynchronization

Sinus tachycardia or atrial fibrillation can result from elevated left atrial pressure and sympathetic stimulation. Tachycardia itself can also limit LV filling time and further increase left atrial pressure. Although relief of pulmonary congestion slows the sinus rate or ventricular response in atrial fibrillation, a primary tachyarrhythmia may require cardioversion. In patients with reduced LV function and without atrial contraction or with lack of synchronized AV contraction, placement of an AV sequential pacemaker should be considered.

Stimulation of Alveolar Fluid Clearance

Recent mechanistic studies on alveolar epithelial ion transport have defined a variety of ways to upregulate the clearance of solute and water from the alveolar space. In patients with acute lung injury (noncardiogenic pulmonary edema) IV β-adrenergic agonist treatment decreases extravascular lung water.

SPECIAL CONSIDERATIONS

The Risk of Iatrogenic Cardiogenic Shock

In the treatment of patients with pulmonary edema, vasodilators lower BP, and, particularly when used in combination, their use may lead to hypotension, coronary artery hypoperfusion, and shock (see Fig. 31-1). In general, patients with a *hypertensive* response to pulmonary edema tolerate and benefit from these medications. In normotensive patients, low doses of single agents should be instituted sequentially as needed.

Acute Coronary Syndromes

(See also Chap. 34) Acute STEMI complicated by pulmonary edema is associated with in-hospital mortality rates of 20–40%. After immediate stabilization, coronary artery blood flow must be reestablished rapidly. When available, primary PCI is preferable; alternatively, a fibrinolytic agent should be administered. Early coronary angiography and revascularization by PCI or CABG are also indicated for patients with non-ST elevation acute coronary syndrome. IABP use may be required to stabilize patients for coronary angiography if hypotension develops or for refractory pulmonary edema in patients with LV failure who are candidates for revascularization.

Unusual Types of Edema

Patients with specific causes of pulmonary edema may require particular therapy. Reexpansion pulmonary edema can develop after removal of air or fluid that has been in the pleural space for some time. These patients may develop hypotension or oliguria resulting from rapid fluid shifts into the lung.

In contrast to cardiogenic edema, diuretics and preload reduction are contraindicated, and intravascular volume repletion is often needed while oxygenation and gas exchange are supported.

High-altitude pulmonary edema can often be prevented with the use of dexamethasone, calcium channel-blocking drugs, or long-acting inhaled β_2 -adrenergic agonists. Treatment includes descent from altitude; bed rest; oxygen; and, if feasible, inhaled nitric oxide; nifedipine may also be effective.

For pulmonary edema resulting from upper airway obstruction, recognition of the obstructing cause is key because treatment then is to relieve or bypass the obstruction.

FURTHER READINGS

- ANTMAN EM: Treatment of ST elevation myocardial infarction, in *Braunwald's Heart Disease*, 8th ed, P Libby et al (eds). Philadelphia, Saunders, 2008
- et al: ACC/AHA Guidelines for the management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on Management of Acute Myocardial Infarction). *J Am Coll Cardiol* 44:671, 2004
- BABAIEV A et al for the NRMII Investigators: National guidelines and trends in management of patients with acute myocardial infarction complicated by cardiogenic shock: Observations from the National Registry of Myocardial Infarction. *J Am Med Assoc* 294:448, 2005
- GOLDBERG RJ et al: Thirty-year trends (1975 to 2005) in the magnitude of, management of, and hospital death rates associated with cardiogenic shock in patients with acute myocardial infarction: A population-based perspective. *Circulation* 119:1211, 2009
- HOCHMAN JS: Cardiogenic shock complicating acute myocardial infarction: Expanding the paradigm. *Circulation* 107:2998, 2003
- , Ohman EM: *Cardiogenic Shock, American Heart Association Clinical Series*, E. Antman (ed). New York, Wiley-Blackwell, 2008
- et al: Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. *JAMA* 295:2511, 2006
- MATTHAY MA, INGBAR DH (eds): *Pulmonary Edema. Lung Biology in Health and Disease*, vol 116. New York, Marcel Dekker, 1998
- OKUDA M: A multidisciplinary overview of cardiogenic shock. *Shock* 25:557, 2006
- REYNOLDS HR, HOCHMAN JS: Cardiogenic shock: Current concepts and improving outcomes. *Circulation* 117:686, 2008
- WARE LB, MATTHAY MA: Clinical practice: Acute pulmonary edema. *N Engl J Med* 353(26):2788, 2005



CHAPTER 32

CARDIOVASCULAR COLLAPSE, CARDIAC ARREST, AND SUDDEN CARDIAC DEATH

Robert J. Myerburg ■ Agustin Castellanos

■ Overview and Definitions	306
Clinical Definition of Forms of Cardiovascular Collapse	307
■ Etiology, Initiating Events, and Clinical Epidemiology	307
Pathology	308
■ Prediction and Prevention of Cardiac Arrest and Sudden Cardiac Death	308
■ Clinical Characteristics of Cardiac Arrest	311
Prodrome, Onset, Arrest, and Death	311
■ Prevention of Sudden Cardiac Death in High-Risk Individuals without Prior Cardiac Arrest	315
■ Further Readings	315

OVERVIEW AND DEFINITIONS

The vast majority of naturally occurring sudden deaths are caused by cardiac disorders. The magnitude of sudden cardiac death (SCD) as a public health problem is highlighted by the estimate that ~50% of all cardiac deaths are sudden and unexpected, at least two-thirds of which are first cardiac events or occur among population subsets with previously known heart disease considered to be relatively low risk. The total SCD burden is estimated to range from <200,000 to >450,000 deaths each year in the United States. SCD is a direct consequence of cardiac arrest, which may be reversible if responded to promptly. Because resuscitation techniques and emergency rescue systems are available to respond to victims of out-of-hospital cardiac arrest, which was uniformly fatal in the past, understanding the SCD problem has practical importance.

SCD must be defined carefully. In the context of time, “sudden” is defined, for most clinical and epidemiologic purposes, as 1 h or less between a change in clinical status heralding the onset of the terminal clinical event and the cardiac arrest itself. An exception is unwitnessed deaths in which pathologists may expand the definition of time to 24 h after the victim was last seen to be alive and stable.

Because of community-based interventions, victims may remain biologically alive for days or even weeks after a cardiac arrest that has resulted in irreversible central nervous system (CNS) damage. Confusion in terms can be avoided by adhering strictly to definitions of cardiovascular collapse, cardiac arrest, and death (**Table 32-1**). Death is biologically, legally, and literally an absolute and irreversible event. Death may be delayed in a survivor of cardiac arrest, but “survival after sudden death” is an irrational term. A generally accepted definition of SCD is *natural death due to cardiac causes* heralded by abrupt loss of consciousness within 1 hour of the onset of acute symptoms in an individual who may have known *preexisting* heart disease but in whom the *time* and *mode* of death are *unexpected*. When biologic death of the cardiac arrest victim is delayed because of interventions, the relevant pathophysiologic event remains the sudden and unexpected cardiac arrest that leads ultimately to death even though it is delayed by artificial methods. The language used should reflect the fact that the index event was a cardiac arrest and that death was due to its delayed consequences. Accordingly, for statistical purposes, deaths that occur during hospitalization or within 30 days after resuscitated cardiac arrest are counted as sudden deaths.

TABLE 32-1

DISTINCTION BETWEEN CARDIOVASCULAR COLLAPSE, CARDIAC ARREST, AND DEATH

TERM	DEFINITION	QUALIFIERS OR EXCEPTIONS
Cardiovascular collapse	A sudden loss of effective blood flow because of cardiac or peripheral vascular factors that may reverse spontaneously (e.g., neurocardiogenic syncope; vasovagal syncope) or only with interventions (e.g., cardiac arrest)	Nonspecific term that includes cardiac arrest and its consequences as well as events that characteristically revert spontaneously
Cardiac arrest	Abrupt cessation of cardiac pump function that may be reversible by a prompt intervention but will lead to death in its absence	Rare spontaneous reversions; the likelihood of successful interventions relates to mechanism of arrest, clinical setting, and prompt return of circulation
Death	Irreversible cessation of all biologic functions	None

CLINICAL DEFINITION OF FORMS OF CARDIOVASCULAR COLLAPSE

Cardiovascular collapse is a general term connoting loss of effective blood flow caused by acute dysfunction of the heart, peripheral vasculature, or both. Cardiovascular collapse may be caused by vasodepressor syncope (vasovagal syncope, postural hypotension with syncope, neurocardiogenic syncope), a transient severe bradycardia, or cardiac arrest. The latter is distinguished from the transient forms of cardiovascular collapse in that it usually requires an intervention to achieve resuscitation. In contrast, vasodepressor syncope and other primary bradyarrhythmic syncopal events are transient and non-life-threatening events with a spontaneous return of consciousness.

The most common electrical mechanism for cardiac arrest is ventricular fibrillation (VF), which is responsible for 50–80% of cardiac arrests. Severe persistent bradyarrhythmias, asystole, and pulseless electrical activity (PEA; an organized electrical activity without mechanical response, formerly called *electromechanical dissociation*) cause another 20–30% of cardiac arrests. Pulseless sustained ventricular tachycardia (VT) is a less common mechanism. Acute low cardiac output states, having precipitous onset, may also present clinically as a cardiac arrest. These hemodynamic causes include massive acute pulmonary emboli, internal blood loss from ruptured aortic aneurysm, intense anaphylaxis, and cardiac rupture with tamponade after myocardial infarction (MI).

ETIOLOGY, INITIATING EVENTS, AND CLINICAL EPIDEMIOLOGY

Clinical and epidemiologic studies have identified population subgroups at high risk for SCD. In addition, a large body of pathologic data provides information on the underlying *structural abnormalities* in victims of SCD, and studies of clinical physiology have begun to identify a group of *transient functional factors* that may convert a

long-standing underlying structural abnormality from a stable to an unstable state ([Table 32-2](#)).

Cardiac disorders constitute the most common causes of sudden *natural* death. After an initial peak incidence of sudden death between birth and 6 months of age (sudden infant death syndrome), the incidence of sudden death declines sharply and remains low through childhood and adolescence. Among adolescents and young adults, the incidence of SCD is ~1 per 100,000 population per year. The incidence begins to increase in adults older than 30 years of age, reaching a second peak in the age range of 45–75 years, when the incidence approximates one to two per 1000 per year among the unselected adult population. Increasing age within this range is associated with increasing risk for sudden *cardiac* death ([Fig. 32-1A](#)). From 1 to 13 years of age, only one of five sudden *natural* deaths is attributable to cardiac causes. Between 14 and 21 years of age, the proportion increases to 30% and then to 88% in middle-aged and elderly individuals.

Young and middle-aged men and women have different susceptibilities to SCD, but the gender differences decrease with advancing age. The difference in risk for SCD parallels the differences in age-related risks for other manifestations of coronary heart disease (CHD) between men and women. As the gender gap for manifestations of CHD closes in the sixth to eighth decades of life, the excess risk of SCD in men progressively narrows. Despite the lower incidence among younger women, coronary risk factors such as cigarette smoking, diabetes, hyperlipidemia, and hypertension are highly influential, and SCD remains an important clinical and epidemiologic problem. The incidence of SCD among the African-American population appears to be higher than among the white population; the reasons remain uncertain.

Genetic factors contribute to the risk of SCD. In one sense, they contribute to familial predisposition to CHD and its expression as acute coronary syndromes. In addition, however, data suggest a familial predisposition to SCD as a specific form of expression of CHD. A strong parental

CAUSES OF CARDIAC ARREST AND SUDDEN CARDIAC DEATH**Structural Causes**

- I. Coronary heart disease
 - A. Coronary artery abnormalities
 1. Chronic atherosclerotic lesions
 2. Acute (active) lesions (plaque fissuring, platelet aggregation, acute thrombosis)
 3. Anomalous coronary artery anatomy
 - B. Myocardial infarction
 1. Healed
 2. Acute
- II. Myocardial hypertrophy
 - A. Secondary
 - B. Hypertrophic cardiomyopathy
 1. Obstructive
 2. Nonobstructive
- III. Dilated cardiomyopathy—primary muscle disease
- IV. Inflammatory and infiltrative disorders
 - A. Myocarditis
 - B. Noninfectious inflammatory diseases
 - C. Infiltrative diseases
 - D. Right ventricular dysplasia
- V. Valvular heart disease
- VI. Electrophysiologic abnormalities, structural
 - A. Anomalous pathways in Wolff-Parkinson-White syndrome
 - B. Conducting system disease
- VII. Inherited disorders of molecular structure associated with electrophysiologic abnormalities (e.g., congenital long QT syndromes, Brugada syndrome)

Functional Contributing Factors

- I. Alterations of coronary blood flow
 - A. Transient ischemia
 - B. Reperfusion after ischemia
- II. Low cardiac output states
 - A. Heart failure
 1. Chronic
 2. Acute decompensation
 - B. Shock
- III. Systemic metabolic abnormalities
 - A. Electrolyte imbalance (e.g., hypokalemia)
 - B. Hypoxemia, acidosis
- IV. Neurophysiologic disturbances
 - A. Autonomic fluctuations: central, neural, humoral
 - B. Receptor function
- V. Toxic responses
 - A. Proarrhythmic drug effects
 - B. Cardiac toxins (e.g., cocaine, digitalis intoxication)
 - C. Drug interactions

history of SCD as an initial coronary event increases the probability of a similar expression in the offspring. In a few syndromes, such as hypertrophic cardiomyopathy, congenital long QT interval syndromes, right ventricular dysplasia, and the syndrome of right bundle branch block and

nonischemic ST-segment elevations (Brugada syndrome), there is a specific inherited risk of SCD.

The structural causes of and functional factors contributing to the SCD syndrome are listed in Table 32-2. Worldwide, and especially in Western cultures, coronary atherosclerotic heart disease is the most common structural abnormality associated with SCD in middle-aged and older adults. Up to 80% of all SCDs in the United States are due to the consequences of coronary atherosclerosis. The cardiomyopathies (dilated and hypertrophic, collectively) account for another 10–15% of SCDs, and all the remaining diverse etiologies cause only 5–10% of all SCDs. The inherited arrhythmia syndromes (see earlier and **Table 32-2**) are more common causes in adolescents and young adults. For some of these syndromes, such as hypertrophic cardiomyopathy, the risk of SCD begins to increase after puberty.

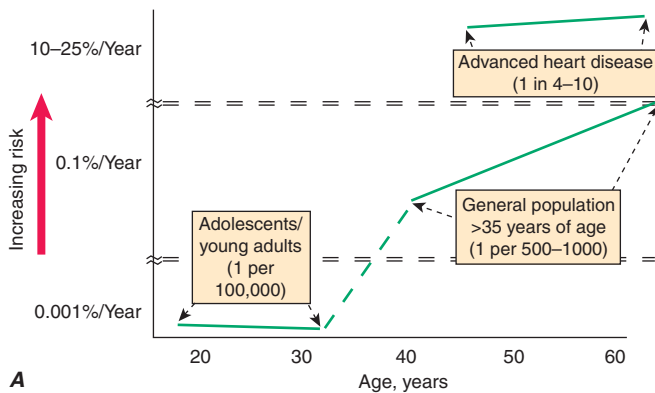
Transient ischemia in a previously scarred or hypertrophied heart, hemodynamic and fluid and electrolyte disturbances, fluctuations in autonomic nervous system activity, and transient electrophysiologic changes caused by drugs or other chemicals (e.g., proarrhythmia) have all been implicated as mechanisms responsible for the transition from electrophysiologic stability to instability. In addition, reperfusion of ischemic myocardium may cause transient electrophysiologic instability and arrhythmias.

PATHOLOGY

Data from postmortem examinations of SCD victims parallel the clinical observations on the prevalence of CHD as the major structural etiologic factor. More than 80% of SCD victims have pathologic findings of CHD. The pathologic description often includes a combination of long-standing, extensive atherosclerosis of the epicardial coronary arteries and unstable coronary artery lesions, which include various permutations of fissured or ruptured plaques, platelet aggregates, hemorrhage, or thrombosis. As many as 70–75% of men who die suddenly have preexisting healed MIs, but only 20–30% have recent acute MIs despite the prevalence of unstable plaques and thrombi. The latter suggests transient ischemia as the mechanism of onset. Regional or global left ventricular (LV) hypertrophy often coexists with prior MIs.

PREDICTION AND PREVENTION OF CARDIAC ARREST AND SUDDEN CARDIAC DEATH

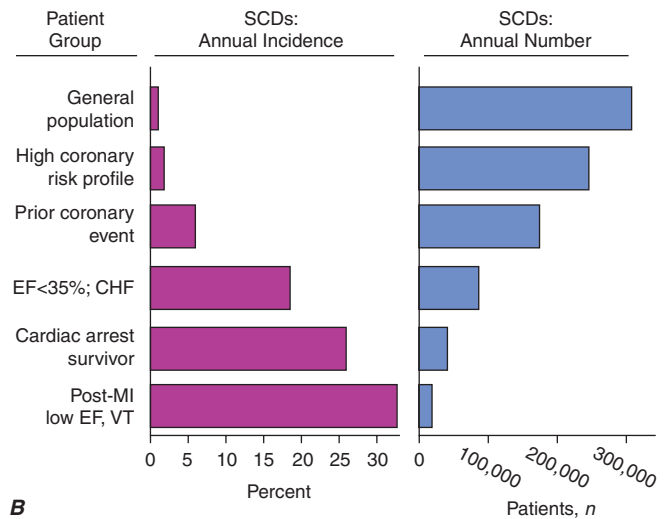
SCD accounts for ~50% the total cardiovascular mortality rate. As shown in **Fig. 32-1B**, the very-high-risk subgroups provide more focused populations (“percent per year”) for predicting cardiac arrest or SCD; but the impact of such subgroups on the overall problem of SCD, indicated by the absolute number of events (“events per



A **FIGURE 32-1**

Panel A demonstrates age-related risk for sudden cardiac death (SCD). For the general population age 35 years and older, the risk of SCD is 0.1–0.2% per year (one per 500–1000 population). Among the general population of adolescents and adults younger than the age of 30 years, the overall risk of SCD is one per 100,000 population, or 0.001% per year. The risk of SCD increases dramatically after age 35 years. The greatest rate of increase is between 40 and 65 years of age (vertical axis is discontinuous). Among patients older than 30 years of age with advanced structural heart disease and markers of high risk for cardiac arrest, the event rate may exceed 25% per year, and age-related risk attenuates.

Panel B demonstrates the incidence of SCD in population subgroups and the relation of total number of events per year to incidence figures. Approximations of subgroup incidence figures and the related population pool from which they are derived are presented. Approximately 50% of all



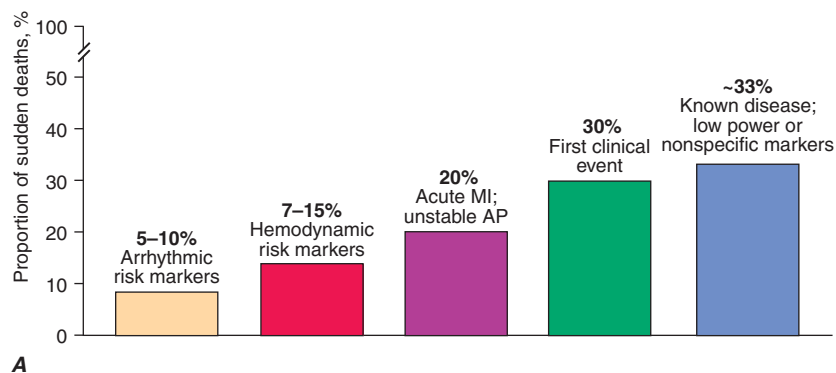
B

cardiac deaths are sudden and unexpected. The incidence triangle on the left (“percent/year”) indicates the approximate percentage of sudden and nonsudden deaths in each of the population subgroups indicated, ranging from the lowest percentage in unselected adult populations (0.1–2% per year) to the highest percentage in patients with ventricular tachycardia (VT) or ventricular fibrillation (VF) during convalescence after a myocardial infarction (MI), ~50% per year. The triangle on the right indicates the total number of events per year in each of these groups, to reflect incidence in context with the size of the population subgroups. The highest risk categories identify the smallest number of total annual events, and the lowest incidence category accounts for the largest number of events per year. CHF, congestive heart failure; EF, ejection fraction. [Adapted from RJ Myerburg et al, *Circulation* 85(Suppl 1):2, 1992. Reproduced with permission of the American Heart Association.]

year”), is relatively small. The requirements for achieving a major population impact are effective prevention of underlying diseases or new epidemiologic probes that will allow better resolution of subgroups at specific risk within the large general populations.

Strategies for predicting and preventing SCD are categorized as primary and secondary, in addition to responses intended to abort cardiac arrests. *Primary prevention*, as defined in various implantable defibrillator trials, refers to the attempt to identify individual patients at specific risk for SCD and institute preventive strategies. *Secondary prevention* refers to measures taken to prevent recurrent cardiac arrest or death in individuals who have survived a previous cardiac arrest. The primary prevention strategies currently used depend on the magnitude of risk among the various population subgroups. Because the annual incidence of SCD among the unselected adult population is limited to 1–2 per 1000 population per year (Fig. 32-1) and more than 30% of all SCDs attributable to coronary

artery disease occur as the first clinical manifestation of the disease (Fig. 32-2A), the only practical strategies are profiling for risk of developing CHD and risk factor control (Fig. 32-2B). The most powerful long-term risk factors include age, cigarette smoking, elevated serum cholesterol, diabetes mellitus, elevated blood pressure, LV hypertrophy, and nonspecific electrocardiographic (ECG) abnormalities. Markers of inflammation (e.g., C-reactive protein levels) that may predict plaque destabilization have been added to risk classifications. The presence of multiple risk factors progressively increases incidence but not sufficiently or specifically enough to warrant therapies targeted to potentially fatal arrhythmias (Fig. 32-1A). However, recent studies offer the hope that genetic markers for specific risk may become available. These studies suggest that a family history of SCD associated with acute coronary syndromes predicts a higher likelihood of cardiac arrest as the initial manifestation of coronary artery disease in first-degree family members.



A

Target	Examples	Goal	Sensitivity
<ul style="list-style-type: none"> • ASHD risk factors • Anatomic screening • Clinical markers 	<ul style="list-style-type: none"> • Framingham risk index • Electron beam tomography • EF; angiography 	<ul style="list-style-type: none"> • Predict evolution of disease • Identify CAD • Define extent of disease 	<ul style="list-style-type: none"> • Very low • Very low • Variable; extent of disease; low specificity
<ul style="list-style-type: none"> • Transient risk predictors 	<ul style="list-style-type: none"> • EPS • EPS combined with EF • T-wave alternans; QT dispersions • Pathophysiologic controls (e.g., HRV) • Inflammatory markers 	<ul style="list-style-type: none"> • Identify arrhythmia markers • Define high-risk groups • ECG markers of risk 	<ul style="list-style-type: none"> • Low to intermediate for screening • High for specific groups • Primary predictive value unknown
<ul style="list-style-type: none"> • Individual risk predictors 	<ul style="list-style-type: none"> • Familial or genetic profiles 	<ul style="list-style-type: none"> • Quantify autonomic regulation • Predict unstable plaques • Predict specific SCD risk before disease expression 	<ul style="list-style-type: none"> • Uncertain; some measures useful • Unknown; potentially high • High potential for future profiling

B

FIGURE 32-2

Population subsets, risk predictors, and distribution of sudden cardiac deaths (SCDs) according to clinical circumstances.

A. The population subset with high-risk arrhythmia markers in conjunction with low ejection fraction (EF) is a group at high risk of SCD but accounts for <10% of the total SCD burden attributable to coronary artery disease. In contrast, nearly two-thirds of all SCD victims present with SCD as the first and only manifestation of underlying disease or have known disease but are considered at relatively low risk because of the absence of high-risk markers. **B.** Risk profile for prediction and prevention of SCD is difficult. The highest

absolute numbers of events occur among the general population who may have risk factors for coronary heart disease or expressions of disease that do not predict high risk. This results in a low sensitivity for predicting and preventing SCD. New approaches that include epidemiologic modeling of transient risk factors and methods of predicting individual patient risk offer hope for greater sensitivity in the future. AP, angina pectoris; ASHD, arteriosclerotic heart disease; CAD, coronary artery disease; ECG, electrocardiographic; EPS, electrophysiologic study; HRV, heart rate variability. (From Myerburg, reproduced with permission of the publisher.)

After coronary artery disease has been identified in a patient, additional strategies for risk profiling become available (Fig. 32-2B), but the majority of SCDs occur among the large unselected groups rather than in the specific high-risk subgroups that become evident among populations with established disease (compare events per year with percent per year in Fig. 32-1B). Under most conditions of higher level of risk, particularly those indexed to a major recent cardiovascular event (e.g., MI, recent onset of heart failure, survival after out-of-hospital cardiac arrest), the highest risk of death occurs during the initial 6–18 months and then plateaus toward the baseline risk of the underlying disease. However, many of the early deaths are nonsudden, diluting the potential benefit of strategies targeted specifically to SCD. Thus,

even though post-MI β -blocker therapy has an identifiable benefit for both early SCD and nonsudden mortality risk, a total mortality benefit for ICD therapy early after MI has not been observed.

Among patients in the acute, convalescent, and chronic phases of MI (Chap. 34), subgroups at high absolute risk of SCD can be identified. During the acute phase, the potential risk of cardiac arrest from onset through the first 48 h may be as high as 15%, emphasizing the importance for patients to respond promptly to the onset of symptoms. Those who survive acute-phase VF, however, are not at continuing risk for recurrent cardiac arrest indexed to that event. During the convalescent phase after MI (3 days to ~6 weeks), an episode of sustained VT or VF, associated with a large infarct, predicts a natural history mortality risk

of up to 50% at 12 months. At least 50% of the deaths are sudden. Aggressive intervention techniques may reduce this incidence.

After passage into the chronic phase of MI, the longer-term risk for total and SCD mortality is predicted by a number of factors (Fig. 32-2B). The most important for both SCD and nonsudden death is the extent of myocardial damage sustained as a result of the acute MI. This is measured by the magnitude of reduction of the ejection fraction (EF), functional capacity, or the occurrence of heart failure. Various studies have demonstrated that ventricular arrhythmias identified by ambulatory monitoring contribute significantly to this risk, especially in patients with an EF <40%. In addition, inducibility of VT or VF during electrophysiologic testing of patients who have ambient ventricular arrhythmias [premature ventricular contractions (PVCs) and nonsustained VT] and an EF <35 or 40% is a strong predictor of SCD risk. Patients in this subgroup are now considered candidates for implantable cardioverter defibrillators (ICDs) (see later). Risk falls off sharply with EFs >40% after MI and the absence of ambient arrhythmias and conversely is high with EFs <30% even without the ambient arrhythmia markers.

The cardiomyopathies (dilated and hypertrophic) are the second most common category of diseases associated with risk of SCD after CHD (Table 32-2). Some risk factors have been identified, largely related to extent of disease, documented ventricular arrhythmias, and symptoms of arrhythmias (e.g., unexplained syncope). The less common causes of SCD include valvular heart disease (primarily aortic) and inflammatory and infiltrative disorders of the myocardium. The latter include viral myocarditis, sarcoidosis, and amyloidosis.

Among adolescents and young adults, rare inherited disorders, such as hypertrophic cardiomyopathy, the long QT interval syndromes, right ventricular dysplasia, and the Brugada syndrome, have received attention as important causes of SCD because of advances in genetics and the ability to identify some individuals at risk before a fatal event. The subgroup of young competitive athletes has received special attention. The incidence of SCD among athletes appears to be higher than the general adolescent and young adult population, perhaps up to one in 75,000. Hypertrophic cardiomyopathy is the most common cause in the United States compared with Italy, where more comprehensive screening programs remove potential victims from the population of athletes.

Secondary prevention strategies should be applied to surviving victims of a cardiac arrest that was not associated with an acute MI or a transient risk of SCD (e.g., drug exposures, correctable electrolyte imbalances). Multivessel coronary artery disease or dilated cardiomyopathy with left ventricular EF <40% or the presences of life-threatening arrhythmias with long QT syndromes or right ventricular dysplasia predict a

1- to 2-year risk of recurrence of a SCD or cardiac arrest of up to 30% in the absence of specific interventions (see below).

CLINICAL CHARACTERISTICS OF CARDIAC ARREST

PRODROME, ONSET, ARREST, AND DEATH

SCD may be presaged by days, weeks, or months of increasing angina, dyspnea, palpitations, easy fatigability, and other nonspecific complaints. However, these *prodromal complaints* are generally predictive of any major cardiac event; they are not specific for predicting SCD.

The *onset of the clinical transition*, leading to cardiac arrest, is defined as an acute change in cardiovascular status preceding cardiac arrest by up to 1 h. When the onset is instantaneous or abrupt, the probability that the arrest is cardiac in origin is >95%. Continuous ECG recordings, fortuitously obtained at the onset of a cardiac arrest, commonly demonstrate changes in cardiac electrical activity during the minutes or hours before the event. There is a tendency for the heart rate to increase and for advanced grades of PVCs to evolve. Most cardiac arrests that are caused by VF begin with a run of sustained or nonsustained VT, which then degenerates into VF.

The probability of achieving successful resuscitation from cardiac arrest is related to the interval from onset to institution of resuscitative efforts, the setting in which the event occurs, the mechanism (VF/VT, pulseless electrical activity, asystole), and the clinical status of the patient before the cardiac arrest. Return of circulation and survival rates as a result of defibrillation decrease linearly from the first minute to 10 min. By 5 min, survival rates are no better than 25–30% in out-of-hospital settings. Settings in which it is possible to institute prompt cardiopulmonary resuscitation (CPR) with rapid defibrillation of VF provide a better chance of a successful outcome. However, the outcome in intensive care units (ICUs) and other in-hospital environments is heavily influenced by the patient's preceding clinical status. The immediate outcome is good for cardiac arrest occurring in the ICU in the presence of an acute cardiac event or transient metabolic disturbance, but survival among patients with far-advanced chronic cardiac disease or advanced noncardiac diseases (e.g., renal failure, pneumonia, sepsis, diabetes, cancer) is low and not much more successful in the in-hospital than in the out-of-hospital setting.

The success rate for initial resuscitation and survival to hospital discharge after an out-of-hospital cardiac arrest depends heavily on the mechanism of the event. When the mechanism is VT, the outcome is best; VF is the next most successful; and asystole and pulseless electrical activity (PEA) generate dismal outcome statistics. Advanced age also adversely influences the chances of successful resuscitation.

Progression to biologic death is a function of the mechanism of cardiac arrest and the length of the delay before interventions. VF or asystole without CPR within the first 4–6 min has a poor outcome even if defibrillation is successful because of superimposed brain damage; there are few survivors among patients who had no life support activities for the first 8 min after onset. Outcome statistics are improved by lay bystander intervention (basic life support; see below) before definitive interventions (advanced life support), and even more by early defibrillation. In regard to the latter, evaluations of deployment of automatic external defibrillators (AEDs) in communities (e.g., police vehicles, large buildings, airports, and stadiums) are beginning to generate encouraging data. Increased deployment is to be encouraged.

Death during the hospitalization after a successfully resuscitated cardiac arrest relates closely to the severity of CNS injury. Anoxic encephalopathy and infections subsequent to prolonged respirator dependence account for 60% of the deaths. Another 30% occur as a consequence of low cardiac output states that fail to respond to interventions. Recurrent arrhythmias are the least common cause of death, accounting for only 10% of in-hospital deaths.

In the setting of acute MI (Chap. 34), it is important to distinguish between primary and secondary cardiac arrests. *Primary cardiac arrests* refer to those that occur in the absence of hemodynamic instability, and *secondary cardiac arrests* are those that occur in patients in whom abnormal hemodynamics dominate the clinical picture before cardiac arrest. The success rate for immediate resuscitation in primary cardiac arrest during acute MI in a monitored setting should approach 100%. In contrast, as many as 70% of patients with secondary cardiac arrest succumb immediately or during the same hospitalization.

Rx Treatment: **CARDIAC ARREST**

An individual who collapses suddenly is managed in five stages: (1) the initial response and basic life support, (2) public access defibrillation (if available), (3) advanced life support, (4) postresuscitation care, and (5) long-term management. The initial response, including basic life support and public access defibrillation, can be carried out by physicians, nurses, paramedical personnel, or trained laypersons. There is a requirement for increasingly specialized skills as the patient moves through the stages of advanced life support, postresuscitation care, and long-term management.

INITIAL RESPONSE AND BASIC LIFE SUPPORT The initial evaluation will confirm whether a sudden collapse is indeed attributable to a cardiac arrest. Observations of the state of consciousness, respiratory

movements, skin color, and the presence or absence of pulses in the carotid or femoral arteries can promptly determine whether a life-threatening cardiac arrest has occurred. For lay responders, the pulse check is no longer recommended. As soon as a cardiac arrest is suspected, confirmed, or even considered to be impending, calling an emergency rescue system (e.g., 911) is the immediate priority. With the development of AEDs that are easily used by nonconventional emergency responders, an additional layer for response has evolved (see below).

Agonal respiratory movements may persist for a short time after the onset of cardiac arrest, but it is important to observe for severe stridor with a persistent pulse as a clue to aspiration of a foreign body or food. If this is suspected, the Heimlich maneuver (see below) may dislodge the obstructing body. A precordial blow, or “thump,” delivered firmly by the clenched fist to the junction of the middle and lower third of the sternum may occasionally revert VT or VF, but there is concern about converting VT to VF. Therefore, it is recommended to use precordial thumps as an advanced life support technique when monitoring and defibrillation are available. This conservative application of the technique remains controversial.

The third action during the initial response is to clear the airway. The head is tilted back and the chin lifted so that the oropharynx can be explored to clear the airway. Dentures or foreign bodies are removed, and the Heimlich maneuver is performed if there is reason to suspect that a foreign body is lodged in the oropharynx. If respiratory arrest precipitating cardiac arrest is suspected, a second precordial thump is delivered after the airway has been cleared.

Basic life support, more popularly known as CPR, is intended to maintain organ perfusion until definitive interventions can be instituted. The elements of CPR are the maintenance of ventilation of the lungs and compression of the chest. Mouth-to-mouth respiration may be used if no specific rescue equipment is immediately available (e.g., plastic oropharyngeal airways, esophageal obturators, masked Ambu bag). Conventional ventilation techniques during single-responder CPR require the lungs to be inflated twice in succession every 30 chest compressions.

Chest compression is based on the assumption that cardiac compression allows the heart to maintain a pump function by sequential filling and emptying of its chambers, with competent valves maintaining forward direction of flow. The palm of one hand is placed over the lower sternum, with the heel of the other resting on the dorsum of the lower hand. The sternum is depressed, with the arms remaining straight, at a rate of ~100 per minute. Sufficient force is applied to depress the sternum 4–5 cm, and relaxation is abrupt.

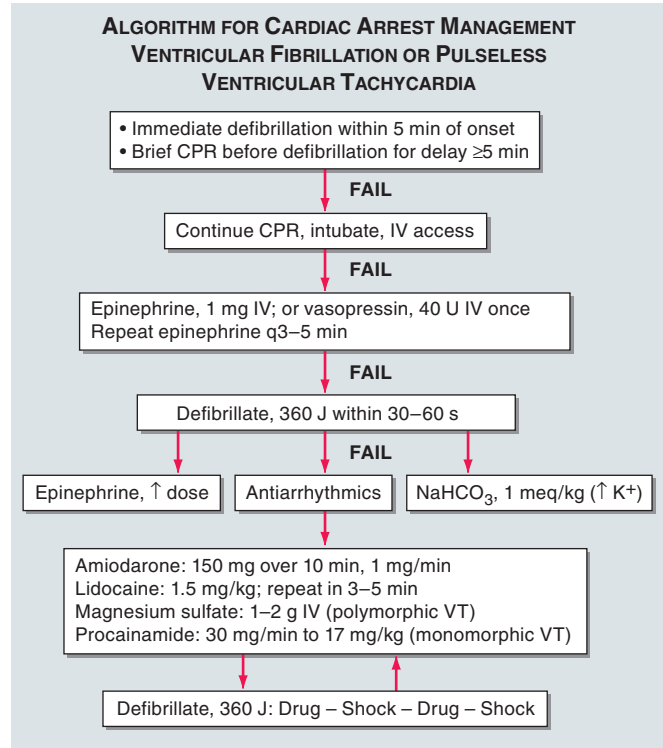
AUTOMATED EXTERNAL DEFIBRILLATION

AEDs that are easily used by nonconventional responders, such as nonparamedic firefighters, police, ambulance drivers, trained security guards, and minimally trained or untrained laypersons, have been developed. This advance has inserted another level of response into the cardiac arrest paradigm. A number of studies have demonstrated that AED use by nonconventional and lay responders in strategic response systems can improve cardiac arrest survival rates. This strategy is based on shortening the time to first defibrillation attempt while awaiting arrival of advanced life support.

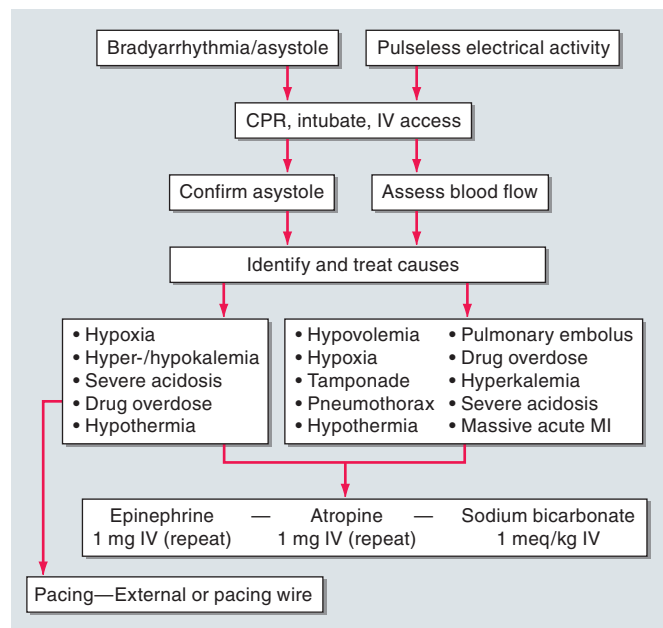
ADVANCED LIFE SUPPORT Advanced life support is intended to achieve adequate ventilation, control cardiac arrhythmias, stabilize blood pressure and cardiac output, and restore organ perfusion. The activities carried out to achieve these goals include (1) defibrillation/cardioversion, pacing, or both; (2) intubation with an endotracheal tube; and (3) insertion of an IV line. The speed with which defibrillation/cardioversion is carried out is an important element for successful resuscitation, both for restoration of spontaneous circulation and protection of the CNS. Immediate defibrillation should precede intubation and insertion of an IV line; CPR should be carried out while the defibrillator is being charged. As soon as a diagnosis of VF or VT is established, a shock of at least 300 J should be delivered. Additional shocks, up to a maximum of 360 J, are tried if the initial shock does not successfully abolish VT or VF, but it is now recommended that 60–90 s of CPR be carried out before repeated shocks if the first shock fails to restore an organized rhythm, or before the first shock if 5 min has elapsed between the onset of cardiac arrest and ability to deliver a shock. Epinephrine, 1 mg IV, is given after failed defibrillation, and attempts to defibrillate are repeated. The dose of epinephrine may be repeated after intervals of 3–5 min (Fig. 32-3A). Vasopressin (a single 40-U dose given IV) has been suggested as an alternative to epinephrine.

If the patient is less than fully conscious upon reversion or if two or three attempts fail, prompt intubation, ventilation, and arterial blood gas analysis should be carried out. Ventilation with O₂ (room air if O₂ is not immediately available) may promptly reverse hypoxemia and acidosis. A patient who is persistently acidotic after successful defibrillation and intubation should be given 1 meq/kg NaHCO₃ initially and an additional 50% of the dose repeated every 10–15 min. However, it should not be used routinely.

After initial unsuccessful defibrillation attempts or with persistent or recurrent electrical instability, antiarrhythmic therapy should be instituted. IV amiodarone has emerged as the initial treatment of choice (150 mg over 10 min followed by 1 mg/min for up to 6 h and 0.5 mg/min thereafter; Fig. 32-3A). For cardiac arrest



A



B

FIGURE 32-3

A. The algorithm of ventricular fibrillation or pulseless ventricular tachycardia (VT) begins with defibrillation attempts. If that fails, it is followed by administration of epinephrine and then antiarrhythmic drugs. See text for details. **B.** The algorithms for bradyarrhythmia/asystole (left) or pulseless electrical activity (right) is dominated first by continued life support and a search for reversible causes. Subsequent therapy is nonspecific and accompanied by a low success rate. See text for details. CPR, cardiopulmonary resuscitation; MI, myocardial infarction.

caused by VF in the early phase of an acute coronary syndrome, a bolus of 1 mg/kg of lidocaine may be given IV as an alternative, and the dose may be repeated in 2 min. It may also be tried in those patients in whom amiodarone is unsuccessful. IV procainamide (loading infusion of 100 mg/5 min to a total dose of 500–800 mg followed by continuous infusion at 2–5 mg/min) is now rarely used in this setting but may be tried for patients with persisting, hemodynamically stable arrhythmias. IV calcium gluconate is no longer considered safe or necessary for routine administration. It is used only in patients in whom acute hyperkalemia is known to be the triggering event for resistant VF, in the presence of known hypocalcemia, and in patients who have received toxic doses of calcium channel antagonists.

Patients with cardiac arrest secondary to bradyarrhythmias or asystole are managed differently (Fig. 32-3B). The patient is promptly intubated, CPR is continued, and an attempt is made to control hypoxemia and acidosis. Epinephrine, atropine, or both are given IV or by an intracardiac route. External pacing devices are now available to attempt to establish a regular rhythm, but the prognosis is generally very poor in this form of cardiac arrest, even with successful electrical pacing. Patients with PEA are treated similarly to those with bradyarrhythmias, but the outcome is also dismal. The one exception is bradyarrhythmic or asystolic cardiac arrest secondary to airway obstruction. Patients with this form of cardiac arrest may respond promptly to removal of foreign bodies by the Heimlich maneuver or in hospitalized patients by intubation and suctioning of obstructing secretions in the airway.

POSTRESUSCITATION CARE This phase of management is determined by the clinical setting of the cardiac arrest. Primary VF in patients with acute MI (Chap. 34) are generally very responsive to life support techniques and are easily controlled after the initial event. In the in-hospital setting, respirator support is usually not necessary or is needed for only a short time, and hemodynamics stabilize promptly after defibrillation or cardioversion. In secondary VF in acute MI (events in which hemodynamic abnormalities predispose to the potentially fatal arrhythmia), resuscitative efforts are less often successful, and in patients who are successfully resuscitated, the recurrence rate is high. The clinical picture and outcome are dominated by hemodynamic instability and the ability to control hemodynamic dysfunction. Bradyarrhythmias, asystole, and PEA are commonly secondary events in hemodynamically unstable patients. The in-hospital phase of care of the out-of-hospital cardiac arrest survivor is dictated by specific clinical circumstances. The most difficult is the presence of anoxic encephalopathy, which is a strong predictor of in-hospital death. A recent addition to the

management of this condition is induced hypothermia to reduce metabolic demands and cerebral edema.

The outcome after in-hospital cardiac arrest associated with noncardiac diseases is poor, and in the few successfully resuscitated patients, the postresuscitation course is dominated by the nature of the underlying disease. Patients with end-stage cancer, renal failure, acute CNS disease, and uncontrolled infections, as a group, have a survival rate of <10% after in-hospital cardiac arrest. Some major exceptions are patients with transient airway obstruction, electrolyte disturbances, proarrhythmic effects of drugs, and severe metabolic abnormalities, most of whom may have an excellent chance of survival if they can be resuscitated promptly and maintained while the transient abnormalities are being corrected.

LONG-TERM MANAGEMENT AFTER SURVIVAL OF OUT-OF-HOSPITAL CARDIAC ARREST

Patients who survive cardiac arrest without irreversible damage to the CNS and who achieve hemodynamic stability should have extensive diagnostic testing and appropriate therapeutic interventions for their long-term management. This aggressive approach is driven by the fact that survival after out-of-hospital cardiac arrest was followed by a 25–30% mortality rate during the first 2 years after the event, and data suggest that significant reductions in risk can be achieved by implantation of an internal cardiac defibrillator (ICD).

Among patients in whom an acute transmural MI is identified as the specific mechanism triggering an out-of-hospital cardiac arrest, the management is dictated partly by the transient nature of life-threatening arrhythmia risk in the acute phase of MI and partly by the extent of permanent myocardial damage that results. Several clinical trials have now documented an improved survival rate among cardiac arrest survivors who have EFs <40% and receive ICDs.

For patients with cardiac arrest that is thought to be caused by a transient ischemic mechanism, particularly with higher EFs, anti-ischemic therapy by pharmacologic or interventional methods is generally accepted as appropriate management. However, despite the absence of supportive clinical trial evidence, some adopt a more aggressive attitude about the use of ICDs in this group of cardiac arrest survivors as well, given the unpredictability of recurrent ischemia.

The principles guiding therapy for patients with coronary artery disease who survive a cardiac arrest generally apply to the other cardiac disorders as well, with the exception that there is less focus on the extent of disease in certain disorders. Generally, cardiac arrest survivors from other categories of disease, such as the hypertrophic or dilated cardiomyopathies and various rare inherited disorders (e.g., RV dysplasia, long QT syndrome, Brugada syndrome, arrhythmic VF) are all considered ICD candidates.

PREVENTION OF SUDDEN CARDIAC DEATH IN HIGH-RISK INDIVIDUALS WITHOUT PRIOR CARDIAC ARREST

Post-MI patients have been the subject of clinical trials for ICD benefit. It is now established that for post-MI patients with EFs <40%, ambient ventricular arrhythmias, and inducible ventricular tachyarrhythmias in the electrophysiology laboratory, ICDs provide a significant reduction in relative risk of SCD and total mortality. Total mortality benefits in the range of a 20–30% reduction over 2–3 years have been observed, and ICD has emerged as preferred therapy for such patients. One study suggests that when the EF <30%, electrophysiologic testing is not necessary to identify ICD benefit, and another demonstrates benefit for patients with functional class 2 or 3 heart failure and EFs ≤35%, regardless of the cause (ischemic or nonischemic) or ambient or induced arrhythmias.

Decision making for primary prevention in disorders other than coronary artery disease and dilated cardiomyopathy is generally driven by observational data and judgment based on clinical observations. Controlled clinical trials providing evidence-based indicators for ICDs are lacking for these smaller population subgroups. In general, for the rare disorders listed above, indicators of arrhythmic risk, such as syncope, documented ventricular tachyarrhythmias, aborted cardiac arrest or perhaps a family history of premature SCD, and a number of other clinical or ECG markers, may be used as indicators for ICDs.

FURTHER READINGS

- GOLDBERGER Z, LAMPERT R: Implantable cardioverter-defibrillators: Expanding indications and technologies. *JAMA* 295:809, 2006
- HUIKURI H et al: Sudden death due to cardiac arrhythmias. *N Engl J Med* 345:1473, 2001
- INTERNATIONAL LIAISON COMMITTEE ON RESUSCITATION: 2005 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Circulation* 112(Suppl III):III-1–III-136, 2005
- KOKOLIS S et al: Ventricular arrhythmias and sudden cardiac death. *Prog Cardiovasc Dis* 48:426, 2006
- MARENCO JP et al: Improving survival from sudden cardiac arrest: The role of the automated external defibrillator. *JAMA* 285:1193, 2001
- MARON BJ, PELLICCIA A: The heart of trained athletes: Cardiac remodeling and the risks of sports, including sudden death. *Circulation* 114:1633, 2006
- MYERBURG RJ, CASTELLANOS A: Cardiac arrest and sudden cardiac death, in *Braunwald's Heart Disease*, 8th ed, P Libby et al (eds). Philadelphia, Saunders, 2008
- , et al: Indications for implantable cardioverter-defibrillators based on evidence and judgment. *J Am Coll Cardiol* 54:747, 2009
- NOSEWORTHY PA, NEWTON-CHEH C: Genetic determinants of sudden cardiac death. *Circulation* 118:854, 2008
- ROBERTS R: Genomics and cardiac arrhythmias. *J Am Coll Cardiol* 47:9, 2006
- WIK L et al: Delaying defibrillation to give basic cardiopulmonary resuscitation to patients with out-of-hospital ventricular fibrillation: A randomized trial. *JAMA* 289:1389, 2003



CHAPTER 33

UNSTABLE ANGINA AND NON-ST-ELEVATION MYOCARDIAL INFARCTION

Christopher P. Cannon ■ Eugene Braunwald

Definition	316
Pathophysiology	316
Clinical Presentation	317
Diagnostic Evaluation	317
Risk Stratification and Prognosis	318
Long-Term Management	321
Prinzmetal's Variant Angina	322
■ Further Readings	323

Patients with ischemic heart disease fall into two large groups: patients with chronic coronary artery disease (CAD) who most commonly present with stable angina and patients with acute coronary syndromes (ACS). The latter group, in turn, is composed of patients with acute myocardial infarction (MI) with ST-segment elevation on their presenting electrocardiogram (STEMI; Chap. 34) and those with unstable angina and non-ST-segment elevation MI (UA/NSTEMI; see Fig. 34-1). Every year in the United States, ~1.3 million patients are admitted to hospitals with UA/NSTEMI compared with ~300,000 patients with acute STEMI. The relative incidence of UA/NSTEMI compared with STEMI appears to be increasing. Almost 50% of patients with UA/NSTEMI are women, and more than 75% of patients with STEMI are men.

DEFINITION

The diagnosis of UA is based largely on the clinical presentation. *Stable* angina pectoris is characterized by chest or arm discomfort that may not be described as pain but is reproducibly associated with physical exertion or stress and is relieved within 5–10 min by rest, sublingual nitroglycerin, or both. UA is defined as angina pectoris or equivalent ischemic discomfort with at least one of three

features: (1) it occurs at rest (or with minimal exertion), usually lasting >10 min; (2) it is severe and of new onset (i.e., within the prior 4–6 weeks); or (3) it occurs with a crescendo pattern (i.e., distinctly more severe, prolonged, or frequent than previously). The diagnosis of NSTEMI is established if a patient with the clinical features of UA develops evidence of myocardial necrosis, as reflected in elevated cardiac biomarkers.

PATHOPHYSIOLOGY

UA/NSTEMI is most commonly caused by a reduction in oxygen supply or by an increase in myocardial oxygen demand superimposed on an atherosclerotic coronary plaque, with varying degrees of obstruction. Four pathophysiologic processes that may contribute to the development of UA/NSTEMI have been identified: (1) plaque rupture or erosion with superimposed nonocclusive thrombus, believed to be the most common cause—NSTEMI may occur with downstream embolization of platelet aggregates or atherosclerotic debris; (2) dynamic obstruction (e.g., coronary spasm, as in Prinzmetal's variant angina); (3) progressive mechanical obstruction [e.g., rapidly advancing coronary atherosclerosis or restenosis after percutaneous coronary intervention (PCI)]; and (4) secondary UA related to increased myocardial oxygen

demand or decreased supply (e.g., tachycardia, anemia). More than one of these processes may be involved.

Among patients with UA/NSTEMI studied at angiography, approximately 5% have left main stenosis, 15% have three-vessel CAD, 30% have two-vessel disease, 40% have single-vessel disease, and 10% have no critical coronary stenosis; some of the latter have Prinzmetal's variant angina (see later). The "culprit lesion" on angiography may show an eccentric stenosis with scalloped or overhanging edges and a narrow neck. Angioscopy may reveal "white" (platelet-rich) thrombi, as opposed to "red" thrombi, more often seen in patients with acute STEMI. Patients with UA/NSTEMI often have multiple plaques that are vulnerable to disruption.

CLINICAL PRESENTATION

History and Physical Examination

The clinical hallmark of UA/NSTEMI is chest pain, typically located in the substernal region or sometimes in the epigastrium, that radiates to the neck, left shoulder, and left arm. This discomfort is usually severe enough to be considered painful. Anginal "equivalents" such as dyspnea and epigastric discomfort may also occur, and these appear to occur more often in women. The examination resembles that in patients with stable angina and may be unremarkable. If the patient has a large area of myocardial ischemia or a large NSTEMI, the physical findings can include diaphoresis, pale cool skin, sinus tachycardia, a third or fourth heart sound, basilar rales, and sometimes hypotension, resembling the findings of large STEMI.

Electrocardiography

In UA, ST-segment depression, transient ST-segment elevation, or T-wave inversion occurs in 30–50% of patients, depending on the severity of the clinical presentation. In patients with the clinical features of UA, the presence of new ST-segment deviation, even of only 0.05 mV, is an important predictor of adverse outcome. T-wave changes are sensitive for ischemia but less specific, unless they are new, deep T-wave inversions (≥ 0.3 mV).

Cardiac Biomarkers

Patients with UA who have elevated biomarkers of necrosis, such as CK-MB and troponin (a much more specific and sensitive marker of myocardial necrosis), are at increased risk for death or recurrent MI. Elevated levels of these markers distinguish patients with NSTEMI from those with UA. There is a direct relationship between the degree of troponin elevation and mortality. However, in patients *without* a clear clinical history of myocardial ischemia, minor troponin elevations have been reported and can be caused by congestive heart failure, myocarditis, or pulmonary embolism, or they may be false-positive

readings. Thus, in patients with an *unclear* history, small troponin elevations may not be diagnostic of an ACS.

DIAGNOSTIC EVALUATION

Approximately 6–7 million persons per year in the United States present to hospital emergency departments (EDs) with a complaint of chest pain or other symptoms suggestive of ACS. A diagnosis of an ACS is established in 20–25% of such patients. The first step in evaluating patients with possible UA/NSTEMI is to determine the *likelihood* that CAD is the cause of the presenting symptoms. The American College of Cardiology/American Heart Association (ACC/AHA) Guidelines include, among the factors associated with a high likelihood of ACS, a clinical history typical of ischemic discomfort, a history of established CAD by angiography, prior MI, congestive heart failure, new electrocardiographic (ECG) changes, or elevated cardiac biomarkers. Factors associated with an intermediate likelihood of ACS in patients with the clinical features of this condition but without the above high-risk factors are age older than 70 years, male gender, diabetes mellitus, known peripheral arterial or cerebrovascular disease, and old ECG abnormalities.

Diagnostic Pathways

Four major diagnostic tools are used in the diagnosis of UA/NSTEMI in the ED: the clinical history, the ECG, cardiac markers, and stress testing. The goals are to (1) recognize or exclude MI (using cardiac markers), (2) evaluate for rest ischemia (chest pain at rest, serial or continuous ECGs), and (3) evaluate for significant CAD (using provocative stress testing). Typical pathways begin with assessment of the likelihood that the presenting symptoms are attributable to ischemia. Patients with a low likelihood of ischemia are usually managed with an ED-based critical pathway (which is carried out in a "chest pain unit" in some institutions (Fig. 33-1). Evaluation of such patients includes clinical monitoring for recurrent ischemic discomfort, serial ECGs, and cardiac markers, typically performed at baseline and at 4–6 h and 12 h after presentation. If new elevations in cardiac markers (CK-MB, troponin, or both) or ECG changes are noted, the patient is admitted to the hospital. If the patient remains pain free and the markers are negative, the patient may go on to stress testing. This may be performed as early as 6 h after presentation in the ED or chest pain center or on an outpatient basis within 72 h. For most patients, standard treadmill ECG stress testing is used, but for patients with fixed abnormalities on the ECG (e.g., left bundle branch block), perfusion or echocardiographic imaging is used. For patients who cannot walk, pharmacologic stress is used. By demonstrating normal myocardial perfusion, sestamibi or thallium imaging can reduce unnecessary hospitalizations by

Critical Pathway for ED Evaluation of Chest Pain/ "Rule Out MI"

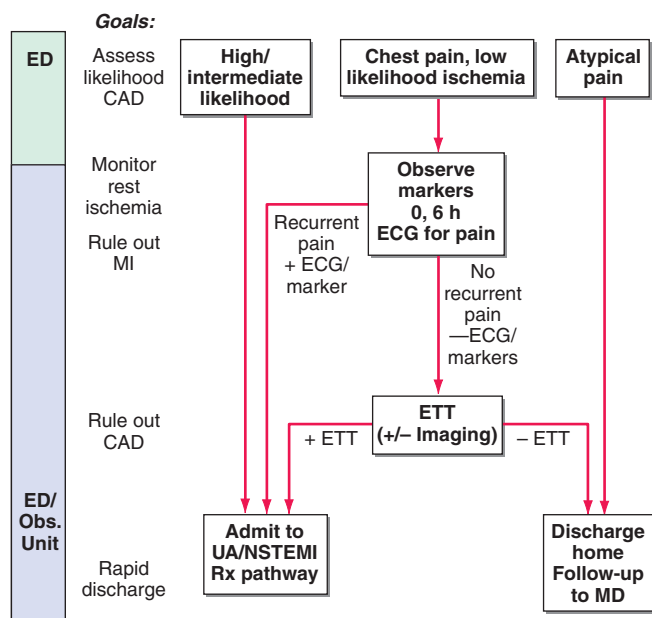


FIGURE 33-1

Diagnostic evaluation of patients presenting with suspected unstable angina and non-ST-segment elevation MI (UA/NSTEMI).

The first step is to assess the likelihood of coronary artery disease (CAD). Patients at *high or intermediate* likelihood are admitted to the hospital. Those with clearly atypical chest pain are sent home. Patients with a *low* likelihood of ischemia enter the pathway and are observed in a monitored bed in the emergency department (ED) or observation unit over a period of 6 h, and 12-lead electrocardiograms (ECGs) are performed if the patient has recurrent chest discomfort. A panel of cardiac markers (e.g., troponin and CK-MB) is drawn at baseline and 6 h later. If the patient develops recurrent pain, has ST-segment or T-wave changes, or has positive cardiac markers, he or she is admitted to the hospital and treated for UA/NSTEMI. If the patient has negative markers and no recurrence of pain, he or she is sent for exercise treadmill testing, with imaging reserved for patients with abnormal baseline ECGs (e.g., left bundle branch block or left ventricular hypertrophy). If the results are positive, the patient is admitted; if the results are negative, the patient is discharged with follow-up to his or her primary care physician (PCP). ETT, exercise tolerance test; MI, myocardial infarction; Rx, treatment. [Adapted from Cannon CP, Braunwald E, in *Heart Disease: A Textbook of Cardiovascular Medicine*, 6th ed, E Braunwald et al (eds). Philadelphia, Saunders, 2001.]

excluding acute ischemia. CT angiography is used with increasing frequency to exclude obstructive CAD.

RISK STRATIFICATION AND PROGNOSIS

Patients with documented UA/NSTEMI exhibit a wide spectrum of early (30 days) risk of death, ranging from

1–10%, and of new or recurrent infarction of 3–10%. Assessment of “global risk” can be accomplished by clinical risk scoring systems such as that developed from in the Thrombolysis in Myocardial Infarction (TIMI) Trials, which includes seven independent risk factors: age ≥ 65 years, three or more risk factors for CAD, documented CAD at catheterization, development of UA/NSTEMI while taking aspirin, more than two episodes of angina within the preceding 24 h, ST deviation ≥ 0.5 mm, and an elevated cardiac marker (Fig. 33-2). Other risk factors include diabetes mellitus; left ventricular dysfunction; and elevated levels of creatinine, atrial natriuretic peptides, and C-reactive protein (CRP). Early risk assessment (especially using troponin, ST-segment changes, or a global risk scoring system) is useful both in predicting the risk of recurrent cardiac events and in identifying patients who would derive the greatest benefit from antithrombotic therapies more potent than unfractionated heparin (UFH), such as low-molecular-weight heparin (LMWH) and glycoprotein (GP) IIb/IIIa inhibitors, and from an early invasive strategy. For example, in the TACTICS-TIMI 18 Trial, whereas an early invasive strategy conferred a 40% reduction in recurrent cardiac events in patients with positive troponin levels, no benefit was observed in those with negative troponin levels.

CRP, a marker of vascular inflammation, and B-type natriuretic peptide, a marker of increased myocardial wall tension, correlate independently with increased mortality (and, in some studies, recurrent cardiac events) in patients presenting with UA/NSTEMI. Multimarker strategies are now gaining favor both to define the pathophysiologic mechanisms underlying a given patient’s presentation more fully and to stratify the patient’s risk further.

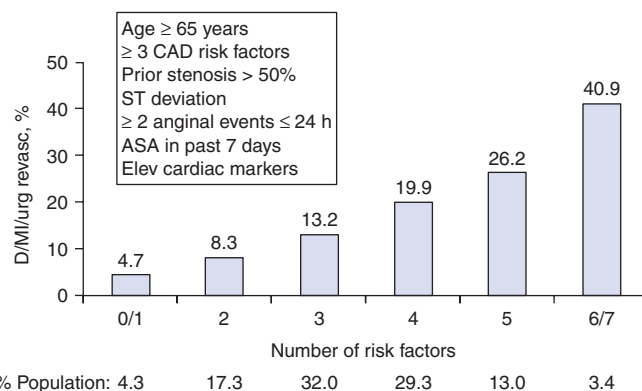


FIGURE 33-2

The Thrombolysis in Myocardial Infarction (TIMI) Risk Score for unstable angina and non-ST-segment elevation MI (UA/NSTEMI), a simple but comprehensive clinical risk stratification score used to identify increasing risk of death, myocardial infarction, or urgent revascularization (urg revasc) to day 14. ASA, aspirin; CAD, coronary artery disease. (Adapted from Antman et al.)

Rx Treatment:
UNSTABLE ANGINA AND NON-ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

MEDICAL TREATMENT Patients with UA/NSTEMI should be placed on bed rest with continuous ECG monitoring for ST-segment deviation and cardiac rhythm. Ambulation is permitted if the patient shows no recurrence of ischemia (discomfort or ECG changes) and does not develop a biomarker of necrosis for 12–24 h. Medical therapy involves simultaneous anti-ischemic treatment and antithrombotic treatment.

ANTI-ISCHEMIC TREATMENT (Table 33-1) To provide relief and prevention of recurrence of chest pain, initial treatment should include bed rest, nitrates, and β -blockers.

Nitrates Nitrates should first be given sublingually or by buccal spray (0.3–0.6 mg) if the patient is experiencing ischemic pain. If pain persists after three doses given 5 min apart, IV nitroglycerin (5–10 μ g/min using nonabsorbing tubing) is recommended. The rate of the infusion may be increased by 10 μ g/min every 3–5 min until symptoms are relieved or systolic arterial pressure decreases to <100 mmHg. Topical or oral nitrates can be used after the pain has resolved, or they may replace IV nitroglycerin when the patient has been pain free for 12–24 h. The only absolute contraindications to the use of nitrates are hypotension or the use of sildenafil (Viagra) or other drugs in that class within the previous 24 h.

β -Adrenergic Blockade These agents are the other mainstay of anti-ischemic treatment. IV β blockade followed by oral β blockade targeted to a heart rate of 50–60 bpm is recommended. Heart rate–slowing calcium channel blockers (e.g., verapamil or diltiazem) are recommended in patients who have persistent or recurrent symptoms after treatment with full-dose nitrates and β -blockers and in patients with contraindications to β blockade. Additional medical therapy includes angiotensin-converting enzyme (ACE) inhibition and HMG-CoA reductase inhibitors (statins) for long-term secondary prevention.

If pain persists despite IV nitroglycerin and β blockade, morphine sulfate (1–5 mg IV) can be administered every 5–30 min as needed.

ANTITHROMBOTIC THERAPY (Table 33-2) Antithrombotic therapy is the other main component of treatment of patients with UA/NSTEMI. Initial treatment should begin with the platelet cyclooxygenase inhibitor aspirin (Fig. 33-3). The typical initial dose is 325 mg/d with lower doses (75–162 mg/d) recommended for long-term therapy. “Aspirin resistance” has been noted in research studies in 5–10% of patients and more

frequently in patients treated with lower doses of aspirin. No clear guidelines are available regarding evaluation or treatment, but the use of higher doses of aspirin, a thienopyridine (clopidogrel), or both appears to be logical in this situation.

The thienopyridine clopidogrel, which blocks the platelet P2Y₁₂ (adenosine) receptor (in combination with aspirin), was shown in the CURE trial to confer a 20% relative reduction in cardiovascular death, MI, or stroke compared with aspirin alone in both low- and high-risk patients with UA/NSTEMI but to be associated with a moderate (absolute 1%) increase in major bleeding, which is more common in patients who undergo coronary artery bypass grafting (CABG). Pretreatment with clopidogrel (a 300- or 600-mg loading dose followed by 75 mg qd) has also been shown in three studies to reduce adverse outcomes associated with and following PCI and has a class I, grade A evidence recommendation in the PCI Guidelines. Continued benefit of long-term (~1 year) treatment with the combination of clopidogrel and aspirin has been observed both in patients treated conservatively and in those who underwent PCI. This combination is recommended for all patients with UA/NSTEMI who are not at excessive risk for bleeding.

Four options are available for anticoagulation therapy to be added to aspirin and clopidogrel. UFH is the mainstay of therapy. The LMWH enoxaparin has been shown in several studies to be superior to UFH in reducing recurrent cardiac events, especially in conservatively managed patients. The factor Xa inhibitor fondaparinux is equivalent for early efficacy compared with enoxaparin but appears to have a lower risk of major bleeding and thus may have the best risk:benefit ratio. However, UFH, LMWH, or a direct thrombin inhibitor such as bivalirudin should be used during cardiac catheterization or PCI. Preliminary data indicate that bivalirudin is equivalent (for both efficacy and safety) to either UFH or enoxaparin among patients treated with a GP IIb/IIIa inhibitor, but use of bivalirudin alone had less bleeding than the combination of a heparin and GP IIb/IIIa inhibitor in patients with UA/NSTEMI undergoing PCI.

IV GP IIb/IIIa inhibitors have also been shown to be beneficial in treating patients with UA/NSTEMI. For “upstream” management of high-risk patients in whom an invasive management is intended (i.e., initiating therapy when the patient first presents to the hospital), the small molecule inhibitors eptifibatide and tirofiban show benefit, but the monoclonal antibody abciximab appears not to be effective in patients treated conservatively (i.e., in those not undergoing coronary angiography or PCI). However, abciximab has been shown to be beneficial in patients with UA/NSTEMI undergoing PCI, even among troponin-positive patients pretreated with clopidogrel. The ACC/AHA Guidelines note that these

DRUGS COMMONLY USED IN INTENSIVE MEDICAL MANAGEMENT OF PATIENTS WITH UNSTABLE ANGINA AND NON-ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

DRUG CATEGORY	CLINICAL CONDITION	WHEN TO AVOID ^a	DOSAGE
Nitrates	Administer IV when symptoms are not fully relieved with three SL nitroglycerin tablets and initiation of β -blocker therapy	Hypotension Patient receiving sildenafil or other PDE-5 inhibitor	5–10 μ g/min by continuous infusion Titrated up to 75–100 μ g/min until relief of symptoms or limiting side effects (headache or hypotension with a SBP <90 mmHg or >30% below starting mean arterial pressure levels if significant hypertension is present) Topical, oral, or buccal nitrates are acceptable alternatives for patients without ongoing or refractory symptoms
β -blockers ^b	Unstable angina	PR interval (ECG) >0.24 s Second- or third-degree AV block Heart rate <60 bpm BP <90 mmHg Shock LV failure with congestive heart failure Severe reactive airway disease	Metoprolol ^c 5-mg increments by slow (over 1–2 min IV administration) Repeated every 5 min for a total initial dose of 15 mg Followed in 1–2 h by 25–50 mg by mouth every 6 h If a very conservative regimen is desired, initial doses can be reduced to 1–2 mg Esmolol ^c Starting maintenance dose of 0.1 mg/kg per min IV Titration in increments of 0.05 mg/kg per min every 10–15 min as tolerated by BP until the desired therapeutic response has been obtained, limiting symptoms develop, or a dose of 0.20 mg/kg per min is reached Optional loading dose of 0.5 mg/kg may be given by slow IV administration (2–5 min) for more rapid onset of action Dependent on specific agent
Calcium channel blockers	Patients whose symptoms are not relieved by adequate doses of nitrates and β -blockers, in patients unable to tolerate adequate doses of one or both of these agents, or in patients with variant angina	Pulmonary edema Evidence of LV dysfunction (for diltiazem or verapamil)	Dependent on specific agent
Morphine sulfate	Patients whose symptoms are not relieved after three serial SL nitroglycerin tablets or whose symptoms recur with adequate anti-ischemic therapy	Hypotension Respiratory depression Confusion Obtundation	2–5 mg IV dose May be repeated every 5–30 min as needed to relieve symptoms and maintain patient comfort

^aAllergy or prior intolerance is a contraindication for all categories of drugs listed in this chart.

^bThe choice of the specific agent is not as important as ensuring that appropriate candidates receive this therapy. If there are concerns about patient intolerance owing to existing pulmonary disease, especially asthma, left ventricular (LV) dysfunction, risk of hypotension or severe bradycardia, initial selection should favor a short-acting agent, such as propranolol or metoprolol or the ultra-short-acting agent esmolol. Mild wheezing or a history of chronic obstructive pulmonary disease should prompt a trial of a short-acting agent at a reduced dose (e.g., 2.5 mg IV metoprolol, 12.5 mg oral metoprolol, or 25 g/kg per min esmolol as the initial doses) rather than complete avoidance of β -blocker therapy.

^cMetoprolol and esmolol are two of several β -blockers that may be used.

Note: Some of the recommendations in this guide suggest the use of agents for purposes or in doses other than those specified by the U.S. Food and Drug Administration. Such recommendations are made after consideration of concerns regarding nonapproved indications. Where made, such recommendations are based on more recent clinical trials or expert consensus.

AV, atrioventricular; BP, blood pressure; ECG, electrocardiogram; LV, left ventricular; PDE, phosphodiesterase; SBP, systolic blood pressure; SL, sublingual.

Source: Modified from E Braunwald et al: *Circulation* 1994;90:613–622.

TABLE 33-2

CLINICAL USE OF ANTITHROMBOTIC THERAPY	
Oral Antiplatelet Therapy	
Aspirin	Initial dose of 162–325 mg nonenteric formulation followed by 75–162 mg/d of an enteric or a nonenteric formulation
Clopidogrel (Plavix)	Loading dose of 300 mg followed by 75 mg/d
Intravenous Antiplatelet Therapy	
Abciximab (ReoPro)	0.25 mg/kg bolus followed by infusion of 0.125 µg/kg per min (maximum, 10 µg/min) for 12–24 h
Eptifibatid (Integrilin)	180 µg/kg bolus followed by infusion of 2.0 µg/kg per min for 72–96 h
Tirofiban (Aggrastat)	0.4 µg/kg per min for 30 min followed by infusion of 0.1 µg/kg per min for 48–96 h
Heparins^a	
Heparin (UFH)	Bolus 60–70 U/kg (maximum 5000 U) IV followed by infusion of 12–15 U/kg per h (initial maximum 1000 U/h) titrated to a PTT 50–70 s
Enoxaparin (Lovenox)	1 mg/kg SC every 12 h; the first dose may be preceded by a 30-mg IV bolus; renal adjustment to 1 mg/kg once daily if creatine Cl <30 cc/min
Fondaparinux	2.5 mg SC qd
Bivalirudin	Initial bolus IV bolus of 0.1 mg/kg and an infusion of 0.25 mg/kg per hour. Before PCI, an additional IV bolus of 0.5 mg/kg was administered, and the infusion was increased to 1.75 mg/kg per h.

^aOther low-molecular-weight heparins exist beyond those listed.

Note: IV, intravenous; PCI, percutaneous coronary intervention; SC, subcutaneous; UFH, unfractionated heparin.

Source: Modified from Braunwald E et al: J Am Coll Cardiol 36:970–1056, 2000.

agents can be started either in the ED or during PCI. As with all antithrombotic agents, bleeding is the most important adverse effect of antiplatelet drugs, especially their combination. Thus, patients with a history of bleeding must be screened carefully and given fewer antithrombotic agents.

INVASIVE VERSUS CONSERVATIVE STRATEGY Multiple clinical trials have shown the benefit of an early invasive strategy in high-risk patients—i.e., patients with multiple clinical risk factors, ST-segment deviation, or positive biomarkers (Table 33-3). In this strategy, after treatment with anti-ischemic and antithrombotic agents, coronary arteriography is carried out within ~48 h of admission followed by coronary revascularization (PCI or CABG), depending on the coronary anatomy.

In low-risk patients, the outcomes from an invasive strategy are similar to those obtained from a conservative strategy, which consists of anti-ischemic and antithrombotic therapy followed by “watchful waiting,” in which coronary arteriography is carried out only if rest pain or ST-segment changes recur or there is evidence of ischemia on a stress test.

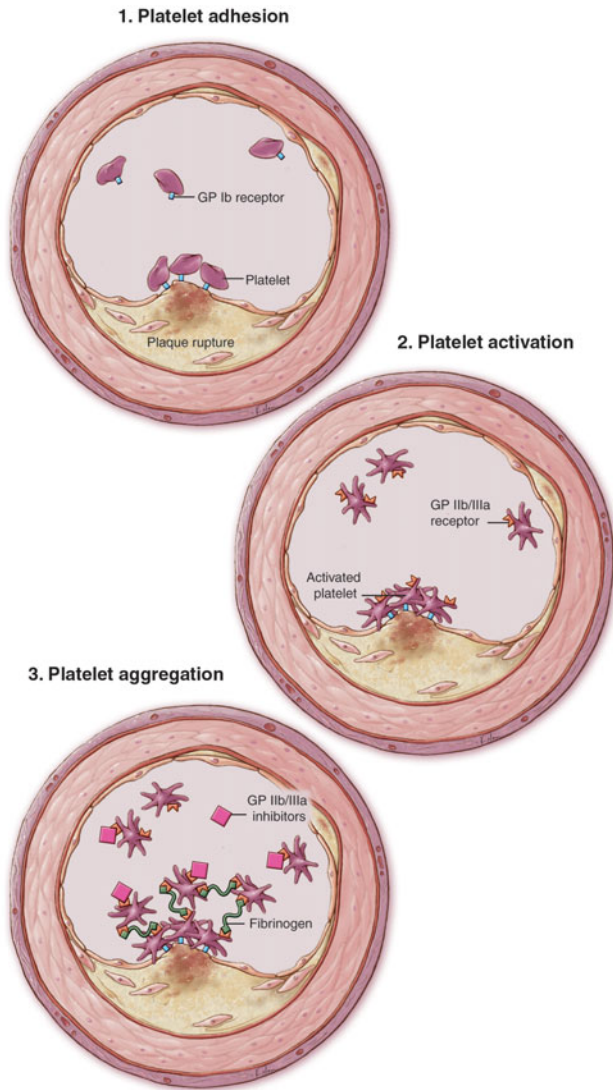
LONG-TERM MANAGEMENT

The time of hospital discharge is a “teachable moment” for the patient with UA/NSTEMI, when the physician can

review and optimize the medical regimen. Risk factor modification is key, and the physician should discuss with the patient the importance of smoking cessation, achieving optimal weight, daily exercise following an appropriate diet, blood pressure control, tight control of hyperglycemia (for diabetic patients), and lipid management, as recommended for patients with chronic stable angina.

There is evidence of benefit with long-term therapy with five classes of drugs that are directed at different components of the atherothrombotic process. B-blockers are appropriate anti-ischemic therapy and may help decrease triggers for MI. Statins (at a high dose, e.g., atorvastatin 80 mg/d) and ACE inhibitors are recommended for long-term plaque stabilization. Antiplatelet therapy, now recommended to be the combination of aspirin and clopidogrel for at least 9–12 months with aspirin continued thereafter, prevents or reduces the severity of any thrombosis that would occur if a plaque does rupture. Thus, a multifactorial approach to long-term medical therapy is directed at preventing the various components of atherothrombosis. This therapy should be begun early (i.e. within 1 week of the event) whenever possible.

Observational registries have shown that patients with UA/NSTEMI at high risk, including women and elderly individuals as well as racial minorities, are less likely to receive evidence-based pharmacologic and interventional therapies with resultant poorer clinical outcomes and quality of life.

**FIGURE 33-3**

Platelets initiate thrombosis at the site of a ruptured plaque with denuded endothelium: *platelet adhesion* occurs via (1) the glycoprotein (GP) 1b receptor in conjunction with von Willebrand factor. This is followed by *platelet activation* (2), which leads to a shape change in the platelet, degranulation of the α and dense granules, and expression of GP IIb/IIIa receptors on the platelet surface with activation of the receptor, such that it can bind fibrinogen. The final step is *platelet aggregation* (3), in which fibrinogen (or von Willebrand factor) binds to the activated GP IIb/IIIa receptors. Whereas aspirin (ASA) and clopidogrel act to decrease platelet activation, the GP IIb/IIIa inhibitors inhibit the final step of platelet aggregation. [Modified from Cannon CP, Braunwald E, in Heart Disease: A Textbook of Cardiovascular Medicine, 8th ed, P Libby et al (eds). Philadelphia, Saunders, 2008.]

PRINZMETAL'S VARIANT ANGINA

In 1959, Prinzmetal et al. described a syndrome of ischemic pain that occurs at rest but not usually with exertion and is associated with transient ST-segment

TABLE 33-3

CLASS I RECOMMENDATIONS FOR USE OF AN EARLY INVASIVE STRATEGY^a

Class I (level of evidence: A) indications

- Recurrent angina at rest and low-level activity despite treatment
- Elevated TnT or TnI
- New ST-segment depression
- Recurrent angina or ischemia with CHF symptoms, rales, MR
- Positive stress test
- EF <0.40
- Decreased BP
- Sustained VT
- PCI <6 months, prior CABG

^aAny one of the high-risk indicators.

Note: BP, blood pressure; CABG, coronary artery bypass grafting; CHF, congestive heart failure; EF, ejection fraction; MR, mitral regurgitation; PCI, percutaneous coronary intervention; TnI, troponin I; TnT, troponin T; VT, ventricular tachycardia.

Source: Adapted from Braunwald E et al: Circulation 106:1893, 2002.

elevation. This syndrome is caused by focal spasm of an epicardial coronary artery, leading to severe myocardial ischemia. The exact cause of the spasm is not well defined, but it may be related to hypercontractility of vascular smooth muscle caused by vasoconstrictor mitogens, leukotrienes, or serotonin. In some patients, it is a manifestation of a vasospastic disorder and is associated with migraine, Raynaud's phenomenon, or aspirin-induced asthma.

Clinical and Angiographic Manifestations

Patients with variant angina are generally younger and have fewer coronary risk factors (with the exception of cigarette smoking) than patients with UA secondary to coronary atherosclerosis. The anginal discomfort is often extremely severe and has usually not progressed from a period of chronic stable angina. Cardiac examination is usually normal in the absence of ischemia.

The clinical diagnosis of variant angina is made with the detection of transient ST-segment *elevation* with rest pain. Many patients also exhibit multiple episodes of asymptomatic ST-segment elevation (*silent ischemia*). Small elevations of CK-MB and troponin may occur in patients with prolonged attacks of variant angina. Exercise testing in patients with variant angina is of limited value because the patients can demonstrate ST elevation, depression, or no ST changes.

Coronary angiography demonstrates transient coronary spasm as the diagnostic hallmark of Prinzmetal's angina. Atherosclerotic plaques, which do not usually cause critical obstruction, in at least one proximal coronary artery occur in the majority of patients, and in them, spasm usually occurs within 1 cm of the plaque. Focal spasm is

most common in the right coronary artery, and it may occur at one or more sites in one artery or in multiple arteries simultaneously. Ergonovine, acetylcholine, other vasoconstrictor medications, and hyperventilation have been used to provoke and demonstrate focal coronary stenosis to establish the diagnosis. Hyperventilation has also been used to provoke rest angina, ST-segment elevation, and spasm on coronary arteriography.

Rx Treatment: **PRINZMETAL'S VARIANT ANGINA**

Nitrates and calcium channel blockers are the main treatments for patients with variant angina. Sublingual or IV nitroglycerin often abolishes episodes of variant angina promptly, and long-acting nitrates are useful in preventing recurrences. Calcium antagonists are extremely effective in preventing the coronary artery spasm of variant angina, and they should be prescribed in maximally tolerated doses. Similar efficacy rates have been noted among the various types of calcium antagonists. Prazosin, a selective α -adrenoreceptor blocker, has also been found to be of value in some patients, but aspirin may actually increase the severity of ischemic episodes. The response to β -blockers is variable. Coronary revascularization may be helpful in patients with variant angina who also have discrete, proximal fixed obstructive lesions.

Prognosis

Many patients with Prinzmetal's angina pass through an acute, active phase, with frequent episodes of angina and cardiac events during the first 6 months after presentation. Long-term survival at 5 years is excellent (~90–95%). Patients with no or mild fixed coronary obstruction tend to experience a more benign course than do patients with associated severe obstructive lesions. Nonfatal MI occurs in up to 20% of patients by 5 years. Patients with variant angina who develop serious arrhythmias during spontaneous episodes of pain are at a higher risk for sudden death. In most patients who survive an infarction or the initial 3–6-month period of frequent episodes, the condition stabilizes, and there is a tendency for symptoms and cardiac events to diminish with time.

FURTHER READINGS

- ALEXANDER KP et al: Excess dosing of antiplatelet and antithrombin agents in the treatment of non-ST-segment elevation acute coronary syndromes. *JAMA* 294: 3108, 2005
- ANDERSON JL et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 116:e148, 2007
- ANTMAN EM et al: The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. *JAMA* 284:835, 2000
- BRAUNWALD E et al: ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST segment elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Unstable Angina). Available at http://www.acc.org/qualityandscience/clinical/guidelines/unstable/update_index.htm
- CANNON CP, BRAUNWALD E: Unstable angina, in *Braunwald's Heart Disease*, 8th ed, P Libby et al (eds). Philadelphia, Saunders, 2008
- : Unstable angina, in *Braunwald's Heart Disease*, 9th ed, R Bonow et al (eds). Philadelphia, Saunders, 2010
- et al: Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 350:1495, 2004
- CLOPIDOGREL IN UNSTABLE ANGINA TO PREVENT RECURRENT EVENTS TRIAL INVESTIGATORS: Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 345:494, 2001
- GIUGLIANO RP et al: Early versus delayed, provisional eptifibatide in acute coronary syndromes. *N Engl J Med* 360:2176, 2009
- GIUGLIANO RP, BRAUNWALD E: The year in non-ST segment elevation acute coronary syndromes. *J Am Coll Cardiol* (in press)
- KASTRATI A et al: Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: The ISAR-REACT 2 randomized trial. *JAMA* 295:1531, 2006
- MEHTA SR et al: Routine vs selective invasive strategies in patients with acute coronary syndromes: A collaborative meta-analysis of randomized trials. *JAMA* 293:2908, 2005
- O'DONOGHUE M et al: Early invasive vs. conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: A meta-analysis. *JAMA* 300:71, 2008
- WALLENIN LT et al: Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 361:1045, 2009
- WIVIOTT SD et al: Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 357:2001, 2007
- YUSUF S et al: Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med* 354:1464, 2006



CHAPTER 34

ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

Elliott M. Antman ■ Eugene Braunwald

■ Pathophysiology: Role of Acute Plaque Rupture	324	Antithrombotic Agents	334
■ Clinical Presentation	325	β-Adrenoceptor Blockers	335
Physical Findings	326	Inhibition of the Renin–Angiotensin– Aldosterone System	336
■ Laboratory Findings	326	Other Agents	336
Electrocardiography	326	■ Complications and Their Management	336
Serum Cardiac Biomarkers	327	Ventricular Dysfunction	336
Cardiac Imaging	328	Hemodynamic Assessment	336
■ Initial Management	328	Cardiogenic Shock	337
Prehospital Care	328	Right Ventricular Infarction	337
Management in the Emergency Department	328	Arrhythmias	338
Control of Discomfort	329	Other Complications	340
Management Strategies	330	■ Postinfarction Risk Stratification and Management	341
Limitation of Infarct Size	330	■ Secondary Prevention	341
■ Hospital Phase Management	333	■ Further Readings	342
Coronary Care Units	333		
■ Pharmacotherapy	334		

Acute myocardial infarction (AMI) is one of the most common diagnoses in hospitalized patients in industrialized countries. In the United States, approximately 650,000 patients experience a new AMI and 450,000 experience a recurrent AMI each year. The early (30-day) mortality rate from AMI is ~30%, with more than half of these deaths occurring before the individual reaches the hospital. Although the mortality rate after admission for AMI has declined by ~30% over the past two decades, approximately one of every 25 patients who survives the initial hospitalization dies in the first year after AMI. Mortality is approximately fourfold higher in elderly patients (older than age 75 years) compared with younger patients.

When patients with prolonged ischemic discomfort at rest are first seen, the working clinical diagnosis is that they have an acute coronary syndrome (ACS) (Fig. 34-1). The 12-lead electrocardiogram (ECG) is a pivotal diagnostic and triage tool since it is at the center of the decision pathway for management. It permits distinction of those

patients presenting with ST-segment elevation from those presenting without ST-segment elevation. Serum cardiac biomarkers are obtained to distinguish unstable angina (UA) from non-ST-segment MI (NSTEMI) and to assess the magnitude of an ST-segment elevation MI (STEMI). This chapter focuses on the evaluation and management of patients with STEMI; Chap. 33 discusses UA/NSTEMI.

PATHOPHYSIOLOGY: ROLE OF ACUTE PLAQUE RUPTURE

STEMI usually occurs when coronary blood flow decreases abruptly after a thrombotic occlusion of a coronary artery previously affected by atherosclerosis. Slowly developing, high-grade coronary artery stenoses do not typically precipitate STEMI because of the development of a rich collateral network over time. Instead, STEMI occurs when a coronary artery thrombus develops rapidly at a site of vascular injury. This injury is produced or

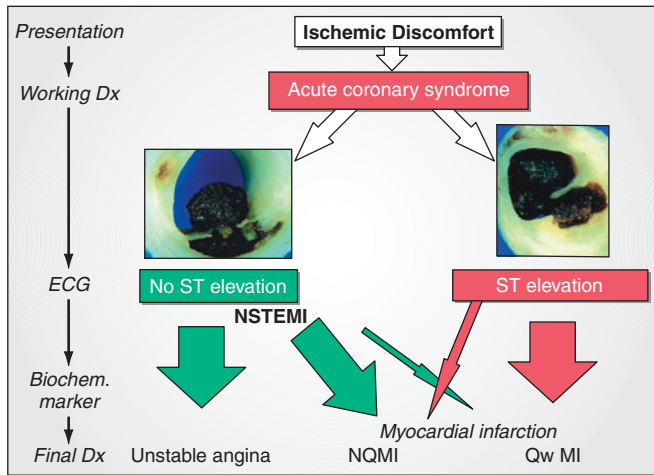


FIGURE 34-1

Acute coronary syndromes. After disruption of a vulnerable plaque, patients experience ischemic discomfort resulting from a reduction of flow through the affected epicardial coronary artery. The flow reduction may be caused by a completely occlusive thrombus (*right*) or subtotally occlusive thrombus (*left*). Patients with ischemic discomfort may present with or without ST-segment elevation. Of patients with ST-segment elevation, the majority (*wide red arrow*) ultimately develop a Q-wave on the ECG (QwMI), but a minority (*thin red arrow*) do not develop Q-wave and in older literature were said to have sustained a non-Q-wave MI (NQMI). Patients who present without ST-segment elevation have either unstable angina or a non-ST-segment elevation MI (NSTEMI) (*wide green arrows*), a distinction that is ultimately made on the presence or absence of a serum cardiac marker such as the MB isoenzyme of creatine phosphokinase (CKMB) or a cardiac troponin detected in the blood. The majority of patients presenting with NSTEMI do not develop a Q-wave on the ECG; a minority develop a QwMI (*thin green arrow*). Dx, diagnosis. (*Adapted from Hamm CW et al: Acute coronary syndrome without ST elevation: implementation of new guidelines. Lancet 358:1533, 2001, and Davies MJ: The pathophysiology of acute coronary syndromes. Heart 83:361, 2000; with permission from the BMJ Publishing Group.*)

facilitated by factors such as cigarette smoking, hypertension, and lipid accumulation. In most cases, STEMI occurs when the surface of an atherosclerotic plaque becomes disrupted (exposing its contents to the blood) and conditions (local or systemic) favor thrombogenesis. A mural thrombus forms at the site of plaque disruption, and the involved coronary artery becomes occluded. Histologic studies indicate that the coronary plaques prone to disruption are those with a rich lipid core and a thin fibrous cap. After an initial platelet monolayer forms at the site of the disrupted plaque, various agonists (collagen, ADP, epinephrine, serotonin) promote platelet activation. After agonist stimulation of platelets, thromboxane A₂ (a potent local vasoconstrictor) is released, further platelet

activation occurs, and potential resistance to fibrinolysis develops.

In addition to the generation of thromboxane A₂, activation of platelets by agonists promotes a conformational change in the glycoprotein (GP) IIb/IIIa receptor. After it has been converted to its functional state, this receptor develops a high affinity for amino acid sequences on soluble adhesive proteins (i.e., integrins) such as fibrinogen. Because fibrinogen is a multivalent molecule, it can bind to two different platelets simultaneously, resulting in platelet cross-linking and aggregation.

The coagulation cascade is activated on exposure of tissue factor in damaged endothelial cells at the site of the disrupted plaque. Factors VII and X are activated, ultimately leading to the conversion of prothrombin to thrombin, which then converts fibrinogen to fibrin (Chap. 41). Fluid-phase and clot-bound thrombin participate in an autoamplification reaction, leading to further activation of the coagulation cascade. The culprit coronary artery eventually becomes occluded by a thrombus containing platelet aggregates and fibrin strands.

In rare cases, STEMI may be due to coronary artery occlusion caused by coronary emboli, congenital abnormalities, coronary spasm, and a wide variety of systemic—particularly inflammatory—diseases. The amount of myocardial damage caused by coronary occlusion depends on (1) the territory supplied by the affected vessel, (2) whether or not the vessel becomes totally occluded, (3) the duration of coronary occlusion, (4) the quantity of blood supplied by collateral vessels to the affected tissue, (5) the demand for oxygen of the myocardium whose blood supply has been suddenly limited, (6) native factors that can produce early spontaneous lysis of the occlusive thrombus, and (7) the adequacy of myocardial perfusion in the infarct zone when flow is restored in the occluded epicardial coronary artery.

Patients at increased risk of developing STEMI include those with multiple coronary risk factors and those with UA (Chap. 33). Less common underlying medical conditions predisposing patients to STEMI include hypercoagulability, collagen vascular disease, cocaine abuse, and intracardiac thrombi or masses that can produce coronary emboli.

CLINICAL PRESENTATION

In up to 50% of cases, a precipitating factor, such as vigorous physical exercise, emotional stress, or a medical or surgical illness, appears to be present before STEMI. Although STEMI may commence at any time of the day or night, circadian variations have been reported such that clusters are seen in the morning within a few hours of awakening.

Pain is the most common presenting complaint in patients with STEMI. The pain is deep and visceral;

326 adjectives commonly used to describe it are *heavy*, *squeezing*, and *crushing*, although occasionally it is described as stabbing or burning. It is similar in character to the discomfort of angina pectoris but commonly occurs at rest, is usually more severe, and lasts longer. Typically, the pain involves the central portion of the chest or the epigastrium, and it occasionally radiates to the arms. Less common sites of radiation include the abdomen, back, lower jaw, and neck. The frequent location of the pain beneath the xiphoid and epigastrium and the patient's denial that he or she may be suffering a heart attack are chiefly responsible for the common mistaken impression of indigestion. The pain of STEMI may radiate as high as the occipital area but not below the umbilicus. It is often accompanied by weakness, sweating, nausea, vomiting, anxiety, and a sense of impending doom. The pain may commence when the patient is at rest, but when it begins during a period of exertion, it does not usually subside with cessation of activity, in contrast to angina pectoris.

The pain of STEMI can simulate pain from acute pericarditis, pulmonary embolism (Chap. 20), acute aortic dissection, costochondritis, and gastrointestinal disorders. These conditions should therefore be considered in the differential diagnosis. Radiation of discomfort to the trapezius is not seen in patients with STEMI and may be a useful distinguishing feature that suggests pericarditis is the correct diagnosis. However, *pain is not uniformly present in patients with STEMI*. The proportion of painless STEMIs is greater in patients with diabetes mellitus, and it increases with age. In elderly individuals, STEMI may present as sudden-onset breathlessness, which may progress to pulmonary edema. Other less common presentations, with or without pain, include sudden loss of consciousness, a confusional state, a sensation of profound weakness, the appearance of an arrhythmia, evidence of peripheral embolism, or merely an unexplained decrease in arterial pressure.

PHYSICAL FINDINGS

Most patients are anxious and restless, attempting unsuccessfully to relieve the pain by moving about in bed, altering their position, and stretching. Pallor associated with perspiration and coolness of the extremities occurs commonly. The combination of substernal chest pain persisting for >30 min and diaphoresis strongly suggests STEMI. Although many patients have a normal pulse rate and blood pressure within the first hour of STEMI, about one-fourth of patients with anterior infarction have manifestations of sympathetic nervous system hyperactivity (tachycardia, hypertension, or both), and up to one-half with inferior infarction show evidence of parasympathetic hyperactivity (bradycardia, hypotension, or both).

The precordium is usually quiet, and the apical impulse may be difficult to palpate. In patients with anterior wall infarction, an abnormal systolic pulsation caused by dyskinetic bulging of infarcted myocardium may develop

in the periapical area within the first days of the illness and may then resolve. Other physical signs of ventricular dysfunction include fourth and third heart sounds, decreased intensity of the first heart sound, and paradoxical splitting of the second heart sound. A transient midsystolic or late systolic apical systolic murmur caused by dysfunction of the mitral valve apparatus may be present. A pericardial friction rub is heard in many patients with transmural STEMI at some time in the course of the disease if they are examined frequently. The carotid pulse is often decreased in volume, reflecting reduced stroke volume. Temperature elevations up to 38°C may be observed during the first week after STEMI. The arterial pressure is variable; in most patients with transmural infarction, systolic pressure declines by approximately 10–15 mmHg from the preinfarction state.

LABORATORY FINDINGS

Myocardial infarction (MI) progresses through the following temporal stages: (1) acute (first few hours–7 days), (2) healing (7–28 days), and (3) healed (≥ 29 days). When evaluating the results of diagnostic tests for STEMI, the temporal phase of the infarction must be considered. The laboratory tests of value in confirming the diagnosis may be divided into four groups: (1) ECG, (2) serum cardiac biomarkers, (3) cardiac imaging, and (4) nonspecific indices of tissue necrosis and inflammation.

ELECTROCARDIOGRAPHY

During the initial stage, total occlusion of an epicardial coronary artery produces ST-segment elevation. Most patients initially presenting with ST-segment elevation ultimately evolve Q waves on the ECG (Fig. 34-1). However, Q waves in the leads overlying the infarct zone may vary in magnitude and even appear only transiently, depending on the reperfusion status of the ischemic myocardium and restoration of transmembrane potentials over time. A small proportion of patients initially presenting with ST-segment elevation will not develop Q waves when the obstructing thrombus is not totally occlusive, obstruction is transient, or if a rich collateral network is present. Among patients presenting with ischemic discomfort but *without* ST-segment elevation, if a serum cardiac biomarker of necrosis (see later) is detected, the diagnosis of NSTEMI is ultimately made (Fig. 34-1). A minority of patients who present initially without ST-segment elevation may develop a Q-wave MI. Previously, it was believed that transmural MI is present if the ECG demonstrates Q waves or loss of R waves, and nontransmural MI may be present if the ECG shows only transient ST-segment and T-wave changes. However, ECG-pathologic correlations are far from perfect, and terms such as *Q-wave MI*, *non-Q-wave MI*, *transmural MI*, and *nontransmural MI*, have been replaced by *STEMI* and *NSTEMI* (Fig. 34-1).

SERUM CARDIAC BIOMARKERS

Certain proteins, called *serum cardiac biomarkers*, are released from necrotic heart muscle after STEMI. The rate of liberation of specific proteins differs depending on their intracellular location, their molecular weight, and the local blood and lymphatic flow. Cardiac biomarkers become detectable in the peripheral blood after the capacity of the cardiac lymphatics to clear the interstitium of the infarct zone is exceeded and spillover into the venous circulation occurs. The temporal pattern of protein release is of diagnostic importance, but contemporary urgent reperfusion strategies necessitate making a decision (based largely on a combination of clinical and ECG findings) before the results of blood tests have returned from the laboratory. Rapid whole-blood bedside assays for serum cardiac markers are now available and may facilitate management decisions, particularly in patients with nondiagnostic ECGs.

Cardiac-specific troponin T (cTnT) and *cardiac-specific troponin I (cTnI)* have amino acid sequences different from those of the skeletal muscle forms of these proteins. These differences permitted the development of quantitative assays for cTnT and cTnI with highly specific monoclonal antibodies. Because cTnT and cTnI are not normally detectable in the blood of healthy individuals but may increase after STEMI to levels >20 times higher than the upper reference limit (the highest value seen in 99% of a reference population without MI), the measurement of cTnT or cTnI is of considerable diagnostic usefulness, and they are now the preferred biochemical markers for MI (Fig. 34-2). The cardiac troponins are particularly valuable when there is clinical suspicion of either skeletal muscle injury or a small MI that may be below the detection limit for creatine phosphokinase (CK) and CKMB measurements, and they are therefore of particular value in distinguishing UA from NSTEMI. Levels of cTnI and cTnT may remain elevated for 7–10 days after STEMI.

CK increases within 4–8 h and generally returns to normal by 48–72 h (see Fig. 34-2). An important drawback of total CK measurement is its lack of specificity for STEMI because CK may be elevated with skeletal muscle disease or trauma, including intramuscular injection. The MB isoenzyme of CK has the advantage over total CK that it is not present in significant concentrations in extracardiac tissue and therefore is considerably more specific. However, cardiac surgery, myocarditis, and electrical cardioversion often result in elevated serum levels of the MB isoenzyme. A ratio (relative index) of CKMB mass:CK activity ≥ 2.5 suggests but is not diagnostic of a myocardial rather than a skeletal muscle source for the CKMB elevation.

Many hospitals use cTnT or cTnI rather than CKMB as the routine serum cardiac marker for diagnosis of STEMI, although any of these analytes remains clinically acceptable. It is *not* cost effective to measure both a cardiac-specific troponin and CKMB at all time points in every patient.

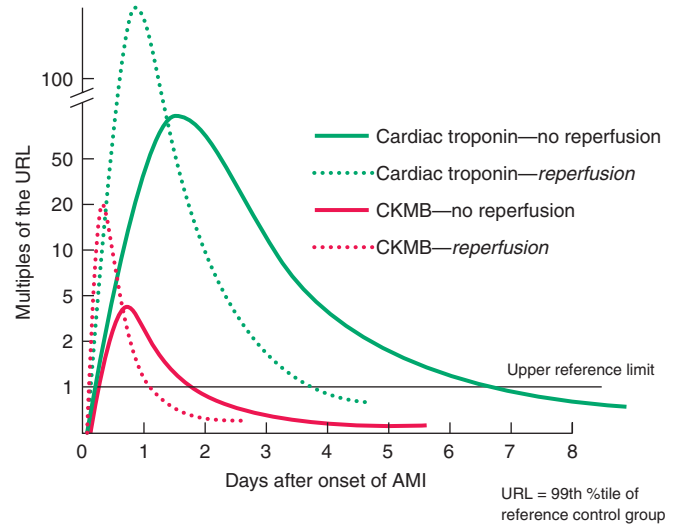


FIGURE 34-2

Typical cardiac biomarkers that are used to evaluate patients with ST-segment elevation myocardial infarction include the MB isoenzyme of creatine phosphokinase (CKMB) and cardiac-specific troponins. The black horizontal line depicts the upper reference limit (URL) for the cardiac biomarker in the clinical chemistry laboratory. The kinetics of release of CKMB and cardiac troponin in patients who do not undergo reperfusion are shown in the solid green and red curves as multiples of the URL. When patients with STEMI undergo reperfusion, as depicted in the dashed green and red curves, the cardiac biomarkers are detected sooner, rise to a higher peak value, but decline more rapidly, resulting in a smaller area under the curve and limitation of infarct size. AMI, acute myocardial infarction. (Adapted from Alpert JS et al: *Myocardial infarction redefined: A consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction*. *J Am Coll Cardiol* 36:959, 2000, and Wu AH et al: *National Academy of Clinical Biochemistry Standards of Laboratory Practice: recommendations for the use of cardiac markers in coronary artery diseases*. *Clin Chem* 45:1104, 1999.)

Although it has long been recognized that the total quantity of protein released correlates with the size of the infarct, the peak protein concentration correlates only weakly with infarct size. Recanalization of a coronary artery occlusion (either spontaneously or by mechanical or pharmacologic means) in the early hours of STEMI causes earlier and higher peaking (at about 8–12 h after reperfusion) of serum cardiac biomarkers (see Fig. 34-2) because of a rapid washout from the interstitium of the infarct zone, quickly overwhelming lymphatic clearance of the proteins.

The nonspecific reaction to myocardial injury is associated with polymorphonuclear leukocytosis, which appears within a few hours after the onset of pain and persists for 3–7 days; the white blood cell count often reaches levels of 12,000–15,000/ μL . The erythrocyte sedimentation rate increases more slowly than the white blood cell count, peaking during the first week and sometimes remaining elevated for 1 or 2 weeks.

Abnormalities of wall motion on *two-dimensional echocardiography* are almost universally present. Although acute STEMI cannot be distinguished from an old myocardial scar or from acute severe ischemia by echocardiography, the ease and safety of the procedure make its use appealing as a screening tool in the emergency department (ED) setting. When the ECG is not diagnostic of STEMI, early detection of the presence or absence of wall motion abnormalities by echocardiography can aid in management decisions, such as whether the patient should receive reperfusion therapy [e.g., fibrinolysis or a percutaneous coronary intervention (PCI)]. Echocardiographic estimation of left ventricular (LV) function is useful prognostically; detection of reduced function serves as an indication for therapy with an inhibitor of the renin-angiotensin-aldosterone system. Echocardiography may also identify the presence of right ventricular (RV) infarction, ventricular aneurysm, pericardial effusion, and LV thrombus. In addition, Doppler echocardiography is useful in the detection and quantitation of a ventricular septal defect and mitral regurgitation, two serious complications of STEMI.

Several *radionuclide imaging techniques* are available for evaluating patients with suspected STEMI. However, these imaging modalities are used less often than echocardiography because they are more cumbersome and lack sensitivity and specificity in many clinical circumstances. Myocardial perfusion imaging with ^{201}Tl or $^{99\text{m}}\text{Tc}$ -sestamibi, which are distributed in proportion to myocardial blood flow and concentrated by viable myocardium, reveal a defect (“cold spot”) in most patients during the first few hours after development of a transmural infarct. Although perfusion scanning is extremely sensitive, it cannot distinguish acute infarcts from chronic scars and thus is not specific for the diagnosis of *acute MI*. Radionuclide ventriculography, carried out with $^{99\text{m}}\text{Tc}$ -labeled red blood cells, frequently demonstrates wall motion disorders and reduction in the ventricular ejection fraction in patients with STEMI. Although of value in assessing the hemodynamic consequences of infarction and in aiding in the diagnosis of RV infarction when the RV ejection fraction is depressed, this technique is nonspecific because many cardiac abnormalities other than MI alter the radionuclide ventriculogram.

Myocardial infarction can be detected accurately with high-resolution cardiac MRI using a technique referred to as *late enhancement*. A standard imaging agent (gadolinium) is administered, and images are obtained after a 10-min delay. Because little gadolinium enters normal myocardium where there are tightly packed myocytes but does percolate into the expanded intercellular region of the infarct zone, a bright signal in areas of infarction appears in stark contrast to the dark areas of normal myocardium.

INITIAL MANAGEMENT

PREHOSPITAL CARE

The prognosis for patients with STEMI is largely related to the occurrence of two general classes of complications: (1) electrical complications (arrhythmias) and (2) mechanical complications (“pump failure”). Most out-of-hospital deaths from STEMI are caused by the sudden development of ventricular fibrillation. The vast majority of deaths caused by ventricular fibrillation occur within the first 24 h of the onset of symptoms, and of these, more than half occur in the first hour. Therefore, the major elements of prehospital care of patients with suspected STEMI include (1) recognition of symptoms by the patient and prompt seeking of medical attention; (2) rapid deployment of an emergency medical team capable of performing resuscitative maneuvers, including defibrillation; (3) expeditious transportation of the patient to a hospital facility that is continuously staffed by physicians and nurses skilled in managing arrhythmias and providing advanced cardiac life support; and (4) expeditious implementation of reperfusion therapy (**Fig. 34-3**). The biggest delay usually occurs not during transportation to the hospital but rather between the onset of pain and the patient’s decision to call for help. This delay can best be reduced by health care professionals educating the public concerning the significance of chest discomfort and the importance of seeking early medical attention. Regular office visits with patients having a history of or who are at risk for ischemic heart disease are important “teachable moments” for clinicians to review the symptoms of STEMI and the appropriate action plan.

Increasingly, monitoring and treatment are carried out by trained personnel in the ambulance, further shortening the time between the onset of the infarction and appropriate treatment. General guidelines for initiation of fibrinolysis in the prehospital setting include the ability to transmit 12-lead ECGs to confirm the diagnosis, the presence of paramedics in the ambulance, training of paramedics in the interpretation of ECGs and management of STEMI, and online medical command and control that can authorize the initiation of treatment in the field.

MANAGEMENT IN THE EMERGENCY DEPARTMENT

In the ED, the goals for the management of patients with suspected STEMI include control of cardiac discomfort, rapid identification of patients who are candidates for urgent reperfusion therapy, triage of lower-risk patients to the appropriate location in the hospital, and avoidance of inappropriate discharge of patients with STEMI. Many aspects of the treatment of patients with STEMI are

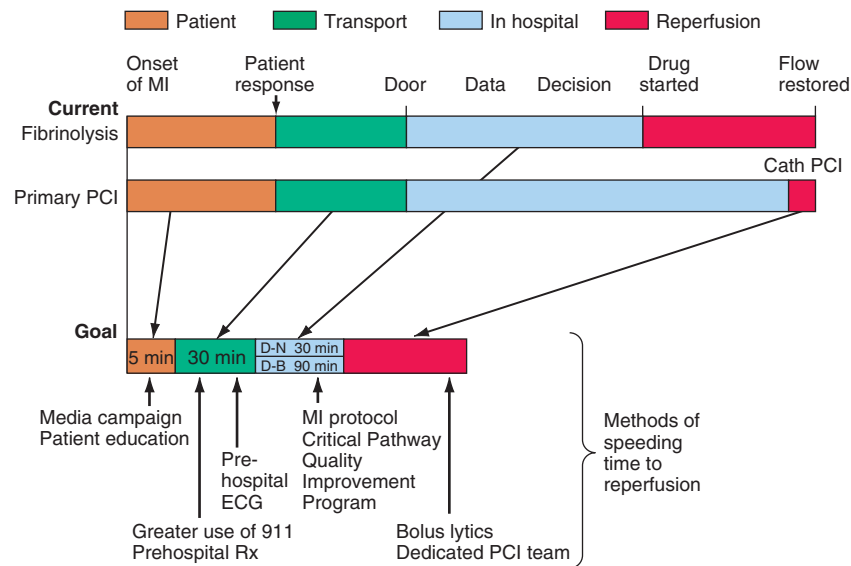


FIGURE 34-3

Major components of time delay between the onset of symptoms from ST-segment elevation myocardial infarction (STEMI) and restoration of flow in the infarct-related artery. Plotted sequentially from left to right are the times for patients to recognize symptoms and seek medical attention, transportation to the hospital, in-hospital decision making, implementation of reperfusion strategy, and restoration of flow after the reperfusion strategy has been initiated. The time to initiate fibrinolytic therapy is the “door-to-needle” (D-N) time; this is followed by the period of time required for pharmacologic restoration of flow. More time is required to move the

patient to the catheterization laboratory for a percutaneous coronary interventional (PCI) procedure, referred to as the “door-to-balloon” (D-B) time, but restoration of flow in the epicardial infarct-related artery occurs promptly after PCI. At the bottom are shown a variety of methods for speeding the time to reperfusion along with the goals for the time intervals for the various components of the time delay. ECG, electrocardiography; Rx, treatment. (Adapted from Cannon CP et al: *Time as an adjunctive agent to thrombolytic therapy. J Thromb Thrombolysis* 1:27, 1994.)

initiated in the ED and then continued during the in-hospital phase of management.

Aspirin is essential in the management of patients with suspected STEMI and is effective across the entire spectrum of ACS (Fig. 34-1). Rapid inhibition of cyclooxygenase-1 in platelets followed by a reduction of thromboxane A₂ levels is achieved by buccal absorption of a chewed 160–325-mg tablet in the ED. This measure should be followed by daily oral administration of aspirin in a dose of 75–162 mg.

In patients whose arterial O₂ saturation is normal, supplemental O₂ is of limited, if any, clinical benefit and therefore is not cost effective. However, when hypoxemia is present, O₂ should be administered by nasal prongs or a face mask (2–4 L/min) for the first 6–12 h after infarction; the patient should then be reassessed to determine if there is a continued need for such treatment.

CONTROL OF DISCOMFORT

Sublingual *nitroglycerin* can be given safely to most patients with STEMI. Up to three doses of 0.4 mg should be administered at about 5-min intervals. In addition to diminishing or abolishing chest discomfort, nitroglycerin may be capable of both decreasing myocardial oxygen

demand (by lowering preload) and increasing myocardial oxygen supply (by dilating infarct-related coronary vessels or collateral vessels). In patients whose initially favorable response to sublingual nitroglycerin is followed by the return of chest discomfort, particularly if accompanied by other evidence of ongoing ischemia such as further ST-segment or T-wave shifts, the use of IV nitroglycerin should be considered. Therapy with nitrates should be avoided in patients who present with low systolic arterial pressure (<90 mmHg) or in whom there is clinical suspicion of RV infarction (inferior infarction on ECG, elevated jugular venous pressure, clear lungs, and hypotension). Nitrates should not be administered to patients who have taken the phosphodiesterase-5 inhibitor sildenafil for erectile dysfunction within the preceding 24 h because it may potentiate the hypotensive effects of nitrates. An idiosyncratic reaction to nitrates consisting of sudden marked hypotension sometimes occurs but can usually be reversed promptly with the rapid administration of IV atropine.

Morphine is a very effective analgesic for the pain associated with STEMI. However, it may reduce sympathetically mediated arteriolar and venous constriction, and the resulting venous pooling may reduce cardiac output and arterial pressure. These hemodynamic disturbances usually

330 respond promptly to elevation of the legs, but in some patients, volume expansion with IV saline is required. The patient may experience diaphoresis and nausea, but these events usually pass and are replaced by a feeling of well-being associated with the relief of pain. Morphine also has a vagotonic effect and may cause bradycardia or advanced degrees of heart block, particularly in patients with posterior-inferior infarction. These side effects usually respond to atropine (0.5 mg IV). Morphine is routinely administered by repetitive (every 5 min) IV injection of small doses (2–4 mg) rather than by the subcutaneous administration of a larger quantity because absorption may be unpredictable by the latter route.

IV β -blockers are also useful in the control of the pain of STEMI. These drugs control pain effectively in some patients, presumably by diminishing myocardial O_2 demand and hence ischemia. More important, evidence suggests that IV β -blockers reduce the risks of reinfarction and ventricular fibrillation (see β -Adrenoceptor Blockers later). A commonly used regimen is metoprolol, 5 mg every 2–5 min for a total of three doses, provided the patient has a heart rate >60 bpm, systolic pressure >100 mmHg, a PR interval <0.24 s, and rales that are no higher than 10 cm up from the diaphragm. Fifteen minutes after the last IV dose, an oral regimen is initiated of 50 mg every 6 h for 48 h followed by 100 mg every 12 h.

Unlike β -blockers, calcium antagonists are of little value in the acute setting, and evidence suggests that short-acting dihydropyridines may be associated with an increased mortality risk.

MANAGEMENT STRATEGIES

The primary tool for screening patients and making triage decisions is the initial 12-lead ECG. When ST-segment elevation of at least 2 mm in two contiguous precordial leads and 1 mm in two adjacent limb leads is present, a patient should be considered a candidate for reperfusion therapy (Fig. 34-4). The process of selecting patients for fibrinolysis versus primary PCI (angioplasty, or stenting) is discussed below. In the absence of ST-segment elevation, fibrinolysis is not helpful, and evidence suggests that it may be harmful.

LIMITATION OF INFARCT SIZE

The quantity of myocardium that becomes necrotic as a consequence of a coronary artery occlusion is determined by factors other than just the site of occlusion. Although the central zone of the infarct contains necrotic tissue that is irretrievably lost, the fate of the surrounding ischemic myocardium may be improved by timely restoration of coronary perfusion, reduction of myocardial O_2 demands, prevention of the accumulation of noxious metabolites, and blunting of the impact of mediators of reperfusion injury (e.g., calcium overload and oxygen-derived free radicals). Up to one-third of patients with STEMI may

achieve *spontaneous* reperfusion of the infarct-related coronary artery within 24 h and experience improved healing of infarcted tissue. Reperfusion, either pharmacologically (by fibrinolysis) or by PCI, accelerates the opening of infarct-related arteries in patients in whom spontaneous fibrinolysis ultimately would have occurred and greatly increases the number of patients in whom restoration of flow in the infarct-related artery is accomplished. Timely restoration of flow in the epicardial infarct-related artery combined with improved perfusion of the downstream zone of infarcted myocardium results in a limitation of infarct size. Protection of the ischemic myocardium by the maintenance of an optimal balance between myocardial O_2 supply and demand through pain control, treatment of congestive heart failure (CHF), and minimization of tachycardia and hypertension extends the “window” of time for the salvage of myocardium by reperfusion strategies.

Glucocorticoids and nonsteroidal anti-inflammatory agents, with the exception of aspirin, should be avoided in patients with STEMI. They can impair infarct healing and increase the risk of myocardial rupture, and their use may result in a larger infarct scar. In addition, they can increase coronary vascular resistance, thereby potentially reducing flow to ischemic myocardium.

Primary Percutaneous Coronary Intervention

PCI, usually angioplasty or stenting without preceding fibrinolysis, referred to as *primary PCI*, is effective in restoring perfusion in STEMI when carried out on an emergency basis in the first few hours of MI. It has the advantage of being applicable to patients who have contraindications to fibrinolytic therapy (see below) but otherwise are considered appropriate candidates for reperfusion. It appears to be more effective than fibrinolysis in opening occluded coronary arteries and, *when performed by experienced operators* [≥ 75 PCI cases (not necessarily primary) per year] in dedicated medical centers (≥ 36 primary PCI cases per year), is associated with better short- and long-term clinical outcomes. Compared with fibrinolysis, primary PCI is generally preferred when the diagnosis is in doubt, cardiogenic shock is present, bleeding risk is increased, or symptoms have been present for at least 2–3 h when the clot is more mature and less easily lysed by fibrinolytic drugs. However, PCI is expensive in terms of personnel and facilities, and its applicability is limited by its availability, around the clock, in only a minority of hospitals.

Fibrinolysis

If no contraindications are present (see later), fibrinolytic therapy should ideally be initiated within 30 minutes of presentation (i.e., door-to-needle time ≤ 30 min). The principal goal of fibrinolysis is prompt restoration of full coronary arterial patency. The fibrinolytic agents

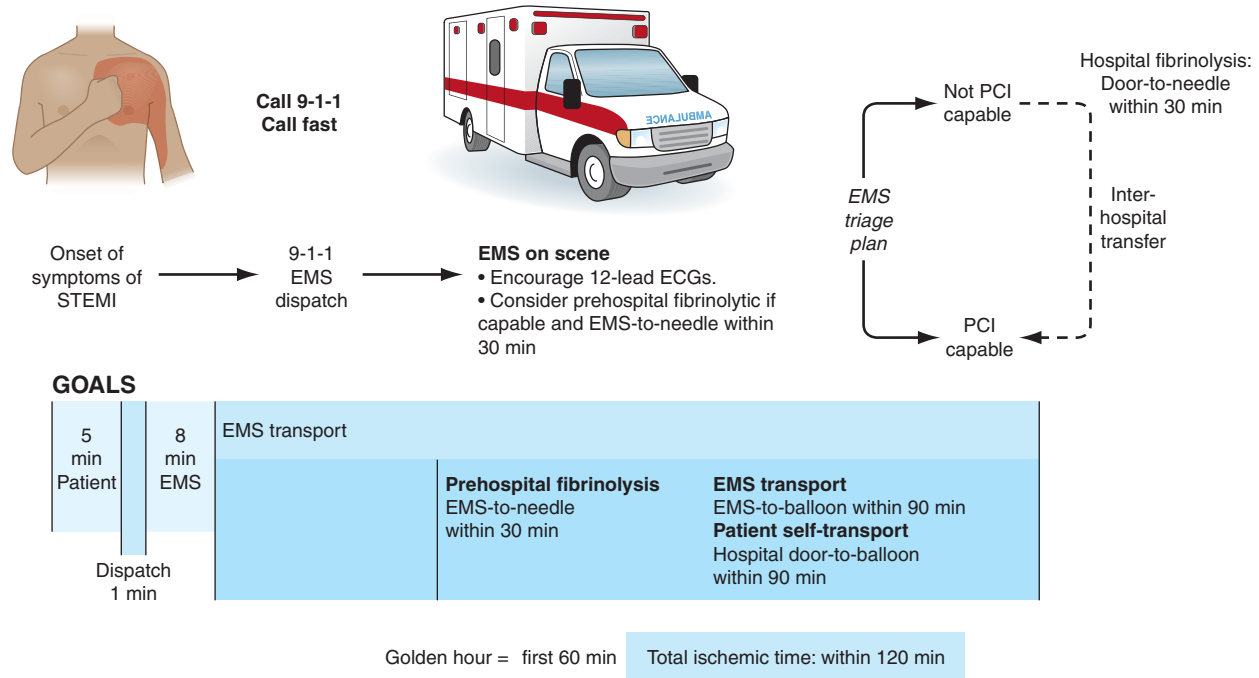


FIGURE 34-4

Options for transportation of patients with ST-segment elevation myocardial infarction (STEMI) and initial reperfusion treatment. Patient transported by Emergency Medical Services (EMS) after calling 911: Reperfusion in patients with STEMI can be accomplished by the pharmacologic (fibrinolysis) or catheter-based (primary percutaneous coronary intervention [PCI]) approaches. Implementation of these strategies varies based on the mode of transportation of the patient and capabilities at the receiving hospital. Transport time to the hospital is variable from case to case, but the goal is to keep total ischemic time within 120 min. There are three possibilities: (1) If EMS has fibrinolytic capability and the patient qualifies for therapy, prehospital fibrinolysis should be started within 30 min of EMS arrival on scene. (2) If EMS is not capable of administering prehospital fibrinolysis and the patient is transported to a non-PCI-capable hospital, the hospital door-to-needle (D-N) time should be within 30 min for patients in whom fibrinolysis is indicated. (3) If EMS is not capable of administering prehospital fibrinolysis and the patient is transported to a PCI-capable hospital, the hospital door-to-balloon (D-B) time should be within 90 min.

Interhospital transfer: It is also appropriate to consider emergency interhospital transfer of the patient to a PCI-capable

hospital for mechanical revascularization if (1) there is a contraindication to fibrinolysis; (2) PCI can be initiated promptly (within 90 min after the patient presented to the initial receiving hospital or within 60 min compared with when fibrinolysis with a fibrin-specific agent could be initiated at the initial receiving hospital); (3) fibrinolysis is administered and is unsuccessful (i.e., “rescue PCI”). Secondary nonemergency interhospital transfer can be considered for recurrent ischemia.

Patient self-transport: Patient self-transportation is discouraged. If the patient arrives at a non-PCI-capable hospital, the D-N time should be within 30 min. If the patient arrives at a PCI-capable hospital, the D-B time should be within 90 min. The treatment options and time recommended after first hospital arrival are the same. ECG, electrocardiography. [Reproduced with permission from Antman et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Available at <http://www.acc.org/clinical/guidelines/stemi/index.pdf>.]

tissue plasminogen activator (tPA), streptokinase, tenecteplase (TNK), and reteplase (rPA) have been approved by the U.S. Food and Drug Administration for IV use in patients with STEMI. These drugs all act by promoting the conversion of plasminogen to plasmin, which subsequently lyses fibrin thrombi. Although considerable emphasis was first placed on a distinction between more fibrin-specific agents, such as tPA, and non-fibrin-specific agents, such as streptokinase, it is now recognized that these differences are only relative because some degree of systemic fibrinolysis

occurs with the former agents. TNK and rPA are referred to as *bolus fibrinolytics* because their administration does not require a prolonged IV infusion.

When assessed angiographically, flow in the culprit coronary artery is described by a simple qualitative scale called the *Thrombolysis in Myocardial Infarction (TIMI) grading system*: grade 0 indicates complete occlusion of the infarct-related artery; grade 1 indicates some penetration of the contrast material beyond the point of obstruction but without perfusion of the distal coronary

332 bed; grade 2 indicates perfusion of the entire infarct vessel into the distal bed but with flow that is delayed compared with that of a normal artery; and grade 3 indicates full perfusion of the infarct vessel with normal flow. The latter is the goal of reperfusion therapy because full perfusion of the infarct-related coronary artery yields far better results in terms of limiting infarct size, maintenance of LV function, and reduction of both short- and long-term mortality rates. Additional methods of angiographic assessment of the efficacy of fibrinolysis include counting the number of frames on the cine film required for dye to flow from the origin of the infarct-related artery to a landmark in the distal vascular bed (*TIMI frame count*) and determining the rate of entry and exit of contrast dye from the microvasculature in the myocardial infarct zone (*TIMI myocardial perfusion grade*). These methods have an even tighter correlation with outcomes after STEMI than the more commonly used TIMI flow grade.

Fibrinolytic therapy can reduce the relative risk of in-hospital death by up to 50% when administered within the first hour of the onset of symptoms of STEMI, and much of this benefit is maintained for at least 10 years. When appropriately used, fibrinolytic therapy appears to reduce infarct size, limit LV dysfunction, and reduce the incidence of serious complications such as septal rupture, cardiogenic shock, and malignant ventricular arrhythmias. Because myocardium can be salvaged only before it has been irreversibly injured, the timing of reperfusion therapy, by fibrinolysis or a catheter-based approach, is of extreme importance in achieving maximum benefit. Although the upper time limit depends on specific factors in individual patients, it is clear that “every minute counts” and that patients treated within 1–3 h of the onset of symptoms generally benefit most. Although reduction of the mortality rate is more modest, the therapy remains of benefit for many patients seen 3–6 h after the onset of infarction, and some benefit appears to be possible up to 12 h, especially if chest discomfort is still present and ST segments remain elevated. Compared with PCI for STEMI (primary PCI), fibrinolysis is generally the preferred reperfusion strategy for patients presenting in the first hour of symptoms, if there are logistical concerns about transportation of the patient to a suitable PCI center (experienced operator and team with a track record for a “door-to-balloon” time of <2 h), or there is an anticipated delay of at least 1 h between the time that fibrinolysis could be started versus implementation of PCI. Although patients <75 years achieve a greater relative reduction in the mortality rate with fibrinolytic therapy than do older patients, the higher *absolute* mortality rate (15–25%) in the latter results in similar absolute reductions in the mortality rates for both age groups.

tPA and the other relatively fibrin-specific plasminogen activators, rPA and TNK, are more effective than streptokinase at restoring full perfusion (i.e., TIMI

grade 3 coronary flow) and have a small edge in improving survival as well. The current recommended regimen of tPA consists of a 15-mg bolus followed by 50 mg IV over the first 30 min, followed by 35 mg over the next 60 min. Streptokinase is administered as 1.5 million units (MU) IV over 1 h. rPA is administered in a double-bolus regimen consisting of a 10-MU bolus given over 2–3 min followed by a second 10-MU bolus 30 min later. TNK is given as a single weight-based IV bolus of 0.53 mg/kg over 10 s. In addition to the fibrinolytic agents discussed above, pharmacologic reperfusion typically involves adjunctive antiplatelet and antithrombotic drugs, as discussed subsequently.

Alternative pharmacologic regimens for reperfusion combine an IV GP IIb/IIIa inhibitor with a reduced dose of a fibrinolytic agent. Compared with fibrinolytic agents that involve a prolonged infusion (e.g., tPA), such combination reperfusion regimens facilitate the rate and extent of fibrinolysis by inhibiting platelet aggregation, weakening the clot structure, and allowing penetration of the fibrinolytic agent deeper into the clot. However, combination reperfusion regimens have similar efficacy compared with bolus fibrinolytics and are associated with an increased risk of bleeding, especially in patients >75 years of age. Therefore, combination reperfusion regimens are not recommended for routine use. In an experimental strategy called *facilitated PCI*, GP IIb/IIIa inhibitors given alone (i.e., without any fibrinolytic agent) are being investigated as a preparatory pharmacologic regimen in STEMI patients who are referred promptly for PCI. Another experimental strategy that has been proposed but not yet rigorously evaluated is a *pharmacoinvasive* approach in which STEMI patients are first treated with a pharmacologic reperfusion regimen followed by routine angiography and PCI after a delay of 12–24 h to minimize the risks of performing PCI while the effects of the lytic agent are still present.

Contraindications and Complications

Clear contraindications to the use of fibrinolytic agents include a history of cerebrovascular hemorrhage at any time, a nonhemorrhagic stroke or other cerebrovascular event within the past year, marked hypertension (a reliably determined systolic arterial pressure >180 mmHg or a diastolic pressure >110 mmHg) at any time during the acute presentation, suspicion of aortic dissection, and active internal bleeding (excluding menses). Although advanced age is associated with an increase in hemorrhagic complications, the benefit of fibrinolytic therapy in elderly patients appears to justify its use if no other contraindications are present and the amount of myocardium in jeopardy appears to be substantial.

Relative contraindications to fibrinolytic therapy, which require assessment of the risk:benefit ratio, include current use of anticoagulants (International Normalized

Ratio ≥ 2), a recent (< 2 weeks) invasive or surgical procedure or prolonged (> 10 min) cardiopulmonary resuscitation, known bleeding diathesis, pregnancy, a hemorrhagic ophthalmic condition (e.g., hemorrhagic diabetic retinopathy), active peptic ulcer disease, and a history of severe hypertension that is currently adequately controlled. Because of the risk of an allergic reaction, patients should not receive streptokinase if that agent had been received within the preceding 5 days to 2 years.

Allergic reactions to streptokinase occur in $\sim 2\%$ of patients who receive it. Although a minor degree of hypotension occurs in 4–10% of patients given this agent, marked hypotension occurs, although rarely, in association with severe allergic reactions.

Hemorrhage is the most frequent and potentially the most serious complication. Because bleeding episodes that require transfusion are more common when patients require invasive procedures, unnecessary venous or arterial interventions should be avoided in patients receiving fibrinolytic agents. Hemorrhagic stroke is the most serious complication and occurs in $\sim 0.5\text{--}0.9\%$ of patients being treated with these agents. This rate increases with advancing age, with patients > 70 years of age experiencing roughly twice the rate of intracranial hemorrhage as those < 65 years. Large-scale trials have suggested that the rate of intracranial hemorrhage with tPA or rPA is slightly higher than with streptokinase.

Cardiac catheterization and coronary angiography should be carried out after fibrinolytic therapy if there is evidence of either (1) failure of reperfusion (persistent chest pain and ST-segment elevation > 90 min), in which case a *rescue PCI* should be considered, or (2) coronary artery reocclusion (re-elevation of ST segments or recurrent chest pain) or the development of recurrent ischemia (e.g., recurrent angina in the early hospital course or a positive exercise stress test result before discharge), in which case an *urgent PCI* should be considered. The potential benefits of routine angiography and *elective PCI* even in asymptomatic patients after administration of fibrinolytic therapy are controversial, but such an approach may have merit given the numerous technological advances that have occurred in the catheterization laboratory and the increasing number of skilled interventionists. Coronary artery bypass surgery should be reserved for patients whose coronary anatomy is unsuited to PCI but in whom revascularization appears to be advisable because of extensive jeopardized myocardium or recurrent ischemia.

HOSPITAL PHASE MANAGEMENT

CORONARY CARE UNITS

These units are routinely equipped with a system that permits continuous monitoring of the cardiac rhythm of

each patient and hemodynamic monitoring in selected patients. Defibrillators, respirators, noninvasive transthoracic pacemakers, and facilities for introducing pacing catheters and flow-directed balloon-tipped catheters are also usually available. Equally important is the organization of a highly trained team of nurses who can recognize arrhythmias; adjust the dosage of antiarrhythmic, vasoactive, and anticoagulant drugs; and perform cardiac resuscitation, including electroshock, when necessary.

Patients should be admitted to a coronary care unit early in their illness when it is expected that they will derive benefit from the sophisticated and expensive care provided. The availability of ECG monitoring and trained personnel outside the coronary care unit has made it possible to admit lower-risk patients (e.g., those not hemodynamically compromised and without active arrhythmias) to “intermediate care units.”

The duration of stay in the coronary care unit is dictated by the ongoing need for intensive care. If symptoms are controlled with oral therapy, the patient may be transferred out of the coronary care unit. Also, patients who have a confirmed STEMI but who are considered to be at low risk (no prior infarction and no persistent chest discomfort, CHF, hypotension, or cardiac arrhythmias) may be safely transferred out of the coronary care unit within 24 h.

Activity

Factors that increase the work of the heart during the initial hours of infarction may increase the size of the infarct. Therefore, patients with STEMI should be kept on bed rest for the first 12 h. However, in the absence of complications, patients should be encouraged, under supervision, to resume an upright posture by dangling their feet over the side of the bed and sitting in a chair within the first 24 h. This practice is psychologically beneficial and usually results in a reduction in the pulmonary capillary wedge pressure. In the absence of hypotension and other complications, by the second or third day, patients typically are ambulating in their room with increasing duration and frequency, and they may shower or stand at the sink to bathe. By day 3 after infarction, patients should be increasing their ambulation progressively to a goal of 185 m (600 ft) at least three times a day.

Diet

Because of the risk of emesis and aspiration soon after STEMI, patients should receive either nothing or only clear liquids by mouth for the first 4–12 h. The typical coronary care unit diet should provide $\leq 30\%$ of total calories as fat and have a cholesterol content of ≤ 300 mg/d. Complex carbohydrates should make up 50–55% of total calories. Portions should not be unusually large, and the menu should be enriched with foods that are

334 high in potassium, magnesium, and fiber but low in sodium. Patients with diabetes mellitus and hypertriglyceridemia are managed by restriction of concentrated sweets in the diet.

Bowels

Bed rest and the effect of the narcotics used for the relief of pain often lead to constipation. A bedside commode rather than a bedpan, a diet rich in bulk, and the routine use of a stool softener such as dioctyl sodium sulfosuccinate (200 mg/d) are recommended. If the patient remains constipated despite these measures, a laxative can be prescribed. Contrary to prior belief, it is safe to perform a gentle rectal examination on patients with STEMI.

Sedation

Many patients require sedation during hospitalization to withstand the period of enforced inactivity with tranquility. Diazepam (5 mg), oxazepam (15–30 mg), or lorazepam (0.5–2 mg), given three or four times daily, is usually effective. An additional dose of any of the above medications may be given at night to ensure adequate sleep. Attention to this problem is especially important during the first few days in the coronary care unit, where the atmosphere of 24-h vigilance may interfere with the patient's sleep. However, sedation is no substitute for reassuring, quiet surroundings. Many drugs used in the coronary care unit, such as atropine, H₂ blockers, and narcotics, can produce delirium, particularly in elderly patients. This effect should not be confused with agitation, and it is wise to conduct a thorough review of the patient's medications before arbitrarily prescribing additional doses of anxiolytics.

PHARMACOTHERAPY

ANTITHROMBOTIC AGENTS

The use of antiplatelet and antithrombin therapy during the initial phase of STEMI is based on extensive laboratory and clinical evidence that thrombosis plays an important role in the pathogenesis of this condition. The primary goal of treatment with antiplatelet and antithrombin agents is to establish and maintain patency of the infarct-related artery in conjunction with reperfusion strategies. A secondary goal is to reduce the patient's tendency to thrombosis and thus the likelihood of mural thrombus formation or deep venous thrombosis, either of which could result in pulmonary embolization. The degree to which antiplatelet and antithrombin therapy achieves these goals partly determines how effectively it reduces the risk of mortality from STEMI.

As noted previously (see Management in the Emergency Department earlier in this chapter), aspirin is the

standard antiplatelet agent for patients with STEMI. The most compelling evidence for the benefits of antiplatelet therapy (mainly with aspirin) in STEMI is found in the comprehensive overview by the Antiplatelet Trialists' Collaboration. Data from nearly 20,000 patients with MI enrolled in 15 randomized trials were pooled and revealed a relative reduction of 27% in the mortality rate, from 14.2% in control patients to 10.4% in patients receiving antiplatelet agents.

Inhibitors of the P2Y₁₂ ADP receptor prevent activation and aggregation of platelets. The addition of the P2Y₁₂ inhibitor clopidogrel to background treatment with aspirin to STEMI patients reduces the risk of clinical events (death, reinfarction, stroke), and in patients receiving fibrinolytic therapy, it has been shown to prevent reocclusion of a successfully reperfused infarct artery (**Fig. 34-5**). GP IIb/IIIa receptor inhibitors appear useful for preventing thrombotic complications in patients with STEMI undergoing PCI.

The standard antithrombin agent used in clinical practice is unfractionated heparin (UFH). The available data suggest that when UFH is added to a regimen of aspirin and a non-fibrin-specific thrombolytic agent such as streptokinase, additional mortality benefit occurs (~5 lives saved per 1000 patients treated). It appears that the immediate administration of IV UFH, in addition to a regimen of aspirin and relatively fibrin-specific fibrinolytic agents (tPA, rPA, or TNK), helps to maintain the patency of the infarct-related artery. This effect is achieved at the cost of a small increased risk of bleeding. The recommended dose of UFH is an initial bolus of 60 U/kg (maximum, 4000 U) followed by an initial infusion of 12 U/kg/h (maximum, 1000 U/h). The activated partial thromboplastin time during maintenance therapy should be 1.5–2 times the control value.

An alternative to UFH for anticoagulation of patients with STEMI are the low-molecular-weight heparin (LMWH) preparations, which are formed by enzymatic or chemical depolymerization to produce saccharide chains of varying length but with a mean molecular weight of about 5000 Da. Advantages of LMWHs include high bioavailability permitting administration subcutaneously, reliable anticoagulation without monitoring, and greater antiXa:IIa activity. Enoxaparin has been shown to significantly reduce the composite endpoints of death/nonfatal reinfarction (**Fig. 34-6**) and death/nonfatal reinfarction, and urgent revascularization compared with UFH in STEMI patients who receive fibrinolysis. Although treatment with enoxaparin is associated with higher rates of serious bleeding, net clinical benefit—a composite endpoint that combines efficacy and safety—strongly favors enoxaparin over UFH.

Patients with an anterior location of the infarction, severe LV dysfunction, heart failure, a history of embolism, two-dimensional echocardiographic evidence of mural thrombus, or atrial fibrillation are at increased risk of

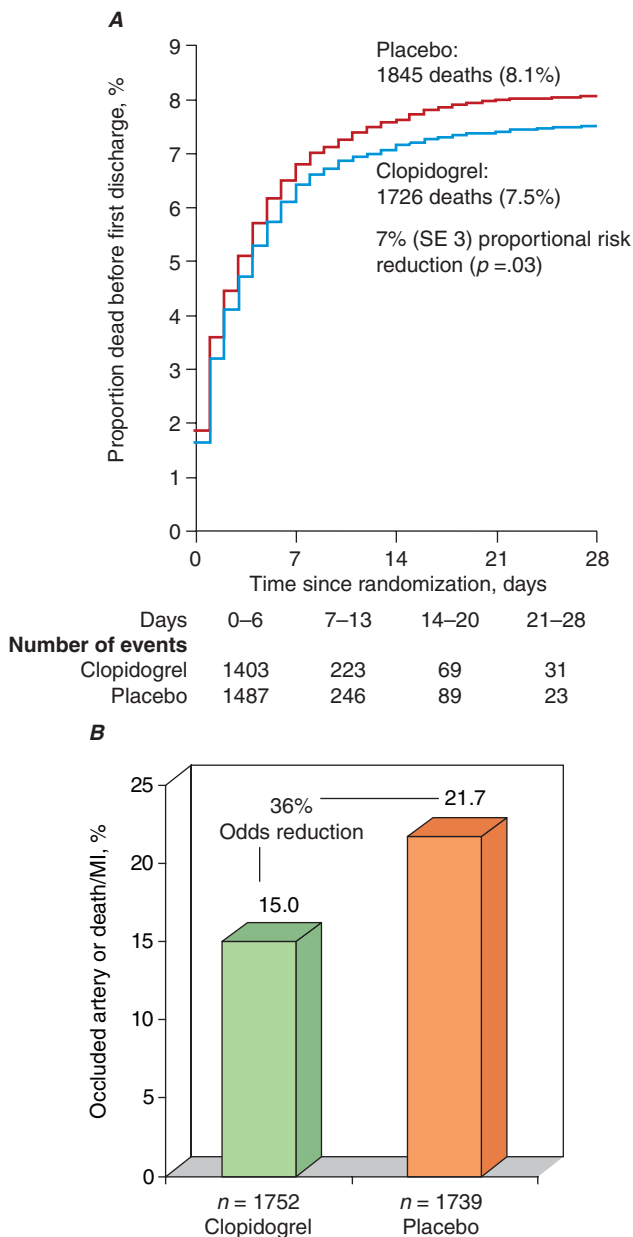


FIGURE 34-5

A. Effect of the addition of clopidogrel on in-hospital mortality after ST-segment elevation myocardial infarction (STEMI). These time-to-event curves show a 0.6% reduction in mortality in the group receiving clopidogrel plus aspirin ($n = 22,961$) compared with placebo plus aspirin ($n = 22,891$) in the COMMIT trial. **B.** Effects of the addition of clopidogrel in patients receiving fibrinolysis for STEMI. Patients in the clopidogrel group ($n = 1752$) had a 36% reduction in the odds of dying, sustaining a recurrent infarction, or having an occluded infarct artery compared with the placebo group ($n = 1739$) in the CLARITY-TIMI 28 trial ($p < .001$). MI, myocardial infarction; SE, standard error. (Part A reproduced with permission from Chen ZM et al: Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 366:1607, 2005; part B adapted from Sabatine MS et al: Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 352:1179, 2005.)

systemic or pulmonary thromboembolism. Such individuals should receive full therapeutic levels of antithrombin therapy (LMWH or UFH) while hospitalized followed by at least 3 months of warfarin therapy.

β -ADRENOCEPTOR BLOCKERS

The benefits of β -blockers in patients with STEMI can be divided into those that occur immediately when the drug is given acutely and those that accrue over the long term when the drug is given for secondary prevention after an infarction. Acute IV β blockade improves the myocardial O_2 supply–demand relationship, decreases pain, reduces infarct size, and decreases the incidence of serious ventricular arrhythmias. In patients who undergo fibrinolysis soon after the onset of chest pain, no incremental reduction in mortality rate is seen with β blockers, but recurrent ischemia and reinfarction are reduced.

Thus, β -blocker therapy after STEMI is useful for most patients [including those treated with an angiotensin-converting enzyme (ACE) inhibitor] except those in whom it is specifically contraindicated (patients with heart failure or severely compromised LV function, heart block, orthostatic hypotension, or a history of asthma) and perhaps those whose excellent long-term prognosis (defined as an expected mortality rate of $<1\%$ per year, patients younger than age 55 years, no previous MI, with normal ventricular function, no complex ventricular ectopy, and no angina) markedly diminishes any potential benefit.

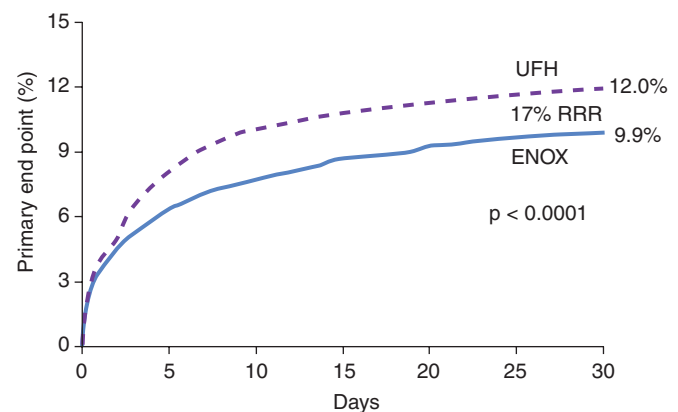


FIGURE 34-6

Enoxaparin (ENOX) is superior to unfractionated heparin (UFH) in ST-segment elevation myocardial infarction (STEMI) patients receiving fibrinolysis. In the ExTRACT-TIMI 25 trial, patients receiving the low-molecular-weight heparin enoxaparin in addition to a fibrinolytic agent plus aspirin ($n = 10,256$) had a significantly lower rate of the composite endpoint of death or nonfatal reinfarction compared to patients receiving UFH in combination with a fibrinolytic plus aspirin ($n = 10,223$). RRR, relative risk reduction. (Reproduced with permission from Antman EM et al: Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med* 354:1477, 2006.)

ACE inhibitors reduce the mortality rate after STEMI, and the mortality benefits are additive to those achieved with aspirin and β -blockers. The maximum benefit is seen in high-risk patients (those who are elderly or who have an anterior infarction, a prior infarction, or globally depressed LV function), but evidence suggests that a short-term benefit occurs when ACE inhibitors are prescribed unselectively to all hemodynamically stable patients with STEMI (i.e., those with a systolic pressure >100 mmHg). The mechanism involves a reduction in ventricular remodeling after infarction (see Ventricular Dysfunction later in the chapter) with a subsequent reduction in the risk of CHF. The rate of recurrent infarction may also be lower in patients treated chronically with ACE inhibitors after infarction.

Before hospital discharge, LV function should be assessed with an imaging study. ACE inhibitors should be continued indefinitely in patients who have clinically evident CHF, in patients in whom an imaging study shows a reduction in global LV function or a large regional wall motion abnormality, or in those who have hypertension.

Angiotensin receptor blockers (ARBs) should be administered to STEMI patients who are intolerant of ACE inhibitors and who have either clinical or radiologic signs of heart failure. Long-term aldosterone blockade should be prescribed for STEMI patients without significant renal dysfunction (creatinine ≥ 2.5 mg/dL in men and ≥ 2.0 mg/dL in women) or hyperkalemia (potassium ≥ 5.0 mEq/L) who are already receiving therapeutic doses of an ACE inhibitor, an LV ejection fraction (LVEF) $\leq 40\%$, and either symptomatic heart failure or diabetes mellitus. A multidrug regimen for inhibiting the renin-angiotensin-aldosterone system has been shown to reduce both heart failure-related and sudden cardiac death-related cardiovascular mortality after STEMI but has not been as thoroughly explored as ACE inhibitors in STEMI patients.

OTHER AGENTS

Favorable effects on the ischemic process and ventricular remodeling (see later) previously led many physicians to routinely use *IV nitroglycerin* (5–10 $\mu\text{g}/\text{min}$ for the initial dose and ≤ 200 $\mu\text{g}/\text{min}$ as long as hemodynamic stability is maintained) for the first 24–48 h after the onset of infarction. However, the benefits of routine use of *IV nitroglycerin* are less in the contemporary era because β -adrenoceptor blockers and ACE inhibitors are routinely prescribed for patients with STEMI.

Results of multiple trials of different calcium antagonists have failed to establish a role for these agents in the treatment of most patients with STEMI. Therefore, the routine use of calcium antagonists cannot be recommended. Strict control of blood glucose in diabetic

patients with STEMI has been shown to reduce the mortality rate. Serum magnesium should be measured in all patients on admission, and any demonstrated deficits should be corrected to minimize the risk of arrhythmias.

COMPLICATIONS AND THEIR MANAGEMENT

VENTRICULAR DYSFUNCTION

After STEMI, the LV undergoes a series of changes in shape, size, and thickness in both the infarcted and noninfarcted segments. This process is referred to as *ventricular remodeling* and generally precedes the development of clinically evident CHF in the months to years after infarction. Soon after STEMI, the LV begins to dilate. Acutely, this results from expansion of the infarct—i.e., slippage of muscle bundles, disruption of normal myocardial cells, and tissue loss within the necrotic zone—resulting in disproportionate thinning and elongation of the infarct zone. Later, lengthening of the noninfarcted segments occurs as well. The overall chamber enlargement that occurs is related to the size and location of the infarct, with greater dilation after infarction of the anterior wall and apex of the LV and causing more marked hemodynamic impairment, more frequent heart failure, and a poorer prognosis. Progressive dilatation and its clinical consequences may be ameliorated by therapy with ACE inhibitors and other vasodilators (e.g., nitrates). In patients with an ejection fraction $<40\%$, regardless of whether or not heart failure is present, ACE inhibitors or ARBs should be prescribed (see Inhibition of the Renin-Angiotensin-Aldosterone System earlier in the chapter).

HEMODYNAMIC ASSESSMENT

Pump failure is now the primary cause of in-hospital death from STEMI. The extent of infarction correlates well with the degree of pump failure and with mortality, both early (within 10 days of infarction) and later. The most common clinical signs are pulmonary rales and S_3 and S_4 gallop sounds. Pulmonary congestion is also frequently seen on the chest radiogram. Elevated LV filling pressure and elevated pulmonary artery pressure are the characteristic hemodynamic findings, but these findings may result from a reduction of ventricular compliance (diastolic failure) or a reduction of stroke volume with secondary cardiac dilation (systolic failure).

A classification originally proposed by Killip divides patients into four groups: class I, no signs of pulmonary or venous congestion; class II, moderate heart failure as evidenced by rales at the lung bases, S_3 gallop, tachypnea, or signs of failure of the right side of the heart, including venous and hepatic congestion; class III, severe heart failure, pulmonary edema; and class IV, shock with systolic pressure <90 mmHg and evidence of peripheral vasoconstriction, peripheral cyanosis, mental confusion,

and oliguria. When this classification was established in 1967, the expected hospital mortality rate of patients in these classes was as follows: class I, 0–5%; class II, 10–20%; class III, 35–45%; and class IV, 85–95%. With advances in management, the mortality rate in each class has fallen, perhaps by as much as one-third to one-half.

Hemodynamic evidence of abnormal global LV function appears when contraction is seriously impaired in 20–25% of the LV. Infarction of $\geq 40\%$ of the LV usually results in cardiogenic shock (Chap. 31). Positioning of a balloon flotation (Swan-Ganz) catheter in the pulmonary artery permits monitoring of LV filling pressure; this technique is useful in patients who exhibit hypotension or clinical evidence of CHF. Cardiac output can also be determined with a pulmonary artery catheter. With the addition of intraarterial pressure monitoring, systemic vascular resistance can be calculated as a guide to adjusting vasopressor and vasodilator therapy. Some patients with STEMI have markedly elevated LV filling pressures (>22 mmHg) and normal cardiac indices [$2.6\text{--}3.6$ L/(min/m²)], but others have relatively low LV filling pressures (<15 mmHg) and reduced cardiac indices. The former patients usually benefit from diuresis, and the latter may respond to volume expansion.

Hypovolemia

Hypovolemia is an easily corrected condition that may contribute to the hypotension and vascular collapse associated with STEMI in some patients. It may be secondary to previous diuretic use, reduced fluid intake during the early stages of the illness, to vomiting associated with pain or medications. Consequently, hypovolemia should be identified and corrected in patients with STEMI and hypotension before more vigorous forms of therapy are begun. Central venous pressure reflects RV rather than LV filling pressure and is an inadequate guide for adjustment of blood volume because LV function is almost always affected much more adversely than RV function in patients with STEMI. The optimal LV filling or pulmonary artery wedge pressure may vary considerably among patients. Each patient's ideal level (generally ~ 20 mmHg) is reached by cautious fluid administration during careful monitoring of oxygenation and cardiac output. Eventually, the cardiac output level plateaus, and further increases in LV filling pressure only increase congestive symptoms and decrease systemic oxygenation without increasing arterial pressure.

Rx Treatment: CONGESTIVE HEART FAILURE

The management of patients with CHF in association with STEMI is similar to that for patients with acute heart failure secondary to other forms of heart disease (avoidance of hypoxemia, diuresis, afterload reduction, inotropic

support) except that the benefits of digitalis administration to patients with STEMI are unimpressive. By contrast, diuretic agents are extremely effective because they diminish pulmonary congestion in the presence of systolic or diastolic heart failure. LV filling pressure decreases, and orthopnea and dyspnea improve after the IV administration of furosemide or other loop diuretics. These drugs should be used with caution, however, because their use can result in a massive diuresis with associated decreases in plasma volume, cardiac output, systemic blood pressure, and hence coronary perfusion. Nitrates in various forms may be used to decrease preload and congestive symptoms. Oral isosorbide dinitrate, topical nitroglycerin ointment, and IV nitroglycerin all have the advantage over a diuretic of lowering preload through venodilation without decreasing the total plasma volume. In addition, nitrates may improve ventricular compliance if ischemia is present because ischemia causes an elevation of LV filling pressure. Vasodilators must be used with caution to prevent serious hypotension. As noted earlier, ACE inhibitors are an ideal class of drugs managing patients with ventricular dysfunction after STEMI, especially for the long term (see Inhibition of the Renin-Angiotensin-Aldosterone System earlier in the chapter).

CARDIOGENIC SHOCK

Prompt reperfusion, efforts to reduce the infarct size, and treatment of ongoing ischemia and other complications of MI appear to have reduced the incidence of cardiogenic shock from 20% to about 7%. Only 10% of patients with this condition present with it on admission; 90% develop it during hospitalization. Typically, patients who develop cardiogenic shock have severe multivessel coronary artery disease with evidence of “piecemeal” necrosis extending outward from the original infarct zone. The evaluation and management of patients with cardiogenic shock and severe power failure after STEMI are discussed in detail in Chap. 31.

RIGHT VENTRICULAR INFARCTION

Approximately one-third of patients with inferior infarction demonstrate at least a minor degree of RV necrosis. An occasional patient with inferoposterior LV infarction also has extensive RV infarction, and rare patients present with infarction limited primarily to the RV. Clinically significant RV infarction causes signs of severe RV failure (jugular venous distention, Kussmaul's sign, hepatomegaly) with or without hypotension. ST-segment elevations of right-sided precordial ECG leads, particularly lead V_{4R}, are frequently present in the first 24 h in patients with RV infarction. Two-dimensional echocardiography is helpful in determining the degree of RV dysfunction. Catheterization of the right side of the heart often

338 reveals a distinctive hemodynamic pattern resembling constrictive pericarditis (steep right atrial “y” descent and an early diastolic dip and plateau in RV waveforms). Therapy consists of volume expansion to maintain adequate RV preload and efforts to improve LV performance with attendant reduction in pulmonary capillary wedge and pulmonary arterial pressures.

ARRHYTHMIAS

The incidence of arrhythmias after STEMI is higher in patients seen early after the onset of symptoms. The mechanisms responsible for infarction-related arrhythmias include autonomic nervous system imbalance, electrolyte disturbances, ischemia, and slowed conduction in zones of ischemic myocardium. An arrhythmia can usually be managed successfully if trained personnel and appropriate equipment are available when it develops. Because most deaths from arrhythmia occur during the first few hours after infarction, the effectiveness of treatment relates directly to the speed with which patients come under medical observation. The prompt management of arrhythmias constitutes a significant advance in the treatment of patients with STEMI.

Ventricular Premature Beats

Infrequent, sporadic ventricular premature depolarizations occur in almost all patients with STEMI and do not require therapy. Whereas in the past, patients with frequent, multifocal, or early diastolic ventricular extrasystoles (so-called *warning arrhythmias*) were routinely treated with antiarrhythmic drugs to reduce the risk of development of ventricular tachycardia and ventricular fibrillation, pharmacologic therapy is now reserved for patients with sustained ventricular arrhythmias. Prophylactic antiarrhythmic therapy (either IV lidocaine early or oral agents later) is contraindicated for ventricular premature beats in the absence of clinically important ventricular tachyarrhythmias because such therapy may actually increase the mortality rate. β -adrenoceptor blocking agents are effective in abolishing ventricular ectopic activity in patients with STEMI and in the prevention of ventricular fibrillation. As described above (see β -Adrenoceptor Blockers, earlier), they should be used routinely in patients without contraindications. In addition, hypokalemia and hypomagnesemia are risk factors for ventricular fibrillation in patients with STEMI; the serum potassium concentration should be adjusted to approximately 4.5 mmol/L and magnesium to about 2.0 mmol/L.

Ventricular Tachycardia and Fibrillation

Within the first 24 h of STEMI, ventricular tachycardia and fibrillation can occur without prior warning

arrhythmias. The occurrence of ventricular fibrillation can be reduced by prophylactic administration of IV lidocaine. However, prophylactic use of lidocaine has not been shown to reduce overall mortality from STEMI. In fact, in addition to causing possible noncardiac complications, use of lidocaine may predispose patients to an excess risk of bradycardia and asystole. For these reasons and with earlier treatment of patients with active ischemia, more frequent use of β -blocking agents, and the nearly universal success of electrical cardioversion or defibrillation, routine prophylactic antiarrhythmic drug therapy *is no longer recommended*.

Patients with sustained ventricular tachycardia that is well tolerated hemodynamically should be treated with an IV regimen of amiodarone (bolus of 150 mg over 10 min followed by infusion of 1.0 mg/min for 6 h and then 0.5 mg/min) or procainamide (bolus of 15 mg/kg over 20–30 min; infusion of 1–4 mg/min); if it does not stop promptly, electroversion should be used. An unsynchronized discharge of 200–300 J (monophasic wave form; ~50% of these energies with biphasic wave forms) is used immediately in patients with ventricular fibrillation or when ventricular tachycardia causes hemodynamic deterioration. Ventricular tachycardia or fibrillation that is refractory to electroshock may be more responsive after the patient is treated with epinephrine (1 mg IV or 10 mL of a 1:10,000 solution via the intracardiac route) or amiodarone (a 75–150-mg bolus).

Ventricular arrhythmias, including the unusual form of ventricular tachycardia known as torsades des pointes, may occur in patients with STEMI as a consequence of other concurrent problems (e.g., hypoxia, hypokalemia, or other electrolyte disturbances) or of the toxic effects of an agent being administered to the patient (e.g., digoxin or quinidine). A search for such secondary causes should always be undertaken.

Although the in-hospital mortality rate is increased, the long-term survival is excellent in patients who survive to hospital discharge after *primary* ventricular fibrillation (i.e., ventricular fibrillation that is a primary response to acute ischemia that occurs during the first 48 h and is not associated with predisposing factors such as CHF, shock, bundle branch block, or ventricular aneurysm). This result is in sharp contrast to the poor prognosis for patients who develop ventricular fibrillation *secondary* to severe pump failure. For patients who develop ventricular tachycardia or ventricular fibrillation late in their hospital course (i.e., after the first 48 h), the mortality rate is increased both in-hospital and during long-term follow-up. Such patients should be considered for electrophysiologic study and implantation of a cardioverter/defibrillator (ICD). A more challenging issue is the prevention of sudden cardiac death from ventricular fibrillation late after STEMI in patients who have not exhibited sustained ventricular tachyarrhythmias during their index hospitalization. An algorithm for

selection of patients who warrant prophylactic implantation of an ICD is shown in Fig. 34-7.

Accelerated Idioventricular Rhythm

Accelerated idioventricular rhythm (AIVR; “slow ventricular tachycardia”), a ventricular rhythm with a rate of 60–100 bpm, occurs in 25% of patients with STEMI. It often occurs transiently during fibrinolytic therapy at the time of reperfusion. For the most part, AIVR is benign and does not presage the development of classic ventricular tachycardia. Most episodes of AIVR do not require treatment if the patient is monitored carefully because degeneration into a more serious arrhythmia is rare.

Supraventricular Arrhythmias

Sinus tachycardia is the most common supraventricular arrhythmia. If it occurs secondary to another cause (e.g.,

anemia, fever, heart failure, or a metabolic derangement), the primary problem should be treated first. However, if it appears to be caused by sympathetic overstimulation (e.g., as part of a hyperdynamic state), then treatment with a β -blocker is indicated. Other common arrhythmias in this group are atrial flutter and atrial fibrillation, which are often secondary to LV failure. Digoxin is usually the treatment of choice for patients with supraventricular arrhythmias if heart failure is present. If heart failure is absent, β -blockers, verapamil, or diltiazem are suitable alternatives for controlling the ventricular rate because they may also help to control ischemia. If the abnormal rhythm persists for >2 h with a ventricular rate >120 bpm or if tachycardia induces heart failure, shock, or ischemia (as manifested by recurrent pain or ECG changes), a synchronized electroshock (100–200 J monophasic wave form) should be used.

Accelerated junctional rhythms have diverse causes but may occur in patients with inferoposterior infarction. Digitalis excess must be ruled out. In some patients with severely compromised LV function, the loss of appropriately timed atrial systole results in a marked reduction of cardiac output. Right atrial or coronary sinus pacing is indicated in such instances.

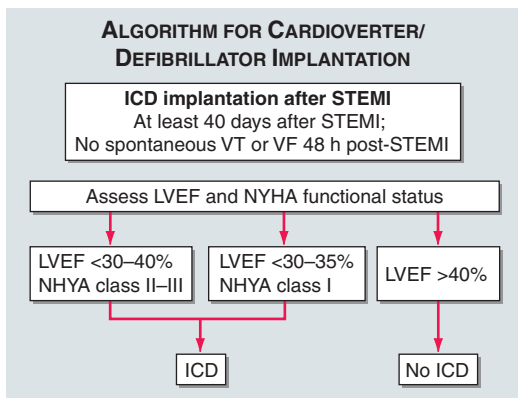


FIGURE 34-7

Algorithm for assessment of need for implantation of a cardioverter/defibrillator (ICD). The appropriate management is selected based on measurement of left ventricular ejection fraction (LVEF) and assessment of the New York Heart Association (NYHA) functional class. Patients with depressed LV function at least 40 days after ST-segment elevation myocardial infarction (STEMI) are referred for insertion of an ICD if the LVEF is <30–40% and they are in NYHA class II to III or if the LVEF is <30–35% and they are in NYHA class I functional status. Patients with preserved LV function (LVEF >40%) do not receive an ICD regardless of NYHA functional class. All patients are treated with medical therapy after STEMI. VF, ventricular fibrillation; VT, ventricular tachycardia. [Adapted from data contained in Zipes DP et al: ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death; a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). *J Am Coll Cardiol* 48:1064, 2006.]

Sinus Bradycardia

Treatment of sinus bradycardia is indicated if hemodynamic compromise results from the slow heart rate. Atropine is the most useful drug for increasing the heart rate and should be given IV in doses of 0.5 mg initially. If the rate remains <50–60 bpm, additional doses of 0.2 mg, up to a total of 2.0 mg, may be given. Persistent bradycardia (<40 bpm) despite atropine may be treated with electrical pacing. Isoproterenol should be avoided.

Atrioventricular and Intraventricular Conduction Disturbances

Both the in-hospital mortality rate and the postdischarge mortality rate of patients who have complete atrioventricular (AV) block in association with anterior infarction are markedly higher than those of patients who develop AV block with inferior infarction. This difference is related to the fact that heart block in inferior infarction is commonly a result of increased vagal tone or the release of adenosine and therefore is transient. In anterior wall infarction, however, heart block is usually related to ischemic malfunction of the conduction system, which is commonly associated with extensive myocardial necrosis.

Temporary electrical pacing provides an effective means of increasing the heart rate of patients with bradycardia caused by AV block. However, acceleration of the heart rate may have only a limited impact on prognosis in patients with anterior wall infarction and complete

340 heart block in whom the large size of the infarct is the major factor determining outcome. It should be carried out if it improves hemodynamics. Pacing does appear to be beneficial in patients with inferoposterior infarction who have complete heart block associated with heart failure, hypotension, marked bradycardia, or significant ventricular ectopic activity. A subgroup of these patients, those with RV infarction, often respond poorly to ventricular pacing because of the loss of the atrial contribution to ventricular filling. In such patients, dual-chamber AV sequential pacing may be required.

External noninvasive pacing electrodes should be positioned in a “demand” mode for patients with sinus bradycardia (rate <50 bpm) that is unresponsive to drug therapy, Mobitz II second-degree AV block, third-degree heart block, or bilateral bundle branch block (e.g., right bundle branch block plus left anterior fascicular block). Retrospective studies suggest that permanent pacing may reduce the long-term risk of sudden death caused by bradyarrhythmias in rare patients who develop combined persistent bifascicular and transient third-degree heart block during the acute phase of MI.

OTHER COMPLICATIONS

Recurrent Chest Discomfort

Recurrent angina develops in ~25% of patients hospitalized for STEMI. This percentage is even higher in patients who undergo successful fibrinolysis. Because recurrent or persistent ischemia often heralds extension of the original infarct or reinfarction in a new myocardial zone and is associated with a near tripling of mortality after STEMI, patients with these symptoms should be referred for prompt coronary arteriography and mechanical revascularization. Repeat administration of a fibrinolytic agent is an alternative to early mechanical revascularization.

Pericarditis

Pericardial friction rubs and pericardial pain are frequently encountered in patients with STEMI involving the epicardium. This complication can usually be managed with aspirin (650 mg four times daily). It is important to diagnose the chest pain of pericarditis accurately because failure to recognize it may lead to the erroneous diagnosis of recurrent ischemic pain or infarct extension, with resulting inappropriate use of anticoagulants, nitrates, β -blockers, or coronary arteriography. When it occurs, complaints of pain radiating to either trapezius muscle is helpful because such a pattern of discomfort is typical of pericarditis but rarely occurs with ischemic discomfort. Anticoagulants potentially could cause tamponade in the presence of acute pericarditis (as manifested by either pain or persistent rub) and therefore should not be used unless there is a compelling indication.

Thromboembolism

Clinically apparent thromboembolism complicates STEMI in ~10% of cases, but embolic lesions are found in 20% of patients in necropsy series, suggesting that thromboembolism is often clinically silent. Thromboembolism is considered to be an important contributing cause of death in 25% of patients with STEMI who die after admission to the hospital. Whereas arterial emboli originate from LV mural thrombi, most pulmonary emboli arise in the leg veins.

Thromboembolism typically occurs in association with large infarcts (especially anterior), CHF, and an LV thrombus detected by echocardiography. The incidence of arterial embolism from a clot originating in the ventricle at the site of an infarction is small but real. Two-dimensional echocardiography reveals LV thrombi in about one-third of patients with anterior wall infarction but in few patients with inferior or posterior infarction. Arterial embolism often presents as a major complication, such as hemiparesis, when the cerebral circulation is involved or hypertension if the renal circulation is compromised. When a thrombus has been clearly demonstrated by echocardiographic or other techniques or when a large area of regional wall motion abnormality is seen even in the absence of a detectable mural thrombus, systemic anticoagulation should be undertaken (in the absence of contraindications) because the incidence of embolic complications appears to be markedly lowered by such therapy. The appropriate duration of therapy is unknown, but 3–6 months is probably prudent.

Left Ventricular Aneurysm

The term *ventricular aneurysm* is usually used to describe *dyskinesis* or local expansile paradoxical wall motion. Normally functioning myocardial fibers must shorten more if stroke volume and cardiac output are to be maintained in patients with ventricular aneurysm; if they cannot, overall ventricular function is impaired. True aneurysms are composed of scar tissue and neither predispose to nor are associated with cardiac rupture.

The complications of LV aneurysm do not usually occur for weeks to months after STEMI; they include CHF, arterial embolism, and ventricular arrhythmias. Apical aneurysms are the most common and the most easily detected by clinical examination. The physical finding of greatest value is a double, diffuse, or displaced apical impulse. Ventricular aneurysms are readily detected by two-dimensional echocardiography, which may also reveal a mural thrombus in an aneurysm.

Rarely, myocardial rupture may be contained by a local area of pericardium, along with organizing thrombus and hematoma. Over time, this *pseudoaneurysm* enlarges, maintaining communication with the LV cavity through a narrow neck. Because a pseudoaneurysm often

ruptures spontaneously, it should be surgically repaired if recognized.

POSTINFARCTION RISK STRATIFICATION AND MANAGEMENT

Many clinical and laboratory factors have been identified that are associated with an increase in cardiovascular risk after initial recovery from STEMI. Some of the most important factors include persistent ischemia (spontaneous or provoked), depressed LVEF (<40%), rales above the lung bases on physical examination or congestion on chest radiograph, and symptomatic ventricular arrhythmias. Other features associated with increased risk include a history of MI, age >75, diabetes mellitus, prolonged sinus tachycardia, hypotension, ST-segment changes at rest without angina (“silent ischemia”), an abnormal signal-averaged ECG, nonpatency of the infarct-related coronary artery (if angiography is undertaken), and persistent advanced heart block or a new intraventricular conduction abnormality on the ECG. Therapy must be individualized on the basis of the relative importance of the risk(s) present.

The goal of preventing reinfarction and death after recovery from STEMI has led to strategies to evaluate risk after infarction. In stable patients, submaximal exercise stress testing may be carried out before hospital discharge to detect residual ischemia and ventricular ectopy and to provide the patient with a guideline for exercise in the early recovery period. Alternatively, or in addition, a maximal (symptom-limited) exercise stress test may be carried out 4–6 weeks after infarction. Evaluation of LV function is usually warranted as well. Recognition of a depressed LVEF by echocardiography or radionuclide ventriculography identifies patients who should receive medications to inhibit the renin–angiotensin–aldosterone system. Patients in whom angina is induced at relatively low workloads, those who have a large reversible defect on perfusion imaging or a depressed ejection fraction, those with demonstrable ischemia, and those in whom exercise provokes symptomatic ventricular arrhythmias should be considered at high risk for recurrent MI or death from arrhythmia (Fig. 34-7). Cardiac catheterization with coronary angiography, invasive electrophysiologic evaluation, or both is advised.

Exercise tests also aid in formulating an individualized exercise prescription, which can be much more vigorous in patients who tolerate exercise without any of the above-mentioned adverse signs. Additionally, pre-discharge stress testing may provide an important psychological benefit, building the patient’s confidence by demonstrating a reasonable exercise tolerance.

In many hospitals, a cardiac rehabilitation program with progressive exercise is initiated in the hospital and continued after discharge. Ideally, such programs should

include an educational component that informs patients about their disease and its risk factors.

The usual duration of hospitalization for an uncomplicated STEMI is about 5 days. The remainder of the convalescent phase may be accomplished at home. During the first 1–2 weeks, the patient should be encouraged to increase activity by walking around the house and outdoors in good weather. Normal sexual activity may be resumed during this period. After 2 weeks, the physician must regulate the patient’s activity on the basis of exercise tolerance. Most patients will be able to return to work within 2–4 weeks.

SECONDARY PREVENTION

Various secondary preventive measures are at least partly responsible for the improvement in the long-term mortality and morbidity rates after STEMI. Long-term treatment with an antiplatelet agent (usually aspirin) after STEMI is associated with a 25% reduction in the risk of recurrent infarction, stroke, or cardiovascular mortality (36 fewer events for every 1000 patients treated). An alternative antiplatelet agent that may be used for secondary prevention in patients intolerant of aspirin is clopidogrel (75 mg/d orally). ACE inhibitors or ARBs and, in appropriate patients, aldosterone antagonists should be used indefinitely by patients with clinically evident heart failure, a moderate decrease in global ejection fraction, or a large regional wall motion abnormality to prevent late ventricular remodeling and recurrent ischemic events.

The chronic routine use of oral β -adrenoceptor blockers for at least 2 years after STEMI is supported by well-conducted placebo-controlled trials.

Evidence suggests that warfarin lowers the risk of late mortality and the incidence of reinfarction after STEMI. Most physicians prescribe aspirin routinely for all patients without contraindications and add warfarin for patients at increased risk of embolism (see Thromboembolism earlier in the chapter). Several studies suggest that in patients younger than 75 years of age, a low dose of aspirin (75–81 mg/d) in combination with warfarin administered to achieve an INR >2.0 is more effective than aspirin alone for preventing recurrent MIs and embolic cerebrovascular accidents. However, there is an increased risk of bleeding and a high rate of discontinuation of warfarin that has limited clinical acceptance of combination antithrombotic therapy. There is increased risk of bleeding when warfarin is added to dual antiplatelet therapy (aspirin and clopidogrel). However, patients who have had a stent implanted and have an indication for anticoagulation should receive dual antiplatelet therapies in combination with warfarin. Such patients should also receive a proton pump inhibitor to minimize the risk of gastrointestinal bleeding and should have regular

342 monitoring of their hemoglobin levels and stool Hematest while on combination antithrombotic therapy.

Finally, risk factors for *atherosclerosis* should be discussed with the patient and, when possible, favorably modified.

FURTHER READINGS

AMERICAN HEART ASSOCIATION: *Heart and Stroke Facts: 2005 Statistical Supplement*. Dallas, American Heart Association, 2006

ANTMAN EM: ST-elevation myocardial infarction: Management, in *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 8th ed, P Libby et al (eds). Philadelphia, Saunders Elsevier, 2008, pp 1233–1299

———: Time is muscle: Translation into practice. *J Am Coll Cardiol* 52:1216, 2008

———, BRAUNWALD E: Acute myocardial infarction, in *Braunwald's Heart Disease*, 8th ed, P Libby et al (eds). Philadelphia, Saunders, 2008

——— et al: 2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the Canadian Cardiovascular Society endorsed by the American Academy of Family Physicians: 2007 Writing Group to Review New Evidence and Update the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction, writing on behalf of the 2004 Writing Committee. *Circulation* 117(2):296, 2008

BOERSMA E et al: Acute myocardial infarction. *Lancet* 361:847, 2003

BRAUNWALD E, ANTMAN EM: ST-elevation myocardial infarction: Pathology, pathophysiology, and clinical features, in *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 8th ed, P Libby et al (eds). Philadelphia, Saunders Elsevier, 2008, pp 1207–1232

FALK E et al: Coronary plaque disruption. *Circulation* 92:657, 1995

JACOBS AK et al: Development of systems of care for ST-elevation myocardial infarction patients: executive summary. *Circulation* 116:217, 2007

LLOYD-JONES D et al: Heart disease and stroke statistics—2009 update: A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 119:e21, 2009

MEHRAN R et al: Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction (HORIZONS-AMI): 1-year results of a randomised controlled trial. *Lancet* 374:1149, 2009

MICHAELS AD, GOLDSCHLAGER N: Risk stratification after acute myocardial infarction in the reperfusion era. *Prog Cardiovasc Dis* 42:273, 2000

MONTALESCOT G et al: Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med* 344:1895, 2001

WHITE HD, CHEW DP: Acute myocardial infarction. *Lancet* 372:570, 2008

WIVIOTT SD et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 357:2001, 2007



CHAPTER 35

COMA

Allan H. Ropper

The Anatomy and Physiology of Coma	344
Laboratory Studies and Imaging	349
Differential Diagnosis of Coma	350
Brain Death	351
Prognosis	352
■ Further Readings	352

Coma is among the most common and striking problems in general medicine. It accounts for a substantial portion of admissions to emergency wards and occurs on all hospital services. Because coma demands immediate attention, the physician must use an organized approach.

There is a continuum of states of reduced alertness, the severest form being *coma*, a deep sleeplike state from which the patient cannot be aroused. *Stupor* refers to a higher degree of arousability in which the patient can be awakened only by vigorous stimuli, accompanied by motor behavior that leads to avoidance of uncomfortable or aggravating stimuli. *Drowsiness*, which is familiar to all persons, simulates light sleep and is characterized by easy arousal and the persistence of alertness for brief periods. Drowsiness and stupor are usually attended by some degree of confusion. A narrative description of the level of arousal and of the type of responses evoked by various stimuli, precisely as observed at the bedside, is preferable to ambiguous terms such as *lethargy*, *semicoma*, or *obtundation*.

Several other neurologic conditions render patients apparently unresponsive and thereby simulate coma, and certain subsyndromes of coma must be considered separately because of their special significance. Among the latter, the *vegetative state* signifies an awake but nonresponsive state. These patients have emerged from coma after a period of days or weeks to a state in which the eyelids are open, giving the appearance of wakefulness. Yawning, coughing, swallowing, as well as limb and head movements persist, but there are few, if any, meaningful responses to

the external and internal environment—in essence, an “awake coma.” Respiratory and autonomic functions are retained. The term “vegetative” is unfortunate because it is subject to misinterpretation by laypersons. The possibility of incorrectly attributing meaningful behavior to these patients has created inordinate problems. There are always accompanying signs that indicate extensive damage in both cerebral hemispheres (e.g., decerebrate or decorticate limb posturing and absent responses to visual stimuli; see later).

In the closely related but less severe *minimally conscious state*, the patient may make intermittent rudimentary vocal or motor responses. Cardiac arrest with cerebral hypoperfusion and head injuries are the most common causes of the vegetative and minimally conscious states (Chaps. 32 and 36). The prognosis for regaining mental faculties after the vegetative state has supervened for several months is very poor, and after 1 year, almost nil, hence the term *persistent vegetative state*. Most reports of dramatic recovery, when investigated carefully, are found to yield to the usual rules for prognosis, but there have been rare instances in which recovery has occurred to a demented condition and, in rare childhood cases, to an even better state.

Quite apart from the above conditions, certain syndromes that affect alertness are prone to be misinterpreted as stupor or coma. *Akinetic mutism* refers to a partially or fully awake state in which the patient is able to form impressions and think but remains virtually immobile and mute. The condition results from damage in the regions of

344 the medial thalamic nuclei or the frontal lobes (particularly lesions situated deeply or on the orbitofrontal surfaces) or from hydrocephalus. The term *abulia* is in essence a milder form of akinetic mutism used to describe mental and physical slowness and diminished ability to initiate activity. It is also generally the result of damage to the frontal lobe network. *Catatonia* is a curious hypomobile and mute syndrome that arises as part of a major psychosis, usually schizophrenia or major depression. Catatonic patients make few voluntary or responsive movements, although they blink, swallow, and may not appear distressed. There are nonetheless signs that the patient is responsive, although it may take some ingenuity on the part of the examiner to demonstrate them. For example, eyelid elevation is actively resisted, blinking occurs in response to a visual threat, and the eyes move concomitantly with head rotation, all of which are inconsistent with the presence of a brain lesion. It is characteristic but not invariable in catatonia for the limbs to retain the postures in which they have been placed by the examiner (“waxy flexibility,” or catalepsy). Upon recovery, such patients have some memory of events that occurred during their catatonic stupor. The appearance is superficially similar to akinetic mutism, but clinical evidence of cerebral damage such as Babinski signs and hypertonicity of the limbs is lacking. The singular problem of brain death is discussed later.

The *locked-in state* describes yet another type of pseudocoma in which an awake patient has no means of producing speech or volitional movement but retains voluntary vertical eye movements and eyelid elevation, thus allowing the patient to signal with a clear mind. The pupils are normally reactive. Such individuals have written entire treatises using Morse code. The usual cause is an infarction or hemorrhage of the ventral pons, which transects all descending corticospinal and corticobulbar pathways. A similar awake but de-efferented state occurs as a result of total paralysis of the musculature in severe cases of Guillain-Barré syndrome, critical illness neuropathy (Chap. 36), and pharmacologic neuromuscular blockade.

THE ANATOMY AND PHYSIOLOGY OF COMA

Almost all instances of diminished alertness can be traced to widespread abnormalities of the cerebral hemispheres or to reduced activity of a special thalamocortical alerting system termed the *reticular activating system* (RAS). The proper functioning of this system, its ascending projections to the cortex, and the cortex itself are required to maintain alertness and coherence of thought. It follows that the principal causes of coma are (1) lesions that damage the RAS or its projections; (2) destruction of large portions of both cerebral hemispheres; and (3) suppression of reticulo-cerebral function by drugs, toxins, or metabolic derangements such as hypoglycemia, anoxia, uremia, and hepatic failure.

The proximity of the RAS to structures that control pupillary function and eye movements permits clinical localization of the cause of coma in many cases. Pupillary enlargement with loss of light reaction and loss of vertical and adduction movements of the eyes suggests that the likely location of the lesion is in the upper brainstem. Conversely, preservation of pupillary reactivity and eye movements absolves the upper brainstem and indicates that widespread structural lesions or metabolic suppression of the cerebral hemispheres is responsible.

Coma Caused by Cerebral Mass Lesions and Herniations

The cranial cavity is separated into compartments by infoldings of the dura. The two cerebral hemispheres are separated by the falx and the anterior and posterior fossae by the tentorium. *Herniation* refers to displacement of brain tissue into a compartment that it normally does not occupy. Many of the signs associated with coma, and indeed coma itself, can be attributed to these tissue shifts, and certain clinical configurations are characteristic of specific herniations (Fig. 35-1). They are in essence “false localizing” signs because they derive from compression of brain structures at a distance from the mass.

The most common herniations are from the supratentorial to the infratentorial compartments through the tentorial opening, hence *transtentorial*. *Uncal transtentorial herniation* refers to impaction of the anterior medial temporal gyrus (the uncus) into the tentorial opening

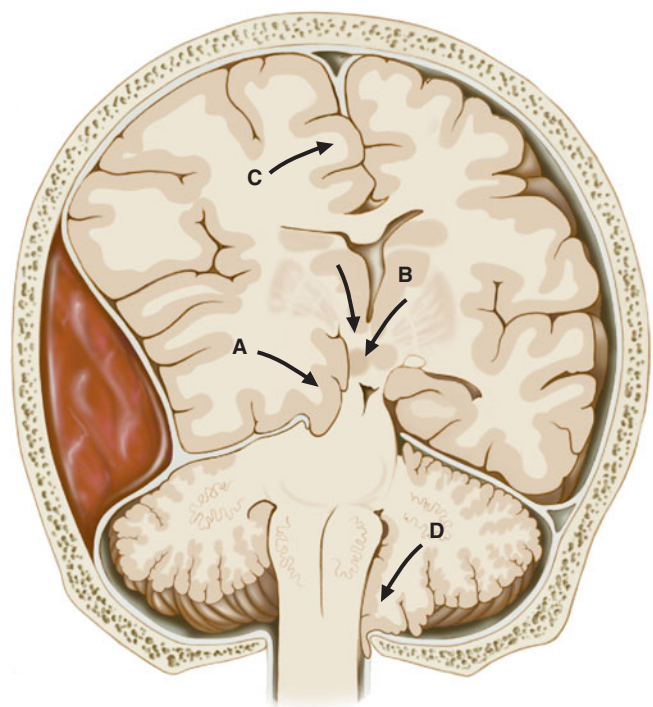


FIGURE 35-1
Types of cerebral herniation. A. Uncal. B. Central. C. Transfalcineal. D. Foraminal.

just anterior to and adjacent to the midbrain (Fig. 35-1A). The displaced brain tissue compresses the third nerve as it traverses the subarachnoid space and results in enlargement of the ipsilateral pupil (putatively because the fibers subserving parasympathetic pupillary function are located peripherally in the nerve). The coma that follows is caused by compression of the midbrain against the opposite tentorial edge by the displaced parahippocampal gyrus (Fig. 35-2). In some cases, the lateral displacement of the midbrain causes compression of the opposite cerebral peduncle, producing a Babinski sign and hemiparesis contralateral to the original hemiparesis (the Kernohan-Woltman sign). In addition to compressing the upper brainstem, tissue shifts, including herniations, may compress major blood vessels, particularly the anterior and posterior cerebral arteries as they pass over the tentorial reflections, thus producing brain infarctions. The distortions may also entrap portions of the ventricular system, resulting in regional hydrocephalus.

Central transtentorial herniation denotes a symmetric downward movement of the thalamic medial structures through the tentorial opening with compression of the upper midbrain (Fig. 35-1B). Miotic pupils and drowsiness are the heralding signs. Both temporal and central herniations have classically been considered to cause a progressive compression of the brainstem from above in an orderly manner: first the midbrain, then the pons, and finally the medulla. The result is a sequence of neurologic signs that corresponds to each affected level. Other

forms of herniation are *transfalcial herniation* (displacement of the cingulate gyrus under the falx and across the midline; Fig. 35-1C), and *foraminal herniation* (downward forcing of the cerebellar tonsils into the foramen magnum; Fig. 35-1D), which causes compression of the medulla and respiratory arrest.

A direct relationship between the various configurations of transtentorial herniations and coma is not always found. Drowsiness and stupor typically occur with moderate horizontal shifts at the level of the diencephalon (thalami) well before transtentorial or other herniations are evident. Lateral shift may be quantified on axial images of CT and MRI scans (see Fig. 35-2). In cases of *acutely appearing masses*, horizontal displacement of the pineal calcification of 3–5 mm is generally associated with drowsiness, 6–8 mm with stupor, and >9 mm with coma. Intrusion of the medial temporal lobe into the tentorial opening may be apparent on MRI and CT scans by an obliteration of the cisterns that surround the upper brainstem.

Coma Caused by Metabolic Disorders

Many systemic metabolic abnormalities cause coma by interrupting the delivery of energy substrates (hypoxia, ischemia, hypoglycemia) or by altering neuronal excitability (drug and alcohol intoxication, anesthesia, and epilepsy). The same metabolic abnormalities that produce coma may in milder form induce widespread cortical dysfunction and an acute confusional state. Thus, in metabolic encephalopathies, clouded consciousness and coma are in a continuum.

Cerebral neurons are fully dependent on cerebral blood flow (CBF) and the related delivery of oxygen and glucose. CBF is ~75 mL per 100 g/min in gray matter and 30 mL per 100 g/min in white matter (mean, 55 mL per 100 g/min); oxygen consumption is 3.5 mL per 100 g/min, and glucose utilization is 5 mg per 100 g/min. Brain stores of glucose provide energy for ~2 min after blood flow is interrupted, and oxygen stores last 8–10 s after the cessation of blood flow. Simultaneous hypoxia and ischemia exhaust glucose more rapidly. The electroencephalogram (EEG) rhythm in these circumstances becomes diffusely slowed, typical of metabolic encephalopathies, and as conditions of substrate delivery worsen, eventually all recordable brain electrical activity ceases. In almost all instances of metabolic encephalopathy, the global metabolic activity of the brain is reduced in proportion to the degree of diminished consciousness.

Conditions such as hypoglycemia, hyponatremia, hyperosmolarity, hypercapnia, hypercalcemia, and hepatic and renal failure are associated with a variety of alterations in neurons and astrocytes. Unlike hypoxia-ischemia, which causes neuronal destruction, metabolic disorders generally cause only minor neuropathologic changes. The reversible effects of these conditions on the brain are not

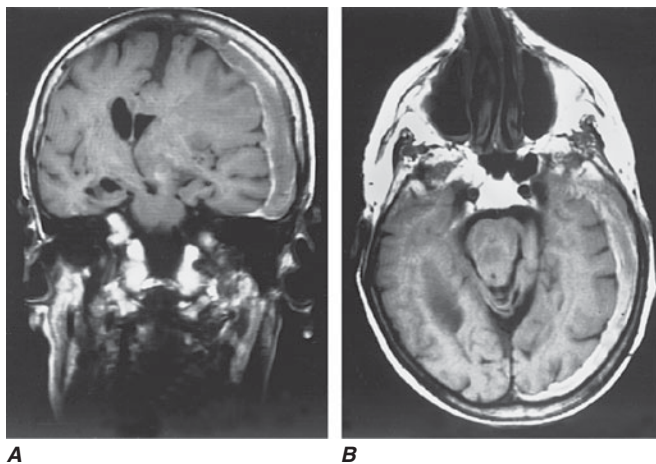


FIGURE 35-2
Coronal (A) and axial (B) MRIs from a stuporous patient with a left third nerve palsy as a result of a large left-sided subdural hematoma (seen as a gray-white rim). The upper midbrain and lower thalamic regions are compressed and displaced horizontally away from the mass, and there is transtentorial herniation of the medial temporal lobe structures, including the uncus anteriorly. The lateral ventricle opposite to the hematoma has become enlarged as a result of compression of the third ventricle.

346 understood but may result from impaired energy supplies, changes in ion fluxes across neuronal membranes, and neurotransmitter abnormalities. For example, the high brain ammonia concentration of hepatic coma interferes with cerebral energy metabolism and with the Na⁺, K⁺-ATPase pump, increases the number and size of astrocytes, alters nerve cell function, and causes increased concentrations of potentially toxic products of ammonia metabolism; it may also result in abnormalities of neurotransmitters, including putative “false” neurotransmitters that are active at receptor sites. Apart from hyperammonemia, which of these mechanisms is of critical importance is not clear. The mechanism of the encephalopathy of renal failure is also not known. Unlike ammonia, urea itself does not produce central nervous system (CNS) toxicity. A multifactorial causation has been proposed, including increased permeability of the blood–brain barrier to toxic substances such as organic acids and an increase in brain calcium or cerebrospinal fluid (CSF) phosphate content.

Coma and seizures are a common accompaniment of any large shifts in sodium and water balance in the brain. These changes in osmolarity arise from systemic medical disorders, including diabetic ketoacidosis, the nonketotic hyperosmolar state, and hyponatremia from any cause (e.g., water intoxication, excessive secretion of antidiuretic hormone or atrial natriuretic peptides). Sodium levels <125 mmol/L induce confusion, and <115 mmol/L are associated with coma and convulsions. In hyperosmolar coma, the serum osmolarity is generally >350 mosmol/L. Hypercapnia depresses the level of consciousness in proportion to the increase in the CO₂ tension in the blood. *In all of these metabolic encephalopathies, the degree of neurologic change depends to a large extent on the rapidity with which the serum changes occur.* The pathophysiology of other metabolic encephalopathies, such as hypercalcemia, hypothyroidism, vitamin B₁₂ deficiency, and hypothermia, are incompletely understood but must also reflect derangements of CNS biochemistry and membrane function.

Epileptic Coma

Continuous, generalized electrical discharges of the cortex (*seizures*) are associated with coma even in the absence of epileptic motor activity (*convulsions*). The self-limited coma that follows seizures, termed the *postictal state*, may be caused by exhaustion of energy reserves or effects of locally toxic molecules that are the byproduct of seizures. The postictal state produces a pattern of continuous, generalized slowing of the background EEG activity similar to that of other metabolic encephalopathies.

Toxic Drug–Induced Coma

This common class of encephalopathy is in large measure reversible and leaves no residual damage providing hypoxia does not supervene. Many drugs and toxins are

capable of depressing nervous system function. Some produce coma by affecting both the brainstem nuclei, including the RAS, and the cerebral cortex. The combination of cortical and brainstem signs, which occurs in certain drug overdoses, may lead to an incorrect diagnosis of structural brainstem disease. Overdose of medications that have atropinic actions produces physical signs such as dilated pupils, tachycardia, and dry skin.

Coma Caused by Widespread Damage to the Cerebral Hemispheres

This special category, comprising a number of unrelated disorders, results from widespread structural cerebral damage, thereby simulating a metabolic disorder of the cortex. The effect of prolonged hypoxia–ischemia is perhaps the best known and one in which it is not possible to distinguish the acute effects of hypoperfusion of the brain from the further effects of generalized neuronal damage. Similar bihemispherical damage is produced by disorders that occlude small blood vessels throughout the brain; examples include cerebral malaria, thrombotic thrombocytopenic purpura, and hyperviscosity. The presence of seizures and the bihemispherical damage is sometimes an indication of this class of disorder.

Approach to the Patient: COMA

Acute respiratory and cardiovascular problems should be attended to before neurologic assessment. In most instances, a complete medical evaluation, except for vital signs, funduscopy, and examination for nuchal rigidity, may be deferred until the neurologic evaluation has established the severity and nature of coma.

HISTORY In many cases, the cause of coma is immediately evident (e.g., trauma, cardiac arrest, or known drug ingestion). In the remainder, certain points are especially useful: (1) the circumstances and rapidity with which neurologic symptoms developed; (2) the antecedent symptoms (confusion, weakness, headache, fever, seizures, dizziness, double vision, or vomiting); (3) the use of medications, illicit drugs, or alcohol; and (4) chronic liver, kidney, lung, heart, or other medical disease. Direct interrogation of family members and observers on the scene, in person or by telephone, is an important part of the initial evaluation. Ambulance technicians often provide the most useful information.

GENERAL PHYSICAL EXAMINATION The temperature, pulse, respiratory rate and pattern, and blood pressure should be measured quickly. Fever suggests a systemic infection, bacterial meningitis,

or encephalitis; only rarely is it attributable to a brain lesion that has disturbed hypothalamic temperature-regulating centers (“*central fever*”). A slight elevation in temperature may occur after vigorous convulsions. High body temperature (42°–44°C) associated with dry skin should arouse the suspicion of heat stroke or anticholinergic drug intoxication. Hypothermia is observed with alcoholic, barbiturate, sedative, or phenothiazine intoxication; hypoglycemia; peripheral circulatory failure; and hypothyroidism. Hypothermia itself causes coma only when the temperature is <31°C. Tachypnea may indicate systemic acidosis or pneumonia. Aberrant respiratory patterns that reflect brainstem disorders are discussed later. Marked hypertension either indicates hypertensive encephalopathy or is the result of a rapid increase in intracranial pressure (ICP; the Cushing response), most often after cerebral hemorrhage or head injury. Hypotension is characteristic of coma from alcohol or barbiturate intoxication, internal hemorrhage, myocardial infarction, sepsis, profound hypothyroidism, or Addisonian crisis.

The fundoscopic examination can detect subarachnoid hemorrhage (subhyaloid hemorrhages), hypertensive encephalopathy (exudates, hemorrhages, vessel-crossing changes, papilledema), and increased ICP (papilledema). Cutaneous petechiae suggest thrombotic thrombocytopenic purpura, meningococemia, or a bleeding diathesis from which an intracerebral hemorrhage has arisen.

NEUROLOGIC EXAMINATION First, the patient should be observed without intervention by the examiner. Tossing about in the bed, reaching up toward the face, crossing the legs, yawning, swallowing, coughing, and moaning denote a state close to normal awakeness. Lack of restless movements on one side or an outturned leg suggests a hemiplegia. Intermittent twitching movements of a foot, finger, or facial muscle may be the only sign of seizures. Multifocal myoclonus almost always indicates a metabolic disorder, particularly uremia, anoxia, or drug intoxication (lithium and haloperidol are particularly likely to cause this sign), or the rare conditions of a prion disease or “Hashimoto encephalopathy.” In a drowsy and confused patient, bilateral *asterixis* is a certain sign of metabolic encephalopathy or drug intoxication.

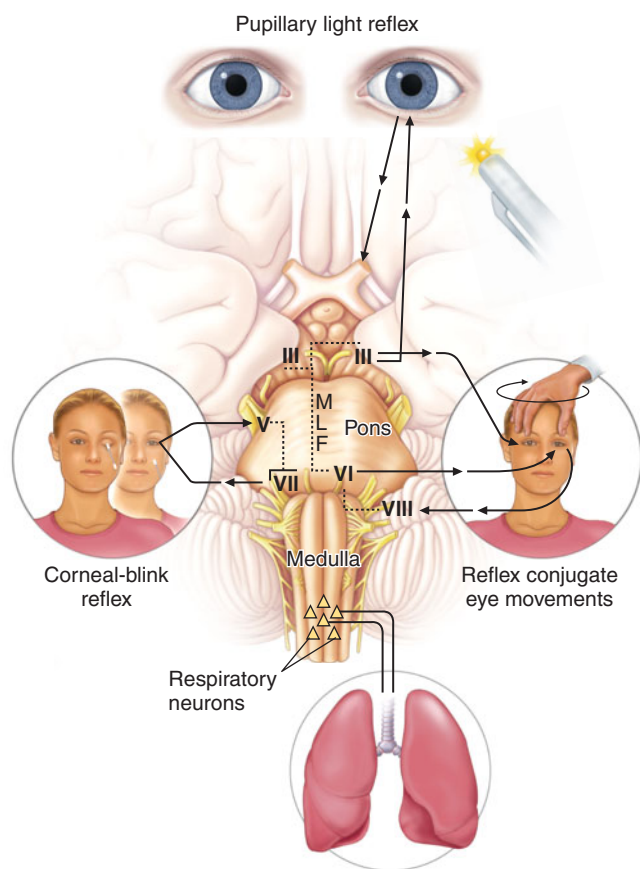
The terms *decorticate rigidity* and *decerebrate rigidity*, or “posturing,” describe stereotyped arm and leg movements that occur spontaneously or elicited by sensory stimulation. Flexion of the elbows and wrists and supination of the arm (decortication) suggests bilateral damage rostral to the midbrain, and extension of the elbows and wrists with pronation (decerebration) indicates damage to motor tracts in the midbrain or caudal diencephalon. The less frequent

combination of arm extension with leg flexion or flaccid legs is associated with lesions in the pons. These concepts have been adapted from animal work and cannot be applied with the same precision to coma in humans. In fact, acute and widespread disorders of any type, regardless of their location, frequently cause limb extension, and almost all such extensor posturing becomes predominantly flexor as time passes. Posturing may also be unilateral and may coexist with purposeful limb movements, usually reflecting incomplete damage to the motor system.

LEVEL OF AROUSAL A sequence of increasingly intense stimuli is used to determine the threshold for arousal and the optimal motor response of each side of the body. The results of testing may vary from minute to minute and serial examinations are most useful. Tickling the nostrils with a cotton wisp is a moderate stimulus to arousal—all but deeply stuporous and comatose patients will move the head away and rouse to some degree. Using the hand to remove the offending stimulus represents an even greater degree of responsiveness. Stereotyped posturing in response to noxious stimuli indicates severe dysfunction of the corticospinal system. Abduction-avoidance movement of a limb is usually purposeful and denotes an intact corticospinal system. Pressure on the knuckles or bony prominences and pinprick stimulation are humane forms of noxious stimuli; pinching the skin causes unsightly ecchymoses and is generally not necessary but may be useful in eliciting abduction withdrawal movements of the limbs.

BRAINSTEM REFLEXES Assessment of brainstem function is essential to localization of the lesion in coma (**Fig. 35-3**). The brainstem reflexes that are conveniently examined are pupillary responses to light, spontaneous and elicited eye movements, corneal responses, and the respiratory pattern. As a rule, when these brainstem activities are preserved, particularly the pupil reactions and eye movements, coma must be ascribed to bilateral hemispherical disease. The converse, however, is not always true because a mass in the hemispheres may be the underlying cause of coma but nonetheless produce brainstem signs by inducing transtentorial herniation.

Pupillary Signs Pupillary reactions are examined with a bright, diffuse light (not an ophthalmoscope); if the response is absent, this should be confirmed by observation through a magnifying lens. Normally reactive and round pupils of midsize (2.5–5 mm) essentially exclude midbrain damage, either primary or secondary to compression. Reaction to light is often difficult to appreciate in pupils <2 mm in diameter, and bright room lighting mutes pupillary reactivity.

**FIGURE 35-3**

Examination of brainstem reflexes in coma. Midbrain and third nerve function are tested by pupillary reaction to light, pontine function by spontaneous and reflex eye movements and corneal responses, and medullary function by respiratory and pharyngeal responses. Reflex conjugate, horizontal eye movements are dependent on the medial longitudinal fasciculus (MLF) interconnecting the sixth and contralateral third nerve nuclei. Head rotation (oculocephalic reflex) or caloric stimulation of the labyrinths (oculovestibular reflex) elicits contraversive eye movements (for details, see text).

One unreactive and enlarged pupil (>6 mm) or one that is poorly reactive signifies compression of the third nerve from the effects of a mass above. Enlargement of the pupil contralateral to a mass may occur first but is infrequent. An oval and slightly eccentric pupil is a transitional sign that accompanies early midbrain–third nerve compression. The most extreme pupillary sign, bilaterally dilated and unreactive pupils, indicates severe midbrain damage, usually from compression by a supratentorial mass. Ingestion of drugs with anticholinergic activity, the use of mydriatic eye drops, and direct ocular trauma are among the causes of misleading pupillary enlargement.

Unilateral miosis in coma has been attributed to dysfunction of sympathetic efferents originating in

the posterior hypothalamus and descending in the tegmentum of the brainstem to the cervical cord. It is an occasional finding with a large cerebral hemorrhage that affects the thalamus. Reactive and bilaterally small (1–2.5 mm) but not pinpoint pupils are seen in metabolic encephalopathies and in deep bilateral hemispherical lesions such as hydrocephalus and thalamic hemorrhage. Very small but reactive pupils (<1 mm) characterize narcotic and barbiturate overdoses but also occur with extensive pontine hemorrhage. The response to naloxone and the presence of reflex eye movements (see below) distinguish these.

Ocular Movements The eyes are first observed by elevating the eyelids and noting the resting position and spontaneous movements of the globes. Eyelid tone, which is tested by lifting the eyelids and noting their resistance to opening and the speed of closure, is reduced progressively as coma deepens. Horizontal divergence of the eyes at rest is normal in drowsiness. As coma deepens, the ocular axes may become parallel again.

Spontaneous eye movements in coma often take the form of conjugate horizontal roving. This finding alone exonerates the midbrain and pons and has the same significance as normal reflex eye movements (see below). Conjugate horizontal ocular deviation to one side indicates damage to the pons on the opposite side or, alternatively, to the frontal lobe on the same side. This phenomenon is summarized by the following maxim: *The eyes look toward a hemispherical lesion and away from a brainstem lesion.* Seizures also drive the eyes to one side. On rare occasions, the eyes may turn paradoxically away from the side of a deep hemispherical lesion (“wrong-way eyes”). The eyes turn down and inward as a result of thalamic and upper midbrain lesions, typically with thalamic hemorrhage. “Ocular bobbing” describes brisk downward and slow upward movements of the eyes associated with loss of horizontal eye movements and is diagnostic of bilateral pontine damage, usually from thrombosis of the basilar artery. “Ocular dipping” is a slower, arrhythmic downward movement followed by a faster upward movement in patients with normal reflex horizontal gaze; it indicates diffuse cortical anoxic damage. Many other complex eye movements are known but do not have the same clinical importance as those mentioned earlier.

The oculocephalic reflexes depend on the integrity of the ocular motor nuclei and their interconnecting tracts that extend from the midbrain to the pons and medulla. These reflexes are elicited by moving the head from side to side or vertically and observing evoked eye movements in the direction opposite to the head movement (Fig. 35–3). The movements,

called somewhat inappropriately “doll’s eyes” (which refers more accurately to the reflex elevation of the eyelids with flexion of the neck), are normally suppressed in awake patients. The ability to elicit them therefore indicates a reduced cortical influence on the brainstem. Furthermore, preservation of evoked reflex eye movements signifies the integrity of the brainstem and implies that the origin of unconsciousness lies in the cerebral hemispheres. The opposite, an absence of reflex eye movements, usually signifies damage within the brainstem but can be produced infrequently by profound overdoses of certain drugs. Normal pupillary size and light reaction distinguishes most drug-induced comas from structural brainstem damage.

Thermal, or “caloric,” stimulation of the vestibular apparatus (oculovestibular response) provides a more intense stimulus for the oculocephalic reflex but gives fundamentally the same information. The test is performed by irrigating the external auditory canal with cool water to induce convection currents in the labyrinths. After a brief latency period, the result is tonic deviation of both eyes to the side of cool-water irrigation and nystagmus in the opposite direction. (The acronym “COWS” has been used to remind generations of medical students of the direction of nystagmus—“cold water opposite, warm water same.”) The loss of conjugate ocular movements indicates brainstem damage. The absence of nystagmus despite conjugate deviation of the globes indicates that the cerebral hemispheres are damaged or metabolically suppressed.

By touching the cornea with a wisp of cotton, a response consisting of brief bilateral eyelid closure is normally observed. The corneal reflexes depend on the integrity of pontine pathways between the fifth (afferent) and both seventh (efferent) cranial nerves; although rarely useful alone, in conjunction with reflex eye movements, they are important clinical tests of pontine function. CNS depressant drugs diminish or eliminate the corneal responses soon after reflex eye movements are paralyzed but before the pupils become unreactive to light. The corneal (and pharyngeal) response may be lost for a time on the side of an acute hemiplegia.

Respiratory Patterns Respiratory patterns are of less localizing value compared with other brainstem signs. Shallow, slow, but regular breathing suggests metabolic or drug depression. Cheyne–Stokes respiration in its classic cyclic form, ending with a brief apneic period, signifies bihemispherical damage or metabolic suppression and commonly accompanies light coma. Rapid, deep (Kussmaul) breathing usually implies metabolic acidosis but may also occur with

pontomesencephalic lesions. Agonal gasps are the result of lower brainstem (medullary) damage and are well known as the terminal respiratory pattern of severe brain damage. A number of other cyclic breathing variations have been described but are of lesser significance.

LABORATORY STUDIES AND IMAGING

The studies that are most useful in the diagnosis of coma are chemical-toxicologic analysis of blood and urine, cranial CT or MRI, EEG, and CSF examination. Arterial blood gas analysis is helpful in patients with lung disease and acid–base disorders. The metabolic aberrations commonly encountered in clinical practice require measurements of electrolytes, glucose, calcium, osmolality, and renal (blood urea nitrogen) and hepatic (NH_3) function. Toxicologic analysis is necessary in any case of coma where the diagnosis is not immediately clear. However, the presence of exogenous drugs or toxins, especially alcohol, does not exclude the possibility that other factors, particularly head trauma, are also contributing to the clinical state. An ethanol level of 43 mmol/L (0.2 g/dL) in nonhabituated patients generally causes impaired mental activity and of >65 mmol/L (0.3 g/dL) is associated with stupor. The development of tolerance may allow a chronic alcoholic to remain awake at levels >87 mmol/L (0.4 g/dL).

The availability of CT and MRI has focused attention on causes of coma that are radiologically detectable (e.g., hemorrhages, tumors, or hydrocephalus). Resorting primarily to this approach, although at times expedient, is imprudent because most cases of coma (and confusion) are metabolic or toxic in origin. The notion that a normal CT scan excludes anatomic lesions as the cause of coma is also erroneous. Bilateral hemisphere infarction, acute brainstem infarction, encephalitis, meningitis, mechanical shearing of axons as a result of closed head trauma, sagittal sinus thrombosis, and subdural hematomas that are isodense to adjacent brain are some of the disorders that may not be detected. Nevertheless, if the source of coma remains unknown, a scan should be obtained.

The EEG is useful in metabolic or drug-induced states but is rarely diagnostic, except when coma is caused by clinically unrecognized seizures, to herpesvirus encephalitis, or to prion (Creutzfeldt–Jakob) disease. The amount of background slowing of the EEG is a reflection of the severity of any diffuse encephalopathy. Predominant high-voltage slowing (δ or triphasic waves) in the frontal regions is typical of metabolic coma, as from hepatic failure, and widespread fast (β) activity implicates sedative drugs (e.g., diazepam, barbiturates). A special pattern of “ α coma,” defined by widespread, variable 8- to 12-Hz

350 activity, superficially resembles the normal α rhythm of waking but is unresponsive to environmental stimuli. It results from pontine or diffuse cortical damage and is associated with a poor prognosis. Most importantly, EEG recordings may reveal clinically inapparent epileptic discharges in a patient with coma. Normal α activity on the EEG, which is suppressed by stimulating the patient, also alerts the clinician to the locked-in syndrome or to hysteria or catatonia.

Lumbar puncture is performed less frequently than in the past for coma diagnosis because neuroimaging effectively excludes intracerebral and extensive subarachnoid hemorrhage. However, examination of the CSF remains indispensable in the diagnosis of meningitis and encephalitis. Lumbar puncture should therefore not be deferred if meningitis is a possibility.

DIFFERENTIAL DIAGNOSIS OF COMA

(Table 35-1) The causes of coma can be divided into three broad categories: those without focal neurologic signs (e.g., metabolic encephalopathies); meningitis syndromes, characterized by fever or stiff neck and an excess of cells in the spinal fluid (e.g., bacterial meningitis, subarachnoid hemorrhage); and conditions associated with prominent focal signs (e.g., stroke, cerebral hemorrhage). In most instances, coma is part of an obvious medical problem such as drug ingestion, hypoxia, stroke, trauma, or liver or kidney failure. Conditions that cause sudden coma include drug ingestion, cerebral hemorrhage, trauma, cardiac arrest, epilepsy, or basilar artery embolism. Coma that appears subacutely is usually related to a preceding medical or neurologic problem,

TABLE 35-1

DIFFERENTIAL DIAGNOSIS OF COMA

1. Diseases that cause no focal or lateralizing neurologic signs, usually with normal brainstem functions; the CT scan and cellular content of the CSF are normal
 - a. Intoxications: alcohol, sedative drugs, opiates, and so on
 - b. Metabolic disturbances: anoxia, hyponatremia, hypernatremia, hypercalcemia, diabetic acidosis, nonketotic hyperosmolar hyperglycemia, hypoglycemia, uremia, hepatic coma, hypercarbia, Addisonian crisis, hypo- and hyperthyroid states, profound nutritional deficiency
 - c. Severe systemic infections: pneumonia, septicemia, typhoid fever, malaria, Waterhouse-Friderichsen syndrome
 - d. Shock from any cause
 - e. Postseizure states, status epilepticus, subclinical epilepsy
 - f. Hypertensive encephalopathy, eclampsia
 - g. Severe hyperthermia, hypothermia
 - h. Concussion
 - i. Acute hydrocephalus
2. Diseases that cause meningeal irritation with or without fever and with an excess of WBCs or RBCs in the CSF, usually without focal or lateralizing cerebral or brainstem signs; CT or MRI shows no mass lesion
 - a. Subarachnoid hemorrhage from ruptured aneurysm, arteriovenous malformation, trauma
 - b. Acute bacterial meningitis
 - c. Viral encephalitis
 - d. Miscellaneous: fat embolism, cholesterol embolism, carcinomatous and lymphomatous meningitis, and so on
3. Diseases that cause focal brainstem or lateralizing cerebral signs with or without changes in the CSF; CT and MRI are abnormal
 - a. Hemispherical hemorrhage (basal ganglionic, thalamic) or infarction (large middle cerebral artery territory) with secondary brainstem compression
 - b. Brainstem infarction caused by basilar artery thrombosis or embolism
 - c. Brain abscess, subdural empyema
 - d. Epidural and subdural hemorrhage, brain contusion
 - e. Brain tumor with surrounding edema
 - f. Cerebellar and pontine hemorrhage and infarction
 - g. Widespread traumatic brain injury
 - h. Metabolic coma (see earlier) with preexisting focal damage
 - i. Miscellaneous: cortical vein thrombosis, herpes simplex encephalitis, multiple cerebral emboli caused by bacterial endocarditis, acute hemorrhagic leukoencephalitis, acute disseminated (postinfectious) encephalomyelitis, thrombotic thrombocytopenic purpura, cerebral vasculitis, gliomatosis cerebri, pituitary apoplexy, intravascular lymphoma, and so on

Note: CSF, cerebrospinal fluid; RBC, red blood cell; WBC, white blood cell.

including the secondary brain swelling of a mass lesion such as a tumor or cerebral infarction.

Cerebrovascular diseases cause the greatest difficulty in coma diagnosis. The most common categories are (1) basal ganglia and thalamic hemorrhage (acute but not instantaneous onset, vomiting, headache, hemiplegia, and characteristic eye signs), (2) pontine hemorrhage (sudden onset, pinpoint pupils, loss of reflex eye movements and corneal responses, ocular bobbing, posturing, hyperventilation, and excessive sweating), (3) cerebellar hemorrhage (occipital headache, vomiting, gaze paresis, and inability to stand), (4) basilar artery thrombosis (neurologic prodrome or warning spells, diplopia, dysarthria, vomiting, eye movement and corneal response abnormalities, and asymmetric limb paresis), and (5) subarachnoid hemorrhage (precipitous coma after headache and vomiting). The most common stroke, infarction in the territory of the middle cerebral artery, does not generally cause coma, but edema surrounding large infarcts may expand during the first few days and act as a mass. The syndrome of acute hydrocephalus accompanies many intracranial diseases, particularly subarachnoid hemorrhage. It is characterized by headache and sometimes vomiting that may progress quickly to coma, with extensor posturing of the limbs, bilateral Babinski signs, small unreactive pupils, and impaired oculocephalic movements in the vertical direction.

If the history and examination do not indicate the cause of coma, then information obtained from CT or MRI may be needed. The majority of medical causes of coma can be established without a neuroimaging study.

BRAIN DEATH

Brain death is a state of cessation of cerebral function while somatic function is maintained by artificial means and the heart continues to pump. It is the only type of brain damage that is recognized as equivalent to death. Several similar criteria have been advanced for the diagnosis of brain death, and it is essential to adhere to the standards endorsed by the local medical community. Ideal criteria are simple, can be assessed at the bedside, and allow no chance of diagnostic error. They contain three essential elements of clinical evidence: (1) widespread cortical destruction that is reflected by deep coma and unresponsiveness to all forms of stimulation, (2) global brainstem damage demonstrated by absent pupillary light reaction and by the loss of oculocephalic and corneal reflexes, and (3) destruction of the medulla manifested by complete apnea. The pulse rate is invariant and unresponsive to atropine. Diabetes insipidus is often present but may develop hours or days after the other clinical signs of brain death. The pupils are often enlarged but may be midsized; they should not, however, be constricted. The absence of deep tendon reflexes is not required because the spinal cord remains functional. There may or may not be Babinski signs.

Demonstration that apnea is caused by irreversible medullary damage requires that the PCO_2 be high enough to stimulate respiration during a test of spontaneous breathing. *Apnea testing* can be done safely by the use of diffusion oxygenation before removing the ventilator. This is accomplished by preoxygenation with 100% oxygen, which is then sustained during the test by oxygen administered through a tracheal cannula. CO_2 tension increases $\sim 0.3\text{--}0.4$ kPa/min ($2\text{--}3$ mmHg/min) during apnea. At the end of the period of observation, typically several minutes, arterial PCO_2 should be at least $>6.6\text{--}8.0$ kPa ($50\text{--}60$ mmHg) for the test to be valid. Apnea is confirmed if no respiratory effort is observed in the presence of a sufficiently elevated PCO_2 .

The possibility of profound drug-induced or hypothermic depression of the nervous system should be excluded, and some period of observation, usually 6–24 h, is desirable during which the signs of brain death are sustained. It is advisable to delay clinical testing for at least 24 h if a cardiac arrest has caused brain death or if the inciting disease is not known. An isoelectric EEG may be used as a confirmatory test for total cerebral damage. Radionuclide brain scanning, cerebral angiography, or transcranial Doppler measurements may also be used to demonstrate the absence of CBF, but they have not been extensively correlated with pathologic changes.

Although it is largely accepted in Western society that the respirator can be disconnected from a brain-dead patient, problems frequently arise because of poor communication and inadequate preparation of the family by the physician. Reasonable medical practice allows the removal of support or transfer out of an intensive care unit of patients who are not brain dead but whose condition is nonetheless hopeless and are likely to live for only a brief time.

Rx Treatment: COMA

The immediate goal in a comatose patient is prevention of further nervous system damage. Hypotension, hypoglycemia, hypercalcemia, hypoxia, hypercapnia, and hyperthermia should be corrected rapidly. An oropharyngeal airway is adequate to keep the pharynx open in drowsy patients who are breathing normally. Tracheal intubation is indicated if the patient has apnea, upper airway obstruction, hypoventilation, or emesis, or if the patient is liable to aspirate because of coma. Mechanical ventilation is required if there is hypoventilation or a need to induce hypocapnia to lower ICP, as described later. IV access is established, and naloxone and dextrose are administered if narcotic overdose and hypoglycemia are even remote possibilities; thiamine is given along with glucose to avoid provoking Wernicke disease in malnourished patients. In cases of suspected basilar thrombosis with brainstem ischemia, IV heparin

or a thrombolytic agent is often used after cerebral hemorrhage has been excluded by a neuroimaging study. Physostigmine may awaken patients with anticholinergic-type drug overdoses but should be used only by experienced physicians and with careful monitoring; many physicians believe that it should only be used to treat anticholinergic overdose-associated cardiac arrhythmias. The use of benzodiazepine antagonists offers some prospect of improvement after overdoses of soporific drugs and has transient benefit in patients with hepatic encephalopathy. IV administration of hypotonic solutions should be monitored carefully in patients with serious acute brain illness because of the potential for exacerbating brain swelling. Cervical spine injuries must not be overlooked, particularly before attempting intubation or evaluating of oculocephalic responses. Fever and meningismus indicate an urgent need for examination of the CSF to diagnose meningitis. If the lumbar puncture in a case of suspected meningitis is delayed for any reason, an antibiotic such as a third-generation cephalosporin should be administered as soon as possible, preferably after obtaining blood cultures. The management of patients with increased ICP is discussed in Chapter 36.

PROGNOSIS

One hopes to avoid the emotionally painful, hopeless outcome of a patient who is left severely disabled or vegetative. The uniformly poor outcome of the persistent

vegetative state has already been mentioned. Children and young adults may have ominous early clinical findings such as abnormal brainstem reflexes and yet recover, so temporization in offering a prognosis in this group of patients is wise. Patients in metabolic comas have a far better prognosis than those in traumatic ones. All systems for estimating prognosis in adults should be taken as approximations, and medical judgments must be tempered by factors such as age, underlying systemic disease, and general medical condition. In an attempt to collect prognostic information from large numbers of patients with head injury, the Glasgow Coma Scale was devised; empirically, it has predictive value in cases of brain trauma. For anoxic and metabolic coma, clinical signs such as the pupillary and motor responses after 1 day, 3 days, and 1 week have been shown to have predictive value (Fig. 36-4). The absence of the cortical waves of the somatosensory evoked potentials has also proved a strong indicator of poor outcome in coma from any cause.

FURTHER READINGS

- LAUREYS S et al: Brain function in coma, vegetative state, and related disorders. *Lancet Neurol* 3:537, 2004
- PARVIZI J AR: Neuroanatomical correlates of brainstem coma. *Brain* 126:1524, 2003
- POSNER JB et al: *Plum and Posner's Diagnosis of Stupor and Coma*, 4th ed. New York and London, Oxford University Press, 2007
- ROPPER AH: *Neurological and Neurosurgical Intensive Care*, 4th ed. New York, Lippincott Williams & Wilkins, 2004
- WIJDICKS EFM: Current concepts: The diagnosis of brain death. *N Engl J Med* 344:1215, 2001



CHAPTER 36

NEUROLOGIC CRITICAL CARE, INCLUDING HYPOXIC-ISCHEMIC ENCEPHALOPATHY AND SUBARACHNOID HEMORRHAGE

J. Claude Hemphill, III ■ Wade S. Smith

Pathophysiology	353	Wernicke's Disease	361
■ Critical Care Disorders of the Central Nervous System	358	■ Critical Care Disorders of the Peripheral Nervous System	362
Hypoxic-Ischemic Encephalopathy	358	Neuropathy	362
Delayed Postanoxic Encephalopathy	360	Disorders of Neuromuscular Transmission	363
Metabolic Encephalopathies	360	Myopathy	363
Septic Encephalopathy	360	■ Subarachnoid Hemorrhage	363
Central Pontine Myelinolysis	361	■ Further Readings	368

Life-threatening neurologic illness may be caused by a primary disorder affecting any region of the neuraxis or may occur as a consequence of a systemic disorder such as hepatic failure, multisystem organ failure, or cardiac arrest (**Table 36-1**). Neurologic critical care focuses on preservation of neurologic tissue and prevention of secondary brain injury caused by ischemia, edema, and elevated intracranial pressure (ICP).

PATHOPHYSIOLOGY

Brain Edema

Swelling, or edema, of brain tissue occurs with many types of brain injury. The two principal types of edema are vasogenic and cytotoxic. *Vasogenic edema* refers to the influx of fluid and solutes into the brain through an incompetent blood–brain barrier (BBB). In the normal cerebral vasculature, endothelial tight junctions associated with astrocytes create an impermeable barrier (the BBB), through which access into the brain interstitium is dependent on specific transport mechanisms. The BBB may be compromised in patients with ischemia, trauma, infection, and metabolic derangements. Typically, vasogenic edema develops rapidly after injury. *Cytotoxic edema*

refers to cellular swelling and occurs in a variety of settings, including brain ischemia and trauma. Early astrocytic swelling is a hallmark of ischemia. Brain edema that is clinically significant usually represents a combination of vasogenic and cellular components. Edema can lead to increased ICP as well as tissue shifts and brain displacement from focal processes (Chap. 35). These tissue shifts can cause injury by mechanical distraction and compression in addition to the ischemia of impaired perfusion consequent to the elevated ICP.

Ischemic Cascade and Cellular Injury

When delivery of substrates, principally oxygen and glucose, is inadequate to sustain cellular function, a series of interrelated biochemical reactions known as the *ischemic cascade* is initiated. The release of excitatory amino acids, especially glutamate, leads to influx of calcium and sodium ions, which disrupt cellular homeostasis. An increased intracellular calcium concentration may activate proteases and lipases, which then lead to lipid peroxidation and free radical–mediated cell membrane injury. Cytotoxic edema ensues, and ultimately necrotic cell death and tissue infarction occur. This pathway to irreversible cell death is common to ischemic stroke, global cerebral

NEUROLOGIC DISORDERS IN CRITICAL ILLNESS

LOCALIZATION ALONG NEUROAXIS	SYNDROME
Central Nervous System	
Brain: cerebral hemispheres	Global encephalopathy Sepsis Organ failure: hepatic, renal Medication related Sedatives, hypnotics, analgesics H ₂ blockers, antihypertensives Drug overdose Electrolyte disturbance: hyponatremia, hypoglycemia Hypotension or hypoperfusion Hypoxia Meningitis Subarachnoid hemorrhage Wernicke's disease Seizure: postictal or nonconvulsive status Hypertensive encephalopathy Hypothyroidism: myxedema Focal deficits Ischemic stroke Tumor Abscess, subdural empyema Subdural or epidural hematoma
Brainstem	Mass effect and compression Ischemic stroke, intraparenchymal hemorrhage Hypoxia
Spinal cord	Mass effect and compression Disc herniation Epidural hematoma Ischemia: hypotension or embolic Subdural empyema Trauma, central cord syndrome
Peripheral Nervous System	
Peripheral nerve	
Axonal	Critical illness polyneuropathy Possible neuromuscular blocking agent complication Metabolic disturbances, uremia, hyperglycemia Medication effects: chemotherapeutic, antiretroviral
Demyelinating	Guillain-Barré syndrome Chronic inflammatory demyelinating polyneuropathy
Neuromuscular junction	Prolonged effect of neuromuscular blockade Medication effects: aminoglycosides Myasthenia-gravis, Lambert-Eaton syndrome
Muscle	Critical illness myopathy Septic myopathy Cachectic myopathy with or without disuse atrophy Electrolyte disturbances: hypokalemia or hyperkalemia, hypophosphatemia Acute quadriplegic myopathy

ischemia, and traumatic brain injury (TBI). *Penumbra* refers to ischemic brain tissue that has not yet undergone irreversible infarction, implying that the region is potentially salvageable if ischemia can be reversed. Factors that may exacerbate ischemic brain injury include systemic hypotension and hypoxia, which further reduce substrate delivery to vulnerable brain tissue, and fever, seizures, and hyperglycemia, which can increase cellular metabolism outstripping compensatory processes. Clinically, these events are known as *secondary brain insults* because they lead to exacerbation of the primary brain injury. Prevention, identification, and treatment of secondary brain insults are fundamental goals of management.

An alternative pathway of cellular injury is *apoptosis*. This process implies programmed cell death, which may occur in the setting of ischemic stroke, global cerebral ischemia, TBI, and possibly intracerebral hemorrhage. Apoptotic cell death can be distinguished histologically from the necrotic cell death of ischemia and is mediated through a different set of biochemical pathways. At present, interventions for prevention and treatment of apoptotic cell death remain less well defined than those for ischemia.

Cerebral Perfusion and Autoregulation

Brain tissue requires constant perfusion to ensure adequate delivery of substrate. The hemodynamic response of the brain has the capacity to preserve perfusion across a wide range of systemic blood pressures. Cerebral perfusion pressure (CPP), defined as the mean systemic arterial pressure (MAP) minus the ICP, provides the driving force for circulation across the capillary beds of the brain. *Autoregulation* refers to the physiologic response whereby cerebral blood flow (CBF) remains relatively constant over a wide range of blood pressures as a consequence of alterations of cerebrovascular resistance (Fig. 36-1). If systemic blood pressure decreases, cerebral perfusion is preserved through vasodilatation of arterioles in the brain; likewise, arteriolar vasoconstriction occurs at high systemic pressures to prevent hyperperfusion. At the extreme limits of MAP or CPP (high or low), flow becomes directly related to perfusion pressure. These autoregulatory changes occur in the microcirculation and are mediated by vessels below the resolution of those seen on angiography. CBF is also strongly influenced by pH and P_{CO}₂. CBF increases with hypercapnia and acidosis and decreases with hypocapnia and alkalosis. This forms the basis for the use of hyperventilation to lower ICP, and this effect on ICP is mediated through a decrease in intracranial blood volume. Cerebral autoregulation is critical to the normal homeostatic functioning of the brain, and this process may be disordered focally and unpredictably in disease states such as TBI and severe focal cerebral ischemia.

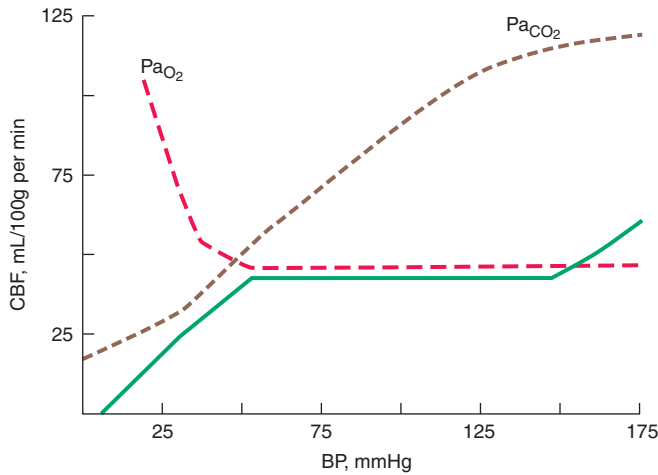


FIGURE 36-1

Autoregulation of cerebral blood flow (solid line). Cerebral perfusion is constant over a wide range of systemic blood pressure. Perfusion is increased in the setting of hypoxia or hypercarbia. BP, blood pressure; CBF, cerebral blood flow; PaCO₂, arterial partial pressure of carbon dioxide. (Reprinted with permission from *Anesthesiology* 43:447, 1975. Copyright 1975, Lippincott Company.)

Cerebrospinal Fluid and Intracranial Pressure

The cranial contents consist essentially of brain, cerebrospinal fluid (CSF), and blood. CSF is produced principally in the choroid plexus of each lateral ventricle, exits the brain via the foramina of Luschka and Magendi, and flows over the cortex to be absorbed into the venous system along the superior sagittal sinus. Approximately 150 mL of CSF is contained within the ventricles and surrounding the brain and spinal cord; the cerebral blood volume is also ~150 mL. The bony skull offers excellent protection for the brain but allows little tolerance for additional volume. Significant increases in volume eventually result in increased ICP. Obstruction of CSF outflow, edema of cerebral tissue, or increases in volume from tumor or hematoma may increase ICP. Elevated ICP diminishes cerebral perfusion and can lead to tissue ischemia. Ischemia in turn may lead to vasodilatation via autoregulatory mechanisms designed to restore cerebral perfusion. However, vasodilatation also increases cerebral blood volume, which in turn then increases ICP, lowers CPP, and provokes further ischemia (Fig. 36-2). This vicious cycle is commonly seen in TBI, massive intracerebral hemorrhage, and large hemispheric infarcts with significant tissue shifts.

Approach to the Patient:

SEVERE CENTRAL NERVOUS SYSTEM DYSFUNCTION

Critically ill patients with severe central nervous system dysfunction require rapid evaluation and intervention

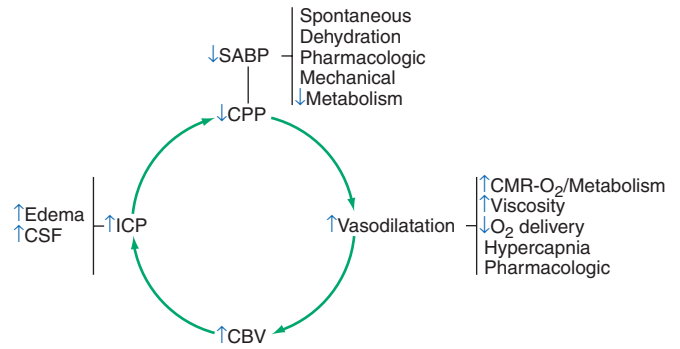


FIGURE 36-2

Ischemia and vasodilatation. Reduced cerebral perfusion pressure (CPP) leads to increased ischemia, vasodilatation, increased intracranial pressure (ICP), and further reductions in CPP, a cycle leading to further neurologic injury. CBV, cerebral blood volume; CMR, cerebral metabolic rate; CSF, cerebrospinal fluid; SABP, systolic arterial blood pressure. (Adapted from Rosner MJ et al: *Cerebral perfusion pressure: Management protocol and clinical results. J Neurosurg* 83:949, 1995, with permission.)

to limit primary and secondary brain injury. The initial neurologic evaluation should be performed concurrent with stabilization of basic respiratory, cardiac, and hemodynamic parameters. Significant barriers may exist to neurologic assessment in the critical care unit, including endotracheal intubation and the use of sedative or paralytic agents to facilitate procedures.

An impaired level of consciousness is common in critically ill patients. The essential first task in assessment is to determine whether the cause of dysfunction is related to a diffuse, usually metabolic, process or whether a focal, usually structural, process is implicated. Examples of diffuse processes include metabolic encephalopathies related to organ failure, drug overdose, or hypoxia-ischemia. Focal processes include ischemic and hemorrhagic stroke and TBI, especially with intracranial hematomas. Because these two categories of disorders have fundamentally different causes, treatments, and prognoses, the initial focus is on making this distinction rapidly and accurately. The approach to comatose patients is discussed in Chap. 35; etiologies are listed in Table 35-1.

Minor focal deficits may be present on the neurologic examination in patients with metabolic encephalopathies. However, the finding of prominent focal signs such as pupillary asymmetry, hemiparesis, gaze palsy, or paraplegia should suggest the possibility of a structural lesion. All patients with a decreased level of consciousness associated with focal findings should undergo an urgent neuroimaging procedure,

as should all patients with coma of unknown etiology. CT scanning is usually the most appropriate initial study because it can be performed quickly in critically ill patients and demonstrates hemorrhage, hydrocephalus, and intracranial tissue shifts well. MRI may provide more specific information in some situations, such as acute ischemic stroke [diffusion-weighted imaging (DWI)] and cerebral venous sinus thrombosis [magnetic resonance venography (MRV)]. Any suggestion of trauma from the history or examination should alert the examiner to the possibility of cervical spine injury and prompt an imaging evaluation using plain x-rays, MRI, or CT.

Other diagnostic studies are best used in specific circumstances, usually when neuroimaging studies fail to reveal a structural lesion and the cause of the altered mental state remains uncertain. Electroencephalography (EEG) can be important in the evaluation of critically ill patients with severe brain dysfunction. The EEG of metabolic encephalopathy typically reveals generalized slowing. One of the most important uses of EEG is to help exclude inapparent seizures, especially nonconvulsive status epilepticus. Untreated continuous or frequently recurrent seizures may cause neuronal injury, making the diagnosis and treatment of seizures crucial in this patient group. Lumbar puncture (LP) may be necessary to exclude infectious processes, and an elevated opening pressure may be an important clue to cerebral venous sinus thrombosis. In patients with coma or profound encephalopathy, it is preferable to perform a neuroimaging study before LP. If bacterial meningitis is suspected, an LP may be performed first or antibiotics may be empirically administered before the diagnostic studies are completed. Standard laboratory evaluation of critically ill patients should include assessment of serum electrolytes (especially sodium and calcium), glucose, renal and hepatic function, complete blood count, and coagulation. Serum or urine toxicology screens should be performed in patients with encephalopathy of unknown cause. EEG, LP, and other specific laboratory tests are most useful when the mechanism of the altered level of consciousness is uncertain; they are not routinely performed in clear-cut cases of stroke or TBI.

Monitoring of ICP can be an important tool in selected patients. In general, patients who should be considered for ICP monitoring are those with primary neurologic disorders, such as stroke or TBI, who are at significant risk for secondary brain injury because of elevated ICP and decreased CPP. Included are patients with severe TBI [Glasgow Coma Scale (GCS) score ≤ 8 ; [Table 36-2](#)]; large tissue shifts from supratentorial ischemic or hemorrhagic stroke; or hydrocephalus from subarachnoid hemorrhage (SAH), intraventricular hemorrhage, or posterior fossa stroke.

TABLE 36-2**GLASGOW COMA SCALE FOR HEAD INJURY**

Eye Opening (E)		Verbal Response (V)	
Spontaneous	4	Oriented	5
To loud voice	3	Confused, disoriented	4
To pain	2	Inappropriate words	3
Nil	1	Incomprehensible sounds	2
Best motor response (M)		Nil	1
Obeys	6		
Localizes	5		
Withdraws (flexion)	4		
Abnormal flexion posturing	3		
Extension posturing	2		
Nil	1		

Note: Coma score = E + M + V. Patients scoring 3 or 4 have an 85% chance of dying or remaining vegetative; scores >11 indicate only a 5–10% likelihood of death or vegetative state and 85% chance of moderate disability or good recovery. Intermediate scores correlate with proportional chances of recovery.

Source: From Ropper AH: Concussion and other head injuries in Fauci AS, Braunwald E, Kasper L, et al (eds). *Harrison's Principles of Internal Medicine*, 17th ed. New York: McGraw-Hill, 2008, p. 2601.

An additional disorder in which ICP monitoring can add important information is fulminant hepatic failure, in which elevated ICP may be treated with barbiturates or, eventually, liver transplantation. In general, ventriculostomy is preferable to ICP monitoring devices that are placed in the brain parenchyma because ventriculostomy allows CSF drainage as a method of treating elevated ICP. However, parenchymal ICP monitoring is most appropriate for patients with diffuse edema and small ventricles (which may make ventriculostomy placement more difficult) or any degree of coagulopathy (in which ventriculostomy carries a higher risk of hemorrhagic complications) ([Fig 36-3](#)).

TREATMENT OF ELEVATED INTRACRANIAL PRESSURE

Elevated ICP may occur in a wide range of disorders, including head trauma, intracerebral hemorrhage, SAH with hydrocephalus, and fulminant hepatic failure. Because CSF and blood volume can be redistributed initially, by the time elevated ICP occurs, intracranial compliance is severely impaired. At this point, any small increase in the volume of CSF, intravascular blood, edema, or a mass lesion may result in a significant increase in ICP and a decrease in cerebral perfusion. This is a fundamental mechanism of secondary ischemic brain injury and constitutes an emergency that requires immediate attention. In general,

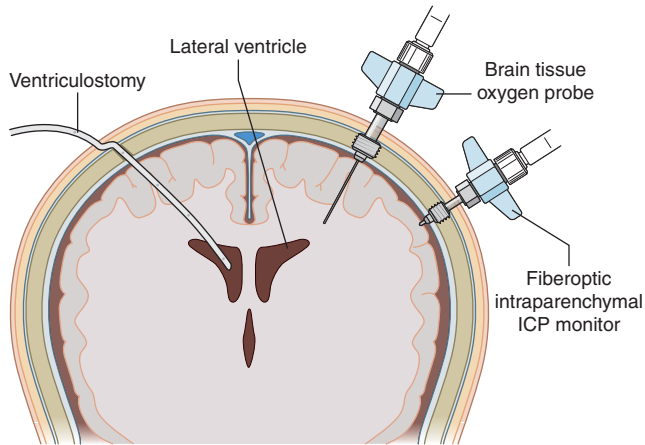


FIGURE 36-3

Intracranial pressure (ICP) and brain tissue oxygen monitoring. A ventriculostomy allows for drainage of cerebrospinal fluid to treat elevated ICP. Fiberoptic ICP and brain tissue oxygen monitors are usually secured using a screwlike skull bolt. Cerebral blood flow and microdialysis probes (not shown) may be placed in a manner similar to the brain tissue oxygen probe.

ICP should be maintained at <20 mmHg, and CPP should be maintained at ≥ 60 mmHg.

Interventions to lower ICP are ideally based on the underlying mechanism responsible for the elevated ICP (Table 36-3). For example, in hydrocephalus from SAH, the principal cause of elevated ICP is impairment of CSF drainage. In this setting, ventricular drainage of CSF is likely to be sufficient and most appropriate. In head trauma and stroke, cytotoxic edema may be most responsible, and the use of osmotic diuretics such as mannitol becomes an appropriate early step. As described above, elevated ICP may cause tissue ischemia, and, if cerebral autoregulation is intact, the resulting vasodilatation can lead to a cycle of worsening ischemia. Paradoxically, administration of vasopressor agents to increase mean arterial pressure (MAP) may actually lower ICP by improving perfusion, thereby allowing autoregulatory vasoconstriction as ischemia is relieved and ultimately decreasing intracranial blood volume.

Early signs of elevated ICP include drowsiness and a diminished level of consciousness. Neuroimaging studies may reveal evidence of edema and mass effect. Hypotonic IV fluids should be avoided, and elevation of the head of the bed is recommended. Patients must be carefully observed for risk of aspiration and compromise of the airway as the level of alertness declines. Coma and unilateral pupillary changes are late signs and require immediate intervention. Emergent treatment of patients with elevated ICP is most quickly achieved by intubation and hyperventilation, which

TABLE 36-3

STEPWISE APPROACH TO TREATMENT OF ELEVATED INTRACRANIAL PRESSURE^a

Insert ICP monitor (ventriculostomy versus parenchymal device)

General goals: maintain ICP <20 mmHg and CPP ≥ 60 mmHg

For ICP >20 – 25 mmHg for >5 min:

1. Drain CSF via ventriculostomy (if in place)
2. Elevate head of the bed; midline head position
3. Osmotherapy: mannitol 25–100 g q4h as needed (maintain serum osmolality <320 mosmol) or hypertonic saline (30 mL, 23.4% NaCl bolus)
4. Glucocorticoids: dexamethasone 4 mg q6h for vasogenic edema from tumor, abscess (avoid glucocorticoids in head trauma, ischemic and hemorrhagic stroke)
5. Sedation: morphine, propofol, or midazolam; add neuromuscular paralysis if necessary (patient will require endotracheal intubation and mechanical ventilation at this point, if not before)
6. Hyperventilation: to $Paco_2$ 30–35 mmHg
7. Pressor therapy: phenylephrine, dopamine, or norepinephrine to maintain adequate MAP to ensure CPP ≥ 60 mmHg (maintain euolemia to minimize deleterious systemic effects of pressors)
8. Consider second-tier therapies for refractory elevated ICP
 - a. High-dose barbiturate therapy (“pentobarb coma”)
 - b. Aggressive hyperventilation to $Paco_2$ <30 mmHg
 - c. Hypothermia
 - d. Hemicraniectomy

^aThroughout the intracranial pressure (ICP) treatment algorithm, consider repeat head CT to identify mass lesions amenable to surgical evacuation.

Note: CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; MAP, mean arterial pressure; $Paco_2$, arterial partial pressure of carbon dioxide.

causes vasoconstriction and reduces cerebral blood volume. To avoid provoking or worsening cerebral ischemia, hyperventilation is best used for short periods of time until a more definitive treatment can be instituted. Furthermore, the effects of hyperventilation on ICP are short lived, often lasting only for several hours because of the buffering capacity of the cerebral interstitium, and rebound elevations of ICP may accompany abrupt discontinuation of hyperventilation. As the level of consciousness declines to coma, the ability to follow the neurologic status of the patient by examination deteriorates, and measurement of ICP assumes greater importance. If a ventriculostomy device is in place, direct drainage of CSF to reduce ICP is possible. Finally, high-dose barbiturates, decompressive hemicraniectomy, or hypothermia is sometimes used for refractory elevations of ICP, although these interventions

have significant side effects and have not been proven to improve outcome.

SECONDARY BRAIN INSULTS Patients with primary brain injuries, whether caused by trauma or stroke, are at risk for ongoing secondary ischemic brain injury. Because secondary brain injury can be a major determinant of a poor outcome, strategies for minimizing secondary brain insults are an integral part of the critical care of all patients. Although elevated ICP may lead to secondary ischemia, most secondary brain injury is mediated through other clinical events that exacerbate the ischemic cascade already initiated by the primary brain injury. Episodes of secondary brain insults are usually not associated with apparent neurologic worsening. Rather, they lead to cumulative injury, which manifests as higher mortality or worsened long-term functional outcome. Thus, close monitoring of vital signs is important, as is early intervention to prevent secondary ischemia. Avoiding hypotension and hypoxia is critical because significant hypotensive events (systolic blood pressure <90 mmHg) as short as 10 min in duration have been shown to adversely influence outcome after TBI. Even in patients with stroke or head trauma who do not require ICP monitoring, close attention to adequate cerebral perfusion is warranted. Hypoxia (pulse oximetry saturation <90%), particularly in combination with hypotension, also leads to secondary brain injury. Likewise, fever and hyperglycemia both worsen experimental ischemia and have been associated with a worsened clinical outcome after stroke and head trauma. Aggressive control of fever with a goal of normothermia is warranted but may be difficult to achieve with antipyretic medications and cooling blankets. The value of newer surface or intravascular temperature control devices for the management of refractory fever is under investigation. The use of IV insulin infusion is encouraged for control of hyperglycemia because this allows better regulation of serum glucose levels than subcutaneous insulin. A reasonable goal is to maintain the serum glucose level at <7.8 mmol/L (<140 mg/dL), although some have suggested that even tighter control is warranted. New cerebral monitoring tools that allow continuous evaluation of brain tissue oxygen tension, CBF, and metabolism (via microdialysis) may further improve the management of secondary brain injury.

CRITICAL CARE DISORDERS OF THE CENTRAL NERVOUS SYSTEM

HYPOXIC-ISCHEMIC ENCEPHALOPATHY

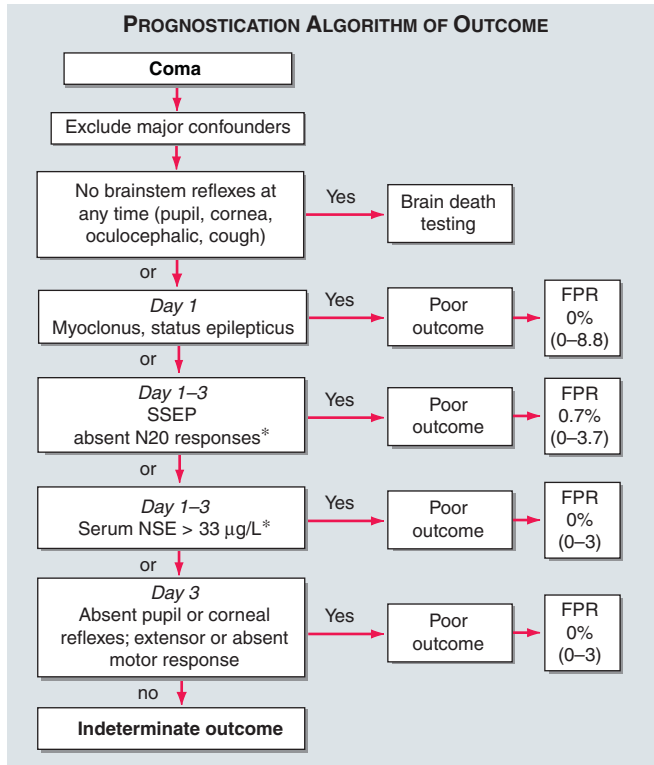
This occurs from lack of delivery of oxygen to the brain because of hypotension or respiratory failure. Causes

include myocardial infarction, cardiac arrest, shock, asphyxiation, paralysis of respiration, and carbon monoxide or cyanide poisoning. In some circumstances, hypoxia may predominate. Carbon monoxide and cyanide poisoning are termed *histotoxic hypoxia* because they cause a direct impairment of the respiratory chain.

Clinical Manifestations

Mild degrees of pure hypoxia, such as occur at high altitudes, cause impaired judgment, inattentiveness, motor incoordination, and sometimes euphoria. However, with hypoxia-ischemia, such as occurs with circulatory arrest, consciousness is lost within seconds. If circulation is restored within 3–5 min, full recovery may occur, but if hypoxia-ischemia lasts beyond 3–5 min, some degree of permanent cerebral damage is the rule. Except in extreme cases, it may be difficult to judge the precise degree of hypoxia-ischemia, and some patients make a relatively full recovery after even 8–10 min of global cerebral ischemia. The distinction between pure hypoxia and hypoxia-ischemia is important because a PaO₂ as low as 20 mmHg (2.7 kPa) can be well tolerated if it develops gradually and normal blood pressure is maintained, but short durations of very low or absent cerebral circulation may result in permanent impairment.

Clinical examination at different time points after a hypoxic-ischemic insult (especially cardiac arrest) is useful in assessing prognosis for long-term neurologic outcome. The prognosis is better for patients with intact brainstem function, as indicated by normal pupillary light responses and intact oculocephalic (“doll’s eyes”), oculovestibular (caloric), and corneal reflexes (Fig. 36-4). Absence of these reflexes and the presence of persistently dilated pupils that do not react to light are grave prognostic signs. A uniformly dismal prognosis from hypoxic-ischemic coma is conveyed by an absent pupillary light reflex or extensor or absent motor response to pain on day 3 after the injury. Electrophysiologically, the bilateral absence of the N20 component of the somatosensory evoked potentials (SSEPs) in the first several days also conveys a poor prognosis. A very elevated serum level (>33 µg/L) of the biochemical marker neuron-specific enolase (NSE) is indicative of brain damage after resuscitation from cardiac arrest and predicts a poor outcome. However, at present, SSEPs and NSE levels may be difficult to obtain in a timely fashion, with SSEP testing requiring substantial expertise in interpretation and NSE measurements not yet standardized. Whether administration of mild hypothermia after cardiac arrest (see Treatment) will alter the usefulness of these clinical and electrophysiologic predictors is unknown. Long-term consequences of hypoxic-ischemic encephalopathy include persistent coma or a vegetative state (Chap. 35), dementia, visual agnosia, parkinsonism, choreoathetosis, cerebellar ataxia, myoclonus, seizures, and an amnesic

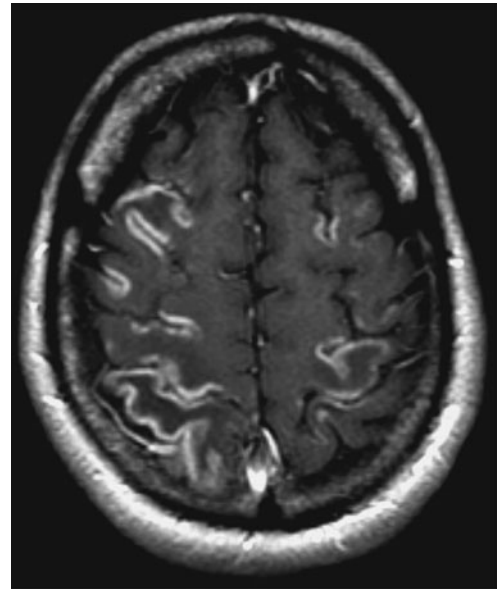
**FIGURE 36-4**

Prognostication of outcome in comatose survivors of cardiopulmonary resuscitation. Numbers in parentheses are 95% confidence intervals. Confounders could include use of sedatives or neuromuscular blocking agents, hypothermia therapy, organ failure, or shock. Tests denoted with an * may not be available in a timely and standardized manner. FPR, false-positive rate; NSE, neuron-specific enolase; SSEP, somatosensory evoked potentials. (From Wijdicks et al, with permission.)

state, which may be a consequence of selective damage to the hippocampus.

Pathology

Principal histologic findings are extensive multifocal or diffuse laminar cortical necrosis (Fig. 36-5), with almost invariable involvement of the hippocampus. The hippocampal CA1 neurons are vulnerable to even brief episodes of hypoxia-ischemia, perhaps explaining why selective persistent memory deficits may occur after brief cardiac arrest. Scattered small areas of infarction or neuronal loss may be present in the basal ganglia, hypothalamus, or brainstem. In some cases, extensive bilateral thalamic scarring may affect the pathways that mediate arousal, and this pathology may be responsible for the persistent vegetative state. A specific form of hypoxic-ischemic encephalopathy—so-called *watershed infarcts*—occurs at the distal territories between the major cerebral arteries and can cause cognitive deficits, including visual

**FIGURE 36-5**

Cortical laminar necrosis in hypoxic-ischemic encephalopathy. T1-weighted postcontrast MRI shows cortical enhancement in a watershed distribution consistent with laminar necrosis.

agnosia, and weakness that is greater in proximal than in distal muscle groups.

Diagnosis

Diagnosis is based on the history of a hypoxic-ischemic event such as cardiac arrest. Blood pressure <70 mmHg systolic or PaO₂ <40 mmHg is usually necessary, although both absolute levels as well as the duration of exposure are important determinants of cellular injury. Carbon monoxide intoxication can be confirmed by measurement of carboxyhemoglobin and is suggested by a cherry red color of the skin, although the latter is an inconsistent clinical finding.

Rx Treatment: HYPOXIC-ISCHEMIC ENCEPHALOPATHY

Treatment should be directed at restoration of normal cardiorespiratory function. This includes securing a clear airway, ensuring adequate oxygenation and ventilation, and restoring cerebral perfusion, whether by cardiopulmonary resuscitation, fluid, pressors, or cardiac pacing. Hypothermia may target the neuronal cell injury cascade and has substantial neuroprotective properties in experimental models of brain injury. In two trials, mild hypothermia (33°C) improved functional outcome in patients who remained comatose after resuscitation from a cardiac arrest. Treatment was initiated within

minutes of cardiac resuscitation and continued for 12 h in one study and 24 h in the other. Potential complications of hypothermia include coagulopathy and an increased risk of infection. Based on these studies, the International Liaison Committee on Resuscitation issued the following advisory statement in 2003: "Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°–34°C for 12–24 h when the initial rhythm was ventricular fibrillation."

Severe carbon monoxide intoxication may be treated with hyperbaric oxygen. Anticonvulsants may be needed to control seizures, although they are not usually given prophylactically. Patients with posthypoxic myoclonus may respond to oral administration of clonazepam at doses of 1.5–10 mg daily or valproate at doses of 300–1200 mg/day in divided doses. Myoclonic status epilepticus within 24 h after a primary circulatory arrest portends a universally poor prognosis, even if seizures are controlled.

DELAYED POSTANOXIC ENCEPHALOPATHY

Delayed postanoxic encephalopathy is an uncommon phenomenon in which patients appear to make an initial recovery from hypoxic-ischemic insult but then develop a relapse characterized by apathy, confusion, and agitation. Progressive neurologic deficits may include a shuffling gait; diffuse rigidity and spasticity; persistent parkinsonism or myoclonus; and, on occasion, coma and death after 1–2 weeks. Widespread cerebral demyelination may be present.

Carbon monoxide and cyanide intoxication can also cause a delayed encephalopathy. Little clinical impairment is evident when the patient first regains consciousness, but a parkinsonian syndrome characterized by akinesia and rigidity without tremor may develop. Symptoms can worsen over months, accompanied by increasing evidence of damage in the basal ganglia as seen on both CT and MRI.

METABOLIC ENCEPHALOPATHIES

Altered mental states, variously described as confusion, delirium, disorientation, and encephalopathy, are present in many patients with severe illness in an intensive care unit (ICU). Older patients are particularly vulnerable to delirium, a confusional state characterized by disordered perception, frequent hallucinations, delusions, and sleep disturbance. This is often attributed to medication effects, sleep deprivation, pain, and anxiety. The term *ICU psychosis* has been used to describe a mental state with profound agitation occurring in this setting. The presence of family members in the ICU may help to calm and orient agitated patients, and in severe cases, low doses of neuroleptics (e.g., haloperidol 0.5–1.0 mg)

can be useful. Ultimately, the psychosis resolves with improvement in the underlying illness and a return to familiar surroundings.

In the ICU setting, several metabolic causes of an altered level of consciousness predominate. Hypercarbic encephalopathy can present with headache, confusion, stupor, or coma. Hypoventilation syndrome occurs most frequently in patients with a history of chronic CO₂ retention who are receiving oxygen therapy for emphysema or chronic pulmonary disease (Chap. 22). The elevated PaCO₂ leading to CO₂ narcosis may have a direct anesthetic effect, and cerebral vasodilatation from increased PaCO₂ can lead to increased ICP. Hepatic encephalopathy is suggested by asterix and may occur in patients with chronic liver failure or acute fulminant hepatic failure. Both hyperglycemia and hypoglycemia can cause encephalopathy, as can hypernatremia and hyponatremia. Confusion, impairment of eye movements, and gait ataxia are the hallmarks of acute Wernicke's disease (see later).

SEPTIC ENCEPHALOPATHY

Pathogenesis

In patients with sepsis, the systemic response to infectious agents leads to the release of circulating inflammatory mediators that appear to contribute to encephalopathy. Critical illness, in association with the systemic inflammatory response syndrome (SIRS), can lead to multisystem organ failure. This syndrome can occur in the setting of apparent sepsis, severe burns, or trauma, even without clear identification of an infectious agent. Many patients with critical illness, sepsis, or SIRS develop encephalopathy without obvious explanation. This condition is broadly termed *septic encephalopathy*. Although the specific mediators leading to neurologic dysfunction remain uncertain, it is clear that the encephalopathy is not simply the result of metabolic derangements of multiorgan failure. The cytokines tumor necrosis factor and interleukin (IL) 1, IL-2, and IL-6 are thought to play a role in this syndrome.

Diagnosis

Septic encephalopathy presents clinically as a diffuse dysfunction of the brain without prominent focal findings. Confusion, disorientation, agitation, and fluctuations in the level of alertness are typical. In more profound cases, especially with hemodynamic compromise, the decrease in level of alertness can be more prominent, at times resulting in coma. Hyperreflexia and frontal release signs such as a grasp or snout reflex can be seen. Abnormal movements such as myoclonus, tremor, or asterix can occur. Septic encephalopathy is quite common, occurring in the majority of patients with sepsis and multisystem organ failure. Diagnosis is often difficult because of the multiple potential

causes of neurologic dysfunction in critically ill patients and requires exclusion of structural, metabolic, toxic, and infectious (e.g., meningitis or encephalitis) causes. The mortality of patients with septic encephalopathy severe enough to produce coma approaches 50%, although this principally reflects the severity of the underlying critical illness and is not a singular result of the septic encephalopathy. Patients dying from severe sepsis or septic shock may have elevated levels of the serum brain injury biomarker S-100 β and neuropathologic findings of neuronal apoptosis and cerebral ischemic injury. However, successful treatment of the underlying critical illness almost always results in complete resolution of the encephalopathy, with profound long-term cognitive disability being uncommon.

CENTRAL PONTINE MYELINOLYSIS

This disorder typically presents in a devastating fashion as quadriplegia and pseudobulbar palsy. Predisposing factors include severe underlying medical illness or nutritional deficiency; most cases are associated with rapid correction of hyponatremia or with hyperosmolar states. The pathology consists of demyelination without inflammation in the base of the pons, with relative sparing of axons and nerve cells. MRI is useful in establishing the diagnosis (Fig. 36-6) and may also identify partial forms that present as confusion, dysarthria, or disturbances of conjugate gaze without quadriplegia. Occasional patients present with lesions outside of the brainstem. Therapeutic guidelines for the restoration of severe hyponatremia should aim for gradual correction—i.e., by ≥ 10 mmol/L (10 meq/L) within 24 h and 20 mmol/L (20 meq/L) within 48 h.

WERNICKE'S DISEASE

Wernicke's disease is a common and preventable disorder caused by a deficiency of thiamine. In the United States, alcoholics account for most cases, but patients with malnutrition caused by a hyperemesis, starvation, renal dialysis, cancer, AIDS, or (rarely) gastric surgery are also at risk. The characteristic clinical triad is ophthalmoplegia, ataxia, and global confusion. However, only one-third of patients with acute Wernicke's disease present with the classic clinical triad. Most patients are profoundly disoriented, indifferent, and inattentive, although rarely they have an agitated delirium related to ethanol withdrawal. If the disease is not treated, stupor, coma, and death may ensue. Ocular motor abnormalities include horizontal nystagmus on lateral gaze, lateral rectus palsy (usually bilateral), conjugate gaze palsies, and (rarely) ptosis. Gait ataxia probably results from a combination of polyneuropathy, cerebellar involvement, and vestibular paresis. The pupils are usually spared, but they may become miotic with advanced disease.

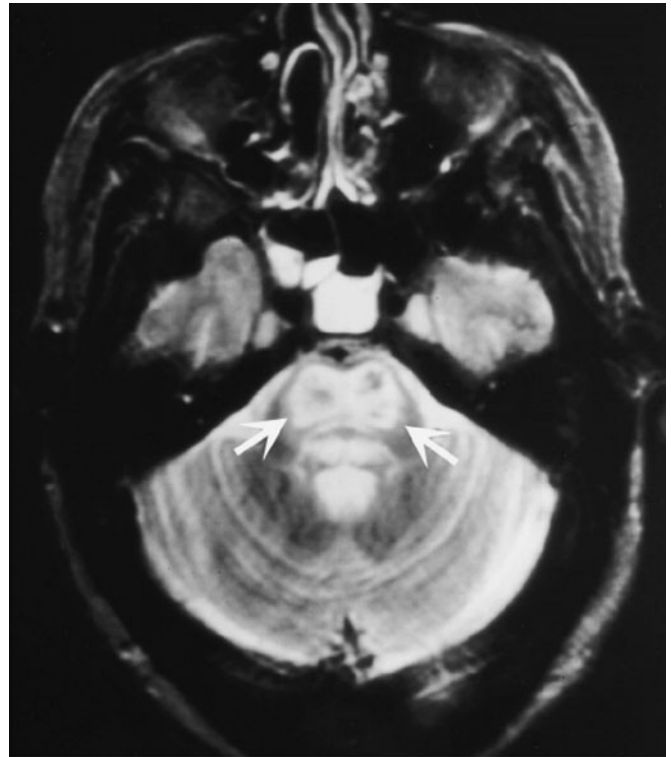


FIGURE 36-6

Central pontine myelinolysis. Axial T2-weighted MR scan through the pons reveals a symmetric area of abnormal high signal intensity within the basis pontis (arrows).

Wernicke's disease is usually associated with other manifestations of nutritional disease, such as polyneuropathy. Rarely, amblyopia or myelopathy occurs. Tachycardia and postural hypotension may be related to impaired function of the autonomic nervous system or to the coexistence of cardiovascular beriberi. Patients who recover show improvement in ocular palsies within hours after the administration of thiamine, but horizontal nystagmus may persist. Ataxia improves more slowly than the ocular motor abnormalities. Approximately 50% of patients recover incompletely and are left with a slow, shuffling, wide-based gait and an inability to tandem walk. Apathy, drowsiness, and confusion improve more gradually. As these symptoms recede, an amnesic state with impairment in recent memory and learning may become more apparent (*Korsakoff's psychosis*). Korsakoff's psychosis is frequently persistent; the residual mental state is characterized by gaps in memory, confabulation, and disordered temporal sequencing.

Pathology

Periventricular lesions surround the third ventricle, aqueduct, and fourth ventricle, with petechial hemorrhages in occasional acute cases and atrophy of the mamillary bodies in most chronic cases. There is frequently endothelial proliferation, demyelination, and some neuronal loss. These changes may be detected by MRI scanning (Fig. 36-7).

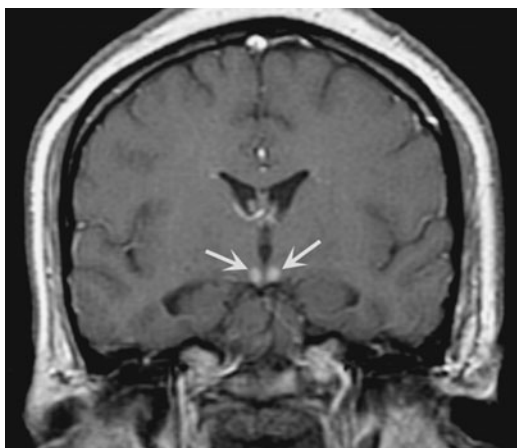


FIGURE 36-7

Wernicke's disease. Coronal T1-weighted postcontrast MRI reveals abnormal enhancement of the mammillary bodies (arrows), typical of acute Wernicke's encephalopathy.

The amnesic defect is related to lesions in the dorsal medial nuclei of the thalamus.

Pathogenesis

Thiamine is a cofactor of several enzymes, including transketolase, pyruvate dehydrogenase, and α -ketoglutarate dehydrogenase. Thiamine deficiency produces a diffuse decrease in cerebral glucose utilization and results in mitochondrial damage. Glutamate accumulates owing to impairment of α -ketoglutarate dehydrogenase activity and, in combination with the energy deficiency, may result in excitotoxic cell damage.

Rx Treatment: **WERNICKE'S DISEASE**

Wernicke's disease is a medical emergency and requires immediate administration of thiamine in a dose of 100 mg either IV or IM. The dose should be given daily until the patient resumes a normal diet and should be begun before treatment with IV glucose solutions. Glucose infusions may precipitate Wernicke's disease in a previously unaffected patient or cause a rapid worsening of an early form of the disease. For this reason, thiamine should be administered to all alcoholic patients requiring parenteral glucose.

CRITICAL CARE DISORDERS OF THE PERIPHERAL NERVOUS SYSTEM

Critical illness with disorders of the peripheral nervous system (PNS) arises in two contexts: (1) primary neurologic diseases that require critical care interventions,

such as intubation and mechanical ventilation, and (2) secondary PNS manifestations of systemic critical illness, often involving multisystem organ failure. The former include acute polyneuropathies such as Guillain-Barré syndrome; neuromuscular junction disorders, including myasthenia gravis and botulism; and primary muscle disorders such as polymyositis. The latter results either from the systemic disease itself or as a consequence of interventions.

General principles of respiratory evaluation in patients with PNS involvement, regardless of cause, include assessment of pulmonary mechanics, such as maximal inspiratory force (MIF) and vital capacity (VC), and evaluation of strength of bulbar muscles. Regardless of the cause of weakness, endotracheal intubation should be considered when the MIF decreases to <-25 cmH₂O or the VC is <1 L. Also, patients with severe palatal weakness may require endotracheal intubation to prevent acute upper airway obstruction or recurrent aspiration. Arterial blood gases and oxygen saturation from pulse oximetry are used to follow patients with potential respiratory compromise from PNS dysfunction. However, intubation and mechanical ventilation should be undertaken based on clinical assessment rather than waiting until oxygen saturation decreases or CO₂ retention develops from hypoventilation. Noninvasive mechanical ventilation may be considered initially in lieu of endotracheal intubation but is generally insufficient in patients with severe bulbar weakness or ventilatory failure with hypercarbia. Principles of mechanical ventilation are discussed in Chap. 27.

NEUROPATHY

Although encephalopathy may be the most obvious neurologic dysfunction in critically ill patients, dysfunction of the PNS is also quite common. It is typically present in patients with prolonged critical illnesses lasting several weeks and involving sepsis; clinical suspicion is aroused when there is failure to wean from mechanical ventilation despite improvement of the underlying sepsis and critical illness. *Critical illness polyneuropathy* refers to the most common PNS complication related to critical illness; it is seen in the setting of prolonged critical illness, sepsis, and multisystem organ failure. Neurologic findings include diffuse weakness, decreased reflexes, and distal sensory loss. Electrophysiologic studies demonstrate a diffuse, symmetric, distal axonal sensorimotor neuropathy, and pathologic studies have confirmed axonal degeneration. The precise mechanism of critical illness polyneuropathy remains unclear, but circulating factors such as cytokines, which are associated with sepsis and SIRS, are thought to play a role. It has been reported that up to 70% of patients with the sepsis syndrome have some degree of neuropathy, although far fewer have a clinical syndrome profound enough to cause severe respiratory muscle weakness requiring prolonged mechanical ventilation or resulting in

failure to wean. Recent studies suggest that aggressive glycemic control with insulin infusions decreases the risk of critical illness polyneuropathy. Treatment is supportive, with specific intervention directed at treating the underlying illness. Although spontaneous recovery is usually seen, the time course may extend over weeks to months and necessitate long-term ventilatory support and care even after the underlying critical illness has resolved.

DISORDERS OF NEUROMUSCULAR TRANSMISSION

A defect in neuromuscular transmission may be a source of weakness in critically ill patients. Myasthenia gravis may be a consideration; however, persistent weakness secondary to impaired neuromuscular junction transmission is almost always caused by administration of drugs. A number of medications, including antibiotics, especially aminoglycosides, and β -blocking agents, impair neuromuscular transmission. In the ICU, the nondepolarizing neuromuscular blocking agents (nd-NMBAs), also known as muscle relaxants, are most commonly responsible. Included in this group of drugs are pancuronium, vecuronium, rocuronium, and atracurium. They are often used to facilitate mechanical ventilation or other critical care procedures, but with prolonged use, persistent neuromuscular blockade may result in weakness even after discontinuation of these agents hours or days earlier. Risk factors for this prolonged action of neuromuscular blocking agents include female gender, metabolic acidosis, and renal failure.

Prolonged neuromuscular blockade does not appear to produce permanent damage to the PNS. After the offending medications are discontinued, full strength is restored, although this may take days. In general, the lowest dose of neuromuscular blocking agent should be used to achieve the desired result, and when these agents are used in the ICU, a peripheral nerve stimulator should be used to monitor neuromuscular junction function.

MYOPATHY

Critically ill patients, especially those with sepsis, frequently develop muscle wasting, often in the face of seemingly adequate nutritional support. The assumption has been that this represents a catabolic myopathy brought about as a result of multiple factors, including elevated cortisol and catecholamine release and other circulating factors induced by the SIRS. In this syndrome, known as *cachectic myopathy*, serum creatine kinase levels and electromyography (EMG) results are normal. Muscle biopsy shows type II fiber atrophy. Panfascicular muscle fiber necrosis may also occur in the setting of profound sepsis. This so-called *septic myopathy* is characterized clinically by weakness progressing to a profound level over just a few days. There may be associated

elevations in serum creatine kinase and urine myoglobin. Both EMG and muscle biopsy may be normal initially but eventually show abnormal spontaneous activity and panfascicular necrosis with an accompanying inflammatory reaction. Both of these myopathic syndromes may be considered under the broader heading of *critical illness myopathy*.

Acute quadriplegic myopathy describes a clinical syndrome of severe weakness seen in the setting of glucocorticoid and nd-NMBA use. The most frequent scenario in which this is encountered is an asthmatic patient who requires high-dose glucocorticoids and nd-NMBA to facilitate mechanical ventilation. This muscle disorder is not caused by prolonged action of nd-NMBAs at the neuromuscular junction but, rather, is an actual myopathy with muscle damage; it has occasionally been described with high-dose glucocorticoid use alone. Clinically, this syndrome is most often recognized when a patient fails to wean from mechanical ventilation despite resolution of the primary pulmonary process. Pathologically, there may be vacuolar changes in both type I and type II muscle fibers with evidence of regeneration. Patients with acute quadriplegic myopathy have a good prognosis. If patients survive their underlying critical illness, the myopathy invariably improves, and most patients return to normal. However, because this syndrome is a result of true muscle damage, not just prolonged blockade at the neuromuscular junction, this process may take weeks or months, and tracheostomy with prolonged ventilatory support may be necessary. Some patients do have residual long-term weakness, with atrophy and fatigue limiting ambulation. At present, it is unclear how to prevent this myopathic complication except by avoiding use of nd-NMBAs, a strategy that is not always possible. Monitoring with a peripheral nerve stimulator can help to avoid the overuse of these agents. However, this is more likely to prevent the complication of prolonged neuromuscular junction blockade than it is to prevent this myopathy.

SUBARACHNOID HEMORRHAGE

SAH renders the brain critically ill from both primary and secondary brain insults. Excluding head trauma, the most common cause of SAH is rupture of a saccular aneurysm. Other causes include bleeding from a vascular malformation (arteriovenous malformation or dural arterial-venous fistula) and extension into the subarachnoid space from a primary intracerebral hemorrhage. Some idiopathic SAHs are localized to the perimesencephalic cisterns and are benign; they probably have a venous or capillary source, and angiography is unrevealing.

Saccular ("Berry") Aneurysm

Autopsy and angiography studies have found that about 2% of adults harbor intracranial aneurysms, for a prevalence of

364 4 million persons in the United States; the aneurysm will rupture, producing SAH, in 25,000–30,000 people per year. For patients who arrive alive at hospital, the mortality rate over the next month is about 45%. Of those who survive, more than half are left with major neurologic deficits as a result of the initial hemorrhage, cerebral vasospasm with infarction, or hydrocephalus. If the patient survives but the aneurysm is not obliterated, the rate of rebleeding is about 20% in the first 2 weeks, 30% in the first month, and about 3% per year afterward. Given these alarming figures, the major therapeutic emphasis is on preventing the predictable early complications of the SAH.

Unruptured, asymptomatic aneurysms are much less dangerous than a recently ruptured aneurysm. The annual risk of rupture for aneurysms <10 mm in size is ~0.1%, and for aneurysms ≥10 mm in size, it is ~0.5–1%; the surgical morbidity far exceeds these percentages. Because of the longer length of exposure to risk of rupture, younger patients with aneurysms >10 mm in size may benefit from prophylactic treatment. As with the treatment of patients with asymptomatic carotid stenosis, the risk:benefit analysis strongly depends on the complication rate of treatment.

Giant aneurysms (those >2.5 cm in diameter) occur at the same sites (see below) as small aneurysms and account for 5% of cases. The three most common locations are the terminal internal carotid artery, middle cerebral artery (MCA) bifurcation, and top of the basilar artery. Their risk of rupture is ~6% in the first year after identification and may remain high indefinitely. They often cause symptoms by compressing the adjacent brain or cranial nerves.

Mycotic aneurysms are usually located distal to the first bifurcation of major arteries of the circle of Willis. Most result from infected emboli caused by bacterial endocarditis causing septic degeneration of arteries and subsequent dilatation and rupture. Whether these lesions should be sought and repaired before rupture or left to heal spontaneously is controversial.

Pathophysiology

Saccular aneurysms occur at the bifurcations of the large-to medium-sized intracranial arteries; rupture is into the subarachnoid space in the basal cisterns and often into the parenchyma of the adjacent brain. Approximately 85% of aneurysms occur in the anterior circulation, mostly on the circle of Willis. About 20% of patients have multiple aneurysms, many at mirror sites bilaterally. As an aneurysm develops, it typically forms a neck with a dome. The length of the neck and the size of the dome vary greatly and are important in planning neurosurgical obliteration or endovascular embolization. The arterial internal elastic lamina disappears at the base of the neck. The media thins, and connective tissue replaces smooth muscle cells. At the site of rupture (most often the dome), the wall thins, and the tear that allows bleeding is

often ≤0.5 mm long. The size and site of the aneurysm are important in predicting the risk of rupture. Aneurysms >7 mm in diameter and those at the top of the basilar artery and at the origin of the posterior communicating artery are at greater risk of rupture.

Clinical Manifestations

Most unruptured intracranial aneurysms are completely asymptomatic. Symptoms are usually caused by rupture and resultant SAH, although some present with mass effect on cranial nerves or brain parenchyma. At the moment of aneurysmal rupture with major SAH, the ICP suddenly increases. This may account for the sudden transient loss of consciousness that occurs in nearly half of patients. Sudden loss of consciousness may be preceded by a brief moment of excruciating headache, but most patients first complain of headache upon regaining consciousness. In 10% of cases, aneurysmal bleeding is severe enough to cause loss of consciousness for several days. In ~45% of cases, severe headache associated with exertion is the presenting complaint. The patient often calls the headache “the worst headache of my life”; however, the most important characteristic is its sudden onset. Occasionally, these ruptures may present as headache of only moderate intensity or as a change in the patient’s usual headache pattern. The headache is usually generalized, often with neck stiffness, and vomiting is common.

Although sudden headache in the absence of focal neurologic symptoms is the hallmark of aneurysmal rupture, focal neurologic deficits may occur. Anterior communicating artery or MCA bifurcation aneurysms may rupture into the adjacent brain or subdural space and form a hematoma large enough to produce mass effect. The common deficits that result include hemiparesis, aphasia, and abulia.

Occasionally, prodromal symptoms suggest the location of a progressively enlarging unruptured aneurysm. A third cranial nerve palsy, particularly when associated with pupillary dilatation, loss of ipsilateral (but retained contralateral) light reflex, and focal pain above or behind the eye, may occur with an expanding aneurysm at the junction of the posterior communicating artery and the internal carotid artery. A sixth nerve palsy may indicate an aneurysm in the cavernous sinus, and visual field defects can occur with an expanding supraclinoid carotid or anterior cerebral artery aneurysm. Occipital and posterior cervical pain may signal a posterior inferior cerebellar artery or anterior inferior cerebellar artery aneurysm. Pain in or behind the eye and in the low temple can occur with an expanding MCA aneurysm. Thunderclap headache is a variant of migraine that simulates a SAH. Before concluding that a patient with sudden, severe headache has thunderclap migraine, a definitive workup for aneurysm or other intracranial pathology is required.

Aneurysms can undergo small ruptures and leaks of blood into the subarachnoid space, so-called *sentinel*

TABLE 36-4

GRADING SCALES FOR SUBARACHNOID HEMORRHAGE

GRADE	HUNT-HESS SCALE	WORLD FEDERATION OF NEUROSURGICAL SOCIETIES (WFNS) SCALE
1	Mild headache, normal mental status, no cranial nerve or motor findings	GCS ^a score 15, no motor deficits
2	Severe headache, normal mental status, may have cranial nerve deficit	GCS 13–14, no motor deficits
3	Somnolent, confused, may have cranial nerve or mild motor deficit	GCS 13–14, with motor deficits
4	Stupor, moderate to severe motor deficit, may have intermittent reflex posturing	GCS 7–12, with or without motor deficits
5	Coma, reflex posturing or flaccid	GCS 3–6, with or without motor deficits

^aGlasgow Coma Scale (GSC): See Table 36-2.

bleeds. Sudden unexplained headache at any location should raise suspicion of SAH and be investigated because a major hemorrhage may be imminent.

The initial clinical manifestations of SAH can be graded using the Hunt-Hess or World Federation of Neurosurgical Societies classification schemes (Table 36-4). For ruptured aneurysms, the prognosis for good outcomes decreases as the grade increases. For example it is unusual for a patient with a Hunt-Hess grade 1 SAH to die if the aneurysm is treated, but the mortality for patients with grade 4 and 5 SAHs may be as high as 80%.

Delayed Neurologic Deficits

The four major causes of delayed neurologic deficits are rerupture, hydrocephalus, vasospasm, and hyponatremia.

1. *Rerupture.* The incidence of rerupture of an untreated aneurysm in the first month after SAH is ~30%, with the peak in the first 7 days. Rerupture is associated with a 60% mortality and a poor outcome. Early treatment eliminates this risk.
2. *Hydrocephalus.* Acute hydrocephalus can cause stupor and coma and can be mitigated by placement of an external ventricular drain. More often, subacute hydrocephalus may develop over a few days or weeks and causes progressive drowsiness or slowed mentation (abulia) with incontinence. Hydrocephalus is differentiated from cerebral vasospasm with a CT scan, CT angiography, transcranial Doppler (TCD) ultrasound, or conventional x-ray angiography. Hydrocephalus may clear spontaneously or require temporary ventricular drainage. Chronic hydrocephalus may develop weeks to months after SAH and manifest as gait difficulty, incontinence, or impaired mentation. Subtle signs may be a lack of initiative in conversation or a failure to recover independence.
3. *Vasospasm.* Narrowing of the arteries at the base of the brain after SAH causes symptomatic ischemia and

infarction in ~30% of patients and is the major cause of delayed morbidity and death. Signs of ischemia appear 4–14 days after the hemorrhage, most often at 7 days. The severity and distribution of vasospasm determine whether infarction will occur.

Delayed vasospasm is believed to result from direct effects of clotted blood and its breakdown products on the arteries within the subarachnoid space. In general, the more blood that surrounds the arteries, the greater is the chance of symptomatic vasospasm. Spasm of major arteries produces symptoms referable to the appropriate vascular territory. All of these focal symptoms may present abruptly, fluctuate, or develop over a few days. In most cases, focal spasm is preceded by a decline in mental status.

Vasospasm can be detected reliably with conventional x-ray angiography, but this invasive procedure is expensive and carries the risk of stroke and other complications. TCD ultrasound is based on the principle that the velocity of blood flow within an artery will increase as the lumen diameter is narrowed. By directing the probe along the MCA and proximal anterior cerebral artery (ACA), carotid terminus, and vertebral and basilar arteries on a daily or every-other-day basis, vasospasm can be reliably detected and treatments initiated to prevent cerebral ischemia (see below). CT angiography is another method that can detect vasospasm.

Severe cerebral edema in patients with infarction from vasospasm may increase the ICP enough to reduce CCP. Treatment may include mannitol, hyperventilation, and hemicraniectomy; moderate hypothermia may have a role as well.

4. *Hyponatremia.* Hyponatremia may be profound and can develop quickly in the first 2 weeks after SAH. There is both natriuresis and volume depletion with SAH, so patients become both hyponatremic and hypovolemic. Both atrial natriuretic peptide and brain natriuretic

peptide have a role in producing this “cerebral salt-wasting syndrome.” Typically, it clears over the course of 1–2 weeks and, in the setting of SAH, should not be treated with free-water restriction because this may increase the risk of stroke (see below).

Laboratory Evaluation and Imaging

(Fig. 36-8) The hallmark of aneurysmal rupture is blood in the CSF. More than 95% of cases have enough blood to be visualized on a high-quality noncontrast CT scan obtained within 72 h. If the scan fails to establish the diagnosis of SAH and no mass lesion or obstructive hydrocephalus is found, an LP should be performed to establish the presence of subarachnoid blood. Lysis of the red blood cells and subsequent conversion of hemoglobin to bilirubin stains the spinal fluid yellow within 6–12 h. This xanthochromic spinal fluid peaks in intensity at 48 h and lasts for 1–4 weeks, depending on the amount of subarachnoid blood.

The extent and location of subarachnoid blood on noncontrast CT scan help locate the underlying aneurysm, identify the cause of any neurologic deficit,

and predict delayed vasospasm. A high incidence of symptomatic vasospasm in the MCA and ACA has been found when early CT scans show subarachnoid clots $>5 \times 3$ mm in the basal cisterns or layers of blood >1 mm thick in the cerebral fissures. CT scans less reliably predict vasospasm in the vertebral, basilar, or posterior cerebral arteries.

LP before an imaging procedure is indicated only if a CT scan is not available at the time of the suspected SAH. After the diagnosis of hemorrhage from a ruptured saccular aneurysm is suspected, four-vessel conventional x-ray angiography (of both carotid and both vertebral arteries) is generally performed to localize and define the anatomic details of the aneurysm and to determine if other unruptured aneurysms exist (Fig. 36-8C). At some centers, the ruptured aneurysm can be treated using endovascular techniques at the time of the initial angiography as a way to expedite treatment and minimize the number of invasive procedures. CT angiography is an alternative method for locating the aneurysm and may be sufficient to plan definitive therapy.

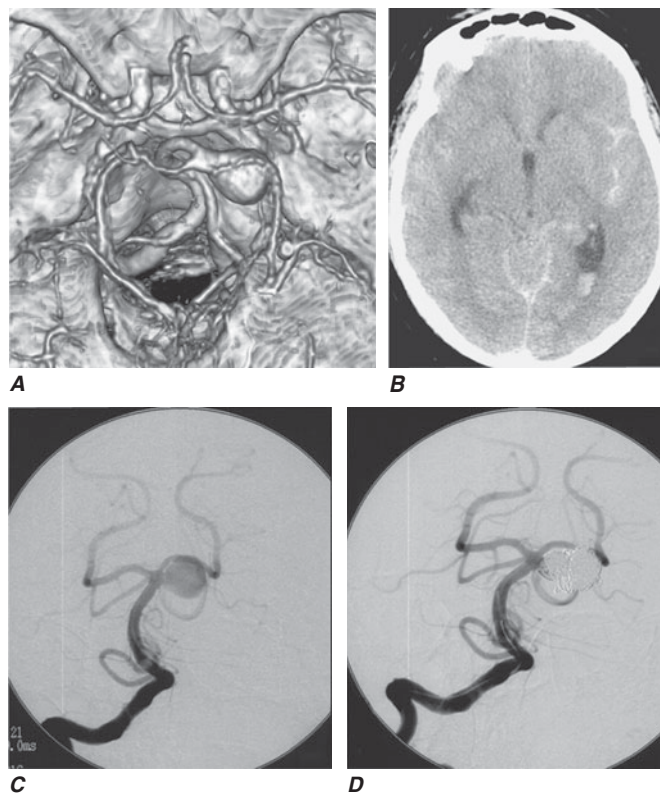


FIGURE 36-8

Subarachnoid hemorrhage. **A.** CT angiography revealing an aneurysm of the left superior cerebellar artery. **B.** Noncontrast CT scan at the level of the third ventricle revealing subarachnoid blood (*bright*) in the left sylvian fissure and within the left lateral ventricle. **C.** Conventional anteroposterior x-ray angiogram of the right vertebral and basilar artery

showing the large aneurysm. **D.** Conventional angiogram after coil embolization of the aneurysm, whereby the aneurysm body is filled with platinum coils delivered through a microcatheter navigated from the femoral artery into the aneurysm neck.

Close monitoring (daily or twice daily) of electrolytes is important because hyponatremia can occur precipitously during the first 2 weeks after SAH (see earlier).

The electrocardiogram (ECG) frequently shows ST-segment and T-wave changes similar to those associated with cardiac ischemia. Prolonged QRS complex, increased QT interval, and prominent “peaked” or deeply inverted symmetric T waves are usually secondary to the intracranial hemorrhage. Evidence suggests that structural myocardial lesions produced by circulating catecholamines and excessive discharge of sympathetic neurons may occur after SAH, causing these ECG changes and a reversible cardiomyopathy sufficient to cause shock or congestive heart failure. Echocardiography reveals a pattern of regional wall motion abnormalities that follow the distribution of sympathetic nerves rather than the major coronary arteries, with relative sparing of the ventricular wall apex. The sympathetic nerves themselves appear to be injured by direct toxicity from the excessive catecholamine release. An asymptomatic troponin elevation is common. Serious ventricular dysrhythmias are unusual.

Rx Treatment: **SUBARACHNOID HEMORRHAGE**

Early aneurysm repair prevents rerupture and allows the safe application of techniques to improve blood flow (e.g., induced hypertension and hypervolemia) if symptomatic vasospasm develops. An aneurysm can be “clipped” by a neurosurgeon or “coiled” by an endovascular surgeon. Surgical repair involves placing a metal clip across the aneurysm neck, thereby immediately eliminating the risk of rebleeding. This approach requires craniotomy and brain retraction, which is associated with neurologic morbidity. Endovascular techniques involve placing platinum coils or other embolic material within the aneurysm via a catheter that is passed from the femoral artery. The aneurysm is packed tightly to enhance thrombosis and over time is walled off from the circulation (Fig. 36-8D). The only prospective randomized trial of surgery versus endovascular treatment for ruptured aneurysm, the International Subarachnoid Aneurysm Trial (ISAT), was terminated early when 24% of patients treated with endovascular therapy were dead or dependent at 1 year compared with 31% treated with surgery, a significant 23% relative reduction. Follow-up for these patients, which is now complete, reveals that the benefit of endovascular therapy is durable. However, some aneurysms have a morphology that is not amenable to endovascular treatment. Thus, surgery remains an important treatment option. Centers that combine both endovascular and neurosurgical expertise likely offer the best outcomes for patients, and good data show that centers that specialize in aneurysm treatment have improved mortality rates.

The medical management of patients with SAH focuses on protecting the airway, managing blood pressure before and after aneurysm treatment, preventing rebleeding before treatment, managing vasospasm, treating hydrocephalus, treating hyponatremia, and preventing pulmonary embolus.

Intracranial hypertension after aneurysmal rupture occurs secondary to subarachnoid blood, parenchymal hematoma, acute hydrocephalus, or loss of vascular autoregulation. Patients who are stuporous should undergo emergent ventriculostomy to measure ICP and to treat high ICP in order to prevent cerebral ischemia. Medical therapies designed to combat increased ICP (e.g., mild hyperventilation, mannitol, and sedation) can also be used as needed. High ICP refractory to treatment is a poor prognostic sign.

Before definitive treatment of the ruptured aneurysm, care is required to maintain adequate CCP while avoiding excessive elevation of arterial pressure. If the patient is alert, it is reasonable to lower the blood pressure to normal using nicardipine, labetalol, or esmolol. If the patient has a depressed level of consciousness, ICP should be measured and the CCP targeted to 60–70 mmHg.

Because rebleeding is common, all patients who are not candidates for early aneurysm repair are put on bed rest in a quiet room and are given stool softeners to prevent straining. If headache or neck pain is severe, mild sedation and analgesia are prescribed. Extreme sedation is avoided because it can obscure changes in neurologic status. Adequate hydration is necessary to avoid a decrease in blood volume predisposing patients to brain ischemia.

Seizures are uncommon at the onset of aneurysmal rupture. The quivering, jerking, and extensor posturing that often accompany loss of consciousness with SAH are probably related to the sharp increase in ICP or, perhaps, acute generalized vasospasm rather than seizure. However, phenytoin is often given as prophylactic therapy because a seizure may promote rebleeding.

Glucocorticoids may help reduce the head and neck ache caused by the irritative effect of the subarachnoid blood. There is no good evidence that they reduce cerebral edema, are neuroprotective, or reduce vascular injury, and their routine use therefore is not recommended.

Antifibrinolytic agents are not routinely prescribed but may be considered in patients in whom aneurysm treatment cannot proceed immediately. They are associated with a reduced incidence of aneurysmal rerupture but may also increase the risk of delayed cerebral infarction and deep vein thrombosis (DVT).

Vasospasm remains the leading cause of morbidity and mortality after aneurysmal SAH. Treatment with the calcium channel antagonist nimodipine (60 mg PO every 4 h) improves outcome, perhaps by preventing ischemic

injury rather than reducing the risk of vasospasm. Nimodipine can cause significant hypotension in some patients, which may worsen cerebral ischemia in patients with vasospasm. Symptomatic cerebral vasospasm can also be treated by increasing the CCP by increasing MAP through plasma volume expansion and the judicious use of IV vasopressor agents, usually phenylephrine or norepinephrine. Increased perfusion pressure has been associated with clinical improvement in many patients, but high arterial pressure may promote rebleeding in unprotected aneurysms. Treatment with induced hypertension and hypervolemia generally requires monitoring of arterial and central venous pressures; it is best to infuse pressors through a central venous line as well. Volume expansion helps prevent hypotension, augments cardiac output, and reduces blood viscosity by reducing the hematocrit. This method is called “triple-H” (hypertension, hemodilution, and hypervolemic) therapy.

If symptomatic vasospasm persists despite optimal medical therapy, intraarterial vasodilators and percutaneous transluminal angioplasty are considered. Vasodilatation by direct angioplasty appears to be permanent, allowing triple-H therapy to be tapered sooner. The pharmacologic vasodilators (verapamil and nicardipine) do not last more than 8–24 h therefore, multiple treatments may be required until the subarachnoid blood is reabsorbed. Although intraarterial papaverine is an effective vasodilator, evidence suggests that papaverine may be neurotoxic, so its use should be reserved for refractory cases.

Acute hydrocephalus can cause stupor or coma. It may clear spontaneously or require temporary ventricular drainage. When chronic hydrocephalus develops, ventricular shunting is the treatment of choice.

Free-water restriction is contraindicated in patients with SAH at risk for vasospasm because hypovolemia and hypotension may occur and precipitate cerebral ischemia. Many patients continue to experience a decline in serum sodium despite receiving parenteral fluids containing normal saline. Frequently, supplemental oral salt coupled with normal saline will mitigate hyponatremia, but patients often also require hypertonic saline. Care must be taken not to correct serum sodium too quickly in patients with marked hyponatremia of several days' duration because central pontine myelinolysis may occur.

All patients should have pneumatic compression stockings applied to prevent pulmonary embolism. Unfractionated heparin administered subcutaneously for DVT prophylaxis can be initiated immediately after endovascular treatment and within days after craniotomy and surgical clipping and is a useful adjunct to pneumatic compression stockings. Treatment of pulmonary embolus depends on whether the aneurysm has been treated and whether or not the patient has had a craniotomy. Systemic anticoagulation with heparin is contraindicated in patients with ruptured and untreated aneurysms. It is a relative contraindication after craniotomy for several days or perhaps weeks, and it may delay thrombosis of a coiled aneurysm. After craniotomy, use of inferior vena cava filters is preferred to prevent further pulmonary emboli; systemic anticoagulation with heparin is preferred after successful endovascular treatment.

FURTHER READINGS

- LATRONICO N et al: Neuromuscular sequelae of critical illness. *Curr Opin Crit Care* 11:381, 2005
- LIU AK et al: To die or not to die for neurons in ischemia, traumatic brain injury and epilepsy: A review on the stress-activated signaling pathways and apoptotic pathways. *Prog Neurobiol* 69:103, 2003
- MOLYNEUX A et al: International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: A randomized trial. *Lancet* 360:1267, 2002
- NOLAN JP et al: Therapeutic Hypothermia After Cardiac Arrest: An Advisory Statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation. *Circulation* 108:118, 2003
- POSNER JB et al: *Plum and Posner's Diagnosis of Stupor and Coma*, 4th ed. New York, Oxford University Press, 2007
- SAFE STUDY INVESTIGATORS et al: Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *N Engl J Med* 357:874, 2007
- VAN DEN BERGHE G et al: Insulin therapy protects the central and peripheral nervous system of intensive care patients. *Neurology* 64:1348, 2005
- WJIDICKS EFM et al: Practice parameter: Prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review). *Neurology* 67:203, 2006

SECTION V

DISORDERS COMPLICATING CRITICAL ILLNESSES AND THEIR MANAGEMENT





CHAPTER 37

ACUTE RENAL FAILURE

Kathleen D. Liu ■ Glenn M. Chertow

■ Etiology and Pathophysiology	370	Renal Failure Indices	379
Prerenal Azotemia	370	Laboratory Findings	379
Intrinsic ARF	372	Radiologic Findings	380
Postrenal ARF	374	Renal Biopsy	380
■ Clinical Features and Differential Diagnosis	375	■ Complications	380
Clinical Assessment	375	■ Outcome and Long-Term Prognosis	385
Urinalysis	375	■ Further Readings	385

Acute renal failure (ARF) is characterized by a rapid decline in glomerular filtration rate (GFR) over hours to days. Depending on the exact definition used, ARF complicates approximately 5–7% of hospital admissions and up to 30% of admissions to intensive care units. Retention of nitrogenous waste products, oliguria (urine output <400 mL/d contributing to extracellular fluid overload), and electrolyte and acid–base abnormalities are frequent clinical features. ARF is usually asymptomatic and diagnosed when biochemical monitoring of hospitalized patients reveals a new increase in blood urea and serum creatinine concentrations. For purposes of diagnosis and management, causes of ARF are generally divided into three major categories: (1) diseases that cause renal hypoperfusion, resulting in decreased function without frank parenchymal damage (*prerenal ARF*, or azotemia; ~55%); (2) diseases that directly involve the renal parenchyma (*intrinsic ARF*; ~40%); and (3) diseases associated with urinary tract obstruction (*postrenal ARF*; ~5%). ARF is often considered to be reversible, although a return to baseline serum creatinine concentrations after injury might not be sufficiently sensitive to detect clinically significant irreversible damage that may ultimately contribute to chronic kidney disease. ARF is associated with significant in-hospital morbidity and mortality rates, the latter in the range of 30–60%, depending on the clinical setting and the presence or absence of nonrenal organ system failure.

ETIOLOGY AND PATHOPHYSIOLOGY

PRERENAL AZOTEMIA

The most common form of ARF is prerenal ARF, which occurs in the setting of renal hypoperfusion. Prerenal ARF is generally reversible when renal perfusion pressure is restored. By definition, renal parenchymal tissue is not damaged. More severe or prolonged hypoperfusion may lead to ischemic injury, often termed *acute tubular necrosis* (ATN). Thus, prerenal ARF and ischemic ATN fall along a spectrum of manifestations of renal hypoperfusion. As shown in [Table 37-1](#), prerenal ARF can complicate any disease that induces hypovolemia, low cardiac output, systemic vasodilatation, or selective intrarenal vasoconstriction.

Hypovolemia leads to a decrease in mean systemic arterial pressure, which is detected as reduced stretch by arterial (e.g., carotid sinus) and cardiac baroreceptors. In turn, this triggers a coordinated series of neurohormonal responses that aim to restore blood volume and arterial pressure. These include activation of the sympathetic nervous system and renin–angiotensin–aldosterone system, as well as release of arginine vasopressin. Relatively “nonessential” vascular beds (e.g., the musculocutaneous and splanchnic circulations) undergo vasoconstriction in an attempt to preserve cardiac and cerebral perfusion pressure. In addition, salt loss through sweat glands is

TABLE 37-1

CLASSIFICATION AND MAJOR CAUSES OF ACUTE RENAL FAILURE

Prerenal Acute Renal Failure

- I. Hypovolemia
 - A. Increased extracellular fluid losses: hemorrhage
 - B. Gastrointestinal fluid loss: vomiting, diarrhea, enterocutaneous fistula
 - C. Renal fluid loss: diuretics, osmotic diuresis, hypoadrenalism, nephrogenic diabetes insipidus
 - D. Extravascular sequestration: burns, pancreatitis, severe hypoalbuminemia (hypoproteinemia)
 - E. Decreased intake: dehydration, altered mental status
- II. Altered renal hemodynamics resulting in hypoperfusion
 - A. Low cardiac output state: diseases of the myocardium, valves, and pericardium (including tamponade); pulmonary hypertension or massive pulmonary embolism leading to right and left heart failure; impaired venous return (e.g., abdominal compartment syndrome or positive pressure ventilation)
 - B. Systemic vasodilation: sepsis, antihypertensives, afterload reducers, anaphylaxis
 - C. Renal vasoconstriction: hypercalcemia, catecholamines, calcineurin inhibitors, amphotericin B
 - D. Impairment of renal autoregulatory responses: cyclooxygenase inhibitors (e.g., NSAIDs), ACE inhibitors, or ARBs
 - E. Hepatorenal syndrome

Intrinsic Acute Renal Failure

- I. Renovascular obstruction (bilateral, or unilateral in the setting of one kidney)
 - A. Renal artery obstruction: atherosclerotic plaque, thrombosis, embolism, dissection aneurysm, large vessel vasculitis
 - B. Renal vein obstruction: thrombosis or compression
- II. Diseases of the glomeruli or vasculature
 - A. Glomerulonephritis or vasculitis
 - B. Other: thrombotic microangiopathy, malignant hypertension, collagen vascular diseases (SLE, scleroderma), DIC, preeclampsia
- III. Acute tubular necrosis
 - A. Ischemia: causes are the same as for prerenal ARF, but generally the insult is more severe or more prolonged
 - B. Infection with or without sepsis syndrome
 - C. Toxins
 1. Exogenous: radiocontrast, calcineurin inhibitors, antibiotics (e.g., aminoglycosides), chemotherapy (e.g., cisplatin), antifungals (e.g., amphotericin B), ethylene glycol
 2. Endogenous: rhabdomyolysis, hemolysis
- IV. Interstitial nephritis
 - A. Allergic: antibiotics (β -lactams, sulfonamides, quinolones, rifampin), NSAIDs, diuretics, other drugs
 - B. Infection: pyelonephritis (if bilateral)
 - C. Infiltration: lymphoma, leukemia, sarcoidosis
 - D. Inflammatory, nonvascular: Sjögren's syndrome, tubulointerstitial nephritis with uveitis
- V. Intratubular obstruction
 - A. Endogenous: myeloma proteins, uric acid (tumor lysis syndrome), systemic oxalosis
 - B. Exogenous: acyclovir, ganciclovir, methotrexate, indinavir

Postrenal Acute Renal Failure (Obstruction)

- I. Ureteric (bilateral, or unilateral in the case of one kidney): calculi, blood clots, sloughed papillae, cancer, external compression (e.g., retroperitoneal fibrosis)
- II. Bladder neck: neurogenic bladder, prostatic hypertrophy, calculi, blood clots, cancer
- III. Urethra: stricture or congenital valves

Note: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ARF, acute renal failure; DIC, disseminated intravascular coagulation; NSAID, nonsteroidal antiinflammatory drug; SLE, systemic lupus erythematosus.

inhibited, and thirst and salt appetite are stimulated. Renal salt and water retention also occur.

In states of mild hypoperfusion, glomerular perfusion and the filtration fraction are preserved through several compensatory mechanisms. In response to the reduction in perfusion pressure, stretch receptors in afferent arterioles trigger afferent arteriolar vasodilatation through a local myogenic reflex (autoregulation). Angiotensin II

increases biosynthesis of vasodilator prostaglandins (e.g., prostaglandin E_2 and prostacyclin), also resulting in afferent arteriolar vasodilation. In addition, angiotensin II induces preferential constriction of efferent arterioles. As a result, the fraction of plasma flowing through glomerular capillaries that is filtered is increased (filtration fraction), intraglomerular pressure is maintained, and GFR is preserved. With more severe hypoperfusion, these

372 compensatory responses are overwhelmed, and GFR decreases, leading to prerenal ARF.

Autoregulatory dilatation of afferent arterioles allows for maintenance of GFR despite systemic hypotension; however, when hypotension is severe or prolonged, these autoregulatory mechanisms fail, resulting in a precipitous decline in GFR. Lesser degrees of hypotension may provoke prerenal ARF in those at risk, including elderly individuals and patients with diseases that affect the integrity of afferent arterioles (e.g., hypertensive nephrosclerosis, diabetic vasculopathy and other forms of occlusive [including atherosclerotic] renovascular disease). In addition, drugs that interfere with adaptive responses to hypoperfusion may convert compensated renal hypoperfusion into overt prerenal ARF or ATN. Pharmacologic inhibitors of renal prostaglandin biosynthesis [nonsteroidal antiinflammatory drugs (NSAIDs)] or angiotensin-converting enzyme (ACE) activity (ACE inhibitors) and angiotensin II receptor blockers (ARBs) are major culprits. Although NSAIDs do not compromise GFR in healthy individuals, these medications may precipitate prerenal ARF in patients with volume depletion and in those with chronic kidney disease (in whom GFR is maintained, in part, through prostaglandin-mediated hyperfiltration by the remaining functional nephrons). ACE inhibitors should be used with special care in patients with bilateral renal artery stenosis or unilateral stenosis in a solitary functioning kidney. In these settings, glomerular perfusion and filtration may be exquisitely dependent on the actions of angiotensin II. Angiotensin II preserves GFR in these circumstances by increasing systemic arterial pressure and triggering selective constriction of efferent arterioles. ACE inhibitors and ARBs blunt these responses and can precipitate ARF.

Hepatorenal Syndrome

Hepatorenal syndrome (HRS) is a unique form of prerenal ARF that frequently complicates advanced cirrhosis as well as acute liver failure. In HRS, the kidneys are structurally normal but fail because of splanchnic vasodilation and arteriovenous shunting, resulting in profound renal vasoconstriction. Correction of the underlying liver disease (e.g., by liver transplantation) results in resolution of the ARF. There are two forms of HRS, type I and type II, that differ in their clinical course. In type I HRS, the more aggressive form of the disease, ARF progresses even after optimization of systemic hemodynamics and carries a mortality rate of >90%.

INTRINSIC ARF

Intrinsic causes of ARF can be conceptually divided based on the predominant compartment of the kidney that is affected: (1) ischemic or nephrotoxic tubular injury, (2) tubulointerstitial diseases, (3) diseases of the renal

microcirculation and glomeruli, and (4) diseases of larger renal vessels (Table 37-1). Ischemia and nephrotoxins classically induce acute tubular injury. Although many patients with ischemic or nephrotoxic ARF do not have morphologic evidence of cellular necrosis, this disease is often referred to as ATN. More recently, because of the important role of sublethal injury to tubular epithelial and other renal cells (e.g., endothelial cells) in the pathogenesis of this syndrome, the term *acute kidney injury* (AKI) has been proposed.

Etiology and Pathophysiology of Ischemic Acute Tubular Necrosis

Prerenal ARF and ischemic ATN are part of a spectrum of manifestations of renal hypoperfusion. In its most extreme form, ischemia leads to bilateral renal cortical necrosis and irreversible renal failure. ATN differs from prerenal ARF in that the renal tubular epithelial cells are injured in the latter. ATN occurs most frequently in patients undergoing major cardiovascular surgery or who have severe trauma, hemorrhage, sepsis, or volume depletion (Table 37-1). Patients with other risk factors for ARF (e.g., exposure to nephrotoxins or preexisting chronic kidney disease) are at increased risk for ATN. Recovery typically takes 1–2 weeks after normalization of renal perfusion because it requires repair and regeneration of renal cells.

The course of ischemic ATN is typically characterized by four phases: initiation, extension, maintenance, and recovery (Fig. 37-1). These phases are often preceded by a period of prerenal azotemia. During the *initiation phase* (lasting hours to days), GFR declines because (1) glomerular ultrafiltration pressure is reduced as renal blood flow decreases, (2) the flow of filtrate within tubules is obstructed by casts composed of shed epithelial cells and necrotic debris, and (3) there is backleak of glomerular filtrate through injured tubular epithelium. Ischemic injury is most prominent in the S₃ segment of the proximal tubule and the medullary portion of the thick ascending limb of the loop of Henle. These segments of the tubule are particularly sensitive to ischemia because of high rates of active [adenosine triphosphate (ATP)-dependent] solute transport and location in the outer medulla, where the partial pressure of oxygen is low even under basal conditions. Cellular ischemia results in ATP depletion, inhibition of active sodium transport, cytoskeletal disruption, loss of cell polarity, cell–cell and cell–matrix attachment, and oxygen free radical formation. Renal injury may be limited by restoration of renal blood flow during this period. If severe, cell injury results in apoptosis or necrosis.

The *extension phase* occurs after the initiation phase and is characterized by continued ischemic injury and inflammation. It has been proposed that endothelial damage (resulting in vascular congestion) contributes to

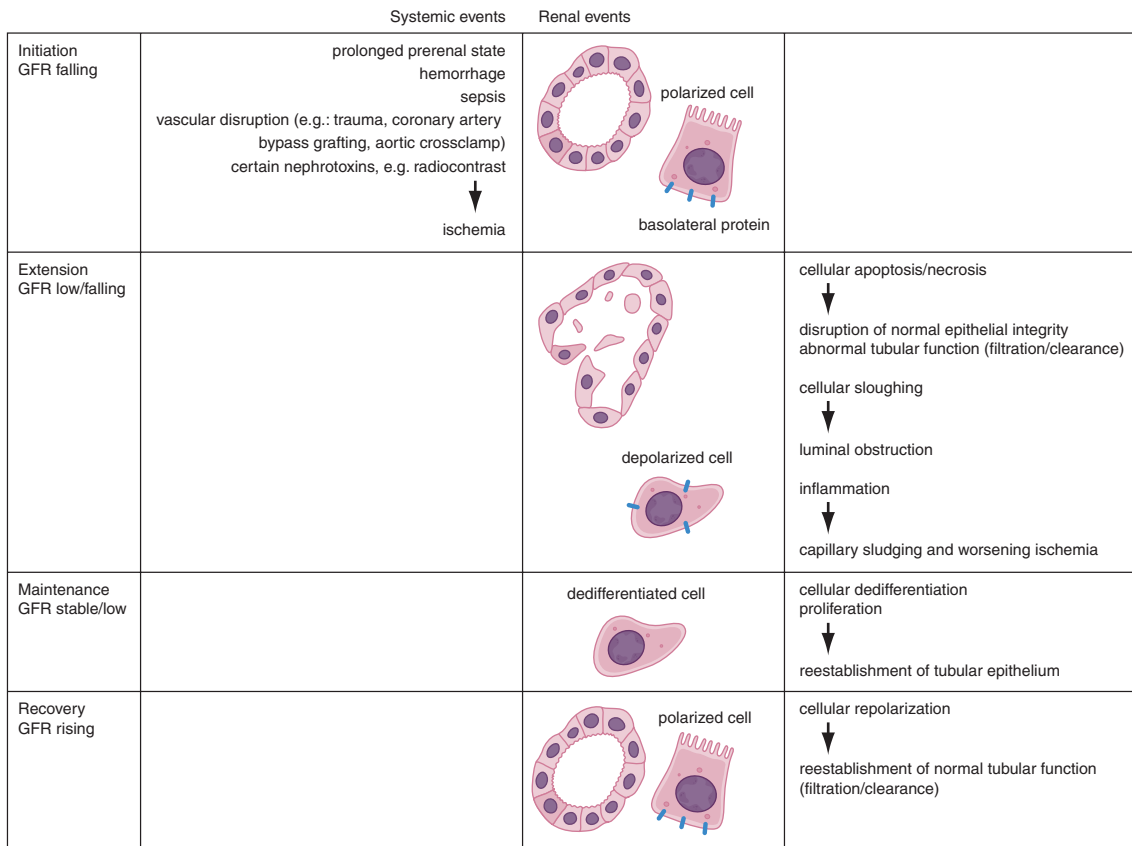


FIGURE 37-1

Four phases of acute tubular necrosis.

both of these processes. During the *maintenance phase* (typically 1–2 weeks), GFR stabilizes at its nadir (typically 5–10 mL/min), urine output is lowest, and uremic complications may arise (see later). It is not clear why the GFR remains low during this phase despite correction of systemic hemodynamics. Proposed mechanisms include persistent intrarenal vasoconstriction and medullary ischemia triggered by dysregulated release of vasoactive mediators from injured endothelial cells, congestion of medullary blood vessels, and reperfusion injury induced by reactive oxygen species and inflammatory mediators released by leukocytes or renal parenchymal cells. In addition, epithelial cell injury may contribute to persistent intrarenal vasoconstriction through *tubuloglomerular feedback*. Specialized epithelial cells in the macula densa region of distal tubules detect increases in distal salt delivery that occur as a consequence of impaired reabsorption by more proximal nephron segments. Macula densa cells, in turn, stimulate constriction of adjacent afferent arterioles by a poorly defined mechanism and further compromise glomerular perfusion and filtration, thereby contributing to a vicious circle.

The *recovery phase* is characterized by tubular epithelial cell repair and regeneration as well as a gradual return of GFR toward pre-morbid levels. The recovery

phase may be complicated by a marked diuretic phase because of delayed recovery of epithelial cell function (solute and water reabsorption) relative to glomerular filtration (see below).

Etiology and Pathophysiology of Nephrotoxic Acute Renal Failure

Nephrotoxic ATN may complicate exposure to many structurally diverse pharmacologic agents (Table 37-1). With most nephrotoxins, the incidence of ARF is increased in elderly individuals and in patients with pre-existing chronic kidney disease, true or “effective” hypovolemia, or concomitant exposure to other toxins.

Radiocontrast agents, cyclosporine, and tacrolimus (FK506) cause kidney injury through intrarenal vasoconstriction. Consequently, ATN in association with these medications is characterized by an acute decrease in renal blood flow and GFR, a relatively benign urine sediment, and a low fractional excretion of sodium (see later). Severe cases may show clinical or pathologic evidence of tubular cell necrosis. Contrast nephropathy is also thought to result from the generation of reactive oxygen species that are directly toxic to renal tubular epithelial cells. Contrast nephropathy classically presents

as an acute (onset within 24–48 h) but reversible (peak, 3–5 days; resolution within 1 week) increase in blood urea nitrogen (BUN) and serum creatinine. Contrast nephropathy is most common in individuals with preexisting chronic kidney disease, diabetes mellitus, congestive heart failure, hypovolemia, or multiple myeloma. The type (low versus iso-osmolar contrast) and dose of contrast also influence the likelihood of injury associated with its administration.

Antibiotics and anticancer drugs typically cause ATN through direct toxicity to the tubular epithelial cells or intratubular obstruction. ARF complicates 10–30% of courses of *aminoglycoside antibiotics*. Aminoglycosides accumulate in renal tubular epithelial cells, where they cause oxidative stress and cell injury; thus, ARF usually occurs after several days of aminoglycoside therapy. Damage may occur in both the proximal and distal tubule; defects in the distal tubule may result in decreased concentrating ability. *Amphotericin B* causes dose-related ARF through intrarenal vasoconstriction and direct toxicity to proximal tubule epithelium. Newer (liposomal) formulations of amphotericin B may be associated with less nephrotoxicity. Acyclovir may precipitate in the renal tubules and cause ARF. Foscarnet and pentamidine are less commonly prescribed antimicrobials also frequently associated with ARF. Cisplatin and carboplatin, similar to the aminoglycosides, are accumulated by proximal tubule cells and typically provoke ARF after 7–10 days of exposure, typically in association with potassium and magnesium wasting. Ifosfamide administration may lead to hemorrhagic cystitis, manifested by hematuria, as well as acute and chronic renal failure. Type II renal tubular acidosis (Fanconi syndrome) often accompanies ifosfamide-associated ARF.

Endogenous nephrotoxins include calcium, myoglobin, hemoglobin, urate, oxalate, and myeloma light chains. Hypercalcemia can compromise GFR, predominantly by inducing intrarenal vasoconstriction as well as volume depletion from obligate water loss. Both *rhabdomyolysis* and *hemolysis* can induce ARF. Common causes of rhabdomyolysis include traumatic crush injury, acute muscle ischemia, prolonged seizure activity, excessive exercise, heat stroke or malignant hyperthermia, and infectious or metabolic disorders (e.g., hypophosphatemia, severe hypothyroidism). ARF caused by hemolysis is relatively rare and is observed after blood transfusion reactions. It has been postulated that myoglobin and hemoglobin promote intrarenal oxidative stress, resulting in injury to tubular epithelial cells and inducing intratubular cast formation. In addition, cell-free hemoglobin and myoglobin are potent inhibitors of nitric oxide bioactivity and may trigger intrarenal vasoconstriction and ischemia. Hypovolemia or acidosis may further promote intratubular cast formation. Intratubular casts containing filtered immunoglobulin light chains and other proteins (including Tamm-Horsfall protein produced by thick ascending

limb cells) cause ARF in patients with *multiple myeloma* (myeloma cast nephropathy). Light chains are also directly toxic to tubule epithelial cells. Intratubular obstruction is an important cause of ARF in patients with severe *hyperuricosuria* or *hyperoxaluria*. Acute uric acid nephropathy can complicate the treatment of patients with selected lymphoproliferative or myeloproliferative disorders (e.g., Burkitt's lymphoma, acute myelogenous leukemia), especially after the administration of chemotherapy, resulting in increased cell lysis ("tumor lysis syndrome").

Pathology of Ischemic and Nephrotoxic Acute Tubular Necrosis

The classic pathologic features of ischemic ATN are patchy and focal necrosis of the tubular epithelium, with detachment of cells from the basement membrane, and occlusion of tubule lumens with casts composed of intact or degenerating epithelial cells, Tamm-Horsfall protein, and pigments. Leukocyte accumulation is frequently observed in vasa recta; however, the morphology of the glomeruli and renal vasculature is characteristically normal. Necrosis is most severe in the S3 segment of proximal tubules but may also affect the medullary thick ascending limb of the loop of Henle.

With exposure to nephrotoxins, morphologic changes tend to be most prominent in both the convoluted and straight portions of proximal tubules. Cellular necrosis is less pronounced than in ischemic ATN.

Other Causes of Intrinsic ARF

Virtually any pharmacologic agent may trigger allergic interstitial nephritis, which is characterized by infiltration of the tubulointerstitium by granulocytes (typically but not invariably eosinophils), macrophages, or lymphocytes and by interstitial edema. The most common offenders are antibiotics (e.g., penicillins, cephalosporins, quinolones, sulfonamides, rifampin) and NSAIDs (Table 37-1).

Patients with advanced atherosclerosis can develop ARF after manipulation of the aorta or renal arteries during surgery or angiography; after trauma; or rarely, spontaneously (atheroembolic ARF). Cholesterol crystals embolize to the renal vasculature, lodge in small- and medium-sized arteries, and incite a giant cell and fibrotic reaction in the vessel wall with narrowing or obstruction of the vessel lumen. Atheroembolic ARF is often associated with hypocomplementemia and eosinophiluria, and it is frequently irreversible. The acute glomerulonephritides are immune-mediated diseases characterized by proliferative or crescentic glomerular inflammation (glomerulonephritis).

POSTRENAL ARF

Urinary tract obstruction accounts for fewer than 5% of cases of hospital-acquired ARF. Because one kidney has

sufficient reserve to handle generated nitrogenous waste products, ARF from obstruction requires obstruction to urine flow between the external urethral meatus and bladder neck, bilateral ureteric obstruction, or unilateral ureteric obstruction in a patient with one functioning kidney or with significant preexisting chronic kidney disease. Bladder neck obstruction is the most common cause of postrenal ARF and is usually caused by prostatic disease (e.g., hypertrophy, neoplasia, or infection), neurogenic bladder, or therapy with anticholinergic drugs. Less common causes of acute lower urinary tract obstruction include blood clots, calculi, and urethritis with spasm. Ureteric obstruction may result from intraluminal obstruction (e.g., calculi, blood clots, sloughed renal papillae), infiltration of the ureteric wall (e.g., neoplasia), or external compression (e.g., retroperitoneal fibrosis, neoplasia or abscess, inadvertent surgical ligation). During the early stages of obstruction (hours to days), continued glomerular filtration leads to increased intraluminal pressure upstream to the site of obstruction. As a result, there is gradual distention of the proximal ureter, renal pelvis, and calyces and a decrease in GFR.

CLINICAL FEATURES AND DIFFERENTIAL DIAGNOSIS

The first step in evaluating a patient with renal failure is to determine if the disease is acute or chronic. If a review of laboratory records demonstrates that the increase in BUN and creatinine is recent, this suggests that the process is acute. However, previous measurements are not always available. Findings that suggest chronic kidney disease include anemia; evidence of renal osteodystrophy (radiologic or laboratory); and small, scarred kidneys. However, anemia may also complicate ARF (see later), and renal size may be normal or increased in several chronic renal diseases (e.g., diabetic nephropathy, amyloidosis, polycystic kidney disease, HIV-associated nephropathy). After a diagnosis of ARF has been established, the cause of ARF needs to be determined. Depending on the cause, specific therapies may need to be instituted. If the cause is believed to be an exogenous nephrotoxin (often a medication), the nephrotoxin should be eliminated or discontinued. Last, the prevention and management of complications should be instituted.

CLINICAL ASSESSMENT

Symptoms of *prerenal* ARF include thirst and orthostatic dizziness. Physical signs of orthostatic hypotension, tachycardia, reduced jugular venous pressure, decreased skin turgor, and dry mucous membranes suggest prerenal ARF. Careful clinical examination may reveal stigmata of chronic liver disease and portal hypertension, advanced cardiac failure, sepsis, or other causes of reduced “effective”

arterial blood volume (Table 37-1). Case records should be reviewed for documentation of a progressive decrease in urine output and body weight and recent initiation of treatment with diuretics, NSAIDs, ACE inhibitors, or ARBs.

Hypovolemia, septic shock, and major surgery are important risk factors for ischemic ATN. The risk of ischemic ATN is increased further if ARF persists despite normalization of systemic hemodynamics. Diagnosis of nephrotoxic ATN requires careful review of the clinical data and records for evidence of recent exposure to nephrotoxic medications, radiocontrast agents, or endogenous toxins.

Although ischemic and nephrotoxic ATN account for >90% of cases of intrinsic ARF, other renal parenchymal diseases must be considered (Table 37-2). Fever, arthralgias, and a pruritic erythematous rash after exposure to a new drug suggest allergic interstitial nephritis, although systemic features of hypersensitivity are frequently absent. Flank pain may be a prominent symptom after occlusion of a renal artery or vein and with other parenchymal diseases distending the renal capsule (e.g., severe glomerulonephritis or pyelonephritis). Subcutaneous nodules, livedo reticularis, bright orange retinal arteriolar plaques, and digital ischemia (“purple toes”) despite palpable pedal pulses suggest atheroembolization. ARF in association with oliguria, edema, and hypertension, with an “active” urine sediment (nephritic syndrome), suggests acute glomerulonephritis or vasculitis. Malignant hypertension may result in ARF, often in association with hypertensive injury to other organs (e.g., papilledema, neurologic dysfunction, left ventricular hypertrophy) and may mimic glomerulonephritis in its other clinical manifestations.

Patients with *postrenal* ARF may present with suprapubic and flank pain because of distention of the bladder and of the renal collecting system and capsule, respectively. Colicky flank pain radiating to the groin suggests acute ureteric obstruction. Prostatic disease is likely if the patient has a history of nocturia, frequency, and hesitancy and enlargement of the prostate on rectal examination. Neurogenic bladder should be suspected in patients receiving anticholinergic medications or with physical evidence of autonomic dysfunction. Definitive diagnosis of postrenal ARF hinges on judicious use of radiologic investigations and rapid improvement in renal function after relief of obstruction.

URINALYSIS

Anuria suggests complete urinary tract obstruction but may complicate severe cases of prerenal or intrinsic renal ARF. Whereas wide fluctuations in urine output raise the possibility of intermittent obstruction, patients with partial urinary tract obstruction may present with polyuria because of impairment of urine concentrating mechanisms.

TABLE 37-2

EPIDEMIOLOGY, CLINICAL FEATURES, AND DIAGNOSTIC STUDIES FOR MAJOR CAUSES OF ACUTE RENAL FAILURE

ETIOLOGY	EPIDEMIOLOGY	CLINICAL FEATURES	SERUM STUDIES	URINE STUDIES	OTHER TESTING
Prerenal ARF	Most common cause of community-acquired ARF; history of poor fluid intake; treatment with NSAIDs, ACE inhibitors, or ARBs; worsening heart failure	Volume depletion (absolute or postural hypotension, low jugular venous pressure, dry mucous membranes) or decreased effective circulatory volume (e.g., heart failure or liver disease)	High BUN/CR ratio (≥ 20) is suggestive but not diagnostic	Hyaline casts FE _{Na} <1% U _{Na} <10 mmol/L SG >1.018	
Intrinsic ARF					
Diseases of large renal vessels					
Renal artery thrombosis	More common in those with atrial fibrillation or arterial thrombosis	Flank or abdominal pain	Elevated LDH	Mild proteinuria Occasional hematuria	Renal angiography or MR angiography is diagnostic
Atheroembolic disease	Vascular disease; classically occurs within days to weeks of manipulation of the aorta or other large vessels, often in the setting of anticoagulation	Retinal plaques, palpable purpura, livedo reticularis	Eosinophilia Hypocomplementemia	Eosinophiluria	Skin or renal biopsy
Renal vein thrombosis	History of nephrotic syndrome or pulmonary embolism	Flank pain		Mild proteinuria Occasional hematuria	Renal venography or MR venography is diagnostic
Diseases of small vessels and glomeruli					
Glomerulonephritis or vasculitis	Associated with recent infection (postinfectious or endocarditis), SLE, liver disease (hepatitis B or C) Anti-GBM disease: typically men in their 20s to 40s ANCA disease: two peaks: 20s to 30s and 50s to 60s	New cardiac murmur (postinfectious) Skin rash or ulcers, arthralgias (lupus) Sinusitis (anti-GBM disease) Lung hemorrhage (anti-GBM, ANCA, lupus)	ANA, ANCA, anti-GBM antibody, hepatitis serologies, cryoglobulins, blood cultures, ASO, complements (positive test results depend on the cause)	Hematuria with RBC casts or dysmorphic RBCs Granular casts Proteinuria (usually <1 g/d)	Renal biopsy
HUS or thrombotic thrombocytopenic	Recent GI infection (<i>Escherichia coli</i>) or use of calcineurin inhibitors (FK506 and cyclosporine)	Fever, neurologic abnormalities	Schistocytes on peripheral blood smear, elevated LDH, anemia, thrombocytopenia	Hematuria Mild proteinuria RBCs (rare)	Renal biopsy

Malignant hypertension	Severe or uncontrolled hypertension	Evidence of damage to other organs: headache, papilledema, heart failure with LVH by echocardiography or ECG Typically resolves with blood pressure control	Hematuria with RBC casts or proteinuria
Acute tubular necrosis Ischemia	Recent hemorrhage or severe hypotension		Muddy brown granular or tubular epithelial cell casts FE _{Na} >1% U _{Na} >20 mmol/L SG <1.015
Exogenous toxins	Recent exposure to nephrotoxic antibiotics or chemotherapy, often in association with sepsis, or volume depletion		Muddy brown granular or tubular epithelial cell casts FE _{Na} >1% U _{Na} >20 mmol/L SG <1.015
	Recent exposure to radiocontrast, often in association with volume depletion, diabetes, or CKD		Muddy brown granular or tubular epithelial cell casts Urinalysis may be normal FE _{Na} often <1% U _{Na} often <20 mmol/L

(Continued)

TABLE 37-2 (CONTINUED)

EPIDEMIOLOGY, CLINICAL FEATURES, AND DIAGNOSTIC STUDIES FOR MAJOR CAUSES OF ACUTE RENAL FAILURE

ETIOLOGY	EPIDEMIOLOGY	CLINICAL FEATURES	SERUM STUDIES	URINE STUDIES	OTHER TESTING
Endogenous toxins	Rhabdomyolysis	Postictal state (seizures), evidence of trauma or prolonged immobilization	Increased myoglobin, CK	U/A positive for heme but no hematuria	
	Hemolysis: recent blood transfusion	Fever, other evidence of transfusion reaction	Pink plasma, increased LDH	Pink, heme-positive urine without hematuria	Transfusion reaction workup
	Tumor lysis: recent chemotherapy Multiple myeloma	Individuals >60 years of age, ongoing constitutional symptoms (fatigue, malaise)	Hyperuricemia, increased LDH Circulating monoclonal spike, anemia	Urate crystals Dipstick-negative proteinuria, monoclonal spike on electrophoresis	Bone marrow or renal biopsy
	Ethylene glycol ingestion	History of alcohol abuse, altered mental status	Metabolic gap acidosis with osmolal gap, positive toxicology results	Oxalate crystals	
Diseases of the tubulointerstitium Allergic interstitial nephritis Acute bilateral pyelonephritis	Recent medication exposure	Fever, rash, arthralgias	Eosinophilia	WBC casts, eosinophiluria	Renal biopsy
		Fever, flank pain and tenderness	Positive blood culture results	Leukocytes, proteinuria, positive urine culture result	
Postrenal ARF	History of renal stones or prostatic disease	Palpable bladder, flank or abdominal pain		Usually normal; hematuria if caused by stones	Imaging to assess obstruction: CT scan and/or ultrasound

Note: ACE, angiotensin-converting enzyme; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; ARBs, angiotensin II receptor blockers; ARF, acute renal failure; ASO, antistreptolysin O; BUN, blood urea nitrogen; CK, creatine kinase; CKD, chronic kidney disease; CR, creatinine; CT, computed tomography; ECG, electrocardiogram; FE_{Na} , fractional excretion of sodium; GBM, glomerular basement membrane; GI, gastrointestinal; HUS, hemolytic-uremic syndrome; LDH, lactate dehydrogenase; LVH, left ventricular hypertrophy; MR, magnetic resonance; NSAIDs, nonsteroidal anti-inflammatory drugs; RBC, red blood cell; SG, specific gravity; SLE, systemic lupus erythematosus; U/A, urinalysis; U_{Na} , urine sodium concentration; WBC, white blood cell.

In prerenal ARF, the sediment is characteristically acellular and contains transparent hyaline casts (“bland,” “benign,” “inactive” urine sediment). Hyaline casts are formed in concentrated urine from normal constituents of urine, principally Tamm–Horsfall protein, which is secreted by epithelial cells of the loop of Henle. Patients with postrenal ARF may also present with an inactive sediment, although hematuria and pyuria are common in patients with intraluminal obstruction or prostatic disease. Pigmented “muddy brown” granular casts and casts containing tubule epithelial cells are characteristic of ATN and suggest an ischemic or nephrotoxic etiology. These casts are usually found in association with mild “tubular” proteinuria (<1 g/d), reflecting impaired reabsorption and processing of filtered proteins by injured proximal tubules. Casts may be absent in 20–30% of patients with ATN and are not required for diagnosis. In general, red blood cell casts indicate glomerular injury or, less often, acute tubulointerstitial nephritis. Whereas white blood cell casts and nonpigmented granular casts suggest interstitial nephritis, broad granular casts are characteristic of chronic kidney disease and probably reflect interstitial fibrosis and dilatation of tubules. Eosinophiluria (>5% of urine leukocytes) is a common finding (~90%) in patients with antibiotic-induced allergic interstitial nephritis and can be detected with Hansel’s stain; however, lymphocytes may predominate in allergic interstitial nephritis induced by NSAIDs and some other drugs (i.e., ampicillin, rifampicin, and interferon α). Occasional uric acid crystals (pleomorphic in shape) are common in the concentrated urine of patients with prerenal ARF but suggest acute urate nephropathy if seen in abundance. Oxalate (envelope-shaped) and hippurate (needle-shaped) crystals raise the possibility of ethylene glycol ingestion and toxicity.

Proteinuria of >1 g/d suggests injury to the glomerular ultrafiltration barrier (“glomerular proteinuria”) or excretion of myeloma light chains. The latter may not be detected by conventional dipstick analysis, and other tests may be needed (e.g., sulfosalicylic acid precipitation, immunoelectrophoresis). Hemoglobinuria or myoglobinuria should be suspected if urine is strongly positive for heme by dipstick but contains few red blood cells and if the supernatant of centrifuged urine is positive for free heme. Bilirubinuria may provide a clue to the presence of HRS.

RENAL FAILURE INDICES

Analysis of urine and blood biochemistry may be useful for distinguishing prerenal ARF from ischemic or nephrotoxic intrinsic renal ARF. The fractional excretion of sodium (FE_{Na}) is most useful in this regard. The FE_{Na} relates sodium clearance to creatinine clearance. Sodium is reabsorbed avidly from glomerular filtrate in patients with prerenal ARF in an attempt to restore intravascular

volume. The FE_{Na} tends to be high in patients with ischemic ATN but is often low in patients with sepsis-induced, pigment-induced, and some forms of nephrotoxic ATN (e.g., contrast associated). In contrast, creatinine is not reabsorbed in either setting. Consequently, patients with prerenal ARF typically have a FE_{Na} of <1.0% (frequently <0.1%). In patients with metabolic alkalosis, in which there may be obligate losses of sodium in the urine to maintain electroneutrality, the fractional excretion of chloride (FE_{Cl}) may be more sensitive than the FE_{Na} in detecting prerenal azotemia. The *urine sodium concentration* is a less sensitive index for distinguishing prerenal ARF from ischemic and nephrotoxic ARF because values overlap between groups. Similarly, indices of urinary concentrating ability, such as urine specific gravity, urine osmolality, urine-to-plasma urea ratio, and blood urea-to-creatinine ratio, are of limited value in the differential diagnosis.

Many caveats apply when interpreting biochemical renal failure indices. The FE_{Na} may be >1.0% in prerenal ARF if patients are receiving diuretics or with preexisting chronic kidney disease, certain salt-wasting syndromes, or adrenal insufficiency.

LABORATORY FINDINGS

Serial serum creatinine measurements can provide useful insights to the cause of ARF. Prerenal ARF is typified by fluctuating serum creatinine levels that parallel changes in hemodynamic status. Creatinine increases rapidly (within 24–48 h) in patients with ARF after renal ischemia, atheroembolization, and radiocontrast exposure. Peak serum creatinine concentrations are observed after 3–5 days with contrast nephropathy and return to baseline after 5–7 days. In contrast, serum creatinine concentrations typically peak later (7–10 days) in patients with ATN and atheroembolic disease. The initial increase in serum creatinine is characteristically delayed until the second week of therapy with many tubular epithelial cell toxins (e.g., aminoglycosides, cisplatin) and is thought to reflect the need for accumulation of these agents within tubular epithelial cells to cause injury.

Hyperkalemia, hyperphosphatemia, hypocalcemia, and elevations in serum uric acid and creatine kinase (MM isoenzyme) levels at presentation suggest a diagnosis of rhabdomyolysis. Hyperuricemia [$>890 \mu\text{mol/L}$ or ($>15 \text{ mg/dL}$)] in association with hyperkalemia, hyperphosphatemia, and increased circulating levels of intracellular enzymes such as lactate dehydrogenase may indicate acute urate nephropathy and tumor lysis syndrome after cancer chemotherapy. A wide anion and osmolal gap [the latter calculated as the difference between the observed (measured) serum osmolality minus the expected osmolality calculated from serum sodium, glucose, and urea concentrations] indicate the presence of an unusual anion or osmole in the circulation (e.g., ingestion of ethylene glycol

or methanol). Severe anemia in the absence of hemorrhage raises the possibility of hemolysis, multiple myeloma, or thrombotic microangiopathy. Systemic eosinophilia suggests allergic interstitial nephritis but is also a feature of atheroembolic disease and polyarteritis nodosa.

RADIOLOGIC FINDINGS

Imaging of the urinary tract by ultrasonography is useful to exclude postrenal ARF. CT and MRI are alternative imaging modalities. Whereas pelvicalyceal dilatation is usual with urinary tract obstruction (98% sensitivity), dilatation may be absent immediately after obstruction or in patients with ureteric encasement (e.g., retroperitoneal fibrosis, neoplasia). Retrograde and antegrade pyelography are more definitive investigations in complex cases and provide precise localization of the site of obstruction. A plain film of the abdomen or unenhanced helical CT scan is a valuable initial screening technique in patients with suspected nephrolithiasis. Magnetic resonance angiography (MRA) is often used to assess the patency of the renal arteries and veins in patients with suspected vascular obstruction. Alternative methods include Doppler ultrasound (which is much more operator dependent than MRA) and CT-based angiography. Catheter-based angiography may be required for definitive diagnosis and treatment.

RENAL BIOPSY

Biopsy is reserved for patients in whom prerenal and postrenal ARF have been excluded and the cause of intrinsic ARF is unclear. Renal biopsy is particularly useful when clinical assessment and laboratory investigations suggest diagnoses other than ischemic or nephrotoxic injury that may respond to disease-specific therapy. Examples include glomerulonephritis, vasculitis, and allergic interstitial nephritis.

COMPLICATIONS

ARF impairs renal excretion of sodium, potassium, and water and perturbs divalent cation homeostasis and urinary acidification mechanisms. As a result, ARF is frequently complicated by intravascular volume overload, hyponatremia, hyperkalemia, hyperphosphatemia, hypocalcemia, hypermagnesemia, and metabolic acidosis. In addition, patients are unable to excrete nitrogenous waste products and are prone to developing the uremic syndrome. The speed of development and the severity of these complications reflect the degree of renal impairment and the catabolic state of the patient.

Expansion of extracellular fluid volume is an inevitable consequence of diminished salt and water excretion in oliguric or anuric individuals. Whereas milder forms are

characterized by weight gain, bibasilar lung rales, increased jugular venous pressure, and dependent edema, continued volume expansion may precipitate life-threatening pulmonary edema. Excessive administration of free water, either through ingestion and nasogastric administration or as hypotonic saline or isotonic dextrose solutions, can induce *hypo-osmolality* and *hyponatremia*, which, if severe, lead to neurologic abnormalities, including seizures.

Hyperkalemia is a frequent complication of ARF. Coexistent metabolic acidosis may exacerbate hyperkalemia by promoting potassium efflux from cells. Hyperkalemia may be particularly severe, even at the time of diagnosis, in patients with rhabdomyolysis, hemolysis, and tumor lysis syndrome. Patients with mild hyperkalemia (<6.0 mmol/L) are usually asymptomatic. Higher levels may trigger electrocardiographic abnormalities or arrhythmias.

ARF is typically complicated by *metabolic acidosis*, often with an increased anion gap (Chap. 40). Acidosis can be particularly severe when endogenous production of hydrogen ions is increased by other mechanisms (e.g., diabetic or fasting ketoacidosis; lactic acidosis complicating generalized tissue hypoperfusion, liver disease, or sepsis; metabolism of ethylene glycol or methanol).

Hyperphosphatemia is an almost invariable complication of ARF. Severe hyperphosphatemia may develop in highly catabolic patients or after rhabdomyolysis, hemolysis, or tissue ischemia. Metastatic deposition of calcium phosphate can lead to *hypocalcemia*, particularly with elevation of serum calcium (mg/dL) and phosphate (mg/dL) concentrations. Other factors that contribute to hypocalcemia include tissue resistance to the actions of parathyroid hormone and reduced levels of 1,25-dihydroxyvitamin D. Hypocalcemia is often asymptomatic but can cause perioral paresthesia, muscle cramps, seizures, altered mental status, prolongation of the QT interval, and other nonspecific T-wave changes on electrocardiography.

Anemia develops rapidly in patients with ARF and is usually multifactorial in origin. Contributing factors include impaired erythropoiesis, hemolysis, bleeding, hemodilution, and reduced red blood cell survival time. Prolongation of the *bleeding time* is also common. Common contributors to the bleeding diathesis include mild thrombocytopenia, platelet dysfunction, or clotting factor abnormalities (e.g., factor VIII dysfunction). *Infection* is a common and serious complication of ARF. It is unclear whether patients with ARF have a clinically significant defect in host immune responses or whether the high incidence of infection reflects repeated breaches of mucocutaneous barriers (e.g., IV cannulae, mechanical ventilation, bladder catheterization). *Cardiopulmonary complications* of ARF include arrhythmias, pericarditis and pericardial effusion, and pulmonary edema.

Protracted periods of severe ARF are invariably associated with the development of the *uremic syndrome*.

A *vigorous diuresis* can occur during the recovery phase of ARF (see earlier), which may be inappropriate on occasion and lead to intravascular volume depletion. *Hypernatremia* can also complicate recovery if water losses via hypotonic urine are not replaced or if losses are inappropriately replaced by relatively hypertonic saline solutions. *Hypokalemia*, *hypomagnesemia*, *hypophosphatemia*, and *hypocalcemia* are less common metabolic complications during this period but may develop in response to injury associated with selected drugs (e.g., use of ifosfamide may lead to Fanconi syndrome or type II renal tubular acidosis associated with hypokalemia, acidosis, hypophosphatemia, and glycosuria).

Rx Treatment: **ACUTE RENAL FAILURE**

PREVENTION Because there are no specific therapies for ischemic or nephrotoxic ARF, prevention is of paramount importance. Many cases of ischemic ARF can be avoided by close attention to cardiovascular function and intravascular volume in high-risk patients, such as elderly individuals and patients with preexisting chronic kidney disease. Indeed, aggressive restoration of intravascular volume has been shown to dramatically reduce the incidence of ischemic ARF after major surgery and trauma, burns, or cholera. The incidence of nephrotoxic ARF can be reduced by tailoring the administration (dose and frequency) of nephrotoxic drugs to the patient's body size and GFR. In this regard, it should be noted that serum creatinine is a relatively insensitive index of GFR and may overestimate GFR considerably in small and elderly patients. For purposes of drug dosing, it is advisable to estimate the GFR using the Cockcroft-Gault formula (which factors in age, gender, and weight) or the simplified Modification of Diet in Renal Disease (MDRD) equation (which factors in age, gender, weight, and race). Of note, these equations cannot be used to estimate GFR when creatinine is not at steady state (e.g., during evolving ARF). Adjusting the drug dosage according to circulating drug levels also appears to limit renal injury in patients receiving aminoglycoside antibiotics, cyclosporine, or tacrolimus. Diuretics, NSAIDs, ACE inhibitors, ARBs, and vasodilators should be used with caution in patients with suspected true or "effective" hypovolemia or renovascular disease because these drugs may precipitate prerenal ARF or convert the latter to ischemic ARF. Allopurinol and forced alkaline diuresis are useful prophylactic measures in patients at high risk for acute urate nephropathy (e.g., cancer chemotherapy in hematologic malignancies) to limit uric acid generation and prevent precipitation of urate crystals in renal tubules. Rasburicase, a recombinant urate-oxidase enzyme, catalyzes enzymatic oxidation of uric acid into a soluble metabolite, allantoin. Forced alkaline diuresis may also

prevent or attenuate ARF in patients receiving high-dose methotrexate and in those with rhabdomyolysis. *N*-acetylcysteine limits acetaminophen-induced renal injury if given within 24 h of ingestion.

A number of preventive measures have been proposed for contrast nephropathy. It is clear that hydration is an effective preventive measure. Other proposed measures include loop diuretics and mannitol, dopamine, fenoldopam, *N*-acetylcysteine, theophylline, and sodium bicarbonate. Despite favorable experimental data, there is insufficient evidence to support the use of loop diuretics or mannitol to prevent radiocontrast nephropathy or any other cause of ARF. Likewise, despite its widespread use, dopamine has proven ineffective as a prophylactic agent. Fenoldopam, a dopamine α -1-specific agonist approved for use as a parenteral antihypertensive agent, has been tested in several clinical trials and does not appear to reduce the incidence of contrast nephropathy. Moreover, fenoldopam is associated with significant side effects, including systemic hypotension, and its use as an agent to prevent radiocontrast nephropathy should be discouraged. In contrast, several (relatively small) randomized clinical trials (RCTs) have suggested a clinical benefit to the use of *N*-acetylcysteine, although meta-analyses have been inconclusive. However, aside from the potential hazards associated with a delay in radiographic imaging, *N*-acetylcysteine appears to be safe, and its use in patients at high risk for radiocontrast nephropathy is reasonable based on its low side effect profile. Larger RCTs will be required to show definitive benefit.

Theophylline and aminophylline (adenosine antagonists) offer the potential advantage of use immediately preceding radiocontrast administration, although the benefit, if present, appears marginal in most studies. Last, volume expansion with bicarbonate-containing IV fluids has been suggested to be superior to sodium chloride (saline) administration and showed a significant benefit in a single-center RCT. Unlike *N*-acetylcysteine, the use of sodium bicarbonate does not obligate a delay in imaging (the published protocol began IV fluids 1 h before the imaging study was begun). Whether a combination of strategies (e.g., *N*-acetylcysteine plus sodium bicarbonate) offers additive benefit and that patients require treatment remain unclear and warrant further study.

SPECIFIC THERAPIES By definition, prerenal ARF is rapidly reversible upon correction of the primary hemodynamic abnormality, and postrenal ARF resolves upon relief of obstruction. To date, there are no specific therapies for patients with established AKI. Management of these disorders should focus on elimination of the causative hemodynamic abnormality or toxin, avoidance of additional insults, and prevention and treatment of complications. Specific treatment of other causes of intrinsic renal ARF depends on the underlying pathology.

Prerenal Acute Renal Failure The composition of replacement fluids for treatment of prerenal ARF caused by hypovolemia should be tailored according to the composition of the lost fluid. Whereas severe hypovolemia caused by hemorrhage should be corrected with packed red blood cells, isotonic saline is usually appropriate replacement for mild to moderate hemorrhage or plasma loss (e.g., burns, pancreatitis). Urinary and gastrointestinal fluids can vary greatly in composition but are usually hypotonic. Hypotonic solutions (e.g., 0.45% saline) are usually recommended as initial replacement in patients with prerenal ARF caused by increased urinary or gastrointestinal fluid losses, although isotonic saline may be more appropriate in severe cases. Subsequent therapy should be based on measurements of the volume and ionic content of excreted or drained fluids. Serum potassium and acid–base status should be monitored carefully and potassium and bicarbonate supplemented as appropriate. Cardiac failure may require aggressive management with inotropic agents, preload- and afterload-reducing agents, antiarrhythmic drugs, and mechanical aids such as intraaortic balloon pumps. Invasive hemodynamic monitoring may be required in selected cases to guide therapy for complications in patients in whom clinical assessment of cardiovascular function and intravascular volume is difficult.

Fluid management may be particularly challenging in patients with cirrhosis complicated by ascites. In this setting, it is important to distinguish between full-blown HRS, which carries a grave prognosis, and reversible ARF caused by true or “effective” hypovolemia induced by overzealous use of diuretics or sepsis (e.g., spontaneous bacterial peritonitis). The contribution of hypovolemia to ARF can be definitively assessed only by administration of a fluid challenge. Fluids should be administered slowly and titrated to jugular venous pressure and, if necessary, central venous and pulmonary capillary wedge pressure. Whereas patients with a reversible prerenal component typically have an increase in urine output and decrease in serum creatinine with fluid challenge, patients with HRS do not. Patients with HRS may have increased ascites formation and pulmonary compromise if they are not monitored closely during fluid challenge. Large volumes of ascitic fluid can usually be drained by paracentesis without deterioration in renal function if IV albumin is administered simultaneously. Indeed, “large-volume paracentesis” may afford an increase in GFR, likely by lowering intraabdominal pressure and improving flow in renal veins. Alternatively, for patients with refractory ascites, transjugular intrahepatic portosystemic shunting is an alternative. Older peritoneal-venous shunts (LaVeen or Denver shunts) have largely fallen out of favor. Transjugular intrahepatic portosystemic shunts may improve renal function through increased central blood volume

and suppression of aldosterone and norepinephrine secretion.

Intrinsic Acute Renal Failure Many different approaches to attenuate injury or hasten recovery have been tested in ischemic and nephrotoxic AKI. These include atrial natriuretic peptide, low-dose dopamine, endothelin antagonists, loop-blocking diuretics, calcium channel blockers, α -adrenoreceptor blockers, prostaglandin analogues, antioxidants, antibodies against leukocyte adhesion molecules, and insulin-like growth factor type I. Although many of these are beneficial in experimental models of ischemic or nephrotoxic ATN, they have either failed to confer consistent benefit or proved ineffective in humans.

Patients with ARF caused by other intrinsic renal diseases such as acute glomerulonephritis or vasculitis may respond to immunosuppressive agents (glucocorticoids, alkylating agents, or plasmapheresis, depending on the primary pathology). Glucocorticoids may also hasten remission in allergic interstitial nephritis, although data are limited to small-case series. Aggressive control of systemic arterial pressure is of paramount importance in limiting renal injury in patients with malignant hypertensive nephrosclerosis. Patients with hypertension and ARF caused by scleroderma may be exquisitely sensitive to treatment with ACE inhibitors.

Postrenal Acute Renal Failure Management of postrenal ARF requires close collaboration between a nephrologist, urologist, and radiologist. Obstruction of the urethra or bladder neck is usually managed initially by transurethral or suprapubic placement of a bladder catheter, which provides temporary relief while the obstructing lesion is identified and treated definitively. Similarly, ureteric obstruction may be treated initially by percutaneous catheterization of the dilated renal pelvis or ureter. Indeed, obstructing lesions can often be removed percutaneously (e.g., calculus, sloughed papilla) or bypassed by insertion of a ureteric stent (e.g., carcinoma). Most patients experience an appropriate diuresis for several days after relief of obstruction. Approximately 5% of patients develop a transient salt-wasting syndrome that may require administration of IV saline to maintain blood pressure.

SUPPORTIVE MEASURES (Table 37-3) After correction of hypovolemia, salt and water intake are tailored to match losses. Hypervolemia can usually be managed by restriction of salt and water intake and diuretics. Indeed, there is, as yet, no proven rationale for administration of diuretics in ARF except to treat this complication. Even though suppressor doses of dopamine may transiently promote salt and water excretion by increasing renal blood flow and GFR and by inhibiting tubule sodium reabsorption, suppressor (“low-dose,” “renal-dose”) dopamine has proven ineffective in clinical trials, may trigger

arrhythmias, and should not be used as a renoprotective agent in this setting. Ultrafiltration or dialysis is used to treat severe hypervolemia when conservative measures fail. Hyponatremia and hypo-osmolality can usually be controlled by restriction of free water intake. Conversely, hypernatremia is treated by administration of water or IV hypotonic saline or isotonic dextrose-containing solutions. The management of hyperkalemia is described in Chap. 39.

Metabolic acidosis is not usually treated unless serum bicarbonate concentration decreases below 15 mmol/L or arterial pH decreases below 7.2. More severe acidosis

is corrected by oral or IV sodium bicarbonate. Initial rates of replacement are guided by estimates of bicarbonate deficit and adjusted thereafter according to serum levels (Chap. 40). Patients should be monitored for complications of sodium bicarbonate administration such as hypervolemia, metabolic alkalosis, hypocalcemia, and hypokalemia. From a practical point of view, most patients who require supplemental sodium bicarbonate administration will need emergency dialysis within days. Hyperphosphatemia is usually controlled by restriction of dietary phosphate and by oral phosphate binders (calcium carbonate, calcium acetate, sevelamer, and

TABLE 37-3

MANAGEMENT OF ISCHEMIC AND NEPHROTOXIC ACUTE RENAL FAILURE^a

MANAGEMENT ISSUE	THERAPY
Reversal of Renal Insult	
Ischemic ATN	Restore systemic hemodynamics and renal perfusion through volume resuscitation and use of vasopressors
Nephrotoxic ATN	Eliminate nephrotoxic agents Consider toxin-specific measures forced alkaline diuresis for rhabdomyolysis, allopurinol or rasburicase for tumor lysis syndrome
Prevention and Treatment of Complications	
Intravascular volume overload	Salt and water restriction Diuretics Ultrafiltration
Hyponatremia	Restriction of enteral free water intake Avoidance of hypotonic IV solutions, including dextrose-containing solutions
Hyperkalemia	Restriction of dietary K ⁺ intake Elimination of K ⁺ supplements and K ⁺ -sparing diuretics Loop diuretics to promote K ⁺ excretion Potassium binding ion-exchange resins (e.g., sodium polystyrene sulfonate or Kayexelate) Insulin (10 units regular) and glucose (50 mL of 50% dextrose) to promote intracellular mobilization Inhaled β-agonist therapy to promote intracellular mobilization Calcium gluconate or calcium chloride (1 g) to stabilize the myocardium Dialysis
Metabolic acidosis	Sodium bicarbonate (maintain serum bicarbonate >15 mmol/L or arterial pH >7.2) Administration of other bases (e.g., THAM) Dialysis
Hyperphosphatemia	Restriction of dietary phosphate intake Phosphate binding agents (calcium carbonate, calcium acetate, sevelamer hydrochloride, aluminum hydroxide)
Hypocalcemia	Calcium carbonate or gluconate (if symptomatic)
Hypermagnesemia	Discontinue Mg ⁺⁺ -containing antacids
Hyperuricemia	Treatment is usually not necessary if <890 μmol/L or <15 mg/dL Allopurinol, forced alkaline diuresis, rasburicase
Nutrition	Protein and calorie intake to avoid net negative nitrogen balance
Dialysis	To prevent complications of acute renal failure
Choice of agents	Avoid other nephrotoxins: ACE inhibitors, ARBs, aminoglycosides, NSAIDs, radiocontrast unless absolutely necessary and no alternative
Drug dosing	Adjust doses and frequency of administration for degree of renal impairment

^aNote that these are general recommendations and need to be tailored to the individual patient.

Note: ATN, acute tubular necrosis; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; NSAID, nonsteroidal anti-inflammatory drug; THAM, tris(hydroxymethyl)aminomethane.

aluminum hydroxide) to reduce gastrointestinal absorption of phosphate. Hypocalcemia does not usually require treatment unless it is severe, as may occur with rhabdomyolysis or pancreatitis or after administration of bicarbonate. Hyperuricemia is typically mild [$<890 \mu\text{mol/L}$ ($<15 \text{ mg/dL}$)] and does not require intervention.

The objective of *nutritional management* during the maintenance phase of ARF is to provide sufficient calories and protein to minimize catabolism. Nutritional requirements vary based on the underlying disease process; for example, those with sepsis-associated AKI are likely to be hypercatabolic. The presence of oliguria complicates nutritional management, and if the patient is not on dialysis, minimizing production of nitrogenous waste is a consideration. Often, the institution of dialysis facilitates the provision of adequate nutritional support. There is no clear benefit of parenteral nutrition compared with enteral nutrition; indeed, those supported with parenteral nutrition are at increased risk of complications, including infection.

Anemia may necessitate blood transfusion if severe. Recombinant human erythropoietin is rarely used in ARF because bone marrow resistance to erythropoietin is common, and more immediate treatment of anemia (if any) is required. Patients with uremic bleeding may respond to administration of desmopressin or estrogens. Often dialysis is instituted to control bleeding that appears to be related to uremia. Gastrointestinal prophylaxis with histamine receptor (H₂) antagonists or proton pump inhibitors should be prescribed, especially in the setting of critical illness. Meticulous care of IV and bladder catheters and other invasive devices is mandatory to avoid infections.

Indications and Modalities of Dialysis (See also Chap. 38) During ARF, dialysis is often used to support renal function until renal repair or recovery occurs. Absolute indications for dialysis include symptoms or signs of the uremic syndrome and management of refractory hypervolemia, hyperkalemia, or acidosis. Many nephrologists also initiate dialysis empirically for blood urea levels of $>100 \text{ mg/dL}$; however, this approach has yet to be validated in controlled clinical trials. Although direct clinical comparisons are limited, hemodialysis appears to be somewhat more effective than peritoneal dialysis for the management of ARF. Peritoneal dialysis may be useful when hemodialysis is unavailable or if it is impossible to obtain vascular access. However, peritoneal dialysis is associated with increased protein losses and is contraindicated in patients who have undergone recent abdominal surgery and those with ongoing infection. Peritoneal dialysis access requires insertion of a cuffed catheter into the peritoneal cavity.

Vascular access for hemodialysis requires insertion of a temporary double-lumen hemodialysis catheter into

the internal jugular or femoral vein. Insertion into the subclavian vein is generally avoided owing to the risk of subclavian stenosis. Hemodialysis may be provided in the form of intermittent hemodialysis (typically performed for 3–4 h/d three or four times per week), slow low-efficiency dialysis (performed for 6–12 h/d three to six times per week), or continuous renal replacement therapy (CRRT). CCRTs are particular valuable techniques in patients in whom intermittent therapy fails to control hypervolemia, uremia, or acidosis and in those who do not tolerate intermittent hemodialysis because of hemodynamic instability. In patients in whom hemodynamic instability is a primary consideration, slow low-efficiency hemodialysis (SLED), a relatively new hybrid mode of dialysis, is an excellent alternative to CRRT.

Continuous arteriovenous modalities—continuous arteriovenous hemofiltration (CAVH), hemodialysis (CAVHD), and hemodiafiltration (CAVHDF)—require both arterial and venous access. The patient's own blood pressure generates an ultrafiltrate of plasma across a porous biocompatible dialysis membrane. With the advent of peristaltic pumps, the arteriovenous modalities have fallen out of favor, partly because of the complications associated with cannulation of a large artery with a large-bore catheter. In continuous venovenous hemodialysis (CVVHD), a blood pump generates ultrafiltration pressure across the dialysis membrane. In continuous venovenous hemofiltration (CVVH), the hemodialysis (diffusive clearance) component is eliminated, and an ultrafiltrate of plasma is removed across the dialysis membrane and replaced by a physiologic crystalloid solution (convective clearance). In continuous venovenous hemodiafiltration (CVVHDF), these two methods of clearance are combined. The bulk of evidence to date suggests that intermittent and continuous dialytic therapies are equally effective for the treatment of patients with ARF. The choice of technique is currently tailored to the specific needs of the patient, the resources of the institution, and the expertise of the physician. Potential disadvantages of continuous techniques include the need for prolonged immobilization, systemic anticoagulation, and prolonged exposure of blood to synthetic (albeit biocompatible) dialysis membranes.

The optimal dose of dialysis for ARF remains unclear at present. Recent evidence (from a single-center, non-randomized trial) suggests that more intensive hemodialysis (e.g., daily rather than alternate-day intermittent dialysis) may be clinically superior and confers improved survival in ARF after dialysis is required. This conclusion may not be as intuitive as it first appears because dialysis itself has been postulated to prolong ARF by inducing hypotension and other adverse effects related to the blood–dialyzer contact (e.g., complement

activation and inflammation). Similarly, data suggest that increased doses of continuous renal replacement therapy may be of benefit for patients with ARF, although these results need to be confirmed in a larger, multicenter study.

OUTCOME AND LONG-TERM PROGNOSIS

The in-hospital mortality rate among patients with ARF ranges from 20–50% or more, depending on underlying conditions, and has declined only marginally over the past 15 years. Most patients who survive an episode of ARF recover sufficient renal function to remain dialysis independent, although a fraction (~10–20%) go on to require maintenance dialysis.



Common causes of ARF vary depending on the availability of health care in a given country. In general, the most common cause of

community-acquired ARF is prerenal azotemia. However, in countries with less well-developed health care systems, infective causes for ARF predominate. In developed countries, postoperative and ischemic or nephrotoxic causes of ARF are more common.

ACKNOWLEDGMENT

We are grateful to Dr. Hugh Brady and Dr. Barry Brenner, authors of this chapter in the 16th edition of Harrison's Principles of Internal Medicine, for contributions to this edition.

FURTHER READINGS

- BRADY HR et al: Acute renal failure, in BM Brenner (ed), *Brenner and Rector's The Kidney*, 7th ed. Philadelphia, Saunders, 2004
- LAMEIRE N: The pathophysiology of acute renal failure. *Crit Care Clin* 21:197, 2005
- et al: Acute renal failure. *Lancet* 365:417, 2005
- PANNU N et al: Prophylaxis strategies for contrast-induced nephropathy. *JAMA* 295:2765, 2006
- STAR RA: Treatment of acute renal failure. *Kidney Int* 54:1817, 1998
- WEISBORD SD, PALEVSKY P: Radiocontrast-induced acute renal failure. *J Intens Care Med* 20:63, 2005



CHAPTER 38

DIALYSIS IN THE TREATMENT OF RENAL FAILURE

Kathleen D. Liu ■ Glenn M. Chertow

■ Treatment Options for Patients with End-stage Renal Disease	.387
■ Hemodialysis	.387
The Dialyzer	.387
Dialysate	.387
Blood Delivery System	.388
Goals of Dialysis	.389
Complications during Hemodialysis	.389
■ Peritoneal Dialysis	.390
Forms of Peritoneal Dialysis	.390
Access to the Peritoneal Cavity	.391
Complications during Peritoneal Dialysis	.391
■ Global Perspective	.392
■ Further Readings	.392

Dialysis may be required for the treatment of patients with either acute or chronic kidney disease. The use of continuous renal replacement therapies (CRRTs) and slow, low-efficiency dialysis (SLED) is specific to the management of acute renal failure (ARF) and is discussed in Chap. 37. These modalities are performed continuously (CRRT) or over 6–12 h per session (SLED) in contrast to the 3–4 h of an intermittent hemodialysis session. The advantages and disadvantages of CRRT and SLED are discussed in Chap. 37.

Peritoneal dialysis is rarely used in developed countries for the treatment of patients with ARF because of the increased risk of infection and (as will be discussed in more detail later) less efficient clearance per unit of time. The focus of the majority of this chapter is on the use of dialysis for end-stage renal disease (ESRD).

With the widespread availability of dialysis, the lives of hundreds of thousands of patients with ESRD have been prolonged. In the United States alone, there are now approximately 450,000 patients with ESRD, the vast majority of whom require dialysis. The incidence rate for ESRD is 330 cases per million population per year.

The incidence of ESRD is disproportionately higher in African Americans (~1000 per million population per year) compared with white Americans (259 per million population per year). In the United States, the leading cause of ESRD is diabetes mellitus, currently accounting for nearly 45% of newly diagnosed cases of ESRD. Twenty-seven percent of patients have ESRD that has been attributed to hypertension, although it is unclear whether hypertension is the cause or a consequence of vascular disease or other unknown causes of kidney failure in these cases. Other important causes of ESRD include glomerulonephritis, polycystic kidney disease, and obstructive uropathy.



Globally, mortality rates for patients with ESRD are the lowest in Europe and Japan but are very high in the developing world because of the limited availability of dialysis. In the United States, the mortality rate of patients on dialysis is approximately 18–20% per year, with a 5-year survival rate of approximately 30–35%. Deaths are mainly caused by cardiovascular diseases and infections (~50 and 15% of deaths, respectively). Older age, male gender, nonblack race, diabetes mellitus,

malnutrition, and underlying heart disease are important predictors of death.

TREATMENT OPTIONS FOR PATIENTS WITH END-STAGE RENAL DISEASE

The commonly accepted criteria for initiating patients on maintenance dialysis include the presence of uremic symptoms, the presence of hyperkalemia unresponsive to conservative measures, persistent extracellular volume expansion despite diuretic therapy, acidosis refractory to medical therapy, a bleeding diathesis, and a creatinine clearance or estimated glomerular filtration rate (GFR) <10 mL/min per 1.73 m². Timely referral to a nephrologist for advanced planning and creation of a dialysis access; education about ESRD treatment options; and management of the complications of advanced chronic kidney disease, including hypertension, anemia, acidosis, and secondary hyperparathyroidism, is advisable.

In ESRD, treatment options include hemodialysis (in center or at home); peritoneal dialysis, as either continuous ambulatory peritoneal dialysis (CAPD) or continuous cyclic peritoneal dialysis (CCPD); or transplantation. Although there are geographic variations, hemodialysis remains the most common therapeutic modality for ESRD ($>90\%$ of patients) in the United States. In contrast to hemodialysis, peritoneal dialysis is continuous, but much less efficient, in terms of solute clearance. Although no large-scale clinical trials have been completed comparing outcomes among patients randomized to either hemodialysis or peritoneal dialysis, outcomes associated with both therapies are similar in most reports, and the decision of which modality to select is often based on personal preferences and quality-of-life considerations.

HEMODIALYSIS

Hemodialysis relies on the principles of solute diffusion across a semipermeable membrane. Movement of metabolic waste products takes place down a concentration gradient from the circulation into the dialysate. The rate of diffusive transport increases in response to several factors, including the magnitude of the concentration gradient, the membrane surface area, and the mass transfer coefficient of the membrane. The latter is a function of the porosity and thickness of the membrane, the size of the solute molecule, and the conditions of flow on the two sides of the membrane. According to the laws of diffusion, the larger the molecule, the slower its rate of transfer across the membrane. A small molecule, such as urea (60 Da), undergoes substantial clearance; a larger molecule, such as creatinine (113 Da), is cleared less efficiently. In addition to diffusive clearance, movement of waste products from the circulation into the dialysate may occur as a result of ultrafiltration. Convective clearance occurs because of solvent drag, with solutes being

swept along with water across the semipermeable dialysis membrane.

THE DIALYZER

There are three essential components to hemodialysis: the dialyzer, the composition and delivery of the dialysate, and the blood delivery system (Fig. 38-1). The dialyzer consists of a plastic device with the facility to perfuse blood and dialysate compartments at very high flow rates. The surface area of modern dialysis membranes in adult patients is usually in the range of 1.5 – 2.0 m². The hollow-fiber dialyzer is the most common in use in the United States. These dialyzers are composed of bundles of capillary tubes through which blood circulates while dialysate travels on the outside of the fiber bundle.

Recent advances have led to the development of many different types of membrane material. Broadly, there are four categories of dialysis membranes: cellulose, substituted cellulose, cellosynthetic, and synthetic. Over the past three decades, there has been a gradual switch from cellulose-derived to synthetic membranes because the latter are more “biocompatible.” *Biocompatibility* is generally defined as the ability of the membrane to activate the complement cascade. Cellulosic membranes are biocompatible because of the presence of free hydroxyl groups on the membrane surface. In contrast, with the substituted cellulose membranes (e.g., cellulose acetate) or the cellosynthetic membranes, the hydroxyl groups are chemically bound to either acetate or tertiary amino groups, resulting in limited complement activation. Synthetic membranes, such as polysulfone, polymethylmethacrylate, and polyacrylonitrile membranes, are even more biocompatible because of the absence of these hydroxyl groups. Polysulfone membranes are now used in $>60\%$ of the dialysis treatments in the United States.

Reprocessing and reuse of hemodialyzers are often used for patients on maintenance hemodialysis in the United States. However, as the manufacturing costs for disposable dialyzers have declined, increasingly more outpatient dialysis facilities are no longer reprocessing dialyzers. In most centers employing reuse, only the dialyzer unit is reprocessed and reused, but in the developing world, blood lines are also frequently reused. The reprocessing procedure can be either manual or automated. It consists of the sequential rinsing of the blood and dialysate compartments with water; a chemical cleansing step with reverse ultrafiltration from the dialysate to the blood compartment; the testing of the patency of the dialyzer; and, finally, disinfection of the dialyzer. Formaldehyde, peracetic acid–hydrogen peroxide, glutaraldehyde, and bleach have all been used as reprocessing agents.

DIALYSATE

The potassium concentration of dialysate may be varied from 0 to 4 mmol/L depending on the predialysis plasma

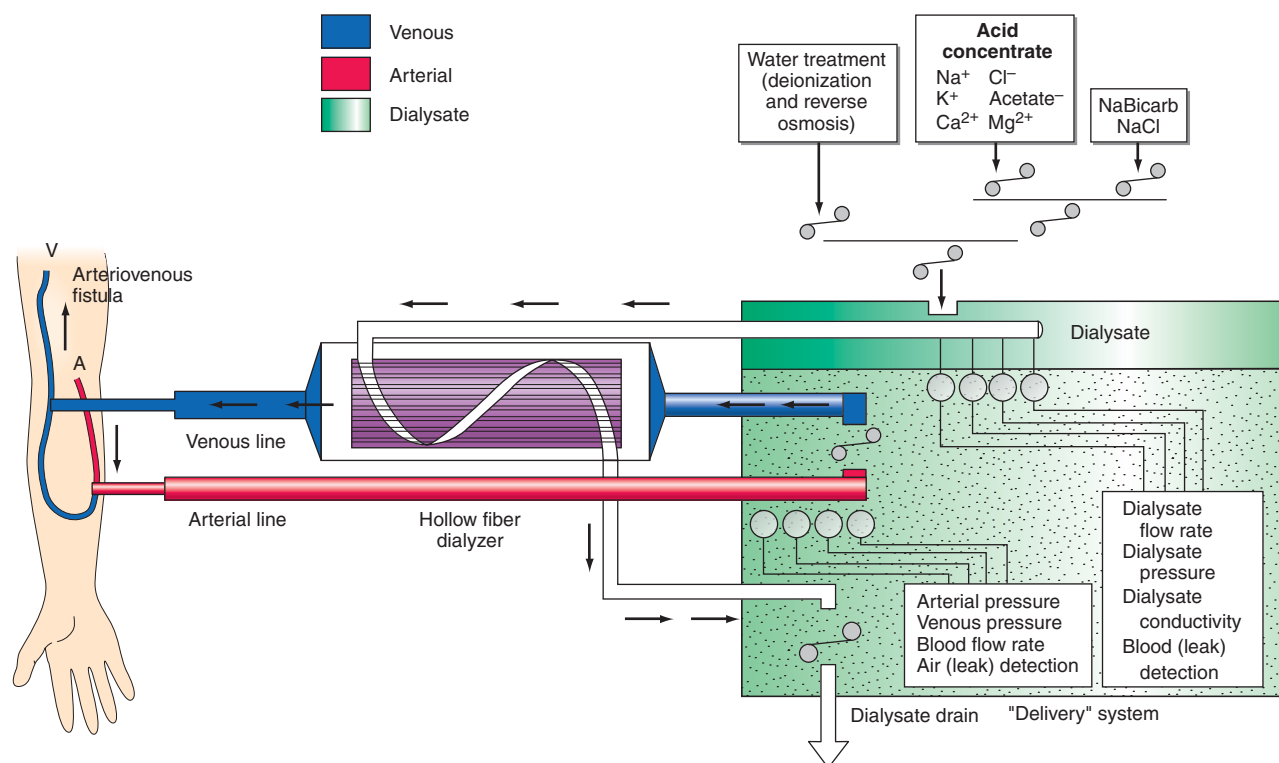


FIGURE 38-1
Schema for hemodialysis.

potassium concentration. The usual dialysate calcium concentration in U.S. hemodialysis centers is 1.25 mmol/L (2.5 meq/L), although modification may be required in selected settings (e.g., higher dialysate calcium concentrations may be used in patients with hypocalcemia associated with secondary hyperparathyroidism or after parathyroidectomy). The usual dialysate sodium concentration is 140 mmol/L. Lower dialysate sodium concentrations are associated with a higher frequency of hypotension, cramping, nausea, vomiting, fatigue, and dizziness. In patients who frequently develop hypotension during their dialysis run, “sodium modeling” to counterbalance urea-related osmolar gradients is often used. When sodium modeling, the dialysate sodium concentration is gradually lowered from the range of 145–155 meq/L to isotonic concentrations (140 meq/L) near the end of the dialysis treatment, typically declining either in steps or in a linear or exponential fashion. Because patients are exposed to approximately 120 L of water during each dialysis treatment, water used for the dialysate is subjected to filtration; softening; deionization; and, ultimately, reverse osmosis. During the reverse osmosis process, water is forced through a semipermeable membrane at very high pressure to remove micro-biologic contaminants and >90% of dissolved ions.

BLOOD DELIVERY SYSTEM

The blood delivery system is composed of the extracorporeal circuit in the dialysis machine and the dialysis

access. The dialysis machine consists of a blood pump, dialysis solution delivery system, and various safety monitors. The blood pump moves blood from the access site, through the dialyzer, and back to the patient. The blood flow rate may range from 250–500 mL/min, depending largely on the type and integrity of the vascular access. Negative hydrostatic pressure on the dialysate side can be manipulated to achieve desirable fluid removal or *ultrafiltration*. Dialysis membranes have different ultrafiltration coefficients (i.e., mL removed/min per mmHg) so that along with hydrostatic changes, fluid removal can be varied. The dialysis solution delivery system dilutes the concentrated dialysate with water and monitors the temperature, conductivity, and flow of dialysate.

Dialysis Access

The fistula, graft, or catheter through which blood is obtained for hemodialysis is often referred to as a *dialysis access*. A native fistula created by the anastomosis of an artery to a vein (e.g., the Brescia-Cimino fistula, in which the cephalic vein is anastomosed end to side to the radial artery) results in arterialization of the vein. This facilitates its subsequent use in the placement of large needles (typically 15 gauge) to access the circulation. Although fistulas have the highest long-term patency rate of all dialysis access options, fistulas are created in a minority of patients in the United States. Many patients undergo placement of an arteriovenous graft (i.e., the interposition of prosthetic material, usually polytetrafluoroethylene,

between an artery and a vein) or a tunneled dialysis catheter. In recent years, nephrologists, vascular surgeons, and health care policy makers in the United States have encouraged creation of arteriovenous fistulas in a larger fraction of patients (the “fistula first” initiative). Unfortunately, even when created, arteriovenous fistulas may not mature sufficiently to provide reliable access to the circulation, or they may thrombose early in their development. Novel surgical approaches (e.g., brachiobasilic fistula creation with transposition of the basilic vein fistula to the arm surface) have increased options for “native” vascular access.

Grafts and catheters tend to be used among persons with smaller-caliber veins, persons whose veins have been damaged by repeated venipuncture, or after prolonged hospitalization. The most important complication of arteriovenous grafts is thrombosis of the graft and graft failure principally because of intimal hyperplasia at the anastomosis between the graft and recipient vein. When grafts (or fistulas) fail, catheter-guided angioplasty can be used to dilate stenoses; monitoring of venous pressures on dialysis and of access flow, although not routinely performed, may assist in the early recognition of impending vascular access failure. In addition to an increased rate of access failure, grafts and (in particular) catheters are associated with much higher rates of infection than fistulas.

IV large-bore catheters are often used in patients with acute and chronic kidney disease. For persons on maintenance hemodialysis, tunneled catheters (either two separate catheters or a single catheter with two lumens) are often used when arteriovenous fistulas and grafts have failed or are not feasible because of anatomical considerations. These catheters are tunneled under the skin; the tunnel reduces bacterial translocation from the skin, resulting in a lower infection rate than with nontunneled temporary catheters. Most tunneled catheters are placed in the internal jugular veins; the external jugular, femoral, and subclavian veins may also be used. Nephrologists, interventional radiologists, and vascular surgeons generally prefer to avoid placement of catheters into the subclavian veins because although flow rates are usually excellent, subclavian stenosis is a frequent complication and, if present, will likely prohibit permanent vascular access (i.e., a fistula or graft) in the ipsilateral extremity. Infection rates may be higher with femoral catheters. For patients with multiple vascular access complications and no other options for permanent vascular access, tunneled catheters may be the last “lifeline” for hemodialysis. Translumbar or transhepatic approaches into the inferior vena cava may be required if the superior vena cava or other central veins draining the upper extremities are stenosed or thrombosed.

GOALS OF DIALYSIS

The hemodialysis procedure is targeted at removing both low- and high-molecular-weight solutes. The procedure

consists of pumping heparinized blood through the dialyzer at a flow rate of 300–500 mL/min while dialysate flows in an opposite *counter-current* direction at 500–800 mL/min. The efficiency of dialysis is determined by blood and dialysate flow through the dialyzer as well as dialyzer characteristics (i.e., its efficiency in removing solute). The *dose* of dialysis, which is currently defined as a derivation of the fractional urea clearance during a single dialysis treatment, is further governed by patient size, residual kidney function, dietary protein intake, the degree of anabolism or catabolism, and the presence of comorbid conditions.

Since the landmark studies of Sargent and Gotch relating the measurement of the dose of dialysis using urea concentrations with morbidity in the National Cooperative Dialysis Study, the *delivered* dose of dialysis has been measured and considered as a quality assurance and improvement tool. Although the fractional removal of urea nitrogen and derivations thereof are considered to be the standard methods by which “adequacy of dialysis” is measured, a large, multicenter, randomized clinical trial (the HEMO Study) failed to show a difference in mortality associated with a large difference in urea clearance. Still, multiple observational studies and widespread expert opinion have suggested that a higher dialysis dose is warranted; current targets include a urea reduction ratio (the fractional reduction in blood urea nitrogen per hemodialysis session) of >65–70% and a body water-indexed clearance \times time product (KT/V) above 1.30 or 1.05, depending on whether urea concentrations are “equilibrated.”

For the majority of patients with ESRD, between 9 and 12 h of dialysis are required each week, usually divided into three equal sessions. Several studies have suggested that longer hemodialysis session lengths may be beneficial, although these studies are confounded by a variety of patient characteristics, including body size and nutritional status. The hemodialysis “dose” should be individualized, and factors other than the urea nitrogen should be considered, including the adequacy of ultrafiltration or fluid removal. Several authors have highlighted improved intermediate outcomes associated with more frequent hemodialysis (i.e., >three times a week), although these studies are also confounded by multiple factors. A randomized clinical trial is currently underway to test whether more frequent dialysis results in differences in a variety of physiologic and functional markers.

COMPLICATIONS DURING HEMODIALYSIS

Hypotension is the most common acute complication of hemodialysis, particularly among patients with diabetes. Numerous factors appear to increase the risk of hypotension, including excessive ultrafiltration with inadequate compensatory vascular filling, impaired vasoactive or autonomic responses, osmolar shifts, overzealous use

of antihypertensive agents, and reduced cardiac reserve. Patients with arteriovenous fistulas and grafts may develop high-output cardiac failure because of shunting of blood through the dialysis access; on rare occasions, this may necessitate ligation of the fistula or graft. Because of the vasodilatory and cardiodepressive effects of acetate, its use as the buffer in dialysate was once a common cause of hypotension. However, since the introduction of bicarbonate-containing dialysate, dialysis-associated hypotension has become less common. The management of hypotension during dialysis consists of discontinuing ultrafiltration, administration of 100–250 mL of isotonic saline or 10 mL of 23% saturated hypertonic saline, and administration of salt-poor albumin. Hypotension during dialysis can frequently be prevented by careful evaluation of the dry weight and by ultrafiltration modeling, such that more fluid is removed at the beginning rather than the end of the dialysis procedure. Additional maneuvers include the performance of sequential ultrafiltration followed by dialysis; the use of midodrine, a selective α_1 -adrenergic pressor agent; cooling of the dialysate during dialysis treatment; and avoiding heavy meals during dialysis.

Muscle cramps during dialysis are also a common complication of the procedure. The cause of dialysis-associated cramps remains obscure. Changes in muscle perfusion because of excessively aggressive volume removal, particularly below the estimated dry weight, and the use of low-sodium-containing dialysate, have been proposed as precipitants of dialysis-associated cramps. Strategies that may be used to prevent cramps include reducing volume removal during dialysis, ultrafiltration profiling, and using higher concentrations of sodium in the dialysate or sodium modeling (see earlier).

Anaphylactoid reactions to the dialyzer, particularly on its first use, have been reported most frequently with the bioincompatible cellulosic-containing membranes. With the gradual phasing out of cuprophane membranes in the United States, dialyzer reactions have become relatively uncommon. Dialyzer reactions can be divided into two types, A and B. Type A reactions are attributed to an IgE-mediated intermediate hypersensitivity reaction to ethylene oxide used in the sterilization of new dialyzers. This reaction typically occurs soon after the initiation of a treatment (within the first few minutes) and can progress to full-blown anaphylaxis if the therapy is not promptly discontinued. Treatment with steroids or epinephrine may be needed if symptoms are severe. The type B reaction consists of a symptom complex of nonspecific chest and back pain, which appears to result from complement activation and cytokine release. These symptoms typically occur several minutes into the dialysis run and typically resolve over time with continued dialysis.

Cardiovascular diseases constitute the major causes of death in patients with ESRD. Cardiovascular mortality and event rates are higher in dialysis patients than in

patients posttransplantation, although rates are extraordinarily high in both populations. The underlying cause of cardiovascular disease is unclear but may be related to shared risk factors (e.g., diabetes mellitus), chronic inflammation, massive changes in extracellular volume (especially with high interdialytic weight gains), inadequate treatment of hypertension, dyslipidemia, anemia, dystrophic vascular calcification, hyperhomocysteinemia, and perhaps alterations in cardiovascular dynamics during the dialysis treatment. Few studies have targeted cardiovascular risk reduction in ESRD patients; none have demonstrated consistent benefit. Nevertheless, most experts recommend conventional cardioprotective strategies (e.g., lipid-lowering agents, aspirin, β -adrenergic antagonists) in dialysis patients based on the individual patient's cardiovascular risk profile, which appears to be increased by more than an order of magnitude relative to persons unaffected by kidney disease.

PERITONEAL DIALYSIS

In peritoneal dialysis, 1.5–3.0 L of a dextrose-containing solution is infused into the peritoneal cavity and allowed to dwell for a set period of time, usually 2–4 h. As with hemodialysis, toxic materials are removed through a combination of convective clearance generated through ultrafiltration and diffusive clearance down a concentration gradient. The clearance of solutes and water during a peritoneal dialysis exchange depends on the balance between the movement of solute and water into the peritoneal cavity versus absorption from the peritoneal cavity. The rate of diffusion diminishes with time and eventually stops when equilibration between plasma and dialysate is reached. Absorption of solutes and water from the peritoneal cavity occurs across the peritoneal membrane into the peritoneal capillary circulation and via peritoneal lymphatics into the lymphatic circulation. The rate of peritoneal solute transport varies from patient to patient and may be altered by the presence of infection (peritonitis), drugs, and physical factors such as position and exercise.

FORMS OF PERITONEAL DIALYSIS

Peritoneal dialysis may be carried out as continuous ambulatory peritoneal dialysis (CAPD), continuous cyclic peritoneal dialysis (CCPD), or a combination of both. In CAPD, dialysis solution is manually infused into the peritoneal cavity during the day and exchanged three to five times daily. A nighttime dwell is frequently instilled at bedtime and remains in the peritoneal cavity through the night. The drainage of spent dialysate is performed manually with the assistance of gravity to move fluid out of the abdomen. In CCPD, exchanges are performed in an automated fashion, usually at night; the patient is connected to an automatedycler that performs

a series of exchange cycles while the patient sleeps. The number of exchange cycles required to optimize peritoneal solute clearance varies by the peritoneal membrane characteristics; as with hemodialysis, experts suggest careful tracking of solute clearances to ensure dialysis “adequacy.”

Peritoneal dialysis solutions are available in volumes typically ranging from 1.5 to 3.0 L. Lactate is the preferred buffer in peritoneal dialysis solutions. The most common additives to peritoneal dialysis solutions are heparin to prevent obstruction of the dialysis catheter lumen with fibrin and antibiotics during an episode of acute peritonitis. Insulin may also be added in patients with diabetes mellitus.

ACCESS TO THE PERITONEAL CAVITY

Access to the peritoneal cavity is obtained through a peritoneal catheter. Catheters used for maintenance peritoneal dialysis are flexible, being made of silicon rubber with numerous side holes at the distal end. These catheters usually have two Dacron cuffs to promote fibroblast proliferation, granulation, and invasion of the cuff. The scarring that occurs around the cuffs anchors the catheter and seals it from bacteria tracking from the skin surface into the peritoneal cavity; it also prevents the external leakage of fluid from the peritoneal cavity. The cuffs are placed in the preperitoneal plane and ~2 cm from the skin surface.

The *peritoneal equilibrium test* is a formal evaluation of peritoneal membrane characteristics that measures the transfer rates of creatinine and glucose across the peritoneal membrane. Patients are classified as low, low-average, high-average, and high “transporters.” Patients with rapid equilibration (i.e., high transporters) tend to absorb more glucose and lose efficiency of ultrafiltration with long daytime dwells. High transporters also tend to lose larger quantities of albumin and other proteins across the peritoneal membrane. In general, patients with rapid transporting characteristics require more frequent, shorter dwell time exchanges, nearly always obligating use of aycler for feasibility. Slower (low and low-average) transporters tend to do well with fewer exchanges. The efficiency of solute clearance also depends on the volume of dialysate infused. Larger volumes allow for greater solute clearance, particularly with CAPD in patients with low and low-average transport characteristics. Interestingly, solute clearance also increases with physical activity, presumably related to more efficient flow dynamics within the peritoneal cavity.

As with hemodialysis, the optimal dose of peritoneal dialysis is unknown. Several observational studies have suggested that higher rates of urea and creatinine clearance (the latter generally measured in L/week) are associated with lower mortality rates and fewer uremic complications. However, a randomized clinical trial (ADEMEX) failed to show a significant reduction in mortality or

complications with a relatively large increment in urea clearance. In general, patients on peritoneal dialysis do well when they retain residual kidney function. The rates of technique failure increase with years on dialysis and have been correlated with loss of residual function to a greater extent than loss of peritoneal membrane capacity. Recently, a nonabsorbable carbohydrate (icodextrin) has been introduced as an alternative osmotic agent. Studies have demonstrated more efficient ultrafiltration with icodextrin than with dextrose-containing solutions. Icodextrin is typically used as the “last fill” for patients on CCPD or for the longest dwell in patients on CAPD. For some patients in whom CCPD does not provide sufficient solute clearance, a hybrid approach can be adopted in which one or more daytime exchanges are added to the CCPD regimen. Although this approach can enhance solute clearance and prolong a patient’s capacity to remain on peritoneal dialysis, the burden of the hybrid approach can be overwhelming to some.

COMPLICATIONS DURING PERITONEAL DIALYSIS

The major complications of peritoneal dialysis are peritonitis, catheter-associated nonperitonitis infections, weight gain and other metabolic disturbances, and residual uremia (especially among patients with no residual kidney function).

Peritonitis typically develops when there has been a break in sterile technique during one or more of the exchange procedures. Peritonitis is usually defined by an elevated peritoneal fluid leukocyte count ($100/\text{mm}^3$, of which at least 50% are polymorphonuclear neutrophils). The clinical presentation typically consists of pain and cloudy dialysate, often with fever and other constitutional symptoms. The most common culprit organisms are gram-positive cocci, including *Staphylococcus*, reflecting the origin from the skin. Gram-negative rod infections are less common; fungal and mycobacterial infections are seen in selected patients, particularly after antibacterial therapy. Most cases of peritonitis can be managed either with intraperitoneal or oral antibiotics, depending on the organism; many patients with peritonitis do not require hospitalization. When peritonitis is caused by hydrophilic gram-negative rods (e.g., *Pseudomonas* spp.) or yeast, antimicrobial therapy is usually not sufficient, and catheter removal is required to ensure complete eradication of infection. Nonperitonitis catheter-associated infections (often termed *tunnel infections*) vary widely in severity. Some cases can be managed with local antibiotic or silver nitrate administration, but others are severe enough to require parenteral antibiotic therapy and catheter removal.

Peritoneal dialysis is associated with a variety of metabolic complications. As noted above, albumin and other proteins can be lost across the peritoneal membrane

in concert with the loss of metabolic wastes. The hypoproteinemia induced by peritoneal dialysis obligates a higher dietary protein intake to maintain nitrogen balance.

Hyperglycemia and weight gain are also common complications of peritoneal dialysis. Several hundred calories in the form of dextrose are absorbed each day, depending on the concentration used. Peritoneal dialysis patients, particularly those with type II diabetes mellitus, are then prone to other complications of insulin resistance, including hypertriglyceridemia. On the positive side, the continuous nature of peritoneal dialysis usually allows for a more liberal diet because of continuous removal of potassium and phosphorus, two major dietary components whose accumulation can be hazardous in patients with ESRD.

GLOBAL PERSPECTIVE



The incidence of ESRD is increasing worldwide with longer life expectancies and improved care of infectious and cardiovascular diseases. The management of patients with ESRD varies widely by country and within country by region, and it is influenced by economic and other major factors. In general, peritoneal dialysis is more commonly performed in poorer countries owing to its lower expense and the high cost of establishing in-center hemodialysis units.

ACKNOWLEDGMENT

We are grateful to Dr. Ajay Singh and Dr. Barry Brenner, authors of "Dialysis in the Treatment of Renal Failure" in the 16th edition of Harrison's Principles of Internal Medicine, for contributions to this chapter.

FURTHER READINGS

- BURKART JM et al: Peritoneal dialysis, in BM Brenner (ed), *Brenner and Rector's The Kidney*, 7th ed. Philadelphia, Saunders, 2004
- EKNOYAN G et al: Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med* 346:2010, 2002
- FORNI LG, HILTON PJ: Current concepts: Continuous hemofiltration in the treatment of acute renal failure. *N Engl J Med* 336:1303, 1997
- HIMMELFARB J, KLIGER AS: End-stage renal disease measures of quality. *Annu Rev Med* 58:387, 2007
- NATIONAL KIDNEY FOUNDATION: *Kidney Disease Quality Initiative Clinical Practice Guidelines: Hemodialysis and Peritoneal Dialysis Adequacy, 2001*. Available at <http://www.kidney.org/professionals/kdoqi/guidelines.cfm>
- PANIAGUA R et al: Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. *J Am Soc Nephrol* 13:1307, 2002
- RAYNER HC et al: Vascular access results from the Dialysis Outcomes and Practice Patterns Study (DOPPS): Performance against Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines. *Am J Kidney Dis*. 44(Suppl):S22, 2004
- U.S. RENAL DATA SYSTEM: *USRDS 2005 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease, 2005



CHAPTER 39

FLUID AND ELECTROLYTE DISTURBANCES

Gary G. Singer ■ Barry M. Brenner

■ Sodium and Water	393
Hypovolemia	395
Hyponatremia	397
Hypernatremia	400
■ Potassium	402
Hypokalemia	403
Hyperkalemia	406
■ Further Readings	409

SODIUM AND WATER

Composition of Body Fluids

Water is the most abundant constituent in the body, comprising approximately 50% of body weight in women and 60% in men. This difference is attributable to differences in the relative proportions of adipose tissue in men and women. Total body water is distributed in two major compartments: 55–75% is intracellular [intracellular fluid (ICF)], and 25–45% is extracellular [extracellular fluid (ECF)]. The ECF is further subdivided into intravascular (plasma water) and extravascular (interstitial) spaces in a ratio of 1:3.

The solute or particle concentration of a fluid is known as its *osmolality* and is expressed as milliosmoles per kilogram of water (mosmol/kg). Water crosses cell membranes to achieve osmotic equilibrium (ECF osmolality = ICF osmolality). The extracellular and intracellular solutes or osmoles are markedly different because of disparities in permeability and the presence of transporters and active pumps. The major ECF particles are Na^+ and its accompanying anions Cl^- and HCO_3^- , and K^+ and organic phosphate esters [adenosine triphosphate (ATP), creatine phosphate, and phospholipids] are the predominant ICF osmoles. Solute particles that are restricted to the ECF or the ICF determine the *effective osmolality*

(or *tonicity*) of that compartment. Because Na^+ is largely restricted to the extracellular compartment, total body Na^+ content is a reflection of ECF volume. Likewise, K^+ and its attendant anions are predominantly limited to the ICF and are necessary for normal cell function. Therefore, the number of intracellular particles is relatively constant, and a change in ICF osmolality is usually attributable to a change in ICF water content. However, in certain situations, brain cells can vary the number of intracellular solutes to defend against large water shifts. This process of *osmotic adaptation* is important in the defense of cell volume and occurs in chronic hyponatremia and hypernatremia. This response is mediated initially by transcellular shifts of K^+ and Na^+ , followed by synthesis, import, or export of organic solutes (so-called *osmolytes*) such as inositol, betaine, and glutamine. During chronic hyponatremia, brain cells lose solutes, thereby defending cell volume and diminishing neurologic symptoms. The converse occurs during chronic hypernatremia. Certain solutes, such as urea, do not contribute to water shift across cell membranes and are known as *ineffective osmoles*.

Fluid movement between the intravascular and interstitial spaces occurs across the capillary wall and is determined by the Starling forces—capillary hydraulic pressure and colloid osmotic pressure. The transcapillary

394 hydraulic pressure gradient exceeds the corresponding oncotic pressure gradient, thereby favoring the movement of plasma ultrafiltrate into the extravascular space. The return of fluid into the intravascular compartment occurs via lymphatic flow.

Water Balance

The normal plasma osmolality is 275–290 mosmol/kg and is kept within a narrow range by mechanisms capable of sensing a 1–2% change in tonicity. To maintain a steady state, water intake must equal water excretion. Disorders of water homeostasis result in hypo- or hypernatremia. Normal individuals have an obligate water loss consisting of urine, stool, and evaporation from the skin and respiratory tract. Gastrointestinal excretion is usually a minor component of total water output except in patients with vomiting, diarrhea, or high enterostomy output states. Evaporative or insensitive water losses are important in the regulation of core body temperature. Obligatory renal water loss is mandated by the minimum solute excretion required to maintain a steady state. Normally, about 600 mosmol must be excreted per day, and because the maximal urine osmolality is 1200 mosmol/kg, a minimum urine output of 500 mL/d is required for neutral solute balance.

Water Intake

The primary stimulus for water ingestion is *thirst*, mediated either by an increase in effective osmolality or a decrease in ECF volume or blood pressure. *Osmoreceptors*, located in the anterolateral hypothalamus, are stimulated by an increase in tonicity. Ineffective osmoles, such as urea and glucose, do not play a role in stimulating thirst. The average osmotic threshold for thirst is ~295 mosmol/kg and varies among individuals. Under normal circumstances, daily water intake exceeds physiologic requirements.

Water Excretion

In contrast to the ingestion of water, its excretion is tightly regulated by physiologic factors. The principal determinant of renal water excretion is *arginine vasopressin* (AVP; formerly antidiuretic hormone), a polypeptide synthesized in the supraoptic and paraventricular nuclei of the hypothalamus and secreted by the posterior pituitary gland. The binding of AVP to V₂ receptors on the basolateral membrane of principal cells in the collecting duct activates adenylyl cyclase and initiates a sequence of events that leads to the insertion of water channels into the luminal membrane. These water channels that are specifically activated by AVP are encoded by the *aquaporin-2* gene. The net effect is passive water reabsorption along an osmotic gradient from the lumen of the collecting duct to the hypertonic medullary interstitium. The major stimulus for AVP secretion is hypertonicity. Because the major ECF solutes are Na⁺

salts, effective osmolality is primarily determined by the plasma Na⁺ concentration. An increase or decrease in tonicity is sensed by hypothalamic osmoreceptors as a decrease or increase in cell volume, respectively, leading to enhancement or suppression of AVP secretion. The osmotic threshold for AVP release is 280–290 mosmol/kg, and the system is sufficiently sensitive that plasma osmolality varies by no more than 1–2%.

Nonosmotic factors that regulate AVP secretion include *effective circulating (arterial) volume*, nausea, pain, stress, hypoglycemia, pregnancy, and numerous drugs. The hemodynamic response is mediated by baroreceptors in the carotid sinus. The sensitivity of these receptors is significantly lower than that of the osmoreceptors. In fact, depletion of blood volume sufficient to result in a decreased mean arterial pressure is necessary to stimulate AVP release, but small changes in effective circulating volume have little effect.

To maintain homeostasis and a normal plasma Na⁺ concentration, the ingestion of solute-free water must eventually lead to the loss of the same volume of electrolyte-free water. Three steps are required for the kidney to excrete a water load: (1) filtration and delivery of water (and electrolytes) to the diluting sites of the nephron; (2) active reabsorption of Na⁺ and Cl⁻ without water in the thick ascending limb of the loop of Henle (TALH) and, to a lesser extent, in the distal nephron; and (3) maintenance of a dilute urine because of impermeability of the collecting duct to water in the absence of AVP. Abnormalities of any of these steps can result in impaired free-water excretion and eventual hyponatremia.

Sodium Balance

Sodium is actively pumped out of cells by the Na⁺, K⁺-ATPase pump. As a result, 85–90% of all Na⁺ is extracellular, and the ECF volume is a reflection of total body Na⁺ content. Normal volume regulatory mechanisms ensure that Na⁺ loss balances Na⁺ gain. If this does not occur, conditions of Na⁺ excess or deficit ensue and are manifest as edematous or hypovolemic states, respectively. It is important to distinguish between disorders of osmoregulation and disorders of volume regulation because water and Na⁺ balance are regulated independently. Whereas changes in Na⁺ concentration generally reflect disturbed water homeostasis, alterations in Na⁺ content are manifest as ECF volume contraction or expansion and imply abnormal Na⁺ balance.

Sodium Intake

Individuals eating a typical Western diet consume approximately 150 mmol of NaCl daily. This normally exceeds basal requirements. As noted above, sodium is the principal extracellular cation. Therefore, dietary intake of Na⁺ results in ECF volume expansion, which

in turn promotes enhanced renal Na^+ excretion to maintain steady-state Na^+ balance.

Sodium Excretion

The regulation of Na^+ excretion is multifactorial and is the major determinant of Na^+ balance. A Na^+ deficit or excess is manifest as a decreased or increased effective circulating volume, respectively. Changes in effective circulating volume tend to lead to parallel changes in glomerular filtration rate (GFR). However, tubule Na^+ reabsorption, not GFR, is the major regulatory mechanism controlling Na^+ excretion. Almost two-thirds of filtered Na^+ is reabsorbed in the proximal convoluted tubule; this process is electroneutral and isoosmotic. Further reabsorption (25–30%) occurs in the TALH via the apical $\text{Na}^+-\text{K}^+-2\text{Cl}^-$ co-transporter; this is an active process and is also electroneutral. Distal convoluted tubule reabsorption of Na^+ (5%) is mediated by the *thiazide-sensitive* Na^+-Cl^- co-transporter. Final Na^+ reabsorption occurs in the cortical and medullary collecting ducts, with the amount excreted being reasonably equivalent to the amount ingested per day.

HYPOVOLEMIA

Etiology

True volume depletion, or hypovolemia, generally refers to a state of combined salt and water loss exceeding intake, leading to ECF volume contraction. The loss of Na^+ may be renal or extrarenal (Table 39-1).

TABLE 39-1

CAUSES OF HYPOVOLEMIA

- I. ECF volume contracted
 - A. Extrarenal Na^+ loss
 1. Gastrointestinal: vomiting, nasogastric suction, drainage, fistula, diarrhea
 2. Skin or respiratory: insensible losses, sweat, burns
 3. Hemorrhage
 - B. Renal Na^+ and water loss
 1. Diuretics
 2. Osmotic diuresis
 3. Hypoaldosteronism
 4. Salt-wasting nephropathies
 - C. Renal water loss
 1. Diabetes insipidus: central or nephrogenic
- II. ECF volume normal or expanded
 - A. Decreased cardiac output
 1. Myocardial, valvular, or pericardial disease
 - B. Redistribution
 1. Hypoalbuminemia (hepatic cirrhosis, nephrotic syndrome)
 2. Capillary leak (acute pancreatitis, ischemic bowel, rhabdomyolysis)
 - C. Increased venous capacitance
 1. Sepsis

Note: ECF, extracellular fluid.

Renal

Many conditions are associated with excessive urinary NaCl and water losses, including use of diuretics. Pharmacologic diuretics inhibit specific pathways of Na^+ reabsorption along the nephron with a consequent increase in urinary Na^+ excretion. Enhanced filtration of non-reabsorbed solutes, such as glucose or urea, can also impair tubular reabsorption of Na^+ and water, leading to an osmotic or solute diuresis. This often occurs in poorly controlled diabetes mellitus and in patients receiving high-protein hyperalimentation. Mannitol is a diuretic that produces an osmotic diuresis because the renal tubule is impermeable to mannitol. Many tubule and interstitial renal disorders are associated with Na^+ wasting. Excessive renal losses of Na^+ and water may also occur during the diuretic phase of acute tubular necrosis (Chap. 37) and after the relief of bilateral urinary tract obstruction. Finally, mineralocorticoid deficiency (hypoaldosteronism) causes salt wasting in the presence of normal intrinsic renal function.

Massive renal water excretion can also lead to hypovolemia. The ECF volume contraction is usually less severe since two-thirds of the volume lost is intracellular. Conditions associated with excessive urinary water loss include *central diabetes insipidus* (CDI) and *nephrogenic diabetes insipidus* (NDI). These two disorders are caused by impaired secretion of and renal unresponsiveness to AVP, respectively, and are discussed later.

Extrarenal

Nonrenal causes of hypovolemia include fluid loss from the gastrointestinal tract, skin, and respiratory system and third-space accumulations (burns, pancreatitis, peritonitis). Approximately 9 L of fluid enters the gastrointestinal tract daily, 2 L by ingestion and 7 L by secretion. Almost 98% of this volume is reabsorbed so that fecal fluid loss is only 100–200 mL/d. Impaired gastrointestinal reabsorption or enhanced secretion leads to volume depletion. Because gastric secretions have a low pH (high H^+ concentration) and biliary, pancreatic, and intestinal secretions are alkaline (high HCO_3^- concentration), vomiting and diarrhea are often accompanied by metabolic alkalosis and acidosis, respectively.

Water evaporation from the skin and respiratory tract contributes to thermoregulation. These *insensible losses* amount to 500 mL/d. During febrile illnesses, prolonged heat exposure, exercise, or increased salt and water loss from skin in the form of sweat can be significant and lead to volume depletion. The Na^+ concentration of sweat is normally 20–50 mmol/L and decreases with profuse sweating because of the action of aldosterone. Because sweat is hypotonic, the loss of water exceeds that of Na^+ . The water deficit is minimized by enhanced thirst. Nevertheless, ongoing Na^+ loss is manifest as hypovolemia. Enhanced evaporative water loss from the respiratory tract

396 may be associated with hyperventilation, especially in mechanically ventilated, febrile patients.

Certain conditions lead to fluid sequestration in a *third space*. This compartment is extracellular but is not in equilibrium with either the ECF or the ICF. The fluid is effectively lost from the ECF and can result in hypovolemia. Examples include the bowel lumen in gastrointestinal obstruction, subcutaneous tissues in severe burns, retroperitoneal space in acute pancreatitis, and peritoneal cavity in peritonitis. Finally, severe hemorrhage from any source can result in volume depletion.

Pathophysiology

ECF volume contraction is manifest as a decreased plasma volume and hypotension. Hypotension is caused by decreased venous return (preload) and diminished cardiac output; it triggers baroreceptors in the carotid sinus and aortic arch and leads to activation of the sympathetic nervous system and the renin–angiotensin system. The net effect is to maintain mean arterial pressure and cerebral and coronary perfusion. In contrast to the cardiovascular response, the renal response is aimed at restoring the ECF volume by decreasing the GFR and filtered load of Na^+ and, most importantly, by promoting tubular reabsorption of Na^+ . Increased sympathetic tone increases proximal tubular Na^+ reabsorption and decreases GFR by causing preferential afferent arteriolar vasoconstriction. Sodium is also reabsorbed in the proximal convoluted tubule in response to increased angiotensin II and altered peritubular capillary hemodynamics (decreased hydraulic and increased oncotic pressure). Enhanced reabsorption of Na^+ by the collecting duct is an important component of the renal adaptation to ECF volume contraction. This occurs in response to increased *aldosterone* and AVP secretion and suppressed *atrial natriuretic peptide* secretion.

Clinical Features

A careful history is often helpful in determining the cause of ECF volume contraction (e.g., vomiting, diarrhea, polyuria, diaphoresis). Most symptoms are nonspecific and secondary to electrolyte imbalances and tissue hypoperfusion and include fatigue, weakness, muscle cramps, thirst, and postural dizziness. More severe degrees of volume contraction can lead to end-organ ischemia manifest as oliguria, cyanosis, abdominal and chest pain, and confusion or obtundation. Diminished skin turgor and dry oral mucous membranes are poor markers of decreased interstitial fluid. Signs of intravascular volume contraction include decreased jugular venous pressure, postural hypotension, and postural tachycardia. Larger and more acute fluid losses lead to hypovolemic shock and manifest as hypotension, tachycardia, peripheral vasoconstriction, and hypoperfusion—cyanosis, cold and clammy extremities, oliguria, and altered mental status.

Diagnosis

A thorough history and physical examination are generally sufficient to diagnose the cause of hypovolemia. Laboratory data usually confirm and support the clinical diagnosis. The blood urea nitrogen (BUN) and plasma creatinine concentrations tend to be elevated, reflecting a decreased GFR. Normally, the BUN:creatinine ratio is about 10:1. However, in *prerenal azotemia*, hypovolemia leads to increased urea reabsorption, a proportionately greater elevation in BUN than plasma creatinine, and a BUN:creatinine ratio of 20:1 or higher. An increased BUN (relative to creatinine) may also be caused by increased urea production that occurs with hyperalimentation (high-protein), glucocorticoid therapy, and gastrointestinal bleeding.

The appropriate response to hypovolemia is enhanced renal Na^+ and water reabsorption, which is reflected in the urine composition. Therefore, the urine Na^+ concentration should usually be <20 mmol/L except in conditions associated with impaired Na^+ reabsorption, as in acute tubular necrosis (Chap. 37). Another exception is hypovolemia caused by vomiting because the associated metabolic alkalosis and increased filtered HCO_3^- impair proximal Na^+ reabsorption. In this case, the urine Cl^- is low (<20 mmol/L). The urine osmolality and specific gravity in hypovolemic subjects are generally >450 mosmol/kg and 1.015, respectively, reflecting the presence of enhanced AVP secretion. However, in hypovolemia, caused by diabetes insipidus, urine osmolality and specific gravity indicate inappropriately dilute urine.

Rx Treatment: HYPOVOLEMIA

The therapeutic goals are to restore normovolemia with fluid similar in composition to that lost and to replace ongoing losses. Symptoms and signs, including weight loss, can help estimate the degree of volume contraction and should also be monitored to assess response to treatment. Mild volume contraction can usually be corrected via the oral route. More severe hypovolemia requires IV therapy. Isotonic or normal saline (0.9% NaCl or 154 mmol/L Na^+) is the solution of choice in normonatremic and most hyponatremic individuals and should be administered initially in patients with hypotension or shock. Hypernatremia reflects a proportionally greater deficit of water than Na^+ , and its correction therefore requires a hypotonic solution such as half-normal saline (0.45% NaCl or 77 mmol/L Na^+) or 5% dextrose in water. Patients with significant hemorrhage, anemia, or intravascular volume depletion may require blood transfusion or colloid-containing solutions (albumin, dextran). Hypokalemia may be present initially or may ensue as a result of increased urinary K^+ excretion; it should be corrected by adding appropriate amounts of KCl to replacement solutions.

HYPONATREMIA

Etiology

A plasma Na^+ concentration <135 mmol/L usually reflects a hypotonic state. However, plasma osmolality may be normal or increased in some cases of hyponatremia. Isotonic or slightly hypotonic hyponatremia may complicate transurethral resection of the prostate or bladder because large volumes of isoosmotic (mannitol) or hypo-osmotic (sorbitol or glycine) bladder irrigation solution can be absorbed and result in a dilutional hyponatremia. The metabolism of sorbitol and glycine to CO_2 and water may lead to hypotonicity if the accumulated fluid and solutes are not rapidly excreted. Hypertonic hyponatremia is usually caused by hyperglycemia or, occasionally, IV administration of mannitol. Relative insulin deficiency causes myocytes to become impermeable to glucose. Therefore, during poorly controlled diabetes mellitus, glucose is an effective osmole and draws water from muscle cells, resulting in hyponatremia. Plasma Na^+ concentration decreases by 1.4 mmol/L for every 100 mg/dL increase in the plasma glucose concentration.

Most causes of hyponatremia are associated with a low plasma osmolality (Table 39-2). In general, hypotonic hyponatremia is caused by either a primary water gain (and secondary Na^+ loss) or a primary Na^+ loss (and secondary water gain). In the absence of water intake or hypotonic fluid replacement, hyponatremia is usually associated with hypovolemic shock caused by a profound sodium deficit and transcellular water shift. Contraction of the ECF volume stimulates thirst and AVP secretion. The increased water ingestion and impaired renal excretion result in hyponatremia. It is important to note that *diuretic-induced hyponatremia* is almost always caused by thiazide diuretics. Loop diuretics decrease the tonicity of the medullary interstitium and impair maximal urinary concentrating capacity. This limits the ability of AVP to promote water retention. In contrast, thiazide diuretics lead to Na^+ and K^+ depletion and AVP-mediated water retention. Hyponatremia can also occur by a process of *desalination*. This occurs when the urine tonicity (the sum of the concentrations of Na^+ and K^+) exceeds that of administered IV fluids (including isotonic saline). This accounts for some cases of acute postoperative hyponatremia and cerebral salt wasting after neurosurgery.

Hyponatremia in the setting of ECF volume expansion is usually associated with edematous states, such as congestive heart failure, hepatic cirrhosis, and nephrotic syndrome. These disorders all have in common a decreased effective circulating arterial volume, leading to increased thirst and increased AVP levels. Additional factors impairing the excretion of solute-free water include a reduced GFR, decreased delivery of ultrafiltrate to the diluting site (because of increased proximal fractional reabsorption of Na^+ and water), and diuretic therapy.

TABLE 39-2

CAUSES OF HYPONATREMIA

- I. Pseudohyponatremia
 - A. Normal plasma osmolality
 1. Hyperlipidemia
 2. Hyperproteinemia
 3. Posttransurethral resection of a prostate or bladder tumor
 - B. Increased plasma osmolality
 1. Hyperglycemia
 2. Mannitol
- II. Hypo-osmolal hyponatremia
 - A. Primary Na^+ loss (secondary water gain)
 1. Integumentary loss: sweating, burns
 2. Gastrointestinal loss: vomiting, tube drainage, fistula, obstruction, diarrhea
 3. Renal loss: diuretics, osmotic diuresis, hypoaldosteronism, salt-wasting nephropathy, postobstructive diuresis, nonoliguric acute tubular necrosis
 - B. Primary water gain (secondary Na^+ loss)
 1. Primary polydipsia
 2. Decreased solute intake (e.g., beer potomania)
 3. AVP release because of pain, nausea, drugs
 4. Syndrome of inappropriate AVP secretion
 5. Glucocorticoid deficiency
 6. Hypothyroidism
 7. Chronic renal insufficiency
 - C. Primary Na^+ gain (exceeded by secondary water gain)
 1. Heart failure
 2. Hepatic cirrhosis
 3. Nephrotic syndrome

Note: AVP, arginine vasopressin.

The degree of hyponatremia often correlates with the severity of the underlying condition and is an important prognostic factor. Oliguric acute and chronic renal failure may be associated with hyponatremia if water intake exceeds the ability to excrete equivalent volumes.

Hyponatremia in the absence of ECF volume contraction, decreased effective circulating arterial volume, or renal insufficiency is usually caused by increased AVP secretion, resulting in impaired water excretion. Ingestion or administration of water is also required because high levels of AVP alone are usually insufficient to produce hyponatremia. This disorder, commonly termed the *syndrome of inappropriate antidiuretic hormone secretion* (SIADH), is the most common cause of normovolemic hyponatremia and is caused by the nonphysiologic release of AVP from the posterior pituitary or an ectopic source. Renal free-water excretion is impaired, but the regulation of Na^+ balance is unaffected. The most common causes of SIADH include neuropsychiatric and pulmonary diseases, malignant tumors, major surgery (postoperative pain), and pharmacologic agents. Severe pain and nausea are physiologic stimuli of AVP secretion; these stimuli are inappropriate in the absence of

hypovolemia or hyperosmolality. The pattern of AVP secretion can be used to classify SIADH into four subtypes: (1) erratic autonomous AVP secretion (ectopic production), (2) normal regulation of AVP release around a lower osmolality set point or *reset osmostat* (cachexia, malnutrition), (3) normal AVP response to hypertonicity with failure to suppress completely at low osmolality (incomplete pituitary stalk section), and (4) normal AVP secretion with increased sensitivity to its actions or secretion of some other antidiuretic factor (rare). Patients with the nephrogenic syndrome of inappropriate antidiuresis have clinical and laboratory features consistent with SIADH but undetectable levels of AVP. It is hypothesized that this disorder is caused by gain of function mutations in the V_2 receptor.

Hormonal excess or deficiency may cause hyponatremia. Adrenal insufficiency and hypothyroidism may present with hyponatremia and should not be confused with SIADH. Although decreased mineralocorticoids may contribute to the hyponatremia of adrenal insufficiency, it is the cortisol deficiency that leads to hypersecretion of AVP both indirectly (secondary to volume depletion) and directly (cosecreted with corticotropin-releasing factor). The mechanisms by which hypothyroidism leads to hyponatremia include decreased cardiac output and GFR and increased AVP secretion in response to hemodynamic stimuli.

Finally, hyponatremia may occur in the absence of AVP or renal failure if the kidney is unable to excrete the dietary water load. In psychogenic or primary polydipsia, compulsive water consumption may overwhelm the normally large renal excretory capacity of 12 L/d. These patients often have psychiatric illnesses and may be taking medications, such as phenothiazines, that enhance the sensation of thirst by causing a dry mouth. The maximal urine output is a function of the minimum urine osmolality achievable and the mandatory solute excretion. Metabolism of a normal diet generates about 600 mosmol/d, and the minimum urine osmolality in humans is 50 mosmol/kg. Therefore, the maximum daily urine output is about 12 L ($600 \div 50 = 12$). A solute excretion rate of greater than ~ 750 mosmol/d is, by definition, an *osmotic diuresis*. A low-protein diet may yield as little as 250 mosmol/d, which translates into a maximal urine output of 5 L/d at a minimum urine tonicity of 50 mosmol/kg. Beer drinkers typically have a poor dietary intake of protein and electrolytes and consume large volumes (of beer), which may exceed the renal excretory capacity and result in hyponatremia. This phenomenon is referred to as *beer potomania*.

Clinical Features

The clinical manifestations of hyponatremia are related to osmotic water shift leading to increased ICF volume, specifically brain cell swelling or cerebral edema. Therefore, the symptoms are primarily neurologic, and their

severity depends on the rapidity of onset and absolute decrease in plasma Na^+ concentration. Patients may be asymptomatic or complain of nausea and malaise. As the plasma Na^+ concentration decreases, the symptoms progress to include headache, lethargy, confusion, and obtundation. Stupor, seizures, and coma do not usually occur unless the plasma Na^+ concentration decreases acutely below 120 mmol/L or decreases rapidly. As described above, adaptive mechanisms designed to protect cell volume occur in chronic hyponatremia. Loss of Na^+ and K^+ , followed by organic osmolytes, from brain cells decreases brain swelling because of secondary transcellular water shifts (from ICF to ECF). The net effect is to minimize cerebral edema and its symptoms.

Diagnosis

(Fig. 39-1) Hyponatremia is not a disease but rather a manifestation of a variety of disorders. The underlying cause can often be ascertained from an accurate history and physical examination, including an assessment of ECF volume status and effective circulating arterial volume. The differential diagnosis of hyponatremia, an expanded ECF volume, and decreased effective circulating volume

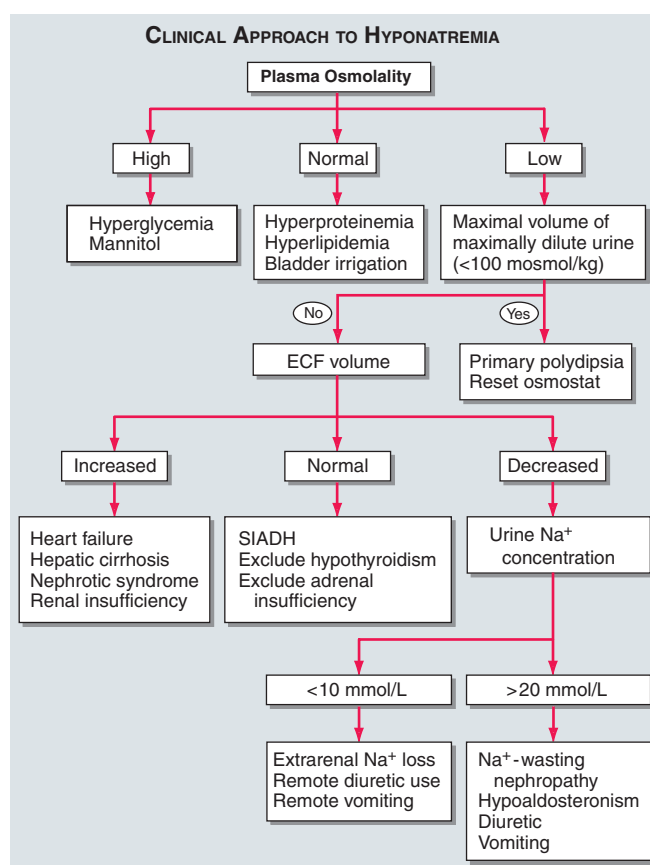


FIGURE 39-1 Algorithm depicting the clinical approach to hyponatremia. ECF, extracellular fluid; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

includes congestive heart failure, hepatic cirrhosis, and the nephrotic syndrome. Patients with hypothyroidism and adrenal insufficiency tend to present with a near-normal ECF volume and decreased effective circulating arterial volume. All of these diseases have characteristic signs and symptoms. Patients with SIADH are usually euvolemic.

Four laboratory findings often provide useful information and can narrow the differential diagnosis of hyponatremia: (1) the plasma osmolality, (2) the urine osmolality, (3) the urine Na^+ concentration, and (4) the urine K^+ concentration. Because ECF tonicity is determined primarily by the Na^+ concentration, most patients with hyponatremia have a decreased plasma osmolality. The appropriate renal response to hypo-osmolality is to excrete the maximum volume of dilute urine (i.e., urine osmolality and specific gravity of <100 mosmol/kg and 1.003, respectively). This occurs in patients with primary polydipsia. If this is not present, it suggests impaired free-water excretion due to the action of AVP on the kidney. The secretion of AVP may be a physiologic response to hemodynamic stimuli or it may be inappropriate in the presence of hyponatremia and euvolemia. Because Na^+ is the major ECF cation and is largely restricted to this compartment, ECF volume contraction represents a deficit in total body Na^+ content. Therefore, volume depletion in patients with normal underlying renal function results in enhanced tubule Na^+ reabsorption and a urine Na^+ concentration <20 mmol/L. The finding of a urine Na^+ concentration >20 mmol/L in a patient with hypovolemic hyponatremia implies a salt-wasting nephropathy, diuretic therapy, hypoaldosteronism, or occasionally vomiting. Both the urine osmolality and the urine Na^+ concentration can be followed serially when assessing the patient's response to therapy.

SIADH is characterized by hypo-osmotic hyponatremia in the setting of an inappropriately concentrated urine (urine osmolality >100 mosmol/kg). Patients are typically normovolemic and have a normal Na^+ balance. They tend to be mildly volume expanded secondary to water retention and have a urine Na^+ excretion rate equal to intake (urine Na^+ concentration usually >40 mmol/L). By definition, they have normal renal, adrenal, and thyroid function and usually have normal K^+ and acid-base balance. SIADH is often associated with hypouricemia caused by the uricosuric state induced by volume expansion. In contrast, patients with hypovolemia tend to be hyperuricemic secondary to increased proximal urate reabsorption.

Rx Treatment: **HYPONATREMIA**

The goals of therapy are twofold: (1) to increase the plasma Na^+ concentration by restricting water intake and promoting water loss and (2) to correct the underlying

disorder. Mild asymptomatic hyponatremia is generally of little clinical significance and requires no treatment. However, the management of asymptomatic hyponatremia associated with ECF volume contraction should include Na^+ repletion, generally in the form of isotonic saline. The direct effect of the administered NaCl on the plasma Na^+ concentration is trivial. However, restoration of euvolemia removes the hemodynamic stimulus for AVP release, allowing the excess free water to be excreted. The hyponatremia associated with edematous states tends to reflect the severity of the underlying disease and is usually asymptomatic. These patients have increased total body water that exceeds the increase in total body Na^+ content. Treatment should include restriction of Na^+ and water intake, correction of hypokalemia, and promotion of water loss in excess of Na^+ . The latter may require the use of loop diuretics with replacement of a proportion of the urinary Na^+ loss to ensure net free-water excretion. Dietary water restriction should be less than the urine output. Correction of the K^+ deficit may increase the plasma Na^+ concentration by favoring a shift of Na^+ out of cells as K^+ moves in. Water restriction is also a component of the therapeutic approach to hyponatremia associated with primary polydipsia, renal failure, and SIADH. The recent development of nonpeptide vasopressin antagonists has introduced a new selective treatment for euvolemic and hypervolemic hyponatremia.

The rate of correction of hyponatremia depends on the absence or presence of neurologic dysfunction. This, in turn, is related to the rapidity of onset and magnitude of the decrease in plasma Na^+ concentration. In asymptomatic patients, the plasma Na^+ concentration should be increased by no more than 0.5–1.0 mmol/L per h and by less than 10–12 mmol/L over the first 24 h. Patients with acute or severe hyponatremia (plasma Na^+ concentration <110 – 115 mmol/L) tend to present with altered mental status, seizures, or both and require more rapid correction. Patients with severe symptomatic hyponatremia should be treated with hypertonic saline, and the plasma Na^+ concentration should be increased by 1–2 mmol/L per hour for the first 3–4 h or until the seizures subside. Again, the plasma Na^+ concentration should probably be increased by no more than 12 mmol/L during the first 24 h. The quantity of Na^+ required to increase the plasma Na^+ concentration by a given amount can be estimated by multiplying the deficit in plasma Na^+ concentration by the total body water.

Under normal conditions, total body water is 50 or 60% of lean body weight in women and men, respectively. Therefore, increasing the plasma Na^+ concentration from 105 to 115 mmol/L in a 70-kg man requires 420 mmol $[(115 - 105) \times 70 \times 0.6]$ of Na^+ . The risk of correcting hyponatremia too rapidly is the development of the *osmotic demyelination syndrome* (ODS). This is a neurologic disorder characterized by flaccid paralysis,

dysarthria, and dysphagia. The diagnosis is usually suspected clinically and can be confirmed by appropriate neuroimaging studies. There is no specific treatment for the disorder, which is associated with significant morbidity and mortality. Patients with chronic hyponatremia are most susceptible to the development of ODS because their brain cell volume has returned to near normal as a result of the osmotic adaptive mechanisms described earlier. Therefore, administration of hypertonic saline to these individuals can cause sudden osmotic shrinkage of brain cells. In addition to rapid or overcorrection of hyponatremia, risk factors for ODS include prior cerebral anoxic injury; hypokalemia; and malnutrition, especially secondary to alcoholism. Water restriction in primary polydipsia and IV saline therapy in ECF volume-contracted patients may also lead to overly rapid correction of hyponatremia as a result of AVP suppression and a brisk water diuresis. This can be prevented by administration of water or use of an AVP analogue to slow down the rate of free-water excretion.

HYPERNATREMIA

Etiology

Hypernatremia is defined as a plasma Na^+ concentration >145 mmol/L. Because Na^+ and its accompanying anions are the major effective ECF osmoles, hypernatremia is a state of hyperosmolality. As a result of the fixed number of ICF particles, maintenance of osmotic equilibrium in hypernatremia results in ICF volume contraction. Hypernatremia may be caused by primary Na^+ gain or water deficit. The two components of an appropriate response to hypernatremia are increased water intake stimulated by thirst and the excretion of the minimum volume of maximally concentrated urine reflecting AVP secretion in response to an osmotic stimulus.

In practice, the majority of cases of hypernatremia result from the loss of water. Because water is distributed between the ICF and the ECF in a 2:1 ratio, a given amount of solute-free water loss will result in a twofold greater reduction in the ICF compartment than the ECF compartment. For example, consider three scenarios: the loss of 1 L of water, isotonic NaCl, or half-isotonic NaCl. If 1 L of water is lost, the ICF volume will decrease by 667 mL, but the ECF volume will decrease by only 333 mL. Because Na^+ is largely restricted to the ECF, this compartment will decrease by 1 L if the fluid lost is isotonic. One liter of half-isotonic NaCl is equivalent to 500 mL of water (one-third ECF, two-thirds ICF) plus 500 mL of isotonic saline (all ECF). Therefore, the loss of 1 L of half-isotonic saline decreases the ECF and ICF volumes by 667 mL and 333 mL, respectively.

The degree of hyperosmolality is typically mild unless the thirst mechanism is abnormal or access to water is

limited. The latter occurs in infants, people with physical disabilities, and patients with impaired mental status; in the postoperative state; and in intubated patients in the intensive care unit. On rare occasions, impaired thirst may be caused by *primary hypodipsia*. This usually occurs as a result of damage to the hypothalamic osmoreceptors that control thirst and tends to be associated with abnormal osmotic regulation of AVP secretion. Primary hypodipsia may be caused by a variety of pathologic changes, including granulomatous disease, vascular occlusion, and tumors. A subset of patients with hypodipsic hypernatremia, referred to as *essential hypernatremia*, do not respond to forced water intake. This appears to be because of a specific osmoreceptor defect resulting in nonosmotic regulation of AVP release. Thus, the hemodynamic effects of water loading lead to AVP suppression and excretion of dilute urine.

The source of free water loss is either renal or extrarenal. Nonrenal loss of water may be caused by evaporation from the skin and respiratory tract (insensible losses) or loss from the gastrointestinal tract. Insensible losses are increased with fever, exercise, heat exposure, and severe burns and in mechanically ventilated patients. Furthermore, the Na^+ concentration of sweat decreases with profuse perspiration, thereby increasing solute-free water loss. Diarrhea is the most common gastrointestinal cause of hypernatremia. Specifically, osmotic diarrheas (induced by lactulose, sorbitol, or malabsorption of carbohydrate) and viral gastroenteritides result in water loss exceeding that of Na^+ and K^+ . In contrast, secretory diarrheas (e.g., cholera, carcinoid, VIPoma) have a fecal osmolality (twice the sum of the concentrations of Na^+ and K^+) similar to that of plasma and present with ECF volume contraction and a normal plasma Na^+ concentration or hyponatremia.

Renal water loss is the most common cause of hypernatremia and is caused by drug-induced or osmotic diuresis or diabetes insipidus. Loop diuretics interfere with the countercurrent mechanism and produce an isoosmotic solute diuresis. This results in a decreased medullary interstitial tonicity and impaired renal concentrating ability. The presence of non-reabsorbed organic solutes in the tubule lumen impairs the osmotic reabsorption of water. This leads to water loss in excess of Na^+ and K^+ , known as an *osmotic diuresis*. The most frequent cause of osmotic diuresis is hyperglycemia and glucosuria in a patient with poorly controlled diabetes mellitus. IV administration of mannitol and increased endogenous production of urea (high-protein diet) can also result in an osmotic diuresis.

Hypernatremia secondary to nonosmotic urinary water loss is usually caused by (1) CDI characterized by impaired AVP secretion or (2) NDI resulting from end-organ (renal) resistance to the actions of AVP. The most common cause of CDI is destruction of the neurohypophysis. This may occur as a result of trauma,

neurosurgery, granulomatous disease, neoplasms, vascular accidents, or infection. In many cases, CDI is idiopathic and may occasionally be hereditary. The familial form of the disease is inherited in an autosomal dominant fashion and has been attributed to mutations in the prorenin (AVP precursor) gene. NDI may be either inherited or acquired. Congenital NDI is an X-linked recessive trait caused by mutations in the V_2 receptor gene. Mutations in the autosomal *aquaporin-2* gene may also result in NDI. The *aquaporin-2* gene encodes the water channel protein whose membrane insertion is stimulated by AVP. The causes of sporadic NDI are numerous and include drugs (especially lithium), hypercalcemia, hypokalemia, and conditions that impair medullary hypertonicity (e.g., papillary necrosis or osmotic diuresis). In the second or third trimester, pregnant women may develop NDI as a result of excessive elaboration of vasopressinase by the placenta.

Finally, although infrequent, a primary Na^+ gain may cause hypernatremia. For example, inadvertent administration of hypertonic $NaCl$ or $NaHCO_3$ or replacing sugar with salt in infant formula can produce this complication.

Clinical Features

As a consequence of hypertonicity, water shifts out of cells, leading to a contracted ICF volume. A decreased brain cell volume is associated with an increased risk of subarachnoid or intracerebral hemorrhage. Hence, the major symptoms of hypernatremia are neurologic and include altered mental status, weakness, neuromuscular irritability, focal neurologic deficits, and occasionally coma or seizures. Patients may also complain of polyuria or thirst. For unknown reasons, patients with polydipsia from CDI tend to prefer ice-cold water. The signs and symptoms of volume depletion are often present in patients with a history of excessive sweating, diarrhea, or osmotic diuresis. As with hyponatremia, the severity of the clinical manifestations is related to the acuity and magnitude of the increase in plasma Na^+ concentration. Chronic hypernatremia is generally less symptomatic as a result of adaptive mechanisms designed to defend cell volume. Brain cells initially take up Na^+ and K^+ salts, later followed by accumulation of organic osmolytes such as inositol. This serves to restore the brain ICF volume toward normal.

Diagnosis

(Fig. 39-2) A complete history and physical examination often provide clues as to the underlying cause of hypernatremia. Relevant symptoms and signs include the absence or presence of thirst, diaphoresis, diarrhea, polyuria, and the features of ECF volume contraction. The history should include a list of current and recent medications,

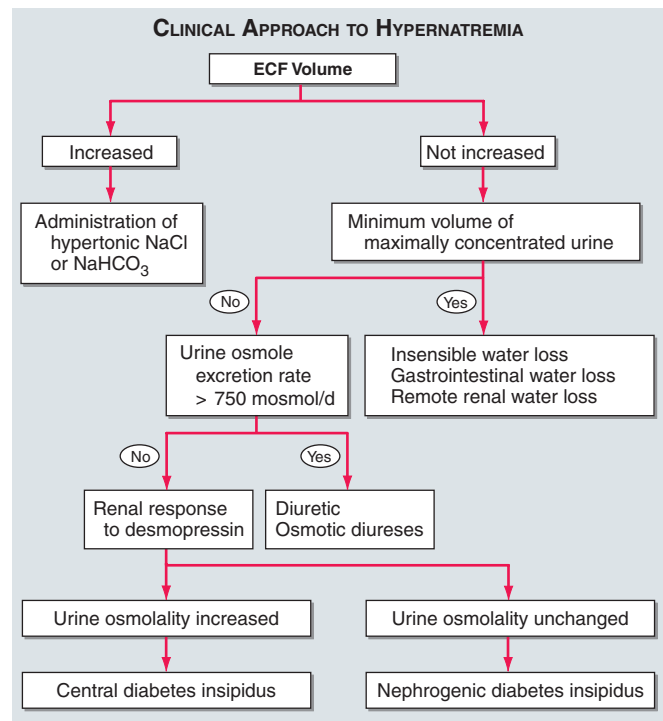


FIGURE 39-2

Algorithm depicting the clinical approach to hypernatremia. ECF, extracellular fluid.

and the physical examination is incomplete without a thorough mental status and neurologic assessment. Measurement of urine volume and osmolality are essential in the evaluation of hyperosmolality. The appropriate renal response to hypernatremia is the excretion of the minimum volume (500 mL/d) of maximally concentrated urine (urine osmolality >800 mosmol/kg). These findings suggest extrarenal or remote renal water loss or administration of hypertonic Na^+ salt solutions. The presence of a primary Na^+ excess can be confirmed by the presence of ECF volume expansion and natriuresis (urine Na^+ concentration usually >100 mmol/L).

Many causes of hypernatremia are associated with polyuria and a submaximal urine osmolality. The product of the urine volume and osmolality (i.e., the solute excretion rate) is helpful in determining the basis of the polyuria (see earlier). To maintain a steady state, total solute excretion must equal solute production. As stated above, individuals eating a normal diet generate ~600 mosmol/d. Therefore, daily solute excretion >750 mosmol defines an osmotic diuresis. This can be confirmed by measuring the urine glucose and urea. In general, patients with both CDI and NDI present with polyuria and hypotonic urine (urine osmolality <250 mosmol/kg). The degree of hypernatremia is usually mild unless there is an associated thirst abnormality. The clinical history, physical examination, and pertinent laboratory data can often rule out causes of acquired NDI. CDI and NDI can generally be distinguished by administering the AVP analogue desmopressin (10 μ g intranasally) after careful water restriction.

402 The urine osmolality should increase by at least 50% in patients with CDI and will not change in those with NDI. Unfortunately, the diagnosis may sometimes be difficult because of partial defects in AVP secretion and action.

Rx Treatment: **HYPERNATREMIA**

The therapeutic goals are to stop ongoing water loss by treating the underlying cause and to correct the water deficit. The ECF volume should be restored in hypovolemic patients. The quantity of water required to correct the deficit can be calculated from the following equation:

$$\text{Water deficit} = \frac{\text{Plasma Na}^+ \text{ concentration} - 140}{140} \times \text{Total body water}$$

In hypernatremia caused by water loss, total body water is approximately 50% and 40% of lean body weight in men and women, respectively. For example, a 50-kg woman with a plasma Na⁺ concentration of 160 mmol/L has an estimated free-water deficit of 2.9 L $\{[(160 - 140) \div 140] \times (0.4 \times 50)\}$. As in hyponatremia, rapid correction of hypernatremia is potentially dangerous. In this case, a sudden decrease in osmolality could potentially cause a rapid shift of water into cells that have undergone osmotic adaptation. This would result in swollen brain cells and increase the risk of seizures or permanent neurologic damage. Therefore, the water deficit should be corrected slowly over at least 48–72 h. When calculating the rate of water replacement, ongoing losses should be taken into account, and the plasma Na⁺ concentration should be lowered by 0.5 mmol/L per h and by no more than 12 mmol/L over the first 24 h.

The safest route of administration of water is by mouth or via a nasogastric tube (or other feeding tube). Alternatively, 5% dextrose in water or half-isotonic saline can be given IV. The appropriate treatment of CDI consists of administering desmopressin intranasally. Other options for decreasing urine output include a low-salt diet in combination with low-dose thiazide diuretic therapy. In some patients with partial CDI, drugs that either stimulate AVP secretion or enhance its action on the kidney have been useful. These include chlorpropamide, clofibrate, carbamazepine, and nonsteroidal antiinflammatory drugs (NSAIDs). The concentrating defect in NDI may be reversible by treating the underlying disorder or eliminating the offending drug. Symptomatic polyuria caused by NDI can be treated with a low-Na⁺ diet and thiazide diuretics, as described above. This induces mild volume depletion, which leads to enhanced proximal reabsorption of salt and water and decreased delivery to the site of action of AVP, the collecting duct. By impairing renal prostaglandin synthesis,

NSAIDs potentiate AVP action and thereby increase urine osmolality and decrease urine volume. Amiloride may be useful in patients with NDI who need to take lithium. The nephrotoxicity of lithium requires the drug to be taken up into collecting duct cells via the amiloride-sensitive Na⁺ channel.

POTASSIUM

Potassium Balance

Potassium is the major intracellular cation. The normal plasma K⁺ concentration is 3.5–5.0 mmol/L; the concentration inside cells is about 150 mmol/L. Therefore, the amount of K⁺ in the ECF (30–70 mmol) constitutes <2% of the total body K⁺ content (2500–4500 mmol). The ratio of ICF to ECF K⁺ concentration (normally 38:1) is the principal result of the resting membrane potential and is crucial for normal neuromuscular function. The basolateral Na⁺, K⁺-ATPase pump actively transports K⁺ in and Na⁺ out of the cell in a 2:3 ratio, and the passive outward diffusion of K⁺ is quantitatively the most important factor that generates the resting membrane potential. The activity of the electrogenic Na⁺, K⁺-ATPase pump may be stimulated as a result of an increased intracellular Na⁺ concentration and inhibited in the setting of digoxin toxicity or chronic illness such as heart failure or renal failure.

The K⁺ intake of individuals on an average Western diet is 40–120 mmol/d, or approximately 1 mmol/kg per day, 90% of which is absorbed by the gastrointestinal tract. Maintenance of the steady state necessitates matching K⁺ ingestion with excretion. Initially, extrarenal adaptive mechanisms, followed later by urinary excretion, prevent a doubling of the plasma K⁺ concentration that would occur if the dietary K⁺ load remained in the ECF compartment. Immediately after a meal, most of the absorbed K⁺ enters cells as a result of the initial elevation in the plasma K⁺ concentration and facilitated by insulin release and basal catecholamine levels. Eventually, however, the excess K⁺ is excreted in the urine (see below). The regulation of gastrointestinal K⁺ handling is not well understood. The amount of K⁺ lost in the stool can increase from 10 to 50 or 60% (of dietary intake) in people with chronic renal insufficiency. In addition, colonic secretion of K⁺ is stimulated in patients with large volumes of diarrhea, resulting in potentially severe K⁺ depletion.

Potassium Excretion

Renal excretion is the major route of elimination of dietary and other sources of excess K⁺. The filtered load of K⁺ (GFR × plasma K⁺ concentration = 180 L/d × 4 mmol/L = 720 mmol/d) is 10- to 20-fold greater than the ECF K⁺ content. About 90% of filtered K⁺ is reabsorbed

by the proximal convoluted tubule and loop of Henle. Proximally, K^+ is reabsorbed passively with Na^+ and water; the luminal $Na^+-K^+-2Cl^-$ co-transporter mediates K^+ uptake in the TALH. Therefore, K^+ delivery to the distal nephron [distal convoluted tubule and cortical collecting duct (CCD)] approximates dietary intake. Net distal K^+ secretion or reabsorption occurs in the setting of K^+ excess or depletion, respectively. The cell responsible for K^+ secretion in the late distal convoluted tubule (or connecting tubule) and CCD is the principal cell. Virtually all regulation of renal K^+ excretion and total body K^+ balance occurs in the distal nephron. Potassium secretion is regulated by two physiologic stimuli—aldosterone and hyperkalemia. Aldosterone is secreted by the zona glomerulosa cells of the adrenal cortex in response to high renin and angiotensin II or hyperkalemia. The plasma K^+ concentration, independent of aldosterone, can directly affect K^+ secretion. In addition to the K^+ concentration in the lumen of the CCD, renal K^+ loss depends on the urine flow rate, a function of daily solute excretion (see above). Because excretion is equal to the product of concentration and volume, increased distal flow rate can significantly enhance urinary K^+ output. Finally, in severe K^+ depletion, secretion of K^+ is reduced and reabsorption in the cortical and medullary collecting ducts is upregulated.

HYPOKALEMIA

Etiology

(Table 39-3) Hypokalemia, defined as a plasma K^+ concentration <3.5 mmol/L, may result from one (or more) of the following: decreased net intake, shift into cells, or increased net loss. Diminished intake is seldom the sole cause of K^+ depletion because urinary excretion can be effectively decreased to <15 mmol/d as a result of net K^+ reabsorption in the distal nephron. With the exception of the urban poor and certain cultural groups, the amount of K^+ in the diet almost always exceeds that excreted in the urine. However, dietary K^+ restriction may exacerbate hypokalemia secondary to increased gastrointestinal or renal loss. An unusual cause of decreased K^+ intake is ingestion of clay (geophagia), which binds dietary K^+ and iron. This custom was previously common among African Americans in the American South.

Redistribution into Cells

Movement of K^+ into cells may transiently decrease the plasma K^+ concentration without altering total body K^+ content. For any given cause, the magnitude of the change is relatively small, often <1 mmol/L. However, a combination of factors may lead to a significant decrease in the plasma K^+ concentration and may amplify the hypokalemia caused by K^+ wasting. Metabolic alkalosis is often associated with hypokalemia. This occurs as a result of K^+ redistribution as well as excessive renal K^+ loss. Treatment of patients with diabetic ketoacidosis

TABLE 39-3

CAUSES OF HYPOKALEMIA

- I. Decreased intake
 - A. Starvation
 - B. Clay ingestion
- II. Redistribution into cells
 - A. Acid–base
 1. Metabolic alkalosis
 - B. Hormonal
 1. Insulin
 2. β_2 -Adrenergic agonists (endogenous or exogenous)
 3. α -Adrenergic antagonists
 - C. Anabolic state
 1. Vitamin B_{12} or folic acid (red blood cell production)
 2. Granulocyte-macrophage colony stimulating factor (white blood cell production)
 3. Total parenteral nutrition
 - D. Other
 1. Pseudohypokalemia
 2. Hypothermia
 3. Hypokalemic periodic paralysis
 4. Barium toxicity
- III. Increased loss
 - A. Nonrenal
 1. Gastrointestinal loss (diarrhea)
 2. Integumentary loss (sweat)
 - B. Renal
 1. Increased distal flow: diuretics, osmotic diuresis, salt-wasting nephropathies
 2. Increased secretion of potassium
 - a. Mineralocorticoid excess: primary hyperaldosteronism, secondary hyperaldosteronism (malignant hypertension, renin-secreting tumors, renal artery stenosis, hypovolemia), apparent mineralocorticoid excess (licorice, chewing tobacco, carbenoxolone), congenital adrenal hyperplasia, Cushing's syndrome, Bartter's syndrome
 - b. Distal delivery of non-reabsorbed anions: vomiting, nasogastric suction, proximal (type 2) renal tubular acidosis, diabetic ketoacidosis, glue-sniffing (toluene abuse), penicillin derivatives
 - c. Other: amphotericin B, Liddle's syndrome, hypomagnesemia

with insulin may lead to hypokalemia because of stimulation of the Na^+-H^+ antiporter and (secondarily) the Na^+ , K^+ -ATPase pump. Furthermore, uncontrolled hyperglycemia often leads to K^+ depletion from an osmotic diuresis (see below). Stress-induced catecholamine release and administration of β_2 -adrenergic agonists directly induce cellular uptake of K^+ and promote insulin secretion by pancreatic islet β cells. *Hypokalemic periodic paralysis* is a rare condition characterized by recurrent episodic weakness or paralysis. Because K^+ is the major ICF cation, anabolic states can potentially result in hypokalemia caused by a K^+ shift into cells. This may occur after rapid cell growth seen in patients with pernicious anemia

404 treated with vitamin B₁₂ or with neutropenia after treatment with granulocyte-macrophage colony stimulating factor. Massive transfusion with thawed washed red blood cells (RBCs) could cause hypokalemia because frozen RBCs lose up to half of their K⁺ during storage.

Nonrenal Loss of Potassium

Excessive sweating may result in K⁺ depletion from increased integumentary and renal K⁺ loss. Hyperaldosteronism secondary to ECF volume contraction enhances K⁺ excretion in the urine. Normally, K⁺ lost in the stool amounts to 5–10 mmol/d in a volume of 100–200 mL. Hypokalemia subsequent to increased gastrointestinal loss can occur in patients with profuse diarrhea (usually secretory), villous adenomas, VIPomas, or laxative abuse. However, the loss of gastric secretions does not account for the moderate to severe K⁺ depletion often associated with vomiting or nasogastric suction. Because the K⁺ concentration of gastric fluid is 5–10 mmol/L, it would take 30–80 L of vomitus to achieve a K⁺ deficit of 300–400 mmol typically seen in these patients. In fact, the hypokalemia is primarily caused by increased renal K⁺ excretion. Loss of gastric contents results in volume depletion and metabolic alkalosis, both of which promote kaliuresis. Hypovolemia stimulates aldosterone release, which augments K⁺ secretion by the principal cells. In addition, the filtered load of HCO₃⁻ exceeds the reabsorptive capacity of the proximal convoluted tubule, thereby increasing distal delivery of NaHCO₃, which enhances the electrochemical gradient favoring K⁺ loss in the urine.

Renal Loss of Potassium

In general, most cases of chronic hypokalemia are due to renal K⁺ wasting. This may be caused by factors that increase the K⁺ concentration in the lumen of the CCD or augment distal flow rate. Mineralocorticoid excess commonly results in hypokalemia. *Primary hyperaldosteronism* is caused by dysregulated aldosterone secretion by an adrenal adenoma (Conn's syndrome) or carcinoma or by adrenocortical hyperplasia. In a rare subset of patients, the disorder is familial (autosomal dominant), and aldosterone levels can be suppressed by administering low doses of exogenous glucocorticoid. The molecular defect responsible for *glucocorticoid-remediable hyperaldosteronism* is a rearranged gene (caused by a chromosomal crossover), containing the 5'-regulatory region of the 11β-hydroxylase gene and the coding sequence of the aldosterone synthase gene. Consequently, mineralocorticoid is synthesized in the zona fasciculata and regulated by corticotropin. A number of conditions associated with hyperreninemia result in secondary hyperaldosteronism and renal K⁺ wasting. High renin levels are commonly seen in both renovascular and malignant hypertension. Renin-secreting tumors of the

juxtaglomerular apparatus are a rare cause of hypokalemia. Other tumors that have been reported to produce renin include renal cell carcinoma, ovarian carcinoma, and Wilms' tumor. Hyperreninemia may also occur secondary to decreased effective circulating arterial volume.

In the absence of elevated renin or aldosterone levels, enhanced distal nephron secretion of K⁺ may result from increased production of non-aldosterone mineralocorticoids in *congenital adrenal hyperplasia*. Glucocorticoid-stimulated kaliuresis does not normally occur because of the conversion of cortisol to cortisone by 11β-hydroxysteroid dehydrogenase (11β-HSDH). Therefore, 11β-HSDH deficiency or suppression allows cortisol to bind to the aldosterone receptor and leads to the *syndrome of apparent mineralocorticoid excess*. Drugs that inhibit the activity of 11β-HSDH include glycyrrhetic acid, which is present in licorice, chewing tobacco, and carbenoxolone. The presentation of Cushing's syndrome may include hypokalemia if the capacity of 11β-HSDH to inactivate cortisol is overwhelmed by persistently elevated glucocorticoid levels.

Liddle's syndrome is a rare familial (autosomal dominant) disease characterized by hypertension, hypokalemic metabolic alkalosis, renal K⁺ wasting, and suppressed renin and aldosterone secretion. Increased distal delivery of Na⁺ with a nonreabsorbable anion (not Cl⁻) enhances K⁺ secretion. Classically, this is seen with *proximal (type 2) renal tubular acidosis* (RTA) and vomiting, associated with bicarbonaturia. Diabetic ketoacidosis and toluene abuse (glue sniffing) can lead to increased delivery of β-hydroxybutyrate and hippurate, respectively, to the CCD and to renal K⁺ loss. High doses of penicillin derivatives administered to volume-depleted patients may likewise promote renal K⁺ secretion as well as an osmotic diuresis. *Classic distal (type 1) RTA* is associated with hypokalemia caused by increased renal K⁺ loss, the mechanism of which is uncertain. Amphotericin B causes hypokalemia because of increased distal nephron permeability to Na⁺ and K⁺ and to renal K⁺ wasting.

Bartter's syndrome is a disorder characterized by hypokalemia, metabolic alkalosis, hyperreninemic hyperaldosteronism secondary to ECF volume contraction, and juxtaglomerular apparatus hyperplasia. Finally, diuretic use and abuse are common causes of K⁺ depletion. Carbonic anhydrase inhibitors, loop diuretics, and thiazides are all kaliuretic. The degree of hypokalemia tends to be greater with long-acting agents and is dose dependent. Increased renal K⁺ excretion is primarily attributable to increased distal solute delivery and secondary hyperaldosteronism (caused by volume depletion).

Clinical Features

The clinical manifestations of K⁺ depletion vary greatly between individual patients, and their severity depends on the degree of hypokalemia. Symptoms seldom occur

unless the plasma K^+ concentration is <3 mmol/L. Fatigue, myalgia, and muscular weakness of the lower extremities are common complaints and are caused by a lower (more negative) resting membrane potential. More severe hypokalemia may lead to progressive weakness, hypoventilation (caused by respiratory muscle involvement), and eventually complete paralysis. Impaired muscle metabolism and the blunted hyperemic response to exercise associated with profound K^+ depletion increase the risk of rhabdomyolysis. Smooth muscle function may also be affected and manifest as paralytic ileus.

The electrocardiographic changes of hypokalemia are due to delayed ventricular repolarization and do not correlate well with the plasma K^+ concentration. Early changes include flattening or inversion of the T wave, a prominent U wave, ST-segment depression, and a prolonged QU interval. Severe K^+ depletion may result in a prolonged PR interval, decreased voltage and widening of the QRS complex, and an increased risk of ventricular arrhythmias, especially in patients with myocardial ischemia or left ventricular hypertrophy. Hypokalemia may also predispose patients to digitalis toxicity. Hypokalemia is often associated with acid–base disturbances related to the underlying disorder. In addition, K^+ depletion results in intracellular acidification and an increase in net acid excretion or new HCO_3^- production. This is a consequence of enhanced proximal HCO_3^- reabsorption, increased renal ammoniogenesis, and increased distal H^+ secretion. This contributes to the generation of metabolic alkalosis frequently present in hypokalemic patients. NDI (see earlier) is not uncommonly seen in K^+ depletion and is manifest as polydipsia and polyuria. Glucose intolerance may also occur with hypokalemia and has been attributed to either impaired insulin secretion or peripheral insulin resistance.

Diagnosis

(Fig. 39-3) In most cases, the cause of K^+ depletion can be determined by a careful history. Diuretic and laxative abuse as well as surreptitious vomiting may be difficult to identify but should be excluded. Rarely, patients with marked leukocytosis (e.g., acute myeloid leukemia) and normokalemia may have a low measured plasma K^+ concentration because of white blood cell uptake of K^+ at room temperature. This *pseudohypokalemia* can be avoided by storing the blood sample on ice or rapidly separating the plasma (or serum) from the cells.

After eliminating decreased intake and intracellular shift as potential causes of hypokalemia, examination of the renal response can help to clarify the source of K^+ loss. The appropriate response to K^+ depletion is to excrete <15 mmol/d of K^+ in the urine because of increased reabsorption and decreased distal secretion. Hypokalemia with minimal renal K^+ excretion suggests

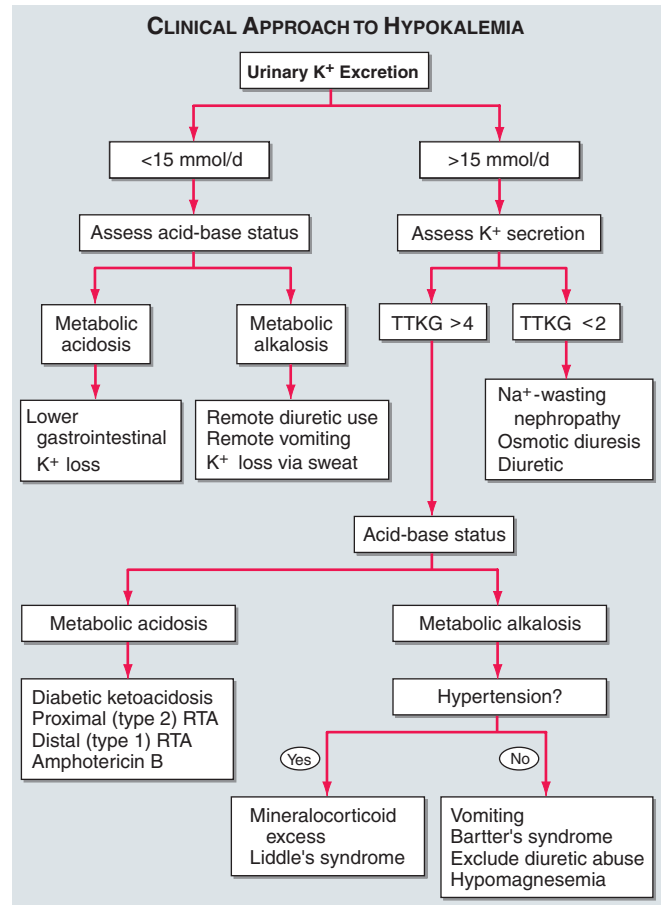


FIGURE 39-3

Algorithm depicting the clinical approach to hypokalemia. RTA, renal tubular acidosis; TTKG, transtubular K^+ concentration gradient.

that K^+ was lost via the skin or gastrointestinal tract or that there is a remote history of vomiting or diuretic use. As described above, renal K^+ wasting may be caused by factors that either increase the K^+ concentration in the CCD or increase the distal flow rate (or both). The ECF volume status, blood pressure, and associated acid–base disorder may help to differentiate the causes of excessive renal K^+ loss. A rapid and simple test designed to evaluate the driving force for net K^+ secretion is the *transtubular K^+ concentration gradient* (TTKG). The TTKG is the ratio of the K^+ concentration in the lumen of the CCD ($[K^+]_{CCD}$) to that in peritubular capillaries or plasma ($[K^+]_p$). The validity of this measurement depends on three assumptions: (1) few solutes are reabsorbed in the medullary collecting duct (MCD), (2) K^+ is neither secreted nor reabsorbed in the MCD, and (3) the osmolality of the fluid in the terminal CCD is known. Significant reabsorption or secretion of K^+ in the MCD seldom occurs, except in profound K^+ depletion or excess, respectively. When AVP is acting ($OSM_U \geq OSM_p$), the osmolality in the terminal CCD is the same as that of plasma, and the K^+ concentration in the lumen of the distal nephron can be estimated by

406 dividing the urine K⁺ concentration ([K⁺]_U) by the ratio of the urine to plasma osmolality (OSM_U/OSM_P):

$$[K^+]_{CCD} = [K^+]_U \div (OSM_U/OSM_P)TTKG \\ = [K^+]_{CCD}/[K^+]_P = [K^+]_U \div (OSM_U/OSM_P)/[K^+]_P$$

Hypokalemia with a TTKG greater than 4 suggests renal K⁺ loss caused by increased distal K⁺ secretion. Plasma renin and aldosterone levels are often helpful in differentiating among the various causes of hyperaldosteronism. Bicarbonaturia and the presence of other non-reabsorbed anions also increase the TTKG and lead to renal K⁺ wasting.

Rx Treatment: **HYPOKALEMIA**

The therapeutic goals are to correct the K⁺ deficit and to minimize ongoing losses. With the exception of periodic paralysis, hypokalemia resulting from transcellular shifts rarely requires IV K⁺ supplementation, which can lead to rebound hyperkalemia. It is generally safer to correct hypokalemia via the oral route. The degree of K⁺ depletion does not correlate well with the plasma K⁺ concentration. A decrement of 1 mmol/L in the plasma K⁺ concentration (from 4.0 to 3.0 mmol/L) may represent a total body K⁺ deficit of 200–400 mmol, and patients with plasma levels under 3.0 mmol/L often require in excess of 600 mmol of K⁺ to correct the deficit. Furthermore, factors promoting K⁺ shift out of cells (e.g., insulin deficiency in diabetic ketoacidosis) may result in underestimation of the K⁺ deficit. Therefore, the plasma K⁺ concentration should be monitored frequently when assessing the response to treatment. Potassium chloride is usually the preparation of choice and promotes more rapid correction of hypokalemia and metabolic alkalosis. Potassium bicarbonate and citrate (metabolized to HCO₃⁻) tend to alkalinize the patient and would be more appropriate for hypokalemia associated with chronic diarrhea or RTA.

Patients with severe hypokalemia or those unable to take anything by mouth require IV replacement therapy with KCl. The maximum concentration of administered K⁺ should be no more than 40 mmol/L via a peripheral vein or 60 mmol/L via a central vein. The rate of infusion should not exceed 20 mmol/h unless paralysis or malignant ventricular arrhythmias are present. Ideally, KCl should be mixed in normal saline because dextrose solutions may initially exacerbate hypokalemia because of insulin-mediated movement of K⁺ into cells. Rapid IV administration of K⁺ should be used judiciously and requires close observation of the clinical manifestations of hypokalemia (electrocardiogram and neuromuscular examination).

HYPERKALEMIA

Etiology

Hyperkalemia, defined as a plasma K⁺ concentration >5.0 mmol/L, occurs as a result of either K⁺ release from cells or decreased renal loss. Increased K⁺ intake is rarely the sole cause of hyperkalemia because the phenomenon of *potassium adaptation* ensures rapid K⁺ excretion in response to increases in dietary consumption. Iatrogenic hyperkalemia may result from overzealous parenteral K⁺ replacement or in patients with renal insufficiency. *Pseudohyperkalemia* represents an artificially elevated plasma K⁺ concentration caused by K⁺ movement out of cells immediately before or after venipuncture. Contributing factors include prolonged use of a tourniquet with or without repeated fist clenching, hemolysis, and marked leukocytosis or thrombocytosis. The latter two result in an elevated serum K⁺ concentration because of release of intracellular K⁺ after clot formation. Pseudohyperkalemia should be suspected in an otherwise asymptomatic patient with no obvious underlying cause. If proper venipuncture technique is used and a plasma (not serum) K⁺ concentration is measured, it should be normal. Intravascular hemolysis, tumor lysis syndrome, and rhabdomyolysis all lead to K⁺ release from cells as a result of tissue breakdown.

Metabolic acidoses, with the exception of those caused by the accumulation of organic anions, can be associated with mild hyperkalemia resulting from intracellular buffering of H⁺ (see earlier). Insulin deficiency and hypertonicity (e.g., hyperglycemia) promote K⁺ shift from the ICF to the ECF. The severity of exercise-induced hyperkalemia is related to the degree of exertion. It is caused by release of K⁺ from muscles and is usually rapidly reversible, often associated with rebound hypokalemia. Treatment with β-blockers rarely causes hyperkalemia but may contribute to the elevation in plasma K⁺ concentration seen with other conditions. *Hyperkalemic periodic paralysis* is a rare autosomal dominant disorder characterized by episodic weakness or paralysis, precipitated by stimuli that normally lead to mild hyperkalemia (e.g., exercise). The genetic defect appears to be a single amino acid substitution caused by a mutation in the gene for the skeletal muscle Na⁺ channel. Hyperkalemia may occur with severe digitalis toxicity because of inhibition of the Na⁺, K⁺-ATPase pump. Depolarizing muscle relaxants such as succinylcholine can increase the plasma K⁺ concentration, especially in patients with massive trauma, burns, or neuromuscular disease.

Chronic hyperkalemia is virtually always associated with decreased renal K⁺ excretion caused by either impaired secretion or diminished distal solute delivery (Table 39-4). The latter is seldom the only cause of impaired K⁺ excretion but may significantly contribute to hyperkalemia in protein-malnourished (low urea

TABLE 39-4

CAUSES OF HYPERKALEMIA

- I. Renal failure
- II. Decreased distal flow (i.e., decreased effective circulating arterial volume)
- III. Decreased K⁺ secretion
 - A. Impaired Na⁺ reabsorption
 1. Primary hypoaldosteronism: adrenal insufficiency, adrenal enzyme deficiency (21-hydroxylase, 3β-hydroxysteroid dehydrogenase, corticosterone methyl oxidase)
 2. Secondary hypoaldosteronism: hyporeninemia, drugs (ACE inhibitors, NSAIDs, heparin)
 3. Resistance to aldosterone: pseudohypoaldosteronism, tubulointerstitial disease, drugs (K⁺-sparing diuretics, trimethoprim, pentamidine)
 - B. Enhanced Cl⁻ reabsorption (chloride shunt)
 1. Gordon's syndrome
 2. Cyclosporine

Note: ACE, angiotensin-converting enzyme; NSAID, nonsteroidal antiinflammatory drug.

excretion) and ECF volume—contracted (decreased distal NaCl delivery) patients. Decreased K⁺ secretion by the principal cells results from either impaired Na⁺ reabsorption or increased Cl⁻ reabsorption.

Hyporeninemic hypoaldosteronism is a syndrome characterized by euolemia or ECF volume expansion and suppressed renin and aldosterone levels. This disorder is commonly seen in patients with mild renal insufficiency, diabetic nephropathy, and chronic tubulointerstitial disease. Patients frequently have an impaired kaliuretic response to exogenous mineralocorticoid administration, suggesting that enhanced distal Cl⁻ reabsorption (electroneutral Na⁺ reabsorption) may account for many of the findings of hyporeninemic hypoaldosteronism. NSAIDs inhibit renin secretion and the synthesis of vasodilatory renal prostaglandins. The resultant decrease in GFR and K⁺ secretion is often manifest as hyperkalemia. As a rule, the degree of hyperkalemia caused by hypoaldosteronism is mild in the absence of increased K⁺ intake or renal dysfunction.

Angiotensin-converting enzyme (ACE) inhibitors block the conversion of angiotensin I to angiotensin II. Angiotensin receptor antagonists directly inhibit the actions of angiotensin II on AT1 angiotensin II receptors. The actions of both of these classes of drugs result in impaired aldosterone release. Patients at increased risk of ACE inhibitor or angiotensin receptor antagonist-induced hyperkalemia include those with diabetes mellitus, renal insufficiency, decreased effective circulating arterial volume, bilateral renal artery stenosis, or concurrent use of K⁺-sparing diuretics or NSAIDs.

Decreased aldosterone synthesis may be caused by *primary adrenal insufficiency* (Addison's disease) or congenital adrenal enzyme deficiency. Heparin (including

low-molecular-weight heparin) inhibits production of aldosterone by the cells of the zona glomerulosa and can lead to severe hyperkalemia in a subset of patients with underlying renal disease or diabetes mellitus or those receiving K⁺-sparing diuretics, ACE inhibitors, or NSAIDs. *Pseudohypoaldosteronism* is a rare familial disorder characterized by hyperkalemia, metabolic acidosis, renal Na⁺ wasting, hypotension, high renin and aldosterone levels, and end-organ resistance to aldosterone. The gene encoding the mineralocorticoid receptor is normal in these patients, and the electrolyte abnormalities can be reversed with suprapharmacologic doses of an exogenous mineralocorticoid (e.g., 9α-fludrocortisone) or an inhibitor of 11β-HSDH (e.g., carbenoxolone). The kaliuretic response to aldosterone is impaired by K⁺-sparing diuretics. Whereas spironolactone is a competitive mineralocorticoid antagonist, amiloride and triamterene block the apical Na⁺ channel of the principal cell. Two other drugs that impair K⁺ secretion by blocking distal nephron Na⁺ reabsorption are trimethoprim and pentamidine. These antimicrobial agents may contribute to the hyperkalemia often seen in patients infected with HIV who are being treated for *Pneumocystis carinii* pneumonia.

Hyperkalemia frequently complicates acute oliguric renal failure because of increased K⁺ release from cells (acidosis, catabolism) and decreased excretion. Increased distal flow rate and K⁺ secretion per nephron compensate for decreased renal mass in chronic renal insufficiency. However, these adaptive mechanisms eventually fail to maintain the K⁺ balance when the GFR decreases below 10–15 mL/min or oliguria ensues. Otherwise asymptomatic urinary tract obstruction is an often overlooked cause of hyperkalemia. Other nephropathies associated with impaired K⁺ excretion include drug-induced interstitial nephritis, lupus nephritis, sickle cell disease, and diabetic nephropathy.

Gordon's syndrome is a rare condition characterized by hyperkalemia, metabolic acidosis, and a normal GFR. These patients are usually volume expanded with suppressed renin and aldosterone levels as well as refractory to the kaliuretic effect of exogenous mineralocorticoids. It has been suggested that these findings could all be accounted for by increased distal Cl⁻ reabsorption (electroneutral Na⁺ reabsorption), also referred to as a *Cl⁻ shunt*. A similar mechanism may be partially responsible for the hyperkalemia associated with cyclosporine nephrotoxicity. *Hyperkalemic distal (type 4) RTA* may be caused by either hypoaldosteronism or a Cl⁻ shunt (aldosterone-resistant).

Clinical Features

Because the resting membrane potential is related to the ratio of the ICF to ECF K⁺ concentration, hyperkalemia partially depolarizes the cell membrane. Prolonged

408 depolarization impairs membrane excitability and is manifest as weakness, which may progress to flaccid paralysis and hypoventilation if the respiratory muscles are involved. Hyperkalemia also inhibits renal ammonia-gene-sis and reabsorption of NH_4^+ in the TALH. Thus, net acid excretion is impaired and results in metabolic acidosis, which may further exacerbate the hyperkalemia because of K^+ movement out of cells.

The most serious effect of hyperkalemia is cardiac toxicity, which does not correlate well with the plasma K^+ concentration. The earliest electrocardiographic changes include increased T-wave amplitude, or peaked T waves. More severe degrees of hyperkalemia result in a prolonged PR interval and QRS duration, atrioventricular conduction delay, and loss of P waves. Progressive widening of the QRS complex and merging with the T wave produces a sine wave pattern. The terminal event is usually ventricular fibrillation or asystole.

Diagnosis

(Fig. 39-4) With rare exceptions, chronic hyperkalemia is always because of impaired K^+ excretion. If the cause is not readily apparent and the patient is asymptomatic,

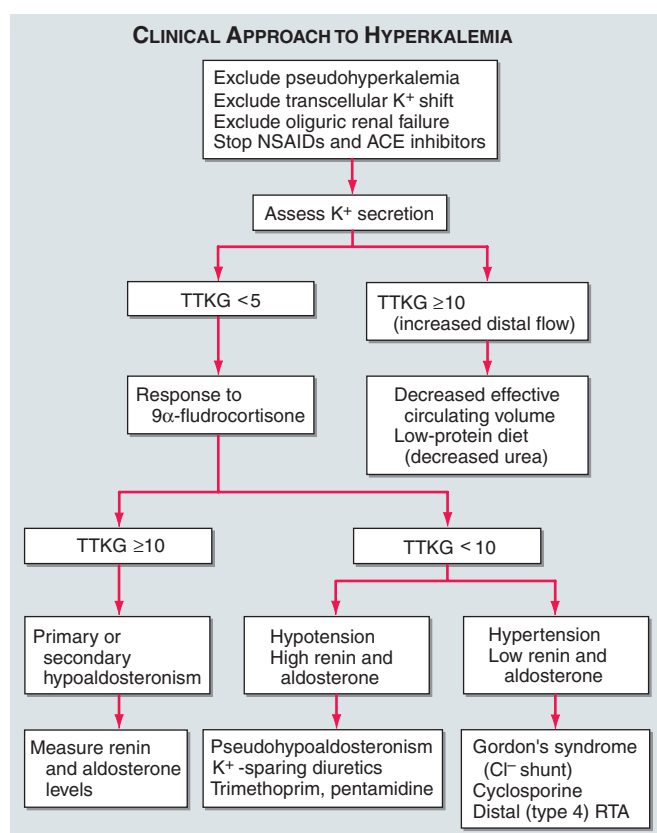


FIGURE 39-4 Algorithm depicting the clinical approach to hyperkalemia. ACE, angiotensin-converting enzyme; NSAID, nonsteroidal anti-inflammatory drug; RTA, renal tubular acidosis; TTKG, transtubular K^+ concentration gradient.

pseudohyperkalemia should be excluded, as described above. Oliguric acute renal failure and severe chronic renal insufficiency should also be ruled out. The history should focus on medications that impair K^+ handling and potential sources of K^+ intake. Evaluation of the ECF compartment, effective circulating volume, and urine output are essential components of the physical examination. The severity of hyperkalemia is determined by the symptoms, plasma K^+ concentration, and electrocardiographic abnormalities.

The appropriate renal response to hyperkalemia is to excrete at least 200 mmol of K^+ daily. In most cases, diminished renal K^+ loss is caused by impaired K^+ secretion, which can be assessed by measuring the transtubular K^+ concentration gradient (TTKG). A TTKG <10 implies a decreased driving force for K^+ secretion caused by either hypoaldosteronism or resistance to the renal effects of mineralocorticoid. This can be determined by evaluating the kaliuretic response to administration of mineralocorticoid (e.g., 9α -fludrocortisone). Primary adrenal insufficiency can be differentiated from hyporeninemic hypoaldosteronism by examining the renin-aldosterone axis. Renin and aldosterone levels should be measured in the supine and upright positions after 3 days of Na^+ restriction (Na^+ intake <10 mmol/d) in combination with a loop diuretic to induce mild volume contraction. Aldosterone-resistant hyperkalemia can result from the various causes of impaired distal Na^+ reabsorption or from a Cl^- shunt. The former leads to salt wasting, ECF volume contraction, and high renin and aldosterone levels. In contrast, enhanced distal Cl^- reabsorption is associated with volume expansion and suppressed renin and aldosterone secretion. As mentioned above, hypoaldosteronism seldom causes severe hyperkalemia in the absence of increased dietary K^+ intake, renal insufficiency, transcellular K^+ shifts, or antidiuretic drugs.

Rx Treatment: HYPERKALEMIA

The approach to therapy depends on the degree of hyperkalemia as determined by the plasma K^+ concentration, associated muscular weakness, and changes on the electrocardiogram. Potentially fatal hyperkalemia rarely occurs unless the plasma K^+ concentration exceeds 7.5 mmol/L and is usually associated with profound weakness and absent P waves, QRS widening, or ventricular arrhythmias on the electrocardiogram.

Severe hyperkalemia requires emergent treatment directed at minimizing membrane depolarization, shifting K^+ into cells, and promoting K^+ loss. In addition, exogenous K^+ intake and antidiuretic drugs should be discontinued. Administration of calcium gluconate decreases membrane excitability. The usual dose is 10 mL of a 10% solution infused over 2–3 min. The effect

begins within minutes but is short lived (30–60 min), and the dose can be repeated if no change in the electrocardiogram is seen after 5–10 min. Insulin causes K^+ to shift into cells by mechanisms described previously and temporarily lowers the plasma K^+ concentration. Although glucose alone stimulates insulin release from normal pancreatic β cells, a more rapid response generally occurs when exogenous insulin is administered (with glucose to prevent hypoglycemia). A commonly recommended combination is 10–20 units of regular insulin and 25–50 g of glucose. Obviously, hyperglycemic patients should not be given glucose. If effective, the plasma K^+ concentration will decrease by 0.5–1.5 mmol/L in 15–30 min, and the effect will last for several hours. Alkali therapy with IV $NaHCO_3$ can also shift K^+ into cells. This is safest when administered as an isotonic solution of 3 ampules per liter (134 mmol/L $NaHCO_3$) and ideally should be reserved for patients with severe hyperkalemia associated with metabolic acidosis. Patients with end-stage renal disease seldom respond to this intervention and may not tolerate the Na^+ load and resultant volume expansion. When administered parenterally or in nebulized form, β_2 -adrenergic agonists promote cellular uptake of K^+ (see earlier). The onset of action is 30 min, lowering the plasma K^+ concentration by 0.5 to 1.5 mmol/L, and the effect lasts 2–4 h.

Removal of K^+ can be achieved using diuretics, cation-exchange resin, or dialysis. Loop and thiazide diuretics, often in combination, may enhance K^+ excretion if renal function is adequate. Sodium polystyrene sulfonate is a cation-exchange resin that promotes the exchange of Na^+ for K^+ in the gastrointestinal tract. Each gram binds 1 mmol of K^+ and releases 2–3 mmol of Na^+ . When given by mouth, the usual dose is 25–50 g mixed with 100 mL of 20% sorbitol to prevent constipation. This generally lowers the plasma K^+ concentration by 0.5–1.0 mmol/L within 1–2 h and lasts for 4–6 h. Sodium polystyrene sulfonate can also be administered as a retention enema consisting of 50 g of resin and 50 mL

of 70% sorbitol mixed in 150 mL of tap water. The sorbitol should be omitted from the enema in postoperative patients because of the increased incidence of sorbitol-induced colonic necrosis, especially after renal transplantation. The most rapid and effective way of lowering the plasma K^+ concentration is hemodialysis. This should be reserved for patients with renal failure and those with severe life-threatening hyperkalemia unresponsive to more conservative measures. Peritoneal dialysis also removes K^+ but is only 15–20% as effective as hemodialysis. Finally, the underlying cause of the hyperkalemia should be treated. This may involve dietary modification, correction of metabolic acidosis, cautious volume expansion, and administration of exogenous mineralocorticoid.

FURTHER READINGS

- ADROGUE HJ, MADIAS NE: Hypernatremia. *N Engl J Med* 342:1493, 2000
- : Hyponatremia. *N Engl J Med* 342:1581, 2000
- BERL T, VERBALIS J: Pathophysiology of water metabolism, in *Brenner & Rector's The Kidney*, 7th ed, BM Brenner (ed). Philadelphia, Saunders, 2004
- COHN JN et al: New guidelines for potassium replacement in clinical practice: A contemporary review by the National Council on Potassium in Clinical Practice. *Arch Intern Med* 160:2429, 2000
- GOLDSZMIDT MA, ILIESCU EA: DDAVP to prevent rapid correction in hyponatremia. *Clin Nephrol* 53:226, 2000
- GREENBERG A, VERBALIS JG: Vasopressin receptor antagonists. *Kidney Int* 69:2124, 2006
- GROSS P: Treatment of severe hyponatremia. *Kidney Int* 60:2417, 2001
- HARRIGAN MR: Cerebral salt wasting syndrome. *Crit Care Clin* 17:125, 2001
- MOUNT DB: Disorders of potassium balance, in *Brenner & Rector's The Kidney*, 7th ed, BM Brenner (ed). Philadelphia, Saunders, 2004
- NIELSEN S et al: Aquaporins in the kidney: From molecules to medicine. *Physiol Rev* 82:205, 2002
- WARNOCK DG: Genetic forms of renal potassium and magnesium wasting. *Am J Med* 112:235, 2002



CHAPTER 40

ACIDOSIS AND ALKALOSIS

Thomas D. DuBose, Jr.

■ Normal Acid–Base Homeostasis	410	Differential Diagnosis	418
■ Diagnosis of General Types of Disturbances	410	Metabolic Alkalosis Associated with Extracellular	
Simple Acid–Base Disorders	411	Fluid Volume Contraction, K ⁺ Depletion, and Secondary	
Mixed Acid–Base Disorders	412	Hyperreninemic Hyperaldosteronism	419
■ Metabolic Acidosis	413	Metabolic Alkalosis Associated with Extracellular Fluid Volume	
High-Anion-Gap Acidoses	414	Expansion, Hypertension, and Hyperaldosteronism	420
Hyperchloremic (Nongap) Metabolic Acidoses	417	■ Respiratory Acidosis	421
■ Metabolic Alkalosis	418	■ Respiratory Alkalosis	422
Pathogenesis	418	■ Further Readings	423

NORMAL ACID–BASE HOMEOSTASIS

Systemic arterial pH is maintained between 7.35 and 7.45 by extracellular and intracellular chemical buffering together with respiratory and renal regulatory mechanisms. The control of arterial CO₂ tension (Pa_{CO₂}) by the central nervous system (CNS) and respiratory system and the control of the plasma bicarbonate by the kidneys stabilize the arterial pH by excretion or retention of acid or alkali. The metabolic and respiratory components that regulate systemic pH are described by the Henderson-Hasselbalch equation:

$$\text{pH} = 6.1 + \log \frac{\text{HCO}_3^-}{\text{Pa}_{\text{CO}_2} \times 0.0301}$$

Under most circumstances, CO₂ production and excretion are matched, and the usual steady-state Pa_{CO₂} is maintained at 40 mmHg. Underexcretion of CO₂ produces hypercapnia, and overexcretion causes hypocapnia. Nevertheless, production and excretion are again matched at a new steady-state Pa_{CO₂}. Therefore, the Pa_{CO₂} is regulated primarily by neural respiratory factors (Chap. 22) and is not subject to regulation by the rate of CO₂ production. Hypercapnia is usually the result of hypoventilation rather than of increased CO₂ production. Increases or decreases in Pa_{CO₂} represent derangements of neural respiratory control or are caused by compensatory changes in response to a primary alteration in the plasma [HCO₃⁻].

The kidneys regulate plasma HCO₃⁻ through three main processes: (1) “reabsorption” of filtered HCO₃⁻, (2) formation of titratable acid, and (3) excretion of NH₄⁺ in the urine. The kidney filters ~4000 mmol of HCO₃⁻ per day. To reabsorb the filtered load of HCO₃⁻, the renal tubules must therefore secrete 4000 mmol of hydrogen ions. Between 80 and 90% of HCO₃⁻ is reabsorbed in the proximal tubule. The distal nephron reabsorbs the remainder and secretes protons, as generated from metabolism, to defend systemic pH. Although this quantity of protons, 40–60 mmol/d, is small, it must be secreted to prevent chronic positive H⁺ balance and metabolic acidosis. This quantity of secreted protons is represented in the urine as titratable acid and NH₄⁺. Metabolic acidosis in the face of normal renal function increases NH₄⁺ production and excretion. NH₄⁺ production and excretion are impaired in chronic renal failure, hyperkalemia, and renal tubular acidosis.

In sum, these regulatory responses, including chemical buffering, the regulation of Pa_{CO₂} by the respiratory system, and the regulation of HCO₃⁻ by the kidneys, act in concert to maintain a systemic arterial pH between 7.35 and 7.45.

DIAGNOSIS OF GENERAL TYPES OF DISTURBANCES

The most common clinical disturbances are simple acid–base disorders (i.e., metabolic acidosis or alkalosis

TABLE 40-1

PREDICTION OF COMPENSATORY RESPONSES ON SIMPLE ACID-BASE DISTURBANCES AND PATTERN OF CHANGES

DISORDER	PREDICTION OF COMPENSATION	RANGE OF VALUES		
		pH	HCO ₃ ⁻	Pa _{CO2}
Metabolic acidosis	$Pa_{CO_2} = (1.5 \times HCO_3^-) + 8 \pm 2$ or Pa _{CO₂} will ↓ 1.25 mmHg per mmol/L ↓ in HCO ₃ ⁻ or $Pa_{CO_2} = HCO_3^- + 15$	Low	Low	Low
Metabolic alkalosis	Pa _{CO₂} will ↑ 0.75 mmHg per mmol/L ↑ in HCO ₃ ⁻ or Pa _{CO₂} will ↑ 6 mmHg per 10 mmol/L ↑ in HCO ₃ ⁻ or $Pa_{CO_2} = HCO_3^- + 15$	High	High	High
Respiratory alkalosis		High	Low	Low
Acute	HCO ₃ ⁻ will ↓ 0.2 mmol/L per mmHg ↓ in Pa _{CO₂}			
Chronic	HCO ₃ ⁻ will ↓ 0.4 mmol/L per mmHg ↓ in Pa _{CO₂}			
Respiratory acidosis		Low	High	High
Acute	HCO ₃ ⁻ will ↑ 0.1 mmol/L per mmHg ↑ in Pa _{CO₂}			
Chronic	HCO ₃ ⁻ will ↑ 0.4 mmol/L per mmHg ↑ in Pa _{CO₂}			

or respiratory acidosis or alkalosis). Because compensation is not complete, the pH is abnormal in simple disturbances. More complicated clinical situations can give rise to mixed acid–base disturbances.

SIMPLE ACID–BASE DISORDERS

Primary respiratory disturbances (primary changes in Pa_{CO₂}) invoke compensatory metabolic responses (secondary changes in HCO₃⁻), and primary metabolic disturbances elicit predictable compensatory respiratory responses. Physiologic compensation can be predicted from the relationships displayed in Table 40-1. Metabolic acidosis caused by an increase in endogenous acids (e.g., ketoacidosis) lowers extracellular fluid (ECF) HCO₃⁻ and decreases extracellular pH. This stimulates the medullary chemoreceptors to increase ventilation and to return the ratio of HCO₃⁻ to Pa_{CO₂}, and thus pH, toward normal, although not to normal. The degree of

respiratory compensation expected in a simple form of metabolic acidosis can be predicted from the relationship: $Pa_{CO_2} = (1.5 \times HCO_3^-) + 8 \pm 2$, i.e., the Pa_{CO₂} is expected to decrease 1.25 mmHg for each mmol per liter decrease in HCO₃⁻. Thus, a patient with metabolic acidosis and HCO₃⁻ of 12 mmol/L would be expected to have a Pa_{CO₂} between 24 and 28 mmHg. Values for Pa_{CO₂} <24 or >28 mmHg define a mixed disturbance (metabolic acidosis and respiratory alkalosis or metabolic alkalosis and respiratory acidosis, respectively). Another way to judge the appropriateness of the response in HCO₃⁻ or Pa_{CO₂} is to use an acid–base nomogram (Fig. 40-1). Although the shaded areas of the nomogram show the 95% confidence limits for normal compensation in simple disturbances, finding acid–base values within the shaded area does not necessarily rule out a mixed disturbance. Imposition of one disorder over another may result in values lying within the area of a third. Thus, the nomogram, although convenient, is not a substitute for the equations in Table 40-1.

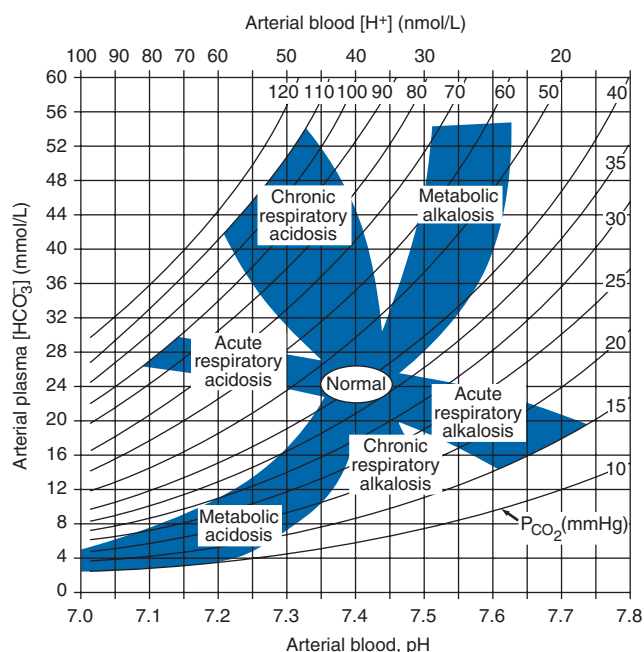


FIGURE 40-1

Acid-base nomogram. Shown are the 90% confidence limits (range of values) of the normal respiratory and metabolic compensations for primary acid-base disturbances. (From DuBose, used with permission.)

MIXED ACID-BASE DISORDERS

Mixed acid-base disorders—defined as independently coexisting disorders, not merely compensatory responses—are often seen in patients in critical care units and can lead to dangerous extremes of pH (Table 40-2). A patient with diabetic ketoacidosis (DKA; metabolic acidosis) may develop an independent respiratory problem leading to respiratory acidosis or alkalosis. Patients with underlying pulmonary disease may not respond to metabolic acidosis with an appropriate ventilatory response because of insufficient respiratory reserve. Such imposition of respiratory acidosis on metabolic acidosis can lead to severe acidemia and a poor outcome. When metabolic acidosis and metabolic alkalosis coexist in the same patient, the pH may be normal or near normal. When the pH is normal, an elevated anion gap (AG; see below) denotes the presence of a metabolic acidosis. A discrepancy in the ΔAG (prevailing minus normal AG) and the ΔHCO_3^- (normal minus prevailing HCO_3^-) indicates the presence of a mixed high-gap acidosis—metabolic alkalosis (see example below). A diabetic patient with ketoacidosis may have renal dysfunction resulting in simultaneous metabolic acidosis. Patients who have ingested an overdose of drug combinations such as sedatives and salicylates may have mixed disturbances as a result of the acid-base response to the individual drugs (metabolic acidosis mixed with respiratory acidosis or respiratory alkalosis, respectively). Even more complex are triple acid-base disturbances. For example,

TABLE 40-2

EXAMPLES OF MIXED ACID-BASE DISORDERS

Mixed Metabolic and Respiratory

Metabolic acidosis—respiratory alkalosis

Key: High- or normal-AG metabolic acidosis; prevailing Pa_{CO_2} below predicted value (Table 40-1)
Example: Na^+ , 140; K^+ , 4.0; Cl^- , 106; HCO_3^- , 14; AG, 20; Pa_{CO_2} , 24; pH, 7.39 (lactic acidosis, sepsis in the ICU)

Metabolic acidosis—respiratory acidosis

Key: High- or normal-AG metabolic acidosis; prevailing Pa_{CO_2} above predicted value (Table 40-1)
Example: Na^+ , 140; K^+ , 4.0; Cl^- , 102; HCO_3^- , 18; AG, 20; Pa_{CO_2} , 38; pH, 7.30 (severe pneumonia, pulmonary edema)

Metabolic alkalosis—respiratory alkalosis

Key: Pa_{CO_2} does not increase as predicted; pH higher than expected
Example: Na^+ , 140; K^+ , 4.0; Cl^- , 91; HCO_3^- , 33; AG, 16; Pa_{CO_2} , 38; pH, 7.55 (liver disease and diuretics)

Metabolic alkalosis—respiratory acidosis

Key: Pa_{CO_2} higher than predicted; pH normal
Example: Na^+ , 140; K^+ , 3.5; Cl^- , 88; HCO_3^- , 42; AG, 10; Pa_{CO_2} , 67; pH, 7.42 (COPD on diuretics)

Mixed Metabolic Disorders

Metabolic acidosis—metabolic alkalosis

Key: Only detectable with high-AG acidosis;
 $\Delta\text{AG} \gg \Delta\text{HCO}_3^-$
Example: Na^+ , 140; K^+ , 3.0; Cl^- , 95; HCO_3^- , 25; AG, 20; Pa_{CO_2} , 40; pH, 7.42 (uremia with vomiting)

Metabolic acidosis—metabolic acidosis

Key: Mixed high-AG–normal-AG acidosis; ΔHCO_3^- accounted for by combined change in ΔAG and ΔCl^-
Example: Na^+ , 135; K^+ , 3.0; Cl^- , 110; HCO_3^- , 10; AG, 15; Pa_{CO_2} , 25; pH, 7.20 (diarrhea and lactic acidosis, toluene toxicity, treatment of diabetic ketoacidosis)

Note: AG, anion gap; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.

patients with metabolic acidosis caused by alcoholic ketoacidosis (AKA) may develop metabolic alkalosis from vomiting and superimposed respiratory alkalosis because of the hyperventilation of hepatic dysfunction or alcohol withdrawal.

Approach to the Patient: ACID-BASE DISORDERS

A stepwise approach to the diagnosis of acid-base disorders follows (Table 40-3). Care should be taken when measuring blood gases to obtain the arterial blood sample without using excessive heparin. Blood for electrolytes and arterial blood gases should be

TABLE 40-3

STEPS IN ACID-BASE DIAGNOSIS

1. Obtain arterial blood gas (ABG) and electrolytes simultaneously.
2. Compare HCO_3^- on ABG and electrolytes to verify accuracy.
3. Calculate anion gap (AG).
4. Know four causes of high-AG acidosis (ketoacidosis, lactic acid acidosis, renal failure, and toxins).
5. Know two causes of hyperchloremic or nongap acidosis (bicarbonate loss from GI tract, renal tubular acidosis).
6. Estimate compensatory response (Table 40-1).
7. Compare ΔAG and ΔHCO_3^- .
8. Compare change in Cl^- with change in Na^+ .

drawn simultaneously before therapy because an increase in HCO_3^- occurs with metabolic alkalosis and respiratory acidosis. Conversely, a decrease in HCO_3^- occurs in metabolic acidosis and respiratory alkalosis. In the determination of arterial blood gases by the clinical laboratory, both pH and Pa_{CO_2} are measured, and the HCO_3^- is calculated from the Henderson-Hasselbalch equation. This calculated value should be compared with the measured HCO_3^- (total CO_2) on the electrolyte panel. These two values should agree within 2 mmol/L. If they do not, the values may not have been drawn simultaneously, a laboratory error may be present, or an error could have been made in calculating the HCO_3^- . After verifying the blood acid-base values, one can then identify the precise acid-base disorder.

CALCULATE THE ANION GAP All evaluations of acid-base disorders should include a simple calculation of the AG; it represents those unmeasured anions in plasma (normally 10–12 mmol/L) and is calculated as follows: $\text{AG} = \text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)$. The unmeasured anions include anionic proteins, phosphate, sulfate, and organic anions. When acid anions, such as acetoacetate and lactate, accumulate in ECF, the AG increases, causing a high-AG acidosis. An increase in the AG is most often caused by an increase in unmeasured anions and less commonly is caused by a decrease in unmeasured cations (calcium, magnesium, potassium). In addition, the AG may increase with an increase in anionic albumin because of either increased albumin concentration or alkalosis, which alters albumin charge. A decrease in the AG can be caused by (1) an increase in unmeasured cations; (2) the addition to the blood of abnormal cations, such as lithium (lithium intoxication) or cationic immunoglobulins (plasma cell dyscrasias); (3) a reduction in the major plasma anion albumin concentration (nephrotic syndrome); (4) a decrease in the effective anionic charge on albumin by acidosis; or (5) hyperviscosity and severe hyperlipi-

demia, which can lead to an underestimation of sodium and chloride concentrations. A decrease in serum albumin by 1 g/dL from the normal value (4.5 g/dL) decreases the AG by 2.5 meq/L. It is important to know the common causes of high-AG acidosis (Table 40-3).

In the face of a normal serum albumin, a high AG is usually caused by non-chloride-containing acids that contain inorganic (phosphate, sulfate), organic (ketoacids, lactate, uremic organic anions), exogenous (salicylate or ingested toxins with organic acid production), or unidentified anions. The high AG is significant even if an additional acid-base disorder is superimposed to modify the HCO_3^- independently. Simultaneous metabolic acidosis of the high-AG variety plus either chronic respiratory acidosis or metabolic alkalosis represents such a situation in which HCO_3^- may be normal or even high (Table 40-2). Compare the change in HCO_3^- (ΔHCO_3^-) and the change in the AG (ΔAG).

Similarly, normal values for HCO_3^- , Pa_{CO_2} , and pH do not ensure the absence of an acid-base disturbance. For instance, an alcoholic who has been vomiting may develop a metabolic alkalosis with a pH of 7.55, Pa_{CO_2} of 48 mmHg, HCO_3^- of 40 mmol/L, Na^+ of 135, Cl^- of 80, and K^+ of 2.8. If such a patient were then to develop a superimposed AKA with a β -hydroxybutyrate concentration of 15 mM, arterial pH would decrease to 7.40, HCO_3^- to 25 mmol/L, and Pa_{CO_2} to 40 mmHg. Although these blood gas levels are normal, the AG is elevated at 30 mmol/L, indicating a mixed metabolic alkalosis and metabolic acidosis. A mixture of high-gap acidosis and metabolic alkalosis is recognized easily by comparing the differences (Δ values) in the normal to prevailing patient values. In this example, the ΔHCO_3^- is 0 (25 – 25 mmol/L) but the ΔAG is 20 (30 – 10 mmol/L). Therefore, 20 mmol/L is unaccounted for in the Δ/Δ value (ΔAG to ΔHCO_3^-).

METABOLIC ACIDOSIS

Metabolic acidosis can occur because of an increase in endogenous acid production (e.g., lactate and ketoacids), loss of bicarbonate (as in diarrhea), or accumulation of endogenous acids (as in renal failure). Metabolic acidosis has profound effects on the respiratory, cardiac, and nervous systems. The decrease in blood pH is accompanied by a characteristic increase in ventilation, especially the tidal volume (Kussmaul respiration). Intrinsic cardiac contractility may be depressed, but inotropic function can be normal because of catecholamine release. Both peripheral arterial vasodilation and central venoconstriction can be present; the decrease in central and pulmonary vascular

CAUSES OF HIGH-ANION-GAP METABOLIC ACIDOSIS

Lactic acidosis	Toxins
Ketoacidosis	Ethylene glycol
Diabetic	Methanol
Alcoholic	Salicylates
Starvation	Propylene glycol
	Pyroglutamic acid
	Renal failure (acute and chronic)

compliance predisposes to pulmonary edema with even minimal volume overload. CNS function is depressed, with headache, lethargy, stupor, and, in some cases, even coma. Glucose intolerance may also occur.

The two major categories of clinical metabolic acidosis are high-AG and normal-AG, or hyperchloremic acidosis (Table 40-3 and Table 40-4).

Rx Treatment: METABOLIC ACIDOSIS

Treatment of metabolic acidosis with alkali should be reserved for severe acidemia except when the patient has no “potential HCO_3^- ” in plasma. Potential HCO_3^- can be estimated from the increment (Δ) in the AG ($\Delta\text{AG} = \text{patient's AG} - 10$). It must be determined if the acid anion in plasma is metabolizable (i.e., β -hydroxybutyrate, acetoacetate, and lactate) or nonmetabolizable (anions that accumulate in chronic renal failure and after toxin ingestion). The latter requires return of renal function to replenish the HCO_3^- deficit, a slow and often unpredictable process. Consequently, patients with a normal AG acidosis (hyperchloremic acidosis), a slightly elevated AG (mixed hyperchloremic and AG acidosis), or an AG attributable to a nonmetabolizable anion in the face of renal failure should receive alkali therapy, either PO (NaHCO_3 or Shohl's solution) or IV (NaHCO_3), in an amount necessary to slowly increase the plasma HCO_3^- into the 20–22 mmol/L range.

Controversy exists, however, regarding the use of alkali in patients with a pure AG acidosis owing to accumulation of a metabolizable organic acid anion (ketoacidosis or lactic acidosis). In general, severe acidosis ($\text{pH} < 7.20$) warrants the IV administration of 50–100 meq of NaHCO_3 over 30–45 min, during the initial 1–2 h of therapy. Provision of such modest quantities of alkali in this situation seems to provide an added measure of safety, but it is essential to monitor plasma electrolytes during the course of therapy because the K^+ may decline as pH increases. The goal is to increase the HCO_3^- to 10 meq/L and the pH to 7.15, not to increase these values to normal.

HIGH-ANION-GAP ACIDOSES**Approach to the Patient: HIGH-ANION-GAP ACIDOSES**

The four principal causes of a high-AG acidosis are lactic acidosis, ketoacidosis, ingested toxins, and acute and chronic renal failure (see Table 40-4). The initial screening to differentiate the high-AG acidoses should include (1) a probe of the history for evidence of drug and toxin ingestion and measurement of arterial blood gas to detect coexistent respiratory alkalosis (salicylates); (2) determination of whether diabetes mellitus is present (DKA); (3) a search for evidence of alcoholism or increased levels of β -hydroxybutyrate (AKA); (4) observation for clinical signs of uremia and determination of the blood urea nitrogen (BUN) and creatinine (uremic acidosis); (5) inspection of the urine for oxalate crystals (ethylene glycol); and (6) recognition of the numerous clinical settings in which lactate levels may be increased (hypotension, shock, cardiac failure, leukemia, cancer, drug or toxin ingestion).

Lactic Acidosis

An increase in plasma L-lactate may be secondary to poor tissue perfusion (type A)—circulatory insufficiency (shock, cardiac failure), severe anemia, mitochondrial enzyme defects, and inhibitors (carbon monoxide, cyanide)—or to aerobic disorders (type B)—malignancies, nucleoside analogue reverse transcriptase inhibitors in HIV, diabetes mellitus, renal or hepatic failure, thiamine deficiency, severe infections (cholera, malaria), seizures, or drugs or toxins (biguanides, ethanol, methanol, propylene glycol, isoniazid, and fructose). Propylene glycol may be used as a vehicle for IV medications, including lorazepam, and toxicity has been reported in several settings. Unrecognized bowel ischemia or infarction in a patient with severe atherosclerosis or cardiac decompensation receiving vasopressors is a common cause of lactic acidosis. Pyroglutamic acidemia has been reported in critically ill patients receiving acetaminophen, which is associated with depletion of glutathione. D-Lactic acid acidosis, which may be associated with jejunoileal bypass, short bowel syndrome, or intestinal obstruction, is caused by formation of D-lactate by gut bacteria.

Approach to the Patient: LACTIC ACID ACIDOSIS

The underlying condition that disrupts lactate metabolism must first be corrected, and tissue perfusion must be restored when inadequate. Vasoconstrictors should be avoided, if possible, because they may worsen tissue perfusion. Alkali therapy is generally advocated for

acute, severe acidemia (pH <7.15) to improve cardiac function and lactate utilization. However, NaHCO₃ therapy may paradoxically depress cardiac performance and exacerbate acidosis by enhancing lactate production (HCO₃⁻ stimulates phosphofructokinase). Although the use of alkali in moderate lactic acidosis is controversial, it is generally agreed that attempts to return the pH or HCO₃⁻ to normal by administration of exogenous NaHCO₃ are deleterious. A reasonable approach is to infuse sufficient NaHCO₃ to increase the arterial pH to no more than 7.2 over 30–40 min.

NaHCO₃ therapy can cause fluid overload and hypertension because the amount required can be massive when accumulation of lactic acid is relentless. Fluid administration is poorly tolerated because of central venoconstriction, especially in patients with oliguria. When the underlying cause of the lactic acidosis can be remedied, blood lactate will be converted to HCO₃⁻ and may result in an overshoot alkalosis.

Ketoacidosis

Diabetic Ketoacidosis

This condition is caused by increased fatty acid metabolism and the accumulation of ketoacids (acetoacetate and β-hydroxybutyrate). DKA usually occurs in patients with insulin-dependent diabetes mellitus in association with cessation of insulin or an intercurrent illness, such as an infection, gastroenteritis, pancreatitis, or myocardial infarction, which increases insulin requirements temporarily and acutely. The accumulation of ketoacids accounts for the increment in the AG and is accompanied most often by hyperglycemia [glucose >17 mmol/L or (>300 mg/dL)]. The relationship between the ΔAG and ΔHCO₃⁻ is ~1:1 in DKA but may decrease in well-hydrated patients with preservation of renal function. Ketoacid excretion in the urine reduces the AG in this situation. It should be noted that because insulin prevents production of ketones, bicarbonate therapy is rarely needed except with extreme acidemia (pH <7.1) and then in only limited amounts. Patients with DKA are typically volume depleted and require fluid resuscitation with isotonic saline. Volume overexpansion is common, however, after IV fluid administration, and contributes to the development of hyperchloremic acidosis during treatment of DKA because volume expansion increases urinary ketoacid anion excretion (loss of potential bicarbonate).

Alcoholic Ketoacidosis

Chronic alcoholics can develop ketoacidosis when alcohol consumption is abruptly curtailed and nutrition is poor. AKA is usually associated with binge drinking, vomiting, abdominal pain, starvation, and volume depletion. The glucose concentration is variable, and acidosis

may be severe because of elevated ketones, predominantly β-hydroxybutyrate. Hypoperfusion may enhance lactic acid production, chronic respiratory alkalosis may accompany liver disease, and metabolic alkalosis can result from vomiting (refer to the relationship between ΔAG and ΔHCO₃⁻). Thus, mixed acid–base disorders are common in patients with AKA. As the circulation is restored by administration of isotonic saline, the preferential accumulation of β-hydroxybutyrate is then shifted to acetoacetate. This explains the common clinical observation of an increasingly positive nitroprusside reaction as the patient improves. The nitroprusside ketone reaction (Acetest) can detect acetoacetic acid but not β-hydroxybutyrate, so the degree of ketosis and ketonuria can not only change with therapy but can also be underestimated initially. Patients with AKA usually present with relatively normal renal function, as opposed to those with DKA, in whom renal function is often compromised because of volume depletion (osmotic diuresis) or diabetic nephropathy. AKA patients with normal renal function may excrete relatively large quantities of ketoacids in the urine, therefore, and may have a relatively normal AG and a discrepancy in the ΔAG/ΔHCO₃⁻ relationship. Typically, insulin levels are low, and concentrations of triglyceride, cortisol, glucagon, and growth hormone are increased.

Rx Treatment: ALCOHOLIC KETOACIDOSIS

ECF deficits almost always accompany AKA and should be repleted by IV administration of saline and glucose (5% dextrose in 0.9% NaCl). Hypophosphatemia, hypokalemia, and hypomagnesemia may coexist and should be corrected. Hypophosphatemia usually emerges 12–24 h after admission; may be exacerbated by glucose infusion; and, if severe, may induce rhabdomyolysis. Upper gastrointestinal hemorrhage, pancreatitis, and pneumonia may accompany this disorder.

Drug- and Toxin-Induced Acidosis

Salicylates

Salicylate intoxication in adults usually causes respiratory alkalosis or a mixture of high-AG metabolic acidosis and respiratory alkalosis. Only a portion of the AG is caused by salicylates. Lactic acid production is also often increased.

Rx Treatment: SALICYLATE-INDUCED ACIDOSIS

Vigorous gastric lavage with isotonic saline (not NaHCO₃) should be initiated immediately followed by administration of activated charcoal per nasogastric tube. In acidotic patients, to facilitate removal of salicylate, IV NaHCO₃ is administered in amounts adequate to alkalinize the

urine and to maintain urine output (urine pH >7.5). Although this form of therapy is straightforward in acidotic patients, a coexisting respiratory alkalosis may make this approach hazardous. Alkalemic patients should not receive NaHCO_3^- . Acetazolamide may be administered in the face of alkalemia, when an alkaline diuresis cannot be achieved, or to ameliorate volume overload associated with NaHCO_3^- administration, but this drug can cause systemic metabolic acidosis if HCO_3^- is not replaced. Hypokalemia should be anticipated with an alkaline diuresis and should be treated promptly and aggressively. Glucose-containing fluids should be administered because of the danger of hypoglycemia. Excessive insensible fluid losses may cause severe volume depletion and hypernatremia. If renal failure prevents rapid clearance of salicylate, hemodialysis can be performed against a bicarbonate dialysate.

Alcohols

Under most physiologic conditions, sodium, urea, and glucose generate the osmotic pressure of blood. Plasma osmolality is calculated according to the following expression: $P_{\text{osm}} = 2\text{Na}^+ + \text{Glu} + \text{BUN}$ (all in mmol/L), or using conventional laboratory values in which glucose and BUN are expressed in milligrams per deciliter: $P_{\text{osm}} = 2\text{Na}^+ + \text{Glu}/18 + \text{BUN}/2.8$. The calculated and determined osmolality should agree within 10–15 mmol/kg H_2O . When the measured osmolality exceeds the calculated osmolality by >15–20 mmol/kg H_2O , one of two circumstances prevails. Either the serum sodium is spuriously low, as with hyperlipidemia or hyperproteinemia (pseudohyponatremia), or osmolytes other than sodium salts, glucose, or urea have accumulated in plasma. Examples include mannitol, radiocontrast media, isopropyl alcohol, ethylene glycol, propylene glycol, ethanol, methanol, and acetone. In this situation, the difference between the calculated osmolality and the measured osmolality (*osmolar gap*) is proportional to the concentration of the unmeasured solute. With an appropriate clinical history and index of suspicion, identification of an osmolar gap is helpful in identifying the presence of poison-associated AG acidosis. Three alcohols may cause fatal intoxications: ethylene glycol, methanol, and isopropyl alcohol. All cause an elevated osmolal gap, but only the first two cause high-AG acidosis.

Ethylene Glycol

Ingestion of ethylene glycol (commonly used in antifreeze) leads to a metabolic acidosis and severe damage to the CNS, heart, lungs, and kidneys. The increased AG and osmolar gap are attributable to ethylene glycol and its metabolites, oxalic acid, glycolic acid, and other organic acids. Lactic acid production increases secondary to inhibition of the tricarboxylic acid cycle and altered intracellular redox state. Diagnosis is facilitated by recognizing oxalate

crystals in the urine, the presence of an osmolar gap in serum, and a high-AG acidosis. If antifreeze containing a fluorescent dye is ingested, a Wood's lamp applied to the urine may be revealing. Treatment should not be delayed while awaiting measurement of ethylene glycol levels in this setting.

Rx Treatment: ETHYLENE GLYCOL-INDUCED ACIDOSIS

Treatment should include prompt institution of a saline or osmotic diuresis, thiamine and pyridoxine supplements, fomepizole or ethanol, and hemodialysis. IV administration of the alcohol dehydrogenase inhibitor fomepizole (4-methylpyrazole; 7 mg/kg as a loading dose) or ethanol IV to achieve a level of 22 mmol/L (100 mg/dL) serves to lessen toxicity because they compete with ethylene glycol for metabolism by alcohol dehydrogenase. Fomepizole, although expensive, offers the advantages of a predictable decline in ethylene glycol levels without excessive obtundation during ethyl alcohol infusion.

Methanol

The ingestion of methanol (wood alcohol) causes metabolic acidosis, and its metabolites formaldehyde and formic acid cause severe optic nerve and CNS damage. Lactic acid, ketoacids, and other unidentified organic acids may contribute to the acidosis. Because of its low molecular weight (32 Da), an osmolar gap is usually present.

Rx Treatment: METHANOL-INDUCED ACIDOSIS

This is similar to that for ethylene glycol intoxication, including general supportive measures, fomepizole or ethanol administration, and hemodialysis.

Isopropyl Alcohol

Ingested isopropanol is absorbed rapidly and may be fatal when as little as 150 mL of rubbing alcohol, solvent, or de-icer is consumed. A plasma level >400 mg/dL is life threatening. Isopropyl alcohol differs from ethylene glycol and methanol in that the parent compound, not the metabolites, causes toxicity, and acidosis is not present because acetone is rapidly excreted.

Rx Treatment: ISOPROPYL ALCOHOL TOXICITY

Isopropanol alcohol toxicity is treated by watchful waiting and supportive therapy; IV fluids, pressors, ventilatory support if needed, and occasionally hemodialysis for prolonged coma or levels >400 mg/dL.

Renal Failure

(See also Chap. 37) The hyperchloremic acidosis of moderate renal insufficiency is eventually converted to the high-AG acidosis of advanced renal failure. Poor filtration and reabsorption of organic anions contribute to the pathogenesis. As renal disease progresses, the number of functioning nephrons eventually becomes insufficient to keep pace with net acid production. Uremic acidosis is characterized, therefore, by a reduced rate of NH_4^+ production and excretion, primarily because of decreased renal mass. HCO_3^- rarely decreases to <15 mmol/L, and the AG is rarely >20 mmol/L. The acid retained in chronic renal disease is buffered by alkaline salts from bone. Despite significant retention of acid (≤ 20 mmol/d), the serum HCO_3^- does not decrease further, indicating participation of buffers outside the extracellular compartment. Chronic metabolic acidosis results in significant loss of bone mass because of reduction in bone calcium carbonate. Chronic acidosis also increases urinary calcium excretion proportional to cumulative acid retention.

Rx Treatment: RENAL FAILURE

Because of the association of renal failure acidosis with muscle catabolism and bone disease, both uremic acidosis and the hyperchloremic acidosis of renal failure require oral alkali replacement to maintain the HCO_3^- between 20 and 24 mmol/L. This can be accomplished with relatively modest amounts of alkali (1.0–1.5 mmol/kg body weight per day). Sodium citrate (Shohl's solution) or NaHCO_3 tablets (650-mg tablets contain 7.8 meq) are equally effective alkalinizing salts. Citrate enhances the absorption of aluminum from the gastrointestinal tract and should never be given together with aluminum-containing antacids because of the risk of aluminum intoxication. When hyperkalemia is present, furosemide (60–80 mg/d) should be added.

HYPERCHLOREMIC (NONGAP) METABOLIC ACIDOSES

Alkali can be lost from the gastrointestinal tract in diarrhea or from the kidneys [renal tubular acidosis (RTA)]. In these disorders (Table 40-5), reciprocal changes in Cl^- and HCO_3^- result in a normal AG. In pure hyperchloremic acidosis, therefore, the increase in Cl^- above the normal value approximates the decrease in HCO_3^- . The absence of such a relationship suggests a mixed disturbance.

TABLE 40-5

CAUSES OF NON-ANION-GAP ACIDOSIS

- I. Gastrointestinal bicarbonate loss
 - A. Diarrhea
 - B. External pancreatic or small bowel drainage
 - C. Ureterosigmoidostomy, jejunal loop, ileal loop
 - D. Drugs
 1. Calcium chloride (acidifying agent)
 2. Magnesium sulfate (diarrhea)
 3. Cholestyramine (bile acid diarrhea)
- II. Renal acidosis
 - A. Hypokalemia
 1. Proximal RTA (type 2)
 2. Distal (classic) RTA (type 1)
 - B. Hyperkalemia
 1. Generalized distal nephron dysfunction (type 4 RTA)
 - a. Mineralocorticoid deficiency
 - b. Mineralocorticoid resistance (autosomal dominant PHA I)
 - c. Voltage defect (autosomal dominant PHA I and PHA II)
 - d. Tubulointerstitial disease
- III. Drug-induced hyperkalemia (with renal insufficiency)
 - A. Potassium-sparing diuretics (amiloride, triamterene, spironolactone)
 - B. Trimethoprim
 - C. Pentamidine
 - D. ACE inhibitors and ARBs
 - E. NSAIDs
 - F. Cyclosporine and tacrolimus
- IV. Other
 - A. Acid loads (ammonium chloride, hyperalimentation)
 - B. Loss of potential bicarbonate: ketosis with ketone excretion
 - C. Expansion acidosis (rapid saline administration)
 - D. Hippurate
 - E. Cation exchange resins

Note: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NSAID, nonsteroidal anti-inflammatory drug; PHA, pseudohypoaldosteronism; RTA, renal tubular acidosis.

Approach to the Patient: HYPERCHLOREMIC METABOLIC ACIDOSES

In diarrhea, stools contain a higher HCO_3^- and decomposed HCO_3^- than plasma so that metabolic acidosis develops along with volume depletion. Instead of an acid urine pH (as anticipated with systemic acidosis), urine pH is usually ~ 6 because metabolic acidosis and hypokalemia increase renal synthesis and excretion of NH_4^+ , thus providing a urinary buffer that increases urine pH. Metabolic acidosis caused by gastrointestinal losses with a high urine pH can be differentiated from RTA because urinary NH_4^+ excretion is typically low in RTA and high with diarrhea. Urinary NH_4^+ levels can be estimated

by calculating the urine AG (UAG): $UAG = [Na^+ + K^+]_u - [Cl^-]_u$. When $[Cl^-]_u > [Na^+ + K^+]_u$, the urine gap is negative by definition. This indicates that the urine ammonium level is appropriately increased, suggesting an extrarenal cause of the acidosis. Conversely, when the urine UAG is positive, the urine ammonium level is low, suggesting a renal cause of the acidosis.

Loss of functioning renal parenchyma by progressive renal disease leads to hyperchloremic acidosis when the glomerular filtration rate (GFR) is between 20 and 50 mL/min and to uremic acidosis with a high AG when the GFR decreases to <20 mL/min. Such a progression occurs commonly with tubulointerstitial forms of renal disease, but hyperchloremic metabolic acidosis can persist with advanced glomerular disease. In advanced renal failure, ammoniogenesis is reduced in proportion to the loss of functional renal mass, and ammonium accumulation and trapping in the outer medullary collecting tubule may also be impaired. Because of adaptive increases in K^+ secretion by the collecting duct and colon, the acidosis of chronic renal insufficiency is typically normokalemic.

Proximal RTA (type 2 RTA) is most often caused by generalized proximal tubular dysfunction manifested by glycosuria, generalized aminoaciduria, and phosphaturia (Fanconi syndrome). With a low plasma HCO_3^- , the urine pH is acidic (pH <5.5). The fractional excretion of HCO_3^- may exceed 10–15% when the serum $HCO_3^- >20$ mmol/L. Because HCO_3^- is not reabsorbed normally in the proximal tubule, therapy with $NaHCO_3$ will enhance renal potassium wasting and hypokalemia.

The typical findings in acquired or inherited forms of classic distal RTA (type 1 RTA) include hypokalemia, hyperchloremic acidosis, low urinary NH_4^+ excretion (positive UAG, low urine $[NH_4^+]$), and inappropriately high urine pH (pH >5.5). Such patients are unable to acidify the urine below a pH of 5.5. Most patients have hypocitraturia and hypercalciuria, so nephrolithiasis, nephrocalcinosis, and bone disease are common. In generalized distal nephron dysfunction (type 4 RTA), hyperkalemia is disproportionate to the reduction in GFR because of coexisting dysfunction of potassium and acid secretion. Urinary ammonium excretion is invariably depressed, and renal function may be compromised, for example, because of diabetic nephropathy, amyloidosis, or tubulointerstitial disease.

Hyporeninemic hypoaldosteronism typically causes hyperchloremic metabolic acidosis, most commonly in older adults with diabetes mellitus or tubulointerstitial disease and renal insufficiency. Patients usually have mild to moderate renal insufficiency (GRF, 20–50 mL/min) and acidosis, with elevation in serum K^+ (5.2–6.0 mmol/L), concurrent hypertension, and

congestive heart failure. Both the metabolic acidosis and the hyperkalemia are out of proportion to impairment in GFR. Nonsteroidal anti-inflammatory drugs, trimethoprim, pentamidine, and angiotensin-converting enzyme inhibitors can also cause hyperkalemia with hyperchloremic metabolic acidosis in patients with renal insufficiency (Table 40-5).

METABOLIC ALKALOSIS

Metabolic alkalosis is manifested by an elevated arterial pH, an increase in the serum HCO_3^- , and an increase in Pa_{CO_2} as a result of compensatory alveolar hypoventilation (Table 40-1). It is often accompanied by hypochloremia and hypokalemia. The arterial pH establishes the diagnosis because it is increased in metabolic alkalosis and decreased or normal in respiratory acidosis. Metabolic alkalosis frequently occurs in association with other disorders such as respiratory acidosis or alkalosis or metabolic acidosis.

PATHOGENESIS

Metabolic alkalosis occurs as a result of net gain of HCO_3^- or loss of nonvolatile acid (usually HCl by vomiting) from the ECF. Because it is unusual for alkali to be added to the body, the disorder involves a generative stage, in which the loss of acid usually causes alkalosis, and a maintenance stage, in which the kidneys fail to compensate by excreting HCO_3^- .

Under normal circumstances, the kidneys have an impressive capacity to excrete HCO_3^- . Continuation of metabolic alkalosis represents a failure of the kidneys to eliminate HCO_3^- in the usual manner. For HCO_3^- to be added to the ECF, it must be administered exogenously or synthesized endogenously, partly or entirely by the kidneys. The kidneys will retain, rather than excrete, the excess alkali and maintain the alkalosis if (1) volume deficiency, chloride deficiency, and K^+ deficiency exist in combination with a reduced GFR, which augments distal tubule H^+ secretion, or (2) hypokalemia exists because of autonomous hyperaldosteronism. In the first example, alkalosis is corrected by administration of NaCl and KCl; in the latter, it is necessary to repair the alkalosis by pharmacologic or surgical intervention, not with saline administration.

DIFFERENTIAL DIAGNOSIS

To establish the cause of metabolic alkalosis (Table 40-6), it is necessary to assess the status of the ECF volume (ECFV), the recumbent and upright blood pressure, the serum K^+ , and the renin–aldosterone system. For example, the presence of chronic hypertension and chronic hypokalemia in an alkalotic patient suggests

TABLE 40-6

CAUSES OF METABOLIC ALKALOSIS

- I. Exogenous HCO_3^- loads
 - A. Acute alkali administration
 - B. Milk-alkali syndrome
- II. Effective ECFV contraction, normotension, K^+ deficiency, and secondary hyperreninemic hyperaldosteronism
 - A. Gastrointestinal origin
 1. Vomiting
 2. Gastric aspiration
 3. Congenital chloridorrhea
 4. Villous adenoma
 - B. Renal origin
 1. Diuretics
 2. Posthypercapnic state
 3. Hypercalcemia or hypoparathyroidism
 4. Recovery from lactic acidosis or ketoacidosis
 5. Nonreabsorbable anions, including penicillin, carbenicillin
 6. Mg^{2+} deficiency
 7. K^+ depletion
 8. Bartter's syndrome (loss of function mutations in TALH)
 9. Gitelman's syndrome (loss of function mutation in $\text{Na}^+\text{-Cl}^-$ cotransporter in DCT)
- III. ECFV expansion, hypertension, K^+ deficiency, and mineralocorticoid excess
 - A. High renin
 1. Renal artery stenosis
 2. Accelerated hypertension
 3. Renin-secreting tumor
 4. Estrogen therapy
 - B. Low renin
 1. Primary aldosteronism
 - a. Adenoma
 - b. Hyperplasia
 - c. Carcinoma
 2. Adrenal enzyme defects
 - a. 11 β -Hydroxylase deficiency
 - b. 17 α -Hydroxylase deficiency
 3. Cushing's syndrome or disease
 4. Other
 - a. Licorice
 - b. Carbenoxolone
 - c. Chewer's tobacco
- IV. Gain-of-function mutation of renal sodium channel with ECFV expansion, hypertension, K^+ deficiency, and hyporeninemic-hypoaldosteronism
 - A. Liddle's syndrome

Note: DCT, distal convoluted tubule; ECFV, extracellular fluid volume; TALH, thick ascending limb of the loop of Henle.

either mineralocorticoid excess or that the hypertensive patient is receiving diuretics. Low plasma renin activity and normal urine Na^+ and Cl^- in a patient who is not taking diuretics indicate a primary mineralocorticoid excess syndrome. The combination of hypokalemia and alkalosis in a normotensive, nonedematous patient may

be attributable to Bartter's or Gitelman's syndrome, magnesium deficiency, vomiting, exogenous alkali, or diuretic ingestion. Determination of urine electrolytes (especially the urine Cl^-) and screening of the urine for diuretics may be helpful. If the urine is alkaline, with an elevated Na^+ and K^+ but low Cl^- , the diagnosis is usually either vomiting (overt or surreptitious) or alkali ingestion. If the urine is relatively acid and has low concentrations of Na^+ , K^+ , and Cl^- , the most likely possibilities are prior vomiting, the posthypercapnic state, or prior diuretic ingestion. If, on the other hand, the urine sodium, potassium, and chloride concentrations are not depressed, magnesium deficiency, Bartter's or Gitelman's syndrome, or current diuretic ingestion should be considered. Bartter's syndrome is distinguished from Gitelman's syndrome because of hypocalciuria and hypomagnesemia in the latter disorder. The genetic and molecular basis of these two disorders has been elucidated recently.

Alkali Administration

Chronic administration of alkali to individuals with normal renal function rarely, if ever, causes alkalosis. However, in patients with coexistent hemodynamic disturbances, alkalosis can develop because the normal capacity to excrete HCO_3^- may be exceeded or there may be enhanced reabsorption of HCO_3^- . Such patients include those who receive HCO_3^- (PO or IV), acetate loads (parenteral hyperalimentation solutions), citrate loads (transfusions), or antacids plus cation-exchange resins (aluminum hydroxide and sodium polystyrene sulfonate).

METABOLIC ALKALOSIS ASSOCIATED WITH EXTRACELLULAR FLUID VOLUME CONTRACTION, K^+ DEPLETION, AND SECONDARY HYPERRENINEMIC HYPERALDOSTERONISM

Gastrointestinal Origin

Gastrointestinal loss of H^+ from vomiting or gastric aspiration results in retention of HCO_3^- . The loss of fluid and NaCl in vomitus or nasogastric suction results in contraction of the ECFV and an increase in the secretion of renin and aldosterone. Volume contraction through a reduction in GFR results in an enhanced capacity of the renal tubule to reabsorb HCO_3^- . During active vomiting, however, the filtered load of bicarbonate is acutely increased to the point that the reabsorptive capacity of the proximal tubule for HCO_3^- is exceeded. The excess NaHCO_3 issuing out of the proximal tubule reaches the distal tubule, where H^+ secretion is enhanced by an aldosterone and the delivery of the poorly reabsorbed anion, HCO_3^- . Correction of the contracted ECFV with NaCl and repair of K^+ deficits corrects the acid-base disorder, and chloride deficiency.

Diuretics

Drugs that induce chloruresis, such as thiazides and loop diuretics (furosemide, bumetanide, torsemide, and ethacrynic acid), acutely diminish the ECFV without altering the total body bicarbonate content. The serum HCO_3^- increases because the reduced ECFV “contracts” the HCO_3^- in the plasma (contraction alkalosis). The chronic administration of diuretics tends to generate an alkalosis by increasing distal salt delivery, so that K^+ and H^+ secretion are stimulated. The alkalosis is maintained by persistence of the contraction of the ECFV, secondary hyperaldosteronism, K^+ deficiency, and the direct effect of the diuretic (as long as diuretic administration continues). Repair of the alkalosis is achieved by providing isotonic saline to correct the ECFV deficit.

Nonreabsorbable Anions and Magnesium Deficiency

Administration of large quantities of nonreabsorbable anions, such as penicillin or carbenicillin, can enhance distal acidification and K^+ secretion by increasing the transepithelial potential difference (lumen negative). Mg^{2+} deficiency results in hypokalemic alkalosis by enhancing distal acidification through stimulation of renin and hence aldosterone secretion.

Potassium Depletion

Chronic K^+ depletion may cause metabolic alkalosis by increasing urinary acid excretion. Both NH_4^+ production and absorption are enhanced and HCO_3^- reabsorption is stimulated. Chronic K^+ deficiency upregulates the renal H^+ , K^+ -ATPase to increase K^+ absorption at the expense of enhanced H^+ secretion. Alkalosis associated with severe K^+ depletion is resistant to salt administration, but repair of the K^+ deficiency corrects the alkalosis.

After Treatment of Lactic Acidosis or Ketoacidosis

When an underlying stimulus for the generation of lactic acid or ketoacid is removed rapidly, as with repair of circulatory insufficiency or with insulin therapy, the lactate or ketones are metabolized to yield an equivalent amount of HCO_3^- . Other sources of new HCO_3^- are additive with the original amount generated by organic anion metabolism to create a surfeit of HCO_3^- . Such sources include (1) new HCO_3^- added to the blood by the kidneys as a result of enhanced acid excretion during the preexisting period of acidosis and (2) alkali therapy during the treatment phase of the acidosis. Acidosis-induced contraction of the ECFV and K^+ deficiency act to sustain the alkalosis.

Posthypercapnia

Prolonged CO_2 retention with chronic respiratory acidosis enhances renal HCO_3^- absorption and the generation of new HCO_3^- (increased net acid excretion). If the

Pa_{CO_2} is returned to normal, metabolic alkalosis results from the persistently elevated HCO_3^- . Alkalosis develops if the elevated Pa_{CO_2} is abruptly returned toward normal by a change in mechanically controlled ventilation. Associated ECFV contraction does not allow complete repair of the alkalosis by correction of the Pa_{CO_2} alone, and alkalosis persists until Cl^- supplementation is provided.

METABOLIC ALKALOSIS ASSOCIATED WITH EXTRACELLULAR FLUID VOLUME EXPANSION, HYPERTENSION, AND HYPERALDOSTERONISM

Increased aldosterone levels may be the result of autonomous primary adrenal overproduction or of secondary aldosterone release caused by renal overproduction of renin. Mineralocorticoid excess increases net acid excretion and may result in metabolic alkalosis, which may be worsened by associated K^+ deficiency. ECFV expansion from salt retention causes hypertension. The kaliuresis persists because of mineralocorticoid excess and distal Na^+ absorption, causing enhanced K^+ excretion, continued K^+ depletion with polydipsia, inability to concentrate the urine, and polyuria.

Liddle's syndrome results from increased activity of the collecting duct Na^+ channel (ENaC) and is a rare inherited disorder associated with hypertension caused by volume expansion manifested as hypokalemic alkalosis and normal aldosterone levels.

Symptoms

With metabolic alkalosis, changes in central and peripheral nervous system function are similar to those of hypocalcemia; symptoms include mental confusion, obtundation, and a predisposition to seizures, paresthesia, muscular cramping, tetany, aggravation of arrhythmias, and hypoxemia in chronic obstructive pulmonary disease. Related electrolyte abnormalities include hypokalemia and hypophosphatemia.

Rx Treatment: METABOLIC ALKALOSIS

Treatment is primarily directed at correcting the underlying stimulus for HCO_3^- generation. If primary aldosteronism, renal artery stenosis, or Cushing's syndrome is present, correction of the underlying cause will reverse the alkalosis. H^+ loss by the stomach or kidneys can be mitigated by the use of proton pump inhibitors or the discontinuation of diuretics. The second aspect of treatment is to remove the factors that sustain the inappropriate increase in HCO_3^- reabsorption, such as ECFV contraction or K^+ deficiency. Although K^+ deficits should be repaired, NaCl therapy is usually sufficient to reverse the

alkalosis if ECFV contraction is present, as indicated by a low urine Cl^- .

If associated conditions preclude infusion of saline, renal HCO_3^- loss can be accelerated by administration of acetazolamide, a carbonic anhydrase inhibitor, which is usually effective in patients with adequate renal function but can worsen K^+ losses. Dilute hydrochloric acid (0.1 N HCl) is also effective but can cause hemolysis and must be delivered centrally and slowly. Hemodialysis against a dialysate low in HCO_3^- and high in Cl^- can be effective when renal function is impaired.

RESPIRATORY ACIDOSIS

Respiratory acidosis can be caused by severe pulmonary disease, respiratory muscle fatigue, or abnormalities in ventilatory control and is recognized by an increase in Pa_{CO_2} and decrease in pH (Table 40-7). In acute respiratory acidosis, there is an immediate compensatory elevation (because of cellular buffering mechanisms) in HCO_3^- , which increases 1 mmol/L for every 10-mmHg increase in Pa_{CO_2} . In chronic respiratory acidosis (>24 h), renal adaptation increases the HCO_3^- by 4 mmol/L for

every 10-mmHg increase in Pa_{CO_2} . The serum HCO_3^- usually does not increase above 38 mmol/L.

The clinical features vary according to the severity and duration of the respiratory acidosis, the underlying disease, and whether accompanying hypoxemia is present. A rapid increase in Pa_{CO_2} may cause anxiety, dyspnea, confusion, psychosis, and hallucinations and may progress to coma. Lesser degrees of dysfunction in chronic hypercapnia include sleep disturbances; loss of memory; daytime somnolence; personality changes; impairment of coordination; and motor disturbances such as tremor, myoclonic jerks, and asterixis. Headaches and other signs that mimic increased intracranial pressure, such as papilledema, abnormal reflexes, and focal muscle weakness, are caused by vasoconstriction secondary to loss of the vasodilator effects of CO_2 .

Depression of the respiratory center by a variety of drugs, injury, or disease can produce respiratory acidosis. This may occur acutely with general anesthetics, sedatives, and head trauma or chronically with sedatives, alcohol, intracranial tumors, and the syndromes of sleep-disordered breathing, including the primary alveolar and obesity-hypoventilation syndromes (Chaps. 22 and 23). Abnormalities or disease in the motor neurons, neuromuscular junction, and skeletal muscle can cause hypoventilation via

TABLE 40-7

RESPIRATORY ACID-BASE DISORDERS

<p>I. Alkalosis</p> <p>A. Central nervous system stimulation</p> <ol style="list-style-type: none"> 1. Pain 2. Anxiety, psychosis 3. Fever 4. Cerebrovascular accident 5. Meningitis, encephalitis 6. Tumor 7. Trauma <p>B. Hypoxemia or tissue hypoxia</p> <ol style="list-style-type: none"> 1. High altitude, $\downarrow \text{Pa}_{\text{CO}_2}$ 2. Pneumonia, pulmonary edema 3. Aspiration 4. Severe anemia <p>C. Drugs or hormones</p> <ol style="list-style-type: none"> 1. Pregnancy, progesterone 2. Salicylates 3. Cardiac failure <p>D. Stimulation of chest receptors</p> <ol style="list-style-type: none"> 1. Hemothorax 2. Flail chest 3. Cardiac failure 4. Pulmonary embolism <p>E. Miscellaneous</p> <ol style="list-style-type: none"> 1. Septicemia 2. Hepatic failure 3. Mechanical hyperventilation 4. Heat exposure 5. Recovery from metabolic acidosis 	<p>II. Acidosis</p> <p>A. Central</p> <ol style="list-style-type: none"> 1. Drugs (anesthetics, morphine, sedatives) 2. Stroke 3. Infection <p>B. Airway</p> <ol style="list-style-type: none"> 1. Obstruction 2. Asthma <p>C. Parenchyma</p> <ol style="list-style-type: none"> 1. Emphysema 2. Pneumoconiosis 3. Bronchitis 4. Adult respiratory distress syndrome 5. Barotrauma <p>D. Neuromuscular</p> <ol style="list-style-type: none"> 1. Poliomyelitis 2. Kyphoscoliosis 3. Myasthenia 4. Muscular dystrophies <p>E. Miscellaneous</p> <ol style="list-style-type: none"> 1. Obesity 2. Hypoventilation 3. Permissive hypercapnia
--	--

respiratory muscle fatigue. Mechanical ventilation, when not properly adjusted and supervised, may result in respiratory acidosis, particularly if CO_2 production suddenly increases (because of fever, agitation, sepsis, or overfeeding) or alveolar ventilation decreases because of worsening pulmonary function. High levels of positive end-expiratory pressure in the presence of reduced cardiac output may cause hypercapnia as a result of large increases in alveolar dead space (Chap. 5). Permissive hypercapnia is being used with increasing frequency because of studies suggesting lower mortality rates than with conventional mechanical ventilation, especially with severe CNS or heart disease. The potential beneficial effects of permissive hypercapnia may be mitigated by correction of the acidemia by administration of NaHCO_3 .

Acute hypercapnia occurs after sudden occlusion of the upper airway or generalized bronchospasm as in severe asthma, anaphylaxis, inhalational burn, or toxin injury. Chronic hypercapnia and respiratory acidosis occur in end-stage obstructive lung disease. Restrictive disorders involving both the chest wall and the lungs can cause respiratory acidosis because the high metabolic cost of respiration causes ventilatory muscle fatigue. Advanced stages of intrapulmonary and extrapulmonary restrictive defects present as chronic respiratory acidosis.

The diagnosis of respiratory acidosis requires, by definition, the measurement of Pa_{CO_2} and arterial pH. A detailed history and physical examination often indicate the cause. Pulmonary function studies (Chap. 5), including spirometry, diffusion capacity for carbon monoxide, lung volumes, and arterial Pa_{CO_2} and O_2 saturation, usually make it possible to determine if respiratory acidosis is secondary to lung disease. The workup for nonpulmonary causes should include a detailed drug history; measurement of hematocrit; and assessment of upper airway, chest wall, pleura, and neuromuscular function.

Rx Treatment: **RESPIRATORY ACIDOSIS**

The management of respiratory acidosis depends on its severity and rate of onset. Acute respiratory acidosis can be life threatening, and measures to reverse the underlying cause should be undertaken simultaneously with restoration of adequate alveolar ventilation. This may necessitate tracheal intubation and assisted mechanical ventilation. Oxygen administration should be titrated carefully in patients with severe obstructive pulmonary disease and chronic CO_2 retention who are breathing spontaneously (Chap. 18). When oxygen is used in judiciously, these patients may experience progression of the respiratory acidosis. Aggressive and rapid correction of hypercapnia should be avoided

because the decreasing Pa_{CO_2} may provoke the same complications noted with acute respiratory alkalosis (i.e., cardiac arrhythmias, reduced cerebral perfusion, and seizures). The Pa_{CO_2} should be lowered gradually in chronic respiratory acidosis, aiming to restore the Pa_{CO_2} to baseline levels and to provide sufficient Cl^- and K^+ to enhance the renal excretion of HCO_3^- .

Chronic respiratory acidosis is frequently difficult to correct, but measures aimed at improving lung function (Chap. 18) can help some patients and forestall further deterioration in most.

RESPIRATORY ALKALOSIS

Alveolar hyperventilation decreases Pa_{CO_2} and increases the $\text{HCO}_3^-/\text{Pa}_{\text{CO}_2}$ ratio, thus increasing pH (see Table 40-7). Nonbicarbonate cellular buffers respond by consuming HCO_3^- . Hypocapnia develops when a sufficiently strong ventilatory stimulus causes CO_2 output in the lungs to exceed its metabolic production by tissues. Plasma pH and HCO_3^- appear to vary proportionately with Pa_{CO_2} over a range from 40–15 mmHg. The relationship between arterial H^+ concentration and Pa_{CO_2} is ~ 0.7 mmol/L per mmHg (or 0.01 pH unit/mmHg), and that for plasma HCO_3^- is 0.2 mmol/L per mmHg. Hypocapnia sustained for >2 –6 h is further compensated by a decrease in renal ammonium and titratable acid excretion and a reduction in filtered HCO_3^- reabsorption. Full renal adaptation to respiratory alkalosis may take several days and requires normal volume status and renal function. The kidneys appear to respond directly to the lowered Pa_{CO_2} rather than to alkalosis per se. In chronic respiratory alkalosis, a 1-mmHg decrease in Pa_{CO_2} causes a 0.4- to 0.5-mmol/L decrease in HCO_3^- and a 0.3-mmol/L decrease (or 0.003-mmol/L increase in pH) in H^+ .

The effects of respiratory alkalosis vary according to duration and severity but are primarily those of the underlying disease. Reduced cerebral blood flow as a consequence of a rapid decline in Pa_{CO_2} may cause dizziness, mental confusion, and seizures, even in the absence of hypoxemia. The cardiovascular effects of acute hypocapnia in conscious humans are generally minimal, but in anesthetized or mechanically ventilated patients, cardiac output and blood pressure may decrease because of the depressant effects of anesthesia and positive-pressure ventilation on heart rate, systemic resistance, and venous return. Cardiac arrhythmias may occur in patients with heart disease as a result of changes in oxygen unloading by blood from a left shift in the hemoglobin-oxygen dissociation curve (Bohr effect). Acute respiratory alkalosis causes intracellular shifts of Na^+ , K^+ , and PO_4^- and reduces free Ca^{2+} by increasing the protein-bound fraction. Hypocapnia-induced hypokalemia is usually minor.

Chronic respiratory alkalosis is the most common acid–base disturbance in critically ill patients and, when severe, portends a poor prognosis. Many cardiopulmonary disorders manifest respiratory alkalosis in their early to intermediate stages, and the finding of normocapnia and hypoxemia in a patient with hyperventilation may herald the onset of rapid respiratory failure and should prompt an assessment to determine if the patient is becoming fatigued. Respiratory alkalosis is common during mechanical ventilation.

The hyperventilation syndrome may be disabling. Paresthesia, circumoral numbness, chest wall tightness or pain, dizziness, inability to take an adequate breath, and (rarely) tetany may themselves be sufficiently stressful to perpetuate the disorder. Arterial blood gas analysis demonstrates an acute or chronic respiratory alkalosis, often with hypocapnia in the range of 15–30 mmHg and no hypoxemia. CNS diseases or injury can produce several patterns of hyperventilation and sustained Pa_{CO_2} levels of 20–30 mmHg. Hyperthyroidism, high caloric loads, and exercise raise the basal metabolic rate, but ventilation usually increases in proportion so that arterial blood gases are unchanged and respiratory alkalosis does not develop. Salicylates are the most common cause of drug-induced respiratory alkalosis as a result of direct stimulation of the medullary chemoreceptor. The methylxanthines, theophylline, and aminophylline stimulate ventilation and increase the ventilatory response to CO_2 . Progesterone increases ventilation and lowers arterial Pa_{CO_2} by as much as 5–10 mmHg. Therefore, chronic respiratory alkalosis is a common feature of pregnancy. Respiratory alkalosis is also prominent in individuals with liver failure, and the severity correlates with the degree of hepatic insufficiency. Respiratory alkalosis is often an early finding in gram-negative septicemia before fever, hypoxemia, or hypotension develops.

The diagnosis of respiratory alkalosis depends on measurement of arterial pH and Pa_{CO_2} . The plasma K^+ is often reduced and the Cl^- increased. In the acute phase, respiratory alkalosis is not associated with increased renal HCO_3^- excretion, but within hours, net acid excretion is reduced. In general, the HCO_3^- concentration decreases by 2.0 mmol/L for each 10-mmHg decrease in Pa_{CO_2} . Chronic hypocapnia reduces the serum HCO_3^-

by 4.0 mmol/L for each 10-mmHg decrease in Pa_{CO_2} . It is unusual to observe a plasma $\text{HCO}_3^- < 12$ mmol/L as a result of a pure respiratory alkalosis.

When a diagnosis of respiratory alkalosis is made, its cause should be investigated. The diagnosis of hyperventilation syndrome is made by exclusion. In difficult cases, it may be important to rule out other conditions such as pulmonary embolism, coronary artery disease, and hyperthyroidism.

Rx Treatment: **RESPIRATORY ALKALOSIS**

The management of respiratory alkalosis is directed toward alleviation of the underlying disorder. If respiratory alkalosis complicates ventilator management, changes in dead space, tidal volume, and frequency can minimize the hypocapnia. Patients with the hyperventilation syndrome may benefit from reassurance, rebreathing from a paper bag during symptomatic attacks, and attention to underlying psychological stress. Antidepressants and sedatives are not recommended. β -Adrenergic blockers may ameliorate peripheral manifestations of the hyperadrenergic state.

FURTHER READINGS

- DUBOSE TD JR: Acid–base disorders, in *Brenner and Rector's The Kidney*, 8th ed, BM Brenner (ed). Philadelphia, Saunders, 2007, pp 505–546
- , ALPERN RJ: Renal tubular acidosis, in *The Metabolic and Molecular Bases of Inherited Disease*, 8th ed, CR Scriver et al (eds). New York, McGraw-Hill, 2001, pp 4983–5021
- GALLA JH: Metabolic alkalosis, in *Acid-Base and Electrolyte Disorders—A Companion to Brenner and Rector's The Kidney*, TD DuBose, LL Hamm (eds). Philadelphia, Saunders, 2002, pp 109–128
- LASKI ME, WESSON DE: Lactic acidosis, in *Acid-Base and Electrolyte Disorders—A Companion to Brenner and Rector's The Kidney*, TD DuBose, LL Hamm (eds). Philadelphia, Saunders, 2002, pp 83–107
- MADIAS NE: Respiratory alkalosis, in *Acid-Base and Electrolyte Disorders—A Companion to Brenner and Rector's The Kidney*, TD DuBose, LL Hamm (eds). Philadelphia, Saunders, 2002, pp 147–164
- WESSON DE et al: Clinical syndromes of metabolic alkalosis, in *The Kidney: Physiology and Pathophysiology*, 3rd ed, DW Seldin, G Gebisch (eds). Philadelphia, Lippincott Williams and Wilkins, 2000, pp 2055–2072



CHAPTER 41

COAGULATION DISORDERS

Valder Arruda ■ Katherine A. High

■ Hemophilia	425	Disseminated Intravascular Coagulation	429
Pathogenesis and Clinical Manifestations	425	Vitamin K Deficiency	432
Factor XI Deficiency	428	Coagulation Disorders Associated with Liver Failure	432
■ Other Rare Bleeding Disorders	428	Acquired Inhibitors of Coagulation Factors	433
Familial Multiple Coagulation Deficiencies	429	■ Further Readings	433

Deficiencies of coagulation factors have been recognized for centuries. Patients with genetic deficiencies of plasma coagulation factors exhibit lifelong recurrent bleeding episodes into joints, muscles, and closed spaces, either spontaneously or after injuries. The most common inherited factor deficiencies are the hemophilias, X-linked diseases caused by deficiency of factor (F) VIII (hemophilia A) or factor IX (FIX, hemophilia B). Rare congenital bleeding disorders caused by deficiencies of other factors, including FII (prothrombin), FV, FVII, FX, FXI, FXIII, and fibrinogen, are usually inherited in an autosomal recessive manner (Table 41-1). Advances in characterization of the molecular bases of clotting factor deficiencies have contributed to a better understanding of the disease phenotypes and may allow more targeted therapeutic approaches through the development of small molecules, recombinant proteins, or cell- and gene-based therapies.

Commonly used tests of hemostasis provide the initial screening for clotting factor activity (Fig. 41-1), and disease phenotype often correlates with the level of clotting activity. Whereas an isolated abnormal prothrombin time (PT) suggests FVII deficiency, a prolonged activated partial thromboplastin time (aPTT) indicates most commonly hemophilia or FXI deficiency (Fig. 41-1). The prolongation of both PT and aPTT suggests deficiency of FV, FX, FII, or fibrinogen abnormalities. The addition of the missing factor to the subject's plasma at a range of doses will correct the abnormal clotting times; the result

is expressed as percent of the activity observed in normal subjects.

Acquired deficiencies of plasma coagulation are more frequent than congenital disorders; the most common disorders include hemorrhagic diathesis of liver disease, disseminated intravascular coagulation (DIC), and vitamin K deficiency. In these disorders, blood coagulation is hampered by the deficiency of more than one clotting factor, and the bleeding episodes result from perturbation of both primary (e.g., platelet and vessel wall interactions) and secondary (coagulation) hemostasis.

The development of antibodies to coagulation plasma proteins, clinically termed *inhibitors*, is a relatively rare problem that most often affects patients with hemophilia A or B and FXI-deficient who receive repeated doses of the missing protein to control bleeding episodes. Inhibitors also occur among subjects without genetic deficiency of clotting factors—e.g., in the postpartum setting, as a manifestation of underlying autoimmune or neoplastic disease, or idiopathically. Rare cases of inhibitors to thrombin or FV have been reported in patients receiving topical bovine thrombin preparation as a local hemostatic agent in complex surgeries. The diagnosis of inhibitors is based on the same tests as those used to diagnose inherited plasma coagulation factor deficiencies. However, the addition of the missing protein to the plasma of a subject with an inhibitor does not correct the abnormal aPTT or PT tests. This is the major laboratory difference between deficiencies and inhibitors.

TABLE 41-1

GENETIC AND LABORATORY CHARACTERISTICS OF INHERITED COAGULATION DISORDERS

CLOTTING FACTOR DEFICIENCY	INHERITANCE	PREVALENCE IN GENERAL POPULATION	LABORATORY ABNORMALITY ^a			MINIMUM HEMOSTATIC LEVELS	TREATMENT	PLASMA HALF-LIFE
			aPTT	PT	TT			
Fibrinogen	AR	1 in 1,000,000	+	+	+	100 mg/dL	Cryoprecipitate	2–4 d
Prothrombin	AR	1 in 2,000,000	+	+	–	20–30%	FFP/PCCs	3–4 d
Factor V	AR	1 in 1,000,000	+/-	+/-	–	15–20%	FFP	36 h
Factor VII	AR	1 in 500,000	–	+	–	15–20%	FFP/PCCs	4–6 h
Factor VIII	X-linked	1 in 5,000	+	–	–	30%	FVIII concentrates	8–12 h
Factor IX	X-linked	1 in 30,000	+	–	–	30%	FIX concentrates	18–24 h
Factor X	AR	1 in 1,000,000	+/-	+/-	–	15–20%	FFP/PCCs	40–60 h
Factor XI	AR	1 in 1,000,000	+	–	–	15–20%	FFP	40–70 h
Factor XII	AR	ND	+	–	–	^b	^b	60 h
HK	AR	ND	+	–	–	^b	^b	150 h
Prekallikrein	AR	ND	+	–	–	^b	^b	35 h
Factor XIII	AR	1 in 2,000,000	–	–	+/-	2–5%	Cryoprecipitate	11–14 d

^a Values within normal range (–) or prolonged (+).

^b No risk for bleeding; treatment is not indicated.

Note: aPTT, activated partial thromboplastin time; AR, autosomal recessive; FFP, fresh-frozen plasma; HK, high-molecular-weight kininogen; ND, not determined; PCCs, prothrombin complex concentrates; PT, prothrombin time; TT, thrombin time.

Additional tests are required to measure the specificity of the inhibitor and its titer.

The treatment of patients with these bleeding disorders often requires replacement of the deficient protein using recombinant or purified plasma-derived products or fresh-frozen plasma (FFP). Therefore, it is imperative to arrive at a proper diagnosis to optimize patient care

without unnecessary exposure to the risks of blood-borne disease.

HEMOPHILIA

PATHOGENESIS AND CLINICAL MANIFESTATIONS

Hemophilia is an X-linked recessive hemorrhagic disease caused by mutations in the *F8* gene (hemophilia A or classic hemophilia) or *F9* gene (hemophilia B). The disease affects one in 10,000 men worldwide in all ethnic groups; hemophilia A represents 80% of all cases. Men are clinically affected; women, who carry a single mutated gene, are generally asymptomatic. Family history of the disease is absent in approximately 30% of cases. In these cases, 80% of the mothers are carriers of the de novo mutated allele. More than 500 different mutations have been identified in the *F8* or *F9* genes. One of the most common hemophilia A mutations results from an inversion of the intron 22 sequence, which is present in 40% of cases of severe hemophilia A. Advances in molecular diagnosis now permit precise identification of mutations, allowing accurate diagnosis of female carriers of the hemophilia gene in affected families.

Clinically, hemophilia A and hemophilia B are indistinguishable. The disease phenotype correlates with the residual activity of FVIII or FIX and can be classified as severe (<1%), moderate (1–5%), or mild (6–30%). In the severe and moderate forms, the disease is characterized by bleeding episodes into the joints (hemarthroses), soft

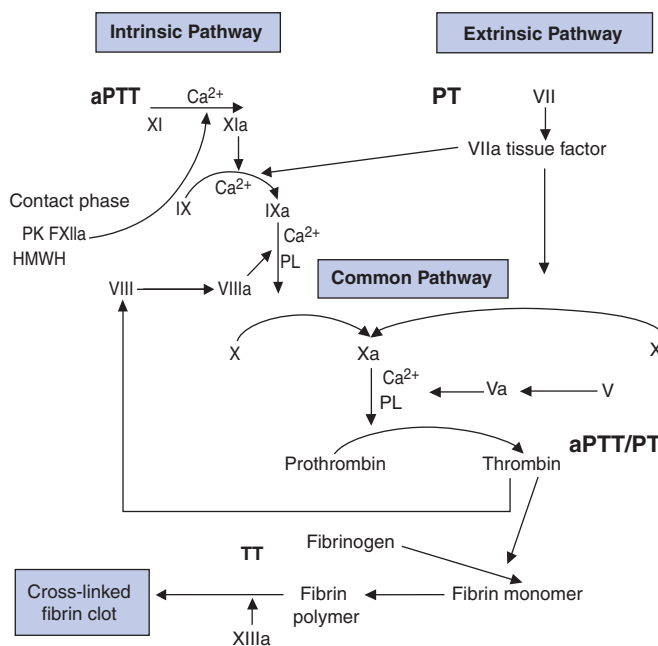


FIGURE 41-1

Coagulation cascade and laboratory assessment of clotting factor deficiency by activated partial prothrombin time (aPTT), prothrombin time (PT), and thrombin time (TT).

tissues, and muscles after minor trauma or even spontaneously. Patients with mild disease experience infrequent bleeding that is usually secondary to trauma. Among those with residual FVIII or FIX activity >25% of normal, the disease is discovered only by bleeding after major trauma or during routine presurgery laboratory tests. Typically, the global tests of coagulation show only an isolated prolongation of the aPTT assay. Patients with hemophilia have normal bleeding times and platelet counts. The diagnosis is made after specific determination of FVIII or FIX clotting activity.

Early in life, bleeding may present after circumcision or rarely as intracranial hemorrhages. The disease is more evident when children begin to walk or crawl. In the severe form, the most common bleeding manifestations are the recurrent hemarthroses, which can affect every joint but mainly affect knees, elbows, ankles, shoulders, and hips. Acute hemarthroses are painful, and clinical signs are local swelling and erythema. To avoid pain, the patient may adopt a fixed position, which leads eventually to muscle contractures. Very young children who are unable to communicate verbally show irritability and a lack of movement of the affected joint. Chronic hemarthroses are debilitating, with synovial thickening and synovitis in response to the intraarticular blood. After a joint has been damaged, recurrent bleeding episodes result in the clinically recognized “target joint,” which then establishes a vicious cycle of bleeding, resulting in progressive joint deformity that in critical cases requires surgery as the only therapeutic option. Hematomas into the muscle of distal parts of the limbs may lead to external compression of arteries, veins, or nerves, which can evolve to a compartment syndrome.

Bleeding into the oropharyngeal spaces, the central nervous system (CNS), or the retroperitoneum is life-threatening and requires immediate therapy. Retroperitoneal hemorrhages can accumulate large quantities of blood along with formation of masses with calcification and inflammatory tissue reaction (pseudotumor syndrome), and they can also result in damage to the femoral nerve. Pseudotumors can also form in bones, especially the long bones of the lower limbs. Hematuria is frequent among hemophilia patients, even in the absence of genitourinary pathology. It is often self-limited and may not require specific therapy.

Rx Treatment: **HEMOPHILIA**

Without treatment, patients with severe hemophilia have a limited life expectancy. Advances in the blood fractionation industry during World War II resulted in the realization that plasma could be used to treat people with hemophilia, but the volumes required to achieve even modest elevation of circulating factor levels limits

the utility of plasma infusion as an approach to disease management. The discovery in the 1960s that cryoprecipitate fraction of plasma was enriched for FVIII, in addition to the eventual purification of FVIII and FIX from plasma, led to the introduction of home infusion therapy with factor concentrates in the 1970s. The availability of factor concentrates resulted in a dramatic improvement in life expectancy and in quality of life for people with severe hemophilia. However, the contamination of the blood supply with hepatitis viruses and, subsequently, HIV resulted in widespread transmission of these blood-borne infections within the hemophilia population; complications of HIV and of hepatitis C are now the leading causes of death among U.S. adults with severe hemophilia. The introduction of viral inactivation steps in the preparation of plasma-derived products in the mid-1980s greatly reduced the risk of HIV and hepatitis, and the risks were further reduced by the successful production of recombinant FVIII and FIX proteins, both licensed in the 1990s. It is uncommon for hemophilic patients born after 1985 to have contracted either hepatitis or HIV, and for these individuals, life expectancy is in the range of 65 years of age.

Factor replacement therapy for hemophilia can be provided either in response to a bleeding episode or as a prophylactic treatment. Primary prophylaxis is defined as a strategy for maintaining the missing clotting factor at levels ~1% or higher on a regular basis to prevent bleeds, especially the onset of hemarthroses. Hemophilic boys receiving regular infusions of FVIII (3 days/week) or FIX (2 days/week) can reach puberty without detectable joint abnormalities. Although highly recommended, this regimen is performed for <30% of patients because of the high cost, difficulties in accessing peripheral veins in young patients, and the potential infectious and thrombotic risks of long-term central vein catheters.

General considerations regarding the treatment of bleeds in hemophilia include (1) the need to begin the treatment as soon as possible because symptoms often precede objective evidence of bleeding; because of the superior efficacy of early therapeutic intervention, classic symptoms of bleeding into the joint in a reliable patient, headaches, or automobile or other accidents, require prompt replacement and further laboratory investigation; and (2) the need to avoid drugs that hamper platelet function, such as aspirin or aspirin-containing drugs, to control pain, drugs such as ibuprofen or propoxyphene are preferred.

Factors VIII and IX are dosed in units. One unit is by definition the amount of FVIII (100 ng/mL) or FIX (5 µg/mL) in 1 mL of normal plasma. One unit of FVIII per kilogram of body weight increases the plasma FVIII level by 2%. One can calculate the dose needed to increase FVIII levels to 100% in a 70-kg severe hemophilia patient

(<1%) using the simple formula below. Thus, 3500 units of FVIII will increase the circulating level to 100%.

$$\text{FVIII dose (IU)} = \frac{\text{Target FVIII levels} - \text{FVIII baseline levels}}{\text{Body weight (kg)} \times 0.5 \text{ unit/kg}}$$

The doses for FIX replacement are different from those for FVIII, because FIX recovery postinfusion is usually only 50% of the predicted value. Therefore, the formula for FIX replacement is

$$\text{FIX dose (IU)} = \frac{\text{Target FIX levels} - \text{FIX baseline levels}}{\text{Body weight (kg)} \times 1.0 \text{ unit/kg}}$$

The FVIII half-life of 8–12 h requires injections twice a day to maintain therapeutic levels; the FIX half-life is longer (~24 h, so that once-a-day injection is sufficient. In specific situations such as postsurgery, continuous infusion of factor may be desirable because of its safety in achieving sustained factor levels at a lower total cost.

Cryoprecipitate is enriched with FVIII protein (each bag contains ~80 IU of FVIII) and was commonly used for the treatment of patients with hemophilia A decades ago; it is still in use in some developing countries, but because of the risk of bloodborne diseases, this product should be avoided in hemophilia patients when factor concentrates are available.

Mild bleeds such as uncomplicated hemarthroses and superficial hematomas require initial therapy with factor levels of 30–50%. Additional doses to maintain levels of 15–25% for 2 or 3 days are indicated for severe hemarthroses, especially when these episodes affect the “target joint.” Large hematomas, or bleeds into deep muscles, require factor levels of 50% or even higher if the clinical symptoms do not improve, and factor replacement may be required for a period of 1 week or longer. The control of serious bleeds, including those that affect the oropharyngeal spaces, CNS, and the retroperitoneum, require sustained protein levels of 50–100% for 7–10 days. Prophylactic replacement for surgery is aimed at achieving normal factor levels (100%) for a period of 7–10 days; replacement can then be tapered, depending on the extent of the surgical wounds. Oral surgery is associated with extensive tissue damage, which usually requires factor replacement for 1–3 days coupled with oral antifibrinolytic drugs.

NONTRANSFUSION THERAPY IN HEMOPHILIA

DDAVP (1-deamino-8-D-arginine vasopressin) DDAVP is a synthetic vasopressin analogue that causes a transient increase in FVIII and von Willebrand factor (vWF), but not FIX, through a mechanism involving release from endothelial cells. Patients with moderate or mild hemophilia A should be tested to determine if they respond to DDAVP before a therapeutic application.

DDAVP at doses of 0.3 µg/kg body weight infused over a 20-min period is expected to increase FVIII levels by two- to threefold over baseline, peaking between 30–60 min postinfusion. DDAVP does not improve FVIII levels in severe hemophilia A patients because there are no stores to release. Repeated dosing of DDAVP results in tachyphylaxis because the mechanism is an increase in release rather than de novo synthesis of FVIII and vWF. More than three consecutive doses become ineffective, and if further therapy is indicated, FVIII replacement is required to achieve hemostasis.

Antifibrinolytic Drugs Bleeding in the gums, in the gastrointestinal tract, and during oral surgery requires the use of oral antifibrinolytic drugs such as ε-aminocaproic acid (EACA) or tranexamic acid to control local hemostasis. The duration of the treatment depending on the clinical indication is 1 week or longer. Tranexamic acid is given at doses of 25 mg/kg three to four times a day. EACA treatment requires a loading dose of 200 mg/kg (maximum of 10 g) followed by 100 mg/kg (maximum 30 g/d) every 6 h. These drugs are not indicated to control hematuria because of the risk of formation of an occlusive clot in the lumen of genitourinary tract structures.

COMPLICATIONS

Inhibitor Formation The formation of alloantibodies to FVIII or FIX is currently the major complication of hemophilia treatment. The prevalence of inhibitors to FVIII is estimated at 5–10% of all cases and approximately 20% of severe hemophilia A patients. Inhibitors to FIX are detected in only 3–5% of all hemophilia B patients. The high-risk group for inhibitor formation includes severe deficiency (>80% of all cases of inhibitors), familial history of inhibitors, African descent, mutations in the FVIII or FIX gene resulting in deletion of large coding regions, or gross gene rearrangements. Inhibitors usually appear early in life, at a median of 2 years of age, and after 10 cumulative days of exposure.

The clinical diagnosis of inhibitor is suspected when patients do not respond to factor replacement at therapeutic doses. Inhibitors increase both morbidity and mortality in hemophilia. Because early detection of an inhibitor is critical to a successful correction of the bleeding or to eradication of the antibody, most hemophilia centers perform annual screening for inhibitors. The laboratory test required to confirm the presence of an inhibitor is an aPTT mixed with normal plasma. In most hemophilia patients, a 1:1 mix with normal plasma completely corrects the aPTT. In inhibitor patients, the aPTT on a 1:1 mix is abnormally prolonged because the inhibitor neutralizes the FVIII clotting activity of the normal plasma. The Bethesda assay uses a similar principle and defines the specificity of the inhibitor and its titer.

The results are expressed in Bethesda units (BU), in which 1 BU is the amount of antibody that neutralizes 50% of the FVIII or FIX present in normal plasma after 2 h of incubation at 37°C. Clinically, inhibitor patients are classified as low responders or high responders, which provides guidelines for optimal therapy. Therapy for inhibitor patients has two goals: the control of acute bleeding episodes and the eradication of the inhibitor. For the control of bleeding episodes, low responders (those with titers <5 BU) respond well to high doses of human or porcine FVIII (50–100 units/kg) with minimal or no increase in the inhibitor titers. However, high-responder patients (those with initial inhibitor titer >10 BU or an anamnestic response in the antibody titer to >10 BU even if low titer initially) do not respond to FVIII or FIX concentrates. The control of bleeding episodes in high-responder patients can be achieved by using concentrates enriched for prothrombin, FVII, FIX, FX [prothrombin complex concentrates (PCCs) or activated PCCs], and more recently by recombinant activated factor VII (FVIIa) (Fig. 41-1). The rates of therapeutic success have been higher for FVIIa than for PCC or aPCC. For eradication of the inhibitory antibody, immunosuppression is not effective. The most effective strategy is immune tolerance induction (ITI) based on daily infusion of the missing protein until the inhibitor disappears, typically requiring periods longer than 1 year, with success rates in the range of 60%. Promising results have been obtained by adding anti-CD20 monoclonal antibody (rituximab) as a coadjuvant for the eradication of high levels of antibody in patients undergoing ITI.

Infectious Diseases Hepatitis C virus (HCV) infection is the major cause of morbidity and the second leading cause of death in hemophilia patients exposed to older clotting factor concentrates. The vast majority of young patients treated with plasma-derived products from 1970 to 1985 became infected with HCV. It has been estimated that >80% of patients older than 20 years of age were HCV antibody positive as of 2006. The comorbidity of the underlying liver disease in hemophilia patients is clear when these individuals require invasive procedures; correction of both genetic and acquired (secondary to liver disease) deficiencies may be needed. Infection with HIV also swept the population of patients treated with plasma-derived concentrates two decades ago. Co-infection of HCV and HIV, present in almost 50% of hemophilia patients, is an aggravating factor for the evolution of liver disease. The response to HCV antiviral therapy in hemophilia is restricted to <30% of patients and is even poorer among those with both HCV and HIV infection. End-stage liver disease requiring organ transplantation may be curative for both the liver disease and for hemophilia.

FACTOR XI DEFICIENCY

Factor XI is a zymogen of an active serine protease (FXIa) in the intrinsic pathway of blood coagulation that activates FIX (see Fig. 41-1). There are two pathways for the formation of FXIa. In an aPTT-based assay, the protease is the result of activation by FXIIa in conjunction with high-molecular-weight kininogen and kallikrein. Thrombin appears to be the physiologic activator of FXI. The generation of thrombin by the tissue-factor/factor VIIa pathway activates FXI on the platelet surface, which contributes to additional thrombin generation after the clot has formed and thus augments resistance to fibrinolysis through a thrombin-activated fibrinolytic inhibitor (TAFI).

Factor XI deficiency is a rare bleeding disorder that occurs in the general population at a frequency of one in a million. However, the disease is highly prevalent among Ashkenazi and Iraqi Jewish populations, reaching a frequency of 6% as heterozygotes and 0.1–0.3% as homozygotes. More than 65 mutations in the *FXI* gene have been reported, but two to three mutations are found among affected Jewish populations.

Normal FXI clotting activity levels range from 70 to 150 U/dL. In heterozygous patients with moderate deficiency, FXI ranges from 20 to 70 U/dL, but in homozygous or double heterozygote patients, FXI levels are <1–20 U/dL. Patients with FXI levels <10% of normal have a high risk of bleeding, but the disease phenotype does not always correlate with residual FXI clotting activity. A family history is indicative of the risk of bleeding in the propositus. Clinically, the presence of mucocutaneous hemorrhages such as bruises, gum bleeding, epistaxis, hematuria, and menorrhagia are common, especially after trauma. This hemorrhagic phenotype suggests that tissues rich in fibrinolytic activity are more susceptible to FXI deficiency. Postoperative bleeding is common but not always present, even among patients with very low FXI levels.

Rx Treatment: FACTOR XI DEFICIENCY

The treatment of FXI deficiency is based on the infusion of FFP at doses of 15–20 mL/kg to maintain trough levels ranging from 10 to 20%. Because FXI has a half-life of 40–70 h, the replacement therapy can be given on alternate days. The use of antifibrinolytic drugs is beneficial to control bleeds, with the exception of hematuria or bleeds in the bladder. The development of a FXI inhibitor was observed in 10% of severely FXI-deficient patients who received replacement therapy.

OTHER RARE BLEEDING DISORDERS

Collectively, the inherited disorders resulting from deficiencies of clotting factors other than FVIII, FIX, and

FXI (Table 41-1) represent a group of rare bleeding diseases. The bleeding symptoms in these patients vary from asymptomatic (dysfibrinogenemia or FVII deficiency) to life threatening (FX or FXIII deficiency). There is no pathognomonic clinical manifestation that suggests one specific disease, but overall, in contrast to hemophilia, hemarthrosis is a rare event, and bleeding in the mucosal tract or after umbilical cord clamping is common. Individuals heterozygous for plasma coagulation deficiencies are often asymptomatic. The laboratory assessment for the specific deficient factor after screening with general coagulation tests (Table 41-1) will establish the diagnosis.

Replacement therapy using FFP or PCCs (containing prothrombin, FVII, FIX, and FX) provides adequate hemostasis in response to bleeds or as prophylactic treatment. The use of PCCs should be carefully monitored and avoided in patients with underlying liver disease or those at high risk for thrombosis because of the risk of DIC.

FAMILIAL MULTIPLE COAGULATION DEFICIENCIES

Several bleeding disorders are characterized by the inherited deficiency of more than one plasma coagulation factor. To date, the genetic defects in two of these diseases have been characterized, and they provide new insights into the regulation of hemostasis by genes encoding proteins outside blood coagulation.

Combined Deficiency of FV and FVII

Patients with combined FV and FVIII deficiency exhibit ~5% of residual clotting activity of each factor. Interestingly, the disease phenotype is a mild bleeding tendency, often after trauma. An underlying mutation has been identified in the endoplasmic reticulum/Golgi intermediate compartment (*ERGIC-53*) gene, a mannose-binding protein localized in the Golgi apparatus that functions as a chaperone for both FV and FVIII. In other families, mutations in the multiple coagulation factor deficiency 2 (*MCFD2*) gene have been defined; this gene encodes a protein that forms a Ca^{2+} -dependent complex with *ERGIC-53* and provides cofactor activity in the intracellular mobilization of both FV and FVIII.

Multiple Deficiencies of Vitamin K-Dependent Coagulation Factors

Two enzymes involved in vitamin K metabolism have been associated with combined deficiency of all vitamin K-dependent proteins, including the procoagulant proteins prothrombin, VII, IX, and X and the anticoagulants protein C and protein S. Vitamin K is a fat-soluble vitamin that is a cofactor for carboxylation of the gamma carbon of the glutamic acid residues in the vitamin

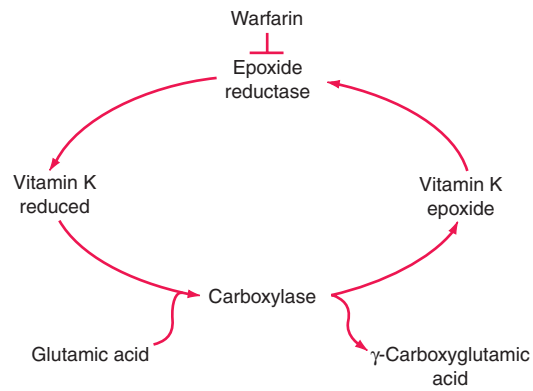


FIGURE 41-2

The vitamin K cycle. Vitamin K is a cofactor for the formation of γ -carboxyglutamic acid residues on coagulation proteins. Vitamin K-dependent γ -glutamylcarboxylase, the enzyme that catalyzes the vitamin K epoxide reductase, regenerates reduced vitamin K. Warfarin blocks the action of the reductase and competitively inhibits the effects of vitamin K.

K-dependent factors, a critical step for calcium and phospholipid binding of these proteins (Fig. 41-2). The enzymes γ -glutamylcarboxylase and epoxide reductase are critical for the metabolism and regeneration of vitamin K. Mutations in the genes encoding the gamma-carboxylase (*GGCX*) or vitamin K epoxide reductase complex 1 (*VKORC1*) result in defective enzymes and thus in vitamin K-dependent factors with reduced activity, varying from 1 to 30% of normal. The disease phenotype is characterized by mild to severe bleeding episodes present from birth. Some patients respond to high doses of vitamin K. For severe bleeding, replacement therapy with FFP or PCCs may be necessary for achieving full hemostatic control.

DISSEMINATED INTRAVASCULAR COAGULATION

DIC is a clinicopathologic syndrome characterized by widespread intravascular fibrin formation in response to excessive blood protease activity that overcomes the natural anticoagulant mechanisms. DIC is associated with several underlying pathologies (Table 41-2). The most common causes are bacterial sepsis, malignant disorders such as solid tumors or acute promyelocytic leukemia (APL), and obstetric causes. DIC is diagnosed in almost half of pregnant women with abruptio placentae or amniotic fluid embolism. Trauma, particularly to the brain, can also result in DIC. The exposure of blood to phospholipids from damaged tissue, hemolysis, and endothelial damage are all contributing factors to the development of DIC in this setting. Purpura fulminans is a severe form of DIC resulting from thrombosis of extensive areas of the skin; it affects predominantly young children after viral or bacterial infection, particularly those with inherited or acquired hypercoagulability

COMMON CLINICAL CAUSES OF DISSEMINATED INTRAVASCULAR COAGULATION
Sepsis

Bacterial
Staphylococci, streptococci, pneumococci, meningococci, gram-negative bacilli
Viral
Mycotic
Parasitic
Rickettsial

Trauma and tissue injury

Brain injury (gunshot)
Extensive burns
Fat embolism
Rhabdomyolysis

Vascular disorders

Giant hemangiomas (Kasabach-Merrit syndrome)
Large vessel aneurysms (e.g., aorta)

Obstetric complications

Abruptio placentae
Amniotic fluid embolism
Dead fetus syndrome
Septic abortion

Cancer

Adenocarcinoma (e.g., prostate, pancreas)
Hematologic malignancies (acute promyelocytic leukemia)

Immunologic disorders

Acute hemolytic transfusion reaction
Organ or tissue transplant rejection
Graft-versus-host disease

Drugs

Fibrinolytic agents
Aprotinin
Warfarin (especially in neonates with protein C deficiency)
Prothrombin complex concentrates
Recreational drugs (amphetamines)

Envenomation

Snake
Insects

Liver disease

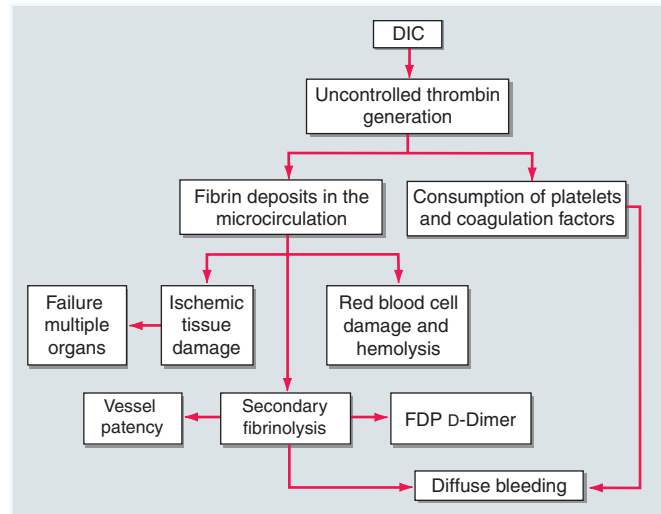
Fulminant hepatic failure
Cirrhosis
Fatty liver of pregnancy

Miscellaneous

Shock
Respiratory distress syndrome
Massive transfusion

caused by deficiencies of the components of the protein C pathway. Neonates homozygous for protein C deficiency also have a high risk for purpura fulminans with or without thrombosis of large vessels.

The central mechanism of DIC is the uncontrolled generation of thrombin by exposure of the blood to pathologic levels of tissue factor (Fig. 41-3). Simultaneous suppression of physiologic anticoagulant mechanisms and abnormal fibrinolysis further accelerate the process. Together these abnormalities contribute to systemic fibrin deposition in small- and mid-sized vessels. The duration and intensity of the fibrin deposition can compromise the blood supply of many organs, especially the lung, kidney, liver, and brain, with consequent organ failure. The sustained activation of coagulation results in consumption of clotting factors and platelets, which in


FIGURE 41-3

The pathophysiology of disseminated intravascular coagulation (DIC). Interactions between coagulation and fibrinolytic pathways result in bleeding and thrombosis in the microcirculation in patients with DIC. FDP, fibrin degradation product; RBC, red blood cell.

turn leads to systemic bleeding. This is further aggravated by secondary hyperfibrinolysis. Studies in animals demonstrate that the fibrinolytic system is indeed suppressed at the time of maximal activation of coagulation. Interestingly, in patients with APL, a severe hyperfibrinolytic state often occurs in addition to the coagulation activation. The release of several proinflammatory cytokines such as interleukin-6 and tumor necrosis factor α play central roles in mediating the coagulation defects in DIC and symptoms associated with systemic inflammatory response syndrome.

Clinical manifestations of DIC are related to the magnitude of the imbalance of hemostasis, to the underlying disease, or to both. The most common findings are bleeding ranging from oozing from venipuncture sites, petechiae, and ecchymoses to severe hemorrhage from the gastrointestinal tract or lung or into the CNS. In chronic DIC, the bleeding symptoms are discrete and restricted to skin or mucosal surfaces. The hypercoagulability of DIC manifests as the occlusion of vessels in the microcirculation and resulting organ failure. Thrombosis of large vessels and cerebral embolism can also occur. Hemodynamic complications and shock are common among patients with acute DIC. The mortality ranges from 30 to >80% depending on the underlying disease, the severity of the DIC, and the age of the patient.

The diagnosis of clinically significant DIC is based on the presence of clinical or laboratory abnormalities of coagulation or thrombocytopenia. The laboratory diagnosis of DIC should prompt a search for the underlying disease if it is not already apparent. No single test establishes the

diagnosis of DIC. The laboratory investigation should include coagulation tests [aPTT, PT, thrombin time (TT)] and markers of fibrin degradation products (FDP) in addition to platelet and red blood cell (RBC) count and analysis of the blood smear. These tests should be repeated over a period of 6–8 h because an initially mild abnormality can be changed dramatically in patients with severe DIC.

Common findings include the prolongation of PT or aPTT; platelet counts $\leq 100,000/\text{mm}^3$, or a rapid decline in platelet numbers; the presence of schistocytes (fragmented RBCs) in the blood smear; and elevated levels of FDP. The most sensitive test for DIC is the FDP level. DIC is an unlikely diagnosis in the presence of normal levels of FDP. The D-dimer test is more specific for detection of fibrin (but not fibrinogen) degradation products and indicates that the cross-linked fibrin has been digested by plasmin. Because fibrinogen has a prolonged half-life, plasma levels diminish acutely only in severe cases of DIC. High-grade DIC is also associated with levels of antithrombin III (ATIII) or plasminogen activity $< 60\%$ of normal.

Chronic Disseminated Intravascular Coagulation

Low-grade, compensated DIC can occur in certain clinical situations, including giant hemangioma, metastatic carcinoma, or the dead fetus syndrome. Plasma levels of FDP or D-dimers are elevated. aPTT, PT, and fibrinogen values are within the normal range or high. Mild thrombocytopenia or normal platelet counts are also common findings. RBC fragmentation is often detected but at a lower degree than in acute DIC.

Differential Diagnosis

The differential diagnosis between DIC and severe liver disease is challenging and requires serial measurements of the laboratory parameters of DIC. Patients with severe liver disease are at risk for bleeding and manifest laboratory features that include thrombocytopenia (caused by platelet sequestration, portal hypertension, or hypersplenism), decreased synthesis of coagulation factors and natural anticoagulants, and elevated levels of FDP because of reduced hepatic clearance. However, in contrast to DIC, these laboratory parameters in patients with liver disease do not change rapidly. Other important differential findings include the presence of portal hypertension or other clinical or laboratory evidence of underlying liver disease.

Microangiopathic disorders such as thrombotic thrombocytopenic purpura present an acute clinical onset of illness accompanied by thrombocytopenia, RBC fragmentation, and multiorgan failure. There is, however, no consumption of clotting factors or hyperfibrinolysis.

Rx Treatment: DISSEMINATED INTRAVASCULAR COAGULATION

The morbidity and mortality associated with DIC are primarily related to the underlying disease rather than the complications of the DIC. The control or elimination of the underlying cause should therefore be the primary concern. Patients with severe DIC require control of hemodynamic parameters, respiratory support, and sometimes invasive surgical procedures. Attempts to treat DIC without accompanying treatment of the causative disease are likely to fail.

MANAGEMENT OF HEMORRHAGIC SYMPTOMS

The control of bleeding in DIC patients with marked thrombocytopenia (platelet counts $< 10,000\text{--}20,000/\text{mm}^3$) and low levels of coagulation factors require replacement therapy. The PT ($> 1.5 \times$ normal) provides a good indicator of the severity of the clotting factor consumption. Replacement with FFP is indicated (1 unit of FFP increases most coagulation factors by 3% in an adult without DIC). Low levels of fibrinogen ($< 100 \text{ mg/dL}$) or brisk hyperfibrinolysis require infusion of cryoprecipitate (plasma fraction enriched for fibrinogen, FVIII, and vWF). The replacement of 10 U of cryoprecipitate for every 2–3 unit of FFP is sufficient to correct the hemostasis. The transfusion scheme must be adjusted according to the patient's clinical and laboratory evolution. Platelet concentrates at a dose of 1–2 U/10 kg body weight are sufficient for most DIC patients with severe thrombocytopenia.

Clotting factor concentrates are not recommended for control of bleeding in patients with DIC because of the limited efficacy afforded by replacement of single factors (factor VIII or IX concentrates) and the high risk of products containing traces of activated blood proteases (PCCs), which further aggravates the disease.

REPLACEMENT OF COAGULATION OR FIBRINOLYSIS INHIBITORS

Drugs to control coagulation such as heparin, ATIII concentrates, or antifibrinolytic drugs have all been tried in the treatment of patients with DIC. Low doses of continuous infusion heparin (5–10 U/kg per h) may be effective in patients with low-grade DIC associated with solid tumor or APL or in a setting with recognized thrombosis. Heparin is also indicated for the treatment of purpura fulminans, during the surgical resection of giant hemangiomas, and during removal of a dead fetus. In acute DIC, the use of heparin is likely to aggravate bleeding. To date, the use of heparin in severe DIC patients is of no proven survival benefit.

The use of antifibrinolytic drugs, EACA, or tranexamic acid to prevent fibrin degradation by plasmin may reduce bleeding episodes in patients with DIC and confirmed hyperfibrinolysis. However, these drugs can

increase the risk of thrombosis, and concomitant use of heparin is indicated. Patients with APL or those with chronic DIC associated with giant hemangiomas are among the few patients who may benefit from this therapy.

The use of protein C concentrates to treat purpura fulminans associated with acquired protein C deficiency or meningococemia has been proven effective. The results from the replacement of ATIII in early-phase studies are promising but require further study.

VITAMIN K DEFICIENCY

Vitamin K–dependent proteins are a heterogeneous group, including clotting factor proteins and proteins found in bone, lung, kidney, and placenta. Vitamin K mediates posttranslational modification of glutamate residues to γ -carboxyglutamate, a critical step for the activity of vitamin K–dependent proteins for calcium binding and proper assembly to phospholipid membranes (Fig. 41-2). Inherited deficiency of the functional activity of the enzymes involved in vitamin K metabolism, notably the GGCX or VKOR-1 (see earlier), results in bleeding disorders. The amount of vitamin K in the diet is often limiting for the carboxylation reaction; thus, recycling of vitamin K is essential to maintain normal levels of vitamin K–dependent proteins. In adults, low dietary intake alone is seldom reason for severe vitamin K deficiency but may become common in association with the use of broad-spectrum antibiotics. Disease or surgical interventions that affect the ability of the intestinal tract to absorb vitamin K, either through anatomic alterations or by changing the fat content of bile salts and pancreatic juices in the proximal small bowel, can result in significant reduction of vitamin K levels. Chronic liver diseases such as primary biliary cirrhosis also deplete vitamin K stores. Neonatal vitamin K deficiency and the resulting hemorrhagic disease of the newborn have been almost entirely eliminated by routine administration of vitamin K to all neonates. Prolongation of PT values is the most common and earliest finding in vitamin K–deficient patients because of reduction in prothrombin, FVII, FIX, and FX levels. FVII has the shortest half-life among these factors, which can prolong the PT before changes in the aPTT. Parenteral administration of vitamin K at a total dose of 10 mg is sufficient to restore normal levels of clotting factor within 8–10 h. In the presence of ongoing bleeding or a need for immediate correction before an invasive procedure, replacement with FFP or PCC is required. PCC should be avoided in patients with severe underlying liver disorders because of their high risk of thrombosis. The reversal of excessive anticoagulant therapy with warfarin or warfarin-like drugs can be achieved by minimal doses of vitamin K (1 mg orally or by IV injection) for asymptomatic patients. This strategy

can diminish the risk of bleeding while maintaining therapeutic anticoagulation for an underlying prothrombotic state.

COAGULATION DISORDERS ASSOCIATED WITH LIVER FAILURE

The liver is central to hemostasis because it is the site of synthesis and clearance of most procoagulant and natural anticoagulant proteins and of essential components of the fibrinolytic system. Liver failure is associated with a high risk of bleeding because of deficient synthesis of procoagulant factors and enhanced fibrinolysis. Thrombocytopenia is common in patients with liver disease and may be caused by congestive splenomegaly (hypersplenism) or immune-mediated shortened platelet life span (primary biliary cirrhosis). In addition, several anatomic abnormalities secondary to underlying liver disease further promote the occurrence of hemorrhage (Table 41-3). Dysfibrinogenemia is a relatively common finding in patients with liver disease caused by impaired fibrin polymerization. The development of DIC concomitant to chronic liver disease is common and may enhance the risk for bleeding. Laboratory evaluation is mandatory for an optimal therapeutic strategy, either to control ongoing bleeding or to prepare patients with liver disease for invasive procedures. Typically, these patients present with prolonged PT, aPTT, and TT,

TABLE 41-3

COAGULATION DISORDERS AND HEMOSTASIS IN LIVER DISEASE

Bleeding

- Portal hypertension
- Esophageal varices
- Thrombocytopenia
- Splenomegaly
- Chronic or acute DIC
- Decreased synthesis of clotting factors
- Hepatocyte failure
- Vitamin K deficiency
- Systemic fibrinolysis
- DIC
- Dysfibrinogenemia

Thrombosis

- Decreased synthesis of coagulation inhibitors: protein C, protein S, antithrombin
- Hepatocyte failure
- Vitamin K deficiency (protein C, protein S)
- Failure to clear activated coagulation proteins (DIC)
- Dysfibrinogenemia
- Iatrogenic: transfusion of prothrombin complex concentrates
- Antifibrinolytic agents: EACA, tranexamic acid

Note: DIC, disseminated intravascular coagulation; EACA, ϵ -aminocaproic acid.

depending on the degree of liver damage; thrombocytopenia; and a normal or slight increase of FDP. Fibrinogen levels are diminished only in those with fulminant hepatitis, decompensated cirrhosis, or advanced liver disease or in the presence of DIC. The presence of prolonged TT, normal fibrinogen, and FDP levels suggests dysfibrinogenemia. FVIII levels are often normal or elevated in patients with liver failure, and decreased levels suggest superimposing DIC. Because FV is only synthesized in the hepatocyte and is not a vitamin K–dependent protein, reduced levels of FV may be an indicator of hepatocyte failure. Normal levels of FV and low levels of FVII suggest vitamin K deficiency. Vitamin K levels may be reduced in patients with liver failure caused by compromised storage in hepatocellular disease, changes in bile acids, or cholestasis that can diminish the absorption of vitamin K. Replacement of vitamin K may be desirable (10 mg given by slow IV injection) to improve hemostasis.

Treatment with FFP is the most effective way to correct hemostasis in patients with liver failure. Infusion of FFP (5–10 mL/kg; each bag contains ~200 mL) is sufficient to ensure 10–20% of normal levels of clotting factors but not correction of PT or aPTT. Even high doses of FFP (20 mL/kg) do not correct the clotting times in all patients. Monitoring for clinical symptoms and clotting times will determine if repeated doses are required 8–12 h after the first infusion. Platelet concentrates are indicated when platelet counts are $<10,000$ – $20,000/\text{mm}^3$ to control an ongoing bleed or immediately before an invasive procedure if counts are $<50,000/\text{mm}^3$. Cryoprecipitate is indicated only when fibrinogen levels are <100 mg/mL; dosing is six bags for a 70-kg patient daily. As noted above, PCC infusion in patients with liver failure should be avoided because of the high risk of thrombotic complications. The safety of antifibrinolytic drugs to control bleeding in patients with liver failure is not yet well defined and should be avoided.

ACQUIRED INHIBITORS OF COAGULATION FACTORS

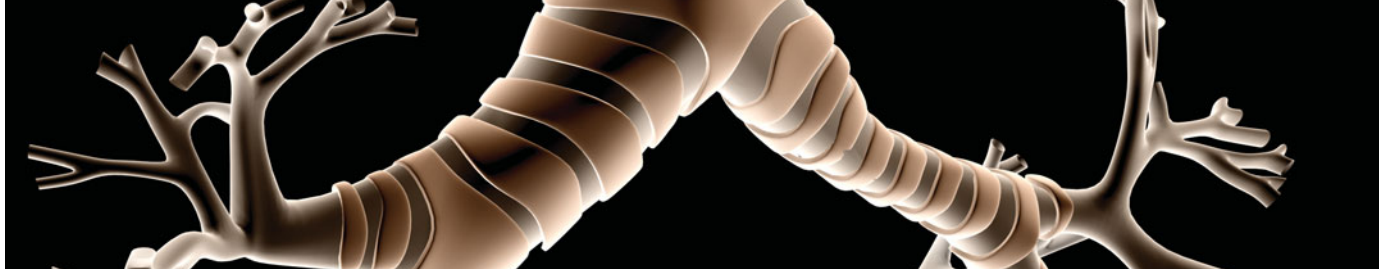
An *acquired inhibitor* is an immune-mediated disease characterized by the presence of an autoantibody against a specific clotting factor. FVIII is the most common target of antibody formation, but inhibitors to prothrombin, FV, FIX, FX, and FXI are also reported. The disease occurs predominantly in older adults (median age, 60 years) but occasionally in pregnant or postpartum women with no previous history of bleeding. In 50% of patients with inhibitors, no underlying disease is identified at the time of diagnosis. In the remaining half, the causes are autoimmune diseases, malignancies (lymphomas, prostate cancer), dermatologic diseases, and pregnancy. Previous

history of open surgery in which topical thrombin is used, especially preparations containing bovine FV, is sometimes associated. Bleeding episodes occur commonly into soft tissues and in the gastrointestinal or urinary tracts and skin. In contrast to hemophilia, hemarthrosis is rare. Retroperitoneal hemorrhages and other life-threatening bleeding may appear suddenly. The overall mortality in untreated patients ranges from 8 to 22%, and most deaths occur within the first few weeks after presentation. The diagnosis is based on the prolonged aPTT with normal PT and TT. The aPTT remains prolonged after mixture of the test plasma with equal amounts of pooled normal plasma for 2 h at 37°C. The Bethesda assay using FVIII-deficient plasma as performed for inhibitor detection in hemophilia will confirm the diagnosis. Major bleeding is treated with high doses of human or porcine FVIII, PCC/PCCa, or recombinant FVIIa. High-dose IV γ -globulin and anti-CD20 monoclonal antibody (rituximab) have been reported to be effective in patients with autoantibodies to FVIII. In contrast to hemophilia, inhibitors in nonhemophilia patients are sometimes responsive to prednisone alone or in association with cytotoxic therapy (e.g., cyclophosphamide).

The presence of lupus anticoagulant can be associated with venous or arterial thrombotic disease. However, bleeding has also been reported in lupus anticoagulant; it is attributable to the presence of antibodies to prothrombin, which results in hypoprothrombinemia. Both disorders show a prolonged PTT that does not correct on mixing. To distinguish acquired inhibitors from lupus anticoagulants, results of the dilute Russell's viper venom test and the hexagonal-phase phospholipids test will be negative in patients with an acquired inhibitor and positive in patients with lupus anticoagulants. Moreover, lupus anticoagulant interferes with the clotting activity of many factors (FVIII, FIX, FXII, FXI); acquired inhibitors are specific to a single factor.

FURTHER READINGS

- CALDWELL SH et al: Coagulation disorders and hemostasis in liver disease: Pathophysiology and critical assessment of current management. *Hepatology* 44:1039, 2006
- DUBOSE TD: Metabolic alkalosis, in *Primer on Kidney Diseases*, 5th ed, A Greenberg (ed). Saunders Elsevier, 2009, pp 84–90
- : Acid-base disorders, in *Brenner and Rector's The Kidney*, 8th ed, BM Brenner (ed). Philadelphia, Saunders, 2008, pp 505–546
- HOYER LW: Hemophilia A. *N Engl J Med* 330:39, 1994
- KEY NS, NEGRIER C: Coagulation factor concentrates: Past, present, and future. *Lancet* 370:439, 2007
- LEVI M, OPAL SM: Coagulation abnormalities in critically ill patients. *Crit Care* 10:222, 2006
- MANNUCCI PM, et al: Recessively inherited coagulation disorders. *Blood* 104:1243, 2004
- STAFFORD DW: The vitamin K cycle. *J Thromb Haemost* 3:1873, 2005



CHAPTER 42

TREATMENT AND PROPHYLAXIS OF BACTERIAL INFECTIONS

Gordon L. Archer ■ Ronald E. Polk

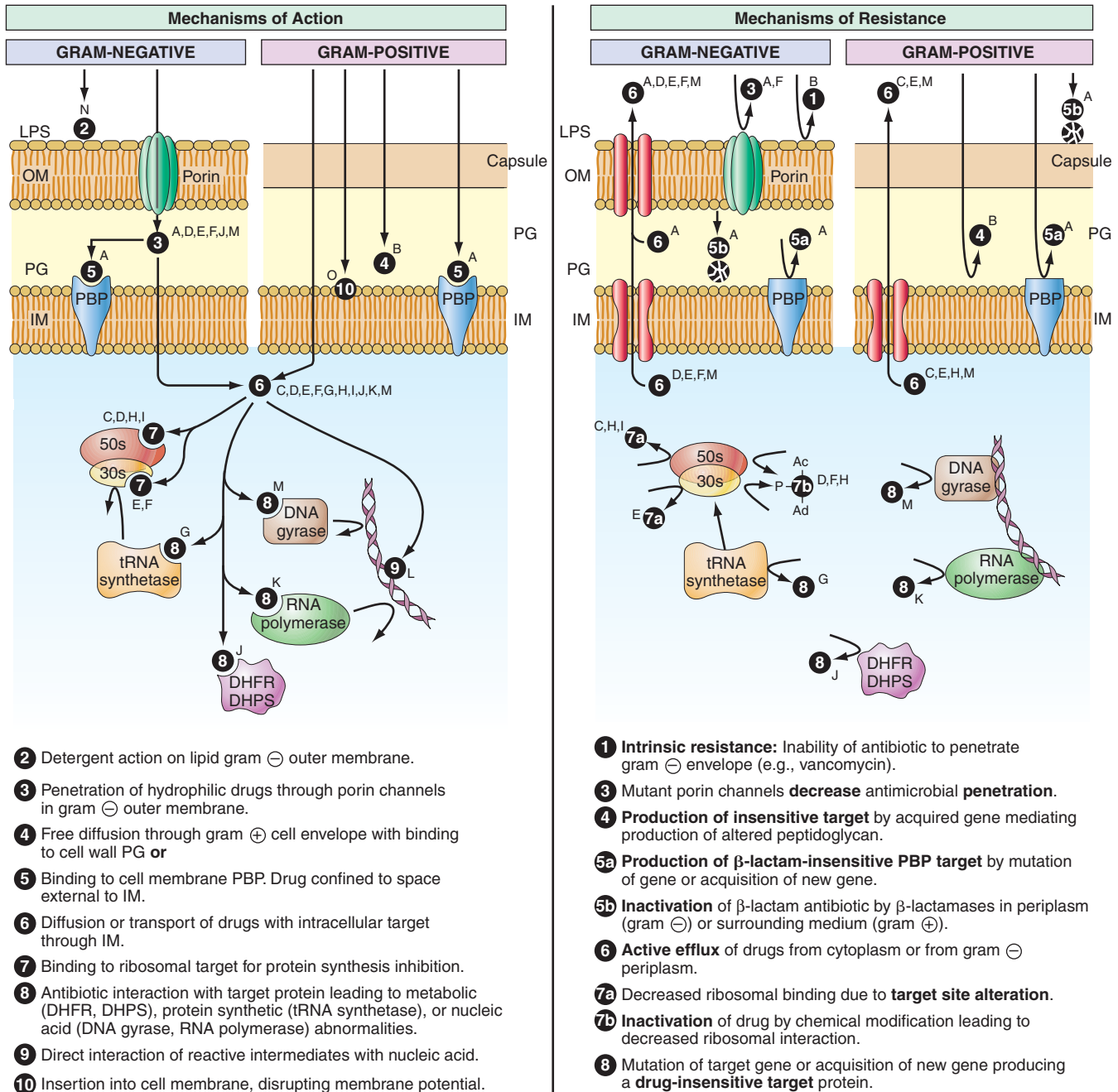
■ Mechanisms of Action	434	■ Principles of Antibacterial Chemotherapy	443
Inhibition of Cell Wall Synthesis	437	Susceptibility of Bacteria to Antibacterial Drugs In Vitro	444
Inhibition of Protein Synthesis	438	Pharmacodynamics: Relationship of Pharmacokinetics and In Vitro Susceptibility to Clinical Response	444
Inhibition of Bacterial Metabolism	439	Status of the Host	445
Inhibition of Nucleic Acid Synthesis or Activity	439	Site of Infection	446
Alteration of Cell-Membrane Permeability	440	Combination Chemotherapy	447
■ Mechanisms of Resistance	440	Empirical Therapy	447
β-Lactam Antibiotics	440	■ Choice of Antibacterial Therapy	448
Vancomycin	441	■ Adverse Reactions	450
Aminoglycosides	441	Drug Interactions	450
Macrolides, Ketolides, Lincosamides, and Streptogramins	441	Macrolides and Ketolides	450
Chloramphenicol	441	Quinupristin/Dalfopristin	450
Tetracyclines and Tigecycline	441	Linezolid	450
Mupirocin	441	Tetracyclines	450
Trimethoprim and Sulfonamides	442	Sulfonamides	451
Quinolones	442	Fluoroquinolones	452
Rifampin	442	Rifampin	452
Linezolid	442	Metronidazole	453
Multiple Antibiotic Resistance	442	■ Prophylaxis of Bacteria Infections	453
■ Pharmacokinetics of Antibiotics	442	■ Duration of Therapy and Treatment Failure	454
Absorption	442	■ Mechanisms to Optimize Antimicrobial Use	454
Distribution	443	■ Further Readings	455
Metabolism and Elimination	443		

The development of vaccines and drugs that prevent and cure bacterial infections was one of the twentieth century's major contributions to human longevity and quality of life. Antibacterial agents are among the most commonly prescribed drugs of any kind worldwide. Used appropriately, these drugs are lifesaving. However, their indiscriminate use drives up the cost of health care, leads to a plethora of side effects and drug interactions; and fosters the emergence of bacterial resistance, rendering previously valuable drugs useless. The rational use of antibacterial agents depends on an understanding of (1) the drugs' mechanisms of action, spectrum of activity, pharmacokinetics, pharmacodynamics, toxicities, and interactions; (2) mechanisms underlying bacterial resistance;

and (3) strategies that can be used by clinicians to limit resistance. In addition, patient-associated parameters, such as infection site, other drugs being taken, allergies, and immune and excretory status, are critically important to appropriate therapeutic decisions. This chapter provides specific data required for making informed choices of antibacterial agents.

MECHANISMS OF ACTION

Antibacterial agents, like all antimicrobial drugs, are directed against unique targets not present in mammalian cells. The goal is to limit toxicity to the host and maximize chemotherapeutic activity affecting

**FIGURE 42-1**

Mechanisms of action of and resistance to antibacterial agents. Black lines trace the routes of drug interaction with bacterial cells, from entry to target site. The letters in each figure indicate specific antibacterial agents or classes of agents, as shown in Table 42-1. The numbers correspond to mechanisms listed beneath each panel. 50s and 30s, large

invading microbes only. *Bactericidal drugs* kill the bacteria that are within their spectrum of activity; *bacteriostatic drugs* only inhibit bacterial growth. Although bacteriostatic activity is adequate for the treatment of most infections, bactericidal activity may be necessary for cure in patients with altered immune systems (e.g.,

and small ribosome subunits; Ac, acetylation; Ad, adenylation; DHFR, dihydrofolate reductase; DHPS, dihydropteroate synthetase; IM, inner (cytoplasmic) membrane; LPS, lipopolysaccharide; OM, outer membrane; P, phosphorylation; PBP, penicillin-binding protein; PG, peptidoglycan.

neutropenia), protected infectious foci (e.g., endocarditis or meningitis), or specific infections (e.g., complicated *Staphylococcus aureus* bacteremia). The mechanisms of action of the antibacterial agents to be discussed in this section are summarized in Table 42-1 and are depicted in Fig. 42-1.

MECHANISMS OF ACTION OF AND RESISTANCE TO MAJOR CLASSES OF ANTIBACTERIAL AGENTS

LETTER FOR FIG. 42-1	ANTIBACTERIAL AGENT ^a	MAJOR CELLULAR TARGET	MECHANISM OF ACTION	MAJOR MECHANISMS OF RESISTANCE
A	β-Lactams (penicillins and cephalosporins)	Cell wall	Inhibit cell wall cross-linking	1. Drug inactivation (β-lactamase) 2. Insensitivity of target (altered PBPs) 3. Decreased permeability (altered gram-negative outer-membrane porins) 4. Active efflux
B	Vancomycin	Cell wall	Interferes with addition of new cell wall subunits (muramyl pentapeptides)	Alteration of target (substitution of terminal amino acid of peptidoglycan subunit)
	Bacitracin	Cell wall	Prevents addition of cell wall subunits by inhibiting recycling of membrane lipid carrier	Not defined
C	Macrolides (erythromycin)	Protein synthesis	Bind to 50S ribosomal subunit	1. Alteration of target (ribosomal methylation and mutation of 23S rRNA) 2. Active efflux
	Lincosamides (clindamycin)	Protein synthesis	Bind to 50S ribosomal subunit	Alteration of target (ribosomal methylation)
D	Chloramphenicol	Protein synthesis	Binds to 50S ribosomal subunit	1. Drug inactivation (chloramphenicol acetyltransferase) 2. Active efflux
E	Tetracycline	Protein synthesis	Binds to 30S ribosomal subunit	1. Decreased intracellular drug accumulation (active efflux) 2. Insensitivity of target
F	Aminoglycosides (gentamicin)	Protein synthesis	Bind to 30S ribosomal subunit	1. Drug inactivation (aminoglycoside-modifying enzyme) 2. Decreased permeability through gram-negative outer membrane 3. Active efflux
G	Mupirocin	Protein synthesis	Inhibits isoleucine tRNA synthetase	Mutation of gene for target protein or acquisition of new gene for drug-insensitive target
H	Quinupristin/dalfopristin (Synercid)	Protein synthesis	Binds to 50S ribosomal subunit	1. Alteration of target (ribosomal methylation: dalfopristin) 2. Active efflux (quinupristin) 3. Drug inactivation (quinupristin and dalfopristin)
I	Linezolid	Protein synthesis	Bind to 50S ribosomal subunit	Alteration of target (mutation of 23S rRNA)
J	Sulfonamides and trimethoprim	Cell metabolism	Competitively inhibit enzymes involved in two steps of folic acid biosynthesis	Production of insensitive targets (dihydropteroate synthetase [sulfonamides] and dihydrofolate reductase [trimethoprim]) that bypass metabolic block
K	Rifampin	Nucleic acid synthesis	Inhibits DNA-dependent RNA polymerase	Insensitivity of target (mutation of polymerase gene)
L	Metronidazole	Nucleic acid synthesis	Intracellularly generates short-lived reactive intermediates that damage DNA by electron transfer system	Not defined
M	Quinolones (ciprofloxacin)	DNA synthesis	Inhibit DNA gyrase (A subunit) I and topoisomerase IV	1. Insensitivity of target (mutation of gyrase genes) 2. Decreased intracellular drug accumulation (active efflux)
	Novobiocin	DNA synthesis	Inhibits DNA gyrase (B subunit)	Not defined

TABLE 42-1 (CONTINUED)

MECHANISMS OF ACTION OF AND RESISTANCE TO MAJOR CLASSES OF ANTIBACTERIAL AGENTS				
LETTER FOR FIG. 42-1	ANTIBACTERIAL AGENT ^a	MAJOR CELLULAR TARGET	MECHANISM OF ACTION	MAJOR MECHANISMS OF RESISTANCE
N	Polymyxins (polymyxin B)	Cell membrane	Disrupt membrane permeability by charge alteration	Not defined
O	Gramicidin Daptomycin	Cell membrane Cell membrane	Forms pores Forms channels that disrupt membrane potential	Not defined Not defined

^a Compounds in parentheses are major representatives for the class.

Note: PBP, penicillin-binding protein.

INHIBITION OF CELL WALL SYNTHESIS

One major difference between bacterial and mammalian cells is the presence in bacteria of a rigid wall external to the cell membrane. The wall protects bacterial cells from osmotic rupture, which would result from the cell's usual marked hyperosmolarity (by ≤ 20 atm) relative to the host environment. The structure conferring cell wall rigidity and resistance to osmotic lysis in both gram-positive and gram-negative bacteria is peptidoglycan, a large, covalently linked sacculus that surrounds the bacterium. In gram-positive bacteria, peptidoglycan is the only layered structure external to the cell membrane and is thick (20–80 nm); in gram-negative bacteria, there is an outer membrane external to a very thin (1-nm) peptidoglycan layer.

Chemotherapeutic agents directed at any stage of the synthesis, export, assembly, or cross-linking of peptidoglycan lead to inhibition of bacterial cell growth and, in most cases, to cell death. Peptidoglycan is composed of (1) a backbone of two alternating sugars, *N*-acetylglucosamine and *N*-acetylmuramic acid; (2) a chain of four amino acids that extends down from the backbone (stem peptides); and (3) a peptide bridge that cross-links the peptide chains. Peptidoglycan is formed by the addition of subunits (a sugar with its five attached amino acids) that are assembled in the cytoplasm and transported through the cytoplasmic membrane to the cell surface. Subsequent cross-linking is driven by cleavage of the terminal stem-peptide amino acid.

Virtually all the antibiotics that inhibit bacterial cell wall synthesis are bactericidal. That is, they eventually result in the cell's death because of osmotic lysis. However, much of the loss of cell wall integrity after treatment with cell wall-active agents is because of the bacteria's own cell wall remodeling enzymes (autolysins) that cleave peptidoglycan bonds in the normal course of cell growth. In the presence of antibacterial agents that

inhibit cell wall growth, autolysis proceeds without normal cell wall repair; weakness and eventual cellular lysis occur.

Antibacterial agents act to inhibit cell wall synthesis in several ways, as described below.

Bacitracin

Bacitracin, a cyclic peptide antibiotic, inhibits the conversion to its active form of the lipid carrier that moves the water-soluble cytoplasmic peptidoglycan subunits through the cell membrane to the cell exterior.

Glycopeptides

Glycopeptides (vancomycin and teicoplanin) are high-molecular-weight antibiotics that bind to the terminal *D*-alanine–*D*-alanine component of the stem peptide while the subunits are external to the cell membrane but still linked to the lipid carrier. This binding sterically inhibits the addition of subunits to the peptidoglycan backbone.

β -Lactam Antibiotics

β -Lactam antibiotics (penicillins, cephalosporins, carbapenems, and monobactams; Table 42-2) are characterized by a four-membered β -lactam ring and prevent the cross-linking reaction called *transpeptidation*. The energy for attaching a peptide cross-bridge from the stem peptide of one peptidoglycan subunit to another is derived from the cleavage of a terminal *D*-alanine residue from the subunit stem peptide. The cross-bridge amino acid is then attached to the penultimate *D*-alanine by transpeptidase enzymes. The β -lactam ring of the antibiotic forms an irreversible covalent acyl bond with the transpeptidase enzyme (probably because of the antibiotic's steric similarity to the enzyme's *D*-alanine–*D*-alanine target), preventing the cross-linking reaction. Transpeptidases and similar enzymes involved in cross-linking are called *penicillin-binding proteins* (PBPs) because they all have active sites that bind β -lactam antibiotics.

TABLE 42-2

CLASSIFICATION OF β -LACTAM ANTIBIOTICS

CLASS	ROUTE OF ADMINISTRATION	
	PARENTERAL	ORAL
Penicillins		
β -Lactamase-susceptible		
Narrow-spectrum	Penicillin G	Penicillin V
Enteric-active	Ampicillin	Amoxicillin, ampicillin
Enteric-active and antipseudomonal	Ticarcillin, piperacillin	None
β -Lactamase-resistant		
Antistaphylococcal	Oxacillin, nafcillin	Cloxacillin, dicloxacillin
Combined with β -lactamase inhibitors	Ticarcillin plus clavulanic acid, ampicillin plus sulbactam, piperacillin plus tazobactam	Amoxicillin plus clavulanic acid
Cephalosporins		
First generation	Cefazolin, cephalothin, cephapirin	Cephalexin, cephadrine, cefadroxil
Second generation		
<i>Haemophilus</i> active	Cefamandole, cefuroxime, cefonicid, ceforanide	Cefaclor, cefuroxime axetil, cefibuten, cefdinir, cefpodoxime, ^a cefprozil, loracarbef
<i>Bacteroides</i> active	Cefoxitin, cefotetan, cefmetazole	None
Third generation		
Extended spectrum	Ceftriaxone, cefotaxime, ceftizoxime	None
Extended spectrum and antipseudomonal	Ceftazidime, cefepime	None
Carbapenems	Imipenem-cilastatin, meropenem, ertapenem	None
Monobactams	Aztreonam	None

^a Some sources classify cefpodoxime as a third-generation oral agent because of a marginally broader spectrum.

INHIBITION OF PROTEIN SYNTHESIS

Most of the antibacterial agents that inhibit protein synthesis interact with the bacterial ribosome. The difference between the composition of bacterial and mammalian ribosomes gives these compounds their selectivity.

Aminoglycosides

Aminoglycosides (gentamicin, kanamycin, tobramycin, streptomycin, neomycin, and amikacin) are a group of structurally related compounds containing three linked hexose sugars. They exert a bactericidal effect by binding irreversibly to the 30S subunit of the bacterial ribosome and blocking initiation of protein synthesis. Uptake of aminoglycosides and their penetration through the cell membrane constitute an aerobic, energy-dependent process. Thus, aminoglycoside activity is markedly reduced in an anaerobic environment. *Spectinomycin*, an aminocyclitol antibiotic, also acts on the 30S ribosomal subunit but has a different mechanism of action from

the aminoglycosides and is bacteriostatic rather than bactericidal.

Macrolides, Ketolides, and Lincosamides

Macrolide antibiotics (erythromycin, clarithromycin, and azithromycin) consist of a large lactone ring to which sugars are attached. *Ketolide antibiotics*, including telithromycin, replace the cladinose sugar on the macrolactone ring with a ketone group. These drugs bind specifically to the 50S portion of the bacterial ribosome and inhibit protein chain elongation. Although structurally unrelated to the macrolides, *lincosamides* (clindamycin and lincomycin) bind to a site on the 50S ribosome nearly identical to the binding site for macrolides.

Streptogramins

Streptogramins [quinupristin (streptogramin B) and dal-fopristin (streptogramin A)], which are supplied as a combination in Synercid, are peptide macrolactones that

also bind to the 50S ribosomal subunit and block protein synthesis. Whereas streptogramin B binds to a ribosomal site similar to the binding site for macrolides and lincosamides, streptogramin A binds to a different ribosomal site, blocking the late phase of protein synthesis. The two streptogramins act synergistically to kill bacteria if the strain is susceptible to both components.

Chloramphenicol

Chloramphenicol consists of a single aromatic ring and a short side chain. This antibiotic binds reversibly to the 50S portion of the bacterial ribosome at a site close to but not identical with the binding sites for the macrolides and lincosamides, inhibiting peptide bond formation.

Linezolid

Linezolid is the only commercially available drug in the oxazolidinone class. Linezolid binds to the 50S ribosomal subunit and blocks the initiation of protein synthesis.

Tetracyclines and Glycylcyclines

Tetracyclines (tetracycline, doxycycline, and minocycline) and glycylcyclines (tigecycline) consist of four aromatic rings with various substituent groups. They interact reversibly with the bacterial 30S ribosomal subunit, blocking the binding of aminoacyl tRNA to the mRNA–ribosome complex. This mechanism is markedly different from that of the aminoglycosides, which also bind to the 30S subunit.

Mupirocin

Mupirocin (pseudomonic acid) inhibits isoleucine tRNA synthetase by competing with bacterial isoleucine for its binding site on the enzyme and depleting cellular stores of isoleucine-charged tRNA.

INHIBITION OF BACTERIAL METABOLISM

The *antimetabolites* are all synthetic compounds that interfere with bacterial synthesis of folic acid. Products of the folic acid synthesis pathway function as coenzymes for the one-carbon transfer reactions that are essential for the synthesis of thymidine, all purines, and several amino acids. Inhibition of folate synthesis leads to cessation of bacterial cell growth and, in some cases, to bacterial cell death. The principal antibacterial antimetabolites are sulfonamides (sulfisoxazole, sulfadiazine, and sulfamethoxazole) and trimethoprim.

Sulfonamides

Sulfonamides are structural analogues of *p*-aminobenzoic acid (PABA), one of the three structural components of folic acid (the other two being pteridine and glutamate). The first step in the synthesis of folic acid is the addition of PABA to pteridine by the enzyme dihydropteroic acid

synthetase. Sulfonamides compete with PABA as substrates for the enzyme. The selective effect of sulfonamides is because of the fact that bacteria synthesize folic acid but mammalian cells cannot synthesize the cofactor and must use exogenous supplies. However, the activity of sulfonamides can be greatly reduced by the presence of excess PABA or by the exogenous addition of end products of one-carbon transfer reactions (e.g., thymidine and purines). High concentrations of the latter substances may be present in some infections as a result of tissue and white blood cell breakdown, compromising sulfonamide activity.

Trimethoprim

Trimethoprim is a diaminopyrimidine, a structural analogue of the pteridine moiety of folic acid. Trimethoprim is a competitive inhibitor of dihydrofolate reductase; this enzyme is responsible for reduction of dihydrofolic acid to tetrahydrofolic acid—the essential final component in the folic acid synthesis pathway. Similar to that of the sulfonamides, the activity of trimethoprim is compromised in the presence of exogenous thymine or thymidine.

INHIBITION OF NUCLEIC ACID SYNTHESIS OR ACTIVITY

Numerous antibacterial compounds have disparate effects on nucleic acids.

Quinolones

The quinolones, including nalidixic acid and its fluorinated derivatives (ciprofloxacin, levofloxacin, and moxifloxacin), are synthetic compounds that inhibit the activity of the A subunit of the bacterial enzyme DNA gyrase as well as topoisomerase IV. DNA gyrase and topoisomerases are responsible for negative supercoiling of DNA—an essential conformation for DNA replication in the intact cell. Inhibition of the activity of DNA gyrase and topoisomerase IV is lethal to bacterial cells. The antibiotic *novobiocin* also interferes with the activity of DNA gyrase, but it interferes with the B subunit.

Rifampin

Rifampin, used primarily against *Mycobacterium tuberculosis*, is also active against a variety of other bacteria. Rifampin binds tightly to the B subunit of bacterial DNA-dependent RNA polymerase, thus inhibiting transcription of DNA into RNA. Mammalian-cell RNA polymerase is not sensitive to this compound.

Nitrofurantoin

Nitrofurantoin, a synthetic compound, causes DNA damage. The nitrofurans, compounds containing a single five-membered ring, are reduced by a bacterial enzyme to highly reactive, short-lived intermediates that are

440 thought to cause DNA strand breakage, either directly or indirectly.

Metronidazole

Metronidazole, a synthetic imidazole, is active only against anaerobic bacteria and protozoa. The reduction of metronidazole's nitro group by the bacterial anaerobic electron-transport system produces a transient series of reactive intermediates that are thought to cause DNA damage.

ALTERATION OF CELL-MEMBRANE PERMEABILITY

Polymyxins

The polymyxins [polymyxin B and colistin (polymyxin E)] are cyclic, basic polypeptides. They behave as cationic, surface-active compounds that disrupt the permeability of both the outer and the cytoplasmic membranes of gram-negative bacteria.

Gramicidin A

Gramicidin A is a polypeptide of 15 amino acids that acts as an ionophore, forming pores or channels in lipid bilayers.

Daptomycin

Insertion of daptomycin, a new bactericidal lipopeptide antibiotic, into the cell membrane of gram-positive bacteria forms a channel that causes depolarization of the membrane by efflux of intracellular ions, resulting in cell death.

MECHANISMS OF RESISTANCE

Some bacteria exhibit *intrinsic resistance* to certain classes of antibacterial agents (e.g., obligate anaerobic bacteria to aminoglycosides and gram-negative bacteria to vancomycin). In addition, bacteria that are ordinarily susceptible to antibacterial agents can acquire resistance. *Acquired resistance* is a major limitation to effective antibacterial chemotherapy. Resistance can develop by mutation of resident genes or by acquisition of new genes. New genes mediating resistance are usually spread from cell to cell by way of mobile genetic elements such as plasmids, transposons, and bacteriophages. The resistant bacterial populations flourish in areas of high antimicrobial use, where they enjoy a selective advantage over susceptible populations.

The major mechanisms used by bacteria to resist the action of antimicrobial agents are inactivation of the compound, alteration or overproduction of the antibacterial target through mutation of the target protein's gene, acquisition of a new gene that encodes a drug-insensitive target, decreased permeability of the cell envelope to the agent, failure to convert an inactive prodrug

to its active derivative, and active efflux of the compound from the periplasm or interior of the cell. Specific mechanisms of bacterial resistance to the major antibacterial agents are outlined below, summarized in Table 42-1, and depicted in Fig. 42-1.

β -LACTAM ANTIBIOTICS

Bacteria develop resistance to β -lactam antibiotics by a variety of mechanisms. The most common is the destruction of the drug by β -lactamases. The β -lactamases of gram-negative bacteria are confined to the periplasm between the inner and outer membranes, whereas the gram-positive bacteria secrete their β -lactamases into the surrounding medium. These enzymes have a higher affinity for the antibiotic than the antibiotic has for its target. Binding results in hydrolysis of the β -lactam ring. Genes encoding β -lactamases have been found in both chromosomal and extrachromosomal locations and in both gram-positive and gram-negative bacteria; these genes are often on mobile genetic elements. Many "advanced-generation" β -lactam antibiotics, such as ceftriaxone and cefepime, are stable in the presence of plasmid-mediated β -lactamases and are active against bacteria resistant to earlier-generation β -lactam antibiotics. However, extended-spectrum β -lactamases (ESBLs), either acquired on mobile genetic elements by gram-negative bacteria (e.g., *Klebsiella pneumoniae* and *Escherichia coli*) or present as stable chromosomal genes in other gram-negative species (e.g., *Enterobacter* spp.), have broad substrate specificity, hydrolyzing virtually all penicillins and cephalosporins. One strategy that has been devised for circumventing resistance mediated by β -lactamases is to combine the β -lactam agent with an inhibitor that avidly binds the inactivating enzyme, preventing its attack on the antibiotic. Unfortunately, the inhibitors (e.g., clavulanic acid, sulbactam, and tazobactam) do not bind all chromosomal β -lactamases (e.g., that of *Enterobacter* spp.) and thus cannot be depended on to prevent the inactivation of β -lactam antibiotics by such enzymes. No β -lactam antibiotic or inhibitor has been produced that can resist all of the many β -lactamases that have been identified.

A second mechanism of bacterial resistance to β -lactam antibiotics is an alteration in PBP targets so that the PBPs have a markedly reduced affinity for the drug. Although this alteration may occur by mutation of existing genes, the acquisition of new PBP genes (as in staphylococcal resistance to methicillin) or of new pieces of PBP genes (as in streptococcal, gonococcal, and meningococcal resistance to penicillin) is more important.

A final resistance mechanism is the coupling, in gram-negative bacteria, of a decrease in outer-membrane permeability with rapid efflux of the antibiotic from the periplasm to the cell exterior. Mutations of genes encoding outer-membrane protein channels called *porins*

decrease the entry of β -lactam antibiotics into the cell, and additional proteins form channels that actively pump β -lactams out of the cell. Resistance of Enterobacteriaceae to some cephalosporins and resistance of *Pseudomonas* spp. to cephalosporins and piperacillin are the best examples of this mechanism.

VANCOMYCIN

Clinically important resistance to vancomycin was first described among enterococci in France in 1988. Vancomycin-resistant enterococci (VRE) have subsequently become disseminated worldwide. The genes encoding resistance are carried on plasmids that can transfer themselves from cell to cell and on transposons that can jump from plasmids to chromosomes. Resistance is mediated by enzymes that substitute D-lactate for D-alanine on the peptidoglycan stem peptide so that there is no longer an appropriate target for vancomycin binding. This alteration does not appear to affect cell wall integrity, however. This type of acquired vancomycin resistance was confined for 14 years to enterococci—more specifically, to *Enterococcus faecium* rather than the more common pathogen *E. faecalis*. However, since 2002, *S. aureus* isolates that are highly resistant to vancomycin have been recovered from four patients in the United States. All of the isolates contain *vanA*, the gene that mediates vancomycin resistance in enterococci. In addition, since 1996, a few isolates of both *S. aureus* and *Staphylococcus epidermidis* that display a four- to eightfold reduction in susceptibility to vancomycin have been found worldwide, and many more isolates may contain subpopulations with reduced vancomycin susceptibility. These isolates have not acquired the genes that mediate vancomycin resistance in enterococci but are mutant bacteria with markedly thickened cell walls. These mutants were apparently selected in patients who were undergoing prolonged vancomycin therapy. The failure of vancomycin therapy in some patients infected with *S. aureus* or *S. epidermidis* strains exhibiting only intermediate susceptibility to this drug is thought to have resulted from this resistance.

AMINOGLYCOSIDES

The most common aminoglycoside resistance mechanism is inactivation of the antibiotic. Aminoglycoside-modifying enzymes, usually encoded on plasmids, transfer phosphate, adenylyl, or acetyl residues from intracellular molecules to hydroxyl or amino side groups on the antibiotic. The modified antibiotic is less active because of diminished binding to its ribosomal target. Modifying enzymes that can inactivate any of the available aminoglycosides have been found in both gram-positive and gram-negative bacteria. A second aminoglycoside resistance mechanism, which has been identified predominantly in

clinical isolates of *Pseudomonas aeruginosa*, is decreased antibiotic uptake, presumably caused by alterations in the bacterial outer membrane.

MACROLIDES, KETOLIDES, LINCOSAMIDES, AND STREPTOGRAMINS

Resistance in gram-positive bacteria, which are the usual target organisms for macrolides, ketolides, lincosamides, and streptogramins, can be caused by the production of an enzyme—most commonly plasmid encoded—that methylates ribosomal RNA, interfering with binding of the antibiotics to their target. Methylation mediates resistance to erythromycin, clarithromycin, azithromycin, clindamycin, and streptogramin B. Resistance to streptogramin B converts quinupristin/dalfopristin from a bactericidal to a bacteriostatic antibiotic. Streptococci can also actively cause the efflux of macrolides, and staphylococci can cause the efflux of macrolides, clindamycin, and streptogramin A. Ketolides such as telithromycin retain activity against most isolates of *Streptococcus pneumoniae* that are resistant to macrolides. In addition, staphylococci can inactivate streptogramin A by acetylation and streptogramin B by either acetylation or hydrolysis. Finally, mutations in 23S ribosomal RNA that alter the binding of macrolides to their targets have been found in both staphylococci and streptococci.

CHLORAMPHENICOL

Most bacteria resistant to chloramphenicol produce a plasmid-encoded enzyme, chloramphenicol acetyltransferase that inactivates the compound by acetylation.

TETRACYCLINES AND TIGECYCLINE

The most common mechanism of tetracycline resistance in gram-negative bacteria is a plasmid-encoded active-efflux pump that is inserted into the cytoplasmic membrane and extrudes antibiotic from the cell. Resistance in gram-positive bacteria is either caused by active efflux or by ribosomal alterations that diminish binding of the antibiotic to its target. Genes involved in ribosomal protection are found on mobile genetic elements. A new parenteral tetracycline derivative (a glycylcycline), tigecycline, is active against tetracycline-resistant bacteria because it is not removed by efflux and can bind to altered ribosomes.

MUPIROCIN

Although the topical compound mupirocin was introduced into clinical use relatively recently; resistance is already becoming widespread in some areas. The mechanism appears to be either mutation of the target isoleucine tRNA synthetase so that it is no longer inhibited by the

442 antibiotic or plasmid-encoded production of a form of the target enzyme that binds mupirocin poorly.

TRIMETHOPRIM AND SULFONAMIDES

The most prevalent mechanism of resistance to trimethoprim and the sulfonamides in both gram-positive and gram-negative bacteria is the acquisition of plasmid-encoded genes that produce a new, drug-insensitive target—specifically, an insensitive dihydrofolate reductase for trimethoprim and an altered dihydropteroate synthetase for sulfonamides.

QUINOLONES

The most common mechanism of resistance to quinolones is the development of one or more mutations in target DNA gyrases and topoisomerase IV that prevent the antibacterial agent from interfering with the enzymes' activity. Some gram-negative bacteria develop mutations that both decrease outer-membrane porin permeability and cause active drug efflux from the cytoplasm. Mutations that result in active quinolone efflux are also found in gram-positive bacteria.

RIFAMPIN

Bacteria rapidly become resistant to rifampin by developing mutations in the B subunit of RNA polymerase that render the enzyme unable to bind the antibiotic. The rapid selection of resistant mutants is the major limitation to the use of this antibiotic against otherwise susceptible staphylococci and requires that the drug be used in combination with another antistaphylococcal agent.

LINEZOLID

Enterococci, streptococci, and staphylococci become resistant to linezolid in vitro by mutation of the 23S rRNA binding site. Clinical isolates of *E. faecium* and *E. faecalis* acquire resistance to linezolid readily by this mechanism, often during therapy, but linezolid-resistant staphylococcal and streptococcal isolates are rare.

MULTIPLE ANTIBIOTIC RESISTANCE

The acquisition by one bacterium of resistance to multiple antibacterial agents is becoming increasingly common. The two major mechanisms are the acquisition of multiple unrelated resistance genes and the development of mutations in a single gene or gene complex that mediates resistance to a series of unrelated compounds. The construction of multiresistant strains by acquisition of multiple genes occurs by sequential steps of gene transfer and environmental selection in areas of high-level antimicrobial use. In contrast, mutations in a

single gene can conceivably be selected in a single step. Bacteria that are multiresistant by virtue of the acquisition of new genes include hospital-associated strains of gram-negative bacteria, enterococci, and staphylococci and community-acquired strains of salmonellae, gonococci, and pneumococci. Mutations that confer resistance to multiple unrelated antimicrobial agents occur in the genes encoding outer-membrane porins and efflux proteins of gram-negative bacteria. These mutations decrease bacterial intracellular and periplasmic accumulation of β -lactams, quinolones, tetracyclines, chloramphenicol, and aminoglycosides. Multiresistant bacterial isolates pose increasing problems in U.S. hospitals; strains resistant to all available antibacterial chemotherapy have already been identified.

PHARMACOKINETICS OF ANTIBIOTICS

The *pharmacokinetic profile* of an antibacterial agent refers to concentrations in serum and tissue versus time and reflects the processes of absorption, distribution, metabolism, and excretion. Important characteristics include peak and trough serum concentrations and mathematically derived parameters such as half-life, clearance, and distribution volume. Pharmacokinetic information is useful for estimating the appropriate antibacterial dose and frequency of administration, adjusting dosages in patients with impaired excretory capacity, and comparing one drug with another. In contrast, the *pharmacodynamic profile* of an antibiotic refers to the relationship between the pharmacokinetics of the antibiotic and its minimal inhibitory concentrations (MICs) for bacteria (see “Principles of Antibacterial Chemotherapy,” later in the chapter).

ABSORPTION

Antibiotic *absorption* refers to the rate and extent of a drug's systemic bioavailability after oral, IM, or IV administration.

Oral Administration

Most patients with infection are treated with oral antibacterial agents in the outpatient setting. Advantages of oral therapy over parenteral therapy include lower cost, generally fewer adverse effects (including complications of indwelling lines), and greater acceptance by patients. The percentage of an orally administered antibacterial agent that is absorbed (i.e., its *bioavailability*) ranges from as little as 10–20% (erythromycin and penicillin G) to nearly 100% [amoxicillin, clindamycin, metronidazole, doxycycline, trimethoprim-sulfamethoxazole (TMP-SMX), linezolid, and most fluoroquinolones]. These differences in bioavailability are not clinically important as long as drug concentrations at the site of infection are sufficient to inhibit or kill the pathogen. However, therapeutic

efficacy may be compromised when absorption is reduced as a result of physiologic or pathologic conditions (e.g., the presence of food for some drugs or the shunting of blood away from the gastrointestinal tract in patients with hypotension), drug interactions (e.g., that of quinolones and metal cations), or noncompliance. The oral route is usually used for patients with relatively mild infections in whom absorption is not thought to be compromised by the preceding conditions. In addition, the oral route can often be used in more severely ill patients after they have responded to parenteral therapy.

Intramuscular Administration

Although the IM route of administration usually results in 100% bioavailability, it is not as widely used in the United States as the oral and IV routes, partly because of the pain often associated with IM injections and the relative ease of IV access in hospitalized patients. IM injection may be suitable for specific indications requiring an “immediate” and reliable effect (e.g., with long-acting forms of penicillin, including benzathine and procaine, and with single doses of ceftriaxone for acute otitis media or uncomplicated gonococcal infection).

Intravenous Administration

The IV route is appropriate when oral antibacterial agents are not effective against a particular pathogen, when bioavailability is uncertain, or when larger doses are required than are feasible with the oral route. After IV administration, bioavailability is 100%; serum concentrations are maximal at the end of the infusion. For many patients in whom long-term antimicrobial therapy is required and oral therapy is not feasible, outpatient parenteral antibiotic therapy (OPAT), including the use of convenient portable pumps, may be cost effective and safe. Alternatively, some oral antibacterial drugs (e.g., fluoroquinolones) are sufficiently active against Enterobacteriaceae to provide potency equal to that of parenteral therapy; oral use of such drugs may allow the patient to return home from the hospital earlier or to avoid hospitalization entirely.

DISTRIBUTION

To be effective, concentrations of an antibacterial agent must exceed the pathogen’s MIC. Serum antibiotic concentrations usually exceed the MIC for susceptible bacteria, but because most infections are extravascular, the antibiotic must also distribute to the site of the infection. Concentrations of most antibacterial agents in interstitial fluid are similar to free-drug concentrations in serum. However, when the infection is located in a “protected” site where penetration is poor, such as cerebrospinal fluid (CSF),

the eye, the prostate, or infected cardiac vegetations, high parenteral doses or local administration for prolonged periods may be required for cure. In addition, even though an antibacterial agent may penetrate to the site of infection, its activity may be antagonized by factors in the local environment, such as an unfavorable pH or inactivation by cellular degradation products. For example, because the activity of aminoglycosides is reduced at acidic pH, the acidic environment in many infected tissues may be partly responsible for the relatively poor efficacy of aminoglycoside monotherapy. In addition, the abscess milieu reduces the penetration and local activity of many antibacterial compounds, so surgical drainage may be required for cure.

Most bacteria that cause human infections are located extracellularly. Intracellular pathogens such as *Legionella*, *Chlamydia*, *Brucella*, and *Salmonella* spp. may persist or cause relapse if the antibacterial agent does not enter the cell. In general, β -lactams, vancomycin, and aminoglycosides penetrate cells poorly, whereas macrolides, ketolides, tetracyclines, metronidazole, chloramphenicol, rifampin, TMP-SMX, and quinolones penetrate cells well.

METABOLISM AND ELIMINATION

Similar to other drugs, antibacterial agents are disposed of by hepatic elimination (metabolism or biliary elimination), renal excretion of the unchanged or metabolized form, or a combination of the two processes. For most of the antibacterial drugs, metabolism leads to loss of in vitro activity, although some agents, such as cefotaxime, rifampin, and clarithromycin, have bioactive metabolites that may contribute to their overall efficacy.

The most practical application of information on the mode of excretion of an antibacterial agent is in adjusting the dosage when elimination capability is impaired (Table 42-3). Direct, non-idiosyncratic toxicity from antibacterial drugs may result from failure to reduce the dosage given to patients with impaired elimination. For agents that are primarily cleared intact by glomerular filtration, drug clearance is correlated with creatinine clearance, and estimates of the latter can be used to guide dosage. For drugs whose elimination is primarily hepatic, no simple marker is useful for dosage adjustment in patients with liver disease. However, in patients with severe hepatic disease, residual metabolic capability is usually sufficient to preclude accumulation and toxic effects.

PRINCIPLES OF ANTIBACTERIAL CHEMOTHERAPY

The choice of an antibacterial compound for a particular patient and a specific infection involves more than just a knowledge of the agent’s pharmacokinetic profile and in vitro activity. The basic tenets of chemotherapy,

TABLE 42-3

ANTIBACTERIAL DRUG DOSE ADJUSTMENTS IN PATIENTS WITH RENAL IMPAIRMENT

ANTIBIOTIC	MAJOR ROUTE OF EXCRETION	DOSAGE ADJUSTMENT WITH RENAL IMPAIRMENT
Aminoglycosides	Renal	Yes
Azithromycin	Biliary	No
Cefazolin	Renal	Yes
Cefepime	Renal	Yes
Ceftazidime	Renal	Yes
Ceftriaxone	Renal/biliary	Modest reduction in severe renal impairment
Ciprofloxacin	Renal/biliary	Only in severe renal insufficiency
Clarithromycin	Renal/biliary	Only in severe renal insufficiency
Daptomycin	Renal	Yes
Erythromycin	Biliary	Only when given in high IV doses
Levofloxacin	Renal	Yes
Linezolid	Metabolism	No
Metronidazole	Biliary	No
Nafcillin	Biliary	No
Penicillin G	Renal	Yes (when given in high IV doses)
Piperacillin	Renal	Only with Cl_{cr} of <40 mL/min
Quinupristin/dalfopristin	Metabolism	No
Ticarcillin	Renal	Yes
Tigecycline	Biliary	No
TMP-SMX	Renal/biliary	Only in severe renal insufficiency
Vancomycin	Renal	Yes

Note: Cl_{cr} , creatinine clearance rate; TMP-SMX, trimethoprim-sulfamethoxazole.

to be elaborated below, include the following: When appropriate, material containing the infecting organism(s) should be obtained before the start of treatment so that presumptive identification can be made by microscopic examination of stained specimens and the organism can be grown for definitive identification and susceptibility testing. Awareness of local susceptibility patterns is useful when the patient is treated empirically. After the organism has been identified and its susceptibility to antibacterial agents have been determined, the regimen with the narrowest effective spectrum should be chosen. The choice of antibacterial agent is guided by the pharmacokinetic and adverse reaction profile of active compounds, the site of infection, the immune status of the host, and evidence of efficacy from well-performed clinical trials. If all other factors are equal, the least expensive antibacterial regimen should be chosen.

SUSCEPTIBILITY OF BACTERIA TO ANTIBACTERIAL DRUGS IN VITRO

Determination of the susceptibility of the patient's infecting organism to a panel of appropriate antibacterial agents is an essential first step in devising a chemotherapeutic regimen. Susceptibility testing is designed to estimate the susceptibility of a bacterial isolate to an antibacterial drug

under standardized conditions. These conditions favor rapidly growing aerobic or facultative organisms and assess bacteriostasis only. Specialized testing is required for the assessment of bactericidal antimicrobial activity; for the detection of resistance among such fastidious organisms as obligate anaerobes, *Haemophilus* spp., and pneumococci; and for the determination of resistance phenotypes with variable expression, such as resistance to methicillin or oxacillin among staphylococci. Antimicrobial susceptibility testing is important when susceptibility is unpredictable, most often as a result of increasing acquired resistance among bacteria infecting hospitalized patients.

PHARMACODYNAMICS: RELATIONSHIP OF PHARMACOKINETICS AND IN VITRO SUSCEPTIBILITY TO CLINICAL RESPONSE

Bacteria have often been considered *susceptible* to an antibacterial drug if the achievable peak serum concentration exceeds the MIC by approximately fourfold. The *breakpoint* is the concentration of the antibiotic that separates susceptible from resistant bacteria (Fig. 42-2). When a majority of the isolates of a given bacterial species are inhibited at concentrations below the breakpoint, the species is considered to be within the spectrum of the antibiotic.

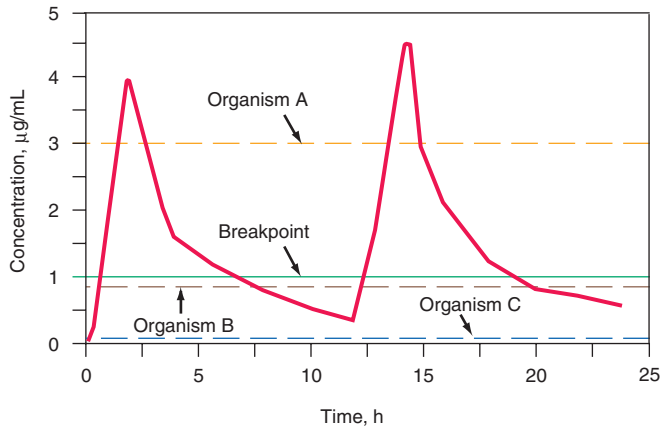


FIGURE 42-2

Relationship between pharmacokinetics of an antibiotic and susceptibility. Organism A is resistant, organism B is moderately susceptible, and organism C is very susceptible. Pharmacodynamic indices include the ratio of the peak serum concentration to minimal inhibitory concentration (MIC) (C_{\max}/MIC), the ratio of the area under the serum concentration vs. time curve to MIC (AUC/MIC), and the time that serum concentrations exceed the MIC ($t > \text{MIC}$).

The pharmacodynamic profile of an antibiotic refers to the quantitative relationships between the time course of antibiotic concentrations in serum and tissue, *in vitro* susceptibility (MIC), and microbial response (inhibition of growth or rate of killing). Three pharmacodynamic parameters quantify these relationships: the ratio of the area under the plasma concentration vs. time curve to MIC (AUC/MIC), the ratio of the maximal serum concentration to the MIC (C_{\max}/MIC), and the time during a dosing interval that plasma concentrations exceed the MIC ($t > \text{MIC}$). The pharmacodynamic profile of an antibiotic class is characterized as either *concentration dependent* (fluoroquinolones, aminoglycosides), such that an increase in antibiotic concentration leads to a more rapid rate of bacterial death, or *time dependent* (β -lactams), such that the reduction in bacterial density is proportional to the time that concentrations exceed the MIC. For concentration-dependent antibiotics, the C_{\max}/MIC or AUC/MIC ratio correlates best with the reduction in microbial density *in vitro* and in animal investigations. Dosing strategies attempt to maximize these ratios by the administration of a large dose relative to the MIC for anticipated pathogens, often at long intervals (relative to the serum half-life). Once-daily dosing of aminoglycoside antibiotics is the most practical consequence of these relationships. In contrast, dosage strategies for time-dependent antibiotics emphasize the administration of doses sufficient to maintain serum concentrations above the MIC for a critical portion of the dose interval. Response to β -lactam antibiotics, measured as the decline in bacterial density at the site of infection, is maximal when serum and tissue concentrations are

TABLE 42-4

PHARMACODYNAMIC INDICES OF MAJOR ANTIMICROBIAL CLASSES

PARAMETER PREDICTING RESPONSE	DRUG OR DRUG CLASS
Time above the MIC	Penicillins, cephalosporins, carbapenems, aztreonam
24-h AUC/MIC	Aminoglycosides, fluoroquinolones, tetracyclines, vancomycin, macrolides, clindamycin, quinupristin/dalfopristin, tigecycline, daptomycin
Peak to MIC	Aminoglycosides, fluoroquinolones

Note: AUC, area under the concentration curve; MIC, minimal inhibitory concentration.

maintained above the MIC for 30–50% of the dose interval. For example, the use of high-dose amoxicillin (90–100 mg/kg per day) in the treatment of acute otitis media increases not only the penetration of amoxicillin into the inner ear but also the duration of time that concentrations exceed the MIC for pneumococci. This approach provides effective therapy in most patients, including those whose pneumococcal isolates are penicillin resistant. The clinical implications of these pharmacodynamic relationships are in the early stages of investigation; their elucidation should eventually result in more rational antibacterial dosage regimens. **Table 42-4** summarizes the pharmacodynamic properties of the major antibiotic classes.

STATUS OF THE HOST

Various host factors must be considered in the devising of antibacterial chemotherapy. The host's antibacterial *immune function* is of importance, particularly as it relates to opsonophagocytic function. Because the major host defense against acute, overwhelming bacterial infection is the polymorphonuclear leukocyte, patients with neutropenia must be treated aggressively and empirically with bactericidal drugs for suspected infection. Likewise, patients who have deficient humoral immunity (e.g., those with chronic lymphocytic leukemia and multiple myeloma) and individuals with surgical or functional asplenia (e.g., sickle cell disease) should be treated empirically for infections with encapsulated organisms, especially the pneumococcus.

Pregnancy increases the risk of toxicity of certain antibacterial drugs for the mother (e.g., hepatic toxicity of tetracycline), affects drug disposition and pharmacokinetics, and—because of the risk of fetal toxicity—severely limits the choice of agents for treating infections. Certain antibacterial agents are contraindicated in

TABLE 42-5

ANTIBACTERIAL DRUGS IN PREGNANCY

ANTIBACTERIAL DRUG	TOXICITY IN PREGNANCY	RECOMMENDATION
Aminoglycosides	Possible 8th-nerve toxicity	Caution ^a
Chloramphenicol	Gray syndrome in newborns	Caution at term
Fluoroquinolones	Arthropathy in immature animals	Caution
Clarithromycin	Teratogenicity in animals	Contraindicated
Ertapenem	Decreased weight in animals	Caution
Erythromycin estolate	Cholestatic hepatitis	Contraindicated
Imipenem/cilastatin	Toxicity in some pregnant animals	Caution
Linezolid	Embryonic and fetal toxicity in rats	Caution
Meropenem	Unknown	Caution
Metronidazole	None known, but carcinogenic in rats	Caution
Nitrofurantoin	Hemolytic anemia in newborns	Caution; contraindicated at term
Quinupristin/dalfopristin	Unknown	Caution
Sulfonamides	Hemolysis in newborns with G6PD ^b deficiency; kernicterus in newborn	Caution; contraindicated at term
Tetracyclines/tigecycline	Tooth discoloration, inhibition of bone growth in fetuses; hepatotoxicity	Contraindicated
Vancomycin	Unknown	Caution

^a Use only for strong clinical indication in the absence of a suitable alternative.

^b G6PD, glucose-6-phosphate dehydrogenase

pregnancy either because their safety has not been established (categories B and C) or because they are known to be toxic (categories D and X). **Table 42-5** summarizes drug safety in pregnancy.

In patients with *concomitant viral infections*, the incidence of adverse reactions to antibacterial drugs may be unusually high. For example, persons with infectious mononucleosis and those infected with HIV experience skin reactions more often to penicillins and folic acid synthesis inhibitors such as TMP-SMX, respectively.

In addition, the patient's age, gender, racial heritage, genetic background, and excretory status all determine the incidence and type of side effects that can be expected with certain antibacterial agents.

SITE OF INFECTION

The location of the infected site may play a major role in the choice and dose of antimicrobial drug. Patients with suspected *meningitis* should receive drugs that can cross the blood–CSF barrier; in addition, because of the relative paucity of phagocytes and opsonins at the site of infection, the agents should be bactericidal. Chloramphenicol, an older drug that is occasionally useful in the treatment of meningitis, is bactericidal for common organisms causing meningitis (i.e., meningococci, pneumococci, and *Haemophilus influenzae*, but *not* enteric gram-negative bacilli), is highly lipid soluble, and enters the CSF well. However, β -lactam drugs, the mainstay of therapy for most of these infections, do not normally reach high levels in the CSF. Their efficacy is based on the increased

permeability of the blood–brain and blood–CSF barriers to hydrophilic molecules during inflammation and the extreme susceptibility of most infectious organisms to even small amounts of β -lactam drug.

The vegetation, which is the major site of infection in *bacterial endocarditis*, is also a focus that is protected from normal host-defense mechanisms. Antibacterial therapy needs to be bactericidal, with the selected agent administered parenterally over a long period and at a dose that produces serum levels at least eight times higher than the minimal bactericidal concentration (MBC) for the infecting organism. Likewise, *osteomyelitis* involves a site that is resistant to opsonophagocytic removal of infecting bacteria; furthermore, avascular bone (sequestrum) represents a foreign body that thwarts normal host-defense mechanisms. *Chronic prostatitis* is exceedingly difficult to cure because most antibiotics do not penetrate through the capillaries serving the prostate, especially when acute inflammation is absent. *Intraocular infections*, especially endophthalmitis, are difficult to treat because retinal capillaries lacking fenestration hinder drug penetration into the vitreous from blood. Inflammation does little to disrupt this barrier. Thus, direct injection into the vitreous is necessary in many cases. Antibiotic penetration into *abscesses* is usually poor, and local conditions (e.g., low pH or the presence of enzymes that hydrolyze the drug) may further antagonize antibacterial activity.

In contrast, *urinary tract infections* (UTIs), when confined to the bladder, are relatively easy to cure, partly because of the higher concentration of most antibiotics

in urine than in blood. Because blood is the usual reference fluid in defining susceptibility (Fig. 42-2), even organisms found to be resistant to achievable serum concentrations may be susceptible to achievable urine concentrations. For drugs that are used only for the treatment of UTIs, such as the urinary tract antiseptics nitrofurantoin and methenamine salts, achievable urine concentrations are used to determine susceptibility. Nitrofurantoin is often active against VRE and is a less expensive alternative to linezolid for the treatment of lower UTIs.

COMBINATION CHEMOTHERAPY

One of the tenets of antibacterial chemotherapy is that if the infecting bacterium has been identified, the most specific chemotherapy possible should be used. The use of a single agent with a narrow spectrum of activity against the pathogen diminishes the alteration of normal flora and thus limits the overgrowth of resistant nosocomial organisms (e.g., *Candida albicans*, enterococci, *Clostridium difficile*, methicillin-resistant staphylococci), avoids the potential toxicity of multiple-drug regimens, and reduces the cost. However, certain circumstances call for the use of more than one antibacterial agent. These are summarized below.

1. *Prevention of the emergence of resistant mutants.* Spontaneous mutations occur at a detectable frequency in certain genes encoding the target proteins for some antibacterial agents. The use of these agents can eliminate the susceptible population, select out resistant mutants at the site of infection, and result in the failure of chemotherapy. Resistant mutants are usually selected when the MIC of the antibacterial agent for the infecting bacterium is close to achievable levels in serum or tissues or when the site of infection limits the access or activity of the agent. Among the most common examples are rifampin for staphylococci, imipenem for *Pseudomonas* spp., and fluoroquinolones for staphylococci and *Pseudomonas* spp. Small-colony variants of staphylococci resistant to aminoglycosides also emerge during monotherapy with these antibiotics. A second antibacterial agent with a mechanism of action different from that of the first is added to prevent the emergence of these resistant mutants (e.g., imipenem plus an aminoglycoside or a fluoroquinolone for systemic *Pseudomonas* infections). However, because resistant mutants have emerged after combination chemotherapy, this approach clearly is not uniformly successful.
2. *Synergistic or additive activity.* Synergistic or additive activity involves a lowering of the MIC or MBC of each or all of the drugs tested in combination against a specific bacterium. In *synergy*, each agent is more active when combined with a second drug than it would be alone, and the drugs' combined activity is

therefore greater than the sum of the individual activities of each drug. In an *additive relationship*, the combined activity of the drugs is equal to the sum of their individual activities. Among the best examples of a synergistic or additive effect, confirmed both in vitro and by animal studies, are the enhanced bactericidal activities of certain β -lactam/aminoglycoside combinations against enterococci, viridans streptococci, and *P. aeruginosa*. The synergistic or additive activity of these combinations has also been demonstrated against selected isolates of enteric gram-negative bacteria and staphylococci. The combination of trimethoprim and sulfamethoxazole has synergistic or additive activity against many enteric gram-negative bacteria. Most other antimicrobial combinations display indifferent activity (i.e., the combination is no *better* than the more active of the two agents alone), and some combinations (e.g., penicillin plus tetracycline against pneumococci) may be antagonistic (i.e., the combination is *worse* than either drug alone).

3. *Therapy directed against multiple potential pathogens.* For certain infections, either a mixture of pathogens is suspected or the patient is desperately ill with an as-yet-unidentified infection (see Empirical Therapy below). In these situations, the most important of the likely infecting bacteria must be covered by therapy until culture and susceptibility results become available. Examples of the former infections are intraabdominal or brain abscesses and infections of the limbs in diabetic patients with microvascular disease. The latter situations include fevers in neutropenic patients, acute pneumonia from aspiration of oral flora by hospitalized patients, and septic shock or sepsis syndrome.

EMPIRICAL THERAPY

In many situations, antibacterial therapy is begun before a specific bacterial pathogen has been identified. The choice of agent is guided by the results of studies identifying the usual pathogens at that site or in that clinical setting, by pharmacodynamic considerations, and by the resistance profile of the expected pathogens in a particular hospital or geographic area. Situations in which empirical therapy is appropriate include the following.

1. *Life-threatening infection.* Any suspected bacterial infection in a patient with a life-threatening illness should be treated presumptively. Therapy is usually begun with more than one agent and is later tailored to a specific pathogen if one is eventually identified. Early therapy with an effective antimicrobial regimen has consistently been demonstrated to improve survival rates.
2. *Treatment of community-acquired infections.* In many situations, it is appropriate to treat non-life-threatening infections without obtaining cultures. These situations

include outpatient infections such as community-acquired upper and lower respiratory tract infections, cystitis, cellulitis or local wound infection, urethritis, and prostatitis. However, if any of these infections recurs or fails to respond to initial therapy, every effort should be made to obtain cultures to guide retreatment.

CHOICE OF ANTIBACTERIAL THERAPY

Infections for which specific antibacterial agents are among the drugs of choice are detailed in [Table 42-6](#). No attempt has been made to include all of the potential situations in which antibacterial agents may be used. A more

TABLE 42-6

INFECTIONS FOR WHICH SPECIFIC ANTIBACTERIAL AGENTS ARE AMONG THE DRUGS OF CHOICE

AGENT	INFECTIONS	COMMON PATHOGEN(S) (RESISTANCE RATE, %) ^a
Penicillin G	Syphilis, yaws, leptospirosis, groups A and B streptococcal infections, pneumococcal infections, actinomycosis, oral and periodontal infections, meningococcal meningitis and meningococcemia, viridans streptococcal endocarditis, clostridial myonecrosis, tetanus, anthrax, rat-bite fever, <i>Pasteurella multocida</i> infections, and erysipeloid (<i>Erysipelothrix rhusiopathiae</i>)	<i>Neisseria meningitidis</i> ^b (intermediate, ^c 15–30; resistant, 0; geographic variation) Viridans streptococci (intermediate, 15–30; resistant, 5–10) <i>Streptococcus pneumoniae</i> (intermediate, 23; resistant, 17)
Ampicillin, amoxicillin	Salmonellosis, acute otitis media, <i>Haemophilus influenzae</i> meningitis and epiglottitis, <i>Listeria monocytogenes</i> meningitis, <i>Enterococcus faecalis</i> UTI	<i>Escherichia coli</i> (37) <i>H. influenzae</i> (35) <i>Salmonella</i> spp. ^b (30–50; geographic variation) <i>Enterococcus</i> spp. (24) <i>S. aureus</i> (46; MRSA) <i>Staphylococcus epidermidis</i> (78; MRSE) <i>P. aeruginosa</i> (6)
Nafcillin, oxacillin	<i>Staphylococcus aureus</i> (non-MRSA) bacteremia and endocarditis	<i>S. aureus</i> (46; MRSA) <i>Staphylococcus epidermidis</i> (78; MRSE) <i>P. aeruginosa</i> (6)
Piperacillin plus tazobactam	Intraabdominal infections (facultative enteric gram-negative bacilli plus obligate anaerobes); infections caused by mixed flora (aspiration pneumonia, diabetic foot ulcers); infections caused by <i>Pseudomonas aeruginosa</i>	<i>E. coli</i> (7) <i>S. aureus</i> (46; MRSA) <i>Bacteroides fragilis</i> (12)
Cefazolin	<i>E. coli</i> UTI, surgical prophylaxis, <i>S. aureus</i> (non-MRSA) bacteremia and endocarditis	<i>E. coli</i> (7) <i>S. aureus</i> (46; MRSA) <i>Bacteroides fragilis</i> (12)
Cefoxitin, cefotetan	Intraabdominal infections and pelvic inflammatory disease	<i>S. pneumoniae</i> (intermediate, 16; resistant, 0) <i>E. coli</i> and <i>Klebsiella pneumoniae</i> (1; ESBL producers)
Ceftriaxone	Gonococcal infections, pneumococcal meningitis, viridans streptococcal endocarditis, salmonellosis and typhoid fever, hospital-acquired infections caused by nonpseudomonal facultative gram-negative enteric bacilli	<i>S. pneumoniae</i> (intermediate, 16; resistant, 0) <i>E. coli</i> and <i>Klebsiella pneumoniae</i> (1; ESBL producers)
Ceftazidime, cefepime	Hospital-acquired infections caused by facultative gram-negative enteric bacilli and <i>Pseudomonas</i> spp.	<i>P. aeruginosa</i> (16) (See ceftriaxone for ESBL producers)
Imipenem, meropenem	Intraabdominal infections, hospital-acquired infections (non-MRSA), infections caused by <i>Enterobacter</i> spp. and ESBL-producing gram-negative bacilli	<i>P. aeruginosa</i> (6) <i>Acinetobacter</i> spp. (35)
Aztreonam	Hospital-acquired infections caused by facultative gram-negative bacilli and <i>Pseudomonas</i> spp. in penicillin-allergic patients	<i>P. aeruginosa</i> (16)
Vancomycin	Bacteremia, endocarditis, and other serious infections caused by MRSA infection; pneumococcal meningitis; antibiotic-associated pseudomembranous colitis ^d	<i>Enterococcus</i> spp. (24)
Daptomycin	VRE infections; MRSA bacteremia	UNK
Gentamicin, amikacin, tobramycin	Combined with a penicillin for staphylococcal, enterococcal, or viridans streptococcal endocarditis; combined with a β -lactam antibiotic for gram-negative bacteremia; pyelonephritis	Gentamicin: <i>E. coli</i> (6) <i>P. aeruginosa</i> (17) <i>Acinetobacter</i> spp. (32)
Erythromycin, clarithromycin, azithromycin	<i>Legionella</i> , <i>Campylobacter</i> , and <i>Mycoplasma</i> infections; CAP; group A streptococcal pharyngitis in penicillin-allergic patients; bacillary angiomatosis (<i>Bartonella henselae</i>); gastric infections caused by <i>Helicobacter pylori</i> infection; <i>Mycobacterium avium-intracellulare</i> infections	<i>S. pneumoniae</i> (28) <i>Streptococcus pyogenes</i> ^b (0–10; geographic variation) <i>H. pylori</i> ^b (2–20; geographic variation)

TABLE 42-6 (CONTINUED)

AGENT	INFECTIONS	COMMON PATHOGEN(S) (RESISTANCE RATE, %) ^a
Clindamycin	Severe, invasive group A streptococcal infections; infections caused by obligate anaerobes; infections caused by susceptible staphylococci	<i>S. aureus</i> (nosocomial, 58; CA-MRSA, 10 ^b)
Doxycycline, minocycline	Acute bacterial exacerbations of chronic bronchitis, granuloma inguinale, brucellosis (with streptomycin), tularemia, glanders, melioidosis, spirochetal infections caused by <i>Borrelia</i> spp. Infection (Lyme disease and relapsing fever; doxycycline), infections caused by <i>Vibrio vulnificus</i> , some <i>Aeromonas</i> infections, infections caused by <i>Stenotrophomonas</i> (minocycline), plague, ehrlichiosis, chlamydial infections (doxycycline), granulomatous skin infections caused by <i>Mycobacterium marinum</i> infection (minocycline), rickettsial infections, mild CAP, skin and soft tissue infections caused by gram-positive cocci (CA-MRSA infections, leptospirosis, syphilis, actinomycosis in penicillin-allergic patients)	<i>S. pneumoniae</i> (17) MRSA (5)
Trimethoprim-sulfamethoxazole	Community-acquired UTI; <i>S. aureus</i> skin and soft tissue infections (CA-MRSA)	<i>E. coli</i> (19) MRSA (3)
Sulfonamides	Nocardial infections, leprosy (dapson, a sulfone), and toxoplasmosis (sulfadiazine)	UNK
Ciprofloxacin, levofloxacin, moxifloxacin	CAP (levofloxacin and moxifloxacin); UTI; bacterial gastroenteritis; hospital-acquired gram-negative enteric infections; <i>Pseudomonas</i> infections (ciprofloxacin and levofloxacin)	<i>S. pneumoniae</i> (1) <i>E. coli</i> (13) <i>P. aeruginosa</i> (23) <i>Salmonella</i> spp. (10–50; geographic variation) <i>Neisseria gonorrhoeae</i> ^b (0–5, non–West Coast U.S.; 10–15, California and Hawaii; 20–70, Asia, England, Wales)
Rifampin	Staphylococcal foreign body infections, in combination with other antistaphylococcal agents; <i>Legionella</i> pneumonia	Staphylococci rapidly develop resistance during rifampin monotherapy.
Metronidazole	Obligate anaerobic gram-negative bacteria (<i>Bacteroides</i> spp.): abscess in the lung, brain, or abdomen; bacterial vaginosis; antibiotic-associated <i>Clostridium difficile</i> disease	UNK
Linezolid	VRE; staphylococcal skin and soft tissue infection (CA-MRSA)	UNK
Polymyxin E (colistin)	Hospital-acquired infection caused by gram-negative bacilli resistant to all other chemotherapy: <i>P. aeruginosa</i> , <i>Acinetobacter</i> spp., <i>Stenotrophomonas maltophilia</i>	UNK
Quinupristin/dalfopristin	VRE	Vancomycin-resistant <i>E. faecalis</i> ^b (100)
Mupirocin	Topical application to nares to eradicate <i>S. aureus</i> carriage	Vancomycin-resistant <i>E. faecium</i> (10) UNK

^a Unless otherwise noted, resistance rates are based on all isolates tested in 2005 in the clinical microbiology laboratory at Virginia Commonwealth University Medical Center. The rates are consistent with those reported by the National Nosocomial Infections Surveillance System (Am J Infect Control 32:470, 2004).

^b Data from recent literature sources.

^c Intermediate resistance.

^d Drug is given orally for this indication.

Note: CA-MRSA, community-acquired methicillin-resistant *S. aureus*; CAP, community-acquired pneumonia; ESBL, extended-spectrum β -lactamase; MRSA, methicillin-resistant *S. aureus*; MRSE, methicillin-resistant *S. epidermidis*; UTI, urinary tract infection; VRE, vancomycin-resistant enterococci; UNK, resistance rates unknown.

detailed discussion of specific bacteria and infections that they cause can be found elsewhere in this volume.

The choice of antibacterial therapy increasingly involves an assessment of the acquired resistance of major microbial pathogens to the antimicrobial agents available to treat them. Resistance rates are dynamic (Table 42-6), both increasing and decreasing in response to the environmental pressure applied by antimicrobial use. For example, a threefold increase in fluoroquinolone use in the community between 1995 and 2002 was associated with increasing rates of quinolone resistance in community-acquired strains of *S. pneumoniae*, *E. coli*, *Neisseria gonorrhoeae*, and *K. pneumoniae*. Fluoroquinolone resistance has also emerged rapidly among nosocomial isolates of *S. aureus* and *Pseudomonas* spp. as hospital use of this drug class has increased. In contrast, staphylococcal resistance to tetracyclines has decreased as the use of these antibiotics has declined. It is important to note that, in many cases, wide variations in worldwide antimicrobial-resistance trends may not be reflected in the values recorded at U.S. hospitals (e.g., for fluoroquinolone resistance in *N. gonorrhoeae*). Therefore, the most important factor in choosing initial therapy for an infection in which the susceptibility of the specific pathogen(s) is not known is information on local resistance rates. This information can be obtained from local clinical microbiology laboratories, state health departments, or publications of the Centers for Disease Control and Prevention (e.g., *Emerging Infectious Diseases* and *Morbidity and Mortality Weekly Report*).

ADVERSE REACTIONS

Adverse drug reactions are frequently classified by mechanism as either *dose related* (“toxic”) or *unpredictable*. Unpredictable reactions are either idiosyncratic or allergic. Dose-related reactions include aminoglycoside-induced nephrotoxicity, linezolid-induced thrombocytopenia, penicillin-induced seizures, and vancomycin-induced anaphylactoid reactions. Many of these reactions can be avoided by reducing the dosage in patients with impaired renal function, limiting the duration of therapy, or reducing the rate of administration. Adverse reactions to antibacterial agents are a common cause of morbidity, requiring alteration in therapy and additional expense, and they occasionally result in death. Elderly patients, often those with the more severe infections, may be especially prone to certain adverse reactions. The most clinically relevant adverse reactions to common antibacterial drugs are listed in [Table 42-7](#).

DRUG INTERACTIONS

Antimicrobial drugs are a common cause of drug–drug interactions. [Table 42-8](#) lists the most common and best-documented interactions of antibacterial agents

with other drugs and characterizes the clinical relevance of these interactions. Coadministration of drugs paired in the tables does not necessarily result in clinically important adverse consequences. Recognition of the potential for an interaction before the administration of an antibacterial agent is crucial to the rational use of these drugs because adverse consequences can often be prevented if the interaction is anticipated. Table 42-8 is intended only to heighten awareness of the potential for an interaction. Additional sources should be consulted to identify appropriate options.

MACROLIDES AND KETOLIDES

Erythromycin, clarithromycin, and telithromycin inhibit CYP3A4, the hepatic P450 enzyme that metabolizes many drugs, including cyclosporine, certain statins (lovastatin, simvastatin), theophylline, carbamazepine, warfarin, certain antineoplastic agents (e.g., vincristine, irinotecan), and ergot alkaloids. In ~10% of patients receiving digoxin, concentrations increase significantly when erythromycin or telithromycin is coadministered, and this increase may lead to digoxin toxicity. Azithromycin has little effect on the metabolism of other drugs.

Many drugs (e.g., azole antifungal drugs, diltiazem, verapamil, and nefazodone) can also increase absorption or inhibit erythromycin metabolism. These effects are associated with prolongation of the QT interval and a fivefold increase in mortality rate. This example serves as a reminder that the true significance of drug–drug interactions may be subtle yet profound and that close attention to the evolving safety literature is important.

QUINUPRISTIN/DALFOPRISTIN

Quinupristin/dalfopristin is an inhibitor of CYP3A4. Its interactions with other drugs should be similar to those of erythromycin.

LINEZOLID

Linezolid is a monoamine oxidase inhibitor. Its concomitant administration with sympathomimetics (e.g., phenylpropanolamine) and with foods with high concentrations of tyramine should be avoided. Many case reports describe serotonin syndrome after coadministration of linezolid with selective serotonin reuptake inhibitors.

TETRACYCLINES

The most important interaction involving tetracyclines is reduced absorption when these drugs are coadministered with divalent and trivalent cations, such as antacids, iron compounds, or dairy products. Food also adversely affects

TABLE 42-7

MOST CLINICALLY RELEVANT ADVERSE REACTIONS TO COMMON ANTIBACTERIAL DRUGS

DRUG	ADVERSE EVENT	COMMENTS
β-Lactams	Allergies in ~1–4% of treatment courses	Cephalosporins cause allergy in 2–4% of penicillin-allergic patients. Aztreonam is safe in β-lactam-allergic patients.
	Nonallergic skin reactions	Ampicillin “rash” is common among patients with Epstein-Barr virus infection.
Vancomycin	Diarrhea, including <i>Clostridium difficile</i> colitis	—
Aminoglycosides	Anaphylactoid reaction (“red man syndrome”)	Give as a 1- to 2-h infusion.
	Nephrotoxicity, ototoxicity, allergy, neutropenia	Rare
Macrolides/ketolides	Nephrotoxicity (generally reversible)	Greatest with prolonged therapy in the elderly or with preexisting renal insufficiency. Monitor serum creatinine every 2–3 days.
	Ototoxicity (often irreversible)	Risk factors similar to those for nephrotoxicity; both vestibular and hearing toxicities
	GI distress	Most common with erythromycin
Clindamycin	Ototoxicity	High-dose IV erythromycin
	Cardiac toxicity	QTc prolongation and torsades de pointes, especially when inhibitors of erythromycin metabolism are given simultaneously
	Hepatic toxicity (telithromycin)	Warning added to prescribing information (July 2006)
Sulfonamides	Respiratory failure in patients with myasthenia gravis (telithromycin)	Warning added to prescribing information (July 2006)
	Diarrhea, including <i>C. difficile</i> colitis	—
Fluoroquinolones	Allergic reactions	Rashes (more common in HIV-infected patients); serious dermal reactions, including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
	Hematologic reactions	Uncommon; include agranulocytosis and granulocytopenia (more common in HIV-infected patients), hemolytic and megaloblastic anemia, thrombocytopenia
Rifampin	Renal insufficiency	Crystalluria with sulfadiazine therapy
	Diarrhea, including <i>C. difficile</i> colitis	—
	Contraindicated for general use in patients <18 years old and pregnant women	Appear safe in treatment of pulmonary infections in children with cystic fibrosis
	CNS adverse effects (e.g., insomnia)	—
Metronidazole	Miscellaneous: allergies, tendon rupture, dysglycemias, QTc prolongation	Rare
	Hepatotoxicity	Rare
	Orange discoloration of urine and body fluids	Common
Tetracyclines/glycylcyclines	Miscellaneous: flulike symptoms, hemolysis, renal insufficiency	Uncommon; usually related to intermittent administration
	GI distress	Common
Linezolid	Esophageal ulceration	≤20% with tigecycline
	Myelosuppression	Doxycycline (take in A.M. with fluids)
Daptomycin	Ocular and peripheral neuritis	Follows long-term treatment
	Distal muscle pain or weakness	Follow long-term treatment
		Weekly creatine phosphokinase measurements, especially in patients also receiving statins

Note: CNS, central nervous system; GI, gastrointestinal.

absorption of most tetracyclines. Inducers of hepatic isoenzymes, such as phenytoin and rifampin, increase the clearance of doxycycline; although the clinical significance of this effect is unknown, use of an alternative antibiotic may be appropriate.

SULFONAMIDES

Sulfonamides, including TMP-SMX, increase the hypoprothrombinemic effect of warfarin by inhibition of its metabolism or by protein-binding displacement.

INTERACTIONS OF ANTIBACTERIAL AGENTS WITH OTHER DRUGS

ANTIBIOTIC	INTERACTS WITH	POTENTIAL CONSEQUENCE (CLINICAL SIGNIFICANCE ^a)	
Erythromycin/ clarithromycin/telithromycin	Theophylline	Theophylline toxicity (1)	
	Carbamazepine	CNS depression (1)	
	Digoxin	Digoxin toxicity (2)	
	Triazolam/midazolam	CNS depression (2)	
	Ergotamine	Ergotism (1)	
	Warfarin	Bleeding (2)	
	Cyclosporine/tacrolimus	Nephrotoxicity (1)	
	Cisapride	Cardiac arrhythmias (1)	
	Statins ^b	Rhabdomyolysis (2)	
	Valproate	Valproate toxicity (2)	
	Vincristine/vinblastine	Excess neurotoxicity (2)	
	Quinupristin/dalfopristin	Similar to erythromycin ^c	
		Theophylline	Theophylline toxicity (2) ^d
Fluoroquinolones	Antacids/sucralfate/iron	Subtherapeutic antibiotic levels (1)	
	Theophylline	Subtherapeutic antibiotic levels (1)	
Tetracycline	Antacids/sucralfate/iron	Subtherapeutic antibiotic levels (1)	
	Phenytoin	Phenytoin toxicity (2)	
Trimethoprim- sulfamethoxazole	Oral hypoglycemics	Hypoglycemia (2)	
	Warfarin	Bleeding (1)	
Metronidazole	Digoxin	Digoxin toxicity (2)	
	Ethanol	Disulfiram-like reactions (2)	
	Fluorouracil	Bone marrow suppression (1)	
Rifampin	Warfarin	Bleeding (2)	
	Warfarin	Clot formation (1)	
	Oral contraceptives	Pregnancy (1)	
	Cyclosporine/tacrolimus	Rejection (1)	
	HIV-1 protease inhibitors	Increased viral load, resistance (1)	
	Nonnucleoside reverse-transcriptase inhibitors	Increased viral load, resistance (1)	
	Glucocorticoids	Loss of steroid effect (1)	
	Methadone	Narcotic withdrawal symptoms (1)	
	Digoxin	Subtherapeutic digoxin levels (1)	
	Itraconazole	Subtherapeutic itraconazole levels (1)	
	Phenytoin	Loss of seizure control (1)	
Statins	Hypercholesterolemia (1)		
Diltiazem	Subtherapeutic diltiazem levels (1)		
Verapamil	Subtherapeutic verapamil levels (1)		

^a1 = a well-documented interaction with clinically important consequences; 2 = an interaction of uncertain frequency but of potential clinical importance.

^bLovastatin and simvastatin are most affected; pravastatin and atorvastatin are less prone to clinically important effects.

^cThe macrolide antibiotics and quinupristin/dalfopristin inhibit the same human metabolic enzyme, CYP3A4, and similar interactions are anticipated.

^dCiprofloxacin only. Levofloxacin and moxifloxacin do not inhibit theophylline metabolism.

Note: New interactions are commonly reported after marketing. Consult the most recent prescribing information for updates.

CNS, central nervous system.

FLUOROQUINOLONES

There are two clinically important drug interactions involving fluoroquinolones. First, similar to tetracyclines, all fluoroquinolones are chelated by divalent and trivalent cations, with a consequential significant reduction in absorption. Second, ciprofloxacin inhibits the hepatic enzyme that metabolizes theophylline. Scattered case reports suggest that quinolones can also potentiate the effects of warfarin, but this effect has not been observed in most controlled trials.

RIFAMPIN

Rifampin is an excellent inducer of many cytochrome P450 enzymes and increases the hepatic clearance of a large number of drugs, including the following (with the indicated predictable outcomes): HIV-1 protease inhibitors (loss of viral suppression), oral contraceptives (pregnancy), warfarin (decreased prothrombin times), cyclosporine and prednisone (organ rejection or exacerbations of any underlying inflammatory condition), and verapamil and diltiazem (increased dosage requirements).

Before rifampin is prescribed for any patient, a review of concomitant drug therapy is essential.

METRONIDAZOLE

Metronidazole can cause a disulfiram-like syndrome when alcohol is ingested. Thus, patients taking metronidazole should be instructed to avoid alcohol. Inhibition of the metabolism of warfarin by metronidazole leads to significant increases in prothrombin times.

PROPHYLAXIS OF BACTERIAL INFECTIONS

Antibacterial agents are occasionally indicated for use in patients who have no evidence of infection but who have been or are expected to be exposed to bacterial

pathogens under circumstances that constitute a major risk of infection. The basic tenets of antimicrobial prophylaxis are as follows. (1) The risk or potential severity of infection should outweigh the risk of side effects from the antibacterial agent. (2) The antibacterial agent should be given for the shortest period necessary to prevent target infections. (3) The antibacterial agent should be given before the expected period of risk (e.g., within 1 h of incision before elective surgery) or as soon as possible after contact with an infected individual (e.g., prophylaxis for meningococcal meningitis).

Table 42-9 lists the major indications for antibacterial prophylaxis in adults. The table includes only those indications that are widely accepted, supported by well-designed studies, or recommended by expert panels. Prophylaxis is also used but is less widely accepted for recurrent cellulitis in conjunction with lymphedema,

TABLE 42-9

PROPHYLAXIS OF BACTERIAL INFECTIONS IN ADULTS

CONDITION	ANTIBACTERIAL AGENT	TIMING OR DURATION OF PROPHYLAXIS
Nonsurgical		
Cardiac lesions susceptible to bacterial endocarditis	Amoxicillin ^a	Before and after procedures causing bacteremia
Recurrent <i>Staphylococcus aureus</i> infections	Mupirocin	5 days (intranasal)
Contact with patient with meningococcal meningitis	Rifampin	2 days
Bite wounds ^b	Fluoroquinolone	Single dose
	Penicillin V or amoxicillin/clavulanic acid	3–5 days
Recurrent cystitis	Trimethoprim-sulfamethoxazole or a fluoroquinolone or nitrofurantoin	3 times per week for ≤1 year or after sexual intercourse
Surgical		
Clean (cardiac, vascular, neurologic, or orthopedic surgery)	Cefazolin (vancomycin) ^c	Before and during procedure
Ocular	Topical combinations and subconjunctival cefazolin	During and at end of procedure
Clean-contaminated (head and neck, high-risk gastroduodenal or biliary tract surgery; high-risk cesarean section; hysterectomy)	Cefazolin (or clindamycin for head and neck)	Before and during procedure
Clean-contaminated (vaginal or abdominal hysterectomy)	Cefazolin or cefoxitin or cefotetan	Before and during procedure
Clean-contaminated (high-risk genitourinary surgery)	Fluoroquinolone	Before and during procedure
Clean-contaminated (colorectal surgery or appendectomy)	Cefoxitin or cefotetan (add oral neomycin + erythromycin for colorectal)	Before and during procedure
Dirty ^b (ruptured viscus)	Cefoxitin or cefotetan ± gentamicin, clindamycin + gentamicin, or another appropriate regimen directed at anaerobes and gram-negative aerobes	Before and for 3–5 days after procedure
Dirty ^b (traumatic wound)	Cefazolin	Before and for 3–5 days after trauma

^a Gentamicin should be added to the amoxicillin regimen for high-risk gastrointestinal and genitourinary procedures; vancomycin should be used in penicillin-allergic patients.

^b In these cases, use of antibacterial agents actually constitutes treatment of infection rather than prophylaxis.

^c Vancomycin is recommended only in institutions that have a high incidence of infection with methicillin-resistant staphylococci.

454 recurrent pneumococcal meningitis in conjunction with deficiencies in humoral immunity or CSF leaks, traveler's diarrhea, gram-negative sepsis in conjunction with neutropenia, and spontaneous bacterial peritonitis in conjunction with ascites. The use of antibacterial agents in children to prevent rheumatic fever and otitis media under certain circumstances is also common practice.

The major use of antibacterial prophylaxis is to prevent infections after surgical procedures. Antibacterial agents are administered just before the surgical procedure—and, for long operations, during the procedure as well—to ensure high drug concentrations in serum and tissues during surgery. The objective is to eradicate bacteria originating from the air of the operating suite, the skin of the surgical team, and the patient's own flora that may contaminate the wound. In all but colorectal surgical procedures, prophylaxis is predominantly directed against staphylococci, and cefazolin is the most commonly recommended drug. Prophylaxis is intended to prevent wound infection or infection of implanted devices, not all infections that may occur during the postoperative period (e.g., UTIs or pneumonia). Prolonged prophylaxis (>24 h) merely alters the normal flora and favors infections with organisms resistant to the antibacterial agents used. A focus on appropriate surgical prophylaxis by the Centers for Medicare and Medicaid Services, coupled with national efforts by surgical societies, appears to be having a favorable impact on the appropriate use of antimicrobial drugs in the surgical setting, although additional improvements are needed.

DURATION OF THERAPY AND TREATMENT FAILURE

Until recently, there was little incentive to establish the most appropriate duration of treatment; patients were instructed to take a 7- or 10-day course of treatment for most common infections. A number of recent investigations have evaluated shorter durations of therapy, especially in patients with community-acquired pneumonia. **Table 42-10** lists common bacterial infections for which treatment duration guidelines have been established or for which there is sufficient clinical experience to establish treatment durations. The ultimate test of cure for a bacterial infection is the absence of relapse when therapy is discontinued. *Relapse* is defined as a recurrence of infection with the identical organism that caused the first infection. In general, therefore, the duration of therapy should be long enough to prevent relapse yet not be excessive. Extension of therapy beyond the limit of effectiveness may increase the medication's side effects and encourage the selection of resistant bacteria. The art of treating bacterial infections lies in the ability to determine the appropriate duration of

TABLE 42-10

DURATION OF THERAPY FOR BACTERIAL INFECTIONS

DURATION OF THERAPY	INFECTIONS
Single dose	Gonococcal urethritis, streptococcal pharyngitis (penicillin G benzathine), primary and secondary syphilis (penicillin G benzathine)
3 days	Cystitis in young women, community- or travel-acquired diarrhea
3–10 days	Community-acquired pneumonia (3–5 days), community-acquired meningitis (pneumococcal or meningococcal), antibiotic-associated diarrhea (10 days), <i>Giardia</i> enteritis, cellulitis, epididymitis
2 weeks	<i>Helicobacter pylori</i> -associated peptic ulcer, neurosyphilis (penicillin IV), penicillin-susceptible viridans streptococcal endocarditis (penicillin plus aminoglycoside), disseminated gonococcal infection with arthritis, acute pyelonephritis, uncomplicated <i>Staphylococcus aureus</i> catheter-associated bacteremia
3 weeks	Lyme disease, septic arthritis (nongonococcal)
4 weeks	Acute and chronic prostatitis, infective endocarditis (penicillin-resistant streptococcal)
>4 weeks	Acute and chronic osteomyelitis, <i>S. aureus</i> endocarditis, foreign-body infections (prosthetic valve and joint infections), relapsing pseudomembranous colitis

therapy for infections that are not covered by established guidelines. Retreatment of infections for which therapy has failed usually requires a prolonged course (>4 weeks) with combinations of antibacterial agents.

MECHANISMS TO OPTIMIZE ANTIMICROBIAL USE

Antibiotic use is often not “rational,” and it is easy to understand why. The diagnosis of bacterial infection is often uncertain, and patients may expect or demand antimicrobial agents in this tenuous situation. There is a bewildering array of drugs, each with claims of superiority over the competition. The rates of resistance for many bacterial pathogens are ever-changing, and even experts may not agree on the clinical significance of resistance in some pathogens. Investigations consistently report that ~50% of antibiotic use is in some way “inappropriate.” Aside from the monetary cost of using unnecessary or overly expensive antibiotics, there are the

more serious costs associated with excess morbidity from superinfections such as *Clostridium difficile* disease, adverse drug reactions, drug interactions, and selection of resistant organisms. Although these costs are not yet well quantified, they add substantially to the overall costs of medical care.

At a time when fewer new antimicrobial drugs are entering the worldwide market than in the past, much has been written about the continued increase in rates of resistant microorganisms and its causes. The message seems clear: the use of existing and new antimicrobial agents must be more judicious and infection control more effective if we are to slow or reverse trends in resistance. The phrase *antimicrobial stewardship* is used to describe the new attitude toward antibacterial agents that must be adopted to preserve their usefulness. Appropriate stewardship requires that these drugs be used only when necessary, at the most appropriate dosage, and for the most appropriate duration. Increasing attention is being given to the relationships between differences in antibiotic consumption and differences in rates of resistance in different countries. Although some newer antibacterial drugs undeniably represent important advances in therapy, many offer no advantage over older, less expensive agents. With rare exceptions, newer drugs are usually found to be no more effective than the comparison antibiotic in controlled trials despite the “high prevalence of resistance” often touted to market the advantage of the new antibiotic over older therapies.

The following suggestions are intended to provide guidance through the antibiotic maze. First, objective evaluation of the merits of newer and older drugs is available. Online references such as the Johns Hopkins website (hopkins-abxguide.org) offer current and practical information regarding antimicrobial drugs and treatment regimens. Evidence-based practice guidelines for most infections are available from the Infectious Diseases Society of America (www.idsociety.org). Second, clinicians should become comfortable using a few drugs recommended by independent experts and professional organizations and should resist the temptation to use a new drug unless the merits are clear. A new antibacterial agent with a “broader spectrum and greater potency” or a “higher serum concentration-to-MIC ratio” will not necessarily be more clinically efficacious. Third, clinicians should become familiar with local bacterial susceptibility profiles. It may not be necessary to use a new drug with “improved activity against *P. aeruginosa*” if that pathogen is rarely encountered or if it retains full susceptibility to older drugs. Fourth, a skeptical attitude toward manufacturers’ claims is still appropriate. For example, increasing rates of penicillin resistance in *S. pneumoniae* have been

used to promote the use of broader-spectrum drugs, notably the fluoroquinolones. However, except in patients with meningitis, amoxicillin is still effective for infections caused by these “penicillin-resistant” strains. Finally, with regard to inpatient treatment with antibacterial drugs, a number of efforts to improve use are under study. The strategy of antibiotic “cycling” or rotation has not proved effective, but other strategies, such as heterogeneity or diversity of antibiotic use, may hold promise. Adoption of other evidence-based strategies to improve antimicrobial use may be the best way to retain the utility of existing compounds. For example, appropriate empirical treatment of a seriously ill patient with one or more broad-spectrum agents is important for improving survival rates, but therapy may often be simplified by switching to a narrower-spectrum agent or even an oral drug after the results of cultures and susceptibility tests become available. Although there is an understandable temptation not to alter effective therapy, switching to a more specific agent after the patient’s clinical condition has improved does not compromise outcome. A promising and active area of research includes the use of shorter courses of antimicrobial therapy. Many antibiotics that once were given for 7–10 days can be given for 3–5 days with no loss of efficacy and no increase in relapse rates (Table 42-10). Adoption of new guidelines for shorter-course therapy will not undermine the care of patients, many unnecessary complications and expenses will be avoided, and the useful life of these valuable drugs will perhaps be extended.

FURTHER READINGS

- BARTLETT JG, PERL TM: The new *Clostridium difficile*—What does it mean? *N Engl J Med* 353:2503, 2005
- COSGROVE SE, CARMELI Y: The impact of antimicrobial resistance on health and economic outcomes. *Clin Infect Dis* 36:1433, 2003
- FISHMAN N: Antimicrobial stewardship. *Am J Med* 119:S53, 2006
- GRUCHALLA RS, PIRMOHAMED M: Antibiotic allergy. *N Engl J Med* 354:601, 2006
- JACOBY GA, MUNOZ-PRICE LS: The new β -lactamases. *N Engl J Med* 352:380, 2005
- KOLLEF M: Appropriate empirical antibacterial therapy for nosocomial infections: Getting it right the first time. *Drugs* 63:2157, 2003
- NAHUM GG et al: Antibiotic use in pregnancy and lactation: What is and is not known about teratogenic and toxic risks. *Obstet Gynecol* 107:1120, 2006
- PETERSON LR: Penicillins for treatment of pneumococcal pneumonia: Does in vitro resistance really matter? *Clin Infect Dis* 42:224, 2006
- POLK HC JR: Continuing refinements in surgical antibiotic prophylaxis. *Arch Surg* 140:1066, 2005
- RAY WA et al: Oral erythromycin and the risk of sudden death from cardiac causes. *N Engl J Med* 351:1089, 2004



CHAPTER 43

ANTIVIRAL CHEMOTHERAPY, EXCLUDING ANTIRETROVIRAL DRUGS

Lindsey R. Baden ■ Raphael Dolin

■ Antiviral Drugs Active against Respiratory Infections	461	Trifluridine	467
Zanamivir and Oseltamivir	461	Vidarabine	467
Amantadine and Rimantadine	462	■ Antiviral Drugs Active against Hepatitis Viruses	467
Ribavirin	463	Lamivudine	467
■ Antiviral Drugs Active against Herpesvirus Infections	463	Adefovir	467
Acyclovir and Valacyclovir	463	Tenofovir	468
Cidofovir	465	Entecavir	468
Fomivirsen	465	Telbivudine	468
Ganciclovir and Valganciclovir	465	■ Interferons	468
Famciclovir and Penciclovir	466	■ Further Readings	469
Foscarnet	466		

The field of antiviral therapy—both the number of antiviral drugs and our understanding of their optimal use—continues to lag behind the field of antibacterial drug treatment, in which >70 years of experience has now been accumulated, but significant progress has been made in recent years on new drugs for several viral infections.

The development of antiviral drugs poses several challenges. Viruses replicate intracellularly and often use host cell enzymes, macromolecules, and organelles for synthesis of viral particles. Therefore, useful antiviral compounds must discriminate between host and viral functions with a high degree of specificity; agents without such selectivity are likely to be too toxic for clinical use.

The development of laboratory assays to assist clinicians in the appropriate use of antiviral drugs is also in its early stages. Phenotypic and genotypic assays for resistance to antiviral drugs are becoming more widely available, and correlations of laboratory results with clinical outcomes in various settings are beginning to be defined. Of particular note has been the development of highly sensitive and specific methods that measure the concentration of virus in blood (*virus load*) and permit direct assessment of the antiviral effect of a given drug

regimen in that compartment in the host. Virus load measurements have been useful in recognizing the risk of disease progression in patients with certain viral infections and in identifying patients to whom antiviral chemotherapy might be of greatest benefit. Similar to any in vitro laboratory test, these tests yield results that are highly dependent on (and likely to vary with) the laboratory techniques used.

Information regarding the pharmacokinetics of some antiviral drugs, particularly in diverse clinical settings, is limited. Assays to measure the concentrations of these drugs, especially of their active moieties within cells, are primarily research procedures and are not widely available to clinicians. Thus, relatively few guidelines are available for adjusting dosages of antiviral agents to maximize antiviral activity and minimize toxicity. Consequently, clinical use of antiviral drugs must be accompanied by particular vigilance with regard to unanticipated adverse effects.

Similar to that of other infections, the course of viral infections is profoundly affected by an interplay of the pathogen with a complex set of host defenses. The presence or absence of preexisting immunity, the ability to mount humoral or cell-mediated immune responses, and

the stimulation of innate immunity are important determinants of the outcome of viral infections. The state of the host's defenses needs to be considered when antiviral agents are used or evaluated.

As with any therapy, the optimal use of antiviral compounds requires a specific and timely diagnosis. For some viral infections, such as herpes zoster, the clinical manifestations are so characteristic that a diagnosis can be made on clinical grounds alone. For other viral infections, such as influenza A, epidemiologic information (e.g., the documentation of a community-wide outbreak) can be used to make a presumptive diagnosis with a high degree of accuracy. However, for most other viral infections, including herpes simplex encephalitis, cytomegaloviral infections

other than retinitis, and enteroviral infections, diagnosis on clinical grounds alone cannot be accomplished with certainty. For such infections, rapid viral diagnostic techniques are of great importance. Considerable progress has been made in recent years in the development of such tests, which are now widely available for a number of viral infections.

Despite these complexities, the efficacy of a number of antiviral compounds has been clearly established in rigorously conducted and controlled studies. As summarized in **Table 43-1**, this chapter reviews the antiviral drugs that are currently approved or are likely to be considered for approval in the near future for use against viral infections other than those caused by HIV.

TABLE 43-1**ANTIVIRAL CHEMOTHERAPY AND CHEMOPROPHYLAXIS**

INFECTION	DRUG	ROUTE	DOSAGE	COMMENTS	
Influenza A and B Prophylaxis	Oseltamivir	Oral	Adults: 75 mg/d Children ≥ 1 yr: 30–75 mg/d, depending on weight	Prophylaxis must continue for the duration of the outbreak and can be administered simultaneously with inactivated vaccine. Unless the sensitivity of isolates is known, neither amantadine nor rimantadine is currently recommended for prophylaxis or therapy because of the high rate of resistance in influenza A/H3N2 viruses since the 2005–2006 season.	
	Zanamivir	Inhaled orally	Adults and children ≥ 5 yrs: 10 mg/d		
	Amantadine ^a or rimantadine ^a	Oral	Adults: 200 mg/d Children 1–9 yrs: 5 mg/kg per day (maximum, 150 mg/d)		
	Treatment	Oseltamivir	Oral		Adults: 75 mg bid for 5 days Children 1–12 yrs: 30–75 mg bid for 5 days
		Zanamivir	Inhaled orally		Adults and children ≥ 7 yrs: 10 mg bid for 5 days
		Amantadine ^a	Oral		Adults: 100 qd or bid Children 1–9 yrs: 5 mg/kg per day (maximum, 150 mg/d) for 5–7 days
		Rimantadine ^a	Oral		100 qd or bid for 5–7 days in adults
	RSV infection	Ribavirin	Small-particle aerosol		Administered continuously from reservoir containing 20 mg/mL for 3–6 days
CMV retinitis in immunocompromised host (AIDS)	Ganciclovir	IV	5 mg/kg bid for 14–21 days; then 5 mg/kg per day as maintenance dose	Ganciclovir, valganciclovir, foscarnet, and cidofovir are approved for treatment of CMV retinitis in patients with AIDS. They are also used for colitis, pneumonia, or “wasting” syndrome associated with CMV and for prevention of CMV disease in transplant recipients.	
		Oral	1 g tid as maintenance dose		

(Continued)

ANTIVIRAL CHEMOTHERAPY AND CHEMOPROPHYLAXIS

INFECTION	DRUG	ROUTE	DOSAGE	COMMENTS	
CMV retinitis (continued)	Valganciclovir	Oral	900 mg bid for 21 days; then 900 mg/d as maintenance dose	Valganciclovir has largely supplanted oral ganciclovir and is frequently used in place of IV ganciclovir.	
	Foscarnet	IV	60 mg/kg q8h for 14–21 days; then 90–120 mg/kg per day as maintenance dose	Foscarnet is not myelosuppressive and is active against acyclovir- and ganciclovir-resistant herpesviruses.	
	Cidofovir	IV	5 mg/kg once weekly for 2 weeks, then once every other week; given with probenecid and hydration		
	Fomivirsen	Intravitreal	330 mg on day 1 and day 15, followed by 330 mg monthly as maintenance	Fomivirsen has reduced the rate of progression of CMV retinitis in patients in whom other regimens have failed or have not been well tolerated. The major form of toxicity is ocular inflammation.	
Varicella					
	Immunocompetent host	Acyclovir	Oral	20 mg/kg (maximum, 800 mg) four or five times daily for 5 days	Treatment confers modest clinical benefit when administered within 24 h of rash onset.
	Immunocompromised host	Acyclovir	IV	10 mg/kg q8h for 7 days	A change to oral valganciclovir can be considered after fever has subsided if there is no evidence of visceral involvement.
Herpes simplex encephalitis	Acyclovir	IV	10 mg/kg q8h for 14–21 days	Results are optimal when therapy is initiated early. Some authorities recommend treatment for 21 days to prevent relapses.	
Neonatal herpes simplex	Acyclovir	IV	10 mg/kg q8h for 14–21 days	Serious morbidity is common despite therapy. Prolonged oral administration of acyclovir after initial IV therapy has been suggested because of long-term sequelae associated with cutaneous recurrences of HSV infection.	
Genital herpes simplex	Primary (treatment)	Acyclovir	IV	5 mg/kg q8h for 5–10 days	The IV route is preferred for infections severe enough to warrant hospitalization or with neurologic complications.
			Oral	200 mg five times daily for 10 days	The oral route is preferred for patients whose condition does not warrant hospitalization. Adequate hydration must be maintained.
		Acyclovir	Topical	5% ointment; four to six applications daily for 7–10 days	Topical use—largely supplemented by oral therapy—may obviate systemic administration to pregnant women. Systemic symptoms and untreated areas are not affected.
		Valacyclovir	Oral	1 g bid for 10 days	Valacyclovir appears to be as effective as acyclovir but can be administered less frequently.
		Famciclovir	Oral	250 mg tid for 5–10 days ^b	Famciclovir appears to be similar in effectiveness to acyclovir.
	Recurrent (treatment)	Acyclovir	Oral	200 mg five times daily for 5 days	Clinical effect is modest and is enhanced if therapy is initiated early.
		Famciclovir Valacyclovir	Oral Oral	1000 mg bid for 1 day 500 mg bid for 3 days	Treatment does not affect recurrence rates.

TABLE 43-1 (CONTINUED)

INFECTION	DRUG	ROUTE	DOSAGE	COMMENTS
Genital herpes (continued)				
Recurrent (suppression)	Acyclovir	Oral	400 mg bid for ≥ 12 months	Suppressive therapy is recommended only for patients with at least 6–10 recurrences per year. “Breakthrough” occasionally takes place, and asymptomatic shedding of virus occurs. The need for suppressive therapy should be reevaluated after 1 year. Suppression with valacyclovir reduces transmission of genital HSV among discordant couples.
	Valacyclovir	Oral	500–1000 mg/d	
	Famciclovir	Oral	125–250 mg bid	
Mucocutaneous herpes simplex in immunocompromised host				
Treatment	Acyclovir	IV	5 mg/kg q8h for 7 days	The choice of the IV or oral route depends on the severity of infection and the patient’s ability to take oral medication. Oral or IV treatment has supplanted topical therapy except for small, easily accessible lesions. Foscarnet is used for acyclovir-resistant viruses. Treatment is administered during periods when intense immunosuppression is expected (e.g., during antitumor chemotherapy or after transplantation) and is usually continued for 2–3 months.
		Oral	400 mg five times daily for 10 days	
Prevention of recurrence during intense immunosuppression	Valacyclovir Famciclovir Acyclovir Valacyclovir Famciclovir	Topical	5% ointment; four to six applications daily for 7 days or until healed	
		Oral	1 g tid for 7 days ^b	
		Oral	500 mg bid for 4 days ^c	
		Oral	200 mg bid	
		IV	5 mg/kg q12h	
		Oral	1 g tid ^b	
		Oral	500 mg bid ^b	
Herpes simplex orolabialis (recurrent)				
	Penciclovir	Topical	1.0% cream applied q2h during waking hours for 4 days	Treatment shortens healing time and symptoms by 0.5–1.0 day (compared with placebo).
	Valacyclovir	Oral	2 g q12h for 1 day	Therapy begun at the earliest symptom reduces disease duration by 1 day.
	Famciclovir ^b	Oral	500 mg tid for 5 days	Therapy begun 48 h after UV light exposure decreases time to healing by 2 days.
	Docosonal ^d	Topical	10% cream five times daily until healed	Application at initial symptoms reduces healing time by 1 day.
Herpes simplex keratitis				
	Trifluridine	Topical	1 drop of 1% ophthalmic solution q2h while awake (maximum, 9 drops daily)	Therapy should be undertaken in consultation with an ophthalmologist.
	Vidarabine	Topical	0.5-in ribbon of 3% ophthalmic ointment five times daily	
Herpes zoster				
Immunocompetent host	Valacyclovir	Oral	1 g tid for 7 days	Valacyclovir may be more effective than acyclovir for pain relief; otherwise, it has a similar effect on cutaneous lesions and should be given within 72 h of rash onset.

(Continued)

ANTIVIRAL CHEMOTHERAPY AND CHEMOPROPHYLAXIS

INFECTION	DRUG	ROUTE	DOSAGE	COMMENTS
Herpes zoster Immunocompetent host (continued)	Famciclovir	Oral	500 mg q8h for 7 days	The duration of postherpetic neuralgia is shorter than with placebo. Famciclovir showed overall efficacy similar to that of acyclovir in a comparative trial. It should be given ≤ 72 h after rash onset.
	Acyclovir	Oral	800 mg five times daily for 7–10 days	Acyclovir causes faster resolution of skin lesions than placebo and provides some relief of acute symptoms if given within 72 h of rash onset. Combined with tapering doses of prednisone, acyclovir improves quality-of-life outcomes.
Immunocompromised host	Acyclovir	IV Oral	10 mg/kg q8h for 7 days 800 mg five times daily for 7 days	Effectiveness in localized zoster is most marked when treatment is given early. Foscarnet may be used for VZV infections that are resistant to acyclovir.
	Famciclovir	Oral	500 mg tid for 10 days ^b	
Herpes zoster ophthalmicus	Acyclovir	Oral	600 mg five times daily for 10 days	Treatment reduces ocular complications, including ocular keratitis and uveitis.
Condyloma acuminatum	IFN- $\alpha 2b$	Intralesional	1 million units per wart (maximum of 5) thrice weekly for 3 weeks	Intralesional treatment frequently results in regression of warts, but lesions often recur. Parenteral administration may be useful if lesions are numerous.
	IFN- $\alpha n3$	Intralesional	250,000 units per wart (maximum of 10) twice weekly for up to 8 weeks	
Chronic hepatitis B	IFN- $\alpha 2b$	SC	5 million units daily or 10 million units thrice weekly for 16–24 weeks	HBeAg and DNA are eliminated in 33–37% of cases. Histopathologic improvement is also seen.
	Pegylated IFN- $\alpha 2a$	SC	180 μ g weekly for 48 weeks	HBeAg and DNA are eliminated in 32–43% of recipients.
	Lamivudine	Oral	100 mg/d for 12–18 months; 150 mg bid as part of therapy for HIV infection	The efficacy of lamivudine is similar to that of IFN, but lamivudine is better tolerated. Resistance develops in 24% of recipients when lamivudine is used as monotherapy for 1 year.
	Adefovir dipivoxil	Oral	10 mg/d for 48 months	A return of ALT levels to normal is documented in 48–72% of recipients and improved liver histopathology in 53–64%. Adefovir is effective in lamivudine-resistant hepatitis B. Renal function should be monitored.
	Entecavir	Oral	0.5 mg/d for 48 weeks (1 mg/d if HBV is resistant to lamivudine)	Normalization of ALT is seen in 68–78% of recipients and loss of HBeAg in 21%. Entecavir is active against lamivudine-resistant HBV.
	Telbivudine	Oral	600 mg/d for 52 weeks	Reduction of HBV DNA by $>5 \log_{10}$ copies/mL along with either normalization of ALT or loss of serum HBeAg is seen in 75% of recipients. Myopathy may occur.

TABLE 43-1 (CONTINUED)

INFECTION	DRUG	ROUTE	DOSAGE	COMMENTS
Chronic hepatitis C	IFN- α 2a or IFN- α 2b	SC	3 million units thrice weekly for 12–18 months	A return of ALT levels to normal is documented in 54% of recipients but is sustained in only 28%. Improvement in liver histopathology is seen.
	IFN- α 2b/ribavirin	SC (IFN)/oral (ribavirin)	3 million units thrice weekly (IFN)/1000–1200 mg daily (ribavirin) for 6–12 months	Combination therapy results in sustained responses in up to 40–50% of all recipients.
	Pegylated IFN- α 2b	SC	1 μ g/kg weekly for 12–24 months	The slower clearance of pegylated IFNs than of standard IFNs permits once-weekly administration. The pegylated formulations appear to be superior to standard IFNs in tolerability and efficacy, both as monotherapy and in combination with ribavirin. Sustained virologic responses were seen in 42–46% of genotype 1 patients and in 76–82% of those infected with genotype 2 or 3.
	Pegylated IFN- α 2a	SC	180 μ g weekly for 12–24 months	
	Pegylated IFN- α 2b/ribavirin	SC (IFN)/oral (ribavirin)	1.5 μ g/kg weekly (IFN)/800–1200 mg daily (ribavirin) ^d for 24–48 weeks	
	Pegylated IFN- α 2a/ribavirin	SC (IFN)/oral (ribavirin)	180 μ g weekly (IFN)/800–1200 mg daily (ribavirin) for 24–48 weeks	
Chronic hepatitis D	IFN- α 2a or IFN- α 2b	SC	9–15 μ g thrice weekly for 6–12 months	Doses of 9 and 15 μ g are equivalent to IFN- α 2a and IFN- α 2b doses of 3 million and 5 million units, respectively.
				The overall efficacy and the optimal regimen and duration of therapy have not been established. Responses usually are not sustained when therapy is stopped.

^a Influenza A only. Unless isolate sensitivity is known, not recommended for prophylaxis or therapy since 2005–2006 because of high rates of resistance in influenza A/H3N2 viruses.

^b Not approved for this indication by the U.S. Food and Drug Administration (FDA).

^c Approved by the FDA for treatment of HIV-infected individuals.

^d Active ingredient: benzyl alcohol. Available without prescription.

Note: ALT, alanine aminotransferase; CMV, cytomegalovirus; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HSV, herpes simplex virus; IFN, interferon; RSV, respiratory syncytial virus; UV, ultraviolet; VZV, varicella-zoster virus.

ANTIVIRAL DRUGS ACTIVE AGAINST RESPIRATORY INFECTIONS

ZANAMIVIR AND OSELTAMIVIR

Zanamivir and oseltamivir are inhibitors of the influenza viral neuraminidase enzyme, which is essential for release of the virus from infected cells and for its subsequent spread throughout the respiratory tract of the infected host. The enzyme cleaves terminal sialic acid residues and thus destroys the cellular receptors to which the viral hemagglutinin attaches. Zanamivir and oseltamivir are sialic acid transition-state analogues and are highly active and specific inhibitors of the neuraminidases of both influenza A and B viruses. The antineuraminidase activity of the two drugs is similar, although zanamivir has somewhat greater in vitro activity against influenza B. Both zanamivir and oseltamivir act through competitive and

reversible inhibition of the active site of influenza A and B viral neuraminidases and have relatively little effect on mammalian cell enzymes.

Oseltamivir phosphate is an ethyl ester prodrug that is converted to oseltamivir carboxylate by esterases in the liver. Orally administered oseltamivir has a bioavailability of >60% and a plasma half-life of 7–9 h. The drug is excreted unmetabolized, primarily by the kidneys. Zanamivir has low oral bioavailability and is administered orally via a handheld inhaler. By this route, ~15% of the dose is deposited in the lower respiratory tract, and low plasma levels of the drug are detected.

Orally inhaled zanamivir is generally well tolerated, although exacerbations of asthma may occur. The toxicities most frequently encountered with orally administered oseltamivir are nausea, gastrointestinal discomfort, and (less commonly) vomiting. Gastrointestinal discomfort is usually transient and is less likely if the drug is administered

with food. Recently, neuropsychiatric events (e.g., delirium, self-injury) have been reported in children who have been taking oseltamivir, primarily in Japan.

Inhaled zanamivir and orally administered oseltamivir have been effective in the treatment of naturally occurring influenza A or B in otherwise healthy adults. In placebo-controlled studies, illness has been shortened by 1.0–1.5 days of therapy with either of these drugs when treatment is administered within 2 days of onset. A recent meta-analysis of clinical studies of oseltamivir suggests that treatment may reduce the likelihood of certain respiratory tract complications of influenza. Once-daily inhaled zanamivir or once-daily orally administered oseltamivir provides effective prophylaxis against laboratory-documented influenza A- and influenza B-associated illness.

The emergence of viruses resistant to zanamivir or oseltamivir occurs but appears to be less frequent than the emergence of resistance to the adamantanes in clinical studies carried out thus far. In one pediatric study, 5.5% of patients treated with oseltamivir developed resistant isolates. A somewhat higher rate of resistance was noted in a recent pediatric study of oseltamivir from Japan. Resistance to the neuraminidase inhibitors may develop by changes in the viral neuraminidase enzyme, by changes in the hemagglutinin that make it more resistant to the actions of the neuraminidase, or by both mechanisms. Some isolates that are resistant to oseltamivir may remain sensitive to zanamivir. Since the mechanisms of action of the neuraminidase inhibitors differ from those of the adamantanes (see below), zanamivir and oseltamivir are active against strains of influenza A virus that are resistant to amantadine and rimantadine.

Zanamivir and oseltamivir have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of influenza in adults and in children (those ≥ 7 years old for zanamivir and those ≥ 1 year of age for oseltamivir) who have been symptomatic for ≤ 2 days. Oseltamivir is approved for prophylaxis of influenza in individuals ≥ 1 year of age and zanamivir for those ≥ 5 years of age (Table 43-1).

AMANTADINE AND RIMANTADINE

Amantadine and the closely related compound rimantadine are primary symmetric amines that display antiviral activity limited to influenza A viruses. Amantadine and rimantadine have been shown to be efficacious in the prophylaxis and treatment of influenza A infections in humans for >40 years. High frequencies of resistance to these drugs were noted among influenza A/H3N2 viruses in the 2005–2006 influenza season and continue to be seen up to the present (2006–2007). Therefore, these agents are no longer recommended unless the sensitivity of the individual influenza A isolate is known, in which case their use may be considered. Amantadine and rimantadine act

through inhibition of the ion channel function of the influenza A M2 matrix protein, on which appropriate uncoating of the virus depends. A substitution of a single amino acid at critical sites in the M2 protein can result in a virus that is resistant to amantadine and rimantadine.

Amantadine and rimantadine have been shown to be effective in the prophylaxis of influenza A in large-scale studies of young adults and in less extensive studies of children and elderly persons. In such studies, efficacy rates of 55–80% in the prevention of influenza-like illness were noted, and even higher rates were reported when virus-specific attack rates were calculated. Amantadine and rimantadine have also been found to be effective in the treatment of influenza A infection in studies involving predominantly young adults and, to a lesser extent, children. Administration of these compounds within 24–72 h after the onset of illness has resulted in a reduction of the duration of signs and symptoms by $\sim 50\%$ from that in placebo recipients. The effect on signs and symptoms of illness is superior to that of commonly used antipyretic-analgesic agents. Only anecdotal reports are available concerning the efficacy of amantadine or rimantadine in the prevention or treatment of complications of influenza (e.g., pneumonia).

Amantadine and rimantadine are available only in oral formulations and are ordinarily administered to adults once or twice daily, with a dosage of 100–200 mg/d. Despite their structural similarities, the two compounds have different pharmacokinetics. Amantadine is not metabolized and is excreted almost entirely by the kidneys, with a half-life of 12–17 h and peak plasma concentrations of 0.4 $\mu\text{g}/\text{mL}$. In contrast, rimantadine is extensively metabolized to hydroxylated derivatives and has a half-life of 30 h. Only 30–40% of an orally administered dose of rimantadine is recovered in the urine. The peak plasma levels of rimantadine are approximately half those of amantadine, but rimantadine is concentrated in respiratory secretions to a greater extent than amantadine. For prophylaxis, the compounds must be administered daily for the period at risk (i.e., the peak duration of the outbreak). For therapy, amantadine or rimantadine is generally administered for 5–7 days.

Although these compounds are generally well tolerated, 5–10% of amantadine recipients experience mild central nervous system (CNS) side effects consisting primarily of dizziness, anxiety, insomnia, and difficulty in concentrating. These effects are rapidly reversible upon cessation of the drug. At a dosage of 200 mg/d, rimantadine is better tolerated than amantadine; in a large-scale study of young adults, adverse effects were no more frequent among rimantadine recipients than among placebo recipients. Seizures and worsening of congestive heart failure have also been reported in patients treated with amantadine, although a causal relationship has not been established. The dosage of amantadine should be reduced to 100 mg/d in patients with renal insufficiency

[i.e., a creatinine clearance rate (Cr_{Cl}) of <50 mL/min] and in elderly patients. A rimantadine dose of 100 mg/d should be used for patients with a Cr_{Cl} of <10 mL/min and, in elderly patients.

RIBAVIRIN

Ribavirin is a synthetic nucleoside analogue that inhibits a wide range of RNA and DNA viruses. The mechanism of action of ribavirin is not completely defined and may be different for different groups of viruses. Ribavirin-5'-monophosphate blocks the conversion of inosine-5'-monophosphate to xanthosine-5'-monophosphate and interferes with the synthesis of guanine nucleotides as well as that of both RNA and DNA. Ribavirin-5'-monophosphate also inhibits capping of virus-specific messenger RNA in certain viral systems. In studies demonstrating the effectiveness of ribavirin in the treatment of respiratory syncytial virus (RSV) infection in infants, the compound was administered as a small-particle aerosol. In infants with RSV infection who were given ribavirin by continuous aerosol for 3–6 days, illness and lower respiratory tract signs resolved more rapidly and arterial oxygen desaturation was less pronounced than in placebo-treated groups. In addition, ribavirin has had a beneficial clinical effect in infants with RSV infection who require mechanical ventilation. Aerosolized ribavirin has also been administered to older children and adults with severe RSV and parainfluenza virus infections (including immunosuppressed patients) and to older children and adults with influenza A or B infection, but the benefit of this treatment, if any, is unclear. In RSV infections in immunosuppressed patients, ribavirin is often given in combination with immunoglobulins.

Orally administered ribavirin has not been effective in the treatment of influenza A virus infections. IV or oral ribavirin has reduced mortality rates among patients with Lassa fever; it has been particularly effective in this regard when given within the first 6 days of illness. IV ribavirin has been reported to be of clinical benefit in the treatment of hemorrhagic fever with renal syndrome caused by Hantaan virus and as therapy for Argentinian hemorrhagic fever. Moreover, oral ribavirin has been recommended for the treatment and prophylaxis of Congo-Crimean hemorrhagic fever. An open-label trial suggested that oral ribavirin may be beneficial in the treatment of Nipah virus encephalitis. Use of IV ribavirin in patients with hantavirus pulmonary syndrome in the United States has not been associated with clear-cut benefits. Oral administration of ribavirin reduces serum aminotransferase levels in patients with chronic hepatitis C virus (HCV) infection; because it appears not to reduce serum HCV RNA levels, the mechanism of this effect is unclear. The drug provides added benefit when given by mouth in doses of 800–1200 mg/d in combination with interferon (IFN) $\alpha 2b$ or $\alpha 2a$ (see later), and

the ribavirin/IFN combination has been approved for the treatment of patients with chronic HCV infection.

Large doses of ribavirin (800–1000 mg/d PO) have been associated with reversible hematopoietic toxicity. This effect has not been observed with aerosolized ribavirin, apparently because little drug is absorbed systemically. Aerosolized administration of ribavirin is generally well tolerated but occasionally is associated with bronchospasm, rash, or conjunctival irritation. Aerosolized ribavirin has been approved for treatment of RSV infection in infants and should be administered under close supervision, particularly in the setting of mechanical ventilation, in which precipitation of the drug is possible. Health care workers exposed to the drug have experienced minor toxicity, including eye and respiratory tract irritation. Because ribavirin is mutagenic, teratogenic, and embryotoxic, its use is generally contraindicated in pregnancy. Its administration as an aerosol poses a risk to pregnant health care workers.

ANTIVIRAL DRUGS ACTIVE AGAINST HERPESVIRUS INFECTIONS

ACYCLOVIR AND VALACYCLOVIR

Acyclovir is a highly potent and selective inhibitor of the replication of certain herpesviruses, including herpes simplex virus (HSV) types 1 and 2, varicella-zoster virus (VZV), and Epstein-Barr virus (EBV). It is relatively ineffective in the treatment of human cytomegalovirus (CMV) infections; however, some studies have indicated its effectiveness in the prevention of CMV-associated disease in immunosuppressed patients. Valacyclovir, the L-valyl ester of acyclovir, is converted almost entirely to acyclovir by intestinal and hepatic hydrolysis after oral administration. Valacyclovir has pharmacokinetic advantages over orally administered acyclovir: it exhibits significantly greater oral bioavailability, results in higher blood levels, and can be given less frequently than acyclovir (two or three rather than five times daily).

The high degree of selectivity of acyclovir is related to its mechanism of action, which requires that the compound first be phosphorylated to acyclovir monophosphate. This phosphorylation occurs efficiently in herpesvirus-infected cells by means of a virus-coded thymidine kinase. In uninfected mammalian cells, little phosphorylation of acyclovir occurs, and the drug is therefore concentrated in herpesvirus-infected cells. Acyclovir monophosphate is subsequently converted by host cell kinases to a triphosphate that is a potent inhibitor of virus-induced DNA polymerase but has relatively little effect on host-cell DNA polymerase. Acyclovir triphosphate can also be incorporated into viral DNA, with early chain termination.

Acyclovir is available in IV, oral, and topical forms, and valacyclovir is available in an oral formulation.

464 IV acyclovir is markedly effective in the treatment of mucocutaneous HSV infections in immunocompromised hosts, in whom it reduces time to healing, duration of pain, and virus shedding. When administered prophylactically during periods of intense immunosuppression (e.g., related to chemotherapy for leukemia or transplantation) and before the development of lesions, IV acyclovir reduces the frequency of HSV-associated disease. After prophylaxis is discontinued, HSV lesions recur. IV acyclovir is also effective in the treatment of HSV encephalitis; two comparative trials have indicated that acyclovir is more effective than vidarabine for this indication (see below).

Because VZV is generally less sensitive to acyclovir than is HSV, higher doses of acyclovir must be used to treat VZV infections. In immunocompromised patients with herpes zoster, IV acyclovir reduces the frequency of cutaneous dissemination and visceral complications and—in one comparative trial—was more effective than vidarabine. Acyclovir, administered at dosages of 800 mg PO five times a day, had a modest beneficial effect on localized herpes zoster lesions in both immunocompromised and immunocompetent patients. Combination of acyclovir with a tapering regimen of prednisone appeared to be more effective than acyclovir alone in terms of quality-of-life outcomes in immunocompetent patients older than age 50 years with herpes zoster. A comparative study of acyclovir (800 mg PO five times daily) and valacyclovir (1 g PO tid) in immunocompetent patients with herpes zoster indicated that the latter drug may be more effective in eliciting the resolution of zoster-associated pain. Orally administered acyclovir (600 mg five times a day) reduced complications of herpes zoster ophthalmicus in a placebo-controlled trial.

In chickenpox, a modest overall clinical benefit is attained when oral acyclovir therapy is begun within 24 h of the onset of rash in otherwise healthy children (20 mg/kg, up to a maximum of 800 mg, four times a day) or adults (800 mg five times a day). IV acyclovir has also been reported to be effective in the treatment of immunocompromised children with chickenpox.

The most widespread use of acyclovir is in the treatment of genital HSV infections. IV or oral acyclovir or oral valacyclovir has shortened the duration of symptoms, reduced virus shedding, and accelerated healing when used for the treatment of primary genital HSV infections. Oral acyclovir and valacyclovir have also had a modest effect in treatment of recurrent genital HSV infections. However, the failure of treatment of either primary or recurrent disease to reduce the frequency of subsequent recurrences has indicated that acyclovir is ineffective in eliminating latent infection. Chronic oral administration of acyclovir for ≥ 1 –6 years or of valacyclovir for ≥ 1 year has reduced the frequency of recurrences markedly during therapy; when the drug is discontinued, lesions recur. In one study, suppressive therapy with valacyclovir (500 mg once daily for 8 months) reduced transmission of HSV-2

genital infections among discordant couples by 50%. A modest effect (i.e., a reduction of disease duration by 1 day) on herpes labialis was seen when valacyclovir was administered upon detection of the first symptom of a lesion at a dosage of 2 g every 12 h for 1 day. In AIDS patients, chronic or intermittent administration of acyclovir has been associated with the development of HSV and VZV strains resistant to the action of the drug and with clinical failures. The most common mechanism of resistance is a deficiency of the virus-induced thymidine kinase. Patients with HSV or VZV infections resistant to acyclovir have frequently responded to foscarnet.

With the availability of the oral and IV forms, there are few indications for topical acyclovir, although treatment with this formulation has been modestly beneficial in primary genital HSV infections and in mucocutaneous HSV infections in immunocompromised hosts.

Overall, acyclovir is remarkably well tolerated and is generally free of toxicity. The most frequently encountered form of toxicity is renal dysfunction because of drug crystallization, particularly after rapid IV administration or with inadequate hydration. CNS changes, including lethargy and tremors, are occasionally reported, primarily in immunosuppressed patients. However, whether these changes are related to acyclovir, to concurrent administration of other therapy, or to underlying infection remains unclear. Acyclovir is excreted primarily unmetabolized by the kidney via both glomerular filtration and tubular secretion. Approximately 15% of a dose of acyclovir is metabolized to 9-[(carboxymethoxy)methyl] guanine or other minor metabolites. Reduction in dosage is indicated in patients with a Cr_{Cl} of < 50 mL/min. The half-life of acyclovir is ~ 3 h in normal adults, and the peak plasma concentration after a 1-h infusion of a dose of 5 mg/kg is 9.8 $\mu\text{g/mL}$. Approximately 22% of an orally administered acyclovir dose is absorbed, and peak plasma concentrations of 0.3–0.9 $\mu\text{g/mL}$ are attained after administration of a 200-mg dose. Acyclovir penetrates relatively well into the cerebrospinal fluid (CSF), with concentrations approaching half of those found in plasma.

Acyclovir causes chromosomal breakage at high doses, but its administration to pregnant women has not been associated with fetal abnormalities. Nonetheless, the potential risks and benefits of acyclovir should be carefully assessed before the drug is used in pregnancy.

Valacyclovir exhibits three to five times greater bioavailability than acyclovir. The concentration-time curve for valacyclovir, given as 1 g PO three times daily, is similar to that for acyclovir, given as 5 mg/kg IV every 8 h. The safety profiles of valacyclovir and acyclovir are similar, although thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome has been reported in immunocompromised patients who have received high doses of valacyclovir (8 g/d). Valacyclovir is approved for the treatment of herpes zoster, initial and recurrent episodes of genital HSV infections in immunocompetent

adults, and herpes labialis as well as for suppressive treatment of genital herpes. Although it has not been extensively studied in other clinical settings involving HSV or VZV infections, many consultants use valacyclovir rather than oral acyclovir in settings where the latter has been approved because of valacyclovir's superior pharmacokinetics and more convenient dosing schedule.

CIDOFOVIR

Cidofovir is a phosphonate nucleotide analogue of cytosine. Its major use is in CMV infections, particularly retinitis, but it is active against a broad range of herpesviruses, including HSV; human herpesvirus (HHV) type 6; HHV-8; and certain other DNA viruses such as polyomaviruses, papillomaviruses, adenoviruses, and poxviruses, including variola (smallpox) and vaccinia. Cidofovir does not require initial phosphorylation by virus-induced kinases; the drug is phosphorylated by host cell enzymes to cidofovir diphosphate, which is a competitive inhibitor of viral DNA polymerases and, to a lesser extent, of host cell DNA polymerases. Incorporation of cidofovir diphosphate slows or terminates nascent DNA chain elongation. Cidofovir is active against HSV isolates that are resistant to acyclovir because of absent or altered thymidine kinase and against CMV isolates that are resistant to ganciclovir because of UL97 phosphotransferase mutations. Cidofovir is usually active against foscarnet-resistant CMV, although cross-resistance to foscarnet as well as to ganciclovir has been described.

Cidofovir has poor oral availability and is administered IV. It is excreted primarily by the kidney and has a plasma half-life of 2.6 h. Cidofovir diphosphate's intracellular half-life of >48 h is the basis for the recommended dosing regimen of 5 mg/kg once a week for the initial 2 weeks and then 5 mg/kg every other week. The major toxic effect of cidofovir is proximal renal tubular injury, as manifested by elevated serum creatinine levels and proteinuria. The risk of nephrotoxicity can be reduced by vigorous saline hydration and concomitant oral administration of probenecid. Neutropenia, rashes, and gastrointestinal tolerance may also occur.

IV cidofovir has been approved for the treatment of CMV retinitis in AIDS patients who are intolerant of ganciclovir or foscarnet or in whom those drugs have failed. In a controlled study, a maintenance dosage of 5 mg/kg per week administered to AIDS patients reduced the progression of CMV retinitis from that seen at 3 mg/kg. IV cidofovir has been reported anecdotally to be effective for treatment of acyclovir-resistant mucocutaneous HSV infections. Likewise, topically administered cidofovir is reportedly beneficial against these infections in HIV-infected patients; it is also being studied for the treatment of anogenital warts. Anecdotal use of IV cidofovir has been described in disseminated adenoviral infections in immunosuppressed patients, but its efficacy,

if any, is not known. An ophthalmic formulation is being studied as treatment for adenoviral keratoconjunctivitis. Intravitreal cidofovir has been used to treat CMV retinitis but has been associated with significant toxicity.

FOMIVIRSEN

Fomivirsen is the first antisense oligonucleotide approved by the FDA for therapy in humans. This phosphorothioate oligonucleotide, 21 nucleotides in length, inhibits CMV replication through interaction with CMV messenger RNA. Fomivirsen is complementary to messenger transcripts of the major immediate early region 2 (IE2) of CMV, which codes for proteins regulating viral gene expression. In addition to its antisense mechanism of action, fomivirsen may exert activity against CMV through inhibition of viral adsorption to cells as well as direct inhibition of viral replication. Because of its different mechanism of action, fomivirsen is active against CMV isolates that are resistant to nucleoside or nucleotide analogues, such as ganciclovir, foscarnet, and cidofovir.

Fomivirsen has been approved for intravitreal administration in the treatment of CMV retinitis in AIDS patients who have failed to respond to other treatments or cannot tolerate them. Injections of 330 mg for two doses 2 weeks apart followed by maintenance doses of 330 mg monthly significantly reduce the rate of progression of CMV retinitis. The major toxicity is ocular inflammation, including vitritis and iritis, which usually responds to topically administered glucocorticoids.

GANCICLOVIR AND VALGANCICLOVIR

An analogue of acyclovir, ganciclovir is active against HSV and VZV and is markedly more active than acyclovir against CMV. Ganciclovir triphosphate inhibits CMV DNA polymerase and can be incorporated into CMV DNA, whose elongation it eventually terminates. In HSV- and VZV-infected cells, ganciclovir is phosphorylated by virus-encoded thymidine kinases; in CMV-infected cells, it is phosphorylated by a viral kinase encoded by the UL97 gene. Ganciclovir triphosphate is present in 10-fold higher concentrations in CMV-infected cells than in uninfected cells. Ganciclovir is approved for the treatment of CMV retinitis in immunosuppressed patients and for the prevention of CMV disease in transplant recipients. It is widely used for the treatment of other CMV-associated syndromes, including pneumonia, esophagogastrintestinal infections, hepatitis, and "wasting" illness.

Ganciclovir is available for IV or oral administration. Because its oral bioavailability is low (5–9%), relatively large doses (1 g three times daily) must be administered by this route. Oral ganciclovir has largely been supplanted by valganciclovir, which is the L-valyl ester of ganciclovir. Valganciclovir is well absorbed orally, with a bioavailability of 60%, and is rapidly hydrolyzed to ganciclovir in the

intestine and liver. The area under the curve for a 900-mg dose of valganciclovir is equivalent to that for 5 mg/kg of ganciclovir given IV, although peak serum concentrations are ~40% lower for valganciclovir. The serum half-life is 3.5 h after IV administration of ganciclovir and 4.0 h after PO administration of valganciclovir. Ganciclovir is excreted primarily by the kidneys in an unmetabolized form, and its dosage should be reduced in cases of renal failure. The most commonly used dosage for initial IV therapy is 5 mg/kg every 12 h for 14–21 days; this regimen is followed by an IV maintenance dose of 5 mg/kg per day or five times per week. For oral therapy with valganciclovir, the dosage is 900 mg twice daily for 21 days followed by 900 mg once a day for maintenance, with dose adjustment in patients with renal dysfunction. Intraocular ganciclovir, given by either intravitreal injection or intraocular implantation, has also been used to treat CMV retinitis.

Ganciclovir is effective as prophylaxis against CMV-associated disease in organ and bone marrow transplant recipients. Oral ganciclovir administered prophylactically to AIDS patients with CD4+T cell counts of <100/μL has provided protection against the development of CMV retinitis. However, the long-term benefits of this approach to prophylaxis in AIDS patients have not been established, and most experts do not recommend the use of oral ganciclovir for this purpose. As already mentioned, valganciclovir has supplanted oral ganciclovir when oral prophylaxis or therapy is considered.

The administration of ganciclovir has been associated with profound bone marrow suppression, particularly neutropenia, which significantly limits the drug's use in many patients. Bone marrow toxicity is potentiated in the setting of renal dysfunction and when other bone marrow suppressants, such as zidovudine, are used concomitantly.

Resistance has been noted in CMV isolates obtained after therapy with ganciclovir, especially in patients with AIDS. Such resistance may develop through a mutation in either the viral *UL97* gene or the viral DNA polymerase. Ganciclovir-resistant isolates are usually sensitive to foscarnet (see later) or cidofovir (see earlier).

FAMCICLOVIR AND PENCICLOVIR

Famciclovir is the diacetyl 6-deoxyester of the guanosine analogue penciclovir. Famciclovir is well absorbed orally, has a bioavailability of 77%, and is rapidly converted to penciclovir by deacetylation and oxidation in the intestine and liver. Penciclovir's spectrum of activity and mechanism of action are similar to those of acyclovir. Thus, penciclovir is usually not active against acyclovir-resistant viruses. However, some acyclovir-resistant viruses with altered thymidine kinase or DNA polymerase substrate specificity may be sensitive to penciclovir. This drug is phosphorylated initially by a virus-encoded thymidine kinase and subsequently by cellular kinases to penciclovir

triphosphate, which inhibits HSV-1, HSV-2, VZV, and EBV as well as hepatitis B virus (HBV). The serum half-life of penciclovir is 2 h, but the intracellular half-life of penciclovir triphosphate is 7–20 h—markedly longer than that of acyclovir triphosphate. The latter is the basis for the less frequent (twice-daily) dosing schedule for famciclovir than for acyclovir. Penciclovir is eliminated primarily in the urine by both glomerular filtration and tubular secretion. The usually recommended dosage interval should be adjusted for renal insufficiency.

Clinical trials involving immunocompetent adults with herpes zoster showed that famciclovir was superior to placebo in eliciting the resolution of skin lesions and virus shedding and in shortening the duration of postherpetic neuralgia; moreover, administered at 500 mg every 8 h, famciclovir was at least as effective as acyclovir administered at a dose of 800 mg PO five times daily. Famciclovir was also effective in the treatment of herpes zoster in immunosuppressed patients. Clinical trials have demonstrated its effectiveness in the suppression of genital HSV infections for ≤1 year and in the treatment of initial and recurrent episodes of genital herpes. Famciclovir is effective as therapy for mucocutaneous HSV infections in HIV-infected patients. Application of a 1% penciclovir cream reduces the duration of signs and symptoms of herpes labialis in immunocompetent patients (by 0.5–1.0 day) and has been approved for that purpose by the FDA. Famciclovir is generally well tolerated, with occasional headache, nausea, and diarrhea reported in frequencies similar to those among placebo recipients. The administration of high doses of famciclovir for 2 years was associated with an increased incidence of mammary adenocarcinomas in female rats, but the clinical significance of this effect is unknown.

FOSCARNET

Foscarnet (phosphonoformic acid) is a pyrophosphate-containing compound that potently inhibits herpesviruses, including CMV. This drug inhibits DNA polymerases at the pyrophosphate binding site at concentrations that have relatively little effect on cellular polymerases. Foscarnet does not require phosphorylation to exert its antiviral activity and is therefore active against HSV and VZV isolates that are resistant to acyclovir because of deficiencies in thymidine kinase as well as against most ganciclovir-resistant strains of CMV. Foscarnet also inhibits the reverse transcriptase of HIV and is active against HIV *in vivo*.

Foscarnet is poorly soluble and must be administered IV via an infusion pump in a dilute solution over 1–2 h. The plasma half-life of foscarnet is 3–5 h and increases with decreasing renal function because the drug is eliminated primarily by the kidneys. It has been estimated that 10–28% of a dose may be deposited in bone, where it can persist for months. The most common initial dosage of foscarnet—60 mg/kg every 8 h for 14–21 days—is

followed by a maintenance dose of 90–120 mg/kg once a day.

Foscarnet is approved for the treatment of CMV retinitis in patients with AIDS and of acyclovir-resistant mucocutaneous HSV infections. In a comparative clinical trial, the drug appeared to be about as efficacious as ganciclovir against CMV retinitis but was associated with a longer survival period, possibly because of its activity against HIV. Intraocular foscarnet has been used to treat CMV retinitis. Foscarnet has also been used to treat acyclovir-resistant HSV and VZV infections as well as ganciclovir-resistant CMV infections, although resistance to foscarnet has been reported in CMV isolates obtained during therapy. Foscarnet has also been used to treat HHV-6 infections in immunosuppressed patients.

The major form of toxicity associated with foscarnet is renal impairment. Thus, renal function should be monitored closely, particularly during the initial phase of therapy. Because foscarnet binds divalent metal ions, hypocalcemia, hypomagnesemia, hypokalemia, and hypo- or hyperphosphatemia can develop. Saline hydration and slow infusion appear to protect the patient against nephrotoxicity and electrolyte disturbances. Although hematologic abnormalities have been documented (most commonly anemia), foscarnet is not generally myelosuppressive and may be administered concomitantly with myelosuppressive medications such as zidovudine.

TRIFLURIDINE

Trifluridine is a pyrimidine nucleoside active against HSV-1, HSV-2, and CMV. Trifluridine monophosphate irreversibly inhibits thymidylate synthetase, and trifluridine triphosphate inhibits viral and, to a lesser extent, cellular DNA polymerases. Because of systemic toxicity, its use is limited to topical therapy. Trifluridine is approved for treatment of HSV keratitis, for which trials have shown that it is more effective than topical idoxuridine but similar in efficacy to topical vidarabine. The drug has benefited some patients with HSV keratitis who have failed to respond to idoxuridine or vidarabine. Topical application of trifluridine to sites of acyclovir-resistant HSV mucocutaneous infections has also been beneficial in some cases.

VIDARABINE

Vidarabine is a purine nucleoside analogue with activity against HSV-1, HSV-2, VZV, and EBV. Vidarabine inhibits viral DNA synthesis through its 5'-triphosphorylated metabolite, although its precise molecular mechanisms of action are not completely understood. IV-administered vidarabine has been shown to be effective in the treatment of herpes simplex encephalitis, mucocutaneous HSV infections, herpes zoster in immunocompromised patients, and neonatal HSV infections. Its use has been

supplanted by that of IV acyclovir, which is more effective and easier to administer. Production of the IV preparation has been discontinued by the manufacturer, but vidarabine is available as an ophthalmic ointment, which is effective in the treatment of HSV keratitis.

ANTIVIRAL DRUGS ACTIVE AGAINST HEPATITIS VIRUSES

LAMIVUDINE

Lamivudine is a pyrimidine nucleoside analogue that is used primarily in combination therapy against HIV infection. It is also active against HBV through inhibition of the viral DNA polymerase and has been approved for the treatment of chronic HBV infection. At dosages of 100 mg/d for 1 year, lamivudine is well tolerated and results in suppression of HBV DNA levels, normalization of serum aminotransferase levels in 50–70% of patients, and reduction of hepatic inflammation and fibrosis in 50–60% of patients. Loss of hepatitis B e antigen (HBeAg) occurs in 30% of patients. Resistance to lamivudine develops in 24% of patients treated for 1 year and is associated with changes in the YMDD motif of HBV DNA polymerase. This is an important limitation of monotherapy with the drug. Lamivudine is being evaluated as a component of combination regimens (with IFNs and other nucleoside or nucleotide analogues listed below) for the treatment of hepatitis B. Lamivudine appears to be useful in the prevention or suppression of HBV infection associated with liver transplantation.

ADEFOVIR

Adefovir dipivoxil is an acyclic nucleotide analogue of adenosine monophosphate that has activity against HBV, HIV, HSV, and CMV. It is phosphorylated by cellular kinases to the active triphosphate moiety, which is a competitive inhibitor of HBV DNA polymerase and results in chain termination after incorporation into nascent viral DNA. Adefovir is administered orally and is eliminated primarily by the kidneys, with a plasma half-life of 7.5 h. In clinical studies, therapy with adefovir at 10 mg/d for 48 weeks resulted in normalization of alanine aminotransferase (ALT) levels in 48–72% of patients and improved liver histology in 53–64%; it also resulted in a 3.6- \log_{10} reduction in the number of HBV DNA copies per milliliter of plasma. Adefovir was effective in treatment-naïve patients as well as in those infected with lamivudine-resistant HBV. Resistance to adefovir appears to develop less readily than that to lamivudine, but adefovir resistance rates of 15–18% have been reported after 192 weeks of treatment. This agent is generally well tolerated. Significant nephrotoxicity attributable to adefovir is uncommon at the dosage used in the treatment of HBV infections (10 mg/d) but is a treatment-limiting

468 adverse effect at the higher doses used in therapy for HIV infections (30–120 mg/d). In any case, renal function should be monitored in patients taking adefovir, even at the lower dose. Adefovir is approved only for treatment of chronic HBV infection.

TENOFOVIR

Tenofovir disoproxil fumarate is a nucleotide analogue of adenosine monophosphate with activity against both retroviruses and hepadnaviruses. In patients co-infected with HIV and HBV, tenofovir reduces HBV loads by 3–4 log₁₀ copies/mL at 24 weeks and is effective against lamivudine-resistant HBV. The drug is approved only for treatment of HIV infection, but its use should be considered in patients co-infected with HIV and HBV.

ENTECAVIR

Entecavir is a cyclopentyl guanosine analogue that inhibits HBV through inhibition of HBV DNA polymerase by entecavir triphosphate and is also active against HIV. In vitro, entecavir is more potent than lamivudine or adefovir against HBV and is also effective against lamivudine-resistant HBV. Administration of entecavir at 0.5 mg/d PO for 48 weeks results in a reduction of HBV DNA by 5.0–6.9 log₁₀ copies/mL, normalization of ALT values in 68–78% of recipients, and loss of HBeAg in 21%. Entecavir is highly bioavailable but should be taken on an empty stomach because food interferes with its absorption. The drug is eliminated primarily in unchanged form by the kidneys, and its dosage should be adjusted for patients with Cr_{Cl} values of <50 mg/min. Overall, entecavir is well tolerated. Resistance to entecavir has not been observed during the treatment of naive patients; however, resistance was noted in 7–10% of lamivudine-refractory patients at 48 weeks of treatment with entecavir. Entecavir-resistant strains appear to be sensitive to adefovir. As with other anti-HBV treatments, exacerbation of hepatitis may occur when entecavir therapy is stopped. Entecavir is approved for treatment of chronic hepatitis B in adults.

TELBIVUDINE

Telbivudine is the β-L enantiomer of thymidine and is a potent inhibitor of HBV. Its active form is telbivudine triphosphate, which inhibits HBV DNA polymerase but has little or no activity against human DNA polymerase. Administration of telbivudine at 600 mg/d PO for 52 weeks to patients with chronic hepatitis B resulted in reduction of HBV DNA by >5 log₁₀ copies/mL along with either loss of serum HBeAg or normalization of ALT in 75% of recipients. After 2 years of therapy, resistance to telbivudine was noted in isolates from 8.6–21.6% of patients. Telbivudine-resistant HBV is usually resistant

to lamivudine as well but is generally susceptible to adefovir.

Telbivudine is eliminated primarily by the kidneys, and the dosage should be reduced in patients with a Cl_{Cr} value of <50 mL/min. Telbivudine is generally well tolerated, but increases in serum creatinine kinases and clinically evident myopathy have been observed. As with other anti-HBV drugs, hepatitis may be exacerbated in patients who have discontinued telbivudine therapy. Telbivudine has been approved for the treatment of adults with chronic hepatitis B who have evidence of viral replication and either persistent elevation in serum aminotransferases or histologically active disease.

INTERFERONS

IFNs are cytokines that exhibit a broad spectrum of antiviral activities as well as immunomodulating and antiproliferative properties. IFNs are not available for oral administration but must be given IM, SC, or IV. Early studies with human leukocyte IFN demonstrated an effect in the prophylaxis of experimentally induced rhinovirus infections in humans and in the treatment of VZV infections in immunosuppressed patients. DNA recombinant technology has made available highly purified α, β, and γ IFNs that have been evaluated in a variety of viral infections. Results of such trials have confirmed the effectiveness of intranasally administered IFN in the prophylaxis of rhinovirus infections, although its use has been associated with nasal mucosal irritation. Studies have also demonstrated a beneficial effect of intralesionally or systemically administered IFNs on genital warts. The effect of systemic administration consists primarily of a reduction in the size of the warts, and this mode of therapy may be useful in persons who have numerous warts that cannot easily be treated by individual intralesional injections. However, lesions frequently recur after either intralesional or systemic IFN therapy is discontinued.

IFNs have undergone extensive study in the treatment of chronic HBV infection. The administration of IFN-α2b (5 million units daily or 10 million units three times a week for 16–24 weeks) to patients with stable chronic HBV infection resulted in loss of markers of HBV replication, such as HBeAg and HBV DNA, in 33–37% of cases; 8% of patients also became negative for hepatitis B surface antigen. In >80% of patients who lose HBeAg and HBV DNA markers, serum aminotransferases return to normal levels, and both short- and long-term improvements in liver histopathology have been described. Predictors of a favorable response to therapy include low pretherapy levels of HBV DNA, high pretherapy serum levels of ALT, a short duration of chronic HBV infection, and active inflammation in liver histopathology. Poor responses are seen in immunosuppressed patients, including those with HIV infection. A longer duration of therapy

(12–24 months) is recommended for HBeAg-negative chronic hepatitis B. Adverse effects of the above doses of IFN are common and include fever, chills, myalgia, fatigue, neurotoxicity (primarily manifested as somnolence, depression, anxiety, and confusion), and leukopenia. Approximately 25% of patients receiving a daily dose of 5 million units require dose reduction, but <5% require discontinuation of therapy. Pegylated IFNs, which are covalently linked with monomethoxy polyethylene glycol, have a markedly reduced clearance rate. Therefore, they can be administered less frequently, are better tolerated, and may be more effective in some settings than standard IFNs (see discussion of hepatitis C below). Pegylated IFN- α 2a is approved for the treatment of patients with chronic hepatitis B who are either positive or negative for HBeAg (Table 43-1).

Several IFN preparations, including IFN- α 2a, IFN- α 2b, IFN-alfacon-1, and IFN- α m1 (lymphoblastoid), have been studied as therapy for chronic HCV infections. A variety of monotherapy regimens have been used, of which the most common is IFN- α 2b or - α 2a at 3 million units three times per week for 12–18 months. The addition of oral ribavirin to IFN- α 2b—either as initial therapy or after failure of IFN therapy alone—results in significantly higher rates of sustained virologic or serum ALT responses (40–50%) than are obtained with monotherapy. Comparative studies indicate that pegylated IFN- α 2b or - α 2a therapy is more effective than standard IFN treatment against chronic HCV infection. The combination of SC pegylated IFN and oral ribavirin is more convenient and appears to be the most effective regimen for treatment of chronic hepatitis C. With this combination regimen, sustained virologic responses were seen in 42–46% of patients with genotype 1 infection and in 76–82% of patients with genotype 2 or 3 infection. Ribavirin appears to have a small antiviral effect in HCV infection but may also be working through an immunomodulatory effect in combination with IFN. Optimal results with ribavirin appear to be associated with weight-based dosing. Prognostic factors for a favorable response include an age of <45 years, a short duration of infection, low levels of HCV RNA, and infection with HCV genotypes other than 1. IFN-alfacon, a synthetic “consensus” α interferon, appears to produce response rates similar to those elicited by IFN- α 2a or - α 2b alone and is also approved in the United States for the treatment of chronic hepatitis C.

The efficacy of IFN- α treatment for chronic hepatitis D remains unestablished. Anecdotal reports suggested that dosages ranging from 5 million U/d to 9 million units three times per week for 12 months elicit biochemical and virologic responses. Results from small controlled trials have been inconsistent, and observed responses have not generally been sustained. Limited experience has been published with the use of pegylated IFN- α 2b for treatment of hepatitis D, but some consultants prefer this agent for this indication because of its pharmacologic advantages over standard IFN.

FURTHER READINGS

- BEUTNER KR et al: Valaciclovir compared with acyclovir for improved therapy for herpes zoster in immunocompetent adults. *Antimicrob Agents Chemother* 39:1546, 1995
- COUCH RB: Drug therapy: Prevention and treatment of influenza. *N Engl J Med* 343:1778, 2000
- CRUMPACKER CS: Ganciclovir. *N Engl J Med* 335:721, 1996
- DOLIN R et al: A controlled trial of amantadine and rimantadine in the prophylaxis of influenza A infection. *N Engl J Med* 307:580, 1982
- FIELD JJ, HOOFNAGLE JH: Mechanism of action of interferon and ribavirin in treatment of hepatitis C. *Nature* 436:967, 2005
- GISH RG et al: Safety and antiviral activity of emtricitabine (FTC) for the treatment of chronic hepatitis B infection: A two-year study. *J Hepatol* 43:60, 2005
- HALL CB et al: Aerosolized ribavirin treatment of infants with respiratory syncytial viral infection: A randomized double-blind study. *N Engl J Med* 308:1443, 1983
- HAYDEN FG: Antiviral drugs (other than antiretrovirals), in *Principles and Practice of Infectious Diseases*, 6th ed, JE Bennett et al (eds). Philadelphia, Elsevier Churchill Livingstone, 2005, pp 514–551
- LAI CL et al: Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 354:186, 2006
- LALEZARI JP et al: Randomized controlled study of the safety and efficacy of IV cidofovir for the treatment of relapsing cytomegalovirus retinitis in patients with AIDS. *J AIDS* 17:339, 1998
- LOK AS et al: Management of hepatitis B: 2000—summary of a workshop. *Gastroenterology* 120:1828, 2001
- MARTIN DF et al: A controlled trial of valganciclovir as induction therapy for cytomegalovirus retinitis. *N Engl J Med* 346:1119, 2002
- NATIONAL INSTITUTES OF HEALTH CONSENSUS DEVELOPMENT CONFERENCE STATEMENT: Management of hepatitis C. September 12, 2002 (available at www.niaid.nih.gov)
- TREANOR JJ et al: Efficacy and safety in treating acute influenza: A randomized controlled trial. U.S. Oral Neuraminidase Study Group. *JAMA* 283:1016, 2000



CHAPTER 44

DIAGNOSIS AND TREATMENT OF FUNGAL INFECTIONS

John E. Edwards, Jr.

Terminology and Microbiology	470
Diagnosis	471
■ Further Readings	474

TERMINOLOGY AND MICROBIOLOGY

Traditionally, fungal infections have been classified into specific categories based on both anatomic location and epidemiology. The most common general anatomic categories are mucocutaneous and deep organ infection; the most common general epidemiologic categories are endemic and opportunistic. Although *mucocutaneous infections* can cause serious morbidity, they are rarely fatal. *Deep organ infections* also cause severe illness in many cases, but in contrast to mucocutaneous infections, they are often fatal. The *endemic mycoses* (e.g., coccidioidomycosis) are infections caused by fungal organisms that are not part of the normal human microbial flora and are acquired from environmental sources. In contrast, *opportunistic mycoses* are caused by organisms (e.g., *Candida* and *Aspergillus* spp.) that frequently are components of the normal human flora and whose ubiquity in nature renders them easily acquired by immunocompromised hosts. Opportunistic fungi cause serious infections when the immunologic response of the host becomes ineffective, allowing the organisms to transition from harmless commensals to invasive pathogens. Frequently, the diminished effectiveness of the immune system is a result of advanced modern therapies that coincidentally either unbalance the host's microflora or directly interfere with immunologic responses. Endemic mycoses cause more severe illness in immunocompromised patients than in immunocompetent individuals.

Patients acquire infection with endemic fungi almost exclusively by inhalation. The soil is the natural reservoir for the vast majority of endemic mycoses. The

dermatophytic fungi may be acquired by human-to-human transmission, but the majority of infections result from environmental contact. In contrast, the opportunistic fungus *Candida* invades the host from normal sites of colonization, usually the mucous membranes of the gastrointestinal tract. In general, innate immunity is the primary defense mechanism against fungi. Although antibodies are formed during many fungal infections (and even during commensalism), they generally do not constitute the primary mode of defense. Nevertheless, in selected infections, as discussed below, measurement of antibody titers may be a useful diagnostic test.

Three other terms frequently used in clinical discussions of fungal infections are *yeast*, *mold*, and *dimorphic fungus*. *Yeasts* are seen as rounded single cells or as budding organisms. *Candida* and *Cryptococcus* spp. are traditionally classified as yeasts. Molds grow as filamentous forms called *hyphae* both at room temperature and when they invade tissue. *Aspergillus*, *Rhizopus* spp. [the species that causes mucormycosis (zygomycosis)], and fungi commonly infecting the skin to cause ringworm and related cutaneous conditions are classified as molds. Variations occur within this classification of yeasts and molds. For instance, when *Candida* spp. infects tissue, both yeasts and filamentous forms may occur (except with *Candida glabrata*, which forms only yeasts in tissue); in contrast, *Cryptococcus* spp. exists only in yeast form. *Dimorphic* is the term used to describe fungi that grow as yeasts or large spherical structures in tissue but

as filamentous forms at room temperature in the environment. Classified in this group are the organisms causing blastomycosis, paracoccidioidomycosis, coccidioidomycosis, histoplasmosis, blastomycosis, and sporotrichosis.

The incidence of fungal infections has increased substantially over the past several decades. Opportunistic infections have increased in frequency as a consequence of intentional immunosuppression in organ and stem cell transplantation and many other diseases, the administration of cytotoxic chemotherapy for cancers, and the liberal use of antibacterial agents. The incidence of endemic mycoses has increased in geographic locations where there has been substantial population growth.

DIAGNOSIS

The definitive diagnosis of any fungal infection requires histopathologic identification of the fungus invading tissue accompanied by evidence of an inflammatory response. The identification of an inflammatory response has been especially important with regard to *Aspergillus* infection. *Aspergillus* spp. is ubiquitous and can float from the air onto biopsy material. Therefore, in rare but important instances, this fungus is an ex vivo contaminant during processing of a specimen for microscopy, with a consequent incorrect diagnosis. The stains most commonly used to identify fungi are periodic acid–Schiff and Gomori methenamine silver. *Candida* spp., unlike other fungi, is visible on gram-stained tissue smears. Hematoxylin and eosin stain is not sufficient to identify *Candida* spp. in tissue specimens. When positive, an India ink preparation of cerebrospinal fluid (CSF) is diagnostic for cryptococcosis. Most laboratories now use calcofluor white staining coupled with fluorescent microscopy to identify fungi in fluid specimens.

Extensive investigations of the diagnosis of deep organ fungal infections have yielded a variety of tests with different degrees of specificity and sensitivity. The most reliable tests are the detection of antibody to *Coccidioides immitis* and *Histoplasma capsulatum* in serum and CSF; the detection of cryptococcal polysaccharide antigen in serum and CSF; and the detection of *Histoplasma* antigen in urine or serum. The test for galactomannan has been used extensively in Europe and is now approved in the United States for diagnosis of aspergillosis. This test requires additional validation before its true usefulness can be determined. Sources of concern are the incidence of false-negative results and the need for multiple serial tests to reduce this incidence. The β -glucan test for *Candida* spp. is also under evaluation, but similar to the galactomannan test, requires additional validation. Numerous polymerase chain reaction assays to detect antigens are in the developmental stages, as are nucleic acid hybridization techniques; however, these methods are not currently used on a widespread basis in major medical centers.

Of the fungal organisms, *Candida* spp. is by far most frequently recovered from blood. Although *Candida* spp. can be detected with any of the automated blood culture systems widely used at present, the lysis–centrifugation technique increases the sensitivity of blood cultures for less common organisms (e.g., *H. capsulatum*) and should be used when disseminated fungal infection is suspected.

Except in the cases of coccidioidomycosis, cryptococcosis, and histoplasmosis, there are no fully validated and widely used tests for serodiagnosis of disseminated fungal infection. Skin tests for the endemic mycoses are no longer available.

Rx Treatment: FUNGAL INFECTIONS

This discussion is intended as a brief overview of general strategies for the use of antifungal agents in the treatment of patients with fungal infections. Details on regimens, schedules, and strategies are discussed in the chapters on specific mycoses.

Because fungal organisms are eukaryotic cells that contain most of the same organelles (with many of the same physiologic functions) as human cells, the identification of drugs that selectively kill or inhibit fungi but are not toxic to human cells has been highly problematic. Far fewer antifungal than antibacterial agents have been introduced into clinical medicine.

AMPHOTERICIN B (AmB) The introduction of AmB in the late 1950s revolutionized the treatment of patients with fungal infections in deep organs. Before AmB became available, cryptococcal meningitis and other disseminated fungal infections were nearly always fatal. For nearly a decade after AmB was introduced, it was the only effective agent for the treatment of patients with life-threatening fungal infections. AmB remains the broadest-spectrum antifungal agent but carries several disadvantages, including significant nephrotoxicity, lack of an oral preparation, and unpleasant side effects (fever, chills, and nausea) during treatment. To circumvent nephrotoxicity and infusion side effects, lipid formulations of AmB were developed and have virtually replaced the original colloidal deoxycholate formulation in clinical use (although the older formulation is still available). The lipid formulations include liposomal AmB (L-AB; 435 mg/kg per day) and AmB lipid complex (ABLC; 5 mg/kg per day). A third preparation, AmB colloidal dispersion (ABCD; 3–4 mg/kg per day), is rarely used because of the high incidence of side effects associated with infusion. (The doses listed are standard doses for adults with invasive infection.)

The lipid formulations of AmB have the disadvantage of being considerably more expensive than the

deoxycholate formulation. Experience is still accumulating on the comparative efficacy, toxicity, and advantages of the different formulations for specific clinical fungal infections [e.g., central nervous system (CNS) infection]. Whether there is a clinically significant difference in these drugs with respect to CNS penetration or nephrotoxicity remains controversial. Despite these issues and despite the expense, the lipid formulations are now much more commonly used than AmB deoxycholate in the United States.

AZOLES This class of antifungal drugs offers important advantages over AmB: the azoles cause little or no nephrotoxicity and are available in oral preparations. Early azoles included ketoconazole and miconazole, which have been replaced by newer agents for the treatment of patients with deep organ fungal infections. The azoles' mechanism of action is inhibition of ergosterol synthesis in the fungal cell wall. Unlike AmB, these drugs are considered fungistatic, not -cidal.

Fluconazole Since its introduction, fluconazole has played an extremely important role in the treatment of a wide variety of serious fungal infections. Its major advantages are the availability of both oral and IV formulations, a long half-life, satisfactory penetration of most body fluids (including ocular fluid and CSF), and minimal toxicity (especially relative to AmB). Its disadvantages include (usually reversible) hepatotoxicity and—at high doses—alopecia, muscle weakness, and dry mouth with a metallic taste. Fluconazole is not effective for the treatment of aspergillosis, mucormycosis, or *Scedosporium apiospermum* infections. It is less effective than the newer azoles against *C. glabrata* and *Candida krusei*.

Fluconazole has become the agent of choice for the treatment of coccidioidal meningitis, although relapses have occurred after therapy with this drug. In addition, fluconazole is useful for both consolidation and maintenance therapy for cryptococcal meningitis. This agent has been shown to be as efficacious as AmB in the treatment of candidemia. The effectiveness of fluconazole in candidemia and the drug's relatively minimal toxicity in conjunction with the inadequacy of diagnostic tests for widespread hematogenously disseminated candidiasis have led to a change in the paradigm for candidemia management. The standard of care is now to treat all candidemic patients with an antifungal agent and to change all their intravascular lines, if feasible, rather than merely to remove a singular suspect intravascular line and then observe the patient. The usual fluconazole regimen for treatment of candidemia is 400 mg/d given until 2 weeks after the last positive blood culture.

Fluconazole is considered effective as fungal prophylaxis in bone marrow transplant recipients and high-risk liver transplant patients. Its use for prophylaxis in patients with leukemia, in AIDS patients with low CD4+

T cell counts, and in patients on surgical intensive care units remains controversial.

Voriconazole Similar to fluconazole, voriconazole is available in both oral and IV formulations. Voriconazole has a broader spectrum than fluconazole against *Candida* spp. (including *C. glabrata* and *C. krusei*) and is active against *Aspergillus*, *Scedosporium*, and *Fusarium* spp. It is generally considered the first-line drug of choice for treatment of aspergillosis. A few case reports have shown voriconazole to be effective in individual patients with coccidioidomycosis, blastomycosis, and histoplasmosis, but (because of limited data) this agent is not recommended for treatment of the endemic mycoses. Among the disadvantages of voriconazole (compared with fluconazole) are its more numerous interactions with many of the drugs used in patients predisposed to fungal infections. Hepatotoxicity, skin rashes (including photosensitivity), and visual disturbances are relatively common. Voriconazole is also considerably more expensive than fluconazole. Moreover, it is advisable to monitor voriconazole levels in certain patients because (1) this drug is completely metabolized in the liver by CYP2C9, CYP3A4, and CYP2C19 and (2) human genetic variability in CYP2C19 activity exists. Dosages should be reduced accordingly in those patients with liver failure. Dose adjustments for renal insufficiency are not necessary; however, because the IV formulation is prepared in cyclodextrin, it should not be given to patients with severe renal insufficiency.

Itraconazole Itraconazole is available in IV and oral (capsule and suspension) formulations. Varying blood levels among patients taking oral itraconazole reflect a disadvantage compared with the other azoles. Itraconazole is the drug of choice for mild to moderate histoplasmosis and blastomycosis and has often been used for chronic mucocutaneous candidiasis. It has been approved by the U.S. Food and Drug Administration (FDA) for use in febrile neutropenic patients. Itraconazole has also proven useful for the treatment of chronic coccidioidomycosis, sporotrichosis, and *S. apiospermum* infection. The mucocutaneous and cutaneous fungal infections that have been treated successfully with itraconazole include oropharyngeal candidiasis (especially in AIDS patients), tinea versicolor, tinea capitis, and onychomycosis. Disadvantages of itraconazole include its poor penetration into the CSF, the use of cyclodextrin in both the oral suspension and the IV preparation, the variable absorption of the capsules, and the need for monitoring of blood levels in patients taking capsules for disseminated mycoses. In recent years, reported cases of severe congestive heart failure in patients taking itraconazole have been a source of concern. Similar to the other azoles, itraconazole can cause hepatic toxicity.

Posaconazole Posaconazole has been approved by the FDA for prophylaxis of aspergillosis and candidiasis in patients at high risk for developing these infections because of severe immunocompromise. This drug has also been evaluated for the treatment of patients with zygomycosis, fusariosis, aspergillosis, and oropharyngeal candidiasis. The relevant studies of posaconazole in zygomycosis, fusariosis, and aspergillosis have examined salvage therapy. A study of >90 patients whose zygomycosis was refractory to other therapy yielded encouraging results. No trials of posaconazole for the treatment of candidemia have yet been reported. Case reports have described the drug's efficacy in coccidioidomycosis and histoplasmosis. Controlled trials have shown its effectiveness as a prophylactic agent in patients with acute leukemia and in bone marrow transplant recipients. In addition, posaconazole has been found to be effective against fluconazole-resistant *Candida* spp. The results of a large-scale study of the use of posaconazole as salvage therapy for aspergillosis have been promising but, as of this writing, have not been published in a peer-reviewed format.

ECHINOCANDINS The echinocandins, including the approved drugs caspofungin, anidulafungin, and micafungin, have added considerably to the antifungal armamentarium. All three of these agents inhibit β -1,3-glucan synthase, which is necessary for cell wall synthesis in fungi and is not a component of human cells. None of these agents is available in an oral formulation. The echinocandins are considered fungicidal for *Candida* spp. and fungistatic for *Aspergillus* spp. Their greatest use to date is against candidal infections. They offer two advantages: broad-spectrum activity against all *Candida* spp. and relatively low toxicity. The minimum inhibitory concentrations (MICs) of all the echinocandins are highest against *C. parapsilosis*; it is not clear whether these higher MIC values represent less clinical effectiveness against this species. The echinocandins are among the safest antifungal agents.

In controlled trials, *caspofungin* has been at least as efficacious as AmB for the treatment of candidemia and invasive candidiasis and as efficacious as fluconazole for the treatment of candidal esophagitis. In addition, caspofungin has been efficacious as salvage therapy for aspergillosis. At present, it is used most extensively for the treatment of candidemic patients, especially before the infecting species is precisely identified.

Anidulafungin has been approved by the FDA as therapy for candidemia in nonneutropenic patients and for *Candida* esophagitis, intraabdominal infection, and peritonitis. In controlled trials, anidulafungin has been more efficacious than fluconazole against candidemia and invasive candidiasis and as efficacious as fluconazole against candidal esophagitis. When anidulafungin is used with cyclosporine, tacrolimus, or voriconazole, no dosage adjustment is required for either drug in the combination.

Micafungin has been approved for the treatment of esophageal candidiasis and for prophylaxis in patients receiving stem cell transplants. Studies thus far have shown that coadministration of micafungin and cyclosporine does not require dose adjustments for either drug. When micafungin is given with sirolimus, the AUC increases for sirolimus, usually necessitating a reduction in its dose. In open-label trials, favorable results have been obtained with micafungin for the treatment of deep-seated *Aspergillus* and *Candida* infections.

FLUCYTOSINE (5-FLUOROCYTOSINE) The use of flucytosine has diminished in recent years as newer antifungal drugs have been developed. Flucytosine has a unique mechanism of action based on intrafungal conversion to 5-fluorouracil, which is toxic to the cell. Development of resistance to the compound has limited its use as a single agent. Flucytosine is nearly always used in combination with AmB. Its good penetration into the CSF makes it attractive for use with AmB for treatment of cryptococcal meningitis. Flucytosine has also been recommended for the treatment of candidal meningitis in combination with AmB; comparative trials with AmB alone have not been done. Significant and frequent bone marrow depression is seen with flucytosine when this drug is used with AmB.

GRISEOFULVIN AND TERBINAFINE Historically, griseofulvin has been useful primarily for ringworm infection. This agent is usually given for relatively long periods. Terbinafine has been used primarily for onychomycosis but also for ringworm. In comparative studies, terbinafine has been as effective as itraconazole and more effective than griseofulvin for both conditions.

TOPICAL ANTIFUNGAL AGENTS A detailed discussion of the agents used for the treatment of cutaneous fungal infections and onychomycosis is beyond the scope of this chapter; readers are referred to the dermatology literature. Many classes of compounds have been used to treat patients with the common fungal infections of the skin. Among the azoles used are clotrimazole, econazole, miconazole, oxiconazole, sulconazole, ketoconazole, tioconazole, butaconazole, and terconazole. In general, topical treatment of vaginal candidiasis has been successful. Because there is considered to be little difference in the efficacy of the various vaginal preparations, the choice of agent is made by the physician, the patient, or both on the basis of preference and availability. Fluconazole given orally at 150 mg has the advantage of not requiring repeated intravaginal application. Nystatin is a polyene that has been used for both oropharyngeal thrush and vaginal candidiasis. Useful agents in other classes include ciclopirox olamine, halprogin, terbinafine, naftifine, tolnaftate, and undecylenic acid.

- BATTI Z et al: Review of epidemiology, diagnosis, and treatment of invasive mould infections in allogeneic hematopoietic stem cell transplant recipients. *Mycopathologia* 162:1, 2006
- CHU JH et al: Hospitalizations for endemic mycoses: A population-based national study. *Clin Infect Dis* 42:822, 2006
- DEPAUW BE: Increasing fungal infections in the intensive care unit. *Surg Infect (Larchmt)* 7(Suppl 2):S93, 2006
- DISMUKES WE: Antifungal therapy: Lessons learned over the past 27 years. *Clin Infect Dis* 42:1289, 2006
- ENOCH DA et al: Invasive fungal infections: A review of epidemiology and management options. *J Med Microbiol* 55:809, 2006
- KAUFFMAN CA: Clinical efficacy of new antifungal agents. *Curr Opin Microbiol* 9:1, 2006
- LIPSETT PA: Surgical critical care: Fungal infections in surgical patients. *Crit Care Med* 34(9 Suppl):S215, 2006
- MANDELL GL et al (eds): Mycoses, in *Principles and Practice of Infectious Diseases*, 6th ed. Philadelphia, Elsevier Churchill Livingstone, 2005, pp 2935–3094
- WHEAT LJ: Antigen detection, serology, and molecular diagnosis of invasive mycoses in the immunocompromised host. *Transpl Infect Dis* 8:128, 2006



CHAPTER 45

ONCOLOGIC EMERGENCIES

Rasim Gucalp ■ Janice P. Dutcher

■ Structural-Obstructive Oncologic Emergencies	475	Syndrome of Inappropriate Secretion of Antidiuretic Hormone	484
Superior Vena Cava Syndrome	475	Lactic Acidosis	484
Pericardial Effusion or Tamponade	476	Hypoglycemia	484
Intestinal Obstruction	478	Adrenal Insufficiency	484
Urinary Obstruction	478	■ Treatment-Related Emergencies	485
Malignant Biliary Obstruction	478	Tumor Lysis Syndrome	485
Spinal Cord Compression	479	Human Antibody Infusion Reactions	486
Increased Intracranial Pressure	481	Hemolytic-Uremic Syndrome	486
Neoplastic Meningitis	481	Neutropenia and Infection	487
Seizures	482	Pulmonary Infiltrates	487
Pulmonary and Intracerebral Leukocytostasis	482	Neutropenic Enterocolitis	488
Hemoptysis	483	Hemorrhagic Cystitis	489
Airway Obstruction	483	Hypersensitivity Reactions to Antineoplastic Drugs	489
■ Metabolic Emergencies	484	■ Further Readings	489
Hypercalcemia	484		

Emergencies in patients with cancer may be classified into three groups: pressure or obstruction caused by a space-occupying lesion, metabolic or hormonal problems (paraneoplastic syndromes), and treatment-related complications.

STRUCTURAL-OBSTRUCTIVE ONCOLOGIC EMERGENCIES

SUPERIOR VENA CAVA SYNDROME

Superior vena cava syndrome (SVCS) is the clinical manifestation of superior vena cava (SVC) obstruction, with severe reduction in venous return from the head, neck, and upper extremities. Malignant tumors, such as lung cancer, lymphoma, and metastatic tumors, are responsible for the majority of SVCS cases. With the expanding use of intravascular devices (e.g., permanent central venous access catheters, pacemaker/defibrillator leads), the prevalence of benign causes of SVCS is increasing. Lung cancer, particularly of small cell and squamous cell histologies, accounts for approximately

85% of all cases of malignant origin. In young adults, malignant lymphoma is a leading cause of SVCS. Hodgkin's lymphoma involves the mediastinum more commonly than other lymphomas but rarely causes SVCS. When SVCS is noted in a young man with a mediastinal mass, the differential diagnosis is lymphoma versus primary mediastinal germ cell tumor. Metastatic cancers to the mediastinum, such as testicular and breast carcinomas, account for a small proportion of cases. Other causes include benign tumors, aortic aneurysm, thyromegaly, thrombosis, and fibrosing mediastinitis from prior irradiation or histoplasmosis.

Patients with SVCS usually present with neck and facial swelling (especially around the eyes), dyspnea, and cough. Other symptoms include hoarseness, tongue swelling, headaches, nasal congestion, epistaxis, hemoptysis, dysphagia, pain, dizziness, syncope, and lethargy. Bending forward or lying down may aggravate the symptoms. The characteristic physical findings are dilated neck veins; an increased number of collateral veins covering the anterior chest wall; cyanosis; and edema of the face, arms, and chest. More severe cases

include proptosis, glossal and laryngeal edema, and obtundation. The clinical picture is milder if the obstruction is located above the azygos vein.

Signs and symptoms of cerebral or laryngeal edema, although rare, are associated with a poorer prognosis and require urgent evaluation. Seizures are more likely related to brain metastases than to cerebral edema from venous occlusion. Patients with small cell lung cancer and SVCS have a higher incidence of brain metastases than those without SVCS.

Cardiorespiratory symptoms at rest, particularly with positional changes, suggest significant airway and vascular obstruction and limited physiologic reserve. Cardiac arrest or respiratory failure can occur, particularly in patients receiving sedatives or undergoing general anesthesia.

The diagnosis of SVCS is a clinical one. The most significant chest radiographic finding is widening of the superior mediastinum, most commonly on the right side. Pleural effusion occurs in only 25% of patients, often on the right side. However, a normal chest radiograph is still compatible with the diagnosis if other characteristic findings are present. CT provides the most reliable view of the mediastinal anatomy. The diagnosis of SVCS requires diminished or absent opacification of central venous structures with prominent collateral venous circulation. MRI has no advantages over CT. Invasive procedures, including bronchoscopy, percutaneous needle biopsy, mediastinoscopy, and even thoracotomy, can be performed by a skilled clinician without any major risk of bleeding. For patients with a known cancer, a detailed workup usually is not necessary, and appropriate treatment may be started after obtaining a CT scan of the thorax. For those with no history of malignancy, a detailed evaluation is essential to rule out benign causes and determine a specific diagnosis to direct the appropriate therapy.

Rx Treatment: **SUPERIOR VENA CAVA SYNDROME**

The one potentially life-threatening complication of a superior mediastinal mass is tracheal obstruction. Upper airway obstruction demands emergent therapy. Diuretics with a low-salt diet, head elevation, and oxygen may produce temporary symptomatic relief. Glucocorticoids may be useful at shrinking lymphoma masses; they are of no benefit in patients with lung cancer.

Radiation therapy is the primary treatment for SVCS caused by non-small cell lung cancer and other metastatic solid tumors. Chemotherapy is effective when the underlying cancer is small cell carcinoma of the lung, lymphoma, or germ cell tumor. SVCS recurs in 10–30% of patients; it may be palliated with the use of intravascular self-expanding stents (Fig. 45-1). Early stenting may be necessary in patients with severe symptoms; however,

the prompt increase in venous return after stenting may precipitate heart failure and pulmonary edema. Surgery may provide immediate relief for patients in whom a benign process is the cause.

Clinical improvement occurs in most patients, although this improvement may be attributable to the development of adequate collateral circulation. The mortality associated with SVCS does not relate to caval obstruction but rather to the underlying cause.

SUPERIOR VENA CAVA SYNDROME AND CENTRAL VENOUS CATHETERS IN ADULTS

The use of long-term central venous catheters has become common practice in patients with cancer. Major vessel thrombosis may occur. In these cases, catheter removal should be combined with anticoagulation to prevent embolization. SVCS in this setting, if detected early, can be treated by fibrinolytic therapy without sacrificing the catheter. The routine use of low-dose warfarin or low-molecular-weight heparin to prevent thrombosis related to permanent central venous access catheters in cancer patients is not recommended.

PERICARDIAL EFFUSION OR TAMPONADE

Malignant pericardial disease is found at autopsy in 5–10% of patients with cancer, most frequently with lung cancer, breast cancer, leukemias, and lymphomas. Cardiac tamponade as the initial presentation of extrathoracic malignancy is rare. The origin is not malignancy in about 50% of cancer patients with symptomatic pericardial disease, but it can be related to irradiation, drug-induced pericarditis, hypothyroidism, idiopathic pericarditis, infection, or autoimmune diseases. Two types of radiation pericarditis occur: (1) an acute inflammatory, effusive pericarditis occurring within months of irradiation, which usually resolves spontaneously, and (2) a chronic effusive pericarditis that may appear up to ≤ 20 years after radiation therapy and is accompanied by a thickened pericardium.

Most patients with pericardial metastasis are asymptomatic. However, the common symptoms are dyspnea, cough, chest pain, orthopnea, and weakness. Pleural effusion, sinus tachycardia, jugular venous distension, hepatomegaly, peripheral edema, and cyanosis are the most frequent physical findings. Relatively specific diagnostic findings, such as paradoxical pulse, diminished heart sounds, pulsus alternans (pulse waves alternating between those of greater and lesser amplitude with successive beats), and friction rub, are less common than with nonmalignant pericardial disease. Chest radiography and electrocardiography (ECG) reveal abnormalities in 90% of patients, but half of these abnormalities are non-specific. Echocardiography is the most helpful diagnostic test. Pericardial fluid may be serous, serosanguineous, or

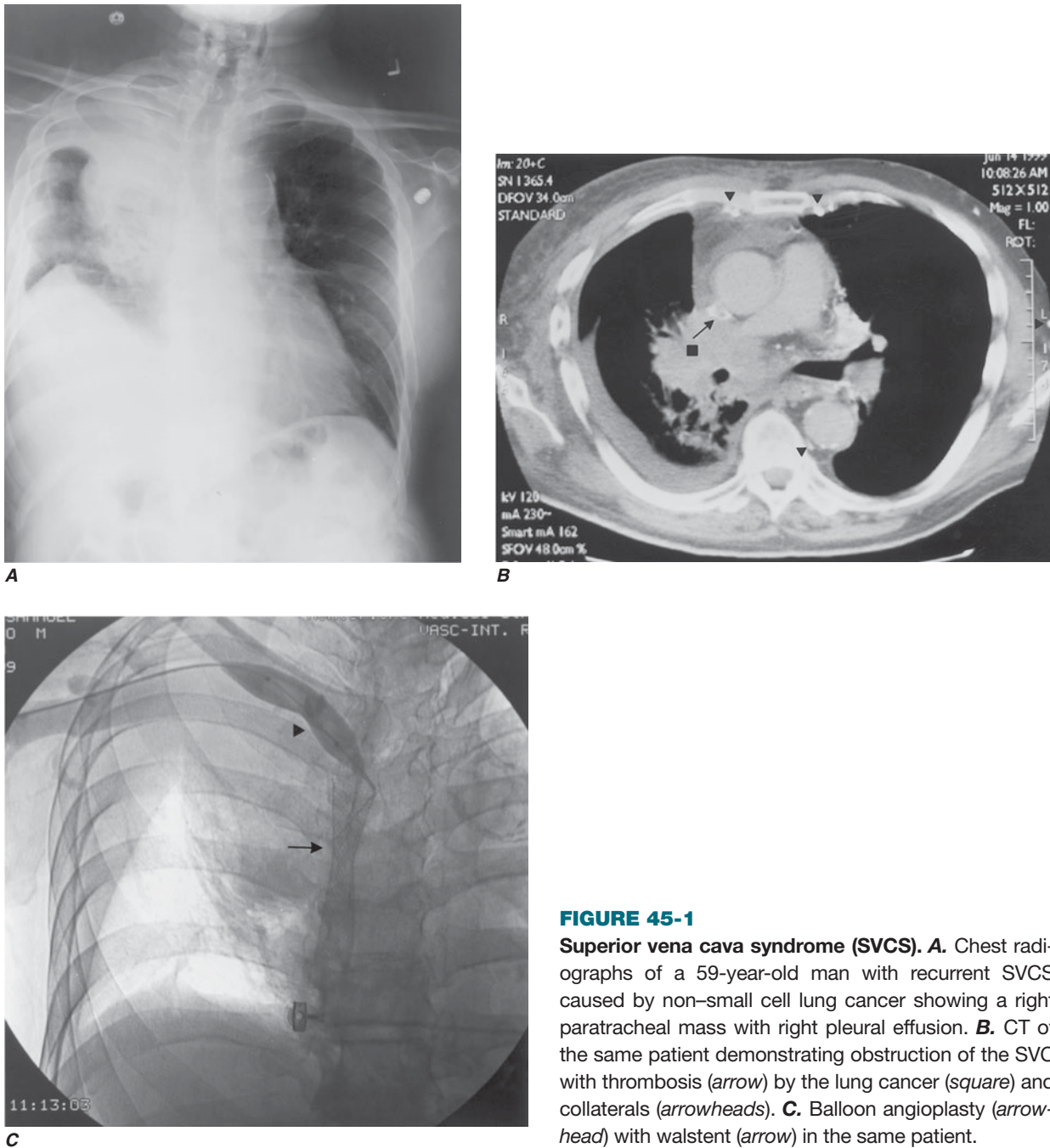


FIGURE 45-1

Superior vena cava syndrome (SVCS). **A.** Chest radiographs of a 59-year-old man with recurrent SVCS caused by non-small cell lung cancer showing a right paratracheal mass with right pleural effusion. **B.** CT of the same patient demonstrating obstruction of the SVC with thrombosis (*arrow*) by the lung cancer (*square*) and collaterals (*arrowheads*). **C.** Balloon angioplasty (*arrowhead*) with walstent (*arrow*) in the same patient.

hemorrhagic, and cytologic examination of pericardial fluid is diagnostic in most patients. Cancer patients with pericardial effusion containing malignant cells on cytology have a very poor survival (~7 weeks).

Rx Treatment:
**PERICARDIAL EFFUSION OR
 TAMPONADE**

Pericardiocentesis with or without the introduction of sclerosing agents, the creation of a pericardial window, complete pericardial stripping, cardiac irradiation, or

systemic chemotherapy are effective treatments. Acute pericardial tamponade with life-threatening hemodynamic instability requires immediate drainage of fluid. This can be quickly achieved by pericardiocentesis. The recurrence rate after percutaneous catheter drainage is around 20%. Sclerotherapy (pericardial instillation of bleomycin, mitomycin C, or tetracycline) may decrease recurrences. Alternatively, subxiphoid pericardiectomy can be performed in 45 min under local anesthesia. Thoracoscopic pericardial fenestration can be used for benign causes; however, 60% of malignant pericardial effusions recur after this procedure.

Intestinal obstruction and reobstruction are common problems in patients with advanced cancer, particularly colorectal or ovarian carcinoma. However, other cancers, such as lung or breast cancer and melanoma, can metastasize within the abdomen, leading to intestinal obstruction. Typically, obstruction occurs at multiple sites. Melanoma has a predilection for involving the small bowel; this involvement may be isolated, and resection may result in prolonged survival. Intestinal pseudoobstruction is caused by infiltration of the mesentery or bowel muscle by tumor, involvement of the celiac plexus, or paraneoplastic neuropathy in patients with small cell lung cancer. Paraneoplastic neuropathy is associated with IgG antibodies reactive to neurons of the myenteric and submucosal plexuses of the jejunum and stomach. Ovarian cancer can lead to authentic luminal obstruction or to pseudoobstruction that results when circumferential invasion of a bowel segment arrests the forward progression of peristaltic contractions.

The onset of obstruction is usually insidious. Pain is the most common symptom and is usually colicky in nature. Pain can also be caused by abdominal distension, tumor masses, or hepatomegaly. Vomiting can be intermittent or continuous. Patients with complete obstruction usually have constipation. The physical examination may reveal abdominal distension with tympany, ascites, visible peristalsis, high-pitched bowel sounds, and tumor masses. Erect plain abdominal films may reveal multiple air-fluid levels and dilation of the small or large bowel. Acute cecal dilation to >12–14 cm is considered a surgical emergency because of the high likelihood of rupture. CT scan is useful in differentiating benign from malignant causes of obstruction in patients who have undergone surgery for malignancy. Malignant obstruction is suggested by a mass at the site of obstruction or prior surgery, adenopathy, or an abrupt transition zone and irregular bowel thickening at the obstruction site. Benign obstruction is more likely when CT shows mesenteric vascular changes, a large volume of ascites, or a smooth transition zone and smooth bowel thickening at the obstruction site. The prognosis for a patient with cancer who develops intestinal obstruction is poor; the median survival is 3–4 months. About 25–30% of patients are found to have intestinal obstruction due to causes other than cancer. Adhesions from previous operations are a common benign cause. Ileus induced by vincristine or other drugs is another reversible cause.

Rx Treatment: **INTESTINAL OBSTRUCTION**

The management of intestinal obstruction in patients with advanced malignancy depends on the extent of the underlying malignancy and the functional status of the major organs. The initial management should include surgical evaluation. Operation is not always

successful and may lead to further complications with a substantial mortality rate (10–20%). Laparoscopy can diagnose and treat malignant bowel obstruction in some cases. Self-expanding metal stents placed in the gastric outlet, duodenum, proximal jejunum, colon, or rectum may palliate obstructive symptoms at those sites without major surgery. Patients known to have advanced intraabdominal malignancy should receive a prolonged course of conservative management, including nasogastric decompression. Treatment with antiemetics, antispasmodics, and analgesics may allow patients to remain outside the hospital. Octreotide may relieve obstructive symptoms through its inhibitory effect on gastrointestinal secretion.

URINARY OBSTRUCTION

Urinary obstruction may occur in patients with prostatic or gynecologic malignancies, particularly cervical carcinoma; metastatic disease from other primary sites such as carcinomas of the breast, stomach, lung, colon, and pancreas; or lymphomas. Radiation therapy to pelvic tumors may cause fibrosis and subsequent ureteral obstruction. Bladder outlet obstruction is usually caused by prostate and cervical cancers and may lead to bilateral hydronephrosis and renal failure.

Flank pain is the most common symptom. Persistent urinary tract infection, persistent proteinuria, or hematuria in patients with cancer should raise suspicion of ureteral obstruction. Total anuria or anuria alternating with polyuria may occur. A slow, continuous increase in the serum creatinine level necessitates immediate evaluation. Renal ultrasonography is the safest and cheapest way to identify hydronephrosis. The function of an obstructed kidney can be evaluated by a nuclear scan. CT scan can reveal the point of obstruction and identify a retroperitoneal mass or adenopathy.

Rx Treatment: **URINARY OBSTRUCTION**

Obstruction associated with flank pain, sepsis, or fistula formation is an indication for immediate palliative urinary diversion. Internal ureteral stents can be placed under local anesthesia. Percutaneous nephrostomy offers an alternative approach for drainage. In the case of bladder outlet obstruction caused by malignancy, a suprapubic cystostomy can be used for urinary drainage.

MALIGNANT BILIARY OBSTRUCTION

This common clinical problem can be caused by a primary carcinoma arising in the pancreas, ampulla of Vater, bile duct, or liver or by metastatic disease to the

periductal lymph nodes or liver parenchyma. The most common metastatic tumors causing biliary obstruction are gastric, colon, breast, and lung cancers. Jaundice, light-colored stools, dark urine, pruritus, and weight loss caused by malabsorption are usual symptoms. Pain and secondary infection are uncommon in patients with malignant biliary obstruction. Ultrasonography, CT scan, or percutaneous transhepatic or endoscopic retrograde cholangiography will identify the site and nature of the biliary obstruction.

Rx Treatment: **MALIGNANT BILIARY OBSTRUCTION**

Palliative intervention is indicated only in patients with disabling pruritus resistant to medical treatment, severe malabsorption, or infection. Stenting under radiographic control, surgical bypass, or radiation therapy with or without chemotherapy may alleviate the obstruction. The choice of therapy should be based on the site of obstruction (proximal versus distal), the type of tumor (sensitive to radiotherapy, chemotherapy, or neither), and the general condition of the patient. In the absence of pruritus, biliary obstruction may be a largely asymptomatic cause of death.

SPINAL CORD COMPRESSION

Malignant spinal cord compression (MSCC) is defined as compression of the spinal cord, cauda equina, or both by an extradural tumor mass. The minimum radiologic evidence for cord compression is indentation of the theca at the level of clinical features. Spinal cord compression occurs in 5–10% of patients with cancer. Epidural tumor is the first manifestation of malignancy in about 10% of patients. The underlying cancer is usually identified during the initial evaluation; lung cancer is the most common cause of MSCC.

Metastatic tumor involves the vertebral column more often than any other part of the bony skeleton. Lung, breast, and prostate cancer are the most frequent offenders. Multiple myeloma also has a high incidence of spine involvement. Lymphomas, melanoma, renal cell cancer, and genitourinary cancers also cause spinal cord compression. The thoracic spine is the most common site (70%) followed by the lumbosacral spine (20%) and the cervical spine (10%). Involvement of multiple sites is most frequent in patients with breast and prostate carcinoma. Cord injury develops when metastases to the vertebral body or pedicle enlarge and compress the underlying dura. Another cause of cord compression is direct extension of a paravertebral lesion through the intervertebral foramen. These cases usually involve lymphoma, myeloma, or pediatric neoplasm. Parenchymal spinal cord metastasis caused by hematogenous spread is rare.

Expanding extradural tumors induce injury through several mechanisms. Obstruction of the epidural venous plexus leads to edema. Local production of inflammatory cytokines enhances blood flow and edema formation. Compression compromises blood flow, leading to ischemia. Production of vascular endothelial growth factor is associated with spinal cord hypoxia and has been implicated as a potential cause of damage after spinal cord injury.

The most common initial symptom in patients with spinal cord compression is localized back pain and tenderness caused by involvement of vertebrae by tumor. Pain is usually present for days or months before other neurologic findings appear. It is exacerbated by movement and by coughing or sneezing. It can be differentiated from the pain of disc disease by the fact that it worsens when the patient is supine. Radicular pain is less common than localized back pain and usually develops later. Radicular pain in the cervical or lumbosacral areas may be unilateral or bilateral. Radicular pain from the thoracic roots is often bilateral and is described by patients as a feeling of tight, band-like constriction around the thorax and abdomen. Typical cervical radicular pain radiates down the arm; in the lumbar region, the radiation is down the legs. *Lhermitte's sign*, a tingling or electric sensation down the back and upper and lower limbs upon flexing or extending the neck, may be an early sign of cord compression. Loss of bowel or bladder control may be the presenting symptom but usually occurs late in the course.

On physical examination, pain induced by straight leg raising, neck flexion, or vertebral percussion may help to determine the level of cord compression. Patients develop numbness and paresthesias in the extremities or trunk. Loss of sensibility to pinprick is as common as loss of sensibility to vibration or position. The upper limit of the zone of sensory loss is often one or two vertebrae below the site of compression. Motor findings include weakness, spasticity, and abnormal muscle stretching. An extensor plantar reflex reflects significant compression. Deep tendon reflexes may be brisk. Motor and sensory loss usually precedes sphincter disturbance. Patients with autonomic dysfunction may present with decreased anal tone, decreased perineal sensibility, and a distended bladder. The absence of the anal wink reflex or the bulbocavernosus reflex confirms cord involvement. In doubtful cases, evaluation of postvoiding urinary residual volume can be helpful. A residual volume of >150 mL suggests bladder dysfunction. Autonomic dysfunction is an unfavorable prognostic factor. Patients with progressive neurologic symptoms should undergo frequent neurologic examinations and rapid therapeutic intervention. Other illnesses that may mimic cord compression include osteoporotic vertebral collapse, disc disease, pyogenic abscess or vertebral tuberculosis, radiation myelopathy, neoplastic leptomeningitis, benign tumors, epidural hematoma, and spinal lipomatosis.

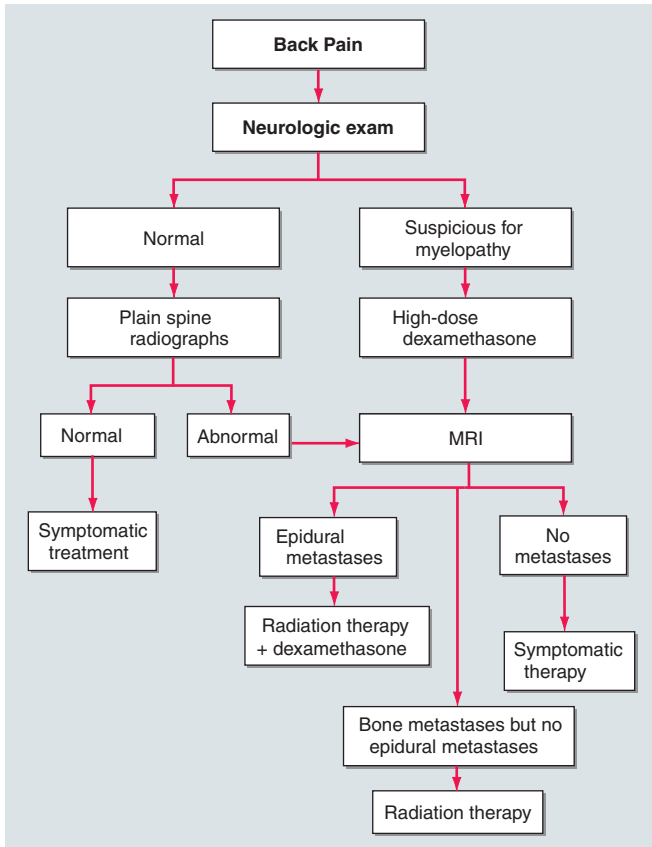


FIGURE 45-2
Management of cancer patients with back pain.

Cauda equina syndrome is characterized by low back pain; diminished sensation over the buttocks, posterior-superior thighs, and perineal area in a saddle distribution; rectal and bladder dysfunction; sexual impotence; absent bulbocavernosus, patellar, and Achilles' reflexes; and variable amount of lower extremity weakness. This reflects compression of nerve roots as they form the cauda equina after leaving the spinal cord.

Patients with cancer who develop back pain should be evaluated for spinal cord compression as quickly as possible (Fig. 45-2). Treatment is more often successful in patients who are ambulatory and still have sphincter control at the time treatment is initiated. Patients should have a neurologic examination and plain films of the spine. Those whose physical examination suggests cord compression should receive dexamethasone (24 mg IV every 6 h), starting immediately.

Erosion of the pedicles (the “winking owl” sign) is the earliest radiologic finding of vertebral tumor. Other radiographic changes include increased intrapedicular distance, vertebral destruction, lytic or sclerotic lesions, scalloped vertebral bodies, and vertebral body collapse. Vertebral collapse is not a reliable indicator of the presence of tumor; about 20% of cases of vertebral collapse, particularly those in older patients and postmenopausal women, are not attributable to cancer but to osteoporosis. Also, a normal appearance on plain films of the spine does not exclude

the diagnosis of cancer. The role of bone scans in the detection of cord compression is not clear; this method is sensitive but less specific than spinal radiography.

The full-length image of the cord provided by MRI is useful. Multiple epidural metastases are noted in 25% of patients with cord compression, and their presence influences treatment plans. On T1-weighted images, good contrast is noted between the cord, cerebrospinal fluid (CSF), and extradural lesions. Owing to its sensitivity in demonstrating the replacement of bone marrow by tumor, MRI can show which parts of a vertebra are involved by tumor. MRI also visualizes intraspinal extradural masses compressing the cord. T2-weighted images are most useful for the demonstration of intramedullary pathology. Gadolinium-enhanced MRI can help to delineate intramedullary disease. MRI is as good as or better than myelography plus postmyelogram CT scan in detecting metastatic epidural disease with cord compression. Myelography should be reserved for patients who have poor MR images or who cannot undergo MRI promptly. CT scan in conjunction with myelography enhances the detection of small areas of spinal destruction.

In patients with cord compression and an unknown primary tumor, a simple workup, including chest radiography, mammography, measurement of prostate-specific antigen, and abdominal CT, usually reveals the underlying malignancy.

Rx Treatment: **SPINAL CORD COMPRESSION**

The treatment of patients with spinal cord compression is aimed at relief of pain and restoration or preservation of neurologic function (Fig. 45-2).

Radiation therapy plus glucocorticoids is generally the initial treatment of choice for most patients with spinal cord compression. Up to 75% of patients treated when still ambulatory remain ambulatory, but only 10% of patients with paraplegia recover walking capacity. Indications for surgical intervention include unknown etiology, failure of radiation therapy, a radioresistant tumor type (e.g., melanoma or renal cell cancer), pathologic fracture dislocation, and rapidly evolving neurologic symptoms. Laminectomy is done for tissue diagnosis and for the removal of posteriorly localized epidural deposits in the absence of vertebral body disease. Because most cases of epidural spinal cord compression are caused by anterior or anterolateral extradural disease, resection of the anterior vertebral body along with the tumor, followed by spinal stabilization, has achieved good results. A randomized trial showed that patients who underwent an operation followed by radiotherapy (within 14 days) retained the ability to walk significantly longer than those treated with radiotherapy alone. Surgically treated patients also

maintained continence and neurologic function significantly longer than patients in the radiation group. The length of survival was not significantly different in the two groups, although there was a trend toward longer survival in the surgery group. The study drew some criticism for the poorer-than-expected results in the patients who did not have surgery. However, patients should be evaluated for surgery.

Conventional radiotherapy has a role after surgery. Chemotherapy may have a role in patients with chemosensitive tumors who have had prior radiotherapy to the same region and who are not candidates for surgery. Most patients with prostate cancer who develop cord compression have already had hormonal therapy; however, for those who have not, androgen deprivation is combined with surgery and radiotherapy.

Patients with metastatic vertebral tumors may benefit from percutaneous vertebroplasty, which is injection of acrylic cement into a collapsed vertebra to stabilize the fracture. Pain palliation is common, and local antitumor effects have been noted. Cement leakage may cause symptoms in about 10% of patients.

The histology of the tumor is an important determinant of both recovery and survival. Rapid onset and progression of signs and symptoms are poor prognostic features.

INCREASED INTRACRANIAL PRESSURE

About 25% of patients with cancer die with intracranial metastases. The cancers that most often metastasize to the brain are lung and breast cancers and melanoma. Brain metastases often occur in the presence of systemic disease, and they frequently cause major symptoms, disability, and early death. The initial presentation of brain metastases from a previously unknown primary cancer is common. Lung cancer is most commonly the primary malignancy. Chest CT scans and brain MRI as the initial diagnostic studies can identify a biopsy site in most patients.

The signs and symptoms of a metastatic brain tumor are similar to those of other intracranial expanding lesions and include headache; nausea; vomiting; behavioral changes; seizures; and focal, progressive neurologic changes. Occasionally, the onset is abrupt, resembling a stroke, with the sudden appearance of headache, nausea, vomiting, and neurologic deficits. This picture is usually caused by hemorrhage into the metastasis. Patients with melanoma, germ cell tumors, and renal cell cancers have a particularly high incidence of intracranial bleeding. The tumor mass and surrounding edema may cause obstruction of the circulation of CSF, with resulting hydrocephalus. Patients with increased intracranial pressure (ICP) may have papilledema with visual disturbances and neck stiffness. As the mass enlarges, brain tissue may be displaced through the fixed cranial openings, producing various herniation syndromes.

CT scan and MRI are equally effective in the diagnosis of brain metastases. CT scan with contrast should be used as a screening procedure. The CT scan shows brain metastases as multiple enhancing lesions of various sizes with surrounding areas of low-density edema. If a single lesion or no metastases are visualized by contrast-enhanced CT, MRI of the brain should be performed. Gadolinium-enhanced MRI is more sensitive than CT at revealing meningeal involvement and small lesions, particularly in the brainstem or cerebellum.

Intracranial hypertension secondary to tretinoin therapy has been reported.

R_x Treatment: **INCREASED INTRACRANIAL PRESSURE**

If signs and symptoms of brain herniation (particularly headache, drowsiness, and papilledema) are present, the patient should be intubated and hyperventilated to maintain P_{CO_2} between 25 and 30 mmHg and should receive infusions of mannitol (1–1.5 g/kg) every 6 h. Dexamethasone is the best initial treatment for all symptomatic patients with brain metastases (see earlier). Patients with multiple lesions should receive whole-brain radiation therapy. Patients with a single brain metastasis and with controlled extracranial disease may be treated with surgical excision followed by whole-brain radiation therapy, especially if they are younger than age 60 years. Radioresistant tumors should be resected if possible. Stereotactic radiosurgery is an effective treatment for inaccessible or recurrent lesions. With a gamma knife or linear accelerator, multiple small, well-collimated beams of ionizing radiation destroy lesions seen on MRI. Some patients with increased ICP associated with hydrocephalus may benefit from shunt placement. If neurologic deterioration is not reversed with medical therapy, ventriculotomy to remove CSF or craniotomy to remove tumors or hematomas may be necessary.

NEOPLASTIC MENINGITIS

Tumor involving the leptomeninges is a complication of both primary central nervous system (CNS) tumors and tumors that metastasize to the CNS. The incidence is estimated at 3–8% of patients with cancer. Melanoma, breast and lung cancer, lymphoma (including that associated with AIDS), and acute leukemia are the most common causes. Synchronous intraparenchymal brain metastases are evident in 11–31% of patients with neoplastic meningitis.

Patients typically present with multifocal neurologic signs and symptoms, including headache, gait abnormality, mental changes, nausea, vomiting, seizures, back or radicular pain, and limb weakness. Signs include cranial

482 nerve palsies, extremity weakness, paresthesia, and decreased deep tendon reflexes.

Diagnosis is made by demonstrating malignant cells in the CSF; however, up to 40% of patients may have false-negative CSF cytology results. An elevated CSF protein level is nearly always present (except in HTLV-1-associated adult T cell leukemia). Patients with neurologic signs and symptoms consistent with neoplastic meningitis who have negative CSF cytology results but an elevated CSF protein level should have the spinal tap repeated at least three times for cytologic examination before the diagnosis is rejected. MRI findings suggestive of neoplastic meningitis include leptomeningeal, subependymal, dural, or cranial nerve enhancement; superficial cerebral lesions; and communicating hydrocephalus. Spinal cord imaging by MRI is a necessary component of the evaluation of nonleukemia neoplastic meningitis because ~20% of patients have cord abnormalities, including intradural enhancing nodules that are diagnostic for leptomeningeal involvement. Cauda equina lesions are common, but lesions may be seen anywhere in the spinal canal. Radio-labeled CSF flow studies are abnormal in up to 70% of patients with neoplastic meningitis; ventricular outlet obstruction, abnormal flow in the spinal canal, or impaired flow over the cerebral convexities may affect distribution of intrathecal chemotherapy, resulting in decreased efficacy or increased toxicity. Radiation therapy may correct CSF flow abnormalities before use of intrathecal chemotherapy. Neoplastic meningitis can also lead to intracranial hypertension and hydrocephalus. Placement of a ventriculoperitoneal shunt may effectively palliate symptoms in these patients.

The development of neoplastic meningitis usually occurs in the setting of uncontrolled cancer outside the CNS; thus, prognosis is poor (median survival 10–12 weeks). However, treatment of the neoplastic meningitis may successfully alleviate symptoms and control the CNS spread.

R_x Treatment:
NEOPLASTIC MENINGITIS

Intrathecal chemotherapy, usually methotrexate, cytarabine, or thiotepa, is delivered by lumbar puncture or by an intraventricular reservoir (Ommaya) three times a week until the CSF is free of malignant cells. Injections are given twice a week for 1 month and then weekly for 1 month. An extended-release preparation of cytarabine (DepoCyt e) has a longer half-life and is more effective than other formulations. Among solid tumors, breast cancer responds best to therapy. Patients with neoplastic meningitis from either acute leukemia or lymphoma may be cured of their CNS disease if the systemic disease can be eliminated.

SEIZURES

Seizures occurring in a patient with cancer can be caused, by the tumor itself, by metabolic disturbances, by radiation injury, by cerebral infarctions, by chemotherapy-related encephalopathies, or by CNS infections. Metastatic disease to the CNS is the most common cause of seizures in patients with cancer. However, seizures occur more frequently in those with primary brain tumors than in those with metastatic brain lesions. Seizures are a presenting symptom of CNS metastasis in 6–29% of cases. Approximately 10% of patients with CNS metastasis eventually develop seizures. The presence of frontal lesions correlates with early seizures, and the presence of hemispheric symptoms increases the risk for late seizures. Both early and late seizures are uncommon in patients with posterior fossa lesions. Seizures are also common in patients with CNS metastases from melanoma. Very rarely, cytotoxic drugs such as etoposide, busulfan, and chlorambucil cause seizures.

R_x Treatment:
SEIZURES

Patients in whom seizures caused by CNS metastases have been demonstrated should receive anticonvulsant treatment with diphenylhydantoin. Prophylactic anticonvulsant therapy is not recommended unless the patient is at a high risk for late seizures (melanoma primary, hemorrhagic metastases, treatment with radiosurgery). In those patients, serum diphenylhydantoin levels should be monitored closely and the dosage adjusted according to serum levels. Phenytoin induces the hepatic metabolism of dexamethasone, reducing its half-life, and dexamethasone may decrease phenytoin levels. Most antiseizure medications induce CYP450, which alters the metabolism of antitumor agents, including irinotecan, taxanes, and etoposide, as well as molecular targeted agents, including imatinib, gefitinib, and tipifarnib.

PULMONARY AND INTRACEREBRAL LEUKOCYTOSTASIS

Hyperleukocytosis and the leukostasis syndrome associated with it is a potentially fatal complication of acute leukemia [particularly acute myeloid leukemia (AML)] that can occur when the peripheral blast cell count is >100,000/mL. The frequency of hyperleukocytosis is 5–13% in AML and 10–30% in acute lymphoid leukemia; however, leukostasis is rare in lymphoid leukemia. At such high blast cell counts, blood viscosity is increased, blood flow is slowed by aggregates of tumor cells, and the primitive myeloid leukemic cells

are capable of invading through endothelium and causing hemorrhage. The brain and lungs are most commonly affected. Patients with brain leukostasis may experience stupor, headache, dizziness, tinnitus, visual disturbances, ataxia, confusion, coma, or sudden death. Administration of 600 cGy of whole-brain irradiation can protect against this complication and can be followed by rapid institution of antileukemic therapy. Pulmonary leukostasis may present as respiratory distress and hypoxemia and progress to respiratory failure. Chest radiographs may be normal but usually show interstitial or alveolar infiltrates. Arterial blood gas results should be interpreted cautiously. Rapid consumption of plasma oxygen by the markedly increased number of white blood cells can cause spuriously low arterial oxygen tension. Pulse oximetry is the most accurate way of assessing oxygenation in patients with hyperleukocytosis. Leukapheresis may be helpful in decreasing circulating blast counts. Treatment of the leukemia can result in pulmonary hemorrhage from lysis of blasts in the lung, called *leukemic cell lysis pneumopathy*. Intravascular volume depletion and unnecessary blood transfusions may increase blood viscosity and worsen the leukostasis syndrome. Leukostasis is not a feature of the high white blood cell counts associated with chronic lymphoid or chronic myeloid leukemia.

When patients with acute promyelocytic leukemia are treated with differentiating agents such as tretinoin and arsenic trioxide, cerebral or pulmonary leukostasis may occur as tumor cells differentiate into mature neutrophils. This complication can be largely avoided by using cytotoxic chemotherapy together with the differentiating agents.

HEMOPTYSIS

Hemoptysis may be caused by nonmalignant conditions, but lung cancer accounts for a large proportion of cases. Up to 20% of patients with lung cancer have hemoptysis some time in their course. Endobronchial metastases from carcinoid tumors, breast cancer, colon cancer, kidney cancer, and melanoma may also cause hemoptysis. The volume of bleeding is often difficult to gauge. Massive hemoptysis is defined as >600 mL of blood produced in 24 h. However, any hemoptysis should be considered massive if it threatens life. When respiratory difficulty occurs, hemoptysis should be treated emergently. The first priorities are to maintain the airway, optimize oxygenation, and stabilize the hemodynamic status. Often patients can tell where the bleeding is occurring. They should be placed bleeding side down and given supplemental oxygen. If large-volume bleeding continues or the airway is compromised, the patient should be intubated and undergo emergency bronchoscopy. If the site of bleeding is detected, either the patient undergoes a definitive

surgical procedure or the lesion is treated with a neodymium:yttrium-aluminum-garnet (Nd:YAG) laser. The surgical option is preferred. Bronchial artery embolization may control brisk bleeding in 75–90% of patients, permitting the definitive surgical procedure to be done more safely. Embolization without definitive surgery is associated with rebleeding in 20–50% of patients. Patients with recurrent hemoptysis usually respond to a second embolization procedure. A postembolization syndrome characterized by pleuritic pain, fever, dysphagia, and leukocytosis may occur; it lasts 5–7 days and resolves with symptomatic treatment. Bronchial or esophageal wall necrosis, myocardial infarction, and spinal cord infarction are rare complications.

Pulmonary hemorrhage with or without hemoptysis in hematologic malignancies is often associated with fungal infections, particularly *Aspergillus* spp. After granulocytopenia resolves, the lung infiltrates in aspergillosis may cavitate and cause massive hemoptysis. Thrombocytopenia and coagulation defects should be corrected if possible. Surgical evaluation is recommended in patients with aspergillosis-related cavitory lesions.

AIRWAY OBSTRUCTION

Airway obstruction refers to a blockage at the level of the mainstem bronchi or above. It may result either from intraluminal tumor growth or from extrinsic compression of the airway. The most common cause of malignant upper airway obstruction is invasion from an adjacent primary tumor, most commonly lung cancer, followed by esophageal, thyroid, and mediastinal malignancies. Extrathoracic primary tumors such as renal, colon, or breast cancer can cause airway obstruction through endobronchial or mediastinal lymph node metastases. Patients may present with dyspnea, hemoptysis, stridor, wheezing, intractable cough, postobstructive pneumonia, or hoarseness. Chest radiographs usually demonstrate obstructing lesions. CT scans reveal the extent of the tumor. Cool, humidified oxygen; glucocorticoids; and ventilation with a mixture of helium and oxygen (Heliox) may provide temporary relief. If the obstruction is proximal to the larynx, a tracheostomy may be lifesaving. For more distal obstructions, particularly intrinsic lesions incompletely obstructing the airway, bronchoscopy with laser treatment, photodynamic therapy, or stenting can produce immediate relief in most patients (**Fig. 45-3**). However, radiation therapy (either external-beam irradiation or brachytherapy) given together with glucocorticoids may also open the airway. Symptomatic extrinsic compression may be palliated by stenting. Patients with primary airway tumors such as squamous cell carcinoma, carcinoid tumor, adenocystic carcinoma, or non-small cell lung cancer should have surgery.

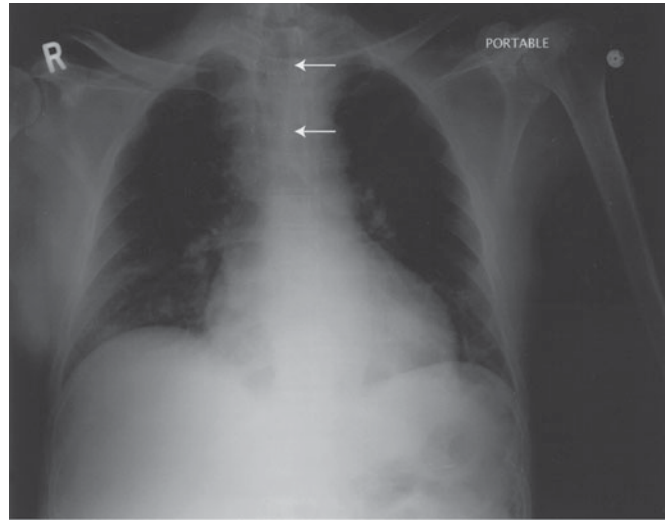


A

FIGURE 45-3

Airway obstruction. **A.** CT scan of a 62-year-old man with tracheal obstruction caused by renal carcinoma showing paratracheal mass with tracheal invasion or obstruction (*arrow*).

B. Chest x-ray of the same patient after stent (*arrows*) placement.



B

METABOLIC EMERGENCIES

HYPERCALCEMIA

Hypercalcemia is the most common paraneoplastic syndrome.

SYNDROME OF INAPPROPRIATE SECRETION OF ANTIDIURETIC HORMONE

Hyponatremia is a common electrolyte abnormality in cancer patients, and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is the most common cause of hyponatremia among patients with cancer.

LACTIC ACIDOSIS

Lactic acidosis is a rare and potentially fatal metabolic complication of cancer. Lactic acidosis associated with sepsis, and circulatory failure is a common preterminal event in many malignancies. Lactic acidosis in the absence of hypoxemia may occur in patients with leukemia, lymphoma, or solid tumors. Extensive involvement of the liver by tumor is present in most cases. Alteration of liver function may be responsible for the lactate accumulation. HIV-infected patients have an increased risk of aggressive lymphoma; lactic acidosis that occurs in such patients may be related either to the rapid growth of the tumor or from toxicity of nucleoside reverse transcriptase inhibitors. Symptoms of lactic acidosis include tachypnea, tachycardia, change of mental status, and hepatomegaly. The serum level of lactic acid may reach 10–20 meq/L (90–180 mg/dL). Treatment is aimed at the underlying disease. The danger from lactic acidosis is from the acidosis, not the lactate. Sodium bicarbonate should be added if acidosis is very severe or if hydrogen ion production is very rapid and uncontrolled. The prognosis is poor.

HYPOGLYCEMIA

Persistent hypoglycemia is occasionally associated with tumors other than pancreatic islet cell tumors. Usually these tumors are large; tumors of mesenchymal origin, hepatomas, or adrenocortical tumors may cause hypoglycemia. Mesenchymal tumors are usually located in the retroperitoneum or thorax. Obtundation, confusion, and behavioral aberrations occur in the postabsorptive period and may precede the diagnosis of the tumor. These tumors often secrete incompletely processed insulin-like growth factor II (IGF-II), a hormone capable of activating insulin receptors and causing hypoglycemia. Tumors secreting incompletely processed big IGF-II are characterized by an increased ratio of IGF-II to IGF-I, suppressed insulin and C peptide level, and inappropriately low growth hormone and β -hydroxybutyrate concentrations. Rarely, hypoglycemia is caused by insulin secretion by a non-islet cell carcinoma. The development of hepatic dysfunction from liver metastases and increased glucose consumption by the tumor can contribute to hypoglycemia. If the tumor cannot be resected, hypoglycemia symptoms may be relieved by the administration of glucose, glucocorticoids, or glucagon.

Hypoglycemia can be artifactual; hyperleukocytosis from leukemia, myeloproliferative diseases, leukemoid reactions, or colony-stimulating factor treatment can increase glucose consumption in the test tube after blood is drawn, leading to pseudohypoglycemia.

ADRENAL INSUFFICIENCY

In patients with cancer, adrenal insufficiency may go unrecognized because the symptoms, such as nausea, vomiting, anorexia, and orthostatic hypotension, are nonspecific and may be mistakenly attributed to progressive cancer or to therapy. Primary adrenal insufficiency may develop owing to replacement of both

glands by metastases (lung, breast, colon, or kidney cancer; lymphoma), to removal of both glands, or to hemorrhagic necrosis in association with sepsis or anticoagulation. Impaired adrenal steroid synthesis occurs in patients being treated for cancer with mitotane, ketoconazole, or aminoglutethimide or undergoing rapid reduction in glucocorticoid therapy. Rarely, metastatic replacement causes primary adrenal insufficiency as the first manifestation of an occult malignancy. Metastasis to the pituitary or hypothalamus is found at autopsy in $\leq 5\%$ of patients with cancer, but associated secondary adrenal insufficiency is rare. Megestrol acetate, which is used to manage cancer and HIV-related cachexia, may suppress plasma levels of cortisol and adrenocorticotropic hormone (ACTH). Patients taking megestrol may develop adrenal insufficiency, and even those whose adrenal dysfunction is not symptomatic may have inadequate adrenal reserve if they become seriously ill. Cranial irradiation for childhood brain tumors may affect the hypothalamus–pituitary–adrenal axis, resulting in secondary adrenal insufficiency.

Acute adrenal insufficiency is potentially lethal. Treatment of suspected adrenal crisis is initiated after the sampling of serum cortisol and ACTH levels.

TREATMENT-RELATED EMERGENCIES

TUMOR LYSIS SYNDROME

Tumor lysis syndrome (TLS) is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia and is caused by the destruction of a large number of rapidly proliferating neoplastic cells. Acidosis may also develop. Acute renal failure occurs frequently.

TLS is most often associated with the treatment of Burkitt's lymphoma, acute lymphoblastic leukemia, and other high-grade lymphomas, but it also may be seen with chronic leukemias and, rarely, with solid tumors. This syndrome has been seen in patients with chronic lymphocytic leukemia after treatment with nucleosides. TLS has been observed with administration of glucocorticoids, hormonal agents such as letrozole and tamoxifen, and monoclonal antibodies such as rituximab and gemtuzumab. TLS usually occurs during or shortly (1–5 days) after chemotherapy. Rarely, spontaneous necrosis of malignancies causes TLS.

Hyperuricemia may be present at the time of chemotherapy. Effective treatment kills malignant cells and leads to increased serum uric acid levels from the turnover of nucleic acids. Owing to the acidic local environment, uric acid can precipitate in the tubules, medulla, and collecting ducts of the kidney, leading to renal failure. Lactic acidosis and dehydration may contribute to the precipitation of uric acid in the renal tubules. The finding of uric acid crystals in the urine is strong evidence for uric acid nephropathy. The ratio of urinary uric acid to

urinary creatinine is >1 in patients with acute hyperuricemic nephropathy and <1 in patients with renal failure from other causes.

Hyperphosphatemia, which can be caused by the release of intracellular phosphate pools by tumor lysis, produces a reciprocal depression in serum calcium, which causes severe neuromuscular irritability and tetany. Deposition of calcium phosphate in the kidney and hyperphosphatemia may cause renal failure. Potassium is the principal intracellular cation, and massive destruction of malignant cells may lead to hyperkalemia. Hyperkalemia in patients with renal failure may rapidly become life threatening by causing ventricular arrhythmias and sudden death.

The likelihood that TLS will occur in patients with Burkitt's lymphoma is related to the tumor burden and renal function. Hyperuricemia and high serum levels of lactate dehydrogenase (LDH >1500 U/L), both of which correlate with total tumor burden, also correlate with the risk of TLS. In patients at risk for TLS, pretreatment evaluations should include a complete blood count, serum chemistry evaluation, and urinalysis. High leukocyte and platelet counts may artificially elevate potassium levels ("pseudohyperkalemia") because of lysis of these cells after the blood is drawn. In these cases, plasma potassium instead of serum potassium should be followed. In pseudohyperkalemia, no ECG abnormalities are present. In patients with abnormal baseline renal function, the kidneys and retroperitoneal area should be evaluated by sonography, CT, or both to rule out obstructive uropathy. Urine output should be watched closely.

Rx Treatment: **TUMOR LYSIS SYNDROME**

Recognition of risk and prevention are the most important steps in the management of patients with this syndrome (Fig. 45-4). The standard preventive approach consists of allopurinol, urinary alkalization, and aggressive hydration. IV allopurinol may be given to patients who cannot tolerate oral therapy. In some cases, uric acid levels cannot be lowered sufficiently with the standard preventive approach. Rasburicase can be effective in these instances. Urate oxidase is missing from primates and catalyzes the conversion of poorly soluble uric acid to readily soluble allantoin. Rasburicase acts rapidly, decreasing uric acid levels within hours; however, it may cause hypersensitivity reactions (HSRs) such as bronchospasm, hypoxemia, and hypotension. Rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency who are unable to break down hydrogen peroxide, an end product of the urate oxidase reaction. Despite aggressive prophylaxis, TLS or oliguric or anuric renal failure may occur. Care should be taken to prevent worsening of symptomatic hypocalcemia by induction of

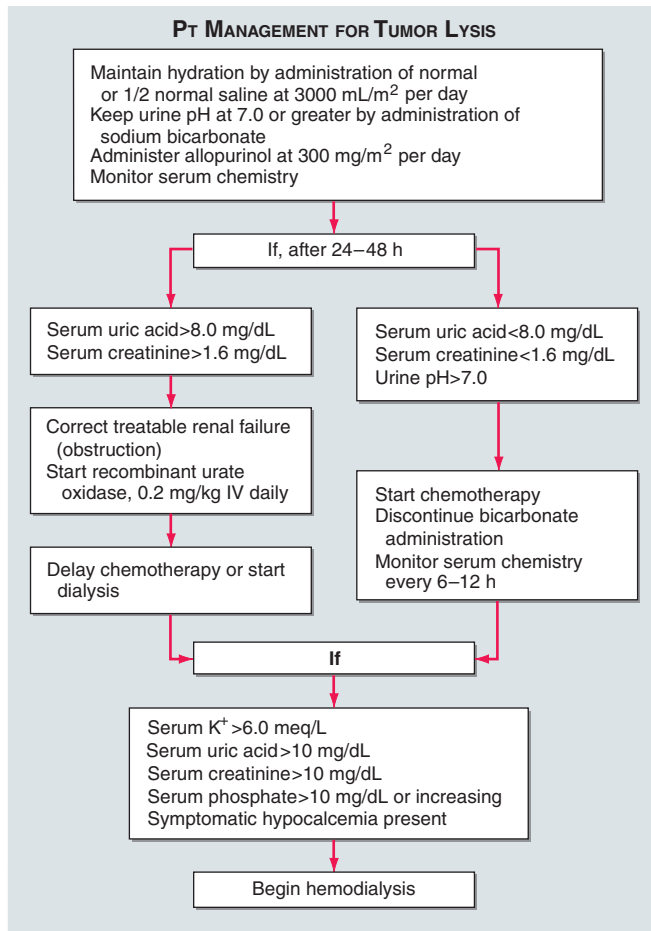


FIGURE 45-4
Management of patients at high risk for the tumor lysis syndrome.

alkalosis during bicarbonate infusion. Administration of sodium bicarbonate may also lead to urinary precipitation of calcium phosphate, which is less soluble at alkaline pH. Dialysis is often necessary and should be considered early in the course. Hemodialysis is preferred. Hemofiltration offers a gradual, continuous method of removing cellular byproducts and fluid. The prognosis is excellent, and renal function recovers after the uric acid level is lowered to ≤ 10 mg/dL.

HUMAN ANTIBODY INFUSION REACTIONS

The initial infusion of human or humanized antibodies (e.g., rituximab, gemtuzumab, trastuzumab) is associated with fever, chills, nausea, asthenia, and headache in $\leq 50\%$ of treated patients. Bronchospasm and hypotension occur in 1% of patients. The pathogenesis is thought to be activation of immune effector processes (cells and complement). In the presence of high levels of circulating lymphoid tumor cells, thrombocytopenia, a rapid decrease in circulating tumor cells, and mild electrolyte evidence of TLS may also occur. In addition, increased

liver enzymes, D-dimer, LDH, and prolongation of the prothrombin time may occur. This syndrome is related to release of inflammatory cytokines, such as tumor necrosis factor (TNF) α and interleukin 6. Diphenhydramine and acetaminophen can often prevent or suppress the symptoms. If they occur, the infusion is stopped and restarted at half the initial infusion rate after the symptoms have abated.

HEMOLYTIC-UREMIC SYNDROME

Hemolytic-uremic syndrome (HUS) and, less commonly, thrombotic thrombocytopenic purpura (TTP) occurring after treatment with antineoplastic drugs have been described. Mitomycin is by far the most common agent causing this peculiar syndrome. Other chemotherapeutic agents, including cisplatin, bleomycin, and gemcitabine, have also been reported to be associated with this syndrome. It occurs most often in patients with gastric, colorectal, pancreatic, and breast carcinoma. In one series, 35% of patients were without evident cancer at the time this syndrome appeared. Secondary HUS/TTP has also been reported as a rare but sometimes fatal complication of bone marrow transplantation (BMT).

HUS usually has its onset 4–8 weeks after the last dose of chemotherapy, but it is not rare to detect it several months later. HUS is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and renal failure. Dyspnea, weakness, fatigue, oliguria, and purpura are also common initial symptoms and findings. Systemic hypertension and pulmonary edema frequently occur. Severe hypertension, pulmonary edema, and rapid worsening of hemolysis and renal function may occur after a blood or blood product transfusion. Cardiac findings include atrial arrhythmias, pericardial friction rub, and pericardial effusion. Raynaud's phenomenon is part of the syndrome in patients treated with bleomycin.

Laboratory findings include severe to moderate anemia associated with red blood cell fragmentation and numerous schistocytes on peripheral smear. Reticulocytosis, decreased plasma haptoglobin, and an LDH level document hemolysis. The serum bilirubin level is usually normal or slightly elevated. The Coombs' test is negative. The white blood cell count is usually normal, and thrombocytopenia ($< 100,000/\mu\text{L}$) is almost always present. Most patients have a normal coagulation profile, although some have mild elevations in thrombin time and in level of fibrin degradation products. The serum creatinine level is elevated at presentation and shows a pattern of subacute worsening within weeks of the initial azotemia. The urinalysis reveals hematuria, proteinuria, and granular or hyaline casts, and circulating immune complexes may be present.

The basic pathologic lesion appears to be deposition of fibrin in the walls of capillaries and arterioles, and these deposits are similar to those seen in HUS from

other causes. These microvascular abnormalities involve mainly the kidneys and rarely occur in other organs. The pathogenesis of chemotherapy-related HUS is unknown. Other forms of HUS/TTP are related to a decrease in processing of von Willebrand factor by a protease called ADAMTS13.

The case fatality rate is high; most patients die within a few months. Plasmapheresis and plasma exchange may normalize the hematologic abnormalities, but renal failure is not reversed in most patients. Immunoperfusion over a staphylococcal protein A column is the most successful treatment. About half of the patients treated with immunoperfusion respond with resolution of thrombocytopenia, improvement in anemia, and stabilization of renal failure. Treatment is well tolerated. It is not clear how the treatment works.

NEUTROPENIA AND INFECTION

These remain the most common, serious complications of cancer therapy.

PULMONARY INFILTRATES

Patients with cancer may present with dyspnea associated with diffuse interstitial infiltrates on chest radiographs. Such infiltrates may be caused by progression of the underlying malignancy, treatment-related toxicities, infection, or unrelated diseases. The cause may be multifactorial; however, most commonly, they occur as a consequence of treatment. Infiltration of the lung by malignancy has been described in patients with leukemia, lymphoma, and breast and other solid cancers. Pulmonary lymphatics may be involved diffusely by neoplasm (pulmonary lymphangitic carcinomatosis), resulting in a diffuse increase in interstitial markings on chest radiographs. The patient is often mildly dyspneic at the onset, but pulmonary failure develops over a period of weeks. In some patients, dyspnea precedes changes on the chest radiographs and is accompanied by a nonproductive cough. This syndrome is characteristic of solid tumors. In patients with leukemia, diffuse microscopic neoplastic peribronchial and peribronchiolar infiltration is frequent but may be asymptomatic. However, some patients present with diffuse interstitial infiltrates, an alveolar capillary block syndrome, and respiratory distress. In these situations, glucocorticoids can provide symptomatic relief, but specific chemotherapy should always be started promptly.

Several cytotoxic agents, such as bleomycin, methotrexate, busulfan, and the nitrosoureas, may cause pulmonary damage. The most frequent presentations are interstitial pneumonitis, alveolitis, and pulmonary fibrosis. Some cytotoxic agents, including methotrexate and procarbazine, may cause an acute HSR. Cytosine arabinoside has been associated with noncardiogenic pulmonary edema. Administration of multiple cytotoxic drugs, as well as

radiotherapy and preexisting lung disease, may potentiate the pulmonary toxicity. Supplemental oxygen may potentiate the effects of drugs and radiation injury. Patients should always be managed with the lowest FI_{O_2} that is sufficient to maintain hemoglobin saturation.

The onset of symptoms may be insidious, with symptoms including dyspnea, nonproductive cough, and tachycardia. Patients may have bibasilar crepitant rales, end-inspiratory crackles, fever, and cyanosis. The chest radiograph generally shows an interstitial and sometimes an intraalveolar pattern that is strongest at the lung bases and may be symmetric. A small effusion may occur. Hypoxemia with decreased carbon monoxide diffusing capacity is always present. Glucocorticoids may be helpful in patients in whom pulmonary toxicity is related to radiation therapy or to chemotherapy. Treatment is otherwise supportive.

Molecular targeted agents, imatinib, erlotinib, and gefitinib are potent inhibitors of tyrosine kinases. These drugs may cause interstitial lung disease. In the case of gefitinib, preexisting fibrosis, poor performance status, and prior thoracic irradiation are independent risk factors; this complication has a high fatality rate. In Japan, the incidence of interstitial lung disease associated with gefitinib is ~4.5%.

Radiation pneumonitis and fibrosis are relatively frequent side effects of thoracic radiation therapy. They may be acute or chronic. Radiation-induced lung toxicity is a function of the irradiated lung volume, dose per fraction, and radiation dose. The larger the irradiated lung field, the higher the risk for radiation pneumonitis. Radiation pneumonitis usually develops from 2 to 6 months after completion of radiotherapy. The clinical syndrome, which varies in severity, consists of dyspnea, cough with scanty sputum, low-grade fever, and an initial hazy infiltrate on chest radiographs. The infiltrate and tissue damage usually are confined to the radiation field. The patients subsequently may develop a patchy alveolar infiltrate and air bronchograms, which may progress to acute respiratory failure that is sometimes fatal. A lung biopsy may be necessary to make the diagnosis. Asymptomatic infiltrates found incidentally after radiation therapy need not be treated. However, prednisone should be administered to patients with fever or other symptoms. The dosage should be tapered slowly after the resolution of radiation pneumonitis because abrupt withdrawal of glucocorticoids may cause an exacerbation of pneumonia. Delayed radiation fibrosis may occur years after radiation therapy and is signaled by dyspnea on exertion. It is often mild, but it can progress to chronic respiratory failure. Therapy is supportive.

Classical radiation pneumonitis that leads to pulmonary fibrosis is caused by radiation-induced production of local cytokines, such as platelet-derived growth factor β , TGF- β , and transforming growth factor β , in the radiation field. An immunologically mediated sporadic

488 radiation pneumonitis occurs in about 10% of patients; bilateral alveolitis mediated by T cells results in infiltrates outside the radiation field. This form of radiation pneumonitis usually resolves without sequelae.

SECTION V

Disorders Complicating Critical Illnesses and Their Management

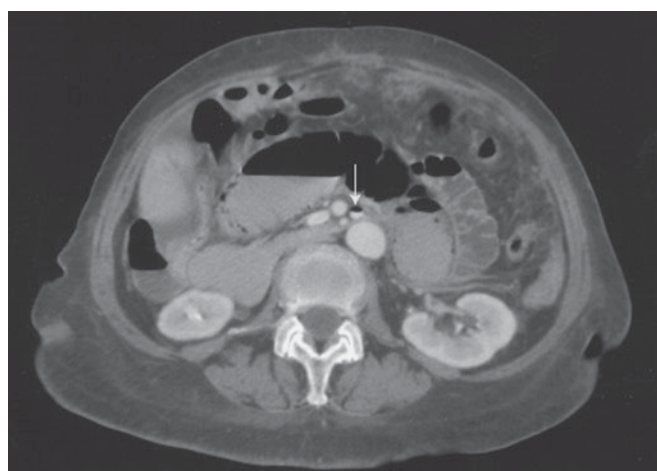
Pneumonia is a common problem in patients undergoing treatment for cancer. Bacterial pneumonia typically causes a localized infiltrate on chest radiographs. Therapy is tailored to the causative organism. When diffuse interstitial infiltrates appear in a febrile patient, the differential diagnosis is extensive and includes pneumonia caused by infection with *Pneumocystis carinii*; viral infections, including cytomegalovirus, adenovirus, herpes simplex virus, herpes zoster, respiratory syncytial virus, or intracellular pathogens such as *Mycoplasma* and *Legionella* spp.; effects of drugs or radiation; tumor progression; nonspecific pneumonitis; and fungal disease. Detection of opportunistic pathogens in pulmonary infections is still a challenge. Diagnostic tools include chest radiographs, CT scans, bronchoscopy with bronchoalveolar lavage (BAL), brush cytology, transbronchial biopsy, fine-needle aspiration, and open lung biopsy. In addition to the culture, evaluation of BAL fluid for *P. carinii* by polymerase chain reaction (PCR) and *Aspergillus* antigen improve the diagnostic yield. Patients with cancer who are neutropenic and have fever and local infiltrates on chest radiographs should be treated initially with broad-spectrum antibiotics, such as ceftazidime or imipenem. A new or persistent focal infiltrate not responding to broad-spectrum antibiotics argues for initiation of empiric antifungal therapy. When diffuse bilateral infiltrates develop in patients with febrile neutropenia, broad-spectrum antibiotics plus trimethoprim-sulfamethoxazole, with or without erythromycin, should be initiated. The addition of an antiviral agent is necessary in some settings, such as patients undergoing allogeneic hematopoietic stem cell transplantation. The empiric administration of trimethoprim-sulfamethoxazole plus erythromycin to patients without neutropenia and these antibiotics plus ceftazidime to patients with neutropenia covers nearly every treatable diagnosis (except tumor progression) and gives as good overall survival as a strategy based on early invasive intervention with BAL or open lung biopsy. If the patient does not improve in 4 days, open lung biopsy is the procedure of choice. Bronchoscopy with BAL may be used in patients who are poor candidates for surgery.

In patients with pulmonary infiltrates who are afebrile, heart failure and multiple pulmonary emboli are in the differential diagnosis.

NEUTROPENIC ENTEROCOLITIS

Neutropenic enterocolitis (typhlitis) is the inflammation and necrosis of the cecum and surrounding tissues that may complicate the treatment of acute leukemia. This complication has also been seen in patients with other forms of cancer treated with taxanes and in patients receiving

high-dose chemotherapy (Fig. 45-5). The patient develops right lower quadrant abdominal pain, often with rebound tenderness and a tense, distended abdomen, in a setting of fever and neutropenia. Watery diarrhea (often containing sloughed mucosa) and bacteremia are common, and bleeding may occur. Plain abdominal films are generally of little value in the diagnosis; the CT scan may show marked bowel wall thickening, particularly in the cecum, with bowel wall edema. Patients with bowel wall thickness >10 mm on ultrasonography have higher mortality rates. However, bowel wall thickening is significantly more prominent in patients with *Clostridium difficile* colitis. Pneumatosis intestinalis is a more specific finding that is seen only in those with neutropenic enterocolitis and ischemia. The combined involvement of the small and large bowel suggests a diagnosis of neutropenic



A



B

FIGURE 45-5

Abdominal CT scans of a 72-year-old woman with neutropenic enterocolitis secondary to chemotherapy. A. Air in the inferior mesenteric vein (arrow) and bowel wall with pneumatosis intestinalis. **B.** CT scan of the upper abdomen demonstrating air in the portal vein (arrows).

enterocolitis. Rapid institution of broad-spectrum antibiotics and nasogastric suction may reverse the process. Surgical intervention should be considered if no improvement is seen by 24 h after the start of antibiotic treatment. If the localized abdominal findings become diffuse, the prognosis is poor.

C. difficile colitis is increasing in incidence. Newer strains of *C. difficile* produce about 20 times more of toxins A and B compared to previously studied strains. *C. difficile* risk is also increased with chemotherapy. Antibiotic coverage for *C. difficile* should be added if pseudomembranous colitis cannot be excluded.

HEMORRHAGIC CYSTITIS

Hemorrhagic cystitis can develop in patients receiving cyclophosphamide or ifosfamide. Both drugs are metabolized to acrolein, which is a strong chemical irritant that is excreted in the urine. Prolonged contact or high concentrations may lead to bladder irritation and hemorrhage. Symptoms include gross hematuria, frequency, dysuria, burning, urgency, incontinence, and nocturia. The best management is prevention. Maintaining a high rate of urine flow minimizes exposure. In addition, 2-mercaptoethanesulfonate (mesna) detoxifies the metabolites and can be coadministered with the instigating drugs. Mesna usually is given three times on the day of ifosfamide administration in doses that are each 20% of the total ifosfamide dose. If hemorrhagic cystitis develops, the maintenance of a high urine flow may be sufficient supportive care. If conservative management is not effective, irrigation of the bladder with a 0.37–0.74% formalin solution for 10 min stops the bleeding in most cases. *N*-acetylcysteine may also be an effective irrigant. Prostaglandins (carboprost) can inhibit the process. In extreme cases, ligation of the hypogastric arteries, urinary diversion, or cystectomy may be necessary.

Hemorrhagic cystitis also occurs in patients who undergo BMT. In the BMT setting, early-onset hemorrhagic cystitis is related to drugs in the treatment regimen (e.g., cyclophosphamide), and late-onset hemorrhagic cystitis is usually caused by the polyoma virus BKV or adenovirus type 11. BKV load in urine alone or in combination with acute graft-versus-host disease correlate with development of hemorrhagic cystitis. Viral causes are usually detected by PCR-based diagnostic tests. Treatment of viral hemorrhagic cystitis is largely

supportive, with reduction in doses of immunosuppressive agents, if possible. No antiviral therapy is approved, although cidofovir is being tested.

HYPERSENSITIVITY REACTIONS TO ANTINEOPLASTIC DRUGS

Many antineoplastic drugs may cause HSR. These reactions are unpredictable and potentially life threatening. Most reactions occur during or within hours of parenteral drug administration. Taxanes; platinum compounds; asparaginase; etoposide; and biologic agents, including rituximab, bevacizumab, trastuzumab, gemtuzumab, cetuximab, and alemtuzumab, are more commonly associated with acute HSR than are other agents. Acute HSRs to some drugs, such as taxanes, occur during the first or second dose administered. HSR from platinum compounds occurs after prolonged exposure. Skin testing may identify patients with high risk for HSR after carboplatin exposure. Premedication with histamine H1 and H2 receptor antagonists and glucocorticoids reduces the incidence of HSR to taxanes, particularly paclitaxel. Despite premedication, HSR may still occur. In these cases, retreatment may be attempted with care, but use of alternative agents may be required.

FURTHER READINGS

- ALBANELL J, BASELGA J: Systemic therapy emergencies. *Semin Oncol* 27:347, 2000
- COIFFIER B, RIOUFFOL C: Management of tumor lysis syndrome in adults. *Expert Rev Anticancer Ther* 7:233, 2007
- DAVIS MP et al: Modern management of cancer-related intestinal obstruction. *Curr Oncol Rep* 2:343, 2000
- GLEISSNER B et al: Neoplastic meningitis. *Lancet Neurol* 5:443, 2006
- GORNIK HL et al: Abnormal cytology predicts poor prognosis in cancer patients with pericardial effusion. *J Clin Oncol* 23:5211, 2005
- GORSCHLUTER M et al: Neutropenic enterocolitis in adults: Systematic analysis of evidence quality. *Eur J Hematol* 75:1, 2005
- LOBLAW DA et al: Systematic review of the diagnosis and management of malignant extradural spinal cord compression: The Cancer Care Ontario Practice Guidelines Initiative's neuro-oncology disease site group. *J Clin Oncol* 23:2028, 2005
- RICE TW et al: The superior vena cava syndrome: Clinical characteristics and evolving etiology. *Medicine* 85:37, 2006
- RIPAMONTI C et al: Respiratory problems in advanced cancer. *Support Care Cancer* 10:204, 2002
- ZANOTTI KM et al: Prevention and management of antineoplastic-induced hypersensitivity reactions. *Drug Saf* 24:767, 2001

This page intentionally left blank



APPENDIX

LABORATORY VALUES OF CLINICAL IMPORTANCE

Alexander Kratz ■ Michael A. Pesce ■ Daniel J. Fink[†]

■ Introductory Comments	491
■ Reference Values for Laboratory Tests	492
■ Reference Values for Specific Analytes	505
■ Special Function Tests	508
■ Miscellaneous	512
■ Further Readings	512

INTRODUCTORY COMMENTS

The following are tables of reference values for laboratory tests, special analytes, and special function tests. A variety of factors can influence reference values. Such variables include the population studied, the duration and means of specimen transport, laboratory methods and instrumentation, and even the type of container used for the collection of the specimen. The reference or “normal” ranges given in this appendix may therefore not be appropriate for all laboratories, and these values should only be used as general guidelines. Whenever possible, reference values provided by the laboratory performing the testing should be used in the interpretation of laboratory data. Values supplied in this Appendix reflect typical reference ranges in adults. Pediatric reference ranges may vary significantly from adult values.

In preparing the Appendix, the authors have taken into account the fact that the system of international units (SI, *Système International d’Unités*) is used in most countries and in some medical journals. However, clinical laboratories may continue to report values in “conventional” units. Therefore, both systems are provided in the Appendix. The dual system is also used in the text except for (1) those instances in which the numbers remain the same but only the terminology is changed (e.g., mmol/L for meq/L or IU/L for mIU/mL), when only the SI units are given and (2) most pressure measurements (e.g., blood and cerebrospinal fluid pressures), when the conventional units (mmHg, mmH₂O) are used. In all other instances in the text, the SI unit is followed by the traditional unit in parentheses.

[†]Deceased.

TABLE A-1

HEMATOLOGY AND COAGULATION

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Activated clotting time	WB	70–180 s	70–180 s
Activated protein C resistance (factor V Leiden)	P	NA	Ratio > 2.1
α_2 Antiplasmin	P	0.87–1.55	87–155%
Antiphospholipid antibody panel			
PTT-LA (lupus anticoagulant screen)	P	Negative	Negative
Platelet neutralization procedure	P	Negative	Negative
Dilute viper venom screen	P	Negative	Negative
Anticardiolipin antibody	S		
IgG		0–15 arbitrary units	0–15 GPL
IgM		0–15 arbitrary units	0–15 MPL
Antithrombin III	P		
Antigenic		220–390 mg/L	22–39 mg/dL
Functional		0.7–1.30 U/L	70–130%
Anti-Xa assay (heparin assay)	P		
Unfractionated heparin		0.3–0.7 kIU/L	0.3–0.7 IU/mL
Low-molecular-weight heparin		0.5–1.0 kIU/L	0.5–1.0 IU/mL
Danaparoid (Orgaran)		0.5–0.8 kIU/L	0.5–0.8 IU/mL
Autohemolysis test	WB	0.004–0.045	0.4–4.50%
Autohemolysis test with glucose	WB	0.003–0.007	0.3–0.7%
Bleeding time (adult)		<7.1 min	<7.1 min
Bone marrow: see Table A-8			
Clot retraction	WB	0.50–1.00/2 h	50–100%/2 h
Cryofibrinogen	P	Negative	Negative
D-Dimer	P	0.22–0.74 μ g/mL	0.22–0.74 μ g/mL
Differential blood count	WB		
Neutrophils		0.40–0.70	40–70%
Bands		0.0–0.05	0–5%
Lymphocytes		0.20–0.50	20–50%
Monocytes		0.04–0.08	4–8%
Eosinophils		0.0–0.6	0–6%
Basophils		0.0–0.02	0–2%
Eosinophil count	WB	150–300/ μ L	150–300/mm ³
Erythrocyte count	WB		
Men		4.30–5.60 $\times 10^{12}$ /L	4.30–5.60 $\times 10^6$ /mm ³
Women		4.00–5.20 $\times 10^{12}$ /L	4.00–5.20 $\times 10^6$ /mm ³
Erythrocyte life span	WB		
Normal survival		120 days	120 days
Chromium labeled, half-life ($t_{1/2}$)		25–35 days	25–35 days
Erythrocyte sedimentation rate	WB		
Women		0–20 mm/h	0–20 mm/h
Men		0–15 mm/h	0–15 mm/h
Euglobulin lysis time	P	7200–14400 s	120–240 min
Factor II, prothrombin	P	0.50–1.50	50–150%
Factor V	P	0.50–1.50	50–150%
Factor VII	P	0.50–1.50	50–150%
Factor VIII	P	0.50–1.50	50–150%
Factor IX	P	0.50–1.50	50–150%
Factor X	P	0.50–1.50	50–150%
Factor XI	P	0.50–1.50	50–150%
Factor XII	P	0.50–1.50	50–150%
Factor XIII screen	P	NA	Present

TABLE A-1 (CONTINUED)

HEMATOLOGY AND COAGULATION

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Factor inhibitor assay	P	<0.5 Bethesda Units	<0.5 Bethesda Units
Fibrin(ogen) degradation products	P	0–1 mg/L	0–1 µg/mL
Fibrinogen	P	2.33–4.96 g/L	233–496 mg/dL
Glucose-6-phosphate dehydrogenase (erythrocyte)	WB	<2400 s	<40 min
Ham's test (acid serum)	WB	Negative	Negative
Hematocrit	WB		
Men		0.388–0.464	38.8–46.4
Women		0.354–0.444	35.4–44.4
Hemoglobin			
Plasma	P	6–50 mg/L	0.6–5.0 mg/dL
Whole blood	WB		
Men		133–162 g/L	13.3–16.2 g/dL
Women		120–158 g/L	12.0–15.8 g/dL
Hemoglobin electrophoresis	WB		
Hemoglobin A		0.95–0.98	95–98%
Hemoglobin A ₂		0.015–0.031	1.5–3.1%
Hemoglobin F		0–0.02	0–2.0%
Hemoglobins other than A, A ₂ , or F		Absent	Absent
Heparin-induced thrombocytopenia antibody	P	Negative	Negative
Joint fluid crystal	JF	NA	No crystals seen
Joint fluid mucin	JF	NA	Only type I mucin present
Leukocytes			
Alkaline phosphatase (LAP)	WB	0.2–1.6 µkat/L	13–100 µ/L
White blood cell count (WBC)	WB	3.54–9.06 × 10 ⁹ /L	3.54–9.06 × 10 ³ /mm ³
Mean corpuscular hemoglobin (MCH)	WB	26.7–31.9 pg/cell	26.7–31.9 pg/cell
Mean corpuscular hemoglobin concentration (MCHC)	WB	323–359 g/L	32.3–35.9 g/dL
Mean corpuscular hemoglobin of reticulocytes (CH)	WB	24–36 pg	24–36 pg
Mean corpuscular volume (MCV)	WB	79–93.3 fL	79–93.3 µm ³
Mean platelet volume (MPV)	WB	9.00–12.95 fL	9.00–12.95 µm ³
Osmotic fragility of erythrocytes	WB		
Direct		0.0035–0.0045	0.35–0.45%
Index		0.0030–0.0065	0.30–0.65%
Partial thromboplastin time, activated	P	26.3–39.4 s	26.3–39.4 s
Plasminogen	P		
Antigen		84–140 mg/L	8.4–14.0 mg/dL
Functional		0.70–1.30	70–130%
Plasminogen activator inhibitor 1	P	4–43 µg/L	4–43 ng/mL
Platelet aggregation	PRP	NA	>65 aggregation in response to adenosine diphosphate, epinephrine, collagen, ristocetin, and arachidonic acid
Platelet count	WB	165–415 × 10 ⁹ /L	165–415 × 10 ³ /mm ³
Platelet, mean volume	WB	6.4–11 fL	6.4–11.0 µm ³
Prekallikrein assay	P	0.50–1.5	50–150%
Prekallikrein screen	P		No deficiency detected
Protein C	P		
Total antigen		0.70–1.40	70–140%
Functional		0.70–1.30	70–130%
Protein S	P		
Total antigen		0.70–1.40	70–140%
Functional		0.65–1.40	65–140%
Free antigen		0.70–1.40	70–140%
Prothrombin gene mutation G20210A	WB	NA	Not present

(Continued)

HEMATOLOGY AND COAGULATION			
ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Prothrombin time	P	12.7–15.4 s	12.7–15.4 s
Protoporphyrin, free erythrocyte	WB	0.28–0.64 $\mu\text{mol/L}$ of RBCs	16–36 $\mu\text{g/dL}$ of RBCs
Red cell distribution width	WB	<0.145	<14.5%
Reptilase time	P	16–23.6 s	16–23.6 s
Reticulocyte count	WB		
Men		0.008–0.023 RBCs	0.8–2.3% RBCs
Women		0.008–0.020 RBCs	0.8–2.0% RBCs
Reticulocyte hemoglobin content	WB	>26 pg/cell	>26 pg/cell
Ristocetin cofactor (functional von Willebrand factor)	P		
Blood group O		0.75 mean of normal	75% mean of normal
Blood group A		1.05 mean of normal	105% mean of normal
Blood group B		1.15 mean of normal	115% mean of normal
Blood group AB		1.25 mean of normal	125% mean of normal
Sickle cell test	WB	Negative	Negative
Sucrose hemolysis	WB	<0.1	<10% hemolysis
Thrombin time	P	15.3–18.5 s	15.3–18.5 s
Total eosinophils	WB	150–300 $\times 10^6/\text{L}$	150–300/ mm^3
Transferrin receptor	S, P	9.6–29.6 nmol/L	9.6–29.6 nmol/L
Viscosity			
Plasma	P	1.7–2.1	1.7–2.1
Serum	S	1.4–1.8	1.4–1.8
Von Willebrand factor (vWF) antigen (factor VIII:R antigen)	P		
Blood group O		0.75 mean of normal	75% mean of normal
Blood group A		1.05 mean of normal	105% mean of normal
Blood group B		1.15 mean of normal	115% mean of normal
Blood group AB		1.25 mean of normal	125% mean of normal
von Willebrand factor multimers	P	Normal distribution	Normal distribution
White blood cells: see “leukocytes”			

Note: GPL, IgG/L; JF, joint fluid; MPL, IgM/L; NA, not applicable; P, plasma; PRP, platelet-rich plasma; PTT-LA, partial thromboplastin time—Lupus anticoagulant screen; RBC, red blood cell; S, serum; SI, Système International d’Unités; WB, whole blood.

TABLE A-2

CLINICAL CHEMISTRY AND IMMUNOLOGY			
ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Acetoacetate	P	20–99 $\mu\text{mol/L}$	0.2–1.0 mg/dL
Adrenocorticotropin hormone (ACTH)	P	1.3–16.7 pmol/L	6.0–76.0 pg/mL
Alanine aminotransferase (AST, SGPT)	S	0.12–0.70 $\mu\text{kat/L}$	7–41 U/L
Albumin	S		
Women		41–53 g/L	4.1–5.3 g/dL
Men		40–50 g/L	4.0–5.0 g/L
Aldolase	S	26–138 nkat/L	1.5–8.1 U/L
Aldosterone (adult)			
Supine, normal-sodium diet	S, P	55–250 pmol/L	2–9 ng/dL
Upright, normal-sodium diet	S, P		2–5-fold increase over supine value
Supine, low-sodium diet	S, P		2–5-fold increase over normal sodium diet level
α fetoprotein (adult)	U	6.38–58.25 nmol/d	2.3–21.0 $\mu\text{g}/24\text{ h}$
α_1 antitrypsin	S	0–8.5 $\mu\text{g/L}$	0–8.5 ng/mL
Ammonia, as NH_3	S	1.0–2.0 g/L	100–200 mg/dL
	P	11–35 $\mu\text{mol/L}$	19–60 $\mu\text{g/dL}$

TABLE A-2 (CONTINUED)

CLINICAL CHEMISTRY AND IMMUNOLOGY			
ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Amylase (method dependent)	S	0.34–1.6 μ kat/L	20–96 U/L
Androstenedione (adult)	S	1.75–8.73 nmol/L	50–250 ng/dL
Angiotensin-converting enzyme (ACE)	S	0.15–1.1 μ kat/L	9–67 U/L
Anion gap	S	7–16 mmol/L	7–16 mmol/L
Apo B/Apo A-1 ratio		0.35–0.98	0.35–0.98
Apolipoprotein A-1	S	1.19–2.40 g/L	119–240 mg/dL
Apolipoprotein B	S	0.52–1.63 g/L	52–163 mg/dL
Arterial blood gases			
(HCO ₃ ⁻)		22–30 mmol/L	22–30 meq/L
P _{CO₂}		4.3–6.0 kPa	32–45 mmHg
pH		7.35–7.45	7.35–7.45
P _{O₂}		9.6–13.8 kPa	72–104 mmHg
Aspartate aminotransferase (AST, SGOT)	S	0.20–0.65 μ kat/L	12–38 U/L
Autoantibodies			
Anti-adrenal antibody	S	NA	Negative at 1:10 dilution
Anti-double-strand (native) DNA	S	NA	Negative at 1:10 dilution
Anti-glomerular basement membrane antibodies	S		
Qualitative		Negative	Negative
Quantitative		<5 kU/L	<5 U/mL
Anti-granulocyte antibody	S	NA	Negative
Anti-Jo-1 antibody	S	NA	Negative
Anti-La antibody	S	NA	Negative
Anti-mitochondrial antibody	S	NA	Negative
Antineutrophil cytoplasmic autoantibodies, cytoplasmic (C-ANCA)	S		
Qualitative		Negative	Negative
Quantitative (antibodies to proteinase 3)		<2.8 kU/L	<2.8 U/mL
Antineutrophil cytoplasmic autoantibodies, perinuclear (P-ANCA)	S		
Qualitative		Negative	Negative
Quantitative (antibodies to myeloperoxidase)		<1.4 kU/L	<1.4 U/mL
Antinuclear antibody	S	NA	Negative at 1:40
Anti-parietal cell antibody	S	NA	Negative at 1:20
Anti-Ro antibody	S	NA	Negative
Anti-platelet antibody	S	NA	Negative
Anti-RNP antibody	S	NA	Negative
Anti-Scl 70 antibody	S	NA	Negative
Anti-Smith antibody	S	NA	Negative
Anti-smooth muscle antibody	S	NA	Negative at 1:20
Anti-thyroglobulin	S	NA	Negative
Anti-thyroid antibody	S	<0.3 kIU/L	<0.3 IU/mL
B type natriuretic peptide (BNP)	P	Age and gender specific: <167 ng/L	Age and gender specific: <167 pg/mL
Bence Jones protein, serum	S	NA	None detected
Bence Jones protein, urine, qualitative	U	NA	None detected in 50 \times concentrated urine
Bence Jones Protein, urine, quantitative	U		
Kappa		<25 mg/L	<2.5 mg/dL
Lambda		<50 mg/L	<5.0 mg/dL
β_2 -Microglobulin	S	<2.7 mg/L	<0.27 mg/dL
	U	<120 μ g/d	<120 μ g/day
Bilirubin	S		
Total		5.1–22 μ mol/L	0.3–1.3 mg/dL
Direct		1.7–6.8 μ mol/L	0.1–0.4 mg/dL
Indirect		3.4–15.2 μ mol/L	0.2–0.9 mg/dL
C peptide (adult)	S, P	0.17–0.66 nmol/L	0.5–2.0 ng/mL

(Continued)

CLINICAL CHEMISTRY AND IMMUNOLOGY

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
C1-esterase-inhibitor protein	S		
Antigenic		124–250 mg/L	12.4–24.5 mg/dL
Functional		Present	Present
CA 125	S	0–35 kU/L	0–35 U/mL
CA 19-9	S	0–37 kU/L	0–37 U/mL
CA-15-3	S	0–34 kU/L	0–34 U/mL
CA27-29	S	0–40 kU/L	0–40 U/mL
Calcitonin	S		
Men		3–26 ng/L	3–26 pg/mL
Women		2–17 ng/L	2–17 pg/mL
Calcium	S	2.2–2.6 mmol/L	8.7–10.2 mg/dL
Calcium, ionized	WB	1.12–1.32 mmol/L	4.5–5.3 mg/dL
Carbon dioxide content (TCO ₂)	P (sea level)	22–30 mmol/L	22–30 meq/L
Carboxyhemoglobin (carbon monoxide content)	WB		
Nonsmokers		0–0.04	0–4%
Smokers		0.04–0.09	4–9%
Onset of symptoms		0.15–0.20	15–20%
Loss of consciousness and death		>0.50	>50%
Carcinoembryonic antigen (CEA)	S		
Nonsmokers		0.0–3.0 µg/L	0.0–3.0 ng/mL
Smokers	S	0.0–5.0 µg/L	0.0–5.0 ng/mL
Ceruloplasmin	S	250–630 mg/L	25–63 mg/dL
Chloride	S	102–109 mmol/L	102–109 meq/L
Cholesterol: see Table A-5			
Cholinesterase	S	5–12 kU/L	5–12 U/mL
Complement			
C3	S	0.83–1.77 g/L	83–177 mg/dL
C4	S	0.16–0.47 g/L	16–47 mg/dL
Total hemolytic complement (CH50)	S	50–150%	50–150%
Factor B	S	0.17–0.42 g/L	17–42 mg/dL
Coproporphyrins (types I and III)	U	150–470 µmol/d	100–300 µg/d
Cortisol			
Fasting, 8 A.M.–12 noon	S	138–690 nmol/L	5–25 µg/dL
12 noon–8 P.M.		138–414 nmol/L	5–15 µg/dL
8 P.M.–8 A.M.		0–276 nmol/L	0–10 µg/dL
Cortisol, free	U	55–193 nmol/24 h	20–70 µg/24 h
C-reactive protein	S	0.2–3.0 mg/L	0.2–3.0 mg/L
Creatine kinase (total)	S		
Women		0.66–4.0 µkat/L	39–238 U/L
Men		0.87–5.0 µkat/L	51–294 U/L
Creatine kinase-MB	S		
Mass		0.0–5.5 µg/L	0.0–5.5 ng/mL
Fraction of total activity (by electrophoresis)		0–0.04	0–4.0%
Creatinine	S		
Women		44–80 µmol/L	0.5–0.9 ng/mL
Men		53–106 µmol/L	0.6–1.2 ng/mL
Cryoproteins	S	NA	None detected
Dehydroepiandrosterone (DHEA) (adult)			
Men	S	6.2–43.4 nmol/L	180–1250 ng/dL
Women		4.5–34.0 nmol/L	130–980 ng/dL
Dehydroepiandrosterone (DHEA) sulfate	S		
Men		100–6190 µg/L	10–619 µg/dL
Premenopausal women		120–5350 µg/L	12–535 µg/dL
Postmenopausal women		300–2600 µg/L	30–260 µg/dL
Deoxycorticosterone (DOC) (adults)	S	61–576 nmol/L	2–19 ng/dL
11-Deoxycortisol (adults) (compound S) (8:00 A.M.)	S	0.34–4.56 nmol/L	12–158 ng/dL

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Dihydrotestosterone			
Men	S, P	1.03–2.92 nmol/L	30–85 ng/dL
Women		0.14–0.76 nmol/L	4–22 ng/dL
Dopamine	P	<475 pmol/L	<87 pg/mL
Dopamine	U	425–2610 nmol/d	65–400 µg/d
Epinephrine	P		
Supine (30 min)		<273 pmol/L	< 50 pg/mL
Sitting		<328 pmol/L	< 60 pg/mL
Standing (30 min)		<491 pmol/L	< 90 pg/mL
Epinephrine	U	0–109 nmol/d	0–20 µg/d
Erythropoietin	S	4–27 U/L	4–27 U/L
Estradiol	S, P		
Premenopausal women			
Follicular phase		74–532 pmol/L	< 20–145 pg/mL
Mid-cycle peak		411–1626 pmol/L	112–443 pg/mL
Luteal phase		74–885 pmol/L	< 20–241 pg/mL
Postmenopausal women		217 pmol/L	< 59 pg/mL
Men		74 pmol/L	< 20 pg/mL
Estrone	S, P		
Premenopausal women			
Follicular phase		55–555 pmol/L	15–150 pg/mL
Luteal phase		55–740 pmol/L	15–200 pg/mL
Postmenopausal women		55–204 pmol/L	15–55 pg/mL
Men		55–240 pmol/L	15–65 pg/mL
Fatty acids, free (nonesterified)	P	<0.28–0.89 mmol/L	< 8–25 mg/dL
Ferritin	S		
Women		10–150 µg/L	10–150 ng/mL
Men		29–248 µg/L	29–248 ng/mL
Follicle-stimulating hormone (FSH)	S, P		
Premenopausal women			
Follicular phase		3.0–20.0 IU/L	3.0–20.0 mIU/mL
Ovulatory phase		9.0–26.0 IU/L	9.0–26.0 mIU/mL
Luteal phase		1.0–12.0 IU/L	1.0–12.0 mIU/mL
Postmenopausal women		18.0–153.0 IU/L	18.0–153.0 mIU/mL
Men		1.0–12.0 IU/L	1.0–12.0 mIU/mL
Free testosterone, adults			
Women	S	2.1–23.6 pmol/L	0.6–6.8 pg/mL
Men		163–847 pmol/L	47–244 pg/mL
Fructosamine	S	< 285 µmol/L	< 285 µmol/L
Gamma glutamyltransferase	S	0.15–0.99 µkat/L	9–58 U/L
Gastrin	S	<100 ng/L	< 100 pg/mL
Glucagon	P	20–100 ng/L	20–100 pg/mL
Glucose (fasting)	P		
Normal		4.2–6.1 mmol/L	75–110 mg/dL
Impaired glucose tolerance		6.2–6.9 mmol/L	111–125 mg/dL
Diabetes mellitus		>7.0 mmol/L	>125 mg/dL
Glucose, 2-h postprandial	P	3.9–6.7 mmol/L	70–120 mg/dL
Growth hormone (resting)	S	0.5–17.0 µg/L	0.5–17.0 ng/mL
Hemoglobin A _{1c}	WB	0.04–0.06 Hb fraction	4.0–6.0%
High-density lipoprotein (HDL) (see Table A-5)			
Homocysteine	P	4.4–10.8 µmol/L	4.4–10.8 µmol/L
Human chorionic gonadotropin (hCG)	S		
Non-pregnant women		<5 IU/L	<5 mIU/mL
1–2 weeks postconception		9–130 IU/L	9–130 mIU/mL
2–3 weeks postconception		75–2600 IU/L	75–2600 mIU/mL
3–4 weeks postconception		850–20,800 IU/L	850–20,800 mIU/mL

(Continued)

CLINICAL CHEMISTRY AND IMMUNOLOGY

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
4–5 weeks postconception		4000–100,200 IU/L	4000–100,200 mIU/mL
5–10 weeks postconception		11,500–289,000 IU/L	11,500–289,000 mIU/mL
10–14 weeks postconception		18,300–137,000 IU/L	18,300–137,000 mIU/mL
Second trimester		1400–53,000 IU/L	1400–53,000 mIU/mL
Third trimester		940–60,000 IU/L	940–60,000 mIU/mL
β-Hydroxybutyrate	P	0–290 μmol/L	0–3 mg/dL
5-Hydroxyindoleacetic acid (5-HIAA)	U	10.5–36.6 μmol/d	2–7 mg/d
17-Hydroxyprogesterone (adult)	S		
Men		0.15–7.5 nmol/L	5–250 ng/dL
Women			
Follicular phase		0.6–3.0 nmol/L	20–100 ng/dL
Midcycle peak		3–7.5 nmol/L	100–250 ng/dL
Luteal phase		3–15 nmol/L	100–500 ng/dL
Postmenopausal		≤2.1 nmol/L	≤70 ng/dL
Hydroxyproline	U, 24 h	38–500 μmol/d	38–500 μmol/d
Immunofixation	S	NA	No bands detected
Immunoglobulin, quantitation (adults)			
IgA	S	0.70–3.50 g/L	70–350 mg/dL
IgD	S	0–140 mg/L	0–14 mg/dL
IgE	S	24–430 μg/L	10–179 IU/mL
IgG	S	7.0–17.0 g/L	700–1700 mg/dL
IgG ₁	S	2.7–17.4 g/L	270–1740 mg/dL
IgG ₂	S	0.3–6.3 g/L	30–630 mg/dL
IgG ₃	S	0.13–3.2 g/L	13–320 mg/dL
IgG ₄	S	0.11–6.2 g/L	11–620 mg/dL
IgM	S	0.50–3.0 g/L	50–300 mg/dL
Insulin	S, P	14.35–143.5 pmol/L	2–20 μU/mL
Iron	S	7–25 μmol/L	41–141 μg/dL
Iron-binding capacity	S	45–73 μmol/L	251–406 μg/dL
Iron-binding capacity saturation	S	0.16–0.35	16–35%
JF crystal	JF	NA	No crystals seen
JF mucin	JF	NA	Only type I mucin present
Ketone (acetone)	S, U	Negative	Negative
17 Ketosteroids	U	0.003–0.012 g/d	3–12 mg/d
Lactate	P, arterial	0.5–1.6 mmol/L	4.5–14.4 mg/dL
	P, venous	0.5–2.2 mmol/L	4.5–19.8 mg/dL
Lactate dehydrogenase	S	2.0–3.8 μkat/L	115–221 U/L
Lactate dehydrogenase isoenzymes	S		
Fraction 1 (of total)		0.14–0.26	14–26%
Fraction 2		0.29–0.39	29–39%
Fraction 3		0.20–0.25	20–25%
Fraction 4		0.08–0.16	8–16%
Fraction 5		0.06–0.16	6–16%
Lipase (method dependent)	S	0.51–0.73 μkat/L	3–43 U/L
Lipids: see Table A-5			
Lipoprotein (a)	S	0–300 mg/L	0–30 mg/dL
Low-density lipoprotein (LDL) (see Table A-5)			
Luteinizing hormone (LH)	S, P		
Premenopausal women			
Menstruating			
Follicular phase		2.0–15.0 U/L	2.0–15.0 U/L
Ovulatory phase		22.0–105.0 U/L	22.0–105.0 U/L
Luteal phase		0.6–19.0 U/L	0.6–19.0 U/L
Postmenopausal women		16.0–64.0 U/L	16.0–64.0 U/L
Men		2.0–12.0 U/L	2.0–12.0 U/L
Magnesium	S	0.62–0.95 mmol/L	1.5–2.3 mg/dL
Metanephrine	P	<0.5 nmol/L	<100 pg/mL

CLINICAL CHEMISTRY AND IMMUNOLOGY			
ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Metanephrine	U	30–211 mmol/mol creatinine	53–367 µg/g creatinine
Methemoglobin	WB	0.0–0.01	0–1%
Microalbumin urine	U		
24-h urine		0.0–0.03 g/d	0–30 mg/24 h
Spot urine		0.0–0.03 g/g creatinine	0–30 µg/mg creatinine
Myoglobin	S		
Men		19–92 µg/L	19–92 µg/L
Women		12–76 µg/L	12–76 µg/L
Norepinephrine	U	89–473 nmol/d	15–80 µg/d
Norepinephrine	P		
Supine (30 min)		650–2423 pmol/L	110–410 pg/mL
Sitting		709–4019 pmol/L	120–680 pg/mL
Standing (30 min)		739–4137 pmol/L	125–700 pg/mL
N-telopeptide (cross linked), NTx	S		
Premenopausal women		6.2–19.0 nmol BCE	6.2–19.0 nmol BCE
Men		5.4–24.2 nmol BCE	5.4–24.2 nmol BCE
Bone collagen equivalent (BCE)			
N-telopeptide (cross linked), NTx	U		
Premenopausal women		17–94 nmol BCE/mmol creatinine	17–94 nmol BCE/mmol creatinine
Postmenopausal women		26–124 nmol BCE/mmol creatinine	26–124 nmol BCE/mmol creatinine
Men		21–83 nmol BCE/mmol creatinine	21–83 nmol BCE/mmol creatinine
Bone collagen equivalent (BCE)			
5' Nucleotidase	S	0.02–0.19 µkat/L	0–11 U/L
Osmolality	P	275–295 mosmol/kg serum water	275–295 mosmol/kg serum water
	U	500–800 mosmol/kg water	500–800 mosmol/kg water
Osteocalcin	S	11–50 µg/L	11–50 ng/mL
Oxygen content	WB		
Arterial (sea level)		17–21	17–21 vol%
Venous (sea level)		10–16	10–16 vol%
Oxygen percent saturation (sea level)	WB		
Arterial		0.97	94–100%
Venous, arm		0.60–0.85	60–85%
Parathyroid hormone (intact)	S	8–51 ng/L	8–51 pg/mL
Phosphatase, alkaline	S	0.56–1.63 µkat/L	33–96 U/L
Phosphorus, inorganic	S	0.81–1.4 mmol/L	2.5–4.3 mg/dL
Porphobilinogen	U	None	None
Potassium	S	3.5–5.0 mmol/L	3.5–5.0 meq/L
Prealbumin	S	170–340 mg/L	17–34 mg/dL
Progesterone	S, P		
Women			
Follicular		<3.18 nmol/L	<1.0 ng/mL
Midluteal		9.54–63.6 nmol/L	3–20 ng/mL
Men		<3.18 nmol/L	<1.0 ng/mL
Prolactin	S	0–20 µg/L	0–20 ng/mL
Prostate-specific antigen (PSA)	S		
Men < 40 years		0.0–2.0 µg/L	0.0–2.0 ng/mL
Men > 40 years		0.0–4.0 µg/L	0.0–4.0 ng/mL
PSA, free; in men 45–75 years, with PSA values 4–20 µg/mL	S	>0.25 associated with benign prostatic hyperplasia	>25% associated with benign prostatic hyperplasia
Protein fractions	S		
Albumin		35–55 g/L	3.5–5.5 g/dL (50–60%)

(Continued)

CLINICAL CHEMISTRY AND IMMUNOLOGY

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Globulin		20–35 g/L	2.0–3.5 g/dL (40–50%)
α_1		2–4 g/L	0.2–0.4 g/dL (4.2–7.2%)
α_2		5–9 g/L	0.5–0.9 g/dL (6.8–12%)
β		6–11 g/L	0.6–1.1 g/dL (9.3–15%)
γ		7–17 g/L	0.7–1.7 g/dL (13–23%)
Protein, total	S	67–86 g/L	6.7–8.6 g/dL
Pyruvate	P, arterial	40–130 μ mol/L	0.35–1.14 mg/dL
	P, venous	40–130 μ mol/L	0.35–1.14 mg/dL
Rheumatoid factor	S, JF	<30 kIU/L	<30 IU/mL
Serotonin	WB	0.28–1.14 μ mol/L	50–200 ng/mL
Serum protein electrophoresis	S	NA	Normal pattern
Sex hormone binding globulin (adults)	S		
Men		13–71 nmol/L	13–71 nmol/L
Women		18–114 nmol/L	18–114 nmol/L
Sodium	S	136–146 mmol/L	136–146 meq/L
Somatomedin-C (IGF-1) (adult)	S		
16–24 years		182–780 μ g/L	182–780 ng/mL
25–39 years		114–492 μ g/L	114–492 ng/mL
40–54 years		90–360 μ g/L	90–360 ng/mL
>54 years		71–290 μ g/L	71–290 ng/mL
Somatostatin	P	<25 ng/L	<25 pg/mL
Testosterone, total, morning sample	S		
Women		0.21–2.98 nmol/L	6–86 ng/dL
Men		9.36–37.10 nmol/L	270–1070 ng/dL
Thyroglobulin	S	0.5–53 μ g/L	0.5–53 ng/mL
Thyroid-binding globulin	S	13–30 mg/L	1.3–3.0 mg/dL
Thyroid-stimulating hormone	S	0.34–4.25 mIU/L	0.34–4.25 μ IU/mL
Thyroxine, free (fT ₄)	S	10.3–21.9 pmol/L	0.8–1.7 ng/dL
Thyroxine, total (T ₄)	S	70–151 nmol/L	5.4–11.7 μ g/dL
(Free) thyroxine index	S	6.7–10.9	6.7–10.9
Transferrin	S	2.0–4.0 g/L	200–400 mg/dL
Triglycerides (see Table A-5)	S	0.34–2.26 mmol/L	30–200 mg/dL
Triiodothyronine, free (fT ₃)	S	3.7–6.5 pmol/L	2.4–4.2 pg/mL
Triiodothyronine, total (T ₃)	S	1.2–2.1 nmol/L	77–135 ng/dL
Troponin I	S		
Normal population, 99 %tile		0–0.08 μ g/L	0–0.08 ng/mL
Cut-off for MI		>0.4 μ g/L	>0.4 ng/mL
Troponin T	S		
Normal population, 99 %tile		0–0.1 μ g/L	0–0.01 ng/mL
Cut-off for MI		0–0.1 μ g/L	0–0.1 ng/mL
Urea nitrogen	S	2.5–7.1 mmol/L	7–20 mg/dL
Uric acid	S		
Women		0.15–0.33 μ mol/L	2.5–5.6 mg/dL
Men		0.18–0.41 μ mol/L	3.1–7.0 mg/dL
Urobilinogen	U	0.09–4.2 μ mol/d	0.05–25 mg/24 h
Vanillylmandelic acid (VMA)	U, 24 h	<30 μ mol/d	<6 mg/d
Vasoactive intestinal polypeptide	P	0–60 ng/L	0–60 pg/mL

Note: JF, joint fluid; MI, myocardial infarction; P, plasma; S, serum; SI, Système International d'Unités; U, urine; WB, whole blood.

DRUG	THERAPEUTIC RANGE		TOXIC LEVEL	
	SI UNITS	CONVENTIONAL UNITS	SI UNITS	CONVENTIONAL UNITS
Acetaminophen	66–199 $\mu\text{mol/L}$	10–30 $\mu\text{g/mL}$	>1320 $\mu\text{mol/L}$	>200 $\mu\text{g/mL}$
Amikacin				
Peak	34–51 $\mu\text{mol/L}$	20–30 $\mu\text{g/mL}$	>60 $\mu\text{mol/L}$	>35 $\mu\text{g/mL}$
Trough	0–17 $\mu\text{mol/L}$	0–10 $\mu\text{g/mL}$	>17 $\mu\text{mol/L}$	>10 $\mu\text{g/mL}$
Amitriptyline/nortriptyline (total drug)	430–900 nmol/L	120–250 ng/mL	>1800 nmol/L	>500 ng/mL
Amphetamine	150–220 nmol/L	20–30 ng/mL	>1500 nmol/L	>200 ng/mL
Bromide	1.3–6.3 mmol/L 9.4–18.8 mmol/L	Sedation: 10–50 mg/dL Epilepsy: 75–150 mg/dL	6.4–18.8 mmol/L >18.8 mmol/L >37.5 mmol/L	51–150 mg/dL : mild toxicity >150 mg/dL : Severe toxicity >300 mg/dL : Lethal
Carbamazepine	17–42 $\mu\text{mol/L}$	4–10 $\mu\text{g/mL}$	85 $\mu\text{mol/L}$	>20 $\mu\text{g/mL}$
Chloramphenicol				
Peak	31–62 $\mu\text{mol/L}$	10–20 $\mu\text{g/mL}$	>77 $\mu\text{mol/L}$	>25 $\mu\text{g/mL}$
Trough	15–31 $\mu\text{mol/L}$	5–10 $\mu\text{g/mL}$	>46 $\mu\text{mol/L}$	>15 $\mu\text{g/mL}$
Chlordiazepoxide	1.7–10 $\mu\text{mol/L}$	0.5–3.0 $\mu\text{g/mL}$	>17 $\mu\text{mol/L}$	>5.0 $\mu\text{g/mL}$
Clonazepam	32–240 nmol/L	10–75 ng/mL	>320 nmol/L	>100 ng/mL
Clozapine	0.6–2.1 $\mu\text{mol/L}$	200–700 ng/mL	>3.7 $\mu\text{mol/L}$	>1200 ng/mL
Cocaine			>3.3 $\mu\text{mol/L}$	>1.0 $\mu\text{g/mL}$
Codeine	43–110 nmol/mL	13–33 ng/mL	>3700 nmol/mL	>1100 ng/mL (lethal)
Cyclosporine				
Renal transplant				
0–6 months	208–312 nmol/L	250–375 ng/mL	>312 nmol/L	>375 ng/mL
6–12 months after transplant	166–250 nmol/L	200–300 ng/mL	>250 nmol/L	>300 ng/mL
>12 months	83–125 nmol/L	100–150 ng/mL	>125 nmol/L	>150 ng/mL
Cardiac transplant				
0–6 months	208–291 nmol/L	250–350 ng/mL	>291 nmol/L	>350 ng/mL
6–12 months after transplant	125–208 nmol/L	150–250 ng/mL	>208 nmol/L	>250 ng/mL
>12 months	83–125 nmol/L	100–150 ng/mL	>125 nmol/L	150 ng/mL
Lung transplant				
0–6 months	250–374 nmol/L	300–450 ng/mL	>374 nmol/L	>450 ng/mL
Liver transplant				
0–7 days	249–333 nmol/L	300–400 ng/mL	>333 nmol/L	>400 ng/mL
2–4 weeks	208–291 nmol/L	250–350 ng/mL	>291 nmol/L	>350 ng/mL
5–8 weeks	166–249 nmol/L	200–300 ng/mL	>249 nmol/L	>300 ng/mL
9–52 weeks	125–208 nmol/L	150–250 ng/mL	>208 nmol/L	>250 ng/mL
>1 year	83–166 nmol/L	100–200 ng/mL	>166 nmol/L	>200 ng/mL
Desipramine	375–1130 nmol/L	100–300 ng/mL	>1880 nmol/L	>500 ng/mL
Diazepam (and metabolite)				
Diazepam	0.7–3.5 $\mu\text{mol/L}$	0.2–1.0 $\mu\text{g/mL}$	>7.0 $\mu\text{mol/L}$	>2.0 $\mu\text{g/mL}$
Nordazepam	0.4–6.6 $\mu\text{mol/L}$	0.1–1.8 $\mu\text{g/mL}$	>9.2 $\mu\text{mol/L}$	>2.5 $\mu\text{g/mL}$
Digoxin	0.64–2.6 nmol/L	0.5–2.0 ng/mL	>3.1 nmol/L	>2.4 ng/mL
Disopyramide	>7.4 $\mu\text{mol/L}$	2.5 $\mu\text{g/mL}$	20.6 $\mu\text{mol/L}$	>7 $\mu\text{g/mL}$
Doxepin and nordoxepin				
Doxepin	0.36–0.98 $\mu\text{mol/L}$	101–274 ng/mL	>1.8 $\mu\text{mol/L}$	>503 ng/mL
Nordoxepin	0.38–1.04 $\mu\text{mol/L}$	106–291 ng/mL	>1.9 $\mu\text{mol/L}$	>531 ng/mL
Ethanol				
Behavioral changes			>4.3 mmol/L	>20 mg/dL
Legal limit			≥ 17 mmol/L	≥ 80 mg/dL
Critical with acute exposure			>54 mmol/L	>250 mg/dL

(Continued)

TOXICOLOGY AND THERAPEUTIC DRUG MONITORING

DRUG	THERAPEUTIC RANGE		TOXIC LEVEL	
	SI UNITS	CONVENTIONAL UNITS	SI UNITS	CONVENTIONAL UNITS
Ethylene glycol				
Toxic			>2 mmol/L	>12 mg/dL
Lethal			>20 mmol/L	>120 mg/dL
Ethosuximide	280–700 µmol/L	40–100 µg/mL	>700 µmol/L	>100 µg/mL
Flecainide	0.5–2.4 µmol/L	0.2–1.0 µg/mL	>3.6 µmol/L	>1.5 µg/mL
Gentamicin				
Peak	10–21 µmol/mL	5–10 µg/mL	>25 µmol/mL	>12 µg/mL
Trough	0–4.2 µmol/mL	0–2 µg/mL	>4.2 µmol/mL	>2 µg/mL
Heroin (diacetyl morphine)			>700 µmol/L	>200 ng/mL (as morphine)
Ibuprofen	49–243 µmol/L	10–50 µg/mL	>97 µmol/L	>200 µg/mL
Imipramine (and metabolite)				
Desimipramine	375–1130 nmol/L	100–300 ng/mL	>1880 nmol/L	>500 ng/mL
Total Imipramine + Desimipramine	563–1130 nmol/L	150–300 ng/mL	>1880 nmol/L	>500 ng/mL
Lidocaine	5.1–21.3 µmol/L	1.2–5.0 µg/mL	>38.4 µmol/L	>9.0 µg/mL
Lithium	0.5–1.3 meq/L	0.5–1.3 meq/L	>2 mmol/L	>2 meq/L
Methadone	1.3–3.2 µmol/L	0.4–1.0 µg/mL	>6.5 µmol/L	>2 µg/mL
Methamphetamine		20–30 ng/mL		0.1–1.0 µg/mL
Methanol			>6 mmol/L	>20 mg/dL
			>16 mmol/L	>50 mg/dL: Severe toxicity
			>28 mmol/L	>89 mg/dL: Lethal
Methotrexate				
Low dose	0.01–0.1 µmol/L	0.01–0.1 µmol/L	>0.1 mmol/L	>0.1 mmol/L
High dose (24 h)	<5.0 µmol/L	<5.0 µmol/L	>5.0 µmol/L	>5.0 µmol/L
High dose (48 h)	<0.50 µmol/L	<0.50 µmol/L	>0.5 µmol/L	>0.5 µmol/L
High dose (72 h)	<0.10 µmol/L	<0.10 µmol/L	>0.1 µmol/L	>0.1 µmol/L
Morphine	35–250 µmol/L	10–70 ng/mL	180–14000 µmol/L	50–4000 ng/mL
Nitroprusside (as thiocyanate)	103–499 µmol/L	6–29 µg/mL	860 µmol/L	>50 µg/mL
Nortriptyline	190–569 nmol/L	50–150 ng/mL	>1900 nmol/L	>500 ng/mL
Phenobarbital	65–172 µmol/L	15–40 µg/mL	>215 µmol/L	>50 µg/mL
Phenytoin	40–79 µmol/L	10–20 µg/mL	>118 µmol/L	>30 µg/mL
Phenytoin, Free % Free	4.0–7.9 µg/mL 0.08–0.14	1–2 µg/mL 8–14%	>13.9 µg/mL	>3.5 µg/mL
Primidone and metabolite				
Primidone	23–55 µmol/L	5–12 µg/mL	>69 µmol/L	>15 µg/mL
Phenobarbital	65–172 µmol/L	15–40 µg/mL	>215 µmol/L	>50 µg/mL
Procainamide				
Procainamide	17–42 µmol/L	4–10 µg/mL	>51 µmol/L	>12 µg/mL
NAPA (<i>N</i> - acetylprocainamide)	22–72 µmol/L	6–20 µg/mL	>126 µmol/L	>35 µg/mL
Quinidine	>6.2–15.4 µmol/L	2.0–5.0 µg/mL	>31 µmol/L	>10 µg/mL
Salicylates	145–2100 µmol/L	2–29 mg/dL	>2172 µmol/L	>30 mg/dL
Sirolimus (trough level)				
Kidney transplant	4.4–13.1 nmol/L	4–12 ng/mL	>16 nmol/L	>15 ng/mL
Tacrolimus (FK506) (trough)				
Kidney and liver				
0–2 months posttransplant	12–19 nmol/L	10–15 ng/mL	>25 nmol/L	>20 ng/mL
>2 months posttransplant	6–12 nmol/L	5–10 ng/mL		

TABLE A-3 (CONTINUED)

DRUG	THERAPEUTIC RANGE		TOXIC LEVEL	
	SI UNITS	CONVENTIONAL UNITS	SI UNITS	CONVENTIONAL UNITS
Heart				
0–2 months posttransplant	19–25 nmol/L	15–20 ng/mL	>25 nmol/L	>20 ng/mL
3–6 months posttransplant	12–19 nmol/L	10–15 ng/mL		
>6 months posttransplant	10–12 nmol/L	8–10 ng/mL		
Theophylline	56–111 µg/mL	10–20 µg/mL	>140 µg/mL	>25 µg/mL
Thiocyanate				
After nitroprusside infusion	103–499 µmol/L	6–29 µg/mL	860 µmol/L	>50 µg/mL
Nonsmoker	17–69 µmol/L	1–4 µg/mL		
Smoker	52–206 µmol/L	3–12 µg/mL		
Tobramycin				
Peak	11–22 µg/L	5–10 µg/mL	>26 µg/L	>12 µg/mL
Trough	0–4.3 µg/L	0–2 µg/mL	>4.3 µg/L	>2 µg/mL
Valproic acid	350–700 µmol/L	50–100 µg/mL	>1000 µmol/L	>150 µg/mL
Vancomycin				
Peak	14–28 µmol/L	20–40 µg/mL	>55 µmol/L	>80 µg/mL
Trough	3.5–10.4 µmol/L	5–15 µg/mL	>14 µmol/L	>20 µg/mL

Note: SI, Système International d'Unités.

SPECIMEN	ANALYTE	REFERENCE RANGE		
		SI UNITS	CONVENTIONAL UNITS	
Aluminum	S	<0.2 µmol/L	<5.41 µg/L	
	U, random	0.19–1.11 µmol/L	5–30 µg/L	
Arsenic	WB	0.03–0.31 µmol/L	2–23 µg/L	
	U, 24 h	0.07–0.67 µmol/d	5–50 µg/d	
Cadmium	WB	<44.5 nmol/L	<5.0 µg/L	
Coenzyme Q10 (ubiquinone)	P	433–1532 µg/L	433–1532 µg/L	
B carotene	S	0.07–1.43 µmol/L	4–77 µg/dL	
Copper	S	11–22 µmol/L	70–140 µg/dL	
	U, 24 h	<0.95 µmol/d	<60 µg/d	
Folic acid	RBC	340–1020 nmol/L cells	150–450 ng/mL cells	
Folic acid	S	12.2–40.8 nmol/L	5.4–18.0 ng/mL	
Lead (adult)	S	<0.5 µmol/L	<10 µg/dL	
Mercury	WB	3.0–294 nmol/L	0.6–59 µg/L	
	U, 24 h	<99.8 nmol/L	<20 µg/L	
Selenium	S	0.8–2.0 µmol/L	63–160 µg/L	
Vitamin A	S	0.7–3.5 µmol/L	20–100 µg/dL	
Vitamin B ₁ (thiamine)	S	0–75 nmol/L	0–2 µg/dL	
Vitamin B ₂ (riboflavin)	S	106–638 nmol/L	4–24 µg/dL	
Vitamin B ₆	P	20–121 nmol/L	5–30 ng/mL	
Vitamin B ₁₂	S	206–735 pmol/L	279–996 pg/mL	
Vitamin C (ascorbic acid)	S	23–57 µmol/L	0.4–1.0 mg/dL	
Vitamin D ₃ , 1,25-dihydroxy	S	60–108 pmol/L	25–45 pg/mL	
Vitamin D ₃ , 25-hydroxy	P	Summer	37.4–200 nmol/L	15–80 ng/mL
		Winter	34.9–105 nmol/L	14–42 ng/mL
Vitamin E	S	12–42 µmol/L	5–18 µg/mL	
Vitamin K	S	0.29–2.64 nmol/L	0.13–1.19 ng/mL	
Zinc	S	11.5–18.4 µmol/L	75–120 µg/dL	

Note: P, plasma; RBC, red blood cell; S, serum; SI, Système International d'Unités; WB, whole blood; U, urine.

TABLE A-5
CLASSIFICATION OF LOW-DENSITY LIPOPROTEIN, TOTAL, AND HIGH-DENSITY LIPOPROTEIN CHOLESTEROL

LDL cholesterol, mg/dL (mmol/L)	
<70 (<1.81)	Therapeutic option for very high-risk patients
<100 (<2.59)	Optimal
100–129 (2.59–3.34)	Near optimal or above optimal
130–159 (3.36–4.11)	Borderline high
160–189 (4.14–4.89)	High
≥190 (≥4.91)	Very high
Total cholesterol, mg/dL (mmol/L)	
<200 (<5.17)	Desirable
200–239 (5.17–6.18)	Borderline high
≥240 (≥6.21)	High
HDL cholesterol, mg/dL (mmol/L)	
<40 (<1.03)	Low
≥60 (≥1.55)	High

Note: HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Source: Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 285:2486, 2001; and Grundy SM et al for the Coordinating Committee of the National Cholesterol Education Program: Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation 110:227, 2004.

TABLE A-6
CEREBROSPINAL FLUID^a

CONSTITUENT	REFERENCE RANGE	
	SI UNITS	CONVENTIONAL UNITS
Osmolarity	292–297 mmol/kg water	292–297 mosmol/L
Electrolytes		
Sodium	137–145 mmol/L	137–145 meq/L
Potassium	2.7–3.9 mmol/L	2.7–3.9 meq/L
Calcium	1.0–1.5 mmol/L	2.1–3.0 meq/L
Magnesium	1.0–1.2 mmol/L	2.0–2.5 meq/L
Chloride	116–122 mmol/L	116–122 meq/L
CO ₂ content	20–24 mmol/L	20–24 meq/L
P _{CO₂}	6–7 kPa	45–49 mmHg
pH	7.31–7.34	
Glucose	2.22–3.89 mmol/L	40–70 mg/dL
Lactate	1–2 mmol/L	10–20 mg/dL
Total protein		
Lumbar	0.15–0.5 g/L	15–50 mg/dL
Cisternal	0.15–0.25 g/L	15–25 mg/dL
Ventricular	0.06–0.15 g/L	6–15 mg/dL
Albumin	0.066–0.442 g/L	6.6–44.2 mg/dL
IgG	0.009–0.057 g/L	0.9–5.7 mg/dL
IgG index ^b	0.29–0.59	
Oligoclonal bands	<2 bands not present in matched serum sample	
Ammonia	15–47 μmol/L	25–80 μg/dL
Creatinine	44–168 μmol/L	0.5–1.9 mg/dL
Myelin basic protein	<4 μg/L	
CSF pressure		50–180 mmH ₂ O
CSF volume (adult)	~150 mL	
Red blood cells	0	0
Leukocytes		
Total	0–5 mononuclear cells per μL	0–5 mononuclear cells per mm ³
Differential		
Lymphocytes	60–70%	
Monocytes	30–50%	
Neutrophils	None	

^aBecause cerebrospinal fluid (CSF) concentrations are equilibrium values, measurements of the same parameters in blood plasma obtained at the same time are recommended. However, there is a time lag in attainment of equilibrium, and cerebrospinal levels of plasma constituents that can fluctuate rapidly (e.g., plasma glucose) may not achieve stable values until after a significant lag phase.

^bIgG index = CSF IgG(mg/dL) × serum albumin(g/dL) / Serum IgG(g/dL) × CSF albumin(mg/dL).

Note: SI, Système International d'Unités.

URINE ANALYSIS

	REFERENCE RANGE	
	SI UNITS	CONVENTIONAL UNITS
Acidity, titratable	20–40 mmol/d	20–40 meq/d
Ammonia	30–50 mmol/d	30–50 meq/d
Amylase		4–400 U/L
Amylase/creatinine clearance ratio ($[Cl_{am}/Cl_{cr}] \times 100$)	1–5	1–5
Calcium (10 meq/d or 200 mg/d dietary calcium)	<7.5 mmol/d	<300 mg/d
Creatine, as creatinine		
Women	<760 μ mol/d	<100 mg/d
Men	<380 μ mol/d	<50 mg/d
Creatinine	8.8–14 mmol/d	1.0–1.6 g/d
Eosinophils	<100,000 eosinophils/L	<100 eosinophils/mL
Glucose (glucose oxidase method)	0.3–1.7 mmol/d	50–300 mg/d
5-Hydroxyindoleacetic acid (5-HIAA)	10–47 μ mol/d	2–9 mg/d
Iodine, spot urine		
WHO classification of iodine deficiency		
Not iodine deficient	>100 μ g/L	>100 μ g/L
Mild iodine deficiency	50–100 μ g/L	50–100 μ g/L
Moderate iodine deficiency	20–49 μ g/L	20–49 μ g/L
Severe iodine deficiency	<20 μ g/L	<20 μ g/L
Microalbumin		
Normal	0.0–0.03 g/d	0–30 mg/d
Microalbuminuria	0.03–0.30 g/d	30–300 mg/d
Clinical albuminuria	>0.3 g/d	>300 mg/d
Microalbumin/creatinine ratio		
Normal	0–3.4 g/mol creatinine	0–30 μ g/mg creatinine
Microalbuminuria	3.4–34 g/mol creatinine	30–300 μ g/mg creatinine
Clinical albuminuria	>34 g/mol creatinine	>300 μ g/mg creatinine
Oxalate		
Men	80–500 μ mol/d	7–44 mg/d
Women	45–350 μ mol/d	4–31 mg/d
pH	5.0–9.0	5.0–9.0
Phosphate (phosphorus) (varies with intake)	12.9–42.0 mmol/d	400–1300 mg/d
Potassium (varies with intake)	25–100 mmol/d	25–100 meq/d
Protein	<0.15 g/d	<150 mg/d
Sediment		
Red blood cells	0–2/high power field	
White blood cells	0–2/high power field	
Bacteria	None	
Crystals	None	
Bladder cells	None	
Squamous cells	None	
Tubular cells	None	
Broad casts	None	
Epithelial cell casts	None	
Granular casts	None	
Hyaline casts	0–5/low power field	
Red blood cell casts	None	
Waxy casts	None	
White cell casts	None	
Sodium (varies with intake)	100–260 mmol/d	100–260 meq/d
Specific gravity	1.001–1.035	1.001–1.035
Urea nitrogen	214–607 mmol/d	6–17 g/d
Uric acid (normal diet)	1.49–4.76 mmol/d	250–800 mg/d

Note: SI, Système International d'Unités; WHO, World Health Organization.

TABLE A-8

DIFFERENTIAL NUCLEATED CELL COUNTS OF BONE MARROW ASPIRATES^a

	OBSERVED RANGE, %	95% CONFIDENCE INTERVALS, %	MEAN, %
Blast cells	0–3.2	0–3.0	1.4
Promyelocytes	3.6–13.2	3.2–12.4	7.8
Neutrophil myelocytes	4–21.4	3.7–10.0	7.6
Eosinophil myelocytes	0–5.0	0–2.8	1.3
Metamyelocytes	1–7.0	2.3–5.9	4.1
Neutrophils			
Men	21.0–45.6	21.9–42.3	32.1
Women	29.6–46.6	28.8–45.9	37.4
Eosinophils	0.4–4.2	0.3–4.2	2.2
Eosinophils plus eosinophil myelocytes	0.9–7.4	0.7–6.3	3.5
Basophils	0–0.8	0–0.4	0.1
Erythroblasts			
Men	18.0–39.4	16.2–40.1	28.1
Women	14.0–31.8	13.0–32.0	22.5
Lymphocytes	4.6–22.6	6.0–20.0	13.1
Plasma cells	0–1.4	0–1.2	0.6
Monocytes	0–3.2	0–2.6	1.3
Macrophages	0–1.8	0–1.3	0.4
M:E ratio			
Men	1.1–4.0	1.1–4.1	2.1
Women	1.6–5.4	1.6–5.2	2.8

^aBased on bone marrow aspirate from 50 healthy volunteers (30 men, 20 women).

Source: From Bain BJ: The bone marrow aspirate of healthy subjects. *Br J Haematol* 94(1):206, 1996.

TABLE A-9

STOOL ANALYSIS

	REFERENCE RANGE	
	SI UNITS	CONVENTIONAL UNITS
Amount	0.1–0.2 kg/d	100–200 g/24 h
Coproporphyrin	611–1832 nmol/d	400–1200 µg/24 h
Fat		
Adults		<7 g/d
Adults on fat-free diet		<4 g/d
Fatty acids	0–21 mmol/d	0–6 g/24 h
Leukocytes	None	None
Nitrogen	<178 mmol/d	<2.5 g/24 h
pH	7.0–7.5	
Occult blood	Negative	Negative
Trypsin		20–95 U/g
Urobilinogen	85–510 µmol/d	50–300 mg/24 h
Uroporphyrins	12–48 nmol/d	10–40 µg/24 h
Water	<0.75	<75%

Note: SI, Système International d'Unités.

Source: Modified from Fishbach FT, Dunning MB III: *A Manual of Laboratory and Diagnostic Tests*, 7th ed. Philadelphia, Lippincott Williams & Wilkins, 2004.

TABLE A-10

RENAL FUNCTION TESTS

	REFERENCE RANGE	
	SI UNITS	CONVENTIONAL UNITS
Clearances (corrected to 1.72 m ² body surface area)		
Measures of glomerular filtration rate		
Inulin clearance (CI)		
Men (mean ± 1 SD)	2.1 ± 0.4 mL/s	124 ± 25.8 mL/min
Women (mean ± 1 SD)	2.0 ± 0.2 mL/s	119 ± 12.8 mL/min
Endogenous creatinine clearance	1.5–2.2 mL/s	91–130 mL/min
Measures of effective renal plasma flow and tubular function		
<i>p</i> -Aminohippuric acid clearance (C _{I_{PAH}})		
Men (mean ± 1 SD)	10.9 ± 2.7 mL/s	654 ± 163 mL/min
Women (mean ± 1 SD)	9.9 ± 1.7 mL/s	594 ± 102 mL/min
Concentration and dilution test		
Specific gravity of urine		
After 12-h fluid restriction	>1.025	>1.025
After 12-h deliberate water intake	≤1.003	≤1.003
Protein excretion, urine	<0.15 g/d	<150 mg/d
Specific gravity, maximal range	1.002–1.028	1.002–1.028
Tubular reabsorption, phosphorus	0.79–0.94 of filtered load	79–94% of filtered load

Note: SI, Système International d'Unités.

TABLE A-11

CIRCULATORY FUNCTION TESTS

TEST	RESULTS: REFERENCE RANGE	
	SI UNITS (RANGE)	CONVENTIONAL UNITS (RANGE)
Arteriovenous oxygen difference	30–50 mL/L	30–50 mL/L
Cardiac output (Fick)	2.5–3.6 L/m ² of body surface area per min	2.5–3.6 L/m ² of body surface area per min
Contractility indexes		
Maximum LV $dp/dt(dp/dt)/DP$ when DP = 5.3 kPa (40 mmHg)	220 kPa/s (176–250 kPa/s) (37.6 ± 12.2)/s	1650 mmHg/s (1320–1880 mmHg/s) (37.6 ± 12.2)/s
Mean normalized systolic ejection rate (angiography)	3.32 ± 0.84 end-diastolic volumes per second	3.32 ± 0.84 end-diastolic volumes per second
Mean velocity of circumferential fiber shortening (angiography)	1.83 ± 0.56 circumferences per second	1.83 ± 0.56 circumferences per second
Ejection fraction: SV/EDV	0.67 ± 0.08 (0.55–0.78)	0.67 ± 0.08 (0.55–0.78)
End-diastolic volume	70 ± 20.0 mL/m ² (60–88 mL/m ²)	70 ± 20.0 mL/m ² (60–88 mL/m ²)
End-systolic volume	25 ± 5.0 mL/m ² (20–33 mL/m ²)	25 ± 5.0 mL/m ² (20–33 mL/m ²)
Left ventricular work		
Stroke work index	50 ± 20.0 (g.m)/m ² (30–110)	50 ± 20.0 (g.m)/m ² (30–110)
LV minute work index	1.8–6.6 [(kg.m)/m ²]/min	1.8–6.6 [(kg.m)/m ²]/min
Oxygen consumption index	110–150 mL	110–150 mL
Maximum oxygen uptake	35 mL/min (20–60 mL/min)	35 mL/min (20–60 mL/min)
Pulmonary vascular resistance	2–12 (kPa.s)/L	20–130 (dyn.s)/cm ⁵
Systemic vascular resistance	77–150 (kPa.s)/L	770–1600 (dyn.s)/cm ⁵

Note: DP, diastolic pressure; EDV, end-diastolic volume; LV, left ventricular; SI, Système International d'Unités; SV, stroke volume.

Source: Braunwald E et al: *Heart Disease*, 6th ed, Philadelphia, Saunders, 2001.

TEST	RESULTS	
	SI UNITS	CONVENTIONAL UNITS
Absorption tests		
D-Xylose: after overnight fast, 25 g xylose given in oral aqueous solution		
Urine, collected for following 5 h	25% of ingested dose	25% of ingested dose
Serum, 2 h after dose	2.0–3.5 mmol/L	30–52 mg/dL
Vitamin A: a fasting blood specimen is obtained and 200,000 U of vitamin A in oil is given PO	Serum level should increase to twice fasting level in 3–5 h	Serum level should increase to twice fasting level in 3–5 h
Bentiromide test (pancreatic function): 500 mg bentiromide (Chymex) PO; <i>p</i> -aminobenzoic acid (PABA) measured		
Plasma		>3.6 (\pm 1.1) μ g/mL at 90 min
Urine	>50% recovered in 6 h	>50% recovered in 6 h
Gastric juice volume		
Volume		
24 h	2–3 L	2–3 L
Nocturnal	600–700 mL	600–700 mL
Basal, fasting	30–70 mL/h	30–70 mL/h
Reaction		
pH	1.6–1.8	1.6–1.8
Titratable acidity of fasting juice	4–9 μ mol/s	15–35 meq/h
Acid output		
Basal		
Women (mean \pm 1 SD)	0.6 \pm 0.5 μ mol/s	2.0 \pm 1.8 meq/h
Men (mean \pm 1 SD)	0.8 \pm 0.6 μ mol/s	3.0 \pm 2.0 meq/h
Maximal (after SC histamine acid phosphate, 0.004 mg/kg body weight, and preceded by 50 mg promethazine, or after betazole, 1.7 mg/kg body weight, or pentagastrin, 6 μ g/kg body weight)		
Women (mean \pm 1 SD)	4.4 \pm 1.4 μ mol/s	16 \pm 5 meq/h
Men (mean \pm 1 SD)	6.4 \pm 1.4 μ mol/s	23 \pm 5 meq/h
Basal acid output/maximal acid output ratio	\leq 0.6	\leq 0.6
Gastrin, serum	0–200 μ g/L	0–200 pg/mL
Secretin test (pancreatic exocrine function): 1 U/kg body weight, IV		
Volume (pancreatic juice) in 80 min	>2.0 mL/kg	>2.0 mL/kg
Bicarbonate concentration	>80 mmol/L	>80 meq/L
Bicarbonate output in 30 min	>10 mmol	>10 meq

Note: SI, Système International d'Unités.

TABLE A-13

NORMAL VALUES OF DOPPLER ECHOCARDIOGRAPHIC MEASUREMENTS IN ADULTS

	RANGE	MEAN
RVD (cm), measured at the base in apical four-chamber view	2.6–4.3	3.5 ± 0.4
LVID (cm), measured in the parasternal long-axis view	3.6–5.4	4.7 ± 0.4
Posterior LV wall thickness (cm)	0.6–1.1	0.9 ± 0.4
IVS wall thickness (cm)	0.6–1.1	0.9 ± 0.4
LA dimension (cm), AP dimension	2.3–3.8	3.0 ± 0.3
Aortic root dimension (cm)	2.0–3.5	2.4 ± 0.4
Aortic cusps separation (cm)	1.5–2.6	1.9 ± 0.4
Percentage of fractional shortening	34–44%	36%
Mitral flow (m/s)	0.6–1.3	0.9
Tricuspid flow (m/s)	0.3–0.7	0.5
Pulmonary artery (m/s)	0.6–0.9	0.75
Aorta (m/s)	1.0–1.7	1.35

Note: AP, anteroposterior; IVS, interventricular septum; LA, left atrium; LV, left ventricle; LVID, left ventricular internal dimension; RVD, right ventricular dimension.

Source: From Weyman A: *Principles and Practice of Echocardiography*, 2d ed, Philadelphia, Lea & Febiger, 1994.

TABLE A-14

SUMMARY OF VALUES USEFUL IN PULMONARY PHYSIOLOGY		TYPICAL VALUES	
	SYMBOL	MAN, AGE 40 YEARS, 75 kg, 175 cm TALL	WOMAN, AGE 40 YEARS, 60 kg, 160 cm TALL
Pulmonary Mechanics			
Spirometry—volume-time curves			
Forced vital capacity	FVC	5.1 L	3.6 L
Forced expiratory volume in 1 s	FEV ₁	4.1 L	2.9 L
FEV ₁ /FVC	FEV ₁ %	80%	82%
Maximal midexpiratory flow	MMF (FEF 25–27)	4.8 L/s	3.6 L/s
Maximal expiratory flow rate	MEFR (FEF 200–1200)	9.4 L/s	6.1 L/s
Spirometry—flow-volume curves			
Maximal expiratory flow at 50% of expired vital capacity	V _{max} 50 (FEF 50%)	6.1 L/s	4.6 L/s
Maximal expiratory flow at 75% of expired vital capacity	V _{max} 75 (FEF 75%)	3.1 L/s	2.5 L/s
Resistance to airflow			
Pulmonary resistance	RL (R _L)	<3.0 (cmH ₂ O/s)/L	
Airway resistance	R _{aw}	<2.5 (cmH ₂ O/s)/L	
Specific conductance	SG _{aw}	>0.13 cmH ₂ O/s	
Pulmonary compliance			
Static recoil pressure at total lung capacity	P _{st} TLC	25 ± 5 cmH ₂ O	
Compliance of lungs (static)	CL	0.2 L cmH ₂ O	
Compliance of lungs and thorax	C(L + T)	0.1 L cmH ₂ O	
Dynamic compliance of 20 breaths/min	C _{dyn} 20	0.25 ± 0.05 L/cmH ₂ O	
Maximal static respiratory pressures			
Maximal inspiratory pressure	MIP	>90 cmH ₂ O	>50 cmH ₂ O
Maximal expiratory pressure	MEP	>150 cmH ₂ O	>120 cmH ₂ O
Lung Volumes			
Total lung capacity	TLC	6.7 L	4.9 L
Functional residual capacity	FRC	3.7 L	2.8 L
Residual volume	RV	2.0 L	1.6 L
Inspiratory capacity	IC	3.3 L	2.3 L
Expiratory reserve volume	ERV	1.7 L	1.1 L
Vital capacity	VC	5.0 L	3.4 L
Gas Exchange (Sea Level)			
Arterial O ₂ tension	Pa _{O₂}	12.7 ± 0.7 kPa (95 ± 5 mmHg)	
Arterial CO ₂ tension	Pa _{CO₂}	5.3 ± 0.3 kPa (40 ± 2 mmHg)	
Arterial O ₂ saturation	Sa _{O₂}	0.97 ± 0.02 (97 ± 2%)	
Arterial blood pH	pH	7.40 ± 0.02	
Arterial bicarbonate	HCO ₃ ⁻	24 ± 2 meq/L	
Base excess	BE	0 ± 2 meq/L	
Diffusing capacity for carbon monoxide (single breath)	DL _{CO}	0.42 mL CO/s/mmHg (25 mL CO/min/mmHg)	
Dead space volume	V _D	2 mL/kg body wt	
Physiologic dead space; dead space-tidal volume ratio	V _D /V _T		
Rest		≤35% V _T	
Exercise		≤20% V _T	
Alveolar-arterial difference for O ₂	P(A-a) _{O₂}	≤2.7 kPa ≤20 kPa (≤20 mmHg)	

TABLE A-15

BODY FLUIDS AND OTHER MASS DATA

	REFERENCE RANGE	
	SI UNITS	CONVENTIONAL UNITS
Ascitic fluid		
Body fluid		
Total volume (lean) of body weight	50–70% (in obese patients)	
Intracellular	0.3–0.4 of body weight	
Extracellular	0.2–0.3 of body weight	
Blood		
Total volume		
Men	69 mL/kg body wt	
Women	65 mL/kg body wt	
Plasma volume		
Men	39 mL/kg body wt	
Women	40 mL/kg body wt	
Red blood cell volume		
Men	30 mL/kg body wt	1.15–1.21 L/m ² of body surface area
Women	25 mL/kg body wt	0.95–1.00 L/m ² of body surface area
Body mass index	18.5–24.9 kg/m ²	18.5–24.9 kg/m ²

Note: SI, Système International d'Unités.

TABLE A-16

RADIATION-DERIVED UNITS

QUANTITY	OLD UNIT	SI UNIT	NAME FOR SI UNIT (ABBREVIATION)	CONVERSION
Activity	Curie (Ci)	Disintegrations per second (dps)	Becquerel (Bq)	1 Ci = 3.7×10^{10} Bq 1 mCi = 37 mBq 1 μ Ci = 0.037 MBq or 37 GBq 1 Bq = 2.703×10^{-11} Ci
Absorbed dose	rad	Joule per kilogram (J/kg)	Gray (Gy)	1 Gy = 100 rad 1 rad = 0.01 Gy 1 mrad = 10^{-3} cGy
Exposure	Roentgen (R)	Coulomb per kilogram (C/kg)	—	1 C/kg = 3876 R 1 R = 2.58×10^{-4} C/kg 1 mR = 258 pC/kg
Dose equivalent	Rem	Joule per kilogram (J/kg)	Sievert (Sv)	1 Sv = 100 rem 1 rem = 0.01 Sv 1 mrem = 10 μ Sv

Note: SI, Système International d'Unités.

ACKNOWLEDGMENT

The authors acknowledge the contributions of Dr. Patrick M. Sluss, Dr. James L. Januzzi, and Dr. Kent B. Lewandrowski to this chapter in previous editions of *Harrison's Principles of Internal Medicine*.

FURTHER READINGS

KRATZ A et al: Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Laboratory reference values. *N Engl J Med* 351(15):1548, 2004

LEHMAN HP, HENRY JB: SI units, in *Henry's Clinical Diagnosis and Management by Laboratory Methods*, 21st ed, RC McPherson, MR Pincus (eds). Philadelphia, Elsevier Saunders, 2007, pp 1404–1418

PESCE MA: Reference ranges for laboratory tests and procedures, in *Nelson's Textbook of Pediatrics*, 18th ed, RM Kliegman et al (eds). Philadelphia, Elsevier Saunders, 2007, pp 2943–2949

SOLBERG HE: Establishment and use of reference values, in *Tietz Textbook of Clinical Chemistry and Molecular Diagnostics*, 4th ed, CA Burtis et al (eds). Philadelphia, Elsevier Saunders, 2006, pp 425–448

REVIEW AND SELF-ASSESSMENT*

Charles Wiener ■ Gerald Bloomfield ■ Cynthia D. Brown
■ Joshua Schiffer ■ Adam Spivak

QUESTIONS

DIRECTIONS: Choose the **one best** response for each question.

1. A patient is evaluated in the emergency department for peripheral cyanosis. Which of the following is not a potential etiology?
 - A. Cold exposure
 - B. Deep venous thrombosis
 - C. Methemoglobinemia
 - D. Peripheral vascular disease
 - E. Raynaud's phenomenon
2. Which of the following associations correctly pairs clinical scenarios and community-acquired pneumonia (CAP) pathogens?
 - A. Aspiration pneumonia: *Streptococcus pyogenes*
 - B. Heavy alcohol use: atypical pathogens and *Staphylococcus aureus*
 - C. Poor dental hygiene: *Chlamydia pneumoniae*, *Klebsiella pneumoniae*
 - D. Structural lung disease: *Pseudomonas aeruginosa*, *S. aureus*
 - E. Travel to the southwestern United States: *Aspergillus* spp.
3. A 54-year-old woman presents to the hospital because of hemoptysis. She has coughed up approximately 1 teaspoon of blood every day for the past 4 days. She has a history of cigarette smoking. A chest radiogram shows diffuse bilateral infiltrates predominantly in the lower lobes. The hematocrit is 30%, and the serum creatinine is 4.0 mg/dL. Both were normal previously. Urinalysis shows 2+ protein and red blood cell casts. The presence of autoantibodies directed against which of the following is most likely to yield a definitive diagnosis?
 - A. Glomerular basement membrane
 - B. Glutamic acid decarboxylase
 - C. Phospholipids
 - D. Smooth muscle
 - E. U1 ribonucleoprotein (RNP)
4. All of the following drugs can cause eosinophilic pneumonia *except*
 - A. nitrofurantoin
 - B. sulfonamides
 - C. nonsteroidal anti-inflammatory drugs (NSAIDs)
 - D. isoniazid
 - E. amiodarone
5. A 24-year-old man presents to the emergency department complaining of shortness of breath and right-sided chest pain. The symptoms began abruptly about 2 h previously. The pain is worse with inspiration. He denies fevers and chills and has not had any leg swelling. He has no past medical history but smokes 1 pack of cigarettes daily. On physical examination, he is tachypneic with a respiratory rate of 24 breaths/min. His oxygen saturation is 94% on room air. Breath sounds are decreased in the right lung, and there is hyperresonance to percussion. A chest radiograph confirms a 50% pneumothorax of the right lung. What is the best approach for treatment of this patient?
 - A. Needle aspiration of the pneumothorax
 - B. Observation and administration of 100% oxygen
 - C. Placement of a large-bore chest tube
 - D. Referral for thoracoscopy with stapling of blebs and pleural abrasion
6. A 53-year-old woman presents to the hospital after an episode of syncope. She has ongoing lightheadedness and shortness of breath. She has a history of antiphospholipid syndrome with prior pulmonary embolism and has been nonadherent to her anticoagulation recently. She has been prescribed warfarin (7.5 mg/d) but reports taking it only intermittently. She does not know her most recent International Normalized Ratio (INR). On presentation to the emergency department, she appears diaphoretic and tachypneic. Her vital signs are blood pressure, 86/44 mmHg; heart rate, 130 bpm; respiratory rate, 30 breaths/min; and

*Questions and answers were taken from Wiener C et al (eds). *Harrison's Principles of Internal Medicine Self-Assessment and Board Review*, 17th ed. New York: McGraw-Hill, 2008.

6. (Continued)

Sa_O₂ 85% on room air. The cardiovascular examination shows a regular tachycardia without murmurs, rubs, or gallops. The lungs are clear to auscultation. On extremity examination, there is swelling of her left thigh with a positive Homan's sign. Chest CT angiography confirms a saddle pulmonary embolus with ongoing clot seen in the pelvic veins on the left. Anticoagulation with unfractionated heparin is administered. After a fluid bolus of 1 L, the patient's blood pressure remains low at 88/50 mmHg. Echocardiogram demonstrates hypokinesis of the right ventricle. On 100% nonrebreather mask, the Sa_O₂ is 92%. What is the next best step in management of this patient?

- A. Continue the current management.
- B. Continue IV fluids at 500 mL/h for a total of 4 L of fluid resuscitation.
- C. Refer the patient for inferior vena cava filter placement and continue the current management.
- D. Refer the patient for surgical embolectomy.
- E. Treat the patient with dopamine and recombinant tissue plasminogen activator (100 mg IV).

7 to 10. Among the following pulmonary function test results, pick those that are the most likely finding in each of the following respiratory disorders:

- A. Increased total lung capacity (TLC), decreased vital capacity (VC), decreased ratio of forced expiratory volume in 1 s (FEV₁) to forced vital capacity (FVC) (FEV₁/FVC ratio)
- B. Decreased TLC, decreased VC, decreased residual volume (RV), increased FEV₁/FVC ratio, normal maximum inspiratory pressure (MIP)
- C. Decreased TLC, increased RV, normal FEV₁/FVC ratio, decreased MIP
- D. Normal TLC, normal RV, normal FEV₁/FVC ratio, normal MIP

7. Myasthenia gravis

8. Idiopathic pulmonary fibrosis

9. Familial pulmonary hypertension

10. Chronic obstructive pulmonary disease

11. A 52-year-old woman presents with a community-acquired pneumonia complicated by pleural effusion.

11. (Continued)

A thoracentesis is performed, with the following results:

Appearance	Viscous, cloudy
pH	7.11
Protein	5.8 g/dL
LDH	285 IU/L
Glucose	66 mg/dL
WBC	3800/mm ³
RBC	24,000/mm ³
PMNs	93%
Gram stain	Many PMNs; no organism seen

Bacterial cultures are sent, but the results are not currently available. Which characteristic of the pleural fluid is most suggestive that the patient will require tube thoracostomy?

- A. Presence of >90% polymorphonucleocytes (PMNs)
- B. Glucose <100 mg/dL
- C. Presence of >1000 white blood cells
- D. pH <7.20
- E. Lactate dehydrogenase (LDH) >two-thirds of the normal upper limit for serum

12. A 63-year-old man with a long history of cigarette smoking comes to see you for a 4-month history of progressive shortness of breath and dyspnea on exertion. The symptoms have been indolent with no recent worsening. He denies fever, chest pain, and hemoptysis. He has a daily cough of 3–6 tablespoons of yellow phlegm. The patient says he has not seen a physician for more than 10 years. Physical examination is notable for normal vital signs, a prolonged expiratory phase, scattered rhonchi, elevated jugular venous pulsation, and moderate pedal edema. The hematocrit is 49%. Which of the following therapies is most likely to prolong his survival?

- A. Atenolol
- B. Enalapril
- C. Oxygen
- D. Prednisone
- E. Theophylline

13. A 23-year-old man is climbing Mount Kilimanjaro. He has no medical problems and takes no medications. Shortly after beginning the climb, he develops severe shortness of breath. Physical examination shows diffuse bilateral inspiratory crackles. Which of the following is the most likely etiology?

13. (*Continued*)
- Acute interstitial pneumonitis
 - Acute respiratory distress syndrome
 - Cardiogenic shock
 - Community-acquired pneumonia
 - High-altitude pulmonary edema
14. Which of the following statements about this condition is true?
- Acetazolamide is indicated for the treatment of this disorder.
 - Older patients are more at risk for this disorder than are younger patients because hypoxic vasoconstriction is more pronounced as patients age.
 - Oxygen is an ineffective therapy for this disorder.
 - Persons who live at high altitudes are not at risk for this disorder even when they return to a high altitude after time spent at sea level.
 - Prevention can be achieved by means of gradual ascent.
15. A 35-year-old man is seen in the clinic for evaluation of infertility. He has never fathered any children, and after 2 years of unprotected intercourse, his wife has not achieved pregnancy. Sperm analysis shows a normal number of sperm, but they are immotile. His medical history is notable for recurrent sinopulmonary infections, and the patient recently was told that he has bronchiectasis. Chest radiography is likely to show which of the following?
- Bihilar lymphadenopathy
 - Bilateral upper lobe infiltrates
 - Normal findings
 - Situs inversus
 - Water balloon-shaped heart
16. A 68-year-old woman presents to the emergency department complaining of dyspnea. She has developed progressive shortness of breath over the past 2 weeks. She has a slight dry cough and a right-sided pleuritic chest pain. There have been no associated fevers or chills. She smokes a pack of cigarettes daily and has done so since 18 years of age. On physical examination, she appears dyspneic at rest. Her vital signs are blood pressure, 138/86 mmHg; heart rate, 92 bpm; temperature, 37.1°C; respiratory rate, 24 breaths/min; and SaO_2 , 94% on room air. There is dullness to percussion halfway up her right lung field with decreased tactile fremitus. Breath sounds are decreased without egophony. The examination is otherwise normal. A chest radiograph shows a large
16. (*Continued*) free-flowing pleural effusion on the right and also suggests mediastinal lymphadenopathy. The patient undergoes thoracentesis, and 1500 mL of bloody-appearing fluid is removed. The results of the pleural fluid are pH, 7.46; red blood cell count, too numerous to count; hematocrit, 3%; white blood cell count, 230/ μL (85% lymphocytes, 10% neutrophils, 5% mesothelial cells); protein, 4.6 g/dL; lactate dehydrogenase (LDH), 340 U/L; and glucose, 35 mg/dL. The corresponding values in the serum are protein, 6.8 g/dL; LDH, 360 U/L; and glucose, 115 mg/dL. A chest CT performed after the thoracentesis shows residual moderate pleural effusion with collapse of the right lower lobe and enlarged mediastinal lymph nodes. Which of the following tests is most likely to yield the cause of the pleural effusion?
- Mammography
 - Mediastinoscopy
 - Pleural fluid cytology
 - Pleural fluid culture
 - Thoracoscopic biopsy of the pleura
17. Which of the following conditions would be expected to increase the residual volume (RV) of the lung?
- Bacterial pneumonia
 - Cryptogenic organizing pneumonia
 - Emphysema
 - Idiopathic pulmonary fibrosis
 - Obesity
18. Match the following vasopressors with the statement that best describes their action on the cardiovascular system.
- Dobutamine
 - Low-dose dopamine (2–4 $\mu\text{g}/\text{kg}$ per min)
 - Norepinephrine
 - Phenylephrine
- Acts solely at α -adrenergic receptors to cause vasoconstriction
 - Acts at β_1 -adrenergic receptors and dopaminergic receptors to increase cardiac contractility and heart rate. It also causes vasodilatation and increased splanchnic and renal blood flow.
 - Acts at β_1 - and, to a lesser extent, β_2 -adrenergic receptors to increase cardiac contractility, heart rate, and vasodilatation
 - Acts at α and β_1 -adrenergic receptors to increase heart rate, cardiac contractility, and vasoconstriction

19. What sleep disorder is depicted in the graphic below (Fig. 19)?

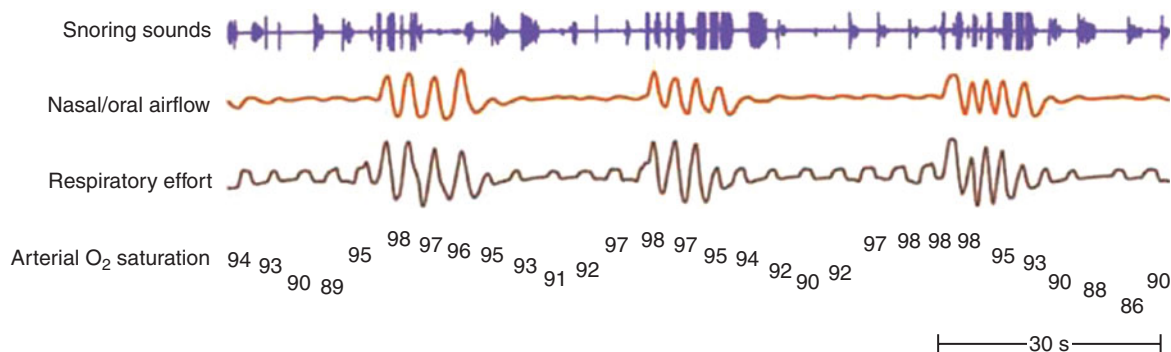


FIGURE 19

- A. Cheyne–Stokes respiration
 B. Central sleep apnea
 C. Obstructive sleep apnea
 D. Periodic limb movement disorder of sleep
20. A 42-year-old man presents with progressive dyspnea on exertion, low-grade fevers, and weight loss over 6 months. He also is complaining of a primarily dry cough, although occasionally he coughs up a thick, mucoid sputum. There is no past medical history. He does not smoke cigarettes. On physical examination, the patient appears dyspneic with minimal exertion. The patient's temperature is 37.9°C (100.3°F). Oxygen saturation is 91% on room air at rest. Faint basilar crackles are heard. On laboratory studies, the patient has polyclonal hypergammaglobulinemia and a hematocrit of 52%. A CT scan reveals bilateral alveolar infiltrates that are primarily perihilar in nature with a mosaic pattern. The patient undergoes bronchoscopy with bronchoalveolar lavage. The effluent appears milky. The cytopathology shows amorphous debris with periodic acid–Schiff (PAS)–positive macrophages. What is the diagnosis?
- A. Bronchiolitis obliterans organizing pneumonia
 B. Desquamative interstitial pneumonitis
 C. Nocardiosis
 D. *Pneumocystis carinii* pneumonia
 E. Pulmonary alveolar proteinosis
21. What treatment is most appropriate at this time?
- A. Prednisone and cyclophosphamide
 B. Trimethoprim-sulfamethoxazole
 C. Prednisone
 D. Whole-lung saline lavage
 E. Doxycycline
22. An 86-year-old nursing home resident is brought by ambulance to the local emergency department (ED). He was found unresponsive in his bed, and 911 was called. Apparently, he had been coughing and complaining of chills for the past few days; no further history is available from the nursing home staff. His medical history is remarkable for Alzheimer's dementia and treated prostate cancer. The emergency responders were able to appreciate a faint pulse and obtained a blood pressure of 91/49 mmHg and a heart rate of 120 bpm. In the emergency room his blood pressure is 88/51 mmHg, and his heart rate is 131 bpm. He is moaning and obtunded, localizes to pain, and has flat neck veins. Skin tenting is noted. A peripheral IV line is placed, specimens for initial laboratory testing are sent off, and an electrocardiogram and chest x-ray are obtained. An anesthesiologist has been called to the bedside and is assessing the patient's airway. What is the best immediate step in management?
- A. Infuse hypertonic saline to increase the rate of vascular filling.
 B. Infuse isotonic crystalloid solution via wide open IV.
 C. Initiate IV pressors starting with Levophed.
 D. Infuse a colloidal solution rapidly.
 E. Transfuse packed red blood cells (pRBCs) until hemoglobin is >10 g/dL.
23. Which of the following is true regarding hypovolemic shock?
- A. Loss of 20–40% of the blood volume leads to shock physiology.
 B. Loss of <20% of the blood volume will manifest as orthostasis.
 C. Oliguria is a crucial prognostic sign of impending vascular collapse.
 D. Symptoms of hypovolemic shock differ from those of hemorrhagic shock.
 E. The first sign of hypovolemic shock is mental obtundation.

24. A 24-year-old woman is brought to the emergency department (ED) after attempting suicide with an overdose of heroin. On arrival at the ED, in Jacksonville, FL, she is obtunded and has a respiratory rate of 6 breaths/min. She is hypotensive with a blood pressure of 84/60 mmHg and a heart rate of 80 bpm. Her oxygen saturation is 70% on room air. An arterial blood gas is performed showing the following: pH, 7.09; PaCO₂, 80 mmHg; PaO₂, and 42 mmHg. Which of the following statements is true regarding the patient's arterial blood gas?
- A. The patient is hypoxic because of hypoventilation with an increased A-a (alveolar-arterial) gradient.
 - B. The patient is hypoxic because of hypoventilation with a normal A-a gradient.
 - C. The patient is hypoxic because of shunt with an increased A-a gradient.
 - D. The patient is hypoxic because of ventilation/perfusion (V/Q) mismatch with an increased A-a gradient.
25. A 49-year-old woman is admitted for an evaluation of weakness. She complains of fatigue with repetitive muscle use, with significant fatigue and dysphagia by the end of the day. Her activities have been significantly limited because of her fatigue, and she has significant orthopnea. During her evaluation, laboratory analysis reveals sodium, 137 meq/L; potassium, 3.8 meq/L; chloride, 94 meq/L; and bicarbonate, 31 meq/L. An arterial blood gas shows a pH of 7.33, PaCO₂ of 60 mmHg, and PaO₂ of 65 mmHg. A chest x-ray is interpreted as "poor inspiratory effort." The oxygen saturation is 92% on room air. A ventilation/perfusion scan has normal perfusion. Which of the following tests will most likely identify the cause of this patient's respiratory acidosis?
- A. CT scan of the brain
 - B. Diffusing capacity for carbon monoxide
 - C. Esophagoscopy
 - D. Forced vital capacity (supine and upright)
 - E. Pulmonary angiogram
26. The most common cause of a pleural effusion is
- A. Cirrhosis
 - B. Left ventricular failure
 - C. Malignancy
 - D. Pneumonia
 - E. Pulmonary embolism
27. A 52-year-old man presents with crushing substernal chest pain. He has a history of coronary artery disease and has had two non-ST-elevation myocardial
27. (Continued)
infarctions in the past 5 years, both requiring percutaneous intervention and intracoronary stent placement. His electrocardiogram shows ST elevations across the precordial leads, and he is taken emergently to the catheterization laboratory. After angioplasty and stent placement, he is transferred to the coronary care unit. His vital signs are stable on transfer; however, 20 min after arrival, he is found to be unresponsive. His radial pulse is thready, extremities are cool, and blood pressure is difficult to obtain; with a manual cuff, it is 65/40 mmHg. The nurse turns to you and asks what you would like to do next. Which of the following accurately represents the physiologic characteristics of this patient's condition?
28. A 19-year-old normal nonsmoking woman has a moderately severe pulmonary embolism while on oral contraceptive pills. Which of the following is the most likely predisposing factor?
- A. Abnormal factor V
 - B. Abnormal protein C
 - C. Diminished protein C level
 - D. Diminished protein S level
 - E. Diminished antithrombin III level
29. A 22-year-old man has cystic fibrosis. He currently is hospitalized about three times yearly for infectious exacerbations. He is colonized with *Pseudomonas aeruginosa* and *Staphylococcus aureus* but has never had *Burkholderia cepacia* complex. He remains active and is in college studying architecture. He requires 2 L of oxygen with exertion. The most recent pulmonary function tests demonstrate a forced expiratory volume in 1 s (FEV₁) that is 28% of the predicted value and an FEV₁/FVC (forced vital capacity) ratio of 44%. Measurement of his arterial blood gas on room air show a pH of 7.38, PaCO₂ of 46 mmHg, and PaO₂ of 62 mmHg. Which of these characteristics is an indication for referral for lung transplantation?
- A. Colonization with *P. aeruginosa*
 - B. FEV₁ <30% predicted
 - C. FEV₁/FVC ratio <50%
 - D. PaCO₂ >40 mmHg
 - E. Use of oxygen with exertion
30. A 42-year-old woman presents to the emergency department (ED) with acute onset of shortness of breath. She recently had been to visit her parents out of state and rode in a car for about 9 h each way. Two days ago, she developed a mild calf pain and swelling, but she thought that this was not

30. (Continued)

unusual after having been sitting with her legs dependent for the recent trip. On arrival to the ED, she is noted to be tachypneic. The vital signs are blood pressure, 98/60 mmHg; heart rate, 114 bpm; respiratory rate, 28 breaths/min; Sa_O₂, 92% on room air; and weight, 89 kg. Her lungs are clear bilaterally. There is pain in the right calf with dorsiflexion of the foot, and the right leg is more swollen than the left. An arterial blood gas measurement shows a pH of 7.22, Pa_{CO}₂ of 18 mmHg, and Pa_O₂ of 68 mmHg. Kidney and liver function are normal. A helical CT scan is performed using shielding of the uterus and confirms a pulmonary embolus. All of the following agents can be used alone as initial therapy in this patient *except*

- A. Enoxaparin, 1 mg/kg SC twice daily
- B. Fondaparinux, 7.5 mg SC once daily
- C. Tinzaparin, 175 units/kg SC once daily
- D. Unfractionated heparin (UFH) IV adjusted to maintain activated partial thromboplastin time (aPTT) two to three times the upper limit of normal
- E. Warfarin, 7.5 mg PO once daily to maintain INR at 2–3

31. Which of the following contacts with a patient infected with tuberculosis is most likely to develop the disease?

- A. The child of a parent with smear-negative, culture-positive pulmonary tuberculosis
- B. The coworker in a small office of a patient with laryngeal tuberculosis
- C. The HIV-negative partner of an HIV-infected patient with pulmonary tuberculosis
- D. The parent of a young child in diapers with renal tuberculosis
- E. The spouse of a patient with miliary tuberculosis

32. A 32-year-old man is brought to the emergency department after developing sudden-onset shortness of breath and chest pain while coughing. He reports a 3-month history of increasing dyspnea on exertion, nonproductive cough, and anorexia with 15 lb of weight loss. He has no past medical history and takes no medications. The patient smokes one or two packs of cigarettes a day, uses alcohol socially, and has no risk factors for HIV infection. A chest radiogram shows a right 80% pneumothorax, and there are nodular infiltrates in the left base that spare the costophrenic angle. After placement of a chest tube, a chest CT shows bilateral small nodular opacities in the lung bases and multiple small cystic spaces in the lung apex. Which of the following interventions is most likely to improve the symptoms and radiograms?

32. (Continued)

- A. IV α_1 antitrypsin
- B. Isoniazid, rifampin, ethambutol, and pyrazinamide
- C. Prednisone and cyclophosphamide
- D. Smoking cessation
- E. Trimethoprim-sulfamethoxazole

33. A 68-year-old man presents for evaluation of dyspnea on exertion. He states that he first noticed the symptoms about 3 years ago. At that time, he had to stop walking the golf course and began to use a cart, but he was still able to complete a full 18 holes. Over the past year, he has stopped golfing altogether because of breathlessness and states that he has difficulty walking to and from his mailbox, which is about 50 yards (46 m) from his house. He also has a dry cough that occurs on most days. It is not worse at night, and he can identify no triggers. He denies wheezing. He has had no fevers, chills, or weight loss. He denies any joint symptoms. He is a former smoker of about 50 pack-years, but he quit 8 years previously after being diagnosed with coronary artery disease. In addition to coronary artery disease, he also has benign prostatic hypertrophy for which he takes tamsulosin. His other medications include aspirin, atenolol, and simvastatin. On physical examination, he appears breathless after walking down the hallway to the examination room, but he quickly recovers upon resting. Vital signs are blood pressure, 118/67 mmHg; heart rate, 88 bpm; respiratory rate, 20 breaths/min; and Sa_O₂, 94% at rest decreasing to 86% after ambulating 300 ft (91 m). His lung examination shows normal percussion and expansion. There are Velcro-like crackles at both bases, and they are distributed halfway through both lung fields. No wheezing is noted. The cardiovascular examination is normal. Digital clubbing is present. A chest CT is performed and is shown in **Fig. 33**. He is referred



FIGURE 33

33. (Continued)
for surgical lung biopsy. Which statement below is most typical of the pathology seen in this disease?
- Dense amorphous fluid within the alveoli diffusely that stains positive with periodic acid-Schiff stain
 - Destruction of alveoli with resultant emphysematous areas, predominantly in the upper lobes
 - Diffuse alveolar damage
 - Formation of noncaseating granulomas
 - Heterogeneous collagen deposition with fibroblast foci and honeycombing
34. A 68-year-old woman has been receiving mechanical ventilation for 10 days for community-acquired pneumonia. You are attempting to decide whether the patient is appropriate for a spontaneous breathing trial. Which of the following factors would indicate that the patient is not likely to be successfully extubated?
- Alert mental status
 - Positive end-expiratory pressure (PEEP) of 5 cmH₂O
 - pH >7.35
 - Rapid shallow breathing index (respiratory rate/tidal volume) >105
 - Sa_{O₂} >90% on Fi_{O₂} <0.5
35. A 34-year-old man presents for evaluation of a cough that has been persistent for the past 3 months. He recalls having an upper respiratory tract infection before the onset of cough with complaints of rhinitis, sore throat, and low-grade fever. After these symptoms resolved, he states that “the cold moved to my chest” about 10 days later. He reports severe coughing episodes that have been associated with posttussive emesis in the past, but these are less frequent now. His biggest complaint has been coughing that awakens him from sleep at night and ultimately has resulted in progressive fatigue. He denies wheezing. Specific triggers for his cough include eating cold foods, especially ice cream. He has no history of asthma or prior history of prolonged cough. He denies symptoms of gastroesophageal reflux disease. He breathes easily through his nose and does not have seasonal rhinitis. He has no past medical history. He works as an accountant in a new office building. He does not have any fume exposure. He does not smoke or drink alcohol. He has no pets. He does not recall his vaccination history but thinks he has not had any vaccinations since graduating from high school. On physical examination, he appears well. He is speaking in full sentences. He is 190 cm tall and weighs 95.5 kg. His temperature is
35. (Continued)
37.5°C, respiratory rate of 14 breaths/min, heart rate is 64 bpm, and blood pressure is 112/72 mmHg. His oxygen saturation is 97% on room air at rest. Head, eyes, ears, nose, and throat examination reveals no enlargement of the nasal turbinates, with open nasal passages. The airway is Mallampati class I without cobblestoning or erythema. The lung examination is clear to auscultation. No forced expiratory wheezes are present. The cardiac, gastrointestinal, extremity, and neurologic examinations are normal. His peak expiratory flow rate is 650 L/min. The forced expiratory volume in 1 s (FEV₁) is 4.86 L (96% predicted) and forced vital capacity (FVC) is 6.26 (99% predicted). The FEV₁/FVC ratio is 78%. Which test is most likely to establish the diagnosis correctly?
- 24-h pH probe
 - Bordetella pertussis* IgG and IgA levels
 - Methacholine challenge testing
 - Peak expiratory flow monitoring in the workplace
 - Skin testing for allergens
36. A 45-year-old man is evaluated in the clinic for asthma. His symptoms began 2 years ago and are characterized by an episodic cough and wheezing that responded initially to inhaled bronchodilators and inhaled corticosteroids but now require nearly constant prednisone tapers. He notes that the symptoms are worst on weekdays, but he cannot pinpoint specific triggers. His medications are an albuterol metered-dose inhaler (MDI), a fluticasone MDI, and prednisone (10 mg/d PO). The patient has no habits and works as a textile worker. Physical examination is notable for mild diffuse polyphonic expiratory wheezing but no other abnormality. Which of the following is the most appropriate next step?
- Exercise physiology testing
 - Measurement of forced expiratory volume in 1 s (FEV₁) before and after work
 - Methacholine challenge testing
 - Skin testing for allergies
 - Sputum culture for *Aspergillus fumigatus*
37. A 46-year-old man is brought to your office by his wife. He is reluctant to admit that he has any health problems. His wife, on the other hand, is adamant that something be done about his sleepiness. He admits that he is frequently sleepy at work and falls asleep while watching television at night, but he attributes this to stress on the job. His wife

37. (Continued)

describes loud snoring at night that begins almost immediately when he falls asleep, punctuated by long periods of no breathing at all. She believes that neither of them is getting enough sleep. On examination, he is a pleasant, obese man in no distress. He is 178 cm tall and weighs 111 kg. His blood pressure is elevated at 146/92 mmHg. He has a normal oropharynx and a short, squat neck. His lung sounds are clear, and he has a protuberant, obese abdomen. Pulses are intact. After completing the physical examination, the patient's wife demands to know what is wrong and what you are going to do about it. What are the next steps in diagnosis and treatment?

- A. He and his wife should be reassured that his symptoms will improve as his work stress lessens.
- B. He meets clinical criteria for obstructive sleep apnea (OSA) and should be referred for surgery.
- C. He should be prescribed a therapeutic trial of modafinil.
- D. He should be started on low-dose continuous-positive airway pressure (CPAP) ventilation at home.
- E. He should undergo polysomnography, potentially followed by a CPAP trial.

38. A 34-year-old woman seeks evaluation for a complaint of cough and dyspnea on exertion that has gradually worsened over 3 months. The patient has no past history of pulmonary complaints and has never had asthma. She started working in a pet store approximately 6 months ago. Her duties there include cleaning the reptile and bird cages. She reports occasional low-grade fevers but has had no wheezing. The cough is dry and nonproductive. Before 3 months ago, the patient had no limitation of exercise tolerance, but now she reports that she gets dyspneic climbing two flights of stairs. On physical examination, the patient appears well. She has an oxygen saturation of 95% on room air at rest but desaturates to 91% with ambulation. Temperature is 37.7°C (99.8°F). The pulmonary examination is unremarkable. No clubbing or cyanosis is present. The patient has a normal chest radiogram. A high-resolution chest CT shows diffuse ground-glass infiltrates in the lower lobes with the presence of centrilobular nodules. A transbronchial biopsy shows an interstitial alveolar infiltrate of plasma cells, lymphocytes, and occasional eosinophils. There are also several loose noncaseating granulomas. All cultures are negative for bacterial, viral, and fungal pathogens. What is the diagnosis?

- A. Sarcoidosis
- B. Psittacosis

38. (Continued)

- C. Hypersensitivity pneumonitis
- D. Nonspecific interstitial pneumonitis related to collagen vascular disease
- E. Aspergillosis

39. What treatment do you recommend?

- A. Glucocorticoids
- B. Doxycycline
- C. Glucocorticoids plus azithioprine
- D. Glucocorticoids plus removal of antigen
- E. Amphotericin

40. A 71-year-old man presents with complaints of cough and sputum production. He describes coughing up a small amount of blood occasionally. He states that his symptoms have worsened over a period of years, and he now gets winded going up one flight of stairs. He has a distant history of treated tuberculosis and has been treated for community-acquired pneumonia two to three times per year for the past several years. He received a flu vaccination this fall. He has never smoked. On examination, his respirations are 16 breaths/min and regular. He has scattered rhonchi and faint expiratory wheezes bilaterally on auscultation. He is not using accessory muscles to breathe. You suspect that this patient may have bronchiectasis to explain his recurrent infections. Which of the following is true regarding making this diagnosis?

- A. Bronchiectasis cannot be diagnosed in the setting of an acute pulmonary infection.
- B. Bronchoscopy is required to definitively diagnose bronchiectasis.
- C. Chest x-ray demonstrating honeycombing pattern will make the diagnosis.
- D. High-resolution chest CT scan is the preferred confirmatory test for bronchiectasis.
- E. Physical examination is sufficient to diagnose bronchiectasis in a patient with this history.

41. All of the following are pulmonary manifestations of systemic lupus erythematosus (SLE) *except*

- A. Pleuritis
- B. Progressive pulmonary fibrosis
- C. Pulmonary hemorrhage
- D. Diaphragmatic dysfunction with loss of lung volumes
- E. Pulmonary vascular disease

42. Which of the following is the most appropriate therapy for a 60-year-old man with 2 weeks of productive cough, fever, shortness of breath, and the chest radiogram as shown in [Fig. 42](#)?

42. (Continued)

- A. Cephalexin
- B. Ciprofloxacin
- C. Clindamycin
- D. Penicillin
- E. Vancomycin

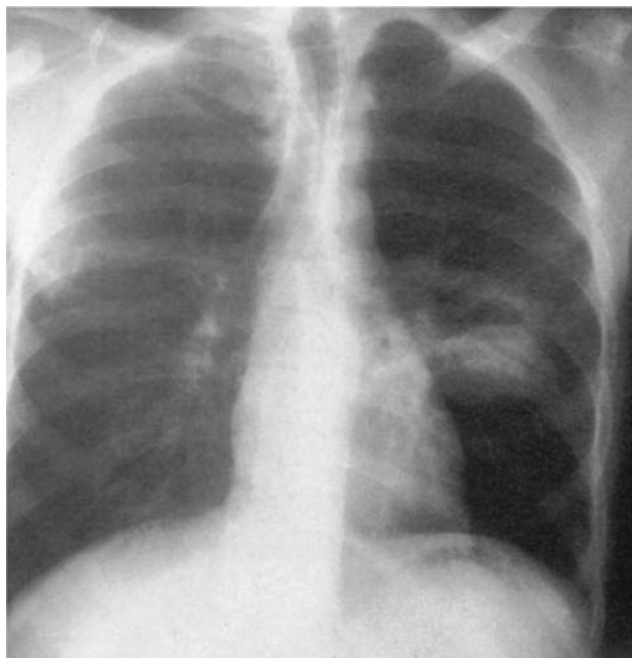


FIGURE 42

43. In the first year after lung transplant, which of the following is the most common cause of mortality?

- A. Acute rejection
- B. Bronchiolitis obliterans
- C. Infection
- D. Posttransplant lymphoproliferative disorder
- E. Primary graft failure

44. A 52-year-old alcoholic man presents to a local emergency department with purulent, productive cough, shortness of breath, right-sided chest pain, and fever. He thinks his symptoms started a few days ago. On examination, he has a temperature of 38.8°C, heart rate of 96 bpm, respirations of 22 breaths/min, oxygen saturation of 85% on room air, and a blood pressure of 115/92 mmHg. He has poor dentition and fetid breath. There is dullness to percussion over the right lower lung field, and rales are auscultated bilaterally. A chest radiograph shows a right-sided opacity in the superior portion of the right lower lobe with an air-fluid level present. There appears to be right-sided parenchymal consolidation as well. Which of the following is the most likely etiologic organism based on this presentation?

44. (Continued)

- A. *Candida glabrata*
- B. Influenza virus
- C. *Mycobacterium tuberculosis*
- D. *Peptostreptococcus*
- E. *Streptococcus pneumoniae*

45. A 45-year-old woman is seen in the clinic for evaluation of a chronic cough. She reports a cough that began in her early twenties that is occasionally productive of yellow or green thick sputum. She has been treated with innumerable courses of antibiotics, all with brief improvements in the symptoms. The patient has been told that she has asthma, and her only medications are fluticasone and albuterol metered-dose inhalers (MDIs). Physical examination is notable for normal vital signs and an oxygen saturation of 92% on room air. The patient's lungs have dullness in the upper lobes bilaterally and diffuse expiratory wheezing. She has mild digital clubbing. The remainder of the physical examination is normal. Pulmonary function testing shows airflow obstruction. Review of the sputum culture data shows that she has had multiple positive cultures for *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Posteroanterior (PA) and lateral chest radiography show bilateral upper lobe infiltrates. Which of the following tests is the most important first step in diagnosing the underlying disease?

- A. Chest CT
- B. Bronchoscopy with transbronchial biopsy
- C. Sweat chloride testing
- D. Blood polymerase chain reaction (PCR) for $\Delta F508$ mutation
- E. Sputum cytology

46. A 23-year-old hospital worker is evaluated for a known contact with a patient with active tuberculosis. One year ago his intermediate-strength purified protein derivative (PPD) had 3 mm of induration; now it has 13 mm of induration at 48 h. He has no significant past medical history and is on no medications. Subsequent management should include

- A. Chest radiography
- B. Isoniazid 300 mg/d for 3 months
- C. Measurement of baseline liver function tests
- D. Measurement of liver function tests every 3 months
- E. Repeated intermediate-strength PPD testing in 2 weeks

47. A 72-year-old man with a long history of tobacco use is seen in the clinic for 3 weeks of progressive dyspnea on exertion. He has had a mild nonproductive cough and anorexia but denies fevers, chills, and

47. (*Continued*)
sweats. On physical examination, he has normal vital signs and normal oxygen saturation on room air. Jugular venous pressure is normal, and cardiac examination shows decreased heart sounds but no other abnormality. The trachea is midline, and there is no associated lymphadenopathy. On pulmonary examination, the patient has dullness over the left lower lung field, decreased tactile fremitus, decreased breath sounds, and no voice transmission. The right lung examination results are normal. After obtaining chest plain film, appropriate initial management at this point would include which of the following?
- IV antibiotics
 - Thoracentesis
 - Bronchoscopy
 - Deep suctioning
 - Bronchodilator therapy
48. Which of the following is the most common underlying medical condition of patients undergoing lung transplantation?
- Chronic obstructive pulmonary disease (COPD)
 - Cystic fibrosis
 - Idiopathic pulmonary fibrosis (IPF)
 - Pulmonary hypertension
 - Sarcoidosis
49. A 34-year-old woman complains of cough productive of green sputum, malaise, and headache over the past week. She notes that two of her children recently had colds, and she thought she caught it from one of them. She smokes two packs of cigarettes a day. On examination, she is afebrile, with a heart rate of 125 bpm and respiratory rate of 32 breaths/min. Oxygen saturation is 94% on room air. She has pronounced use of her accessory respiratory musculature. Physical examination reveals diffuse expiratory wheezing on auscultation of the lungs. There are no areas of bronchophony or egophony. In the proper clinical context, which of the following is necessary to diagnose community-acquired pneumonia (CAP)?
- Abnormal white blood cell (WBC) count
 - Bronchial breath sounds
 - Elevated measures of inflammation (erythrocyte sedimentation rate, C-reactive protein)
 - Infiltrate on chest radiography
 - Supportive microbiologic data
50. (*Continued*)
pulmonary hypertension. She was cytomegalovirus (CMV) seropositive and received CMV prophylaxis immediately after the transplant. On postoperative day 7, she develops a fever and a new infiltrate in the right lung. Which of the following organisms is most likely to be the causative agent of these findings?
- Cytomegalovirus
 - Listeria monocytogenes*
 - Nocardia asteroides*
 - Pneumocystis carinii*
 - Pseudomonas aeruginosa*
51. Patients with chronic hypoventilation disorders often complain of a headache upon waking. What is the cause of this symptom?
- Arousals from sleep
 - Cerebral vasodilation
 - Cerebral vasoconstriction
 - Polycythemia
 - Nocturnal microaspiration and cough
52. Secondhand tobacco smoke has been associated with which of the following?
- Increased risk of lung cancer
 - Increased prevalence of respiratory illness
 - Excess cardiac mortality
 - A and B
 - A, B, and C
53. All of the following are factors that are related to the increased incidence of sepsis in the United States *except*
- Aging of the population
 - Increased longevity of individuals with chronic disease
 - Increased risk of sepsis in individuals without comorbidities
 - Increased risk of sepsis in individuals with AIDS
 - Increased use of immunosuppressive drugs
54. A 28-year-old man comes to the emergency department with complaints of 1–2 days of fever, malaise, cough, green sputum production, and dyspnea. He is a cigarette smoker and works in a restaurant. He has no significant past medical history and takes no medications. He is uncomfortable but alert with temperature of 39.2°C, respiratory rate of 28 breaths/min, blood pressure of 110/70 mmHg, heart rate of 105 bpm, and Sa_O₂ on room air of 94%. His chemistry studies are normal. His white blood cell (WBC) count is 15,500/μL. There are bronchial breath sounds in the right lower lobe, and

54. (Continued)
chest radiography shows consolidation in that area. Which of the following is the most appropriate antibiotic therapy?
- A. Azithromycin
 - B. Ceftriaxone plus clarithromycin
 - C. Fluconazole
 - D. Piperacillin/tazobactam
 - E. Vancomycin
55. A 68-year-old woman comes to the emergency department with complaints of 3 days of fever, malaise, cough with green sputum, dyspnea, and right lower chest pain that is worse on inspiration. She is a smoker of 1 pack of cigarettes a day and works in a retail store. Her only medication is hydrochlorothiazide for hypertension. She is alert but in mild respiratory distress. Her temperature is 39.2°C, respiratory rate 32 breaths/min, blood pressure is 110/70 mmHg, heart rate is 105 bpm, and Sa_O₂ on room air is 91%. Her chemistry studies show a serum glucose of 140 mg/dL and a blood urea nitrogen (BUN) of 32 mg/dL. Her white blood cell (WBC) count is 12,500/μL with a left shift. There are bronchial breath sounds in the right lower lobe, and chest radiography shows consolidation in the right and left lower lobes. Which of the following is the most appropriate antibiotic therapy?
- A. Azithromycin
 - B. Ceftriaxone plus clarithromycin
 - C. Fluconazole
 - D. Piperacillin/tazobactam
 - E. Vancomycin
56. A 45-year-old woman with HIV is admitted to the intensive care unit with pneumonia secondary to *Pneumocystis jiroveci*. She requires mechanical ventilatory support. The ventilator settings are: PC mode; inspiratory pressure, 30 cmH₂O; Fi_O₂, 1.0; and positive end-expiratory pressure (PEEP), 10 cmH₂O. An arterial blood gas measured on these settings shows pH, 7.32; Pa_{CO}₂, 46 mmHg; and Pa_O₂, 62 mmHg. All of the following are important supportive measures for this patient *except*
- A. Frequent ventilator circuit changes
 - B. Gastric acid suppression
 - C. Nutritional support
 - D. Prophylaxis against deep venous thrombosis
 - E. Sedation and analgesia to maintain patient comfort
57. A 68-year-old woman is brought to the emergency department for fever and lethargy. She first felt ill yesterday and experienced generalized body aches. Overnight, she developed a fever of 39.6°C and had shaking chills. By this morning, she was feeling very fatigued. Her son believes that she has had periods of waxing and waning mental status. She denies cough, nausea, vomiting, diarrhea, and abdominal pain. She has a past medical history of rheumatoid arthritis. She takes prednisone 5 mg daily, and methotrexate, 15 mg weekly. On examination, she is lethargic but appropriate. Her vital signs are blood pressure, 85/50 mmHg; heart rate, 122 bpm; temperature, 39.1°C; respiratory rate, 24 breaths/min; and Sa_O₂, 97% on room air. Physical examination shows clear lung fields and a regular tachycardia without murmur. There is no abdominal tenderness or masses. Stool is negative for occult blood. There are no rashes. Hematologic studies show a white blood cell count of 24,200/μL with a differential of 82% polymorphonuclear leukocytes, 8% band forms, 6% lymphocytes, 3% monocytes. Hemoglobin is 8.2 g/dL. A urinalysis has numerous white blood cells with gram-negative bacteria on Gram stain. Chemistries reveal the following: bicarbonate, 16 meq/L; blood urea nitrogen, 60 mg/dL; and creatinine, 2.4 mg/dL. After fluid administration of 2 L, the patient has a blood pressure of 88/54 mmHg and a heart rate of 112 bpm with a central venous pressure of 18 cmH₂O. There is 25 mL of urine output in the first hour. The patient has been initiated on antibiotics with ciprofloxacin. What should be done next for the treatment of this patient's hypotension?
- A. Dopamine, 3 μg/kg per minute IV
 - B. Hydrocortisone, 50 mg IV every 6 h
 - C. Norepinephrine, 2 μg/min IV
 - D. Ongoing colloid administration at 500–1000 mL/h
 - E. Transfusion of 2 units packed red blood cells
57. (Continued)
58. All of the following statements about the epidemiology and pathogenesis of sepsis and septic shock are true *except*
- A. Blood cultures are positive in only 20–40% of cases of severe sepsis.
 - B. Microbial invasion of the bloodstream is not necessary for the development of severe sepsis.
 - C. The hallmark of septic shock is a marked decrease in peripheral vascular resistance that occurs despite increased plasma levels of catecholamines.
 - D. The incidence and mortality from septic shock have declined over the past 20 years.
 - E. Widespread vascular endothelial injury is present in severe sepsis and is mediated by cytokines and procoagulant factors that stimulate intravascular thrombosis.

59. All of the following statements about the physiology of mechanical ventilation are true *except*
- Application of positive end-expiratory pressure (PEEP) decreases preload and afterload.
 - High inspired tidal volumes contribute to the development of acute lung injury because of overdistention of alveoli with resultant alveolar damage.
 - Increasing the inspiratory flow rate increases the ratio of inspiration to expiration (I:E) and allows more time for expiration.
 - Mechanical ventilation provides assistance with inspiration and expiration.
 - PEEP helps prevent alveolar collapse at end-expiration.
60. A 64-year-old man requires endotracheal intubation and mechanical ventilation for chronic obstructive pulmonary disease (COPD). He was paralyzed with rocuronium for intubation. His initial ventilator settings were AC mode; respiratory rate, 10 breaths/min; FI_{O_2} , 1.0; V_t (tidal volume), 550 mL; and positive end-expiratory pressure (PEEP), 0 cmH₂O. On admission to the intensive care unit, the patient remains paralyzed; arterial blood gas is pH 7.22, Pa_{CO_2} is 78 mmHg, and Pa_{O_2} is 394 mmHg. The FI_{O_2} is decreased to 0.6. Thirty minutes later, you are called to the bedside to evaluate the patient for hypotension. Current vital signs are blood pressure, 80/40 mmHg; heart rate, 133 bpm; respiratory rate, 24 breaths/min; and Sa_{O_2} , 92%. Physical examination shows prolonged expiration with wheezing continuing until the initiation of the next breath. Breath sounds are heard in both lung fields. The high-pressure alarm on the ventilator is triggering. What should be done first in treating this patient's hypotension?
- Administer a fluid bolus of 500 mL.
 - Disconnect the patient from the ventilator.
 - Initiate a continuous IV infusion of midazolam.
 - Initiate a continuous IV infusion of norepinephrine.
 - Perform tube thoracostomy on the right side.
61. A 32-year-old man with a history of morbid obesity, active tobacco use, and hypertension is referred for a sleep study by his primary physician. The patient describes falling asleep at work almost every afternoon and is frequently drowsy when driving his car. His girlfriend notes that he snores heavily throughout the night and seems to have intermittent episodes when he is not breathing at all. He undergoes the study, which reveals six to seven hypopneic events and two to three apneic events each hour. Which of the following is true regarding obstructive sleep apnea (OSA)?
61. (*Continued*)
- 85% of patients with OSA have a body mass index (BMI) >30 kg/m².
 - Irregular breathing during sleep without daytime sleepiness qualifies as OSA.
 - The male-to-female ratio is roughly equal in OSA.
 - This patient does not meet criteria for OSA based on having too few apneic events per hour.
 - This patient should be screened for diabetes mellitus.
62. A 53-year-old man is seen in the emergency department with sudden-onset fever, chills, malaise, and shortness of breath but no wheezing. He has no significant past medical history and is a farmer. Of note, he worked earlier in the day stacking hay. Posteroanterior (PA) and lateral chest radiography show bilateral upper lobe infiltrates. Which organism is most likely to be responsible for this presentation?
- Nocardia asteroides*
 - Histoplasma capsulatum*
 - Cryptococcus neoformans*
 - Actinomyces*
 - Aspergillus fumigatus*
63. You are evaluating a patient with a chronic respiratory acidosis. Which of the following tests will be helpful in distinguishing a central nervous system cause of chronic hypoventilation from a pulmonary airway or pulmonary parenchymal cause?
- Alveolar-arterial (A-a) oxygen gradient
 - Diaphragmatic electromyography (EMG)
 - Maximal expiratory pressure
 - Pa_{CO_2}
 - Pa_{O_2}
64. A 45-year-old woman with known rheumatoid arthritis complains of a 1-week history of dyspnea on exertion and dry cough. She had been taking hydroxychloroquine and prednisone 7.5 mg until 3 months ago, when low-dose weekly methotrexate was added because of active synovitis. The patient's temperature is 37.8°C (100°F), and her room air oxygen saturation decreases from 95 to 87% with ambulation. Chest x-ray shows new bilateral alveolar infiltrates.
- Pulmonary function tests reveal the following:
- Forced expiratory volume in 1 s (FEV₁), 3.1 L (70% of predicted)
 Total lung capacity (TLC), 5.3 L (60% of predicted)
 Forced vital capacity (FVC), 3.9 L (68% of predicted)
 Vital capacity (VC), 3.9 L (58% of predicted)

64. (Continued)
FEV₁/FVC ratio, 79%
Diffusion capacity for carbon monoxide (DL_{CO}), 62% of predicted
She had a normal pulmonary function test (PFT) 1 year ago. All but which of the following would be an appropriate next step?
- Start broad-spectrum antibiotics.
 - Increase the methotrexate dose.
 - Perform bronchoalveolar lavage with transbronchial lavage.
 - Increase prednisone to 60 mg/d.
 - Discontinue methotrexate.
65. Which of the following treatments has not been shown to improve mortality in septic shock?
- Activated protein C (drotrecogin α)
 - Administration of antibiotics within 1 h of presentation
 - Bicarbonate therapy for severe acidosis
 - Early goal-directed therapy
66. A 68-year-old man is seen in the clinic for evaluation of chronic cough that has lasted 4 months. He reports that the cough is dry and occurs at any time of the day. He denies hemoptysis and associated constitutional symptoms. Furthermore, he does not have wheezing, acid reflux symptoms, or postnasal drip. His past medical history is notable for a well-compensated ischemic cardiomyopathy that was diagnosed 6 months ago. His current medications include aspirin, carvedilol, furosemide, ramipril, amlodipine, and digoxin. He has no history of tobacco or alcohol abuse and denies occupational exposure. Physical examination shows a normal upper airway, clear lungs, and a normal cardiac examination with the exception of an enlarged point of maximal impulse. Plain radiography of the chest is normal with the exception of cardiomegaly. Which of the following is the most appropriate next step in his management?
- Bronchoscopy
 - Changing furosemide to bumetanide
 - Discontinuing digoxin
 - Changing ramipril to valsartan
 - Giving azithromycin for 5 days
67. Which of the following is true regarding influenza prophylaxis?
- Patients receiving an intramuscular influenza vaccine should be warned of the increased risk of Guillain-Barré syndrome.
 - Patients with hypersensitivity to eggs should not receive the intramuscular vaccine.
67. (Continued)
C. The intramuscular influenza vaccine is a live, attenuated strain of influenza that is based on isolates from the previous year's strains of influenza A and B.
D. The intramuscular influenza vaccine should not be given to immunocompromised hosts.
E. The intranasal spray, "Flu-mist," is an inactivated virus preparation based on the previous year's strains of influenza A and B.
68. A 17-year-old woman with a medical history of mild intermittent asthma presents to your clinic in February with several days of cough, fever, malaise, and myalgias. She notes that her symptoms started 3 days earlier with a headache and fatigue and that several students and teachers at her high school have been diagnosed recently with "the flu." She did not receive a flu shot this year. Which of the following medication treatment plans is the best option for this patient?
- Aspirin and a cough suppressant with codeine
 - Oseltamivir, 75 mg PO bid for 5 days
 - Rimantadine, 100 mg PO bid for 1 week
 - Symptom-based therapy with over-the-counter agents
 - Zanamivir, 10 mg inhaled bid for 5 days
69. Which of the following represents a rare but serious extrapulmonary complication of influenza infection?
- Diffuse eczematous rash
 - Myositis
 - Oligoarthritis
 - Purulent conjunctivitis
 - Secondary bacterial pneumonia caused by *Staphylococcus aureus*
70. Regarding the epidemiology of influenza viruses, which of the following is true?
- Antigenic drift requires a change in both hemagglutinin (H) and neuraminidase (N) antigens.
 - Antigenic shift is defined by an exchange of H and N antigens between influenza A and influenza B viruses.
 - Avian influenza outbreaks in humans occur when human influenza A viruses undergo antigenic shifts with influenza A from poultry.
 - Influenza C virus infections, although uncommon, are more virulent on a population basis because of their increased ability to undergo antigenic shift.
 - The lethality associated with avian influenza is related to its ability to spread via person-to-person contact.
71. A 52-year-old man is brought to the emergency department (ED) complaining of shortness of

71. (*Continued*)
 breath, chest pain, and dizziness. The chest pain began acutely about 90 min ago. He had been working in the yard at that time and thought he might have strained a muscle in his chest. He took an aspirin and lay down, but the symptoms worsened. He soon developed dizziness and shortness of breath. He called 911, and upon arrival to the ED, he was found to be hypotensive and tachycardic. His vital signs on presentation were blood pressure, 75/44 mmHg; heart rate, 132 bpm; respiratory rate, 24 breaths/min; and Sa_O₂, 88% on room air. On physical examination, he appears in distress and is diaphoretic. He is unable to speak in full sentences. His neck veins appear distended. There are crackles throughout both lung fields. The heart sounds are regular and tachycardic. There is no edema. The extremities are cool, and the pulses are thready. An electrocardiogram shows ST elevations in lead V2–V6. The chest radiograph shows diffuse pulmonary edema. Emergency cardiac catheterization is scheduled, and it is estimated that the catheterization laboratory will be available in ~45 min. The patient remains hypotensive with a blood pressure that is now 68/38 mmHg, and the oxygen saturation has decreased to 82% on room air. What is the best management for the patient's hypotension?
- Aortic counterpulsation
 - Dobutamine, 2.5 µg/kg per min IV
 - Furosemide, 40 mg IV
 - Metoprolol, 5 mg IV
 - Norepinephrine, 4 µg/min IV
72. A 64-year-old woman is admitted to the emergency department (ED) with hypotension and chest pain. Her symptoms began 30 min ago, awakening the patient from sleep. She vomited twice and has felt dizzy and lightheaded. Upon arrival in the ED, her blood pressure was 80/40 mmHg, with a heart rate of 64 bpm. She appears in distress and has another episode of emesis in the ED. The lungs are clear to auscultation. Pulses are thready. An electrocardiogram demonstrates elevations in leads II, III, and aV_F. There are ST depressions in V₁ and V₂. The rhythm is sinus with occasional premature ventricular contractions. A chest radiograph is clear. An echocardiogram shows normal left ventricular function and right ventricular dilatation. What is the best immediate treatment for this patient's hypotension?
- Aortic counterpulsation
 - Dobutamine, 5 µg/kg per min
 - Dopamine, 5 µg/kg per min
 - Normal saline bolus, 500 mL
 - Transvenous pacemaker placement
73. All of the following statements regarding sudden cardiac death (SCD) in the United States are true *except*
- A strong parental history of SCD as a presenting history of coronary artery disease increases the likelihood of a similar presentation in an offspring.
 - An estimated 50% of all cardiac deaths are sudden and unexpected.
 - As many as 70–75% of men who die of SCD have evidence of acute myocardial infarction (MI); only 20–30% have preexisting healed MIs.
 - By 5 min after sudden cardiac arrest, the estimated survival rates are no better than 25–30% in the out-of-hospital setting.
74. A 64-year-old man suddenly collapses while playing the sousaphone with his alumni band during half-time of a football game. Emergency medical services with training in advanced cardiac life support are present within 2 min of collapse. Initial rhythm on cardiac monitor is ventricular fibrillation. What is the first step in the treatment of this patient?
- Continue cardiopulmonary resuscitation (CPR) for a full 5 min before attempting defibrillation
 - Endotracheal intubation followed by rapid defibrillation
 - Immediate defibrillation at 300–360 J once followed by CPR for 60–90 s before additional defibrillation
 - Obtain IV access and administer amiodarone, 150 mg
 - Obtain IV access and administer epinephrine, 1 mg
75. Which of the following therapies has been demonstrated to improve survival to hospital discharge with favorable neurologic outcome in out-of-hospital cardiac arrest?
- Amiodarone
 - Epinephrine
 - Hypothermia
 - Time to initial defibrillation <10 min
 - Vasopressin
76. All the following may cause elevation of serum troponin *except*
- Congestive heart failure
 - Myocarditis
 - Myocardial infarction
 - Pneumonia
 - Pulmonary embolism

77. A 54-year-old man presents to the emergency department (ED) with chest pain. He has had three episodes of chest pain in the past 24 h with exertion. Each has lasted 20–30 min and resolved with rest. His past medical history is significant for hypertension, hyperlipidemia, asthma, and chronic obstructive pulmonary disease. He currently smokes one pack a day of cigarettes. His family history is remarkable for early coronary artery disease in a sibling. Home medications include chlorthalidone, simvastatin, aspirin, albuterol, and home oxygen. In the ED, he becomes chest pain free after receiving three sublingual nitroglycerin tablets and IV heparin. Electrocardiography shows 0.8-mm ST-segment depression in V₅, V₆, lead I and aV_L. Cardiac biomarkers are negative. An exercise stress test shows inducible ischemia. Which aspects of this patient's history add to the likelihood that he might have death, myocardial infarction (MI), or urgent revascularization in the next 14 days?
- A. Age
 - B. Aspirin usage
 - C. β -Agonist usage
 - D. Diuretic usage
78. When treating a patient with a non-ST-segment elevation myocardial infarction (NSTEMI), risk stratification and timely administration of anti-ischemic and antithrombotic therapies are paramount. For a patient with unstable angina with negative biomarkers, which medication regimen is most appropriate as initial treatment?
- A. Aspirin, β -blocker, spironolactone, HMG-CoA reductase inhibitor (statin)
 - B. Aspirin, clopidogrel, nitroglycerin, β -blocker, heparin
 - C. Aspirin, nitroglycerin, β -blocker, heparin, glycoprotein (GP) IIB/IIIa inhibitor
 - D. Aspirin, morphine, oxygen, nitrates
79. A 52-year-old man with a history of stable angina presents to the hospital with 30 minutes of chest pain. He reports that over the past 2 weeks, he has developed his typical anginal symptoms of chest pressure radiating to his jaw and left arm with progressively less exertion. He has been using sublingual nitroglycerin more frequently. His other medications include a β -blocker, aspirin, and lovastatin. On the day of admission, he developed pain at rest that was not relieved with three nitroglycerin tablets. On examination, he is anxious and short of breath. His vital signs are notable for a blood pressure of 140/88 mmHg, a heart rate of
79. (Continued)
110/min, and a respiratory rate of 25/min. He has bilateral crackles halfway up both lung fields and has a 3/6 systolic murmur that radiates to his axilla. His electrocardiogram shows 3-mm ST-segment depression in leads V₃–V₅. In addition to his outpatient medications, all of the following additional therapies are indicated *except*
- A. Cardiac catheterization
 - B. Clopidogrel
 - C. Enoxaparin
 - D. Eptifibatid
 - E. Tissue plasminogen activator
80. A 73-year-old woman develops substernal chest pain, severe nausea, and vomiting while mowing the lawn. In the emergency department, she has cool extremities, right arm and left arm blood pressure of 85/70 mmHg, heart rate of 65 bpm, clear lungs, and no murmurs. She has no urine output. A Swan-Ganz catheter is placed and reveals cardiac index of 1.1 L/min per mm², pulmonary artery (PA) pressure of 20/14 mmHg, pulmonary capillary wedge pressure of 6 mmHg, and right atrial (RA) pressure of 24 mmHg. The patient most likely has
- A. Gram-negative sepsis
 - B. Occlusion of the left main coronary artery
 - C. Occlusion of the right coronary artery
 - D. Perforated duodenal ulcer
 - E. Ruptured aortic aneurysm
81. A 62-year-old woman with a history of chronic left bundle branch block is admitted to the coronary care unit with 4 hours of substernal chest pain and shortness of breath. She has elevation of serum troponin-T. She receives urgent catheterization with angioplasty and stent placement of a left anterior descending (LAD) artery lesion. Three days after admission, she develops recurrent chest pain. Which of the following studies is most useful for detecting new myocardial damage since the initial infarction?
- A. Echocardiogram
 - B. Electrocardiogram
 - C. Serum myoglobin
 - D. Serum troponin-I
 - E. Serum troponin-T
82. A patient is brought to the emergency room after a head-on motor vehicle collision. The patient is unresponsive even to painful stimuli and is apneic;

82. (*Continued*)
however, he does have a pulse. Which of the following clinical findings would exclude a diagnosis of brain death?
- Bilateral positive Babinski signs
 - Constricted pupils
 - Invariant pulse rate
 - Positive deep tendon reflexes
 - Presence of diabetes insipidus
83. Which of the following neurologic phenomena is classically associated with herniation of the brain through the foramen magnum?
- Third-nerve compression and ipsilateral papillary dilation
 - Catatonia
 - “Locked-in” state
 - Miotic pupils
 - Respiratory arrest
84. A 56-year-old man is admitted to the intensive care unit with a hypertensive crisis after cocaine use. His initial blood pressure is 245/132 mmHg. On physical examination, the patient is unresponsive except to painful stimuli. He has been intubated for airway protection and is being mechanically ventilated, with a respiratory rate of 14 breaths/min. His pupils are reactive to light, and he has normal corneal, cough, and gag reflexes. The patient has a dense left hemiparesis. When presented with painful stimuli, the patient responds with flexure posturing on the right side. CT reveals a large area of intracranial bleeding in the right frontoparietal area. Over the next several hours, the patient deteriorates. The most recent examination reveals a blood pressure of 189/100 mmHg. The patient now has a dilated pupil on the right side. The patient continues to have corneal reflexes. You suspect increasing intracranial pressure (ICP) related to the intracranial bleed. All but which of the following can be done to decrease the patient’s ICP?
- Administer IV mannitol at a dose of 1 g/kg body weight.
 - Administer hypertonic fluids to achieve a goal sodium level of 155 to 160 meq/L.
 - Consult neurosurgery for an urgent ventriculostomy.
 - Initiate IV nitroprusside to decrease the mean arterial pressure (MAP) to a goal of 100 mmHg.
 - Increase the respiratory rate to 30 breaths/min.
85. (*Continued*)
glomerular filtration rate (GFR) of 33 mL/min per 1.73 m² and poorly controlled diabetes. He is currently taking no nephrotoxic medications, and the nephrologist assures you that the patient does not currently have acute renal failure. The case is due to begin in 4 h, and you would like to prevent contrast nephropathy. Which agent will definitely reduce the risk of contrast nephropathy?
- Dopamine
 - Fenoldopam
 - Indomethacin
 - N*-acetylcysteine
 - Sodium bicarbonate
86. You are consulting to advise on another antihypertensive agent for a patient with difficult-to-control hypertension. Despite high doses of a β -blocker, the patient remains hypertensive. The estimated glomerular filtration rate (GFR) is 75 mL/min per 1.73 m². On physical examination, there is no exophthalmos and no thyroid bruit. The great vessels are without bruit as well. Abdominal examination reveals bruits loudest in the bilateral flanks as well as a left femoral bruit. Peripheral pulses are intact. Ultrasonography confirms the presence of bilateral renal artery stenosis. Which medication class would *not* be a good choice to add to this patient’s regimen?
- Thiazide diuretic
 - Calcium channel blocker
 - Angiotensin II receptor blocker (ARB)
 - Central acting α blocker
87. Which of the following patients in need of dialysis would receive the greatest benefit from placing a peritoneal dialysis catheter rather than a hemodialysis catheter?
- High-peritoneal transporters
 - Patients in developing countries
 - Patients older than 65 years of age
 - Patients with no residual kidney function
 - Patients with prior abdominal surgery
88. Your patient with end-stage renal disease on hemodialysis has persistent hyperkalemia. He has a history of total bilateral renal artery stenosis, which is why he is on hemodialysis. He only has electrocardiogram changes when his potassium increases >6.0 meq/L, which occurs a few times a week. You admit him to the hospital for further

88. (Continued)
evaluation. Your laboratory evaluation, nutrition counseling, and medication adjustments have not impacted his serum potassium level. What is the next reasonable step to undertake for this patient?
- Adjust the dialysate.
 - Administer a daily dose of furosemide.
 - Perform “sodium modeling.”
 - Implant an automatic defibrillator.
 - Perform bilateral nephrectomy.
89. It is hospital day 5 for a 65-year-old patient with prerenal azotemia secondary to dehydration. His creatinine was initially 3.6 mg/dL on admission, but it has improved today to 2.1 mg/dL. He complains of mild lower back pain, and you prescribe naproxen to be taken intermittently. By what mechanism might this drug further impair his renal function?
- Afferent arteriolar vasoconstriction
 - Afferent arteriolar vasodilatation
 - Efferent arteriolar vasoconstriction
 - Proximal tubular toxicity
 - Ureteral obstruction
90. A 63-year-old man with a history of diabetes mellitus is found to have a lung nodule on chest radiography. To stage the disease further, he undergoes a contrast-enhanced CT scan of the chest. One week before the CT scan, his blood urea nitrogen (BUN) is 26 mg/dL, and his creatinine is 1.8 mg/dL. Three days after the study, he complains of dyspnea, pedal edema, and decreased urinary output. Repeat BUN is 86 mg/dL, and creatinine is 4.4 mg/dL. The most likely mechanism of the acute renal failure is
- Acute tubular necrosis
 - Allergic hypersensitivity
 - Cholesterol emboli
 - Immune-complex glomerulonephritis
 - Ureteral outflow obstruction
91. In the patient in Question 90, the urinalysis is most likely to show
- Granular casts
 - Red blood cell (RBC) casts
 - Urinary eosinophils
 - Urinary neutrophils
 - White blood cell (WBC) casts
92. Which of the following is the most potent stimulus for hypothalamic production of arginine vasopressin?
- Hypertonicity
 - Hyperkalemia
 - Hypokalemia
 - Hypotonicity
 - Intravascular volume depletion
93. A 57-year-old man is admitted to the hospital for dehydration and confusion. In the emergency department, he complained of excessive thirst and he was found to have a serum sodium of 162 meq/L and a newly elevated creatinine of 2.2 mg/dL. After receiving IV fluid, his sensorium clears, and he relays to you that he drinks large amounts of fluid each day and makes about 2 L of urine each day. He has noticed that his urine output has no relation to the amount of fluid he drinks. His sodium remains elevated at 150 meq/L, and his urine osmolality returns at 80 mosmol/kg. After careful water restriction, you administer 10 µg of desmopressin intranasally and remeasure his urine osmolality. The osmolality is now 94 mosmol/kg. What is the most likely cause of his hypernatremia?
- Chronic hyperventilation
 - Diabetes insipidus
 - Excessive solute intake
 - Gastrointestinal losses
 - Surreptitious use of diuretics
94. What is the correct long-term treatment for the patient in the preceding scenario?
- Arginine vasopressin (AVP) analogues
 - Brain imaging and, if indicated, resection
 - Lithium carbonate
 - Narcotics
 - Salt restriction and diuretics
95. A 52-year-old diabetic patient is referred to the emergency department from the endoscopy suite. The patient has diabetes and a history of colon cancer that was removed 3 years ago. He also has hyperlipidemia, which is well controlled on atorvastatin. He presented to the endoscopy suite for a scheduled surveillance colonoscopy. Blood drawn upon arrival to shows a sodium of 121 meq/L, and the patient seemed disoriented. On physical examination, the mucous membranes are dry, and there is no axillary moisture. Serum osmolality is

95. (Continued)
checked and is 270 mosmol/kg. What is the most likely cause of this patient's hyponatremia?
- Diabetes insipidus
 - Hyperglycemia
 - Hyperlipidemia
 - Hypovolemia
 - Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
96. An 84-year-old female nursing home resident is brought to the emergency department because of lethargy. At the nursing home, she was found to have a blood pressure of 85/60 mmHg, a heart rate of 101 bpm, and a temperature of 37.8°C. Laboratory data are obtained and show sodium, 137 meq/L; potassium, 2.8 meq/L; HCO_3^- , 8 meq/L; chloride, 117 meq/L; blood urea nitrogen, 17 mg/dL; and creatinine 0.9 mg/dL. An arterial blood gas shows a PaO_2 of 80 mmHg, a PCO_2 of 24 mmHg, and a pH of 7.29. Her urine analysis is clear and has a pH of 4.5. What is the acid-base disorder?
- Anion gap metabolic acidosis
 - Non-anion gap metabolic acidosis
 - Non-anion gap metabolic acidosis and respiratory alkalosis
 - Respiratory acidosis
97. What is the most likely cause of the acid-base disorder of the patient in the preceding scenario?
- Diarrhea
 - Diuretic use
 - Hyperacute renal failure
 - Hypoaldosteronism
 - Proximal renal tubular acidosis
98. A 53-year-old woman with long-standing depression and a history of rheumatoid arthritis is brought in by her daughter, who states that she found an empty bottle of acetylsalicylic acid by her mother's bedside. The patient is found to be confused and lethargic and is unable to provide a definitive history. What is the most likely set of laboratory values?
99. A 34-year-old man is brought to the hospital with altered mental status. He has a history of alcoholism. He is somnolent and does not answer questions. Physical examination reveals blood pressure, 130/80 mmHg; heart rate, 105 bpm; respiratory rate, 24 breaths/min; and temperature, 37°C (98.6°F). The remainder of the physical examination is unremarkable. Microscopic analysis of urine is shown in Fig. 99. Which of the following most likely will be found on further diagnostic evaluation?
- >10,000 bacterial colonies on urine culture
 - Anion gap metabolic acidosis
 - Hydronephrosis on ultrasound
 - Nephrolithiasis on CT scan
 - Positive antinuclear antibodies (ANA)

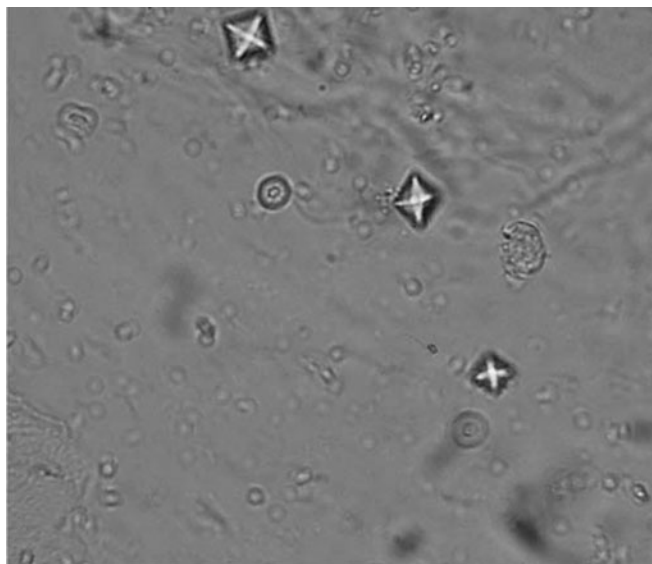


FIGURE 99

100. A 52-year-old man is found at home hypotensive and confused. In the emergency department, his blood pressure is 82/60 mmHg, and his heart rate is 115 bpm. He is confused and lethargic. Laboratory data show sodium, 133 meq/L; potassium, 2.4 meq/L; chloride, 70 meq/L; HCO_3^- , 50 meq/L; blood urea nitrogen, 44 mg/dL; and creatinine, 1.7 mg/dL. An arterial blood gas shows a P_{O_2} of 62 mmHg, a P_{CO_2}

	Na^+	K^+	Cl^-	HCO_3^-	SERUM CREATININE $\mu\text{mol/L}$ (mg/dL)	ROOM AIR ABG		
	(SERUM, meq/L)					P_{O_2}	P_{CO_2}	pH
A	140	3.9	85	26	141 (1.6)	100	40	7.40
B	140	3.9	85	16	141 (1.6)	100	20	7.40
C	140	5.8	100	20	141 (1.6)	100	34	7.38
D	150	2.9	100	36	141 (1.6)	80	46	7.50
E	116	3.7	85	22	141 (1.6)	80	46	7.50

100. (Continued)
of 49 mmHg, and a pH of 7.66. What acid–base disorder is present?
- A. Anion gap metabolic acidosis
 - B. Metabolic alkalosis
 - C. Metabolic alkalosis plus respiratory acidosis
 - D. Respiratory acidosis
 - E. Respiratory alkalosis
101. What is the most likely cause of the acid–base disorder for the patient in the preceding scenario?
- A. Acute myocardial infarction
 - B. Bartter syndrome
 - C. Cushing's disease
 - D. Mineralocorticoid excess
 - E. Vomiting
102. All the following are vitamin K–dependent coagulation factors *except*
- A. Factor X
 - B. Factor VII
 - C. Protein C
 - D. Protein S
 - E. Factor VIII
103. A 31-year-old man with hemophilia A is admitted to the hospital with persistent gross hematuria. He denies recent trauma or any history of genitourinary pathology. The examination is unremarkable. The hematocrit is 28%. All the following are treatments for hemophilia A *except*
- A. Desmopressin (DDAVP)
 - B. Fresh-frozen plasma (FFP)
 - C. Cryoprecipitate
 - D. Recombinant factor VIII
 - E. Plasmapheresis
104. All but which of the following statements about the lupus anticoagulant (LA) are true?
- A. Lupus anticoagulants typically prolong the activated partial thromboplastin time (aPTT).
 - B. A 1:1 mixing study will not correct in the presence of LAs.
 - C. Bleeding episodes in patients with LAs may be severe and life threatening.
 - D. Female patients may experience recurrent midtrimester abortions.
 - E. LAs may occur in the absence of other signs of systemic lupus erythematosus (SLE).
105. The most common inherited prothrombotic disorder is
- A. Activated protein C resistance
 - B. Prothrombin gene mutation
 - C. Protein C deficiency
 - D. Protein S deficiency
 - E. Antithrombin deficiency
106. All the following cause prolongation of the activated partial thromboplastin time (aPTT) that does not correct with a 1:1 mixture with pooled plasma *except*
- A. Lupus anticoagulant
 - B. Factor VIII inhibitor
 - C. Heparin
 - D. Factor VII inhibitor
 - E. Factor IX inhibitor
107. What is the most common side effect of oral ribavirin when used with pegylated interferon for the treatment of hepatitis C?
- A. Drug-associated lupus
 - B. Hemolytic anemia
 - C. Hyperthyroidism
 - D. Leukopenia
 - E. Rash
108. When given as a first-line agent for invasive *Aspergillus* infection, voriconazole commonly causes all of the following side effects *except*
- A. Drug–drug interactions
 - B. Hepatotoxicity
 - C. Photosensitivity skin rashes
 - D. Renal toxicity
 - E. Visual disturbances
109. Caspofungin is a first-line agent for which of the following conditions?
- A. Candidemia
 - B. Histoplasmosis
 - C. Invasive aspergillosis
 - D. Mucormycosis
 - E. Paracoccidiomycosis
110. Sensitive and specific serum or urine diagnostic tests exist for all of the following invasive fungal infections *except*
- A. Blastomycosis
 - B. Coccidioidomycosis
 - C. Cryptococcosis
 - D. Histoplasmosis

111. A 65-year-old man seeks evaluation for nasal congestion, headaches, and dysphagia, most notably when he lies supine for sleeping. These symptoms have been slowly worsening for the past month. He has no nasal discharge or fevers. On review of systems, he reports recent hoarseness and dizziness. His past medical history is significant only for mild hypertension. He worked as a roofing contractor and smoked one pack a day of cigarettes since age 16 years. On physical examination, you note facial edema. His oropharynx is also mildly edematous, and his tonsils are unremarkable. His external and internal jugular veins are engorged bilaterally, and there are prominent veins on his anterior chest. Chest percussion reveals dullness in the right base with decreased tactile fremitus. A chest radiograph shows a right upper lung mass that on biopsy is consistent with non-small cell lung cancer. All of the following treatments may help this patient's symptoms *except*
- Chemotherapy
 - Diuretics
 - Glucocorticoids
 - Radiation therapy
 - Venous stenting
112. Which of the following statements regarding malignant spinal cord compression (MSCC) is true?
- Fewer than 50% of patients who are treated while ambulatory will remain ambulatory.
 - Neurologic abnormalities on physical examination are sufficient to initiate high-dose glucocorticoids.
 - Neurologic findings often appear before pain.
 - Renal cell carcinoma is the most common cause of MSCC.
112. (*Continued*)
- The lumbosacral spine is the most commonly affected site.
113. You are called to the bedside to see a patient with Prinzmetal's angina who is having chest pain. The patient had a cardiac catheterization 2 days earlier showing a 60% stenosis of the right coronary artery with associated spasm during coronary angiogram. At the patient's bedside, which finding is consistent with the diagnosis of Prinzmetal's angina?
- Chest pain reproduced by palpation of the chest wall
 - Nonspecific ST-T-wave abnormalities
 - Relief of pain with drinking cold water
 - ST-segment elevation in II, III, and aV_F
 - ST-segment depression in I, aV_L, and V₆
114. You are managing a patient with suspected disseminated intravascular coagulopathy (DIC). The patient has end-stage liver disease awaiting liver transplantation and was recently in the intensive care unit with *Escherichia coli* bacterial peritonitis. You suspect DIC based on a new upper gastrointestinal bleed in the setting of oozing from venipuncture sites. The platelet count is 43000/ μ L, the International Normalized Ratio (INR) is 2.5, hemoglobin is 6 mg/dL, and D-dimer is elevated to 4.5. What is the best way to distinguish between new-onset DIC and chronic liver disease?
- Blood culture
 - Elevated fibrinogen degradation products
 - Prolonged activated partial thromboplastin time (aPTT)
 - Reduced platelet count
 - Serial laboratory analysis

ANSWERS

1. The answer is C.

(*Chap. 4*) In the evaluation of cyanosis, the first step is to differentiate central from peripheral cyanosis. In central cyanosis, because the cause is either reduced oxygen saturation or abnormal hemoglobin, the physical findings include bluish discoloration of both mucous membranes and skin. In contrast, peripheral cyanosis is associated with normal oxygen saturation but slowing of blood flow and an increased fraction of oxygen extraction from blood; subsequently, the physical findings are present only in the skin and extremities. The mucous membranes are spared. Peripheral cyanosis is commonly caused by cold exposure with vasoconstriction in the digits. Similar physiology is found in Raynaud's phenomenon. Peripheral vascular

disease and deep venous thrombosis result in slowed blood flow and increased oxygen extraction with subsequent cyanosis. Methemoglobinemia causes abnormal hemoglobin that circulates systemically. Consequently, the cyanosis associated with this disorder is systemic. Other common causes of central cyanosis include severe lung disease with hypoxemia, right-to-left intracardiac shunting, and pulmonary arteriovenous malformations.

2. The answer is D.

(*Chap. 11*) Aspiration can lead to anaerobic infection and chemical pneumonitis. The etiologic differential diagnosis of CAP in a patient with a history of recent travel to the southwestern United States should include *Coccidioides* spp.

Aspergillus spp., has a worldwide distribution and is not a cause of CAP syndrome. Alcohol use predisposes patients to anaerobic infection, likely caused by aspiration, as well as *S. pneumoniae*. *Klebsiella* spp. is classically associated with CAP in alcoholic patients, but in reality, it is rarely seen. Patients with structural lung disease, such as cystic fibrosis or bronchiectasis, are at risk for a unique group of organisms that includes *P. aeruginosa* and *S. aureus*. Poor dental hygiene is associated with anaerobic infections.

3. The answer is A.

(Chap. 19) A variety of autoimmune diseases may cause pulmonary or renal disease, including Wegener's granulomatosis, microscopic polyangiitis, systemic lupus erythematosus, and cryoglobulinemia. Goodpasture's syndrome is characterized by the presence of anti-glomerular basement antibodies that cause glomerulonephritis with concurrent diffuse alveolar hemorrhage. The disease typically presents in patients older than age 40 years with a history of cigarette smoking. These patients usually do not have fevers or joint symptoms. Among the listed options, antibodies to glutamic acid decarboxylase are seen in patients with type 1 diabetes or stiff-man syndrome, anti-smooth muscle antibodies in patients with autoimmune hepatitis, and anti-U1 RNP in those with mixed connective tissue disease. Antiphospholipid antibody syndrome may cause renal disease and alveolar hemorrhage, but this usually occurs in the context of a systemic illness with prominent thrombosis in other organ systems (extremities, central nervous system).

4. The answer is E.

(Chap. 9) Multiple drugs have been associated with eosinophilic pulmonary reactions. They include nitrofurantoin, sulfonamides, NSAIDs, penicillins, thiazides, tricyclic antidepressants, hydralazine, and chlorpropamide, among others. Amiodarone can cause an acute respiratory distress syndrome with the initiation of the drug as well as a syndrome of pulmonary fibrosis. Eosinophilic pneumonia is not caused by amiodarone.

5. The answer is A.

(Chap. 21) Primary spontaneous pneumothorax is usually secondary to the rupture of small apical blebs that lie near the pleural surface. The typical patient is a thin young man who smokes. The presenting symptoms are chest pain and dyspnea. The recommended initial approach to treatment is needle aspiration of the pneumothorax. If this fails to fully expand the lung, placement of a small apical tube thoracostomy can be used to continue to drain the air. Large-bore chest tubes are not necessary to drain the air present in a pneumothorax. If ongoing air leak is present after ~5 days, then the patient should be referred for thoracoscopy to staple the blebs and perform pleural abrasion. This procedure is also recommended for individuals who develop recurrent pneu-

mothoraces, which occurs in ~50% of individuals with a primary spontaneous pneumothorax. If the pneumothorax is small (<15%), observation and administration of 100% oxygen is an option for treatment. Use of 100% oxygen speeds reabsorption of the pneumothorax by promoting diffusion of air that is composed of a nitrogen and oxygen mixture back into the lungs.

6. The answer is E.

(Chap. 20) This patient is presenting with massive pulmonary embolus with ongoing hypotension, right ventricular dysfunction, and profound hypoxemia requiring 100% oxygen. In this setting, continuing with anticoagulation alone is inadequate, and the patient should receive circulatory support with fibrinolysis if there are no contraindications to therapy. The major contraindications to fibrinolysis include hypertension >180/110 mmHg, known intracranial disease or prior hemorrhagic stroke, recent surgery, or trauma. The recommended fibrinolytic regimen is recombinant tissue plasminogen activator (rTPA), 100 mg IV over 2 h. Heparin should be continued with the fibrinolytic to prevent a rebound hypercoagulable state with dissolution of the clot. There is a 10% risk of major bleeding with fibrinolytic therapy with a 1–3% risk of intracranial hemorrhage. The only indication approved by the U.S. Food and Drug Administration for fibrinolysis in pulmonary embolus (PE) is for massive PE presenting with life-threatening hypotension, right ventricular dysfunction, and refractory hypoxemia. In submassive PE presenting with preserved blood pressure and evidence of right ventricular dysfunction on echocardiogram, the decision to pursue fibrinolysis is made on a case-by-case basis. In addition to fibrinolysis, the patient should also receive circulatory support with vasopressors. Dopamine and dobutamine are the vasopressors of choice for the treatment of shock in patients with PE. Caution should be taken with ongoing high-volume fluid administration because a poorly functioning right ventricle may be poorly tolerant of additional fluids. Ongoing fluids may worsen right ventricular ischemia and further dilate the right ventricle, displacing the interventricular septum to the left to worsen cardiac output and hypotension. If the patient had contraindications to fibrinolysis and was unable to be stabilized with vasopressor support, referral for surgical embolectomy should be considered. Referral for inferior vena cava filter placement is not indicated at this time. The patient should be stabilized hemodynamically as a first priority. The indications for inferior vena cava filter placement are active bleeding, precluding anticoagulation, and recurrent deep venous thrombosis on adequate anticoagulation.

7, 8, 9, and 10. The answers are C, B, D, and A, respectively.

(Chap. 5) Ventilatory function can be easily measured with lung volume measurement and the FEV₁/FVC ratio.

A decreased FEV₁/FVC ratio diagnoses obstructive lung disease. Alternatively, low lung volumes, specifically decreased TLC, and occasionally decreased RV diagnose restrictive lung disease. With extensive air trapping in obstructive lung disease, TLC is often increased, and RV may also be increased. VC is proportionally decreased. MIP measures respiratory muscle strength and is decreased in patients with neuromuscular disease. Thus, whereas myasthenia gravis produces low lung volumes and decreased MIP, patients with idiopathic pulmonary fibrosis have normal muscle strength and subsequently a normal MIP but decreased TLC and RV. In some cases of pulmonary parenchymal restrictive lung disease, the increase in elastic recoil results in an increased FEV₁/FVC ratio. The hallmark of obstructive lung disease is a decreased FEV₁/FVC ratio; thus, the correct answer for QVI-13 is A.

11. The answer is D.

(Chap. 21) Thoracentesis is indicated for any patient presenting with pneumonia and a pleural effusion >10 mm thick on lateral decubitus imaging because a significant percentage of these patients will show evidence of bacterial invasion and require further intervention. Other indications for thoracentesis for pleural effusions that complicate pneumonias include loculation of the pleural fluid and evidence of thickened parietal pleura on chest CT. The pleural fluid should be sent for cell count, differential, pH, protein, LDH, glucose, and culture with Gram stain. This will allow one to differentiate a simple parapneumonic effusion from a complicated one or from empyema. All effusions complicating pneumonia should be exudative, meeting at least one of Light's criteria: (1) pleural fluid protein/serum protein >0.5, (2) pleural fluid LDH/serum LDH >0.6, and (3) pleural fluid LDH >two-thirds of the normal upper limit for serum. Factors that increase the likelihood that tube thoracostomy will have to be performed include loculated pleural fluid, pH <7.20, pleural fluid glucose <60 mg/dL, positive Gram stain or culture of pleural fluid, and presence of gross pus on aspiration.

12. The answer is C.

(Chap. 18) The only therapy that has been proved to improve survival in patients with chronic obstructive pulmonary disease (COPD) is oxygen in the subset of patients with resting hypoxemia. This patient probably has resting hypoxemia resulting from the presence of an elevated jugular venous pulse, pedal edema, and an elevated hematocrit. Theophylline has been shown to increase exercise tolerance in patients with COPD through a mechanism other than bronchodilation. Glucocorticoids are not indicated in the absence of an acute exacerbation and may lead to complications if they are used indiscriminately. Atenolol and enalapril have no specific role in therapy for patients with COPD but are often used when there is concomitant illness.

13. and 14. The answers are E and E, respectively.

(Chap. 2) The mountain climber is at risk for two well-described altitude-related conditions: high-altitude cerebral edema and high-altitude pulmonary edema. High-altitude pulmonary edema is a well-described subset of pulmonary edema. Other causes of pulmonary edema include cardiogenic, neurogenic, and noncardiogenic (as seen in acute respiratory distress syndrome) factors. Although the exact mechanism of this disorder is unclear, one commonly accepted hypothesis suggests that increased cardiac output and hypoxic vasoconstriction with resultant pulmonary hypertension combine to cause high-pressure pulmonary edema. Persons younger than 25 years old are more likely than older persons to develop this condition, probably because hypoxic vasoconstriction of the pulmonary arteries is more pronounced in this population. Persons who regularly live at high altitudes are still at risk for high-altitude pulmonary edema when they descend to a lower altitude and then return to higher areas. Prevention can be achieved by means of prophylactic administration of acetazolamide and gradual ascent to higher altitudes. After this condition develops, the most important therapy is to descend to a lower altitude. Other therapies include oxygen to decrease hypoxic pulmonary vasoconstriction and diuretic therapy as needed.

15. The answer is D.

(Chap. 16) The combination of infertility and recurrent sinopulmonary infections should prompt consideration of an underlying disorder of ciliary dysfunction called *primary ciliary dyskinesia*. These disorders account for approximately 5–10% of cases of bronchiectasis. A number of deficiencies have been described, including malfunction of dynein arms, radial spokes, and microtubules. All organ systems that require ciliary function are affected. The lungs rely on cilia to beat respiratory secretions proximally and subsequently to remove inspired particles, especially bacteria. In the absence of this normal host defense, recurrent bacterial respiratory infections occur and can lead to bronchiectasis. Otitis media and sinusitis are common for the same reason. In the genitourinary tract, sperm require cilia to provide motility. Kartagener's syndrome is a combination of sinusitis, bronchiectasis, and situs inversus. It accounts for approximately 50% of patients with primary ciliary dyskinesia. Cystic fibrosis is associated with infertility and bilateral upper lobe infiltrates; it causes a decreased number of sperm or absent sperm on analysis because of the congenital absence of the vas deferens. Sarcoidosis, which is often associated with hilar adenopathy, is not generally a cause of infertility. A water balloon-shaped heart is found in those with pericardial effusions, which one would not expect in this patient.

16. The answer is C.

(Chap. 21) This patient is presenting with a large unilateral pleural effusion. By Light's criteria, the effusion is exudative in nature. Light's criteria are (1) pleural fluid

protein/serum protein >0.5 , (2) pleural fluid LDH/serum LDH >0.6 , and (3) pleural fluid LDH $>$ two-thirds of the upper limits of normal. In addition, the pleural fluid has a lymphocytic predominance. In this patient who is a smoker with abnormal lymph nodes in the mediastinum, the most likely cause of an exudative effusion with excess lymphocytes is malignancy, likely caused by lung cancer. Of the choices listed, sending the pleural fluid for cytology is the best test to determine the cause of the pleural effusion. If this is unsuccessful, consideration of thoracoscopic biopsy of the pleura or bronchoscopic biopsy of the mediastinal lymph nodes should be considered. Mediastinoscopy could also be considered. The patient should receive screening mammography yearly as indicated by her age, but this is not the best choice for diagnosis of the pleural effusion. The patient has no symptoms to suggest an infection, and lymphocytic predominance in the pleural fluid is not consistent with a parapneumonic effusion. Thus, pleural fluid culture is unlikely to yield the diagnosis.

17. The answer is C.

(Chap. 5) The RV of the lung is the amount of gas that remains in the lung after a maximal expiratory effort. It is determined by airway closure. RV is elevated in conditions that result in premature airway closure with expiration or caused by an inability to fully exhale because of muscle weakness or chest wall stiffness. Of the choices listed, only emphysema is associated with an increased RV. In emphysema, there is destruction of alveoli usually related to the effects of cigarette smoking. The destruction of alveoli leads to decreased traction on small airways and allows them to collapse at higher lung volumes, resulting in an increased RV. When emphysema occurs concomitantly with chronic bronchitis, the airway inflammation characteristic of chronic bronchitis also leads to increased RV because of decreased airway diameter. Other disorders that lead to increased RV include asthma, diaphragmatic weakness, and kyphoscoliosis. Idiopathic pulmonary fibrosis usually causes a decrease in RV because of airway stiffness. Obesity should not affect the RV.

18. The answers are 1-C; 2-B; 3-D; 4-A.

(Chap. 28) A variety of vasopressor agents are available for hemodynamic support. The effects of these medications depend on their effects on the sympathetic nervous system to produce changes in heart rate, cardiac contractility, and peripheral vascular tone. Stimulation of α -1 adrenergic receptors in the peripheral vasculature causes vasoconstriction and improves mean arterial pressure by increasing systemic vascular resistance. The β_1 receptors are located primarily in the heart and cause increased cardiac contractility and heart rate. The β_2 receptors are found in the peripheral circulation and cause vasodilatation and bronchodilation. Phenylephrine

acts solely as an α -adrenergic agonist. It is considered a second-line agent in septic shock and is often used in anesthesia to correct hypotension after induction of anesthesia. Phenylephrine is also useful for spinal shock. The action of dopamine depends on the dosage used. At high doses, dopamine has a high affinity for the α receptor, but at lower doses ($<5 \mu\text{g}/\text{kg}$ per min), it does not. In addition, dopamine acts at β_1 receptors and dopaminergic receptors. The effect on these receptors is greatest at lower doses. Norepinephrine and epinephrine affect both α and β_1 receptors to increase peripheral vascular resistance, heart rate, and contractility. Norepinephrine has less β_1 activity than epinephrine or dopamine and thus has less associated tachycardia. Norepinephrine and dopamine are the recommended first-line therapies for septic shock. Epinephrine is the drug of choice for anaphylactic shock. Dobutamine is primarily a β_1 agonist with lesser effects at the β_2 receptor. Dobutamine increases cardiac output through improving cardiac contractility and heart rate. Dobutamine may be associated with development of hypotension because of its effects at the β_2 receptor, causing vasodilatation and decreased systemic vascular resistance.

19. The answer is C.

(Chap. 23) Obstructive sleep apnea (OSA) is a common sleep disorder affecting up to 20% of the population, and the incidence of OSA is expected to increase because the incidence of obesity has increased over the past 30 years. OSA is characterized by repetitive events during which the posterior oropharynx collapses with a marked decrease or absence of airflow despite ongoing respiratory effort. Obstructive events are often associated with marked disruptions in sleep continuity with frequent arousals. Recurrent oxygen desaturations, which may be very severe, also occur concurrently with OSA events. The figure illustrates a typical OSA event. In this figure, the nasal/oral airflow channel demonstrates a near absence of airflow despite ongoing respiratory effort. Each obstructive event depicted in this illustration is associated with a concomitant decrease in oxygen saturation from a baseline of 98% to 86–91% and lasts for about 20–30 s. Central sleep apnea is diagnosed when there is an absence of airflow in association with an absence of respiratory effort lasting for at least 10 s. Cheyne–Stokes respiration is a type of central sleep apnea characterized by a crescendo–decrescendo pattern of respiratory effort and airflow. A period of apnea is terminated by a period of hyperpnea. Unlike OSA, arousals during Cheyne–Stokes respiration occur during the hyperpneic phase of respiration rather than at the termination of the apnea. Cheyne–Stokes respiration is frequently seen in congestive heart failure and after cerebrovascular events. Periodic limb movement disorder of sleep is characterized by recurrent leg movements during sleep. The typical periodic limb movement is dorsiflexion of the great toe and ankle. Periodic limb movements become increasingly

frequent with age, and most are not associated with significant sleep disruption or arousals.

20. and 21. The answers are E and D, respectively.

(Chap. 19) Pulmonary alveolar proteinosis (PAP) is a rare disorder with an incidence of approximately one in 1 million. The disease usually presents between ages 30 and 50 years and is slightly more common in men. Three distinct subtypes have been described: congenital, acquired, and secondary (most frequently caused by acute silicosis or hematologic malignancies). Interestingly, the pathogenesis of the disease has been associated with antibodies to granulocyte-macrophage colony-stimulating factor (GM-CSF) in most cases of acquired disease in adults. The pathobiology of the disease is failure of clearance of pulmonary surfactant. These patients typically present with subacute dyspnea on exertion with fatigue and low-grade fevers. Associated laboratory abnormalities include polycythemia, hypergammaglobulinemia, and increased lactate dehydrogenase levels. Classically, the CT appearance is described as “crazy pavement” with ground-glass alveolar infiltrates in a perihilar distribution and intervening areas of normal lung. Bronchoalveolar lavage is diagnostic, with large amounts of amorphous proteinaceous material seen. Macrophages filled with PAS-positive material are also frequently seen. The treatment of choice is whole-lung lavage through a double-lumen endotracheal tube. Survival at 5 years is higher than 95%, although some patients will need a repeat whole-lung lavage. Secondary infection, especially with *Nocardia* spp., is common, and these patients should be followed closely.

22. and 23. The answers are B and C, respectively.

(Chap. 28) Hypovolemic shock is the most common form of shock and occurs either because of hemorrhage or loss of plasma volume in the form of gastrointestinal, urinary, or insensible losses. Symptoms of hemorrhagic and non-hemorrhagic shock are indistinguishable. Mild hypovolemia is considered to be a loss of <20% of the blood volume and usually presents with few clinical signs except for mild tachycardia. Loss of 20–40% of the blood volume typically induces orthostasis. Loss of >40% of the blood volume leads to the classic manifestations of shock—marked tachycardia, hypotension, oliguria, and finally obtundation. Central nervous system perfusion is maintained until shock becomes severe. Oliguria is a very important clinical parameter that should help guide volume resuscitation.

After assessing for an adequate airway and spontaneous breathing, initial resuscitation aims at reexpanding the intravascular volume and controlling ongoing losses. Volume resuscitation should be initiated with rapid IV infusion of isotonic saline or Ringer’s lactate. In head-to-head trials, colloidal solutions have not added any benefit compared with crystalloid and in fact appeared to increase mortality for trauma patients. Patients in hemorrhagic shock

with ongoing blood losses and a hemoglobin ≤ 10 g/dL should be treated with transfusion of pRBCs. After the hemorrhage has been controlled, transfusion of pRBCs should be performed only for hemoglobin ≤ 7 g/dL. Patients who remain hypotensive after volume resuscitation have a very poor prognosis. Inotropic support and intensive monitoring should be initiated in these patients.

24. The answer is B.

(Chap. 5) The patient in this presentation is presenting after a narcotic overdose, which leads to hypoxia because of hypoventilation. The major causes of hypoxemia are hypoventilation, shunt, and \dot{V}/\dot{Q} mismatch. Diffusing defects can also cause hypoxemia but are a much less frequent cause. A final cause of hypoxemia to consider is decreased concentration of oxygen in inspired air, which is only present at altitude or in the setting of medical equipment malfunction. When evaluating a patient with hypoxia, it is important to consider whether the A–a oxygen gradient is normal or elevated. Of the causes of hypoxia, only hypoventilation and decreased fraction of inspired oxygen will cause hypoxia with a normal A–a gradient. The formula for calculating the alveolar oxygen concentration is

$$PA_{O_2} = ((P_{atm} - P_{H_2O}) * (FI_{O_2})) - (Pa_{CO_2}/R)$$

where P_{atm} = atmospheric pressure

P_{H_2O} = water vapor pressure

FI_{O_2} = fraction of inspired oxygen

R = respiratory quotient

When values are substituted assuming usual conditions at sea level and with the patient breathing room air, the equation is simplified to

$$PA_{O_2} = (760 - 47)(0.21) - (Pa_{CO_2}/0.8) = 150 - Pa_{CO_2}/0.8$$

In this patient, the calculated PA_{O_2} is 50. Thus, the A–a gradient is 8 mmHg (normal value <15 mmHg) and is normal. Thus, the correct answer is B.

25. The answer is D.

(Chap. 22) Respiratory muscular disorders rarely cause chronic hypoventilation unless there is significant diaphragmatic weakness. Myasthenia gravis, muscular dystrophy, amyotrophic lateral sclerosis, and other chronic myopathies that involve peripheral musculature as well as the diaphragm should be considered when a patient has signs or symptoms of diaphragmatic weakness. Upright chest radiographs may show diaphragm elevation but are usually normal. When diaphragm weakness is present, forced vital capacity will be >10–15% lower in the supine position than in the upright position, and maximal inspiratory and expiratory pressures will be reduced. Transdiaphragmatic pressure gradients (esophageal minus gastric pressures) can also be measured as a confirmatory test. Diffusing capacity has little diagnostic value; it is mostly

useful as a physiologic measure and a predictor of oxygen desaturation with exercise. The results are usually normal in patients with muscle weakness. A normal perfusion scan result has a high negative predictive value for ruling out pulmonary embolism; an angiogram is not indicated. CT scan of the head would not be useful in diagnosing myasthenia gravis or other motor neuron diseases.

26. The answer is B.

(Chap. 21) The most common cause of pleural effusion is left ventricular failure. Pleural effusions occur in heart failure when increased hydrostatic forces are increasing the pulmonary interstitial fluid and the lymphatic drainage is inadequate to remove the fluid. Right-sided effusions are more common than left-sided effusions in heart failure. Thoracentesis would show a transudative fluid. Pneumonia can be associated with a parapneumonic effusion or empyema. Parapneumonic effusions are the most common cause of exudative pleural effusions and are second only to heart failure as a cause of pleural effusions. Empyema refers to a grossly purulent pleural effusion. Malignancy is the second most common cause of exudative pleural effusion. Breast and lung cancers and lymphoma cause 75% of all malignant pleural effusions. On thoracentesis, the effusion is exudative. Cirrhosis and pulmonary embolus are far less common causes of pleural effusions.

27. The answer is D.

(Chap. 28) The patient is in cardiogenic shock from an ST-elevation myocardial infarction. Shock is a clinical syndrome in which vital organs do not receive adequate perfusion. Understanding the physiology underlying shock is a crucial factor in determining appropriate management. Cardiac output is the major determinant of tissue perfusion and is the product of stroke volume and heart rate. In turn, stroke volume is determined by preload, or ventricular filling, afterload, or resistance to ventricular ejection, and contractility of the myocardium. In this patient, the hypoxic and damaged myocardium has suddenly lost much of its contractile function, and stroke volume will therefore decrease rapidly, decreasing cardiac output. Systemic vascular resistance will increase to improve return of blood to the heart and increase stroke volume. Central venous pressure is elevated as a consequence of increased vascular resistance, decreased cardiac output and poor forward flow, and neuroendocrine-mediated vasoconstriction. The pathophysiology of other forms of shock is shown as a comparison.

28. The answer is A.

(Chap. 20; Ridker P et al, 1995) Many patients who develop pulmonary thromboembolism have an underlying inherited predisposition that remains clinically silent until they are subjected to an additional stress, such as the use of oral contraceptive pills, surgery, or pregnancy.

The most frequently inherited predisposition to thrombosis is so-called activated protein C resistance. The inability of a normal protein C to carry out its anticoagulant function is caused by a missense mutation in the gene coding for factor V in the coagulation cascade. This mutation, which results in the substitution of a glutamine for an arginine residue in position 506 of the factor V molecule, is termed the factor V Leiden gene. Based on the Physicians Health Study, about 3% of healthy male physicians carry this particular missense mutation. Carriers are clearly at an increased risk for deep venous thrombosis and for recurrence after the discontinuation of warfarin. The allelic frequency of factor V Leiden is higher than that of all other identified inherited hypercoagulable states combined, including deficiencies of protein C, protein S, and antithrombin III and disorders of plasminogen.

29. The answer is B.

(Chap. 24) The optimal timing for lung transplantation is critical to improve survival and add quality-adjusted life years. Individuals with cystic fibrosis should be considered for lung transplantation when the FEV₁ is <30% predicted values or is rapidly decreasing. Other indications for referral in cystic fibrosis include PaO₂ <50 mmHg on room air, PaCO₂ >50 mmHg, pulmonary arterial hypertension, increasing hospitalization, and recurrent hemoptysis.

30. The answer is E.

(Chap. 20) Warfarin should not be used alone as initial therapy for the treatment of venous thromboembolic disease (VTE) for two reasons. First, warfarin does not achieve full anticoagulation for at least 5 days because its mechanism of action is to decrease the production of vitamin K-dependent coagulation factors in the liver. Secondly, a paradoxical reaction that promotes coagulation may also occur upon initiation of warfarin because it also decreases the production of the vitamin K-dependent anticoagulants protein C and protein S, which have shorter half-lives than the procoagulant factors. For many years, UFH delivered IV was the treatment of choice for VTE. However, it requires frequent monitoring of aPTT levels and hospitalization until therapeutic International Normalized Ratio (INR) is achieved with warfarin. There are now several safe and effective alternatives to UFH that can be delivered SC. Low-molecular-weight heparins (LMWHs; enoxaparin, tinzaparin) are fragments of UFH with a lower molecular weight. These compounds have a greater bioavailability, longer half-life, and more predictable onset of action. Their use in patients with renal insufficiency should be considered with caution because LMWHs are renally cleared. Fondaparinux is a direct factor Xa inhibitor that, similar to LMWHs, requires no monitoring of anticoagulant effects and has been demonstrated to be safe and effective in treating patients with both deep venous thrombosis and pulmonary embolism.

31. The answer is B.

(Chap. 12) *M. tuberculosis* is spread by droplet nuclei that are aerosolized by coughing, sneezing, or speaking. The droplets dry quickly and may stay airborne and be subject to inhalation for hours. The probability of acquiring tuberculosis is related to the degree of infectiousness and the intimacy and duration of contact. Smear-positive patients have the greatest infectivity. Patients with cavitary, laryngeal, or endobronchial disease produce the most infectious organisms. Patients with smear-negative, culture-positive or disseminated disease are less infectious. Patients with culture-negative (treated) or extrapulmonary tuberculosis are essentially noninfectious. Patients with tuberculosis who are HIV infected also appear to be less infectious because of the lower frequency of cavitary disease. These factors emphasize the importance of public health measures to control the transmission of tuberculosis.

32. The answer is D.

(Chap. 19) This patient's presentation is typical of pulmonary Langerhans cell histiocytosis (eosinophilic granulomas). Cigarette smoking is virtually universal among these patients. The disease may be found incidentally on radiograms or may present with respiratory and systemic complaints. Spontaneous pneumothorax is a common presentation and occurs in approximately 25% of these patients. The radiographic combination of small reticular or nodular opacities in the bases (with sparing of the costophrenic angle) and apical cysts is characteristic and virtually diagnostic. Pulmonary function testing will show a reduced DL_{CO} (carbon monoxide diffusing capacity). Lung volumes may be normal or reduced, depending on the severity. Approximately 33% of these patients improve with smoking cessation, but most develop progressive interstitial disease. Immunosuppressive agents do not appear to influence the course of disease. IV α_1 antitrypsin may benefit patients with deficiency, who will present with lower lobe emphysema. Miliary tuberculosis radiographically appears with multiple small nodules, but cysts are not typical. *Pneumocystis carinii* pneumonia (PCP) may present with spontaneous pneumothorax in patients with HIV infection; however, this patient has no apparent risk factors, and the small nodules on CT are not typical.

33. The answer is E.

(Chap. 19) This patient's clinical presentation and CT imaging are consistent with the diagnosis of idiopathic pulmonary fibrosis (IPF), which is manifested histologically as usual interstitial pneumonitis (UIP). On microscopic examination, UIP is characterized by a heterogeneous appearance on low magnification with normal-appearing alveoli adjacent to severely fibrotic alveoli. There is lymphocytic infiltrate and scattered foci of fibroblasts within the alveolar septae. End-stage

fibrosis results in honeycombing with loss of all alveolar structure. The typical clinical presentation of IPF/UIP is slowly progressive exertional dyspnea with a nonproductive cough. The clinical examination reveals dry crackles and digital clubbing. Patients with IPF are usually older than age 50 years, and more than two-thirds have a history of current or former tobacco use. A high-resolution CT scan of the chest can be diagnostic in the typical clinical situation of an older individual and shows subpleural pulmonary fibrosis that is greatest at the lung bases. As disease progresses, traction bronchiectasis and honeycombing are characteristic on CT scan. The cause of UIP is unknown, and no therapies have been shown to improve survival in patients with this disease with the exception of lung transplantation. Mortality is 50% within 3 years of diagnosis. The presence of a dense periodic acid-Schiff-positive amorphous material in alveolar spaces is characteristic of pulmonary alveolar proteinosis. Pulmonary alveolar proteinosis is an interstitial lung disease that presents with progressive dyspnea, and CT imaging shows characteristic "crazy paving" with ground-glass infiltrates and thickened alveolar septae. Fibrosis is not present. Alveolar destruction with emphysematous changes would be seen in chronic obstructive pulmonary disease (COPD). The presence of crackles without wheezing or hyperinflation on examination does not suggest COPD. Furthermore, clubbing is not seen in COPD. Diffuse alveolar damage is seen in acute interstitial pneumonitis and acute respiratory distress syndrome. These disorders present with a rapid acute course that is not present in this case. The formation of noncaseating granulomas is typical of sarcoidosis, a systemic disease that usually presents in younger individuals. It is more common in African Americans. A typical CT in sarcoidosis would show interstitial infiltrates and hilar lymphadenopathy. End-stage disease may result in pulmonary fibrosis, but it is greatest in the upper lobes.

34. The answer is D.

(Chap. 27) Determining when an individual is an appropriate candidate for a spontaneous breathing trial is important for the care of mechanically ventilated patients. An important initial step in determining if a patient is likely to be successfully extubated is to evaluate the mental status of the patient. This can be difficult if the patient is receiving sedation, and it is recommended that sedation be interrupted on a daily basis for a short period to allow assessment of mental status. Daily interruption of sedation has been shown to decrease the duration of mechanical ventilation. If the patient is unable to respond to any commands or is completely obtunded, he or she is at high risk for aspiration and unlikely to be successfully extubated. In addition, the patient's underlying medical condition should be stable, and the patient should be off vasopressor support. If these conditions are

met, the patient should be on minimal ventilatory support. This includes the ability to maintain the pH between 7.35 and 7.40 and an Sa_{O_2} of $>90\%$ while receiving an $Fi_{O_2} \leq 0.5$ and a PEEP ≤ 5 cmH₂O.

35. The answer is B.

(Chap. 3) *B. pertussis* is becoming an increasingly common cause of cough in adolescents and adults. Some studies have shown that pertussis is associated with 12–30% of prolonged coughing illnesses lasting >2 weeks. The clinical manifestations of pertussis infection are classically described by a catarrhal phase followed by a paroxysmal phase. The catarrhal phase begins after a 7- to 10-day incubation period and lasts 1–2 weeks. This phase is marked by an upper respiratory illness that is similar in symptoms to the common cold, with low-grade fever, rhinitis, mild cough, and lacrimation. This is followed by a prolonged paroxysmal coughing phase during which coughing can become quite severe. The term *whooping cough* as a synonym for *pertussis* is derived from the spasms of coughing that occur during the paroxysmal phase that are often terminated by an audible whoop. Posttussive emesis is frequent. Between paroxysms of cough, the patient is otherwise well. Sleep is often disturbed because the cough tends to be worse at night. This phase usually lasts from 2 to 4 weeks, with cough waning in severity after this point. The convalescent phase marks recovery from the illness and lasts from 1 to 3 months, during which time the cough gradually lessens in severity. Intercurrent viral illnesses that occur over the next year may cause a recurrence of paroxysmal cough. Diagnosis of pertussis in the paroxysmal phase of the illness relies on serologic testing of IgG and IgA antibodies to pertussis with evidence of a two- to fourfold increase in levels suggestive of recent infection. Increasingly, a single specimen for serology can be obtained and compared with established population values. Therapy is not indicated because it does not substantially alter the course of disease except in the catarrhal phase. Other common causes of chronic cough include asthma, allergic rhinitis with postnasal drip, and gastroesophageal reflux disease. Occasionally, asthma may present with cough alone. In these patients, a methacholine challenge test is used to confirm the diagnosis, especially in the setting of normal spirometry. Peak expiratory flow monitoring in the workplace is useful when an occupational cause of asthma or chronic cough is suggested. Typical clinical features include symptoms that increase over the work week and wane significantly during time off work. Individuals with allergic rhinitis often develop cough as a result of postnasal drip, which can become more severe after upper respiratory illnesses. However, the severity of the cough without prior history of chronic rhinitis in this case argues against allergic rhinitis. Thus skin testing for allergens is not indicated. Finally, gastroesophageal reflux disease may also be associated with chronic cough

and would be diagnosed with a 24-h pH probe. The preceding illness and abrupt onset of severe symptoms, however, are inconsistent with this diagnosis.

36. The answer is B.

(Chap. 10) The patient presents with typical asthma symptoms; however, the symptoms are escalating and now require nearly constant use of oral steroids. It is of note that the symptoms are worse during weekdays and better on weekends. This finding suggests that there is an exposure during the week that may be triggering the patient's asthma. Often textile workers have asthma resulting from the inhalation of particles. The first step in diagnosing a work-related asthma trigger is to check the FEV₁ before and after the first shift of the workweek. A decrease in FEV₁ would suggest an occupational exposure. Skin testing for allergies would not be likely to pinpoint the work-related exposure. Although *A. fumigatus* can be associated with worsening asthma from allergic bronchopulmonary aspergillosis, this would not have a fluctuation in symptoms throughout the week. The patient does not require further testing to diagnose that he has asthma; therefore, a methacholine challenge is not indicated. Finally, the exercise physiology test is generally used to differentiate between cardiac and pulmonary causes or deconditioning as causes for shortness of breath.

37. The answer is E.

(Chap. 23) Although the clinical history can suggest a diagnosis of OSA and can be strengthened by the use of objective sleep questionnaires such as the Epworth Sleepiness Score, evidence of recurrent breathing disruptions during sleep is necessary to make the diagnosis. OSA is a condition that requires lifelong therapy; diagnosis should be based on objective findings such as those obtained from polysomnography. Limited sleep studies that measure one or two parameters may be cost effective when interpreted by experts; however, their predictive capacity does not compare favorably to polysomnography. Unfortunately, there are at present no satisfactory pharmacologic options for patients with OSA. Modafinil has shown marginal improvement in patients also using CPAP. It is expensive and not currently recommended as a first-line agent. CPAP ventilation has been shown in double-blind, randomized clinical trials to improve virtually all aspects of disease in patients with OSA, including number of apneas and hypopneas, sleep quality, blood pressure, driving ability, mood, and quality of life. CPAP is often burdensome and uncomfortable at first. The benefits as well as the downsides of CPAP should be covered with patients. Another treatment option is the mandibular repositioning splint, which holds the tongue and lower jaw forward to widen the pharyngeal airway. These can also be difficult to use, and long-term compliance is poor. Several surgical options for patients with narrowed airways are available that are effective in carefully selected patients.

38. The answer is C.

(Chap. 9) The patient has a subacute presentation of hypersensitivity pneumonitis related to exposure to bird droppings and feathers at work. Hypersensitivity pneumonitis is a delayed-type hypersensitivity reaction that has a variety of presentations. Some people develop acute onset of shortness of breath, fevers, chills, and dyspnea within 6–8 h of antigen exposure. Others may present subacutely with worsening dyspnea on exertion and dry cough over weeks to months. Chronic hypersensitivity pneumonitis presents with more severe and persistent symptoms with clubbing. Progressive worsening is common with the development of chronic hypoxemia, pulmonary hypertension, and respiratory failure. The diagnosis relies on a variety of tests. Peripheral eosinophilia is not a feature of this disease, although neutrophilia and lymphopenia are frequently present. Other nonspecific markers of inflammation may be elevated, including the erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, and serum immunoglobulins. If a specific antigen is suspected, serum precipitins directed toward that antigen may be demonstrated. Chest radiography may be normal or show a diffuse reticulonodular infiltrate. High-resolution chest CT is the imaging modality of choice and shows ground-glass infiltrates in the lower lobes. Centrilobular infiltrates are often seen as well. In the chronic stages, patchy emphysema is the most common finding. Histopathologically, interstitial alveolar infiltrates predominate, with a variety of lymphocytes, plasma cells, and occasional eosinophils and neutrophils seen. Loose, noncaseating granulomas are typical.

39. The answer is D.

(Chap. 9) Treatment depends on removing the individual from exposure to the antigen. If this is not possible, the patient should wear a mask that prevents small-particle inhalation during exposure. In patients with mild disease, removal from antigen exposure alone may be sufficient to treat the disease. More severe symptoms require therapy with glucocorticoids at an equivalent prednisone dosage of 1 mg/kg daily for 7–14 days. The steroids are then gradually tapered over 2–6 weeks.

40. The answer is D.

(Chap. 16) Bronchiectasis is defined as an abnormal and permanent dilatation of the bronchi. It can be focal or widespread in the lung. It typically affects older patients and is found more commonly in women than men. Bronchiectasis results from inflammation and destruction of the bronchial wall and is usually triggered by infection. Bacteria such as *Staphylococcus aureus* and *Klebsiella* spp. are common causes. Adenovirus and influenza virus are the main viruses that can cause bronchiectasis. Mycobacteria, including tuberculosis, are major causes worldwide. Patients with impaired immunity to pulmonary infections, such as those with cystic fibrosis or ciliary dysfunction, are highly suscep-

tible to bronchiectasis. Patients frequently complain of recurrent cough and purulent sputum. Frequent lung infections should raise suspicion of this diagnosis. Physical examination findings can be varied and are not sufficient alone for diagnosis. Rhonchi and wheezes can be heard over the affected area; severe cases may present with right-heart failure. Chest radiography often shows nonspecific findings. Honeycomb lung is characteristic of end-stage interstitial lung disease. High-resolution CT of the chest is considered the standard technique to confirm diagnosis of bronchiectasis. It will show the dilated airways beyond the central airways. If focal, it has most likely been caused by prior necrotizing infection; however, mycobacterial infection (*M. tuberculosis*, mycobacteria other than tuberculosis) should be considered. Diffuse bronchiectasis may be caused by cystic fibrosis, immunoglobulin deficiency, ciliary dysfunction syndromes, α_1 antitrypsin deficiency, allergic bronchopulmonary aspergillosis, collagen vascular disease, or HIV infection.

41. The answer is B.

(Chap. 19) Pulmonary complications are common in patients with SLE. The most common manifestation is pleuritis with or without effusion. Other possible manifestations include pulmonary hemorrhage, diaphragmatic dysfunction with loss of lung volumes (the so-called *shrinking lung syndrome*), pulmonary vascular disease, acute interstitial pneumonitis, and bronchiolitis obliterans organizing pneumonia. Other systemic complications of SLE also cause pulmonary complications, including uremic pulmonary edema and infectious complications. Chronic progressive pulmonary fibrosis is not a complication of SLE.

42. The answer is C.

(Chap. 11) The radiograph describes a lung abscess that most likely is caused by an anaerobic infection. The anaerobes involved are most likely oral, but *Bacteroides fragilis* is isolated in $\leq 10\%$ of cases. Vancomycin, ciprofloxacin, and cephalexin have no significant activity against anaerobes. Most oral anaerobic strains have the capacity to produce β -lactamase. For many years, penicillin was considered the standard treatment for patients with anaerobic lung infections. However, clinical studies have demonstrated the superiority of clindamycin over penicillin in the treatment of lung abscess. When there are contraindications to clindamycin, penicillin plus metronidazole is likely to be as effective as clindamycin.

43. The answer is C.

(Chap. 24) Compared with other solid organ transplants, lung transplants have the highest mortality, with only a 50% survival after 5 years. The leading causes of death in the early posttransplant period are infectious complications. Primary graft failure occurs immediately after the transplant and is sometimes called ischemia-reperfusion injury. This can be fatal but can be treated with supportive

care. Acute rejection occurs in ~50% of lung transplant patients within the first year but is rarely fatal. Posttransplant lymphoproliferative disorder is a B cell lymphoma associated with Epstein-Barr virus and is related to the degree of immunosuppression. It is a rare complication of transplant. Bronchiolitis obliterans syndrome denotes chronic rejection and is the leading cause of late mortality in lung transplant.

44. The answer is D.

(Chap. 16) This patient presents with a lung abscess in the setting of pneumonia. Lung abscess is defined as a pulmonary cavitation caused by infection. Aspiration is the predominant means of acquiring infection. The most common anatomic sites of aspiration (when people are lying on their back) and therefore lung abscess include the superior segment of the right lower lobe, posterior segment of the right upper lobe, and superior segment of the left lower lobe. Anaerobic bacteria are the most prevalent isolates from lung abscesses because these are the most common bacteria aspirated from the mouth. Alcoholism is a known risk factor for aspiration. Necrotizing aerobic bacteria such as *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Nocardia* spp. can cause lung abscesses but do so with much less frequency than do anaerobic bacteria. *Peptostreptococcus* spp., an anaerobic organism that is part of normal mouth flora, has been shown to be the most common organism isolated from lung abscesses. Polymicrobial culture results are not uncommon. Management includes antibiotics aimed at treating anaerobes, such as clindamycin.

45. The answer is C.

(Chap. 17) This patient has a history suggestive of cystic fibrosis, with the exception of her age. The persistent asthma, airflow obstruction, and sputum cultures growing *P. aeruginosa* and *S. aureus* coupled with bilateral upper lobe infiltrates should prompt further investigation for this disease. The diagnosis of cystic fibrosis is based on clinical criteria plus laboratory evidence. The laboratory test of choice remains analysis of sweat chloride values. Patients with mutations in the cystic fibrosis transmembrane regulator (CFTR) have increased amounts of chloride in their sweat, and a chloride value >70 meq/L is generally found in these patients. Approximately 1–2% of patients with cystic fibrosis have normal results of sweat chloride testing, and in these cases, the nasal transepithelial potential difference has been used for diagnosis. Although the $\Delta F508$ mutation accounts for the majority of patients with cystic fibrosis, more than 1000 other mutations that can cause this disorder have been described. Thus, the absence of this mutation does not rule out cystic fibrosis. Bronchoscopy with transbronchial biopsy will probably show bronchiectasis and chronic airway inflammation but will not be diagnostic. Similar findings probably will be found on a chest CT but also are not diagnostic.

46. The answer is A.

(Chap. 12) This patient has evidence of recent tuberculosis infection with the change from a negative to a positive PPD. A chest radiogram should be performed to rule out active disease and the presence of latent disease. If there is no abnormality, isoniazid should be prescribed to prevent subsequent development of active disease. The optimal duration of therapy is 6–12 months, with most recommending 9 months to achieve maximal protection from active disease. The major complication of this therapy is hepatitis. Isoniazid should not be given to patients with active liver disease. All of these patients should be educated about the signs and symptoms of hepatitis and should be instructed to discontinue the medication if those symptoms develop. Patients should be questioned about symptoms monthly. Baseline liver function tests need be obtained only in patients with a history of liver disease or daily alcohol use. Serial measurement of liver function is not necessary in the absence of a history of liver disease and alcohol use.

47. The answer is B.

(Chap. 1) This patient presents with subacute-onset dyspnea and an examination consistent with pleural effusion. Dullness to percussion can be seen with consolidation, atelectasis, and pleural effusion. With consolidation, voice transmission is increased during expiration so that one may hear whispered pectoriloquy or egophony. However, in both pleural effusion and atelectasis, breath sounds are diminished, and there is no augmentation of voice transmission. Although this patient could have either atelectasis or pleural effusion, the lack of tracheal deviation points to pleural effusion. Atelectasis would have to be of many segments to account for these findings, and such significant airway collapse would generally cause ipsilateral tracheal deviation. The clinician would expect to find pleural effusion on chest film, and the most appropriate next management step would be thoracentesis to aid in the diagnosis of the cause and for symptomatic relief. With a lack of symptoms to suggest infection, antibiotics are not indicated. Similarly, in the absence of wheezing or significant sputum production, bronchodilators and deep suctioning are unlikely to be helpful. Bronchoscopy may be indicated ultimately in the management of this patient, particularly if malignancy is suspected; however, the most appropriate first attempt at diagnosis is by means of thoracentesis.

48. The answer is A.

(Chap. 24) Lung transplantation has been successfully used in the treatment of patients with end-stage lung disease since the early 1990s. Currently, ~1700 lung transplants are performed yearly worldwide. The most common reason for lung transplant is COPD, accounting for 38.5% of all lung transplants performed between 1995 and 2004. In addition, another 8.6% of lung transplants were performed

because of emphysema caused by α_1 antitrypsin deficiency. IPF and cystic fibrosis are the second and third most common reasons for lung transplantation, respectively. Pulmonary hypertension and sarcoidosis each account for <5% of all lung transplants. Single-lung transplantation is an option for patients with COPD, IPF, and sarcoidosis. Patients with cystic fibrosis and pulmonary hypertension receive double-lung transplants.

49. The answer is D.

(Chap. 11; LA Mandell et al: *Clin Infect Dis* 44[Suppl 2]:S27, 2007) The Infectious Diseases Society of America and the American Thoracic Society state that in the proper clinical context, a new infiltrate on chest imaging should be present to diagnose CAP. An accurate history is important because the differential diagnosis of CAP includes heart disease, chronic bronchitis, pulmonary embolism, and acute bronchitis. At least two clinical symptoms consistent with acute pulmonary infection (any combination of fever, cough, chest pain, or dyspnea) should be present for diagnosis. Cough is the most common symptom in patients presenting with CAP. Physical findings have a sensitivity and specificity of 60–70%, so radiology is recommended to make the diagnosis. Similarly, laboratory studies, including a WBC count and measures of inflammation, are neither sensitive nor specific enough to make a diagnosis. Antibiotics are not recommended for acute bronchitis. In some cases, follow-up radiograph or empirical therapy for CAP should be considered if the clinical suspicion is high and the original chest x-ray results are negative. The microbiologic basis of CAP can usually not be definitively determined on a clinical and radiographic basis. Except for the small minority of patients who are admitted to the intensive care unit, no data exist to show that specific pathogen-directed therapy is superior to empirical therapy. Microbiologic data are not components of the clinical diagnosis of CAP.

50. The answer is E.

(Chap. 25) Patients with lung transplants have the highest risk of pneumonia among all recipients of solid organ transplants. The pathogens causing pulmonary infections vary with the time after transplantation. The most common pathogens in the first 2 weeks (early period) after surgery are the gram-negative bacteria, particularly Enterobacteriaceae and *Pseudomonas*, *Staphylococcus*, *Aspergillus*, and *Candida* spp. Between 1 and 6 months (middle period), most infections are caused by either primary activation or reactivation of CMV. CMV pneumonia is often difficult to distinguish from acute transplant rejection. More than 6 months after a transplant (late period), the chronic suppression of cell-mediated immunity places patients at risk of infection from *Pneumocystis*, *Nocardia*, and *Listeria* spp.; other fungi; and intracellular pathogens. Pretransplant lung donor cultures often guide posttrans-

plant empirical antibiotic choices. Prophylaxis against CMV in seropositive donors or recipients and *Pneumocystis* spp. is routine after lung transplantation.

51. The answer is B.

(Chap. 22) The physiologic effects of hypoventilation are typically magnified during sleep because of a further reduction in central respiratory drive. Hypercapnia causes cerebral vasodilation, which manifests as headache upon awakening. The headache typically resolves soon after awakening as the Pa_{CO_2} decreases with increased ventilation and cerebral vascular tone returns to normal. Patients with frequent arousals from sleep and hypoventilation commonly complain of daytime somnolence and may also exhibit confusion and fatigue. Hypoventilation causes an increase in Pa_{CO_2} and an obligatory decrease in PA_{O_2} . The hypoxemia can stimulate erythropoiesis and result in polycythemia. With central hypoventilation disorders, patients may also have impaired cranial nerve reflexes or muscular function, causing aspiration.

52. The answer is E.

(Chap. 10) Passive cigarette smoking, or secondhand smoking, has been associated in the past 15 years with many adverse outcomes. A correlation has been demonstrated between the number of smokers in a house and the concentration of respirable particulate load. Furthermore, meta-analyses of the best data have shown that persons who receive passive cigarette smoke have a 25% increase in mortality associated with lung cancer, respiratory illness, and cardiac disease compared with persons without such an exposure. Children with smoking parents have been shown to have an increased prevalence of respiratory illness and decreased lung function compared with nonexposed children.

53. The answer is C.

(Chap. 29) The annual incidence of sepsis has increased to >700,000 individuals yearly in the United States, and sepsis accounts for >200,000 deaths yearly. Approximately two-thirds of the cases of sepsis occur in individuals with other significant comorbidities, and the incidence of sepsis increases with age and preexisting comorbidities. In addition, the incidence of sepsis is thought to be increasing as a result of several other factors. These include increased longevity of individuals with chronic disease, including AIDS, and an increased risk for sepsis in individuals with AIDS. The practice of medicine has also influenced the risk of sepsis, with an increased risk of sepsis related to the increased use of antimicrobial drugs, immunosuppressive agents, mechanical ventilation, and indwelling catheters and other hardware.

54. and 55. The answers are A and B, respectively.

(Chap. 11) The first patient is a candidate for outpatient therapy because of his CURB-65 score of 0. As shown

below, an oral macrolide (azithromycin, clarithromycin) is the best choice. Respiratory fluoroquinolones may be used in the presence of comorbidities or recent antibiotics. The second patient has a CURB-65 score of 3 (age, respiratory rate, BUN) and merits consideration for inpatient therapy. Of the listed choices, a β -lactam (ceftriaxone) plus a macrolide (clarithromycin) is best. A respiratory fluoroquinolone may also be used as a single agent unless the patient goes to the intensive care unit, when a β -lactam should also be used. Fluconazole does not have a role for community-acquired pneumonia (CAP); rather, it is used to treat candidal infections. Piperacillin/tazobactam is a consideration when *Pseudomonas* infection is considered likely, such as in patients with cystic fibrosis or bronchiectasis. Vancomycin is only a consideration for CAP when epidemiologic considerations make methicillin-resistant *Staphylococcus aureus* a likely pathogen.

56. The answer is A.

(Chap. 27) Patients initiated on mechanical ventilation require a variety of supportive measures. Sedation and analgesia with a combination of benzodiazepines and narcotics are commonly used to maintain patient comfort and safety while they are mechanically ventilated. In addition, patients are immobilized and are thus at high risk for development of deep venous thrombosis and pulmonary embolus. Prophylaxis with unfractionated heparin or low-molecular-weight heparin SC should be administered. Prophylaxis against diffuse gastrointestinal mucosal injury is also indicated, particularly in individuals with neurologic insult and those with severe respiratory failure and adult respiratory distress syndrome. Gastric acid suppression can be managed with H₂-receptor antagonists, proton pump inhibitors, and Carafate. It is also recommended that individuals who are expected to be intubated for >72 h receive nutritional support. Prokinetic agents are often required. A final supportive measure that should be instituted in all intensive care units is to maintain a protocol that includes frequent positional changes and surveillance for prevention of decubitus ulcers. In the past, frequent ventilator circuit changes had been studied as a measure for prevention of ventilator-associated pneumonia, but they were ineffective and may even have increased the risk of ventilator-associated pneumonia.

57. The answer is B.

(Chap. 29; Dellinger RP et al: *Crit Care Med* 32 858, 2004) Sepsis is a systemic inflammatory response that develops in response to a microbial source. To diagnose the systemic inflammatory response syndrome (SIRS), a patient should have two or more of the following conditions: (1) fever or hypothermia; (2) tachypnea; (3) tachycardia; or (4) leukocytosis, leukopenia, or >10% band forms. This patient fulfills the criteria for sepsis with septic

shock because she meets the above criteria for SIRS with the presence of organ dysfunction and ongoing hypotension despite fluid resuscitation. The patient has received 2 L of IV colloid and now has a central venous pressure of 18 cmH₂O. Ongoing large-volume fluid administration may result in pulmonary edema because the central venous pressure is quite high. At this point, fluid administration should continue but at a lower infusion rate. In this patient, who is receiving chronic glucocorticoids for an underlying inflammatory condition, stress-dose steroids should be administered because adrenal suppression will prevent the patient from developing the normal stress response in the face of SIRS. Glucocorticoids may be given while waiting for results of the cosyntropin stimulation test. If the patient fails to respond to glucocorticoids, she should be started on vasopressor therapy. A single small study has suggested that norepinephrine may be preferred over dopamine for septic shock, but these data have not been confirmed in other trials. The “Surviving Sepsis” guidelines state that either norepinephrine or dopamine should be considered as first-line agent for the treatment of septic shock. Transfusion of red blood cells in critically ill patients has been associated with a higher risk for development of acute lung injury, sepsis, and death. A threshold hemoglobin value of 7 g/dL has been shown to be as safe as a value of 10 g/dL and is associated with fewer complications. In this patient, a blood transfusion is not currently indicated but may be considered if the central venous oxygen saturation is <70% to improve oxygen delivery to tissues. An alternative to blood transfusion in this setting is the use of dobutamine to improve cardiac output.

58. The answer is D.

(Chap. 29) Sepsis is responsible for >200,000 deaths yearly in the United States, and the incidence of sepsis has been increasing over the past 20 years. Approximately two-thirds of patients have underlying comorbidities, and the incidence of sepsis increases markedly with age. Pathophysiologically, sepsis occurs as a result of the inflammatory reaction that develops in response to an infection. Microbial invasion of the bloodstream is not necessary for the development of severe sepsis. In fact, blood cultures are positive in only 20–40% of cases of severe sepsis and in only 40–70% of septic shock. The systemic response to infection classically has been demonstrated by the response to lipopolysaccharide (LPS), which is also called *endotoxin*. LPS binds to receptors on the surfaces of monocytes, macrophages, and neutrophils, causing activation of these cells to produce a variety of inflammatory mediators, including tumor necrosis factor α . This process amplifies the LPS signal, stimulating a process of inflammation that leads to complement activation, increase in procoagulant factors, and cellular injury. The end result of this systemic inflammatory process is widespread intravascular thrombosis. This process is meant to wall off invading

microorganisms to prevent infection from spreading to other tissues, but in cases of severe sepsis, this leads to tissue hypoxia and ongoing cellular injury. In addition, systemic hypotension develops as a reaction to inflammatory mediators and occurs despite increased levels of plasma catecholamines. Physiologically, this is manifested as a marked decrease in systemic vascular resistance despite evidence of increased sympathetic activation. Survival in patients with sepsis has improved in the past decades largely because of advances in supportive care in the intensive care unit. Activated protein C is the only medication currently approved for treatment of patients with sepsis and has been demonstrated to cause a 33% relative risk mortality reduction.

59. The answer is D.

(Chap. 27) Mechanical ventilation is frequently used to support ventilation in individuals with both hypoxemic and hypercarbic respiratory failure. Mechanical ventilators provide warm, humidified gas to the airways in accordance with preset ventilator settings. The ventilator serves as the energy source for inspiration, but expiration is a passive process driven by the elastic recoil of the lungs and chest wall. PEEP may be used to prevent alveolar collapse on expiration. The physiologic consequences of PEEP include decreased preload and decreased afterload. Decreased preload occurs because PEEP decreases venous return to the right atrium and may manifest as hypotension, especially in a volume-depleted individual. In addition, PEEP is transmitted to the heart and great vessels. This complicated interaction leads to a decrease in afterload and may be beneficial to individuals with depressed cardiac function. When using mechanical ventilation, the physician should also be cognizant of other potential physiologic consequences of the ventilator settings. Initial settings chosen by the physician include mode of ventilation, respiratory rate, fraction of inspired oxygen, and tidal volume if volume-cycled ventilation is used or maximum pressure if pressure-cycled ventilation is chosen. The respiratory therapist also has the ability to alter the inspiratory flow rate and waveform for delivery of the chosen mode of ventilation. These choices can have important physiologic consequences for the patient. In individuals with obstructive lung disease, it is important to maximize the time for exhalation. This can be done by decreasing the respiratory rate or decreasing the inspiratory time (increase the I:E ratio, prolong expiration), which is accomplished by increasing the inspiratory flow rate. Care must also be taken in choosing the inspired tidal volume in volume-cycled ventilatory modes because high inspired tidal volumes can contribute to development of acute lung injury because of overdistention of alveoli.

60. The answer is B.

(Chap. 27) Patients intubated for respiratory failure because of obstructive lung disease (asthma or COPD)

are at risk for the development of intrinsic positive end-expiratory pressure (auto-PEEP). Because these conditions are characterized by expiratory flow limitation, a long expiratory time is required to allow a full exhalation. If the patient is unable to exhale fully, auto-PEEP develops. With repeated breaths, the pressure generated from auto-PEEP continues to increase and impedes venous return to the right ventricle. This results in hypotension and increases the risk for pneumothorax. Both of these conditions should be considered when evaluating this patient. However, because breath sounds are heard bilaterally, pneumothorax is less likely, and tube thoracostomy is not indicated at this time.

Development of auto-PEEP has most likely occurred in this patient because the patient is currently agitated and hyperventilating as the effects of the paralytic agent wear off. In AC mode ventilation, each respiratory effort will deliver the full tidal volume of 550 mL, and there is a decreased time for exhalation, allowing auto-PEEP to occur. Immediate management of this patient should include disconnecting the patient from the ventilator to allow him to fully exhale and decrease the auto-PEEP. A fluid bolus may temporarily increase the blood pressure but would not eliminate the underlying cause of the hypotension. After treatment of the auto-PEEP by disconnecting the patient from the ventilator, sedation is important to prevent further occurrence of auto-PEEP by decreasing the respiratory rate to the set rate of the ventilator. Sedation can be accomplished with a combination of benzodiazepines and narcotics or propofol. Initiation of vasopressor support is not indicated unless other measures fail to treat the hypotension and it is suspected that sepsis is the cause of hypotension.

61. The answer is E.

(Chap. 23) OSA is defined by excessive daytime sleepiness and at least five obstructed breathing events (hypopnea or apnea) per hour of sleep. Apneic events are pauses in breathing that last ≥ 10 s. Hypopneic events occur when ventilation is reduced by 50% for ≥ 10 s. It should be stressed that there are two components to diagnosis: symptoms of daytime sleepiness combined with obstructive breathing while asleep. Patients with disordered breathing at night who are asymptomatic while awake *do not have* OSA. The central pathogenesis of sleep apnea is pharyngeal narrowing that leads to airway obstruction when somnolent. Risk factors include male gender, obesity, and a shortened mandible or maxilla. It remains unclear whether smoking is an independent risk factor. The disorder is twice as common in men as in women. About 50% of patients with OSA have BMIs >30 kg/m². There appears to be an association between diabetes mellitus and OSA that is independent of obesity. Insulin resistance has been shown to be related to increasing frequency of apneas and hypopneas. Based on his other cardiac risk factors, including smoking, obesity, and

hypertension, as well as his new diagnosis of OSA, this patient should be screened for diabetes mellitus.

62. The answer is D.

(Chap. 10) The patient presents with acute-onset pulmonary symptoms, including wheezing, with no other medical problems. He is a farmer and was recently handling hay. The clinical presentation and radiogram are consistent with farmer's lung, a hypersensitivity pneumonitis caused by *Actinomyces* spp. In this disorder, moldy hay with spores of actinomycetes are inhaled and produce a hypersensitivity pneumonitis. The disorder is seen most commonly in rainy periods, when the spores multiply. Patients present generally 4–8 h after exposure with fever, cough, and shortness of breath without wheezing. Chest radiograms often show patchy bilateral, often upper lobe infiltrates. The exposure history will differentiate this disorder from other types of pneumonia.

63. The answer is A.

(Chap. 22) Disorders of the respiratory drive, respiratory muscular system, some chest wall disorders, and upper airways obstruction may produce an elevated Pa_{CO_2} despite having normal pulmonary function. In this setting, the A-a oxygen gradient is normal but the minute ventilation is low, producing respiratory acidosis. In pulmonary parenchymal or airways diseases associated with respiratory acidosis (pulmonary fibrosis, chronic obstructive pulmonary disease), the Pa_{CO_2} is elevated, the A-a gradient is commonly increased, and minute ventilation is either elevated or normal. Any cause of respiratory acidosis may produce an obligatory decrease in Pa_{O_2} . Diaphragmatic dysfunction and maximal inspiratory or expiratory pressures are commonly impaired with respiratory neuromuscular dysfunction but may be normal in other disorders of central hypoventilation such as stroke.

64. The answer is B.

(Chap. 19) This patient's clinical–radiologic presentation, in addition to the lung function information, which revealed a moderate restrictive defect and a moderate gas transfer defect, suggests an acute pneumonitis. The differential diagnosis includes various causes of diffuse alveolar hemorrhage, idiopathic bronchiolitis obliterans organizing pneumonia, acute eosinophilic pneumonia, interstitial lung disease secondary to connective tissue disorders (systemic lupus erythematosus, rheumatoid arthritis, polymyositis), and diffuse alveolar damage secondary to other causes (e.g., sepsis, drugs, toxins, infections). Methotrexate has been associated with an idiosyncratic drug reaction, with particular risk in elderly patients and in patients with decreased creatinine clearance. Discontinuing the medicine and in some cases adding high-dose steroids constitute the initial management. Initiating empirical broad-spectrum antibiotics until a more definite result could be obtained via a bronchoscopy would be a reasonable approach.

65. The answer is C.

(Chap. 29) As the mortality from sepsis has increased over the past 20 years, more research has been performed to attempt to limit mortality. Specific therapies have been developed to target the inflammatory response to sepsis, particularly the effect of the inflammatory response on the coagulation system. Activated protein C was the first drug approved by the U.S. Food and Drug Administration for the treatment of patients with septic shock. This drug is an anticoagulant that may also have antiapoptotic and anti-inflammatory properties. In a randomized, controlled trial, activated protein C was associated with an absolute reduction in mortality of 6.1%, and the effect of the drug on mortality was greatest in those who were most critically ill. However, in individuals who are less severely ill, activated protein C may increase mortality. Although it is unethical to randomize individuals to a trial assessing the appropriate timing of antibiotic delivery, retrospective analyses have demonstrated an increased risk of death if antibiotics are not given within 1 h of presentation. A single-center trial of early goal-directed therapy in septic shock showed a survival advantage when this approach was taken. Early goal-directed therapy developed a protocol for fluid administration, institution of vasopressors, and blood transfusion based on physiologic parameters, including mean arterial pressure, central venous oxygen saturation, and presence of acidosis, among others. Bicarbonate therapy is commonly used when severe metabolic acidosis ($\text{pH} < 7.2$) is present in septic shock. However, there is no evidence that bicarbonate improves hemodynamics, response to vasopressors, or outcomes in septic shock.

66. The answer is D.

(Chap. 3) The patient presents with chronic cough because it has lasted for more than 3 weeks. He denies symptoms of the most common causes of chronic cough, such as asthma, gastroesophageal reflux disease, and postnasal drip. However, he does take an angiotensin-converting enzyme (ACE) inhibitor, which is known to cause chronic cough in 5–20% of the patients who take this class of medications. Cough that is caused by use of ACE inhibitors generally begins between 1 week and 6 months after medication initiation. The most appropriate diagnostic and therapeutic step at this point is to discontinue the ramipril. Angiotensin receptor blockers can be used instead of the ACE inhibitor to improve cardiac outcomes but are generally not recommended as first-line therapy. In light of this patient's lack of risk factors for malignancy and lack of sputum production, bronchoscopy would not be helpful in this case. Furosemide and digoxin are not associated with cough. Because the patient denies having infectious or constitutional symptoms, empirical courses of antibiotics are not warranted.

67. The answer is B.

(Chap. 13) There are inactivated and live, attenuated forms of influenza vaccine. The intranasal spray, marketed as “Flu-mist,” is a live, attenuated virus and is not recommended for elderly or immunocompromised patients. This vaccine has similar efficacy to the intramuscular vaccine, which is an inactivated, or “killed,” preparation of the previous year’s strains of influenza A and B. The intramuscular vaccine is manufactured using egg products; patients with true egg hypersensitivity should not receive it. It is safe for elderly and immunocompromised patients. In the past, influenza vaccines have been associated with Guillain-Barré syndrome. This association has not been demonstrated in the past decade despite close surveillance. Patients do not need to be warned of this side effect.

68. The answer is D.

(Chap. 13) The majority of influenza infections are clinically mild and self-limited. Treatment with over-the-counter cough suppressants and analgesics such as acetaminophen is often adequate. Patients who are younger than age 18 years are at risk of developing Reye’s syndrome if they are exposed to salicylates such as aspirin. The neuraminidase inhibitors oseltamivir and zanamivir have activity against influenza A and B. They can be used within 2 days of symptom onset and have been shown to reduce the duration of symptoms by a day or two. This patient has had symptoms for >48 h, so neither drug is likely to be effective. The patient’s history of asthma is an additional contraindication to zanamivir because this drug can precipitate bronchospasm. The M2 inhibitors amantadine and rimantadine have activity against influenza A only. However, in 2005, >90% of A/H3N2 viral isolates demonstrated resistance to amantadine, and these drugs are no longer recommended for use in patients with influenza A.

69. The answer is B.

(Chap. 13) Myositis and subsequent rhabdomyolysis and myoglobinuria represent a rare but severe complication of influenza infection. Renal failure may occur. Myalgias are a prominent symptom of influenza infection, but myositis characterized by elevated creatine phosphokinase and marked tenderness of the muscles is very infrequent. The pathogenesis of this complication is unknown. Other extrapulmonary complications of influenza, including encephalitis, transverse myelitis, and Guillain-Barré syndrome, have been reported, although the etiologic relationship to influenza virus infection is uncertain. Myocarditis and pericarditis were reported during the 1918–1919 influenza pandemic. The most serious complication of influenza is secondary bacterial pneumonia, such as that caused by *S. aureus*. Arthritis, conjunctivitis, and eczematous rashes have not been described as complications of influenza infection.

70. The answer is C.

(Chap. 14) Avian influenza epidemics occur when human influenza A undergoes an antigenic exchange with influenza found in poultry. Recent outbreaks have not been associated with effective human-to-human spread; nearly all patients reported exposure to infected poultry. Past influenza pandemics, including the 1918–1919 pandemic, appear to have originated from antigenic exchange between human and avian influenza viruses. Antigenic shifts are defined as major changes in the hemagglutinin (H) and neuraminidase (N) antigens and occur only with influenza A. Minor antigenic changes are known as antigenic drift and can occur with hemagglutinin alone or with both hemagglutinin (H) and neuraminidase (N). Although influenza A and B are genetically and morphologically similar, the latter virus’ inability to undergo antigenic shifts lessens its virulence and involvement in pandemic flu. Influenza C is a rare cause of disease in humans and is typically a clinically mild, self-limited infection.

71. The answer is A.

(Chap. 31) This patient is presenting in pulmonary edema and cardiogenic shock caused by acute myocardial infarction (MI). Given the distribution of ST-segment elevation, the left anterior descending artery is the most likely artery occluded. Initial management should include high-dose aspirin, heparin, and stabilization of blood pressure. Initial management of acute MI also includes use of nitroglycerin and β -blockers such as metoprolol in most individuals, but these are contraindicated in this individual because of his profound hypotension. In addition, use of furosemide for the treatment of pulmonary edema is also contraindicated because of this patient’s degree of hypotension. IV fluids should be used with caution because the patient also has evidence of pulmonary edema. The best choice for treatment of this patient’s hypotension is aortic counterpulsation. Aortic counterpulsation requires placement of an intraaortic balloon pump percutaneously into the femoral artery. The sausage-shaped balloon inflates during early diastole, augmenting coronary blood flow, and collapses during early systole, markedly decreasing afterload. In contrast to vasopressors and inotropic agents, aortic counterpulsation decreases myocardial oxygen consumption. Both dobutamine and norepinephrine can increase myocardial oxygen demand and worsen ischemia.

72. The answer is D.

(Chap. 31) This patient is presenting with right ventricular (RV) myocardial infarction. The usual clinical features of RV infarction are hypotension, elevated right heart filling pressures, absence of pulmonary congestion, and evidence of RV dilatation and dysfunction. In most cases of RV infarction, the vessel involved is the right coronary

artery, which manifests as ST elevation in leads II, III, and aV_F. When RV infarction occurs, ST depression is commonly seen in V₁ and V₂. An electrocardiogram with the precordial leads placed on the right side of the chest demonstrates ST elevation in RV₄. The initial treatment of hypotension of RV infarction is IV fluids to increase the central venous pressure to 10–15 mmHg. If fluid administration fails to alleviate the hypotension, sympathomimetic agents or aortic counterpulsation can be used. However, care must be taken to avoid excess fluid administration, which would shift the interventricular septum to the left and further impede cardiac output. A transvenous pacemaker would be useful if the hypotension were related to heart block or profound bradycardia, which can be associated with right coronary artery ischemia.

73. The answer is C.

(Chap. 32) SCD is defined as death from cardiac causes heralded by the abrupt loss of consciousness within 1 h of onset of acute symptoms. SCD accounts for about 50% of all cardiac deaths, and of these, two-thirds are initial cardiac events or occur in populations with previously known heart disease who are considered to be relatively low risk. The most common electrical mechanism of SCD is ventricular fibrillation, accounting for 50–80% of cardiac arrests. The risk of SCD rises with age and is greater in men and individuals with a history of coronary artery disease. In addition, several inherited conditions increase the risk of SCD, including hypertrophic cardiomyopathy, right ventricular dysplasia, and long-QT syndromes, among others. A strong parental history of SCD as a presenting history of coronary artery disease increases the likelihood of a similar presentation in an offspring. Interestingly, 70–80% of men who die from SCD have preexisting healed MIs, but only 20–30% have had recent acute MI. On autopsy, individuals who die of SCD most commonly show long-standing atherosclerotic disease as well as evidence of an unstable coronary lesion. When this is considered with the fact that most individuals do not have pathologic evidence of an acute MI by pathology, this suggests that transient ischemia is the mechanism of onset of the fatal arrhythmia. Rapid intervention and restoration of circulation are important for survival in SCD. Within 5 min, the likelihood of surviving SCD is only 25–30% for out-of-hospital arrests.

74. The answer is C.

(Chap. 32) Immediate defibrillation should be the initial choice of action in the treatment of sudden cardiac arrest caused by ventricular fibrillation (VF) or ventricular tachycardia (VT). Defibrillation should occur before endotracheal intubation or placement of IV access. If the time to potential defibrillation is <5 min, the medical team should proceed immediately to defibrillation at 300–360 J if a monophasic defibrillator is used (150 J if

a biphasic defibrillator is used). If there is >5-min delay to defibrillation, then brief cardiopulmonary resuscitation (CPR) should be given before defibrillation. A single shock should be given with immediate resumption of CPR for 60–90 s before delivering additional shocks. After each shock, CPR should be given without delay. Even if there is return of a perfusable rhythm, there is often a delayed return of pulse because of myocardial stunning. If the patient remains in VF or pulseless VT after initial defibrillation, the patient should be intubated and have IV access attained while CPR is performed. After IV access has been obtained, the initial drug of choice is either 1 mg of or 40 units of vasopressin. Amiodarone is a second-line agent.

75. The answer is C.

(Chap. 32; Nolan J et al: *Circulation* 108:118, 2003) In 2002, two studies conducted in Europe and Australia confirmed the benefit of therapeutic hypothermia after out-of-hospital cardiac arrest. In these trials, patients were rapidly cooled to 32–34°C and maintained at these temperatures for the initial 12–24 h. Individuals who received therapeutic hypothermia were 40–85% more likely to have good neurologic outcomes upon hospital discharge. In addition, therapeutic hypothermia also decreased in-hospital mortality rates. Time to initial defibrillation of >5 min is associated with no more than a 25–30% survival rate, and survival continues to decrease linearly from 1 to 10 min. Defibrillation within 5 min has the greatest likelihood for good neurologic outcomes. Of the medications used in treatment of cardiac arrest caused by ventricular fibrillation or pulseless ventricular tachycardia, none have been demonstrated to have any effects on neurologic outcome.

76. The answer is D.

(Chap. 33) Although troponin is a commonly used biomarker for myocardial necrosis in the setting of acute myocardial infarction, it is also associated with and caused by a number of other clinical entities, including pulmonary embolism, myocarditis, and congestive heart failure. Troponin elevations are not known to be caused by pneumonia in the absence of myocardial necrosis.

77. The answer is B.

(Chap. 33) Patients with unstable angina/non-ST-segment elevation myocardial infarction (UA/NSTEMI) exhibit a wide spectrum of risk of death, MI, or urgent revascularization. Risk stratification tools such as the TIMI risk score are useful for identifying patients who benefit from an early invasive strategy and those who are better suited for a more conservative approach. The TIMI risk score is composed of seven independent risk factors: age ≥65, three or more cardiovascular risk factors, prior stenosis >50%, ST-segment deviation ≥0.5 mm, two or more anginal events in <24 h, aspirin usage in

the past 7 days, and elevated cardiac markers. Aspirin resistance can occur in 5–10% of patients and is more common among those taking lower doses of aspirin. Having unstable angina despite aspirin usage suggests aspirin resistance. Use of a β -agonist and a diuretic does not confer an independent risk for death, MI, or need for urgent revascularization.

78. The answer is B.

(Chap. 33) Unstable angina is defined as angina or ischemic discomfort with at least one of three factors: pain at rest lasting >10 min, severe recent pain (within 4–6 weeks), or crescendo angina. NSTEMI is diagnosed when a patient with unstable angina has positive cardiac biomarkers. Anti-ischemic therapy (nitrates, β -blockers) is important for symptom relief and to prevent recurrence of chest pain. Antithrombotic therapy is directed against the platelet aggregation at the site of the ruptured plaque. Initially, this therapy should consist of aspirin. Addition of clopidogrel confers an additional 20% risk reduction in both low- and high-risk NSTEMI patients, as demonstrated in the CURE trial. Continuation of treatment for ≤ 12 months confers additional benefit in patients treated conservatively and among those who underwent percutaneous coronary intervention. The GP IIb/IIIa inhibitors are usually reserved for high-risk (i.e., troponin-positive) patients and may not be beneficial for patients treated conservatively. Statin therapy is important for secondary prevention; however, spironolactone is not a first-line therapy for NSTEMI.

79. The answer is E.

(Chap. 33) Standard therapy for a patient with unstable angina or non-ST-segment elevation myocardial infarction (NSTEMI) includes aspirin and clopidogrel. If an anticoagulant is added, enoxaparin has been shown to be superior to unfractionated heparin in reducing recurrent cardiac events. Glycoprotein IIb/IIIa inhibitors have also been shown to be beneficial in treating unstable angina/NSTEMI. Eptifibatid, tirofiban, and abciximab are beneficial for patients likely to receive percutaneous intervention. Clinical trials have shown benefit of early invasive strategy in the presence of high-risk factors such as recurrent rest angina, elevated troponin, new ST-segment depression, congestive heart failure symptoms, rales, mitral regurgitation, positive stress test, ejection fraction <0.40, decreased blood pressure, sustained ventricular tachycardia, or recent coronary intervention. The presence of ST depressions, rales, and mitral regurgitation puts this patient at high risk. Tissue plasminogen factor is beneficial in ST-segment elevation myocardial infarction, not NSTEMI.

80. The answer is C.

(Chap. 34) This patient has a right ventricular (RV) infarction. The combination of findings consistent with bradycardia, cardiogenic shock, low-normal left ventricular

and PA pressures, and markedly elevated right atrial pressure is consistent with acute RV failure. An acute pulmonary embolus may also cause acute RV failure, but the PA pressure is usually elevated. RV infarction is usually caused by occlusion of the right coronary artery; the bradycardia is caused by sinus or atrioventricular node ischemia. Right-sided precordial electrocardiography will show ST-segment elevation. Occlusion of the left main artery will cause cardiogenic shock, but the PCW pressure will be elevated. Perforated duodenal ulcer and ruptured aortic aneurysm will cause hypovolemic shock with low RA and PCW pressures. Patients with gram-negative sepsis will generally have a normal or increased cardiac index with normal filling pressures and low blood pressure.

81. The answer is C.

(Chap. 34) Myoglobin is released from ischemic myocardial cells and appears in serum within hours. It has a very short half-life in serum because it is excreted rapidly in the urine. Serum myoglobin returns to normal within 24 h after an infarction. Therefore, in this patient, a new elevation of myoglobin would be helpful in distinguishing new myocardial necrosis. Troponin-I and troponin-T are more specific markers of myocardial necrosis but have long half-lives in the circulation. They may remain elevated for more than 1 week after an acute MI. Therefore, they are not as useful for detecting new or recurrent injury. In the presence of a preexisting left bundle branch, ECG is of limited utility in detecting new ischemia. Serial echocardiograms may detect new wall motion abnormalities that suggest new ischemia or infarction, but in the absence of a prior study, a single echocardiogram would have limited utility in this patient.

82. The answer is B.

(Chap. 35) Brain death is defined by the cessation of cerebral function while somatic function is maintained by artificial means and the heart continues to pump. It is the only type of brain damage that is considered equivalent to death. The diagnosis of brain death should be confirmed with the following clinical findings: unresponsiveness to any stimuli, indicating widespread cortical destruction; brainstem damage, as evidenced by enlarged or mid-sized pupils without light reaction; absent corneal and oculo-vestibular reflexes; and apnea, indicating medullary destruction. The heart rate should be invariant. Because the spinal cord is intact, spinal reflexes may be present. The presence or absence of the Babinski sign does not contribute to the diagnosis of brain death. Central diabetes insipidus occurs with dysfunction of the hypothalamus or posterior pituitary. It has been described in patients with brain death but is not a component of the diagnosis.

83. The answer is E.

(Chap. 35) Foramen herniation, which forces the cerebellar tonsils into the foramen magnum, leads to compression

of the medulla and subsequent respiratory arrest. Central transtentorial herniation occurs when the medial thalamus compresses the midbrain as it moves through the tentorial opening; miotic pupils and drowsiness are the classic clinical signs. A locked-in state is usually caused by infarction or hemorrhage of the ventral pons; other causes include Guillain-Barré syndrome and certain neuromuscular blocking agents. Catatonia is a semi-awake state seen most frequently as a manifestation of psychotic disorders such as schizophrenia. Third-nerve palsies arise from an uncus transtentorial herniation where the anterior medial temporal gyrus herniates into the anterior portion of the tentorial opening anterior to the adjacent midbrain. Coma may occur because of compression of the midbrain.

84. The answer is D.

(Chap. 36) This patient has evidence of increased ICP and needs to be managed urgently. A variety of maneuvers may decrease ICP acutely. Hyperventilation causes vasoconstriction, reducing cerebral blood volume and decreasing ICP. However, this can be used only for a short period because the decrease in cerebral blood flow is of limited duration. Mannitol, an osmotic diuretic, is recommended in cases of increased ICP resulting from cytotoxic edema. Hypotonic fluids should be avoided. Instead, hypertonic saline is given to elevate sodium levels and prevent worsening of edema. A more definitive treatment to decrease ICP is to have a ventriculostomy placed by which excessive pressure can be relieved by draining cerebrospinal fluid (CSF). Further decreases in mean arterial pressure may worsen the patient's clinical status. The patient already has had more than a 20% reduction in MAP, which is the recommended reduction in cases of hypertensive emergency. In addition, the patient is exhibiting signs of increased ICP, which indicates that cerebral perfusion pressure (MAP-ICP) has been lowered. Paradoxically, the patient may need a vasopressor agent to increase MAP and thus improve cerebral perfusion. Finally, in cases of increased ICP, nitroprusside is not a recommended IV antihypertensive agent because it causes arterial vasodilation and may decrease cerebral perfusion pressure and worsen neurologic function.

85. The answer is E.

(Chap. 37) Radiocontrast agents cause renal injury through intrarenal vasoconstriction and through generation of oxygen radicals, causing acute tubular necrosis. These medications cause an acute decrease in renal blood flow and GFR. Patients with chronic kidney disease, diabetes mellitus, heart failure, multiple myeloma, and volume depletion are at highest risk of contrast nephropathy. It is clear that hydration with normal saline is an effective measure to prevent contrast nephropathy. Of the other measures mentioned here, only sodium bicarbonate or *N*-acetylcysteine could be recommended for clinical use to reduce the risk of

contrast nephropathy. Dopamine has been proven an ineffective agent to prevent contrast nephropathy. Fenoldopam, a D₁-receptor agonist, has been tested in several clinical trials and does not appear to reduce the incidence of contrast nephropathy. Although several small clinical studies have suggested a clinical benefit to the use of *N*-acetylcysteine, a meta-analysis has been inconclusive, and the medication should be administered well in advance of the procedure. Sodium bicarbonate begun within 1 h of the procedure has shown a significant benefit in a single-center, randomized, controlled trial. Because of the time limitations and based on the evidence, only sodium bicarbonate would be helpful in this patient.

86. The answer is C.

(Chap. 37) In bilateral renal artery stenosis (or unilateral stenosis in a patient with a single kidney), GFR is preserved by the actions of angiotensin II: afferent arteriolar vasodilatation and efferent arteriolar vasoconstriction. Angiotensin-converting enzyme inhibitors and ARBs blunt these responses and can precipitate acute renal failure in this setting. Thiazide diuretics, calcium channel blockers, and centrally acting α blockers are better choices for an antihypertensive agent in a patient with bilateral renal artery stenosis.

87. The answer is B.

(Chap. 38) In peritoneal dialysis, 1.5–3.0 L of dextrose-containing fluid is allowed to dwell in the peritoneum to remove toxic materials and volume. Factors such as infection, drugs, position, and exercise impact solute and water clearance. In the developed world, hemodialysis is often the preferred method for renal replacement for patients. However, in poorer countries where access to hemodialysis centers is limited, peritoneal dialysis is used more commonly. Residual renal function alters the dose of dialysis but does not impact the mode of dialysis. Moreover, patients with no residual renal function who receive peritoneal dialysis are at higher risk of uremia than patients on hemodialysis. High transporters through the peritoneum require more frequent doses of peritoneal dialysis, potentially negating the benefit of this modality. In the developed world, the patient's age does not impact the mode of dialysis. Patients with prior abdominal surgeries often have difficulty with peritoneal dialysis catheter placement and dialysate delivery.

88. The answer is A.

(Chap. 38) The potassium concentration of dialysate is usually 2.5 meq/L but may be varied depending on the predialysis serum potassium. This patient may need a lower dialysate potassium concentration. Sodium modeling is an adjustment of the dialysate sodium that may lessen the incidence of hypotension at the end of a dialysis session. Aldosterone defects, if present, are not likely

to play a role in this patient because his kidneys are not being perfused. Therefore, nephrectomy is not likely to control his potassium. Similarly, because the patient is likely anuric, there is no efficacy in using loop diuretics to effect kaluresis. This patient has no approved indications for implantation of a defibrillator.

89. The answer is A.

(Chap. 38) Nonsteroidal anti-inflammatory drugs (NSAIDs) do not alter glomerular filtration rate in normal individuals. However, in states of mild to moderate hypoperfusion (as in prerenal azotemia) or in the presence of chronic kidney disease, glomerular perfusion and filtration fraction are preserved through several compensatory mechanisms. In response to a reduction in perfusion pressures, stretch receptors in afferent arterioles trigger a cascade of events that lead to afferent arteriolar dilatation and efferent arteriolar vasoconstriction, thereby preserving glomerular filtration fraction. These mechanisms are partly mediated by the vasodilators prostaglandin E₂ and prostacyclin. NSAIDs can impair the kidney's ability to compensate for a low perfusion pressure by interfering with local prostaglandin synthesis and inhibiting these protective responses. Ureteral obstruction is not the mechanism by which NSAID impairs renal function in this scenario. NSAIDs are not known to be proximal tubule toxins.

90. and 91. The answers are A and A, respectively.

(Chap. 38; Solomon R: *Kidney Int* 53:230, 1998) Radiocontrast agents are a common cause of acute renal failure and may result in acute tubular necrosis (contrast nephropathy). It is common for patients receiving IV contrast to develop a transient increase in serum creatinine. These agents cause renal failure by inducing intrarenal vasoconstriction and reducing renal blood flow, mimicking prerenal azotemia, and directly causing tubular injury. The risk of contrast nephropathy may be reduced by initiating newer iso-osmolar agents and minimizing the dose of contrast. When the reduction in renal blood flow is severe or prolonged, tubular injury develops, causing acute renal failure. Patients with intravascular volume depletion, diabetes, congestive heart failure, multiple myeloma, or chronic renal failure have an increased risk of contrast nephropathy. The urine sediment is bland in mild cases, but with acute tubular necrosis, muddy brown granular casts may be seen. Saline hydration plus N-acetylcysteine may decrease the risk and severity of contrast nephropathy. RBC casts indicate glomerular disease, and WBC casts suggest upper urinary tract infection. Urinary eosinophils are seen in allergic interstitial disease caused by many drugs (Tables 90 and 91).

92. The answer is A.

(Chap. 39) Excretion of water is tightly regulated at the collecting duct by arginine vasopressin (AVP, formerly antidiuretic hormone). An increase in plasma tonicity is sensed by hypothalamic osmoreceptors, causing AVP

TABLE 90, 91

GUIDELINES FOR USE OF INTRAVENOUS CONTRAST IN PATIENTS WITH IMPAIRED RENAL FUNCTION

SERUM CREATININE, $\mu\text{mol/L}$ (mg/dL) ^a	RECOMMENDATION
<133 (<1.5)	Use either ionic or nonionic at 2 mL/kg to 150 mL total
133–177 (1.5–2.0)	Nonionic; hydrate diabetics 1 mL/kg/h \times 10 h
>177 (>2.0)	Consider noncontrast CT or MRI; nonionic contrast if required
177–221 (2.0–2.5)	Nonionic only if required (as above); contraindicated in diabetics
>265 (>3.0)	Nonionic IV contrast given only to patients undergoing dialysis within 24 h

^a The risk is greatest in patients with increasing creatinine levels.

secretion from the posterior pituitary. AVP binding to the collecting duct leads to insertion of water channels (aquaporin-2) into the luminal membrane, promoting water reabsorption. Serum sodium is the principal extracellular solute, and so effective osmolality is determined predominantly by the plasma sodium concentration. Plasma osmolality normally is regulated within 1–2% of normal (280–290 mosmol/kg). The sensitivity of the baroreceptors for AVP release is far less than that of the osmoreceptors. Depletion of intravascular volume sufficient to decrease mean arterial pressure is necessary to stimulate AVP secretion.

93. The answer is B.

(Chap. 40) The differential diagnosis for hypernatremia is fairly narrow because it results in a relative loss of water. Water is lost via renal or nonrenal mechanisms. The urine osmolality is a key historic piece of data. If the patient is excreting the minimum amount of maximally concentrated urine, gastrointestinal (osmotic diarrhea), insensible (skin or respiratory loss), or remote renal losses (diabetes mellitus) are the cause. This patient is excreting a large amount of dilute urine. He is not excreting >750 mosm in his urine daily, which would suggest diuretic use. Either central or nephrogenic diabetes insipidus must be the cause. In this patient, the lack of response to desmopressin indicates nephrogenic diabetes insipidus.

94. The answer is E.

(Chap. 39) The patient in the preceding scenario has nephrogenic diabetes insipidus (NDI). Causes of NDI include drugs (particularly lithium carbonate), hypercalcemia, hypokalemia, papillary necrosis, or congenital disorders. Patients with symptomatic polyuria caused by NDI can be treated with a low-sodium diet and thiazide diuretics, which induce mild volume depletion and enhanced proximal reabsorption of salt and water. Narcotics may be useful in patients with gastrointestinal hypermotility and

water loss as a result thereof. AVP analogues are used to treat central diabetes insipidus (CDI) and would have no impact on NDI. If a patient is found to have CDI, brain imaging should be obtained to rule out destruction of the neurohypophysis. Lithium carbonate is a cause of NDI and should be discontinued if causing symptomatic NDI.

95. The answer is D.

(Chap. 39) This patient is most likely hypovolemic from the osmotic preparation for his colonoscopy. Physical examination supports hypovolemic hyponatremia. Hyperglycemia and hyperlipidemia can cause hyponatremia, but these conditions would be associated with a high and normal plasma osmolality, respectively. SIADH is unlikely to be causing the hyponatremia if the extracellular volume status is decreased. Diabetes insipidus is a hypernatremic disorder caused by excess water loss.

96. The answer is B.

(Chap. 40) The pH is <7.35 , so the primary process is an acidosis. The HCO_3^- and P_{CO_2} are low, excluding a primary respiratory acidosis. The anion gap is normal at 12. The expected P_{CO_2} is between 24 and 16 mmHg for appropriate respiratory compensation. The P_{CO_2} in this example represents normal respiratory compensation for metabolic acidosis.

97. The answer is A.

(Chap. 40) Metabolic acidosis occurs because of endogenous acid production or loss of bicarbonate. The anion gap is elevated in the presence of unmeasured anions (or, less commonly, a loss of unmeasured cations) and is normal with bicarbonate loss. A decrease in the serum albumin of 1 g/dL from normal lowers the expected anion gap by 2.5 meq/L. The differential diagnosis for a non-anion gap metabolic acidosis includes gastrointestinal losses, renal acidosis, and drug-induced and other less common causes. Nursing home residents are at risk for institutionally acquired diarrheas, which are often infectious. The urine pH is usually high in proximal renal tubular acidosis, and the patient is usually younger. Defects in the renin-angiotensin system, such as hypoaldosteronism, cause hyperkalemia, not hypokalemia. This patient has no evidence of renal failure. Diuretic use usually causes a metabolic alkalosis.

98. The answer is B.

(Chap. 40; Adrogue HJ, Madias NE: *Management of life-threatening acid-base disorders. First of two parts. N Engl J Med* 338:26–34, 1998.) A respiratory alkalosis with a combined metabolic acidosis is typical of salicylate toxicity. Salicylate intoxication can result in respiratory alkalosis, mixed respiratory alkalosis and metabolic acidosis, or (less commonly) a simple metabolic acidosis. Respiratory alkalosis is caused by direct stimulation of the respiratory center by salicylate. The accumulation of lactic acid and ketoacids leads to the concomitant metabolic acidosis.

The severity of the neurologic manifestations largely depends on the concentration of salicylate in the central nervous system (CNS). Therapy is directed at limiting further drug absorption by administering activated charcoal and promoting the exit of salicylate from the CNS. This can be accomplished by alkalinizing the serum, typically by means of the addition of IV fluids with sodium bicarbonate, with the goal of increasing the serum pH to between 7.45 and 7.50. Increasing the glomerular filtration rate will also enhance salicylate excretion. Hemodialysis is reserved for severe cases, especially those involving fulminant renal failure.

99. The answer is B.

(Chap. 40) The octahedral, or envelope-shaped, crystals are caused by the presence of calcium oxalate in the urine. Calcium oxalate crystals are classically seen in ethylene glycol ingestion, which also causes a high anion gap metabolic acidosis. White blood cell casts indicate an upper urinary tract infection associated with a positive urine culture. Uric acid (rhombohedral-shaped) or struvite (“coffin lid”) crystals may be seen in cases of nephrolithiasis that causes hydronephrosis. Red blood cell casts are indicative of glomerular disease, often associated with a positive ANA.

100. The answer is B.

(Chap. 40) The pH the plasma bicarbonate are high. This is indicative of a metabolic alkalosis, not a primary acidosis. A respiratory alkalosis is not consistent with an elevated P_{CO_2} . Similarly, the P_{CO_2} is elevated appropriately to compensate for the metabolic alkalosis, excluding a primary respiratory acidosis. The respiratory compensation for a metabolic alkalosis is limited by the hypoxic drive. When the P_{CO_2} increases into the 40s and 50s, the hypoxic drive maintains a Pa_{O_2} of >55 – 60 mmHg, preventing further hypoventilation to additionally increase P_{CO_2} .

101. The answer is E.

(Chap. 40) The differential diagnosis for metabolic alkalosis can be divided into those disorders with extracellular fluid contraction and normotension (or hypotension) and those with extracellular fluid expansion and hypertension (see Table 41-6). Cushing’s disease and mineralocorticoid excess cause a metabolic alkalosis with hypertension. Patients with Bartter syndrome are normotensive. This patient has evidence of hypovolemia with altered mental status, hypotension, and tachycardia. Myocardial infarction causing cardiogenic shock would result in an anion gap metabolic acidosis because of lactate accumulation.

102. The answer is E.

(Chap. 41) Vitamin K is a fat-soluble vitamin that plays an essential role in hemostasis. It is absorbed in the small intestine and stored in the liver. It serves as a cofactor in the enzymatic carboxylation of glutamic acid residues on prothrombin-complex proteins. The three major causes of

vitamin K deficiency are poor dietary intake, intestinal malabsorption, and liver disease. The prothrombin complex proteins (factors II, VII, IX, and X and protein C and protein S) all decrease with vitamin K deficiency. Factor VII and protein C have the shortest half-lives of these factors and therefore decrease first. Therefore, vitamin K deficiency manifests with prolongation of the prothrombin time first. With severe deficiency, the aPTT is prolonged as well. Factor VIII is not influenced by vitamin K.

103. The answer is E.

(Chaps. 41) Hemophilia A results from a deficiency of factor VIII. Replacement of factor VIII is the centerpiece of treatment. Cessation of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) is highly recommended. FFP contains pooled plasma from human sources. Cryoprecipitate refers to FFP that is cooled, resulting in the precipitation of material at the bottom of the plasma. This product contains about half the factor VIII activity of FFP in a tenth of the volume. Both agents are therefore reasonable treatment options. DDAVP causes the release of a number of factors and von Willebrand factor from the liver and endothelial cells. This may be useful for patients with mild hemophilia. Recombinant or purified factor VIII (i.e., Humate P) is indicated in patients with more severe bleeding. Therapy may be required for weeks, with levels of factor VIII kept at 50%, for postsurgical or severe bleeding. Plasmapheresis has no role in the treatment of patients with hemophilia A.

104. The answer is C.

(Chap. 41) LAs cause prolongation of coagulation tests by binding to phospholipids. Although most often encountered in patients with SLE, they may develop in normal individuals. The diagnosis is first suggested by prolongation of coagulation tests. Failure to correct with incubation with normal plasma confirms the presence of a circulating inhibitor. Contrary to the name, patients with LA activity have normal hemostasis and are not predisposed to bleeding. Instead, they are at risk for venous and arterial thromboembolisms. Patients with a history of recurrent unplanned abortions or thrombosis should undergo lifelong anticoagulation. The presence of LAs or anticardiolipin antibodies without a history of thrombosis may be observed because many of these patients will not go on to develop a thrombotic event.

105. The answer is A.

(Chap. 41) Factor V Leiden refers to a point mutation in the factor V gene (arginine to glutamine at position 506). This makes the molecule resistant to degradation by activated protein C. This disorder alone may account for $\leq 25\%$ of inherited prothrombotic states, making it the most common of these disorders. Heterozygosity for this mutation increases an individual's lifetime risk of venous

thromboembolism sevenfold. A homozygote has a 20-fold increased risk of thrombosis. Prothrombin gene mutation is probably the second most common condition that causes "hypercoagulability." Antithrombin, protein C, and protein S deficiencies are rarer. Antithrombin complexes with activated coagulation proteins and blocks their biologic activity. Deficiency in antithrombin therefore promotes prolonged activity of coagulation proteins, resulting in thrombosis. Similarly, protein C and protein S are involved in the proteolysis of factors Va and VIIIa, which shuts off fibrin formation. Because proteins C and S are dependent on vitamin K for carboxylation, administration of warfarin anticoagulants may lower the level of proteins C and S more quickly relative to factors II, VII, IX, and X, thereby promoting coagulation. Patients with protein C deficiency may develop warfarin-related skin necrosis.

106. The answer is D.

(Chap. 41) The aPTT involves the factors of the intrinsic pathway of coagulation. Prolongation of the aPTT reflects either a deficiency of one of these factors (e.g., factor VIII, IX, XI, XII) or inhibition of the activity of one of the factors or components of the aPTT assay (i.e., phospholipids). This may be further characterized by the "mixing study," in which the patient's plasma is mixed with pooled plasma. Correction of the aPTT reflects a deficiency of factors that are replaced by the pooled sample. Failure to correct the aPTT reflects the presence of a factor inhibitor or phospholipid inhibitor. Common causes of a failure to correct include the presence of heparin in the sample, factor inhibitors (factor VIII inhibitor being the most common), and the presence of antiphospholipid antibodies. Factor VII is involved in the extrinsic pathway of coagulation. Inhibitors to factor VII would result in prolongation of the prothrombin time.

107. The answer is B.

(Chap. 43) Oral ribavirin combined with pegylated interferon appears to be the most effective regimen for treating patients with hepatitis C. Ribavirin does not exert antiviral effect but may be an immune modulator in combination with the interferon. Hemolytic anemia occurs in nearly 25% of patients receiving this therapy. Common approaches to this problem are dose reduction, cessation of ribavirin therapy, or use of red blood cell growth factors. Rash can occur but is less common. Interferon has common side effects as well, including flulike symptoms, depression, sleep disturbances, personality change, leukopenia, and thrombocytopenia.

108. The answer is D.

(Chap. 44) Voriconazole is an azole antifungal with a broader spectrum of activity than fluconazole against *Candida* spp. (including *Candida glabrata* and *Candida krusei*) and has activity against *Aspergillus* spp. It is available in oral and parenteral forms. Voriconazole's visual

disturbances are common, transient, and harmless, but patients should be warned to expect them. Voriconazole interacts significantly with many other medications, including immunosuppressive agents, such as tacrolimus, that are often used in patients at risk for systemic fungal infections. Voriconazole may also cause liver toxicity and photosensitivity. Renal toxicity is an issue with amphotericin B products rather than the azoles.

109. The answer is A.

(Chap. 44) Caspofungin and the other echinocandins (anidulafungin, micafungin) inhibit fungal synthesis of B-1,3-glucan synthase, a necessary enzyme for fungal cell wall synthesis that does not have a human correlate. These agents are available only parentally, not orally. They are fungicidal for *Candida* spp. and fungistatic against *Aspergillus* spp. Caspofungin is as at least equivalently effective as amphotericin B for disseminated candidiasis and is as effective as fluconazole for candidal esophagitis. It is not a first-line therapy for *Aspergillus* infection but may be used as salvage therapy. The echinocandins, including caspofungin, have an extremely high safety profile. They do not have activity against mucormycosis, paracoccidiomycosis, or histoplasmosis.

110. The answer is A.

(Chap. 44) The definitive diagnosis of an invasive fungal infection generally requires histologic demonstration of fungus invading tissue along with an inflammatory response. However, *Coccidioides* serum complement fixation, cryptococcal serum and cerebrospinal fluid antigen, and urine or serum histoplasma antigen are all tests with good performance characteristics, occasionally allowing for presumptive diagnoses before pathologic tissue sections can be examined or cultures of blood or tissue turn positive. There is no such widely used serologic test for blastomycosis. Serum testing for galactomannan is approved for the diagnosis of *Aspergillus* infection. However, false-negative test results may occur, and further studies of the validity are necessary.

111. The answer is C.

(Chap. 45) Superior vena cava (SVC) syndrome is the clinical manifestation of SVC obstruction with severe reduction in venous return from the head, neck, and upper extremities. Small cell and squamous cell lung cancer account for 85% of all cases of malignant superior vena cava obstruction. Common complaints include neck and facial swelling with dyspnea. Other symptoms include hoarseness, tongue swelling, headaches, nasal congestion, epistaxis, hemoptysis, dysphagia, pain, dizziness, syncope, and lethargy. Temporizing measures include diuretics, a low-salt diet, oxygen, and head elevation. Glucocorticoids may be effective at shrinking the size of lymphomatous masses, but they are of no benefit in patients with primary lung cancer. Radiation therapy

is the primary treatment for SVC syndrome caused by non-small cell lung cancer. Chemotherapy is most effective for small cell lung cancer, lymphoma, or germ cell tumors. Some non-small cell lung tumors are responsive to novel chemotherapy agents. Intravascular stenting is effective for palliation and may be considered to prevent recurrence.

112. The answer is B.

(Chap. 45) MSCC syndrome is defined as compression of the spinal cord, cauda equina, or both by an extradural tumor mass. The minimum radiologic evidence for cord compression is compression of the theca at the level of clinical features. However, radiologic confirmation is not necessary in a patient whose physical examination suggests spinal cord compression. These patients should receive immediate high-dose dexamethasone (24 mg IV every 6 h). Cancers that most commonly cause the MSCC syndrome include prostate, lung, and breast. Renal cell carcinoma, lymphomas, and melanomas may also cause spinal cord compression. The most commonly affected site is the thoracic spine (70% of cases) followed by the sacral spine (20%). Pain is usually present for days or months before the neurologic defects manifest. About 75% percent of patients who are ambulatory at the time of diagnosis will remain ambulatory, but <10% of patients who present with paraplegia will regain the ability to walk despite treatment.

113. The answer is D.

(Chap. 33) Prinzmetal and colleagues described a syndrome of angina that occurs at rest but not usually with exertion associated with transient ST-segment elevation. The pathophysiology is attributable to coronary artery vasospasm. Proximal nonobstructive coronary plaques are usually present. The vasospasm usually occurs within 1 cm of a coronary plaque and is associated with ST-segment elevations on the 12-lead surface electrocardiogram. Because of further vasospasm, cold water ingestion may exacerbate the patient's symptoms. Costochondritis or muscular strain can reproduce the patient's pain. By definition, Prinzmetal's angina is associated with ST-segment elevation, not depression, during the anginal episode.

114. The answer is E.

(Chap. 41) The differentiation between DIC and severe liver disease is challenging. Both entities may manifest with similar laboratory findings: elevated fibrinogen degradation products, prolonged aPTT and prothrombin time, anemia, and thrombocytopenia. When suspecting DIC, these tests should be repeated over a period of 6–8 h because abnormalities may change dramatically in patients with severe DIC. In contrast, the test results should not fluctuate as much in patients with severe liver disease. Bacterial sepsis with positive blood cultures is a common cause of DIC but is not diagnostic.

This page intentionally left blank

INDEX

Bold number indicates the start of the main discussion of the topic; numbers with “f” and “t” refer to figure and table pages.

- A. fumigatus*, 85, 519, 539
 Abciximab, 319, 527, 548
 “ABCs,” traumatic shock and, 274
 Abdominal distension, pain and, 478
 ABG. *See* Arterial blood gas
 Abortions, recurrent mid-trimester, 531, 552
 ABPA. *See* Allergic bronchopulmonary aspergillosis
 Abscesses, 447
 Abulia, 343
 Accelerated idioventricular rhythm (AIVR), 339
 Accelerated junctional rhythm, 339
 ACE inhibitors. *See* Angiotensin-converting enzyme inhibitors
 Acetaminophen, 414, 486
 asthma and, 63
 influenza, 145
 Acetazolamide
 CSA and, **232**
 metabolic alkalosis, 421
 Acetest, 415
 Acid aerosol levels, 96
 Acid amines, 95
 Acid anhydride-exposed workers, 95
 Acid base status, 382
 Acid-base disorders, 410–411, 530, 551
 approach to patient, 412–413
 nomogram, 412f
 Acid-base homeostasis, **410**
 Acidemia, chemoreceptors and, 7
 Acid-fast bacilli (AFB), 115, 116f
 Acid-fast bacilli microscopy, tuberculosis and, 127
 Acidosis, **410**
Acinetobacter spp, antibiotic resistance, 111
 ACMV. *See* Assist control mode ventilation
 Acquired drug resistance, 133
 Acquired inhibitors, of coagulation factors, 433
 Acrocyanosis, 283
 Acrylonitrile, 95
 ACTH. *See* Adrenocorticotropic hormone
Actinomyces, 524, 545
 Activated charcoal, salicylate-induced acidosis and, 415
 Activated partial prothrombin time (aPTT), 424
 prolongation of, 531, 552
 Activated protein C resistance, 531, 552
 Acute asthma, 2
 Acute brain illness, hypotonic solutions and, 352
 Acute coronary syndromes, 304, 314, **316**, 325f
 Acute cough, 15
 Acute deep venous thrombosis (DVT), 208t
 Acute epiglottitis, 158
 Acute fulminant myocarditis, 303
 Acute gastroenteritis, 283
 Acute glomerulonephritis, 382
 Acute hydrocephalus, 368
 Acute hypercapnia, 7, 422
 Acute hypercarbic respiratory failure, 258
 Acute hyperkalemia, 314
 Acute hypersensitivity pneumonitis (HP), 81
 Acute hypoxemia, 9
 Acute hypoxemic respiratory failure, 250
 Acute hypoxia, 20
 Acute interstitial pneumonia, 198, 198f
 Acute ischemic stroke, 255, 356
 Acute kidney injury (AKI), 372
 Acute leukemia, 488
 Acute lung injury (ALI), 269, 290
 diagnostic criteria, 291t
 hypoxic respiratory failure and, 263
 Acute mediastinitis, **220**
 Acute myeloid leukemia (AML), 482
 Acute myocardial infarctions, 312, 324, 526, 547
 cardiogenic shock and
 diagnosis, 299–300
 management, 299f
 patient profile, 298
 timing, 299
 prognosis, 302
 treatment, 300
 aortic counterpulsation, 301
 general measures, 300, 301t
 reperfusion-revascularization, 301–302
 vasopressors, 300–301
 Acute plaque rupture, 324
 Acute pneumonitis, differential diagnosis, 525, 545
 Acute postoperative hyponatremia, 397
 Acute pulmonary edema, 303
 Acute quadriplegic myopathy, 363
 Acute rejection, lung transplantation and, 236–237
 Acute renal failure (ARF), 370, **370**, 376t–378t
 classification and causes, 371t
 clinical features and differential diagnosis, 375, 379–380
 complications of, 380–385
 etiology and pathophysiology, 370–375
 ICU and, 255
 laboratory findings, 379–380
 prevention, 381
 radiologic findings, 380
 renal biopsy, 380
 shock and, 269
 treatment, 381–385
 Acute respiratory distress, treatment of
 clinical trials, 294
 fluid management, 294
 general principles, 293
 glucocorticoids, 294
 mechanical ventilation management, 293–294
 Acute respiratory distress syndrome (ARDS), 100, 122, 153, 198, 253, 258, 269, 283, 284, **290**
 clinical course and pathophysiology
 exudative phase, 290–293, 291f, 293f
 fibrotic phase, 293
 proliferative phase, 293
 clinical disorders associated, 291t
 clinical trials, 295, 295f, 295t
 CT scan of, 50f
 diagnostic criteria, 291t
 etiology of, 290
 ground glass infiltrates with, 51f
 initial management, 295, 295f, 295t
 pressure volume relationship, of lungs, 250f
 prognosis, 295–296
 time course, 290f
 treatment, 158
 Acute respiratory illness, 149
 Acute severe asthma, **75**
 Acute shortness of breath, 2
 Acute silicosis, 90, 91f
 Acute tubular injury, 372
 Acute tubular necrosis (ATN), 269, 370, 375, 529, 550
 etiology and pathophysiology of, 372–373
 phases of, 372–373, 373f
 Acute urate nephropathy, 381
 Acutely appearing masses, 344f355
 Acyclovir, 374, **463**
 mucocutaneous HSV infections, 464
 transplantation and, 243
 Acyclovir-resistant HSV, 467
 Acyclovir-resistant VZV, 467
 ADA. *See* Adenosine deaminase
 ADAM-33 gene, asthma and, 62
 ADAMTS13, 487
 Addison’s disease, 407
 Additive activity, 447
 Additive relationship, 447
 Adefovir, **467**
 Adenoid cystic carcinoma, 56f
 Adenosine deaminase (ADA), 123
 Adenosine triphosphate (ATP)
 hypoxia and, 20
 shock and, 268
 Adenovirus infection, **156**, **158**, 465
 bronchiectasis and, 167
 epidemiology and clinical manifestations, 159
 etiologic agent, 158–159
 laboratory findings and diagnosis, 159–160
 prevention and treatment, 160
 Adjunctive therapies, for shock, 275–276
 Adjunctive ventilator therapies, 294
 Adrenal insufficiency, 286–287
 cancer and, 484–485
 Adrenal tuberculosis, 126
 β -adrenergic agonists, 319, 338, 403, 409
 alveolar hyperventilation and, 226–227
 CF and, 176
 β_2 -adrenergic agonists, for asthma, 61
 β -adrenergic blockers, 76
 asthma and, 68
 β -adrenoceptor blockers, STEMI and, **335**
 Adrenocorticotropic hormone (ACTH), 268
 Adrenocorticotropic hormone stimulation test,
 hypoadrenal shock and, 275
 Adult-onset asthma, 61
 Adult-type tuberculosis, 121–122
 Advanced life support, 313–314
 Adverse (drug) reactions, 450
 AED. *See* Automated external defibrillation
 Aerobic disorders, 414
 Aerosolized recombinant DNase, 169
 AFB smear conversion, 131–132
 Afferent arteriolar vasoconstriction, 529, 550
 Afferent sensory input, 7, 8f
 Afterload, shock and, 268
 Afterload-reducing agents, 382
 Age
 lung transplantation and, 233
 primary tuberculosis and, 118
 SCD and, 307, 309f
 sepsis-related, incidence and mortality rates,
 278, 280
 β agonists, COPD and, 186
 β_2 -adrenergic receptors, 71

- β_2 -agonists, 71, 72
 airways and, 71, 71t
 mode of action, 71
 side effects, 71
 A/H1N1 viral strains, 141–142
 A/H5N1. *See* Avian influenza viruses
 AHR. *See* Airway hyperresponsiveness
 AIDS, 3, 16, 464, 472, 522, 542
 adenovirus infections and, 159
 cidofovir and, 465
 exudative pleural effusions and, 218
 fluconazole and, 472
 ganciclovir prophylaxis and, 466
 neoplastic meningitis, 481–482
 severe sepsis and, 280
 Air contaminants, particle size of, 87
 Air pollution
 asthma and, 62
 asthma triggers, 69
 Air trapping, 82
 Airborne transmission, *Pneumocystis* infection, 161
 Airflow obstruction, 253
 COPD and, 181
 Airway
 anaphylactic reaction of, brittle asthma and, 76
 asthma and, 63
 β_2 -agonists and, 71, 71t
 chronic inflammatory response, 66–67
 complications, lung transplantation and, 236
 disorder, breathing and, 9
 edema, asthma and, 67
 epithelia, in cystic fibrosis, 173–174, 174f
 epithelial shedding, AHR and, 67
 epithelium, inflammation and, 67
 establishing/maintaining, 259
 inflammation
 asthma and, 64, 64f
 bronchiectasis and, 166
 cough and, 14
 lesions, flexible fiberoptic bronchoscopy and, **39**
 mucosa, asthma and, 63
 obstruction, **483**
 remodeling, 67–68
 responsiveness, in COPD, 179
 responsiveness studies, 70
 sensory nerves, neurotrophins and, 67
 Airway hyperresponsiveness (AHR), 69
 airway epithelial shedding and, 67
 asthma and, 64, 64f
 Airway smooth muscle, asthmatic airways and, 67
 Airway smooth muscle cells
 of asthmatics, 65, 66f
 inflammation and, 67
 Airway wall
 bronchiectasis and, 166
 epithelium of, asthma and, 63
 AIVR. *See* Accelerated idioventricular rhythm
 AKA. *See* Alcoholic ketoacidosis
 AKI. *See* Acute kidney injury
 Akinetic mutism, 343
 Albumin, 11–12
 Albuterol, 71
 Alcohol(s), 416
 tuberculosis treatment and, 132
 Alcoholic ketoacidosis (AKA), 412, 415
 Alcoholics, 361
 Alcoholism, 400
 Aldosterone, 396
 shock and, 268
 synthesis, 407
 Aldosterone-resistant hyperkalemia. *See*
 Transtubular K concentration gradient
 Alemtuzumab, 489
 Alfentanil, 259
 ALI. *See* Acute lung injury
 Alkalemia, 226
 Alkali
 administration, 419
 therapy, 409, 414–415
 Alkalosis, **410**
 Allelic polymorphisms, 289
 Allergens, 68
 asthma and, 61, 62–63
 Allergic bronchopulmonary aspergillosis (ABPA),
 83, 84, 167
 diagnostic features of, 84t
 Allergic interstitial nephritis, 380
 Allergic reactions, to streptokinase, 333
 Allergic rhinitis, asthma and, 61
 Allopurinol, 485
 renal injury and, 381
 Alpha activity, on EEG, 350
 Alpha coma fix, 349
 Alternative therapies, asthma and, 74
 Alveolar collapse, 294
 Alveolar diseases, categories of, 191t
 Alveolar edema, 35, 293f
 Alveolar edema, atelectasis, intrinsic positive
 end-expiratory pressure. *See* Auto-PEEP
 Alveolar fluid clearance, 304
 Alveolar gas equation, 31
 Alveolar hemorrhage, 292
 Alveolar hyperventilation, 205
 definition and etiology, 225–226
 diagnosis of, 226–227
 mechanisms involved, 226f
 physiologic and clinical features, 226
 treatment, 227
 Alveolar hypoventilation syndromes
 laboratory test results, 223f
 physiologic and clinical features, 222f
 Alveolar infiltrates, 50f
 Alveolar leak, 100
 Alveolar macrophages
 pathogens and, 100
 silica and, 90
 Alveolar neutrophilia, 82
 Alveolar ventilation
 gas exchange and, 30
 respiratory acidosis and, 422
 ventilator weaning and, 264
 Alveolar-arterial O₂ difference, equation for, 32
 Alveolar-arterial oxygen gradient, 524, 545
 Alveoli
 normal v. injured, 292f
 repair, COPD and, 184
 Amantadine, **462**, 463
 influenza and, 145, 146, 146t, 147
 AmB. *See* Amphotericin B
 Ambient air pollution, COPD and, 179
 Amikacin, 133
 tuberculosis and, 129
 Amiloride, 402
 Aminocaproic acid (EACA), for hemophilia, 427
 Aminoglutethimide, 485
 Aminoglycoside antibiotics, 285, 363, **438**
 ATN and, 374
 bronchiectasis and, 169
 CF lung and, 176
 renal injury and, 381
 tuberculosis and, 129
 Aminoglycoside-resistant bacteria, **441**
 Aminophylline, contrast nephropathy and, 381
 Aminotransferases levels, tuberculosis treatment
 and, 132
 Amiodarone, 313, 314, 513, 533
 Amithiozone
 HIV-associated tuberculosis, 134
 tuberculosis and, 129–130
 AML. *See* Acute myeloid leukemia
 Ammonia, 418
 Amnesia, mechanical ventilation and, 252
 Amoxicillin
 bioavailability of, 442
 bronchiectasis and, 169
 Amoxicillin/clavulanic acid, tuberculosis and, 130
 Amphotericin B (AmB), 374, **471**
 Anaerobes, aspiration and, 101
 Anaerobic bacteria, lung abscess, 169–170
 Anaerobic glycolysis, 20
 Anaerobic infection, clindamycin and, 520–521,
 540
 Anal wink reflex, 479
 Analgesics
 mechanical ventilation and, 251
 withdrawing care, 256
 Anaphylactoid reactions, to dialyzer, 390
 Anatomic dead space, 30
 Anemia, 375, 384
 ARF and, 380–381
 ICU and, 255
 Anemic hypoxia, 21
 Anesthetics
 OSAHS and, 230
 PAH and, 224
 Aneurysmal bleeding, 364
 Aneurysmal rupture, 364
 Aneurysms, 256
 asymptomatic, 364
 repair, 367
 Angina, recurrent, 340
 Angiography, UA/STEMI, 317
 Angiotensin II, 371, 372
 shock and, 267
 Angiotensin receptor blockers (ARBs), 336, 341,
 371, 375, 381, 528, 549
 Angiotensin-converting enzyme inhibitors (ACE
 inhibitors), 15, 304, 319, 321, 341, 371,
 375, 382, 407, 418, 545
 renal injury and, 381
 STEMI and, 335, 336
 Anidulafungin, 473
 Anion gap calculation, 413
 Anion-gap metabolic acidosis, 530, 551
 causes, 414t
 Anoxic cerebral injury, cardiac arrest and, 255
 Anoxic encephalopathy, 312
 Antagonists of chemokine receptors, 74
 β_2 -agonists, brittle asthma, **76**
 Anterior mediastinum, 219
 Antiarrhythmics, 313, 382
 Antibacterial agents, 448, 448t–449t, 450. *See also*
 Antibiotics
 acute influenza and, 146, 146t
 adverse reactions to, 451t
 bacterial intrinsic resistance, 440–442
 distribution of, 443
 inhibition of protein synthesis and, 438–439
 interactions, other drugs, 452t
 mechanisms of action, 434–435, 435f, 436t–437t,
 437–442
 metabolism and elimination of, 443
 pharmacodynamics of, susceptibility and,
 444–445, 445f
 in pregnancy, 445, 446t
 specific, infections for, 448t–449t
 Antibacterial chemotherapy
 acquired resistance and, 440–442
 principles of, 443–448

- Antibacterial drugs. *See* Antibacterial agents
- Antibacterial prophylaxis, 453–454, 453t
- Antibiotic-coated vascular catheters, 254
- Antibiotic-induced allergic interstitial nephritis, 379
- Antibiotics
- absorption, 442
 - acute severe asthma and, 75
 - ATN and, 374
 - bronchiectasis and, 169
 - CF lung and, 176
 - COPD and, acute exacerbations of, 189
 - intramuscular administration, 443
 - intravenous administration, 443
 - lung abscess and, 170
 - oral administration of, 442–443
 - pharmacokinetics of, 442–443
 - quantitative-culture methods and, 110
 - VAP, 113
- Anticholinergics, 71
- acute severe asthma and, 75
 - COPD and, 186
- Anticholinergic-type overdose, 352
- Anticoagulants, 287, 288, 340, 527, 548
- complications of, 211
- Anticoagulation, 319
- duration of, 212
 - PE and, 210, 210t
- Anticyclic depressants, eosinophilic pneumonias and, 84
- Antidepressants, COPD and, 11
- Antidiuretic hormone, 394
- Antifibrinolytic agents, 367, 428, 433
- for hemophilia, 427
- Antifungal agents, topical, 473
- Antigen exposure, 81
- HP and, 83
- Antigen groups, *Pneumocystis* infection, 161
- Antigen removal, 520, 540
- Antigen tests, CAP and, 104
- Antigenic drifts
- influenza A virus and, 140
 - RNA segment and, 141
- Antigenic shifts, influenza A virus and, 140
- Antihistamines, rhinoviruses and, 152
- Anti-IgE, 77
- asthma and, 74
- Anti-inflammatory cytokines, infection and, 281
- Anti-inflammatory drugs, rhinoviruses and, 152
- Anti-ischemic treatment, 319, 321
- Antileukemic therapy, 483
- Antileukotriene, 73, 75, 77
- Antimetabolites, 439
- Antimicrobial(s)
- agents, 285, 289
 - chemotherapy, 285
 - classes, pharmacodynamic indices of, 445f
 - optimizing, mechanisms for, 454–455
 - resistance, CAP treatment and, 104–107
 - stewardship, 454–455
- Antimicrobial regimens (IV therapy), 286t
- Antineoplastic drugs, hypersensitivity reactions and, 489
- Antineuraminidase antibody assay, 142
- Antioxidants
- asthma and, 62
 - traumatic shock, 274
- Antiphospholipid antibody syndrome, 533
- Antiplatelet therapy, 321, 334, 341
- Antiplatelet Trialists' Collaboration, 334
- Anti-pneumocystosis drugs, 164
- Antiretroviral therapy, HIV-associated tuberculosis, 134
- Antiseizure medications, CNS metastases and, 482
- Antithrombotic therapies, 318, 319, 321t, 341
- STEMI and, 334
- Antithrombin therapy, 334–335
- Anti-TNF therapy, refractory asthma, 77
- Anti-TNF- α monoclonal antibody, 84
- α_1 -antitrypsin, 518, 538
- α_1 -antitrypsin deficiency
- bronchiectasis and, 167
 - COPD and, 180
- Antituberculosis treatment regimens, 131t
- Antiviral chemotherapy, 456
- and chemoprophylaxis, 457t–461t
 - interferons, 468–469
- Antiviral drugs
- for hepatitis viruses, 467–468
 - for herpesviruses, 463–467
 - HIV-associated tuberculosis, 134
 - influenza and, 145, 146t
 - as prophylaxis, for influenza, 147
 - for respiratory infections, 461–463
- Anxiety, dyspnea and, 7–8
- Anxiety hyperventilation, 226
- Anxiolysis, withdrawing care, 256
- Anxiolytics, COPD and, 11
- Aortic arch, chest tomogram of, normal, 42f
- Aortic counterpulsation, 526, 546
- MI and, 301
- Aortic dissection, 332
- Aortic knob, normal, 41f
- APACHE II scoring system, 247, 248t, 288, 290, 295
- survival curve, 247, 249f
- APACHE III scoring system, 247
- APACHE scores, 247, 248t
- pneumocystosis and, 164
- aPC. *See* Recombinant activated protein C
- Apical scarring, 43f
- Apnea, 222, 351
- testing, 351
- Apoptotic death, 282
- Apoptosis, 184, 354
- aPTT. *See* Activated partial prothrombin time
- Aquaporin-2 gene, 394
- ARBs. *See* Angiotensin receptor blockers
- ARDS. *See* Acute respiratory distress syndrome
- ARF. *See* Acute renal failure
- Arginine vasopressin (AVP), 275, 370, 394
- Aromatic amines, 95
- Arousal level, 347
- Arrhythmias, 338
- Arsenic compounds, 95
- Arsenic trioxide, 483
- Arterial blood gas (ABG), 31–32, 252
- acute severe asthma and, 75
 - alveolar hyperventilation, 226
 - COPD and, 185
 - ILDs and, 195
 - mixed acid-base disorders, 412t
 - PAH and, 224
- Arterial embolism, 340
- Arterial hypoxemia, 21
- Arterial vascular smooth muscle, shock and, 267
- Arteriovenous fistulas, 389, 390
- Arteriovenous grafts, 389
- Arteriovenous malformation, 363
- Arthralgias, 375
- Asbestos, 88–89
- Asbestosis, 54f, 87, 89, 89f, 90
- Asbestos-related diseases, 88
- bystander exposure, 89
- Ascending aorta, chest tomogram of, normal, 42f
- Ascites
- fluid management and, 382
 - pleural effusions and, 216
- Asparaginase, 489
- Aspergillus fumigatus*, 83, 202, 470
- lung transplant recipients and, 240
- Aspergillus* infection, 531, 552–553
- Aspergillus* spp., 78, 472, 533
- Aspiration, 532–533
- Aspirin, 77, 318, 321, 334, 336, 341, 426, 527, 531, 547–548, 552
- Aspirin-sensitive asthma, 68, 77
- Assist control mode ventilation (ACMV), 259, 261, 261f
- Assisted ventilation, 107
- Asthma, 3, 14–15, 60, 461
- allergens and, 61, 62–63
 - clinical features and diagnosis, 69–70
 - deaths, risk factors, 61
 - differential diagnosis for, 70
 - education, 75
 - elderly and, 77
 - environmental factors, 62–63
 - etiology, 61–63
 - future therapies, 74
 - gold for, 74
 - medications, breastfeeding with, 77
 - mortality, 61
 - Mycoplasma* and, 62
 - nitrogen oxides and, 62
 - pathogenesis of, 63
 - pathology of, 63
 - pathophysiology of, 65f, 69
 - pharmacologic agents and, 68
 - prevalence of, 60–61
 - risk factors, 61t
 - small airway with, histopathology of, 63f
 - therapy, 70–75, 70t
 - treatment, 70–75
 - triggers, 60, 61t, 68–69
 - physical factors for, 68
- Atelectasis, 176
- Atherosclerosis, 342
- Atherosclerotic plaques, 323
- ATN. *See* Acute tubular necrosis
- Atopy, 61
- Atovaquone, 163, 163t
- Atovaquone resistance, pneumocystosis and, 164, 164t
- ATP. *See* Adenosine triphosphate
- Atrial fibrillation, 304
- Atrial natriuretic peptide, 365
- Atrial pressure measurements, 253
- Atrial ventricular resynchronization, 304
- Atrioventricular conduction disturbances, 339–340
- Atropine, 330
- pulse rate and, 351
 - sinus bradycardia and, 339
- Attention-seeking hysterical conversion syndrome, 76
- Attenuated influenza vaccine, 546
- Auscultation of lungs, 4
- Autoimmune connective tissue disorders, 90
- Autoimmune diseases, 533
- Autolysins, 437
- Automated external defibrillation (AED), 313
- Autonomic neural control, 67
- Auto-PEEP (Alveolar edema, atelectasis, intrinsic positive end-expiratory pressure), 251, 253, 253f, 524, 544
- Autoregulation, 354
- shock and, 267
- Avian influenza viruses, 141

- Avian influenza viruses (A/H5N1), 525, 546
 epidemiology, 140–142
 with pneumonia, 145
- AVM. *See* Pulmonary arteriovenous malformations
- AVP. *See* Arginine vasopressin
- Awake coma, 343
- Azathioprine, asthma and, 74
- Azithromycin, 107, 438
 CF lung and, 176
- Azithromycin resistance, 441
- Azoles, **472**
- B. pertussis*, 519, 539
- B adrenoceptor blockers, 341
- Bacille Calmette–Guérin vaccination, 135
- Bacitracin, 437
- Back pain, with cancer, 480–481
- Bacteremia, 280, 283
- Bacteremic pneumococcal pneumonia,
 management of, 106
- Bacteria. *See also* Bacterial pathogens; *specific bacteria
 and bacterial diseases*
 donor kidneys and, 239
 mechanisms of resistance, 440–442
 severe sepsis and, 278, 280
 thermophilic, 85
- Bacterial bronchitis, lung transplantation and, 237
- Bacterial cell death, 439
- Bacterial cell wall synthesis, inhibition of, 437
- Bacterial cell-wall glycolipid lipoarabinomannan,
 tuberculosis and, 119
- Bacterial endocarditis, 446
- Bacterial infections, **434**
 prophylaxis of, 453–454, 453t
 therapy duration for, 454t
 transplanted stem cells and, 239
- Bacterial metabolism, antibacterial compounds
 and, **439**
- Bacterial pathogens, in sputum sample, 38
- Bacterial pneumonia, 488
- Bactericidal drugs, 435
- Bacteriologic evaluation, tuberculosis and, 131
- Bacteriostatic drugs, 435
- Baker's cyst, 208
- BAL. *See* Bronchoalveolar lavage
- Balloon catheter, massive hemoptysis, 18
- Barbiturates
 endotracheal intubation and, 250
 ICP and, 357
- Barotrauma, 264
- Bartter's syndrome, 404, 419, 531, 551
- Basal ganglia hemorrhage, 351
- Baseline Dyspnea Index, 8
- Basic life support, initial response to, 312
- Basilar pneumothorax, 53f
- BCG vaccination. *See* Calmette–Guérin vaccination
- Beclomethasone dipropionate, 75
- Beer potomania, 398
- Beijing/W genotype family, of *M. tuberculosis*, 119
- BeLPT. *See* Beryllium lymphocyte proliferation
 testing
- Benzene, 97
- Benzodiazepines, 259
 endotracheal intubation and, 250
 mechanical ventilation and, 252, 263
 withdrawing care, 256
- “Berry” aneurysm, **363**
- Beryllium, 92
- Beryllium lymphocyte proliferation testing
 (BeLPT), 92
 nuclear workers and, 87
- Beryllium-specific CD4+T cells, on lung biopsy, 92
- Betaconazole, 473
- Bevacizumab, 489
- BG. *See* Bronchocentric granulomatosis
- Bicarbonate, 287, 524–525, 545
- Bicarbonate dialysate, 416
- Bicarbonate-containing dialysate, 390
- Bilirubinuria, 379
- Biomass smoke, 97, 97f
- Biomass smoke-induced interstitial lung
 disease, 97, 97f
- Biopsy
 for chronic beryllium disease, 87
 of distal lung parenchyma, 39
 genitourinary tuberculosis and, 123
 lymph nodes and, 40
 refractory asthma and, 76
 specimens, rhinoviruses and, 151
- Bird fancier's lung, 79
- Birds, 85
- Bivalirudin, 211, 319
- Bladder catheter, 382
- Bladder neck obstruction, 375, 382
- Blastomycosis, 531
- Bleeding, 426–427. *See also* Hemophilia
 from warfarin, cryoprecipitate and, 211
- Bleeding disorders, **428**
- Bleeding time, 380
- Bleomycin, 487
- β blockade, 319, 321
- β blockers, 323, 340, 363
 ventricular rate and, 339
- β -blockers, pain relief and, 330
- Blood, from tracheobronchial tree, 17
- Blood cell transfusions, immunosuppression
 and, 109
- Blood cultures
 CAP and, 103
 severe sepsis and, 278, 280
- Blood delivery system, dialysis and, 388
- Blood glucose levels, 287
- Blood lactate levels, 283
- Blood pressure, 367
- Blood transfusion, hypovolemic shock and, 274
- Blood urea nitrogen (BUN), 375, 396
- Blood-brain barrier, 353, 446
 toxic substances and, 345
- Blood-CSF barrier, 446
- Bloody pleural fluid, 218
- BMT. *See* Bone marrow transplantation
- BNP. *See* Brain natriuretic peptide
- Body fluids, laboratory test values, 512t
- Body mass data, laboratory test values, 512t
- Body plethysmograph, 27
- Bohr effect, 422
- Bolus fibrinolytics, 331
- Bone and joint tuberculosis, 134
- Bone density, ICSs and, 73
- Bone marrow aspirates, differential nucleated cell
 counts of, laboratory test values, 507t
- Bone marrow suppression, ganciclovir prophylaxis
 and, 466
- Bone marrow transplantation (BMT), 85, 486, 489
 fluconazole and, 472
- BOOP. *See* Bronchiolitis obliterans with organizing
 pneumonia
- Borg scale, dyspnea and. *See* Chronic obstructive
 pulmonary disease
- BOS. *See* Bronchiolitis obliterans syndrome
- Bowels, STEMI and, 334
- Boyle's law, 27
- BPA. *See* Bronchopulmonary aspergillosis
- Bradycardias, 307
 SCD and, 340
- Brain, sodium/water balance in, 345
- Brain cell volume, 400, 401
- Brain death, 256, 527–528, 548
 criteria for, 351
- Brain dysfunction, EEG and, 356
- Brain edema, **353**, 398
- Brain injury, 255
- Brain ischemia, 353, 367
- Brain leukostasis, 483
- Brain natriuretic peptide (BNP), 365–366
 shock and, 268
- Brainstem, intact, 358
- Brainstem damage, 351
- Brainstem ischemia, 351
- Brainstem reflexes, coma and, 347–348
- Brainstem signs, 345
- Breast cancer, 481
- Breastfeeding
 asthma medications with, 77
 tuberculosis treatment and, 134
- Breathing, 10, 249
 airway disorder and, 9
 discomfort, 8
 disorders of ventilatory pump and, 7
 inspection, 4
 mineral dusts and, 87
- Brittle asthma, **76**
- Bronchial asthma, eosinophilic pneumonia
 and, 84
- Bronchial breath sounds, 4
- Bronchial circulation, asthma and, 67
- Bronchial wall, 166–167
- Bronchiectasis, 14, 17, 52f, 78, **166**, 169, 534
 definition and pathology of, 166
 infectious v. noninfectious causes, 167
 diagnostic approach to, 169f
 etiology and pathogenesis of, 166–168
 HRCT scan and, 520, 540
 radiographic and laboratory findings,
 168–169, 168f
 “tree in bud” opacities and, 53f
- Bronchiolitis, 53f, 194
 HP and, 82
- Bronchiolitis obliterans, 541
 diacetyl exposure and, 95
- Bronchiolitis obliterans syndrome (BOS), lung
 transplantation and, 237
- Bronchiolitis obliterans with organizing pneumonia
 (BOOP), HP and, 82
- Bronchitis, 18
- Bronchoalveolar lavage (BAL), 39
 HP and, 81, 82
 ILDs and, 195, 196t
 miliary tuberculosis and, 126
Pneumocystis infection, 161, 163
 pulmonary infiltrates and, 488
- Bronchocentric granulomatosis (BG), 202
- Bronchoconstriction, 69
- Bronchodilators, 68, 70–71, 70t
 for asthma, 61
 bronchiectasis and, 169
 COPD and, 186
 acute exacerbations of, 189
 respiratory tract infections and, 16
- Bronchogenic carcinoma, 15
- Bronchograms, on chest CT, 51f
- Bronchophony, 4
- Bronchopulmonary aspergillosis (BPA), 78
- Bronchoscope, 39
- Bronchoscopy, **39**
 asthma and, 63
 bronchiectasis and, 168
 with brushings, *M. tuberculosis* and, 128
 lung abscess with, 170

- Brushing
flexible fiberoptic bronchoscopy and, 39
M. tuberculosis and, 128
- B-type antibiotics, 105
- B-type natriuretic peptide, 318
- Bullous emphysema, 44f
- Bullous lesion, 283
- Burkholderia cepacia*, antibiotic resistance, 111
- Burkitt's lymphoma, 485
- Busulfan, 482, 487
- Bypass membrane oxygenators, 146
- Byssinosis, **92**
- C. difficile* colitis, 489
- C. glabrata*, 472
- C. krusei*, 472
- C reactive protein, HP and, 81
- CABG. *See* Coronary artery bypass graft
- Cachectic myopathy, 363
- CAD. *See* Coronary artery disease
- Cadmium, 97
- Calcified lymphadenopathy, 48f
- Calcium antagonists, 323, 330, 336
- Calcium channel blockers, 367
Prinzmetal's variant angina and, 323
- Calcium gluconate, 314
hyperkalemia and, 408–409
- Calcium homeostasis, shock and, 268
- Calcium influx, hypoxia and, 20
- Calmette–Guérin (BCG) vaccination, 129
- CAM. *See* Confusion Assessment Method
- CA–MRSA. *See* Community-acquired MRSA
- Cancer, 14. *See also specific cancers*
adrenal insufficiency and, 484–485
airway obstruction and, 483, 484f
chemotherapy for, renal injury and, 381
drugs, ATN and, 374
hypoglycemia and, 484
hyponatremia and, 484
ICP and, 481
intestinal obstruction and, 478
lactic acid acidosis and, 484
lactic acidosis and, 484
patients
with back pain, 479–481, 480f
with biliary obstruction, 478
with intestinal obstruction, 478
with pericardial effusion, 476–477
with spinal cord compression, 479
with SVCS, 475–476
with urinary obstruction, 478
pulmonary infiltrates and, 487–488
seizures and, 482
uranium miners and, 95
- Candida* spp., 84, 470, 471, 472, 531–532, 552–553
lung transplant recipients and, 240
- Candidemia, 531, 553
- CAP. *See* Community-acquired pneumonia
- CAPD. *See* Continuous ambulatory peritoneal dialysis
- Capillary leak, 100
- Caplan's syndrome, 92
- Carafate, mechanical ventilation and, 264
- Carbamazepine, 256
- Carbapenem, 169, 437
- Carbon disulfide, 97
- Carbon monoxide intoxication, 21, 95, 359, 360
- Carboplatin, 374
- Carcinoma, 404. *See also* Neoplasm
- Cardiac arrest, 307, 307t, 358
anoxic cerebral injury and, 255
causes, 308t
clinical characteristics, 311–312
- Cardiac arrest (*Cont.*):
outcome after, 311
out-of-hospital, 526, 547
survival of, 314
prediction and prevention, 308–309
sudden collapse with, 312
survivors, 314–315
treatment, 312–315
- Cardiac arrhythmias, 422
- Cardiac biomarkers, UA/NSTEMI and, 317
- Cardiac catheterization, 333, 341
- Cardiac disorders, 306
- Cardiac dysfunction, hypereosinophilic syndrome and, 85
- Cardiac examination, 11
- Cardiac failure, 382
- Cardiac imaging, STEMI and, 328
- Cardiac markers, 317, 318
- Cardiac output, 29
hypoxia and, 14
pulse oximetry and, 32
shock and, 268, 271
- Cardiac rehabilitation program, 341
- Cardiac toxicity, 407t
- Cardiac-specific troponin I (cTnI), 327
- Cardiac-specific troponin T (cTnT), 327
- Cardiogenic pulmonary edema, 12, 292
causes of, 298t
noncardiogenic pulmonary edema v., 12, 12t
- Cardiogenic shock (CS), 247, **297**, 337, 537
causes, 297, 298t
incidence, 297
pathophysiology, 297–298, 298f
patient profile, 298–300, 299f
treatment, 337
- Cardiomyopathies, SCD and, 311
- Cardiopulmonary exercise test, 11
ILDs and, 195
- Cardiopulmonary function, lung transplantation and, 235
- Cardiopulmonary resuscitation (CPR), 311, 312
comatose survivors, 359f
- Cardiorespiratory function, restoration of, 359
- Cardiorespiratory symptoms at rest, 476
- Cardiovascular beriberi, 361
- Cardiovascular collapse, 307t
forms of, 307
- Cardiovascular disease
ESRD and, 390
respiratory system dyspnea v., 11
- Cardiovascular events, OSAHS and, 229
- Cardiovascular function, 381
- Cardiovascular system
alternations in, 8, 9f
vasopressors and, 515–516, 535
- Cardiovascular system dyspnea, 8, 9
- Carina, normal, 41f
- Case-fatality rates, pericardial tuberculosis and, 125
- Caseous necrosis, 120
- Caspofungin, 473, 531, 553
- Catabolic myopathy, 363
- Catalepsy, 343
- Catatonia, 343
- Catheterization, right ventricular infarction and, 337–338
- Catheters, dialysis and, 388–389
- Cauda equina syndrome, 480
- CAVHD. *See* Continuous arteriovenous hemodialysis
- CAVHDF. *See* Continuous arteriovenous hemodiafiltration
- Cavitary disease, 131–132
- Cavities (in lungs), 45f
tuberculosis and, 121–122, 122f
- Cavity lesions, lung abscess with, 170, 170f
- CBD. *See* Chronic beryllium disease
- CBF. *See* Cerebral blood flow
- CCPD. *See* Continuous cyclic peritoneal dialysis
- CD4+T cells, *Mycobacterium tuberculosis* and, 120
- CD8+T cells, *Mycobacterium tuberculosis* and, 120
- Cefotaxime, 443
- Ceftriaxone plus clarithromycin, 522–523, 542–543
- Cell death, COPD and, 184
- Cell membranes, shock and, 268
- Cell necrosis, 20
- Cell-free hemoglobin, 374
- Cell-mediated immunity (CMI), 142
CBD and, 92
HRSV and, 155
lung transplant recipients and, 240
Mycobacterium tuberculosis and, 118
- Cell-membrane permeability, alteration of,
antibacterial compounds and, 440
- Cellular examination, 195–196
- Cellular injury, 353
- Central cyanosis, 23, 532
- Central diabetes insipidus (NDI), 395
- Central fever, 347
- Central nervous system (CNS), 345
critical care disorders of, 358–362
diseases, influenza and, 144–145
drive to breath, diminished, 250
hypoxia and, 20–21
metastasis, 482
neoplastic meningitis, 481–482
respiratory system and, 25
- Central pontine myelinolysis, **361**, 361f, 368
- Central sleep apnea (CSA), 226, **232**, 516, 535
- Central transtentorial herniation, 345, 549
- Central venous catheter, 476
- Central venous pressure, 337
- Centrilobular infiltrates, 540
- Cephalosporins, 111, 374, 437, 441
bronchiectasis and, 169
CF lung and, 176
- Cerebellar hemorrhage, 351
- Cerebral anoxic injury, 400
- Cerebral blood flow (CBF), 354
autoregulation of, 354, 355f
respiratory alkalosis and, 422
- Cerebral edema, 476
- Cerebral hemisphere damage, 345
- Cerebral hemispheres, 344f
- Cerebral hemorrhage, 351–352
- Cerebral herniation, 344f
- Cerebral mass herniations, 344–345
- Cerebral mass lesions, 344–345
- Cerebral neurons, 345
- Cerebral perfusion, **354**, 355f
- Cerebral perfusion pressure (CPP), 354, 355f
- Cerebral salt-wasting syndrome, 366
- Cerebral vasodilation, 522, 542
- Cerebral vasospasm, 256, 368
- Cerebral venous sinus thrombosis, 356
- Cerebrospinal fluid (CSF), **355**
examination, tuberculous meningitis and, 125
laboratory test values, 505t
malignant cells in, 482
- Cerebrovascular diseases, coma diagnosis and, 351
- Cerebrovascular events, OSAHS and, 229
- Cerebrovascular hemorrhage, 332
- Cervical pain, 364
- Cervical spine injuries, 352
- Cetuximab, 489
- CF. *See* Cystic fibrosis
- CFTR gene, genetic mutations in, 173
- CFTR mutation analysis, 175

- CFTR protein, 172–173
 Chamberlain procedure, 40
 Chemical chemistry, laboratory test values, 494t–500t
 Chemical worker's lung, 79
 Chemicals, asthma and, 63
 Chemokines, 100
 Chemoprophylaxis
 for antiviral chemotherapy, 457t–461t
 for influenza, 147
 LTBI and, 135
 Chemoreceptors, 7, 9
 Chemotherapeutic agents, 437
 Chemotherapy, 447, 553
 genitourinary tuberculosis and, 123
 HUS and, 486
 MSCC and, 481
 neutropenic enterocolitis and, 488f
 tuberculous meningitis and, 125
 Chest
 compression, 312
 compressive cardiogenic shock and, 274
 discomfort, recurrent, 340
 examination, 10
 imaging
 atlas of, 41–57
 CBD and, 92
 environmental lung disease and, 87
 roentgenography, PE and, 208
 tightness, 7
 Chest pain, 299, 326, 526, 527, 546, 547–548
 respiratory system diseases and, 3
 UA/NSTEMI and, 317
 Chest radiography, 4–5, 11, 41–57
 ARDS and, 292
 asbestosis diagnosis, 89–90
 cough and, 15
 environmental toxins and, 87
 hemoptysis and, 18
 HP and, 81
 ILDs and, 194
 infiltrate on, 522, 542
 malignant pericardial disease and, 476
 MI and, CS caused by, 300
 normal, 41f
 parainfluenza virus and, 158
 Pneumocystis infection, 162, 162f
 respiratory diagnosis with, 6t
 tuberculosis and, 521, 541
 Chest wall, 26f
 compliance, 251
 Chest x-ray. *See* Chest radiography
 Cheyne–Stokes respiration, 516, 535
 CHF. *See* Congestive heart failure
 Chickenpox, 464
 Childhood brain tumors, 485
 Children (*Cont.*):
 primary tuberculosis and, 118, 122
 rhinoviruses and, 151–152
 rimantadine and, 462
 SARS–CoV and, 153
 of smoking parents, 96–97
 TST and, 136
Chlamydia pneumoniae, COPD and, 189
Chlamydia spp., 15
 asthma and, 62
 Chlorambucil, 482
 Chloramphenicol, **439, 441**, 446–447
 Chlorpropamide, 84, 533
 Cholestasis, mechanical ventilation, 264
 Cholestatic jaundice, 283
 Cholestatic liver disease, 177
 Cholesterol crystals, 374
 Chronic asthma, 74–75
 Chronic beryllium disease (CBD), 92
 biopsy for, 87
 sarcoidosis v., 92
 Chronic bronchitis, biomass smoke and, 97, 97f
 Chronic cardiac disease, 2
 Chronic cough, 15, 525, 545
 Chronic disseminated intravascular coagulation,
 differential diagnosis, 431
 Chronic eosinophilic pneumonia, 85
 Chronic hepatitis B, 469
 Chronic hepatitis C, 463, 469
 Chronic hepatitis D, 469
 Chronic hyperkalemia, 406–407
 Chronic hypervolemia, 401
 Chronic hypersensitivity pneumonitis (HP), 81
 Chronic hypoxemia, 423
 Chronic hyponatremia, 393
 Chronic hypoventilation
 diagnosis of, 222–223
 disease entities and, 221, 222t
 Chronic hypoventilation syndromes, 221, 222t,
 522, 542
 Chronic infection, lung transplantation and, 233
 Chronic inflammatory response, airways and, 66–67
 Chronic interstitial lung disease, 2
 Chronic kidney disease, 375, 386
 Chronic mediastinitis, **220**
 Chronic mountain sickness, 14
 Chronic obstruction pulmonary disease (COPD),
 General medical care, 187
 Chronic obstructive lung disease, 2
 Chronic obstructive pulmonary disease (COPD), 8,
 10, 86, 92, **178**, 518–519, 524, 538, 544
 acute exacerbations of, 189–189
 biomass smoke and, 97, 97f
 clinical presentation
 history, 184
 laboratory findings, 185–186
 physical findings, 184–185
 with concomitant asthma, 76
 exacerbations of, 188–189
 pathogenesis of, 183–184
 pathology of, with cigarette smoke, 182–183
 pathophysiology of, 181
 pulmonary function and, cigarette smoking and,
 180–181
 risk factors, 178–182
 severity of, GOLD criteria for, 185t
 treatment, 11, 186–189
 acute exacerbations, 189
 nonpharmacologic therapies, 187–189
 pharmacotherapies, 186–187
 stable phase, 186
 Chronic rejection, lung transplantation and, 237
 Chronic respiratory acidosis, 224
 Chronic respiratory alkalosis, 423
 Chronic Respiratory Disease Questionnaire, 8
 Chronic respiratory failure, NIV and, 262
 Chronic silicosis, 91f
 Chylothorax, 218
 Ciclopirox, 473
 Cidofovir, **465**
 adenovirus infections, 160
 Cigarette smoke, 16, 92, 93, 96, 108, 309, 325, 514,
 533, 534, 538. *See also* Maternal smoking
 asthma and, 77–78
 coal dust, 91–92
 COPD and, 178–179, 179f, 182–183
 ILDs and, 193
 lung transplantation and, 233
 Cigarette smoke, passive, 522, 542
 asthma and, 62
 COPD and, 180
 Cigarette smoking
 associated ILDs, **198**
 Goodpasture's syndrome and, 193
 pulmonary function and, 180–181
 Cigarette smoking–associated interstitial
 lung disease, **198**
 Ciliary dysfunction, 167
 Ciprofloxacin
 CF lung and, 176
 pneumococcal resistance to, 105
 Circulation, PE and, 212
 Circulatory function tests, laboratory test
 values, 508t
 Circulatory hypoxia, 21
 Cirrhosis
 fluid management and, 382
 pleural effusions and, 216
 Cisplatin, 374
 CKMB (MB isoenzyme of creatine
 phosphokinase), 327, 327f
 Clarithromycin, 438, 443
 resistance, 441
 Clindamycin
 anaerobic infection and, 520–521, 540
 bioavailability of, 442
 Clindamycin plus primaquine, pneumocystosis
 and, 164, 164t
 Clindamycin resistance, 441
 Clinical Pulmonary Infection Score (CPIS),
 110–111, 111t
 Clofazimine, 130
 Clonazepam, 360
 Clopidogrel, 321, 341, 527, 548
 STEMI and, 335f
Clostridium difficile disease, 455, 488
 Clotrimazole, 473
 Clotting, 281
 Clotting factor
 activity, 424, 425f
 deficiency, coagulation cascade and, 425f
 Clubbing of digits, 4, 11, 24, **24**
 CMI. *See* Cell-mediated immunity
 CMV. *See* Cytomegalovirus
 CNS. *See* Central nervous system
 CO₂, pulmonary circulation and, 30
 Coagulation
 cascade, 325
 activation of, 269
 clotting factor deficiency, 425f
 disorders, **424**
 genetic and laboratory characteristics, 425t
 liver failure and, 432–433, 432t
 factors, host defense and, 281
 laboratory test values, 492t–494t
 tests, 431

- Coagulation inhibitor replacement, 431–432
 Coagulation plasma proteins, 424
 Coagulopathy, severe sepsis and, 284
 Coal worker's pneumoconiosis (CWP), 87, **91**
 Cobalt, 92
 Cobalt-induced giant cell interstitial pneumonitis, 92
 Cocaine use, 528, 549
 Coccidioid meningitis, fluconazole and, 472
Coccidioides immitis, 471
 Cockcroft-Gault formula, 381
 Coiled aneurysm, 368
 Colchicine, ILDs and, 196
 Cold abscess, skeletal tuberculosis, 124
 Cold air, asthma and, 68
 Cold-induced vasospasm, peripheral cyanosis and, 23–24
 Collagen, COPD and, 183, 184
 Collagen deposition, asthma and, 63
 Collagen vascular disease, 11, 83
 Collapse, 526, 547
 Coma, **343**, 549
 anatomy and physiology of, 344–349
 approach to patient, 346
 arousal level, 347
 brainstem reflexes, 347–348
 history, 346
 neurologic examination, 347
 physical examination, 346–347
 differential diagnosis, 350–351, 350t
 fundoscopic examination and, 347
 neurologic examination and, 347
 prognosis, 352
 respiratory patterns, 348
 toxic drug-induced, 345
 treatment, 351–352
 Comatose survivors, of cardiopulmonary resuscitation, 359
 Combination inhaler, 71
 Combination therapy
 antithrombotic, 341
 chemotherapy, 447
 HRSV and, 156
 Combined FV and FVIII deficiency, 429
 Common cold, 149, 150, 153
 rhinoviruses and, 151–152
 Community-acquired infections, 447–448
 lung allograft and, 237
 Community-acquired MRSA (CA-MRSA), 101
 epidemiology, 102
 treatment, 105
 Community-acquired pneumonia (CAP), 99,
 101, 101–108, 514–515, 522, 532, 534,
 542, 543
 antibiotic management, initial, 105–107, 106t
 clinical manifestations, 102
 complications, 107
 diagnosis of, clinical and etiologic, 103–104
 differential diagnosis of, 103
 epidemiology, 101–102, 102t
 etiology, 101
 failure to improve, 107
 microbial causes of, by site, 101t
 prognosis and prevention, 108
 treatment, 104–107
 Compliance
 asthma medications and, 76
 treatment regimens, for tuberculosis, 130
 Complicated silicosis, 90
 Compressive cardiogenic shock, **274**
 Computed tomography (CT), 41–57
 bronchiectasis and, 168, 168f
 of bullous emphysema, 44f
 Computed tomography (CT) (*Cont.*):
 chest, PE and, 208, 208f
 COPD and, 185, 186f
 ILDs and, 194–195
 of left upper lobe collapse, 42f
 lung abscess on, 170, 170f
 mediastinal masses, 220
 metastatic brain cancer, 481
 neurologic assessment and, 356
 pulmonary infiltrates and, 488
 for respiratory diseases, 36–37
 SAH and, 366
 Computed tomography angiography, vasospasm and, 365
 Confusion, 360, 529, 550–551
 Confusion Assessment Method (CAM), 255
 Congenital adrenal hyperplasia, 404
 Congenital heart disease, central cyanosis and, 23
 Congenital nephrogenic diabetes insipidus (NDI), 401
 Congenital tuberculosis, 126
 Congestive heart failure (CHF), 46f, 337
 Congo-Crimean hemorrhagic fever, 463
 Connective tissue diseases (CTDs), 190
 Conn's syndrome, 404
 Constipation, 334
 intestinal obstruction and, 478
 "Consumption," 121–122
 Continuous ambulatory peritoneal dialysis (CAPD), 387, 390, 391
 Continuous arteriovenous hemodiafiltration (CAVHDF), 384
 Continuous arteriovenous hemodialysis (CAVHD), 384
 Continuous arteriovenous hemofiltration (CAVH), 384
 Continuous arteriovenous modalities, 384
 Continuous cyclic peritoneal dialysis (CCPD), 387, 390, 391
 Continuous infusion heparin, 431
 Continuous renal replacement therapy (CRRT), 384, 385, 386
 Continuous-positive airway pressure (CPAP), 261–262, 519–520, 539
 CSA and, **232**
 obstructive sleep apnea and, 230
 weaning, 264–265
 Contrast nephropathy, 373–374, 528, 549
 preventive measures, 381
 Contrast phlebography, DVT and, 209
 Contrast-enhanced magnetic resonance imaging, PE and, 209
 Controlled hyperventilation, 259
 Controller, respiratory system dyspnea and, 8, 9
 Controller therapies, asthma and, 72
 Convulsions, 345
 fever and, 347
 COPD. *See* Chronic obstructive pulmonary disease
 cor Pulmonale, CF lung and, 176
 Cork workers pneumonitis, 85
 Corneal reflexes, 358
 Coronary angiography, 300, 333
 Coronary artery bypass graft (CABG), 301–302, 319, 333
 Coronary artery disease (CAD), 317
 risk profiling, 310
 Coronary artery occlusion, 325
 Coronary care unit, STEMI and, 333
 Coronary plaque, 325
 Coronary revascularization, 323
 Coronaviruses, 150, **152**
 clinical manifestations, 153
 epidemiology of, 152–153
 Coronaviruses (*Cont.*):
 etiologic agent, 152
 laboratory findings and diagnosis, 153–154
 pathogenesis of, 153
 prevention, 154–155
 treatment, 154
 Cortical damage, 349
 Cortical laminar necrosis, in hypoxic-ischemic encephalopathy, 359, 359f
 Corticosteroid-resistant asthma, 76
 Corticosteroids
 histone acetylation and, 76
 surgery and, 78
 Cortisone dependent asthma, 76
 Cost, lung transplantation and, 236
 Costochondritis, 553
 Cosyntropin, 287
 Cotton dust, **92**
 Cough, 2, 3, **14**, 519, 522, 539, 542
 adenovirus infections and, 159
 bronchiectasis and, 168
 complications of, 16
 diagnostic algorithm, 16f
 etiology of, 14–16
 HP and, 81
 mechanism of, 14
 treatment of, 16–17
 Cough syncope, 16
 Cough variant asthma, 15
 COX inhibitors (Cyclooxygenase inhibitors), 76
 COX-2 inhibitors (Cyclooxygenase-2 inhibitors), 77
 CPAP. *See* Continuous-positive airway pressure
 CPIS. *See* Clinical Pulmonary Infection Score
 CPP. *See* Cerebral perfusion pressure
 CPR. *See* Cardiopulmonary resuscitation
 Crackles, 4, 194
 Cranial cavity, 344–345
 "Crazy paving," acute silicosis, 90
 C-reactive protein, 280, 281
 levels, 309
 Creatine phosphokinase, 327, 379
 Creatinine levels, 381
 Critical care disorders, of peripheral nervous system, 362–363
 Critical care medicine, **246**
 Critical illness
 complications of, 254–255
 multiorgan system failure syndrome and, 252
 neurologic disorders in, 354t
 neurologic dysfunction and, 255–256
 of peripheral nervous system, disorders of, 362–363
 Critical illness myopathy, 363
 Critical illness polyneuropathy, 362–363
 Cromolyn sodium, 74
 Cromones, 74
 Croup, 149, 150, 158
 CRP, 318
 CRRT. *See* Continuous renal replacement therapy
 Cryoprecipitate, warfarin and, 211
 Cryptic military tuberculosis, 126
Cryptococcus spp., 470
 lung transplant recipients and, 240
 Cryptogenic organizing pneumonia, **198**
 CS. *See* Cardiogenic shock
 CSA. *See* Central sleep apnea
 CT. *See* Computed tomography
 CTDs. *See* Connective tissue diseases
 cTnI. *See* Cardiac-specific troponin I
 cTnT. *See* Cardiac-specific troponin T
 CURB-65 criteria, 104, 543
 CURE trial, 319

- Curvularia*, 84
 Cushing's disease, 531, 551
 Cutaneous perfusion, 32
 Cutaneous petechiae, 283, 347
 CWP. *See* Coal worker's pneumoconiosis
 Cyanide intoxication, 360
 Cyanosis, 22, 194
 acute severe asthma and, 75
 approach to patient, 24
 causes of, 23t
 differential diagnosis, 23–24
 impaired pulmonary function and, 23
 polycythemia and, 22–23
 Cyanotic blue bloaters, 185
 Cyanotic congenital heart disease, 34
 Cycling, ventilator and, 259
 Cyclooxygenase inhibitors. *See* COX inhibitors
 Cyclooxygenase-2 inhibitors. *See* COX-2 inhibitors
 Cyclophosphamide
 and azathioprine, 195–196
 hemorrhagic cystitis and, 489
 Cycloserine, 129
 Cyclosporine, 473
 asthma and, 74
 ILDs and, 196
 kidney injury and, 373
 nephrotoxicity, 407
 renal injury and, 381
 Cylindrical bronchiectasis, 166
 Cylindroma, 56f
 CYP450, theophylline and, 72
 Cysteinyl-leukotrienes, 65–66, 66f
 Cystic bronchiectasis, 52f
 Cystic fibrosis (CF), 172, 521, 534, 541
 with bronchiectasis, 52f
 CFTR protein, 172–173
 clinical features of
 gastrointestinal tract and, 174–175
 genitourinary system and, 175
 respiratory tract, 174–175
 diagnosis, 175–176
 epithelial dysfunction in, 173
 pathogenesis of, genetic considerations, 172
 pathophysiology, organ-specific, 173–174
 treatment, 176–177
 Cysts, thin-walled, 45f
 Cytarabine, 482
 Cytokines, 291–292, 360
 asthma and, 66, 66f
 sepsis and, 280–281
 Cytomegalovirus (CMV), 465
 acyclovir for, 463
 lung allograft and, 237
 lung transplant recipients, 240
 lung transplantation and, 235
 transplantation and, 239
 Cytomegalovirus retinitis, 465, 467
 Cytomegalovirus-associated disease, ganciclovir prophylaxis, 466
 Cytosine arabinoside, pulmonary edema and, 487
 Cytotoxic agents, 482, 487
 Cytotoxic edema, 353

 D-alanine, 437
 Dalfopristin, 438
 Damage-associated molecular patterns (DAMPs), 270
 Daptomycin, 440
 DDAVP, for hemophilia, 427
 D-dimer test, 431
 Death, 307t. *See also* In-hospital death; Sudden cardiac death
 arrhythmias and, 338
 biologic, cardiac arrest and, 312
 Death (*Cont.*):
 HRSV pneumonia and, 156
 thromboembolism, 340
 tuberculosis-related, 117f
 Deaths, out-of-hospital, STEMI, 328
 Decerebrate rigidity, 347
 Decompressive hemicraniectomy, 357
 Decortication, 123, 347
 Decubitus ulcers, 263–264
 Deep leg veins, ultrasonography of, 208t
 Deep organ fungal infections, 471
 Deep venous thrombosis (DVT), 204, 287
 anticoagulation for, 210
 clinical decision rules for, 206t
 diagnosis of, 205–206
 diagnostic imaging for, 206, 206f
 differential diagnosis, clinical syndromes and, 206, 206f
 ICU and, 254
 mechanical ventilation and, 263
 primary therapy v. secondary prevention, 209f
 treatment, 209–214
 Defibrillation, 313
 Defibrillator, 313, 328, 526, 547
 Deficiencies of coagulation factors, 424
 Dehydration, 177, 529, 550
 Delayed postanoxic encephalopathy, 360
 Delayed-type hypersensitivity reaction (DTH reaction), *Mycobacterium tuberculosis* and, 119, 120
 Delirium, 255, 360
 Dendritic cells, asthma and, 64
Dermatophagoides spp., 68
 Desalination, 397
 Descending aorta, chest tomogram of, normal, 42f
 Desquamative interstitial pneumonia, 198
 Developing countries, 528, 549
 asthma in, 60–61
 Dexamethasone, 481, 532, 553
 cord compression and, 480
 Dexamethasone sodium phosphate, hypoadrenal shock and, 275
 Dextrose-containing solution, 390
 Diabetes insipidus, 529, 550
 Diabetes mellitus, 524, 544–545
 OSAHS and, 229–230
 sepsis and, 284
 Diabetic ketoacidosis, 403, 415
 Diacetyl exposure, bronchiolitis obliterans and, 95
 Dialysate, 387, 528–529, 549–550
 Dialysate calcium concentration, 388
 Dialysate sodium concentration, 388
 Dialysis
 goals of, 389
 indications and modalities of, 384–385
 muscle cramps and, 390
 renal failure and, 386–392
 Dialysis access, 388
 Dialysis solution delivery system, 388
 Dialysis-associated hypotension, 389–390
 Dialyzer, 387
 Diaphragm, 517, 536–537
 Diarrhea, 530, 551
 Diastolic dysfunction, 9
 Diastolic failure, 336
 Diazepam, 334
 mechanical ventilation and, 263
 DIC. *See* Disseminated intravascular coagulation
 Diesel particulates, asthma and, 62
 Diet
 asthma and, 62
 STEMI and, 333–334
 Diffuse bronchiectasis, 540
 Diffuse pneumonia, 292
 Diffusing capacity, 31, 34, 35, 195
 Digital clubbing, 4
 Digitalis glycosides, 304, 337
 Digoxin, 338, 545
 Diltiazem, ventricular rate and, 339
 Dilutional hyponatremia, 397
 Dimorphic fungi, 470–471
 Dioctyl sodium sulfosuccinate, 334
 Diphenhydramine, 486
 Diphenylhydantoin, CNS metastases and, 482
 Direct smear examination, pericardial tuberculosis and, 125
 Disability assessment, occupational lung disease, 95–96
 Disability rating scheme, 95–96
 Diseases of airways, 3
 Disorders of neuromuscular apparatus, 5
 Disorders of respiratory pump, 5
 Disorders of ventilatory pump, 7
 Disorders of water homeostasis, 394
 Disseminated intravascular coagulation (DIC), 429, 552, 553
 clinical causes of, 430t
 pathophysiology of, 430, 430f
 treatment, 431–432
 hemorrhagic symptoms, 431
 Distal intestinal obstruction syndrome, 177
 Diuresis, 72, 382
 Diuretic abuse, 405
 Diuretic-induced hyponatremia, 397
 Diuretics, 303, 305, 337, 375, 382, 419
 ECFV and, 420
 K⁺ removal, 409
 renal injury and, 381
 D-Lactic acid acidosis, 414
 DNA
 analysis, 175
 in sputum sample, 38
 vaccination, 74
 viruses, 158–159
 Dobutamine
 hypovolemic shock and, 274
 pulmonary thromboembolism-related shock, 212
 for shock, 275
 Doll's eyes, 358
 Donor kidneys, 239
 Dopamine, 382, 513–514, 533, 535, 549
 contrast nephropathy, 381
 hypovolemic shock and, 274
 pulmonary thromboembolism-related shock, 212
 for shock, 275
 Doppler echocardiographic measurements, normal values of, laboratory test values, 510t
 Doppler imaging, venous flow dynamics, 208
 DOTS strategy, tuberculosis control, 136, 137
 Doxycycline, bioavailability of, 442
 DPP-10 gene, asthma and, 62
 Drotrecogin alfa, for CAP patients, 107
 Drowsiness, 343, 357
 Drug(s). *See also* Pharmacotherapy
 endotracheal intubation and, 250
 ILDs and, 195–196
 interactions, 450
 obstructive sleep apnea and, 230
 overdoses, 345
 regimen, latent tuberculosis infection and, 137t
 resistance, tuberculosis treatment and, 132
 safety
 LABA, 71
 SABA, 71
 susceptibility testing, tuberculosis and, 127–128
 tolerance, 71

- Drug(s) (*Cont.*):
 toxicity, 112
 pregnancy and, 445, 446t
 tuberculosis treatment and, 131–132
- Drug holiday, 271
- Drug–drug interactions, 452t
- Drug-induced acidosis, 415
- Drug-induced delirium, 334
- Drug-induced eosinophilic pneumonias, 84t
- Drug-induced hepatitis, 132
- Drug-induced interstitial lung disease, 200
- Drug-induced lung disease, 83
- Drug-resistant tuberculosis, treatment, 132–134
- DTH reaction. *See* Delayed-type hypersensitivity reaction
- Dual platelet therapy, 341
- Dural arterial–venous fistula, 363
- Dust exposure plus smoking, 92
- Dust mites, asthma and, 61, 63
- DVT. *See* Deep venous thrombosis
- Dynamic hyperinflation. *See* Auto-PEEP
- Dynamic obstruction, 316
- Dysfibrinogenemia, 432
- Dyskinesia, 340–341
- Dysphonia, 73
- Dyspnea, 2, 7, 11, 194, 217, 291–292, 299
 affective dimension of, 8
 approach to patient, 9–11, 10f
 assessing, 7–8
 differential diagnosis, 8–11
 mechanisms of, 7–8
 pathophysiology of, 9f
 sensory inputs in, hypothetical model of, 7, 8f
 treatment, 11
- Dyspnea at rest, alveolar hyperventilation, 226
- E. coli*, fluoroquinolone resistance, 105
- EACA. *See* Aminocaproic acid
- Early goal-directed therapy (EGDT), 249f, 286
- Early invasive strategy, UA/STEMI, 322t
- EBV. *See* Epstein–Barr virus
- ECF. *See* Extracellular fluid
- ECFV. *See* Extracellular fluid volume
- 12-lead ECG, 330
- Echinocandins, 473
- Echocardiography, 300, 303, 328
 PE and, 209
- ECMO. *See* Extracorporeal membrane oxygenation
- Econazole, 473
- Eczema, 61
- Edema, classic pneumonia and, 100
- EEG. *See* Electroencephalogram
- Effective circulating arterial volume, 394
- Effective osmolality, 393
- Efferent sensory input, 7, 8f
- Efferent–reafferent mismatch, 7–8
- Effusions, 11
- EIA. *See* Exercise-induced asthma
- Eicosanoids, 269
- Elastase antielastase hypothesis, 183–184
- Elastin, 183
- Elderly, 336
 amantadine and, 462, 463
 asthma in, 77
 fibrinolytic therapy in, 332
 hypovolemic shock in, 272
 intravascular volume and, 381
 lung biopsy in, 196
 pericardial tuberculosis and, 125
 primary tuberculosis and, 118
 rimantadine and, 462
 STEMI and, 324
 VAP and, 112
- Elective PCI, 333
- Electrocardiography (ECG), 317, 326, 328, 367
 malignant pericardial disease and, 476
 MI and, 300
 SAH and, 367
 STEMI and, 333
 UA/NSTEMI and, 317
- Electroencephalogram (EEG), 345
 brain dysfunction and, 356
- Electrolyte disturbances, 393
- Electrolyte transport, in cystic fibrosis, 173
- Electrolytes, hyponatremia and, 367
- Electromechanical dissociation, 307
- Electrophrenic stimulation, 224
- Electrophysiologic study, 338, 341
 critical illness polyneuropathy, 362
- Electroshock, 338
- ELISA. *See* Enzyme-linked immunosorbent assay
- Embolization, 205
- Emotional support, VTE, 213
- Emphysema, 35, 44f, 53f, 360, 515, 535
 HP and, 82
 pathogenesis of, 183–184, 183f
- Empirical antibiotic treatment, of HCAP, 111t
- Empirical therapy, 447
- Encephalopathy, 345
 of renal failure, 345
 of unknown cause, 356
- Endemic fungi, 470
- Endemic mycoses, 470
- Endobronchial biopsy, 16
- Endobronchial metastasis, hemoptysis and, 483
- Endobronchial tumor, 17
 sputum and, blood in, 16
- Endobronchial ultrasonography, 38
- Endometrium, genitourinary tuberculosis
 and, 123
- End-organ ischemia, 396
- Endothelial injury, multiorgan dysfunction, 282
- Endothelin 1, shock and, 267
- Endothelin antagonists, 382
- Endotoxin, 280, 543
- Endotoxin–neutralizing proteins, 287
- Endotracheal intubation, 259, 264, 524, 544
 drugs used for, 250
 VAT and, 113
- Endotracheal tube (ET)
 contamination, 109
 ventilators and, 259
- Endovascular treatment, 367
- End-stage liver disease, CF and, 177
- End-stage renal disease (ESRD), 386, 528–529,
 549–550
 dialysis, dosing, 389
 global perspective, 392
 treatment options, 387
- ENOX. *See* Enoxaparin
- Enoxaparin (ENOX), 211, 319, 334, 527, 548
 DVT and, 254
 STEMI and, 335f
- Entecavir, 468
- Entecavir-resistant strains, 468
- Enteral feeding, 255
- Enterococcus faecium*, vancomycin-resistant, 441
- Enterotoxin B, 105
- Enterotoxin C, 105
- Environment control, acute HP and, 83
- Environment sampling data, 87
- Environmental allergens, 3
- Environmental contaminants, 85
- Environmental dust, World Trade Center
 disaster, 95
- Environmental exposures, 202
 asthma and, 62–63, 68
 general, 96–97
 ILD and, 193
 measurement of, 87–90
- Environmental lung disease, 86
 chest imaging and, 87
 exposure, measurement of, 87–88
 patient history and, physical examination and,
 86–87
 pulmonary function tests and, 87
- Environmental Protection Agency (EPA), 96
- Environmental respiratory carcinogens, 95
- Environmental toxins, global considerations, 97, 97f
- Environment-induced lung disease. *See* Chronic
 beryllium disease
- Enzyme-linked immunosorbent assay (ELISA), 142
 adenovirus infections and, 160
 coronaviruses and, 153, 154
 HMPV and, 157
 HRSV and, 156
 parainfluenza virus and, 158
- Eosinophilic bronchitis, 16, 63
- Eosinophilic pneumonia, 83, 84, 513, 533
- Eosinophilic pulmonary reactions, 513, 533
- Eosinophils, asthma and, 63, 64–65
- Eotaxin, asthma and, 66, 66f
- EPA. *See* Environmental Protection Agency
- Epidemic disease, influenza A viruses and, 140f
- Epidural venous plexus obstruction, 479
- Epileptic coma, 345
- Epinephrine, 313, 535
- Epithelial cells, of asthmatics, 65, 66f
- Epithelial dysfunction, in cystic fibrosis, 173
- Epithelial-derived relaxant factor, 67
- Epstein–Barr virus (EBV), 541
 lung transplant recipients and, 240
 transplantation and, 239
 types I and II, acyclovir for, 463
- Eptifibatid, 319, 527, 548
- Epworth sleepiness score, 230t, 231
- Erlotinib, 487
- ermB gene, 105
- ERV. *See* Expiratory reserve volume
- Erythrocyte sedimentation rate, 327
 HP and, 81
- Erythrocyte transfusion, 287
- Erythrocyte transit time, exercise and, 31
- Erythromycin, 438
- Erythromycin resistance, 441
- Erythropoietin, 384
- ESBLs. *See* Extended-spectrum β -lactamases
- Esmolol, 367
- Esophagus, chest tomogram of, normal, 42f
- Essential hypernatremia, 400
- Ethambutol, 127, 129, 130t, 133
- Ethionamide, 129
- Ethylene glycol-induced acidosis, 416
- Etomidate, 259
- Etoposide, 482
- Eucapnia. *See* Open lung ventilation
- Eukaryotic cells, 471
- Europe, tuberculosis and, 117
- European CORTICUS trial, 287
- Exercise
 alveolar hyperventilation and, 226–227
 erythrocyte transit time and, 31
 tissue O₂ and, 22
- Exercise testing
 lung transplantation and, 235–236
 post-exercise bronchoconstriction and, 70
- Exercise tolerance, 341
- Exercise-induced asthma (EIA), 67, 68

- Exertional dyspnea, 11, 12
 Expiration, 28
 Expiratory curve, 28, 28f
 Expiratory flow rates, plotting, 27
 Expiratory reserve volume (ERV), 26f, 27
 Extended-spectrum β -lactamases (ESBLs), 105, 440
 Extensive drug-resistant strains, 133
 Extracellular bacteria, lung transplant recipients, 240
 Extracellular fluid (ECF), 393, 398–399
 Extracellular fluid volume (ECFV), 418
 ARF and, 380
 Extracellular fluid volume contraction, 396, 397, 401
 diuretics and, 420
 Extracellular matrix proteolysis, COPD and, 184
 Extracellular osmolarity, 267
 Extracorporeal membrane oxygenation (ECMO), 263, 294
 Extraparenchymal disease, 28, 29t
 Extrapulmonary shunting, hypoxia secondary to, 21
 Extrapulmonary tuberculosis, **122**
 bacteriologic evaluation for, 132
 invasive diagnostic procedures and, 128
 Extravascular spaces, 393
 Extubation, 264, 265
 VAP risk and, 113
 Exudative pleural effusions, 215
 differential diagnosis of, 218t
 Eye examination, miliary tuberculosis and, 126
 Eye signs, 351
- Factor replacement therapy, hemophilia and, 426
 Factor V Leiden, 517, 531, 537, 552
 VTE and, 212
 Factor VII inhibitor, 531, 552
 Factor XI deficiency, **428**
 Factors VIII, 531, 551–552
 Factors IX, 426–427
 complications, 427–428
 dosing, 426–427
 Fallopian tubes, genitourinary tuberculosis and, 123
 False localizing signs, 344, 344f
 Famciclovir, **466**
 Familial multiple coagulation deficiencies, 429
 Fanconi syndrome, 374
 Farmer's lung, 79, 85, **93**
 Fat density, CT scanning and, 36–37, 37f
 Fatigue, 194
 FDC. *See* Fixed drug-combination products
 FE_{Cl} . *See* Fractional excretion of chloride
 FEF. *See* Forced expiratory flow
 FE_{Na} . *See* Fractional excretion of sodium
 Fenoldopam, 549
 contrast nephropathy and, 381
 Fentanyl, 259
 mechanical ventilation and, 263
 Fetal development, anti-asthma medications and, 77
 Fetal liver, prednisolone and, 77
 FEV (Forced expiratory volume), 25
 FEV1. *See* Forced expiratory volume in 1 s
 FEV₁/FVC ratio, 514, 533–534
 Fever, 100
 convulsions and, 347
 tuberculosis and, 122
 FFP. *See* Fresh frozen plasma
 Fiberoptic bronchoscopy, 16
 hemoptysis and, 18
 ILDs and, 195
 Pneumocystis infection, 163
 Fibrinolysis, 212, 330–332
 contraindications to, 212–213
 prehospital setting, 328
 Fibrinolysis inhibitor replacement, 431–432
 Fibrinolytic agents, 334
 contraindications and complications, 332–333
 Fibrin-specific fibrinolytic agents, 334
 Fibroblasts, of asthmatics, 65, 66f
 Fibrosis, 191, 192, 192t, 197
 inflammation and, 67
 Fibrotic lung disease, 89, 89f
 gene cluster analysis and, 83
 Fine-needle aspiration biopsy, mediastinal masses, 220
 Fissures, 49f
 “Fistula first” initiative, 389
 Fixed drug-combination products (FDC), for tuberculosis, 130, 131
 Flank pain, 375
 Flexible fiberoptic bronchoscopy, **39**
 Flow cycling, 259
 Flow-directed pulmonary artery catheter, 271
 Flowing blood, MRI and, 37
 Flow-volume curves, 27–28, 28f
 Flow-volume loop, 28
 “Flu mist,” 525, 546
 Fluconazole, **472**, 473
 Fluocytosine, **473**
 Fluid(s)
 accumulation, mechanisms of, 11–12
 drainage, pericardial tamponade and, 476
 management, 294, 382
 neurogenic shock and, 275
 Fluid disturbances, **393**
 Fluid replacement solutions, 382, 396
 Fluorescence bronchoscopy, 39
 Fluoropolymers, 95
 Fluoroquinolones, 101, 106, 107
 adverse reactions, 452
 CAP and, 103
 pneumococcal resistance, 105
 tuberculosis and, 129
 Focal cerebral ischemia, 354, 355f
 Folic acid synthesis, 163
 Fomivirsen, **465**
 Fondaparinux, 211, 319
 DVT and, 254
 Food, asthma triggers, 68
 Foraminal herniation, 528, 548–549
 Forced expiration, 26f
 Forced expiratory flow (FEF), 25
 Forced expiratory volume (FEV), 69
 Forced expiratory volume in 1 s (FEV₁), 519, 539
 COPD and, 179, 181, 181f
 smokers and, 178–179, 179f
 Forced expiratory volume in 1 s (FEV₁), 517, 537
 Forced vital capacity (FVC), 517, 536–537
 Forced vital capacity (FVC) ratio, 69
 Foreign born patients, primary multidrug-resistant tuberculosis and, 133, 133f
 Formaldehyde, 95
 Foscarnet, 374, **466**
 Fractional excretion of chloride (FE_{Cl}), 379
 Fractional excretion of sodium (FE_{Na}), 379
 Fractionated low-molecular-weight heparin, mechanical ventilation and, 263
 FRC. *See* Functional residual capacity
 Free silica, 90, 91
 Free wall rupture, 302
 Free water restriction
 cerebral ischemia and, 368
 cerebral salt-wasting syndrome and, 366, 366f
 Fresh frozen plasma (FFP), 425, 433, 531, 552
 warfarin and, 211
 Fulminant hepatitis, 433
 Functional residual capacity (FRC), 26, 26f
 Fungal amylase, asthma and, 63
 Fungal ball, 56
 Fungal infections, **470**
 diagnosis of, 471
 lung allograft and, 237
 serum testing for, 531, 553
 terminology and microbiology, 470–471
 treatment, 471–473
 Fungal pathogens, VAP and, 108
 Fungal spores, 79
 Fungi, severe sepsis and, 278, 280
 Furosemide, 303, 417
Fusarium spp., 472
 FVC ratio. *See* Forced vital capacity ratio
 FXIa (Active serum protease), 428
- Gabapentin, seizures, 256
 Gag reflex, 99–100
 Gait ataxia, 361
 Galactomannan test, 471
 Gamma globulin, asthma and, 74
 Ganciclovir, 465, **465**
 Ganciclovir-resistant CMV infections, 467
 Ganciclovir-resistant isolates, 466
 Gas exchange, 205
 COPD and, 182
 disturbances in
 clinical correlations with, 34–35
 measurement of, 31–34
 physiologic features, 30–31
 hemoptysis and, 18
 Gas exchanger, respiratory system dyspnea and, 8, 9
 Gastroesophageal reflux
 asthma triggers and, 69
 cough and, 14
 Gastrointestinal bleeding, 341
 Gastrointestinal discomfort, 461
 Gastrointestinal disease, CF and, treatment for, 177
 Gastrointestinal tests, laboratory test values, 509t
 Gastrointestinal tract
 blood from, 17
 clinical features of, cystic fibrosis, 174, 175
 mechanical ventilation and, 264
 Gastrointestinal tuberculosis, 125
 Gatifloxacin, 129
 Gaucher's disease, 201
 Gefitinib, 482, 487
 Gender, SCD and, 307
 Gene cluster analysis, fibrotic lung disease and, 83
 Gene-environmental interactions, in cystic fibrosis, 173
 General physical examination, respiratory system disorders and, 4
 Genetic diseases, family history and, 3
 Genetic polymorphisms, asthma and, 62
 Genetics
 asthma and, 62
 maternal smoking and, COPD and, 180
 SCD and, 307
 Genital herpes virus infections, 464
 Genital warts, IFNs for, 468
 Genitourinary system, cystic fibrosis and, 175
 Genitourinary tuberculosis, **123**
 Genome scan linkage analysis, COPD and, 180
 GFR. *See* Glomerular filtration rate
 Giant aneurysms, 364
 Gitelman's syndrome, 419
 Glasgow Coma Scale, 352, 356, 356t
 Global LV function, abnormal, 337
 Global tissue perfusion, 254
 Glomerular basement membrane, 513, 533
 Glomerular filtration rate (GFR), 370, 372, 373, 381, 387, 395, 418
 Glomerular proteinuria, 379
 Glottis, 14
 β -glucan test, 471

- Glucocorticoid-remediable hyperaldosteronism, 404
 Glucocorticoids, 16, 281, 287, 289, 294, 330, 367, 382, 476, 520, 532, 540, 543, 553
 acute recurrent HP, 83
 airway obstruction and, 483
 ARDS and, 158
 COPD and, acute exacerbations of, 189
 coronaviruses and, 154
 farmer's lung and, 83
 high-dose, 532, 553
 hypereosinophilic syndrome and, 85
 ILDs and, 195
 inhaled, COPD and, 186–187
 oral, COPD and, 187
 pericardial tuberculosis and, 125
 tuberculous meningitis and, 125
 Glucose infusion, 415
 Glucose solution, 362
 Glutamate, 362
 Glycemic control, 254–255
 Glycocalyx biofilm, on ET, 109
 Glycopeptides, bacterial cell wall synthesis and, 437
 Glycoprotein IIb/IIIa receptor, 325
 Goblet cell metaplasia, 182
 GOLD criteria, COPD and, 185t
 Gold salts, 84
 Gomori methenamine silver, 471
 Goodpasture's syndrome, 3, 17, 18, 35, 196, 201, 533
 cigarette smoking and, 193
 Gordon's syndrome, 407
 Gp IIb/IIIa receptor inhibitors, 334
 GPRA gene, asthma and, 62
 Graft dysfunction, lung transplantation and, 236
 Graft-*versus*-host disease, 243
 SOT and, 241
 Grain dust, **93**
 Grain dust-induced chronic bronchitis, 93
 Grain dust-induced COPD, 93
 Gramicidin A, **440**
 Gram-negative bacilli, 105
 Gram-negative bacteremia, 285
 Gram-negative bacteria, host response and, 280
 Gram's stain, 103
 Granular casts, 529, 550
 Granulocyte colony-stimulating factor, 100
 Granuloma formation, *Mycobacterium tuberculosis* and, 119–120
 Granulomas, miliary tuberculosis and, 126
 Granulomatous disease, transplantation and, 239
 Granulomatous lung disease, 191
 Granulomatous vasculitides, 202
 Gray hepatization, classic pneumonia and, 101
 Griseofulvin, **473**
 Ground glass infiltrates, 82, 82f, 518–519, 538, 540
 ARDS with, 51f
 CT scan of, 50f
 HP and, 82, 82f
 Pneumocystis infection, 162, 162f
 Group A viruses, HRSV and, 155
 Group B viruses, HRSV and, 155
 Guillain-Barré syndrome, 9, 343, 362, 546, 549
 swine influenza vaccine and, 147
 Gynecologic malignancies, 478

H. influenzae, 167
H. influenzae vaccine, transplantation and, 243
 H antigens, 139, 141
 H1N1 viruses, 141
 HACE. *See* High-altitude cerebral edema
Haemophilus influenzae type b conjugate vaccines, HSCT recipients and, 242
 Half-isotonic NaCl, 400
 Haloprogyn, 473
 Hamman-Rich syndrome, **198**
 Hand washing, rhinoviruses and, 152
 Hantavirus pulmonary syndrome, 463
 HAP. *See* Hospital acquired pneumonia
 HAPE. *See* High-altitude pulmonary edema
 Hashimoto encephalopathy, 347
 Hay, moldy, 93
 HBV DNA markers, 468
 HBV DNA polymerase, 468
 HCAP. *See* Health care-associated pneumonia
 Head injury, Glasgow Coma Scale, 356, 356t
 Head trauma, 358
 Headache, 351
 generalized, 364
 Health care workers, SARS and, 154–155
 Health care-associated pneumonia (HCAP), 99, 108–113
 antibiotic treatment of, 111t
 pathogens in, 100t
 Heart, chest tomogram of, normal, 42f
 Heart failure, effusion from, 216
 Heart pressures, elevated, 11
 Heart sounds, 326
 Heavy metal concentrations, in urine, 87
 Heimlich maneuver, 314
 Helical CT scanning, 36–37
 Heliox, airway obstruction and, 483
Helminthosporium spp., 84
 Hemagglutination, parainfluenza virus and, 158
 Hemagglutination inhibition (HI), 142
 Hemagglutinin, 139
 influenza A virus and, 140
 Hematologic tests, for asthma, 70
 Hematology laboratory test values, 492t–494t
 Hematoma, 355
 Hematopoietic stem cell transplantation (HSCT), recipients, 240, 242t
 Hematuria, 379
 Hemiplegia, 351
 HEMO study, 389
 Hemodialysis, **387**, 409, 486
 complications during, 389–390
 components of, 387
 schema for, 388f
 vascular access for, 384
 Hemodynamic assessment, STEMI and, 336–337
 Hemodynamic impairment, 336
 Hemodynamic parameters
 hypovolemic shock and, 274
 normal, 271, 271t
 Hemodynamic support, 285–286
 Hemoglobin concentration, 255
 arterial blood gases and, 31–32
 hypoxia and, 14
 Hemoglobin-oxygen dissociation curve, 422
 Hemolysis, 374
 Hemolytic anemia, 531, 552
 Hemolytic-uremic syndrome (HUS), **486**
 Hemophilia, **425**
 hepatitis and, 426
 hepatitis C and, 428
 inhibitor formation and, 427
 nontransfusion therapy, 427
 treatment of, 426–427
 complications to, 427–428
 Hemophilia A, 425, 531, 552
 Hemophilia B, 425
 Hemoptysis, 3, 14, **17**, 122, **483**, 513, 533
 approach to patient, 18
 BPA and, 78
 bronchiectasis and, 168, 169
 chest radiography and, 18
 classification of, 17
 differential diagnosis of, 17t
 Hemoptysis (*Cont.*):
 endobronchial metastasis, 483
 etiology of, 14
 non massive, evaluation algorithm, 19f
 treatment, 15
 Hemorrhage, 211, 255, 333
 PASG and, 276
 symptoms, management of, 431
 Hemorrhagic cystitis, **489**
 Hemorrhagic effusion, pericardial tuberculosis and, 125
 Hemorrhagic telangiectasia, 35
 Hemothorax, 218
 Henderson-Hasselbalch equation, 410
 Heparin, 407
 acute ischemic stroke and, 255
 DVT and, 254
 indications for, DIC and, 431
 mechanical ventilation and, 263
 PE and, 210
 Hepatic coma, 345
 Hepatic encephalopathy, 360
 Hepatic failure, 225, 345
 Hepatic hydrothorax, 216
 Hepatic toxicity, 472
 Hepatitis B virus, 466
 drugs for, 467–468
 lung transplantation and, 233
 Hepatitis C, 531, 552
 hemophilia and, 428
 lung transplantation and, 233
 Hepatitis vaccines, transplantation and, 242–243
 Hepatitis viruses, antiviral drugs against, 467–468
 Hepatopulmonary syndrome, 10
 Hepatorenal syndrome, **372**
 Hermansky-Pudlak syndrome, 201
 Herniation, 344, 344f
 Herpes simplex virus (HSV), 466
 types I and II, acyclovir for, 463
 Herpes simplex virus keratitis, 467
 Herpes viruses, 150
 antiviral drugs against, 463–467
 transplantation and, 239
 Herpes zoster, with valacyclovir, 464
 Herpes zoster ophthalmicus, 464
 HFOV. *See* High-frequency oscillatory ventilation
 HFV. *See* High-frequency ventilation
 HHV. *See* Human herpesvirus
 HI. *See* Hemagglutination inhibition
 High-altitude cerebral edema (HACE), 20–21
 High-altitude illness, 20
 High-altitude pulmonary edema (HAPE), 20, 305
 High-anion-gap metabolic acidosis, **414**
 approach to patient, 414
 causes, 414t
 lactic acidosis and, 414
 High-density lipoprotein, classification of, laboratory test values, 504t
 High-frequency oscillatory ventilation (HFOV), 263
 High-frequency ventilation (HFV), 294
 High-output hypotension, 247
 High-resolution cardiac MRI, 328
 High-resolution computed tomography (HRCT)
 asbestos exposure and, 89
 bronchiectasis and, 520, 540
 HP and, 81–82
 idiopathic pulmonary fibrosis, 37, 37f, 197
 ILDs and, 191
 lung disease and, 16
 NSIP and, 198, 198f
 silicotic nodules, 90
 toxic exposure and, 87
 Hippocampus, 359

- Histamine, 65–66, 66f, 69
 Histamine challenge, 70
 Histamine receptor antagonists
 mechanical ventilation and, 264
 stress ulcer prophylaxis and, 287
 Histamine-2 antagonists, stress ulcers and, 254
 Histone acetylation, corticosteroids and, 76
 Histone deacetylase-2, 71, 72
Histoplasma capsulatum, 471
 Histotoxic hypoxia, 358
 HIV infection, 15, 39, 102, 118, 193, 457, 466, 468, 484, 485, 538
 amithiozone and, 129–130
 Bacille Calmette–Guérin vaccination and, 135
 bronchiectasis and, 167
 extrapulmonary tuberculosis and, 122, 127
 hemophilia and, 426
 lung transplantation and, 233–234
 lymph node tuberculosis with, 123
 miliary tuberculosis and, 126
 Mycobacterium tuberculosis and, 120
 pericardial tuberculosis and, 125
 Pneumocystis infection, 161, 162
 pneumocystosis and, 164
 primary multidrug-resistant tuberculosis and, 133, 133f
 primary tuberculosis, 122
 tuberculosis and, 117
 HIV-associated nephropathy, 375
 HIV-associated tuberculosis, 117, 126, 128
 antiretroviral therapy, 134
 treatment of, 134
 HMG–CoA reductase inhibitors, 319
 HMPV. *See* Human metapneumovirus
 Home infusion therapy, hemophilia and, 426
 Honeycombing, 47f, 81, 197
 Hormonal level, hyponatremia and, 398
 Hormones
 asthma triggers and, 69
 shock and, 268
 Hospital
 admissions, HRSV and, 155
 CAP and, 104
 discharge, UA/NSTEMI and, 321
 stay
 DVT and, 211–212
 PE and, 211–212
 STEMI, 341
 Hospital acquired pneumonia (HAP), 99, 113
 Hospital-acquired ARF, 374–375
 Host, human, tuberculosis and, 119
 Host cell kinases, 463
 Host defense, 99–100, 280, 456
 bronchiectasis and, 167
 HRSV and, 155
 virus shedding cessation and, 143
 Host immunoinflammatory response, to shock, 269–270, 270f
 Host inflammatory response, 100
 Pneumocystis infection, 161
 Host ligands, 280
 Host pattern-recognition proteins, 280
 Host protein, 280
 Host response
 to influenza, 142
 local, 280–281
 local control mechanisms, 281
 to *M. tuberculosis*, 119
 systemic, 280–281
 systemic control mechanisms, 281
 Host status, antibacterial chemotherapy and, 445–446
 Host-antibacterial immune function, 445–446
 Host-bacterium interaction, 119
 HP. *See* Hypersensitivity pneumonitis
 HRCT. *See* High-resolution computed tomography
 HRSV. *See* Human respiratory syncytial virus infection
 HSCT. *See* Hematopoietic stem cell transplantation
 HSRs. *See* Hypersensitivity reactions
 HSV. *See* Herpes simplex virus
 Human antibody infusion, reactions, 486
 Human herpesvirus (HHV), 239, 465
 Human metapneumovirus (HMPV), 157
 Human respiratory syncytial virus infection (HRSV), 155
 epidemiology and pathogenesis, 155–156
 etiologic agent, 155
 laboratory findings and diagnosis, 156
 prevention, 156
 treatment of, 156
 Human simplex virus (HSV), 465
 Human T cell lymphotropic virus type 1, transplantation and, 239
 Humoral mediators, shock and, 269
 Hunt–Hess classification scale, 365, 365t
 HUS. *See* Hemolytic-uremic syndrome
 Hyaline casts, 379
 Hydralazine, 84, 533
 Hydration, 367
 CAP and, 107
 Hydrocephalus, 256, 343, 365, 367, 481
 Hydrocortisone, 287, 523, 543
 Hydronephrosis, 478
 Hydrostatic pressure, 11–12
 Hygiene hypothesis, asthma and, 62
 Hyperammonemia, 345
 Hyperbaric oxygen, 360
 Hypercalcemia, 484
 Hypercapnia, 9, 34, 345, 354
 Hypercapnic central sleep apnea (CSAs), 232
 Hypercarbic encephalopathy, 360
 Hypercarbic respiratory failure, 258
 Hyperchloremic acidosis, 414
 in renal failure, 417
 Hyperchloremic metabolic acidosis, 417
 approach to patient, 417–418
 Hypereosinophilic syndrome, 85
 Hyperglycemia, 109, 392, 409, 551
 CF and, 177
 Hyperinflation (of lungs), 7, 9
 COPD and, 181
 Hyperkalemia, 406
 ARF and, 380
 causes, 407t
 clinical approach to, 408t
 clinical features, 407–408
 diagnosis, 408
 etiology, 406–407
 treatment, 408–409
 Hyperkalemic distal RTA, 407
 Hyperkalemic periodic paralysis, 406
 Hyperleukocytosis, 482
 Hyponatremia, 360, 393, 400
 clinical approach to, 401f
 clinical features and diagnosis, 401–402
 etiology of, 400–401
 treatment, 402
 Hyperosmolarity, 345
 Hyperoxaluria, 374
 Hyperphosphatemia, 485
 ARF and, 380
 treatment, 383–384
 Hyperplasia, of airway smooth muscle, 67
 Hyperreflexia signs, 360–361
 Hyperreninemia, 404
 Hypersensitivity pneumonitis (HP), 79, 92, 93, 191, 193, 520, 540
 clinical presentation and diagnosis, 81–83
 differential diagnosis, 83
 etiology and pathogenesis of, 79, 81
 examples of, 80t
 global picture of, 85
 subacute form of, 81
 treatment, 83
 Hypersensitivity reactions (HSRs), 485
 antineoplastic drugs and, 489
 tuberculosis treatment and, 132
 Hypertension, 332, 347
 Hypertensive hypovolemic therapy, cerebral vasospasm and, 256
 Hyperthermia, ICP and, 357
 Hypertonic saline, ODS and, 400
 Hypertonicity, 401, 529, 550
 Hypertrophic cardiomyopathy, 308, 311
 Hypertrophic osteoarthropathy, 24
 Hypertrophy, of airway smooth muscle, 67
 Hyperuricemia, 485
 Hyperventilation, 283, 323
 asthma and, 68
 cerebral ischemia and, 357
 Hyperventilation syndrome, 225–227, 226t, 423
 Hypoadrenal shock, 275
 Hypoalbuminemia, 11–12
 Hypoadosteronism, 395
 Hypocalcemia, 314, 380, 381, 384
 Hypocapnia, 226
 Hypoglycemia, 287, 345, 416, 484
 Hypokalemia, 338, 381, 403, 416
 clinical approach, 405f
 clinical features, 404–405
 diagnosis, 405–406
 etiology of, 403–404
 treatment of, 406
 Hypokalemic alkalosis, 420
 Hypokalemic periodic paralysis, 403
 Hypomagnesemia, 338, 381
 Hyponatremia, 345, 360, 365, 368, 380, 393, 394, 397, 484, 551
 causes of, 397t
 clinical approach to, 398f
 clinical features, 398
 diagnosis, 398–399
 differential diagnosis, 399
 electrolytes and, 367
 etiology of, 397–398
 treatment, 399–400
 Hypo-osmolality, 380
 Hypoperfusion (of respiratory muscles), 251
 Hypophosphatemia, 381, 415
 Hypoproteinemia, 392
 Hyporeninemic hypoaldosteronism, 418
 Hyporeninemic hypoaldosteronism syndrome, 407
 Hypotension, 278, 283, 347, 358, 396
 endotracheal intubation and, 250
 mechanical ventilation, 264
 shock and, 268
 Hypotensive molecules, 282
 Hypotensive patients, shock and, 247
 Hypothermia, 347
 complications of, 359–360
 shock and, 276
 Hypotonic fluid replacement, 397
 Hypotonic solutions, 382
 acute brain illness and, 352
 Hypoventilation, 21, 221, 517, 536
 hypoxemia and, 34, 34f
 physiologic and clinical features, 221–222, 222f
 treatment, 223–224

- Hypoventilation syndromes, 224–225, 360
- Hypovolemia, 272, 370, 382–383, **395**, 530, 551
causes, 395t
clinical features and diagnosis, 396
endotracheal intubation and, 250
etiology of
 extrarenal, 395–396
 renal, 395
pathophysiology of, 396
shock and, 267, 268
STEMI and, 337
treatment, 396–397
- Hypovolemic shock, 247, **271**, 272t, 516, 536
diagnosis, 272–273
treatment, 273–274
- Hypoxemia, 30, 201, 205, 225
chemoreceptors and, 7
diagnostic approach to, 34, 34f
oxygen for, 196
- Hypoxemic respiratory failure, 258
NO and, 263
- Hypoxia, 20, **21**, 358
adaptation to, 22
causes of, 20–22
effects of, 20–21
secondary to extrapulmonary shunting, 21
secondary to high altitude, 21
- Hypoxic respiratory failure, ALI and, 263
- Hypoxic-ischemic encephalopathy, **358**
clinical manifestations, 358–359
cortical laminar necrosis in, 359, 359f
diagnosis and treatment, 359–360
- IABP. *See* Intraaortic balloon pump
- Iatrogenic cardiogenic shock, 304
- Ibuprofen, 426
- IC. *See* Inspiratory capacity
- ICAM-1. *See* Intercellular adhesion molecule 1
- ICD. *See* Internal cardioverter/defibrillator
- ICF. *See* Intracellular fluid
- ICP. *See* Increased intracranial pressure; Intracranial pressure
- ICSs. *See* Inhaled corticosteroids
- ICU psychosis, 360
- Idiopathic BOOP, 198
- Idiopathic hypersomnolence, 230
- Idiopathic pulmonary fibrosis (IPF), 37, 37f, 46f, 83, 190, 194f, 195, **197**, 518–519, 538
- IFN- γ , *Mycobacterium tuberculosis* and, 120
- Ifosfamide, 489
- IgE antibody
asthma and, 61, 64
toxic exposure and, 87
- IgM antibody titer, CAP and, 104
- ILDs. *See* Interstitial lung diseases
- ILs. *See* Interleukins
- Imaging studies. *See also* Computed tomography; Doppler echocardiographic measurements; High-resolution cardiac MRI; Magnetic resonance angiography
for asthma, 70
for DVT, 206, 206f
for respiratory diseases, 36–38
- Imatinib, 482, 487
- Immigration, tuberculosis and, 117
- Immune reconstitution inflammatory syndrome (IRIS), 134
- Immune system, of asthmatics, 65
- Immunity
community, influenza A outbreaks, 141–142
impaired, primary tuberculosis and, 122
parainfluenza virus and, 158
- Immunocompromised patients, 470
- Immunoglobulin, HRSV and, 156
- Immunology, laboratory test values, 494t–500t
- Immunomodulatory therapy, for CAP patients, 107
- Immunoperfusion, 487
- Immunosuppressed patients
adenovirus infections and, 159
transplant recipients and, 242–243, 242t
- Immunosuppression, 109
- Immunosuppressive agents, 382, 538
Pneumocystis infection, 161
toxicity, 238
- Immunosuppressive response, 269
- Immunotherapy, asthma and, 74
- In vitro susceptibility (MIC), antibacterial drugs, 444
- Increased intracranial pressure (ICP), 259
cancer and, 481
- Indomethacin, eosinophilic pneumonias and, 84
- Indwelling intravenous catheter infections, lung transplant recipients and, 241
- Indwelling vascular catheters, 289
- Ineffective osmoles, 393
- Infants
Bacille Calmette-Guérin vaccination and, 135
coronaviruses, 153
HRSV and, 156
RSV and, 463
TST and, 136
- Infarct size, 330. *See also* Post-infarction
- Infection(s), 442. *See also specific infections*
ARF and, 380
control practices, 113
in cystic fibrosis, 173
with human host, tuberculosis and, 119
ICU and, 254
life-threatening, 447
lung allograft and, 237–238
secretory antibodies and, 142
source of, removal of, 285
systemic control mechanisms, 281
in transplant recipients, 239–243
- Infection site, antimicrobial drug and, 446–447
- Inferior vena caval filters, indications for, 212
- Infiltrate, on chest radiography, 522, 542
- Inflammation, 192, 192t
asthma and, 64
COPD and, 184
cough and, 14
effects of, airways and, 66–67
- Inflammatory cells
asthma and, 64
shock and, 270
- Inflammatory cytokines, 486
- Inflammatory mediators
asthma and, 65–66, 66f
pneumonia and, 100
- Inflammatory process
alveolar macrophages and, 100
ICSs and, 72
- Influenza, **139**
clinical manifestations, 143
complications of, 143
definition of, 139
differential diagnosis, 145
epidemiology, 140–142
etiologic agent, 139–140
extrapulmonary complications with, 144
laboratory findings and diagnosis, 145
pathogenesis and immunity, 142–143
prophylaxis for, 146–147
systemic symptoms, 143
treatment for, 145–146, 146t
- Influenza A virus, 139, 140f, 461, 462, 546
amantadine and, 462
antigenic subtype of, 140f
antigenic variation of, epidemiology, 140–142
outbreaks of
 epidemiology, 140–142
 inception and termination of, 141–142
 rimantadine, 462
- Influenza AH3N2 viruses, 462
- Influenza B virus, 139, **142**, 461, 462
- Influenza C virus, 139, **142**
- Influenza infection, 103, 525, 546
S. aureus pneumonia with, 101
- Influenza prophylaxis, 525, 546
- Influenza vaccination, 146–148, 147
- Influenza vaccines, 108
- Influenza virus
associated morbidity, 142
associated mortality, 142
bronchiectasis and, 167
with extrapulmonary complications, 144
- Inhaled agents, 3
- Inhaled bronchodilators, brittle asthma, 76
- Inhaled corticosteroids (ICSs), 75–76
for asthma, 61
clinical use and side effects, 73
mode of action, 72
pharmacokinetics of, 73f
- Inhaled environmental agents, 97
- Inhaled hypertonic saline, CF lung and, 176
- Inhaled nitric oxide therapy, 295
- Inherited coagulation disorders, genetic and laboratory characteristics, 425t
- Inherited disorders—interstitial lung diseases, 201–202
- Inhibitors, 424
- In-hospital death, fibrinolytic therapy and, 331
- Innate immunity, 457
- Inorganic dusts, in lungs, 92
- iNOS (Isoform of NO synthase), 270
- Inotropic drugs, 304, 382
- Inspiration, 30
- Inspiratory capacity (IC), 26f, 27
- Inspiratory cycle, SIMV and, 261
- Inspiratory squeaks, 194
- Insulin resistance, 392
- Insulin therapy, 287
- Insulin-like growth factor II, tumors and, 484
- Intensive care unit (ICU)
monitoring, 252–254
multiorgan system failure syndrome and, 252
respiratory failure and, 250
sepsis in, 254
withdrawing care, 256
- Intensive care-acquired weakness, 255
- Intensive insulin therapy, ICU and, 255
- Intercellular adhesion molecule 1 (ICAM-1), rhinoviruses and, 150–151
- Interferon α , 468
- Interferon α 2a, 469
- Interferon γ , 81
- Interferon sprays, rhinoviruses, 152
- Interferons, 463, **468**. *See also specific interferons*
virus shedding and, 143
- Interleukin 1, *Mycobacterium tuberculosis* and, 120
- Interleukin 5, asthma and, 66, 66f
- Interleukin 10, asthma and, 64
- Interleukins (ILs), 100
of asthmatics, 65
shock and, 270
- Internal cardioverter/defibrillator (ICD), 314, 338, 339f
- International Hypersensitivity Pneumonitis Study Group, 82

- International Liaison Committee on Resuscitation, 360
- International Subarachnoid Aneurysm Trial (ISAT), 367
- Interpandemic influenza A, 141–142
- Interstitial edema, 11–12, 35
- Interstitial fibrosis, 293
- Interstitial lung diseases (ILDs), 5, 35, 92, **190**
- associated connective tissue disorders, 199–200
 - BAL in, 195–196, 196t
 - cardiopulmonary exercise testing, 195
 - categories of, 191t
 - chest imaging studies, 194–195
 - cigarette smoking associated, **198**
 - with diffuse alveolar hemorrhage, syndromes of, 201
 - fiberoptic bronchoscopy and, 195
 - frequency of, 192t
 - global considerations, 202
 - with granulomatous response, 202
 - inherited disorders associated with, 201–202
 - laboratory workup, 194
 - pathogenesis of, 191–194
 - age, 192
 - cellular basis for, 193f
 - environmental history, 193
 - family history, 193
 - gender, 192
 - illness duration in, 192
 - smoking history, 193
 - physical examination for, 194
 - pulmonary function testing, 195
 - respiratory symptoms and signs, 194
 - tissue and cellular examination, 195–196
 - treatment for, 196–197
- Interstitial pneumonitis (UIP), 46f, 81, 518–519, 538
- Interstitial pulmonary fibrosis, 11
- Intestinal obstruction
- cancer and, 478
 - treatment, 478
 - with malignancy, 478
- Intestinal pseudoobstruction, 478
- Intraabdominal malignancy, advanced, 478
- Intraaortic balloon pump (IABP), 301, 302
- Intraaortic counterpulsation, 304
- Intraarterial vasodilators, 368
- Intracellular fluid (ICF), 393, 400
- Intracellular pathogens, 443
- Intracerebral leukocytotoxicity, **482**
- Intracranial aneurysms, 363–364
- Intracranial bleeding, 528, 549
- Intracranial hematomas, 355
- Intracranial hemorrhage, fibrinolysis and, 213
- Intracranial hypertension, 367
- Intracranial pressure (ICP), 347, 353, **355**, 355f
- elevated
 - stepwise approach to, 357t
 - treatment of, 356–358
 - monitoring, 358
- Intrapulmonary left-to-right shunting, 21
- Intrathecal chemotherapy, 482
- Intrathoracic airway, acute shortness of breath and, 2
- Intratubular casts, 374
- Intravascular hemolysis, 406
- Intravascular self-expanding stents, 476, 477f
- Intravascular spaces, 393
- Intravascular thrombus, 38, 281
- Intraventricular conduction, disturbances, 339–340
- Intrinsic AREF, 372, 374, 382
- Intrinsic asthma, **61**, 64
- Intubation, 314
- neuromuscular paralysis and, 259
- Invasive diagnostic procedures, extrapulmonary tuberculosis and, 128
- Inverse inspiratory-to-expiratory ratio ventilation (IRV), 262
- Ion transport, in cystic fibrosis, 174f
- IPF. *See* Idiopathic pulmonary fibrosis
- Ipratropium bromide, 71
- Irinotecan, 482
- IRIS. *See* Immune reconstitution inflammatory syndrome
- Irreversible central nervous system damage. *See* Sudden cardiac death
- Irritant triggers, cough and, 14
- IRV. *See* Inverse inspiratory-to-expiratory ratio ventilation
- ISAT. *See* International Subarachnoid Aneurysm Trial
- Ischemia, 337, 355, 355f
- Ischemia-reperfusion injury, lung transplantation and, 236
- Ischemic acute renal failure, 383t
- Ischemic acute tubular necrosis, 374, 375, 381
- Ischemic cascade, **353**, 358
- Ischemic heart disease, **316**
- Isocyanates, 95
- Isoform of NO synthase. *See* iNOS
- Isolated pulmonary capillaritis, 201
- Isoniazid, 136
- eosinophilic pneumonias and, 84
 - LTBI and, 135
 - M. tuberculosis* and, 127
 - toxicity, liver transplantation and, 241–242
 - tuberculosis and, 129, 130t
- Isoniazid, rifampin, pyrazinamide and ethambutol, followed by isoniazid and rifampin, tuberculosis treatment and, 130, 131, 131t
- Isoniazid-related neuropathy, 130
- Isoniazid-resistant tuberculosis, 133, 133f
- Isopropyl alcohol, 416
- Isopropyl alcohol toxicity, 416
- Isopropyl oil, 95
- Isoproterenol, 339
- Isosorbide dinitrate, CHF and, 337
- Isotonic crystalloid solution, 516, 536
- Isotonic saline, 382
- hypovolemic shock and, 274
 - salicylate-induced acidosis and, 415
- Itraconazole, 78, **472**
- J-receptors, 7
- Jugular venous pressure, shock and, 247
- Kanamycin, 129, 133
- Kartagener's syndrome, 167, 534
- Kernohan-Woltman sign, 345
- Ketamine, 259
- Ketoacidosis, **415**
- treatment, 420
- Ketoconazole, 473, 485
- Ketolides, **438**
- drug interactions with, 450
 - resistant bacteria, **441**
- Kidney(s), 372, 410, 418
- acyclovir and, 464
 - telbivudine and, 468
 - water load and, excretion of, 394
- Kidney transplantation, 387
- Killip classification, 336–337
- Kinins, 68
- Klebsiella pneumoniae*, 169
- Klebsiella* spp., 533
- Korsakoff's psychosis, 361
- Kussmaul's sign, 337
- Kyphoscoliosis, 9
- LA. *See* Lupus anticoagulant
- LABAs. *See* Long-acting β_2 -agonists
- Labetalol, 367
- Laboratory test values, **491**
- β -lactam agents, 101, 106, 111, 285, 436t, 437, **440**, 446, 543
- bacterial resistance to, 440–441
 - CAP and, 103
 - classification of, 438t
 - S. aureus* pneumonia resistance, 105
- β -lactam ring, 437
- β -lactamases, 440
- β -lactam/ β -lactamase inhibitor combination, lung abscess and, 170
- Lactate dehydrogenase (LDH), 391
- pleural effusions and, 215–216
- Lactic acid acidosis, 249
- approach to patient, 414–415
 - cancer and, 484
 - treatment, 420
- Laminectomy, MISC and, 480
- Lamivudine, **467**
- Lamivudine-resistant HBV, 468
- Laplace's law, 182
- Large airway, cigarette smoke and, 182
- Large-bore catheters, 389
- Large-volume paracentesis, 382
- Laryngeal edema, 2, 476
- Laryngeal tuberculosis, 518, 538
- Lassa fever, 463
- Late enhancement, 328
- Latent tuberculosis infection (LTBI), 118
- diagnosis of, 128–129
 - revised drug regimen for, 137t
 - treatment, 135–136
 - tuberculin reaction, 135t
- Lavage fluid, polymorphonuclear leukocytes in, 81
- Laxative abuse, 405
- Left heart catheterization, 300
- Left hemi-diaphragm, normal, 41f
- Left hilum, normal, 41f
- Left upper lobe
- collapse, CT of, 42f
 - scarring, with hilar retraction, 43f
- Left upper lobe bronchus, normal, 41f
- Left ventricle, normal, 41f
- Left ventricular aneurysm, 340–341
- Left ventricular failure, 297
- pleural effusion and, 517, 537
- Left-to-right intracardiac shunts, 9
- Leg
- edematous, 206
 - pain, differential diagnosis for, 206, 206t
- Legionella* antigens, 104
- Legionella pneumophila* test, 104
- Legionella* spp, 488
- Lesion biopsy, 40
- Lethargy, 343
- Leukemic cell lysis pneumopathy, 483
- Leukostasis syndrome, 482
- Level of consciousness, 355–356, 357
- altered, 360
- Levofloxacin
- bronchiectasis and, 169
 - pneumococcal resistance to, 105
 - tuberculosis and, 129
- Liddle's syndrome, 404
- Lidocaine, 314, 338

- Light's criteria, 534–535
Limiting factors, ventilation and, 259
Lincosamides, **438**
Linear opacities, asbestos exposure and, 89
Linezolid, **439**, 442
 bioavailability of, 442
 CA-MRSA ad, 107
 drug interactions with, 450
 tuberculosis and, 129–130
Lipid envelope, of influenza A virus, 139
Lipid formulations, 471
Live attenuated vaccine, 147
Liver
 lactic acidosis and, 484
 OSAHs and, 230
 theophylline and, 72
Liver failure
 coagulation disorders and, 432–433, 432t
 pyrazinamide and, 134
Liver function, tuberculosis treatment and, 132
Liver transplantation, isoniazid toxicity and, 241–242
LMWH. *See* Low-molecular-weight heparin
Lobectomy, tuberculosis and, 132
Local antibacterial factors, 100
Local passive congestion, 23
Locked-in state, 343
Loeffler's syndrome, 84–85
Long QT interval syndromes, 311
Long-acting β_2 -agonists (LABAs), 71, 75
Long-term aldosterone blockade. *See* Angiotensin receptor blockers
Long-term therapy, UA/NSTEMI and, 321
Loop diuretics, 303, 337, 382, 399
 contrast nephropathy and, 381
Lorazepam, 334
 mechanical ventilation and, 252, 263
 status epilepticus and, 256
Low-affinity IgE receptors, 64
Low-density lipoprotein, classification of, laboratory test values, 504t
Low-dose heparin, 254
Lower airways, toxic agents in, 88
Lower lobe collapse, 42f
Lower respiratory tract, microorganisms in, 99
Lower respiratory tract defenses, 100, 109
Low-molecular-weight heparin (LMWH), **210**, 318, 319, 334, 407, 517–518, 537
 DVT and, 254
Low-pressure pulmonary edema, 250
LTBI. *See* Latent tuberculosis infection
Lumbar puncture, 124, 350, 356
Lung(s)
 alveoli repair and, COPD and, 184
 collapse, 53f
 expansion, 4
 function
 decortication and, 123
 respiratory acidosis and, 422
 hyperinflation, 69
 inflammatory cells in, mechanisms for, 81
 injury, 250
 mass, 56f
 left upper lobe, 55f
 mechanoreceptors in, 7
 pathophysiology, in cystic fibrosis, 173–174
 resection, radioisotope scan and, 38
 scanning, PE and, 208–209
 sections, *Pneumocystis* infection and, 162, 162f
 Lung abscess, **169**
 clinical manifestations and diagnosis, 170, 170f
 microbiology of, 169–170
 treatment, 170
 Lung apex, MRI and, 37
 Lung atelectasis, 251
 Lung biopsy
 beryllium-specific CD4+T cells on, 92
 HP and, 82
 ILDs and, 195–196
 Lung cancer, 55f, 481
 asbestos exposure and, 90
 CT and, 36–37
 hemoptysis and, 483
 neoplastic meningitis, 481–482
 staging, bronchoscopy and, 39
 SVCS and, 475
 Lung carcinogen, silica as, 91
 Lung compliance, 269
 reduced, 251, 253
 Lung disease
 biologic specimens and, obtaining, 38–40
 CF and, treatment for, 176–177
 historic information and, 3
 Lung function tests, 70
 Lung parenchyma, COPD and, 182–183
 Lung replacement therapy, 294
 Lung transplantation, **233**, 517, 521–522, 537, 541–542
 CF and, 177
 complications, 237t
 COPD and, 188
 cost of, 236
 idiopathic pulmonary fibrosis, 197
 ILDs and, 196
 indications, 233, 234t
 infections in, miscellaneous, 241–242
 organ allocation and, 234
 outcomes, 235–238
 procedure, 234–235
 pulmonary eosinophilia and, 85
 recipient selection, 233–234
 recipients
 infections
 early, 240–241
 late, 241
 middle-period, 241
 infections in, 240–241
 selecting candidates for, disease-specific guidelines, 235t
 waiting list for, 234
 Lung volume reduction surgery (LVRS), COPD and, 187
 Lung volumes, 15, 25, 26f
 assessment of, 11
 ILDs and, 195
 mineral dusts, 87
 Lung water, 12
 Lupus anticoagulant (LA), 433, 531, 552
 LVRS. *See* Lung volume reduction surgery
 Lymph node tuberculosis (Tuberculous lymphadenitis), 122–123
 associated pulmonary disease and, 122–123
 Lymph nodes
 enlarged, 4
 requiring biopsy, 40
 Lymphangioliomyomatosis, 45f
 Lymphoblastoid, 469
 Lymphocytic infiltrative disorders, 202
 Lymphocytic interstitial pneumonitis, 202
 Lymphomas, 220, 479
 neoplastic meningitis, 481–482
 Lymphomatoid granulomatosis, 202
 Lymphopenia, 153
 Lysis-centrifugation technique, 471
 M. africanum, 115
 M. avium complex (MAC), 128
 M. bovis, 115
 M. caprae, 115
 Macrolide antibiotic, *C. pneumoniae*, 76
 Macrolide-resistant bacteria, **441**
 Macrolides, 101, 106, **438**
 drug interactions with, 450
 pneumococcal resistance to, 105
 Macrophage invasion, tuberculosis and, 119
 Macrophage-activating response, *Mycobacterium tuberculosis* and, 119, 120
 Macrophages
 asthma and, 64
 Mycobacterium tuberculosis and, 120
 Magnesium deficiency, 420
 Magnetic resonance angiography (MRA), ARF and, 380
 Magnetic resonance imaging (MRI)
 metastatic brain cancer, 481
 MSCC and, 480
 neoplastic meningitis, 482
 respiratory system disease and, 37
 Main pulmonary artery, chest tomogram of, normal, 42f
 Malignancy, 537
 hemoptysis and, 18
 intestinal obstruction and, treatment, 478
 lung transplantation and, 233
 SVCS and, 475
 Malignant biliary obstruction, **478**
 Malignant cells, in CSF, 482
 Malignant lesions (in lung), PET scan, 38
 Malignant obstruction, 478
 Malignant pericardial disease, **476**
 Malignant pleural effusions, 217
 Malignant spinal cord compression (MSCC), **479**, 532, 553
 treatment, 480–481
 Malnourishment, *Pneumocystis* infection and, 162, 162f
 Malnutrition, 361
 Mammography, 535
 Mandibular repositioning splint, obstructive sleep apnea and, 230
 Mannitol, 397
 contrast nephropathy, 381
 MAP. *See* Mean systemic arterial pressure;
 Mitogen-activated protein
 Mass, soft tissue, 56f
 Massive hemoptysis, 17
 treatment, 18
 Massive pulmonary embolism, 206, 513–514, 533
 anticoagulation for, 210
 MAST. *See* Military antishock trousers
 Mast cells
 asthma and, 64
 of asthmatics, 65
 Mastadenovirus, 159
 Material Safety Data Sheets, 86–87
 Maternal smoking
 asthma and, 62
 COPD and, 180
 Matrix protein antigens, 139
 Maximal expiratory pressure (MEP), 28
 Maximal inspiratory force (MIF), PNS disorders and, 362
 Maximal inspiratory pressure (MIP), 28, 28f
 Maximal midexpiratory flow rate (MMFR), 25, 26f
 Maximum inspiratory pressure (MIP), 514, 533–534
 MBC. *See* Minimal bactericidal concentration
 MCA bifurcation aneurysms, 364

- MDR pathogens. *See* Multidrug-resistant pathogens
- Mean aortic pressure, 29
- Mean pulmonary arterial pressure (PAP), 29
measurement of, 30
- Mean systemic arterial pressure (MAP), 354
- Mechanical revascularization, 340
- Mechanical ventilation, 112, **249**, 258–265, 303, 422, 523, 524, 543, 544
cholestasis, 264
complications of, 264
pulmonary, 264
COPD and, acute exacerbations of, 189
failure to wean, 362
hypoventilation and, 223
idiopathic pulmonary fibrosis, 197
indications for, 258–259
modes of, clinical characteristics of, 260t
patient, care of, 251–252
physiology of, 259
pneumonia and, 108
prone positioning during, 263
support during, 263–264
weaning from, 264–265
- Mediastinal mass, of heterogeneous density, CT
scanning and, 36–37, 37f
- Mediastinal masses, 219–220
- Mediastinoscopy, 40, 535
- Mediastinotomy, 40
specimens and, 40
- Mediastinum, compartments of, 219
- Mediastinum disorders, 215–220, **219**
- Medical history
cough and, 15
potassium depletion and, 405
- Megalodiatrizoate, 177
- Megestrol acetate, 485
- Melanoma, 479, 481
neoplastic meningitis, 481–482
small bowel resection and, 478
- Meningitis, 352, 446–447
- Meniscus, clear, 54f
- MEP. *See* Maximal expiratory pressure
- Mesenchymal tumors, 484
- Mesotheliomas, 217
asbestos exposure and, 90
- Metabolic acidosis, 380, 383, 406, **413**, 530–531, 551
differential diagnosis, 531, 551
high-anion-gap, causes, 414t
treatment, 414
- Metabolic alkalosis, **418**
causes of, 419t
differential diagnosis, 418–419
of gastrointestinal origin, 419
hypoventilation and, 223
pathogenesis of, 418
of renal origin, 419
treatment, 420–421
- Metabolic disorders, causing coma, 345–346
- Metabolic encephalopathies, 345, 355, **360**
- Metabolic support, 285–286
- Metabolism, shock and, 269
- Metal fume fever, 95
- Metallic acidosis, alveolar hyperventilation, 225
- Metallic mercury, 97
- Metalloproteinase-9 (MMP-9), COPD and, 184
- Metapneumoviruses, 150
- Metastatic brain cancer, 481
- Metastatic disease, pleural effusions and, 217
- Metastatic lung cancer, 24
- Metastatic sarcoma, 55f
- Metastatic tumor, vertebral column and, 479
- Metastatic vertebral tumors, percutaneous
vertebroplasty and, 481
- Metered dose inhaler, 71, 71t
- Methacholine, 69
- Methacholine challenge, 70, 96
- Methanol, 416
- Methanol-induced acidosis, 416
- Methemoglobin, central cyanosis and, 23
- Methemoglobinemia, 513, 532
- Methenamine salts, 447
- Methicillin-resistant *Staphylococcus aureus*. *See* MRSA
- Methotrexate, 381, 482, 487, 524–525, 545
asthma and, 74
ILDs and, 196
- Methylprednisolone, 201
- Methylxanthines
COPD and, acute exacerbations of, 189
hypoventilation and, 223
- Metronidazole, **440**
adverse reactions, 452
bioavailability of, 442
- MIC. *See* Minimal inhibitory concentration
- Miconazole, 473
- Microaspiration, 109, 113
- Microbes, sensing, host mechanisms for, 280
- Microbial molecules, host defense and, 280
- Microcirculation, shock and, 266–267
- Microorganisms, severe sepsis and, 278, 279t
- Midazolam, mechanical ventilation and,
252, 263
- Midbrain, 344f, 345
- Middle mediastinum, 219
- MIF. *See* Maximal expiratory pressure
- Mild hypoperfusion, 371
- Mild hypovolemia, 272
- Miliary tuberculosis, **126**, 538
- Military antishock trousers (MAST), 276
- Mineral dusts, breathing and lung volumes, 87
- Mineral fiber, 89
- Mineralocorticoids, 407
- Minimal bactericidal concentration
(MBC), 446
- Minimal inhibitory concentration (MIC),
of penicillin, 104–105
- Minimally conscious state, 343
- Mining, 95
- MIP. *See* Maximal inspiratory pressure
- Mitogen-activated protein (MAP), 72
- Mitotane, 485
- Mitral regurgitation, 302
- Mixed acid-base disorders, **412**
examples, 412t
- Mixed viral and bacterial pneumonia, with
influenza, 144
- MMP-9. *See* Metalloproteinase-9
- Modafinil, 539
obstructive sleep apnea and, 230
- Mode, ventilator, 259, 260t
- Moderate hypovolemia, 272
- Monday chest tightness, 93
- Monitoring
ICP, 356, 358
of ICU, 252–254
shock and, 270–271
- Monobactams, 437
- Monocytes, *Mycobacterium tuberculosis* and, 120
- Monotherapy, tuberculosis and, 129
- Morbidity
acute respiratory illness and, 149
HRSV pneumonia and, 156
- Morphine, 304
asthma and, 259
mechanical ventilation and, 263
STEMI and, 329–330
- Mortality, 340
ARDS and, 295–296
lung transplantation and, 521, 540–541
septic shock and, 523–524, 543–544
severe sepsis, 288
VAP and, 113
- Mortality rates
avian influenza viruses and, 141
for ESRD, 386–387
idiopathic pulmonary fibrosis, 197
lung abscess and, 170
- Motor efferents, 7
- Mouth-to-mouth respiration, 312
- Moxifloxacin, 129
- MRA. *See* Magnetic resonance angiography
- MRI. *See* Magnetic resonance imaging
- MRSA (Methicillin-resistant *Staphylococcus aureus*),
101, 108
vancomycin and, 112
- MSCC. *See* Malignant spinal cord compression
- Mucociliary clearance, 100
- Mucocutaneous HSV infections, acyclovir and, 464
- Mucocutaneous infections, 470
- Mucosal blood flow, asthma and, 67
- Mucus
clearance
CF lung and, 176
in cystic fibrosis, 173
hypersecretion, asthma and, 67
- Multidetector-row spiral CT, chest images, 208
- Multidrug-resistance tuberculosis cases, 133, 133f
- Multidrug-resistant pathogens (MDR pathogens),
99, 111–112
ICU and, 254
- Multiorgan dysfunction, endothelial injury and, 282
- Multiorgan system failure syndrome, 252, 360–361
- Multiple antibiotic resistance, 442
- Multiple inflammatory genes, asthma and, 66, 66f
- Multiple myeloma, 479
- Multiple potential pathogens, therapy against, 447
- Multiresistant bacterial isolates, 442
- Multisystem organ failure, 266, 267f, 362
- Multivessel coronary artery disease, 311
- Mupirocin, **439**, 441
- Muscarinic receptor antagonists, 71
- Muscle tremor, steroid responsiveness, 77
- Muscle wasting, shock and, 269
- Mushroom worker's disease, 79
- Mushrooms, HP and, 85
- Myasthenia gravis, 9, 362, 363, 517, 536–537
- Mycetoma, 56
- Mycobacterial culture, 127
- Mycobacterium tuberculosis*, 103, 115, 120–121
from exposure to infection, 117–118
host response to, 119
infection, innate resistance to, 119
from infection to disease, 118
mycobacterial lipids, 120–121
transplantation and, 239
- Mycoplasma*, 15, 62, 488
- Mycoplasma pneumoniae*, 159
COPD and, acute exacerbations of, 189
- Mycotic aneurysms, 364
- Myocardial compliance, shock and, 268
- Myocardial contractility, shock and, 268
- Myocardial disease, 9
- Myocardial dysfunction, 284
- Myocardial infarctions (MI), 308, 310–311. *See also*
Acute myocardial infarctions
- Myocardial perfusion imaging, 328
- Myocardial rupture, 340
- Myocarditis, influenza and, 144
- Myoclonic status epilepticus, 360

- Myoglobin, 374, 527, 548
 Myoglobinuria, 144
 Myopathy, **363**
 Myositis, 144, 525, 546
 Myxoma, 10
- N antigen, 139
N-acetylcysteine, contrast nephropathy, 381
 NaCl therapy, metabolic alkalosis, 420–421
 Nafifine, 473
 NaHCO₃ therapy, 415
 Naive immune system, of asthmatics, 65
 Naloxone, 351–352
 Narcolepsy, 230
 Narcotic overdose, 351–352, 517, 536
 Nasal ipratropium spray, 16
 Nasogastric decompression, 478
 National Cooperative Dialysis Study, 389
 National Emphysema Treatment trial, 187–188
 Natural killer CD4+ T cells, 65, 66f
 NDI. *See* Central diabetes insipidus; Nephrogenic diabetes insipidus
 nd-NMBAs. *See* Nondepolarizing neuromuscular blocking agents
 Nd:YAG laser, hemoptysis and, 483
 Neck stiffness, 364
 Necrotic cell death, 353–354
 Necrotizing pneumonia, 112
 Nedocromil sodium, 74
 Needle aspiration, primary spontaneous pneumothorax and, 513, 533
Neisseria meningitidis, 283
Neisseria meningitidis polysaccharide, transplant recipients and, 242
- Neoplasm
 bleeding and, 17
 CAP and, 107
 cough and, 15
 Neoplastic meningitis, 481–482
 Nephrogenic diabetes insipidus (NDI), 395, 400, 401, 529, 550–551
 Nephrotic syndrome, 11–12
 Nephrotoxic acute renal failure, 375
 etiology and pathophysiology of, 373–374
 management of, 383t
 prevention, 381
 Nephrotoxic acute tubular necrosis, 374
 Nephrotoxic drugs, 381
 Nephrotoxicity, cidofovir and, 465
 Nephrotoxin, 375
 Neuraminidase inhibitors, resistance to, 462
 Neurogenic bladder, 375
 Neurogenic shock, 275
 Neuroleptics, 360
 Neurologic assessment, 355, 479
 Neurologic critical care, **353**
 Neuromuscular blockade. *See* Nondepolarizing neuromuscular blocking agents
 Neuromuscular blocking agents, mechanical ventilation and, 251
 Neuromuscular disease, pulmonary extraparenchymal disease with, 28–29, 29t
 Neuromuscular paralysis, intubation and, 259
 Neuromuscular transmission disorders, 363
 Neuron-specific enolase (NSE), 358
 Neuropathy, 130, **362**
 Neurotrophins, 67
 Neutropenia, 289
 Neutropenic enterocolitis, 488–489
 chemotherapy and, 488f
 Neutrophils, 65
 NFκB. *See* Nuclear factor κB
- Nicardipine, 367, 368
 Niemann-Pick disease, 201
 Night sweats, 122
 Nimodipine, 367, 368
 Nitrates, 303, 319, 329
 Prinzmetal's variant angina and, 323
 Nitric oxide (NO)
 asthma and, 66
 cigarette smoking, 78
 hypoxic respiratory failure and, 263
 shock and, 267
 Nitrofurantoin, **439**, 447
 Nitrogen dioxide, environmental exposure to, 87
 Nitroglycerin, 303–304, 329, 336
 CHF and, 337
 Nitroprusside, 528, 549
 Nitrosoureas, 487
 NIV. *See* Noninvasive ventilation
 NO. *See* Nitric oxide
Nocardia spp., 169, 536
 Nocturnal dyspnea, 10
 Nocturnal nasal positive-pressure ventilation, CSA and, **232**
 Nodular fibrosis, 90
 Nodular opacities, 46f
 Nodular parenchymal infiltrates, 48f
 Nodules, affecting one lobe, 6
 Non-anion gap metabolic acidosis, 530, 551
 Non-anion-gap acidosis, causes, 417t
 Noncardiogenic pulmonary edema, cardiogenic pulmonary edema v., 12, 12t
 Noncaseating granulomas, in lung tissue, CBD and, 92
 Noncontrast CT scan, subarachnoid blood and, 366
 Nondepolarizing neuromuscular blocking agents (nd-NMBAs), 363
 Noninvasive ventilation (NIV), 251, 262–263, 362
 Nonosmotic urinary waterloss, hyponatremia secondary to, 400–401
 Nonpositive pressure ventilation, lung atelectasis and, 251
 Non-Q-wave MI, 326
 Nonreabsorbable anions, 420
 Nonreactive miliary tuberculosis, 126
 Nonrespiratory disease, respiratory system complications and, 3
 Nonspecific inflammatory responses, 143
 Nonspecific interstitial pneumonia (NSIP), **197**
 Nonspecific reaction, to myocardial injury, 327
 Nonsteroidal anti-inflammatory drugs. *See* NSAIDs
 Non-ST-segment elevation myocardial infarction. *See* NSTEMI
 Nontransmural MI, 326
 Norepinephrine, 535
 hypovolemic shock and, 274
 neurogenic shock and, 275
 for shock, 267, 275
 NRAMP1 gene, mycobacteria and, 119
 NSAIDs (Nonsteroidal anti-inflammatory drugs), 330, 371, 374, 375, 402, 407, 418, 513, 531, 533, 552
 allergic interstitial nephritis and, 379
 renal injury and, 381
 NSE. *See* Neuron-specific enolase
 NSTEMI (Non-ST-segment elevation myocardial infarction), 527, 548
 Nuclear factor κB (NFκB), 66
 Nuclear workers, beryllium lymphocyte proliferation testing, 87
 Nucleic acid amplification test, tuberculosis and, 127
 Nucleic acid synthesis, antibacterial compounds and, 439
- Nucleoprotein antigens, 139
 Nutrition, ICU and, 254–255
 Nutritional management, ARF, 384
 Nylon flock exposure, 95
 Nystatin, 473
- Obesity, asthma and, 62
 Obesity hypoventilation-sleep apnea syndrome, 30
 Obesity-hypoventilation syndrome, 225
 Obstructive lung disease, 27
 Obstructive pattern (of ventilatory function), 28–29
 Obstructive sleep apnea (OSA), 228, 516, 524, 535, 544–545
 Obstructive sleep apnea/hypopnea syndrome (OSAHS)
 clinical features, 229–231
 diagnosis of, 230–231
 differential diagnosis, 230
 epidemiology, 229
 health resources, 232
 mechanism of obstruction, 228–229
 treatment, 231–232
 choice of, 231–232
 how to treat, 231
 whom to treat, 231
 when to refer, 230
- Obtundation, 343
 Occupational lung disease, 10
 categories of, associated respiratory conditions, 88t
 disability assessment, 95–96
 exposures, 3
 asthma and, 63, 87, 179
 asthma triggers and, 69
 COPD and, 87, 179
 pulmonary disease association, 88–93, 88t, 95–96
 patient history and, physical examination and, 86–87
- Octreotide, 478
 Oculovestibular reflexes, 358
 ODS. *See* Osmotic demyelination syndrome
 ODS. *See* Organic dust toxic syndrome
 Olamine, 473
 Oligonucleotides, 74
 Oliguria, 516, 536
 OLV. *See* Open lung ventilation
 Omalizumab
 asthma and, 74
 refractory asthma, 77
 Ommaya, 482
 Oncologic emergencies, **475**
 metabolic, 484
 structural-obstructive, 475–483
 treatment-related, 485
 Oncotic pressure, 11–12
 Onset of clinical transition, to cardiac arrest, 311–312
- Opacities, 197
 OPAT. *See* Outpatient parenteral antibiotic therapy
 Open lung biopsy, 40, 82, 82f
 Open lung ventilation (OLV), 263
 Opiates
 endotracheal intubation and, 250
 mechanical ventilation and, 251, 263
 withdrawing care, 256
 Oral alkali replacement, uremic acidosis and, 417
 Oral candidiasis, 73
 Oral corticosteroids, 73, 78
 Oral therapy, 442–443
 Ores, 95
 Organ allocation, lung transplantation and, 234
 Organ failure, 252

- Organ hypoperfusion, 286
 Organ hypoxia, specific, 21
 Organ injury, shock and, 269
 Organ perfusion, 285–286
 Organ transplantation, 239. *See also* Solid organ transplantation
 CF and, 177
 pretransplantation evaluation, 239
 Organic dust toxic syndrome (ODTS), 83
 Organic dusts, 92
 Oropharyngeal decontamination, 113
 Oropharyngeal thrush, 473
 Orthomyxoviridae, 139
 Orthopnea, 9–11, 12
 Orthostatic dizziness, 375
 OSA. *See* Obstructive sleep apnea
 OSAHS. *See* Obstructive sleep apnea/hypopnea syndrome
 Oseltamivir, 461, 546
 CAP and, 108
 influenza and, 145, 146, 146t
 resistance to, 462
 Osler-Rendu-Weber syndrome, 35
 Osmolality, 393
 Osmotic adaptation, 393
 Osmotic demyelination syndrome (ODS), 399–400
 Osmotic diuresis, 398
 Osmotic water shifting, 398
 Osteomyelitis, 446
 Otitis media, 534
 Outdoor air pollution, 96
 Outpatient parenteral antibiotic therapy (OPAT), 443
 Over the counter agents, 525, 546
 Oxazepam, 334
 Oxiconazole, 473
 Oxidative stress
 asthma and, 66
 HP and, 81
 Oximetric studies, 22
 Oxygen, 303, 514, 534
 acute severe asthma and, 75
 CAP and, 107
 COPD and, 187
 acute exacerbations of, 189
 CSA and, 232
 diffusion of, 31
 humidified, airway obstruction and, 483
 hypoventilation and, 223
 for hypoxemia, 196
 improper utilization, 22
 increased requirement, hypoxia and, 21–22
 pulmonary circulation and, 30
 supplementation
 dyspnea and, 11
 hypovolemic shock and, 274
 Oxygen delivery (QO₂), 254
 Oxygen tension, *Mycobacterium tuberculosis* and, 119–120
 Oxygen transport calculations, 271, 272t
 Oxygenation, 294
 Oxyhemoglobin dissociation curve, 32–33
 Ozone, 62, 96

P. aeruginosa, 107, 108, 283, 455, 533
 antibiotic resistance, 111
P. jiroveci pneumonia, in sputum sample, 38
 Pacing electrodes, sinus bradycardia and, 340
 PAH. *See* Primary alveolar hypoventilation
 Pain, 122, 375, 532, 553
 back, with cancer, 480
 β-blockers, 330
 cervical, 364
 chest, 299, 326, 526, 527, 546, 547–548

 Pain (Cont.):
 cord compression and, 479
 intestinal obstruction and, 478
 leg, differential diagnosis for, 206, 206t
 mechanical ventilation and, 251
 palliation, 481
 shock and, 268
 from STEMI, 326
 Palatal weakness, 362
 Palivizumab, 156
 Palliative urinary diversion, 479
 Palpation, 4
 PAMPs. *See* Pathogen-associated molecular patterns
 Pancreatic enzyme replacement, 177
 Pancreatic islet cell tumors, 484
 Pancytopenia, 126
 Pandemic strains, avian influenza viruses and, 141
 Pandemics, influenza A virus, 140, 140f, 141–142
 Panton-Valentine leukocidin, 105
 PAP. *See* Mean pulmonary arterial pressure;
 Pulmonary alveolar proteinosis
 Papanicolaou method, sputum staining and, 38
 Para-aminosalicylic acid (PAS), 129
 Paracentesis, 382
 tuberculous peritonitis and, 125
 Parahippocampal gyrus, 345, 345f
 Parainfluenza virus, 150, 157
 epidemiology of, 157–158
 laboratory findings and diagnosis, 158
 pathogenesis and clinical manifestations, 158
 treatment of, 158
 Paraneoplastic neuropathy, 478
 Parapneumonic effusion, 216
 Parasitic infections, 193, 239
 Parenchyma (of lung), 190
 bronchiectasis and, 166
 Parenchymal cavity, 46f
 Parenchymal infection, 2
 Parenchymal lung diseases, 3, 15, 37, 40
 Parenchymal spinal cord metastasis, 479
 Parenteral antibiotic therapy, 391
 Paresis of cranial nerves, 124
 Parkinsonian syndrome, 360
 Partial liquid ventilation (PLV), 294
 Particles, characteristics of, 87, 88
 Particulate exposures, 96
 PAS. *See* Para-aminosalicylic acid
 PASG. *See* Pneumatic antishock garment
 Patchy fibrosis, 93
 Pathogen resistance, 111
 Pathogen-associated molecular patterns (PAMPs), 270
 Pathogens
 alveolar macrophages and, 100
 in HCAP, 100t
 Patient history
 ILDs and, 192
 UA/NSTEMI and, 317
 Patient illness, severity of, assessment of, 246–247
 Patient positioning
 for shock, 275–276
 ventilation and, 294
 Patient-ventilatory dyssynchrony, 253
 PBPs. *See* Penicillin-binding proteins
 PCI. *See* Percutaneous coronary intervention
 PcP. *See* Pneumocystis pneumonia
 PCR. *See* Polymerase chain reaction
 PCV. *See* Pressure-control ventilation
 PDD. *See* Tuberculin purified protein derivative
 PE. *See* Pulmonary embolism
 PEA. *See* Pulseless electrical activity
 Peak airway pressure, mechanical ventilation and, 252
 Peak expiratory flow (PEF), 69

 PEEP (Positive end-expiratory pressure), 259, 294, 296
 PEF. *See* Peak expiratory flow
 Pegylated interferon, 531, 552
 Penciclovir, 466
 Penicillin, 105, 106, 374, 437, 513, 533

 CAP and, 103
 CF lung and, 176
 eosinophilic pneumonias and, 84
 ILDs and, 196
 minimal inhibitory concentration of,
 pneumococcal resistance and, 104
 plus metronidazole, 540
 Penicillin-binding proteins (PBPs), 437
 Penicillium, 84
 Pentamidine, 164, 164t, 374, 418
 Penumbra, 354
 Peptide macrolactones, 438–439
 Peptidoglycan, 437
 Peptostreptococcus spp., 521, 541
 Percussion assessment, 4
 Percutaneous coronary intervention (PCI), 301, 302f, 316
 Percutaneous needle aspiration, lung disease and, 38–39
 Percutaneous transluminal angioplasty, 368
 Percutaneous vertebroplasty, metastatic vertebral tumors and, 481
 Perfluorocarbon, 294
 Pericardia tamponade, compressive cardiogenic shock and, 274
 Pericardial effusion, 476
 Pericardial fluid, pericardial tuberculosis and, 125
 Pericardial metastasis, 476
 Pericardial tamponade, 476
 Pericardial tuberculosis (Tuberculous pericarditis), 125
 treatment for, 126
 Pericardiocentesis, 476, 477
 Pericarditis, 144, 340
 Pericardium, chest tomogram of, normal, 42f
 Periodic acid-Schiff, 471
 Periodic limb movement disorder of sleep, 516, 535–536
 Perioperative mortality, 235
 Perioperative respiratory failure, 251
 Peripheral cyanosis, 23–24, 513
 Peripheral eosinophilia, 83
 Peripheral leukocytosis, 100
 Peripheral nerve stimulator, 363
 Peripheral nervous system (PNS), critical care disorders of, 362–363
 Peripheral vascular resistance, 282
 Peritoneal cavity, 390–391
 Peritoneal dialysis, 384, 390, 528, 549
 complications during, 391–392
 forms of, 390–391
 Peritoneal dialysis solutions, additives to, 391
 Peritoneal fluid leukocyte count, 391
 Peritoneal solute transport, 390
 Peritonitis, 391, 396
 Permissive hypercapnia, 258–259, 422
 Persistent vegetative state, 343
 prognosis, 352
 Pertussis infection, 14–15
 Pets, asthma and, 63
 pH, 412, 514, 534
 Mycobacterium tuberculosis and, 119–120
 Phagocytosis, 119
 Pharmacokinetic profile, of antibacterial agent, 442
 Pharmacotherapy
 COPD, 186–187
 for STEMI, 334–336

- Pharyngeal surgery, obstructive sleep apnea and, 230
- Phase alteration syndromes, 230
- Phenobarbital, 256
- Phenylephrine, 535
neurogenic shock and, 275
- Phenytoin
CNS metastases and, 482
seizures, 256
- Phosgene, environmental exposure to, 87
- Phosphodiesterase inhibition, 72
- Physical examination
dyspnea and, 10
hemoptysis and, 18
UA/NSTEMI and, 317
- Physiologic dead space, 205
- Pigeon breeder's disease, 193
- Piperacillin, 441
- Plaque rupture, 316
- Plasma HCO₃, regulation of, 410
- Plasma osmolality, 394, 397
- Plasma potassium concentration, 408
- Plasma sodium concentrations, 399
- Plasmapheresis, 487, 531, 552
- Plateau pressure, mechanical ventilation and, 252
- Platelet adhesion, 322f
- Platinum compounds, 489
- Platypnea, 10
- PLCH. *See* Pulmonary Langerhans cell histiocytosis
- Pleural disorders, 215–220
- Pleural effusion(s), 6, 12, 54f, **215**, 514, 515, 521–522, 534–535, 541
algorithm, 216f
asbestos exposure and, 89
diagnostic approach, 215–216
etiology, 215
left, with clear meniscus, 54f
left ventricular failure and, 517, 537
miscellaneous causes, 218–219, 218t
pleural tuberculosis v., 123
secondary to viral infection, 217–218
- Pleural effusions, protein levels and, 215–216
- Pleural fluid, 217
- Pleural friction rub, 4
- Pleural liquid, ultrasonography, 38
- Pleural plaques, asbestos exposure and, 89
- Pleural thickening, 54f
- Pleural tuberculosis, **123**
- Pleural tumor, asbestos exposure and, 90
- Pleuritic chest pain, 122
- Pluses paradoxus, 274
- PLV. *See* Partial liquid ventilation
- PM/DM. *See* Polymyositis/dermatomyositis
- PMF. *See* Progressive massive fibrosis
- Pneumatic antishock garment (PASG), 276
- Pneumatic compression stockings, 263, 368
- Pneumatoxis intestinalis, 488
- Pneumococcal pneumonia, 101
- Pneumococcal resistance, 104
to fluoroquinolones, 105
to macrolides, 105
- Pneumococcal urine antigen test, 104
- Pneumococcal vaccines, 108, 242
- Pneumocystis carinii* pneumonia, 407, 488, 522, 538, 542
- Pneumocystis* infection, **161**
clinical features and diagnosis, 162–163
course and prognosis of, 163
definition and description, 161
developmental stages, 161
epidemiology of, 161
lung transplant recipients and, 240
pathogenesis and pathology, 161–162
treatment, 163, 163t
- Pneumocystis pneumonia (PcP), 161
- Pneumocystosis
prophylaxis of, 164t
treatment, 163, 163t
- Pneumonectomy, 132
- Pneumonia, 35, **99**, 488, 526, 547
central cyanosis and, 23
community-acquired, 101–108
definition of, 99
health care-associated, 108–113
hospital acquired, 113–114
influenza and, 143–144
lung allograft and, 237
lung transplant recipients and, 240
pathology of, 100–101
pathophysiology of, 99–100
right lower lobe, 50f
- Pneumonia Severity Index (PSI), 104
- Pneumothorax, 6, 53f, **219**, 264
bronchoscopy and, 39
right-sided, 53f
- PNS. *See* Peripheral nervous system
- Poliomyelitis vaccine, 242–243
- Pollutants
indoor exposures, 96–97
outdoor air, 96
- Polyclonal immunoglobulins, 287
- Polycythemia vera, 22
- Polydipsia, 401
- Polymer fume fever, 95
- Polymerase chain reaction (PCR)
amplification, in sputum sample, 38
CAP and, 104
HMPV and, 157
P. carinii and, 488
Pneumocystis infection, 162
rhinoviruses and, 151
tuberculous meningitis and, 125
- Polymyositis, 200
- Polymyositis/dermatomyositis (PM/DM), 200
- Polymyxins, **440**
- Polyneuropathy, 361
- Polypeptide capreomycin, 129
- Polyuria, 401
- Pontine hemorrhage, 351
- Porins, 440–441
- Posaconazole, **473**
- Positive end-expiratory pressure. *See* PEEP
- Positive pressure ventilation, 224, 264, 303
- Post nasal drip, 15
- Post renal ARF, 375
- Posterior mediastinum, 219
- Posthypercapnia, 420
- Postictal state, 345
- Post-infarction, 315
risk stratification and management, 341
- Postphlebotic syndrome, 206
prevention, 213
- Postprimary tuberculosis, clinical manifestations of, 122–123
- Postrenal ARF, 374–375
treatment, 382
- Postresuscitation care, 314
- Posttransplant lymphoproliferative disorder, 541
- Potassium, **402**
depletion, metabolic alkalosis and, 420
nonrenal loss of, 404
renal loss of, 404
supplementation, 406
- Potassium bicarbonate, 406
- Potassium channels, 20
- Potassium excretion, **402**
impaired, 408
- Pott's disease, 124, 124f, 128
- Prazosin, 323
- Prednisolone, fetal liver and, 77
- Prednisone
lung disease and, 83
pericardial tuberculosis and, 125
- Pregnancy
acyclovir and, 464
antibacterial agents and, 445, 446t
asthmatics in, 77
drug toxicity and, 445, 446t
pyrazinamide and, 134
ribavirin and, 463
warfarin and, 211
- Preload
reduction of, 303
shock and, 268
- Preload reduction, 305
- Preloading agents, 382
- Preload-reducing agents, 304
- Premature ventricular contractions, 311
- Prerenal acute renal failure (Prerenal ARF), 375, 379
symptoms of, 375
therapies, 381–382
- Prerenal ARF. *See* Prerenal acute renal failure
- Prerenal azotemia, **370**, 372–373, 373f, 529, 550
- Pressure cycling, 259
- Pressure-control ventilation (PCV), 262, 262f
- Pressure-support ventilation (PSV), 262
weaning from, 265
- Pressure-volume curves, 26, 26f
- Prevention
ARF and, 381
CAP and, 514–515, 534
of VAP, 109t, 113
- Primary adrenal insufficiency, 407
- Primary airway tumors, 483
- Primary alveolar hypoventilation (PAH), 224
- Primary biliary cirrhosis, 432
- Primary brain tumors, 482
- Primary ciliary dyskinesia, 167, 534
- Primary drug resistance, 133
- Primary graft failure, 540
- Primary hyperaldosteronism, 404
- Primary hypodipsia, 400
- Primary infection, 283
- Primary influenza viral pneumonia, 143–144
- Primary multidrug-resistant tuberculosis, 133
- Primary percutaneous intervention (PCI), 330, 331
- Primary spontaneous pneumothorax, 219
needle aspiration of, 513, 533
- Primary tuberculosis, 118, 122
- Primary ventricular fibrillation, 338
- Prinzmetal's variant angina, **322**, 323, 532, 553
- Prodromal complaints, 311–312
- Prodromal symptoms, 364
- Progesterone, hypoventilation and, 223
- Progressive lung injury, 293f
- Progressive massive fibrosis (PMF), 90
- Progressive mechanical obstruction, 316
- Progressive primary tuberculosis, 121
- Progressive systemic sclerosis, 199
- Prophylactic antiarrhythmic drugs, 338
- Prophylactic intubation, acute severe asthma and, 75
- Propofol, 252, 259
- Propoxyphene, 426
- Propylene glycol, 414
- Prostaglandin, 267
- Prostaglandin analogues, 382
- Prostaglandins, 65–66
- Prostate cancer, 481
- Prostatic disease, 375
- Prostatic malignancies, 478
- Protamine sulfate, for intracranial hemorrhage, 211

- Protease inhibitor, 180, 282
 Proteinuria, 379
 Proton pump inhibitors, metabolic alkalosis, 420–421
 Provocative stress testing, 317
 Provoked proximal leg DVT, 212
 Pruritic erythematous rash, 375
 Pseudoaneurysm, 340
 Pseudohyperkalemia, 406, 408, 485
 Pseudohypoaldosteronism, 407
Pseudomonas aeruginosa, 167, 264, 532
 in cystic fibrosis, 173
 lung allograft and, 237
Pseudomonas infection, 112, 113
Pseudomonas spp., 240, 447
 PSI. *See* Pneumonia Severity Index
 PSV. *See* Pressure-support ventilation
 Psychogenic hyperventilation, 226
 Psychogenic polydipsia, 398
 Public health resources, SARS and, 154
 Pulmonary alveolar proteinosis (PAP), 193, **200**, 516, 518–519, 536, 538
 Pulmonary angiography, 38
 PE and, 209
 Pulmonary arteries, enlarged, 57f
 Pulmonary arteriovenous fistulae, central cyanosis and, 23
 Pulmonary arteriovenous malformations (AVM), 56f, 532
 Pulmonary artery catheter, 253
 Pulmonary artery catheterization, 303
 MI and, CS caused by, 300
 Pulmonary artery hypertension, 11
 Pulmonary blood volume, 35
 Pulmonary capillary pressures, 9
 Pulmonary capillary wedge pressure, measurement of, 30
 Pulmonary circulation, disturbances in, 29–30
 Pulmonary compliance, 205
 Pulmonary complications, influenza and, 143–145
 Pulmonary congestion, 336
 Pulmonary dead space, 293
 Pulmonary defense mechanisms, 167
 Pulmonary disease, occupational exposures and, 88–93, 95–96
 Pulmonary edema, **7**, **11**, 34–35, 46f, 303
 central cyanosis and, 23
 cytosine arabinoside and, 487
 early signs, 12
 types of, 304–305
 Pulmonary embolectomy, 213
 Pulmonary embolism (PE), 57f, 204, 205, 368
 effusion secondary to, 217
 integrated diagnostic modalities, 206f, 209
 invasive diagnostic modalities, 209
 nonthrombotic, 206–207
 scintigraphic imaging of, 37
 treatment, risk stratification for, 210
 Pulmonary embolus, 367
 Pulmonary eosinophilia, 85
 Pulmonary fibrosis, 190, 201
 ARDS and, 293
 HP and, 81
 pathogenesis of, 192f
 Pulmonary function testing, 15, 524–525, 538, 545
 bronchiectasis and, 168
 byssinosis and, 93
 CBD and, 92
 COPD and, 181
 environmental lung disease and, 87
 HP and, 82
 ILDs and, 195
 Pulmonary hemorrhage
 hemoptysis and, 483
 necrotizing pneumonia and, 112
 Pulmonary hypertension, 30, 194
 Pulmonary infarction, PE with, 206f
 Pulmonary infiltrates with eosinophilia, 84–85, 84t
 Pulmonary inflammation, 294
 Pulmonary Langerhans cell histiocytosis (PLCH), 3, 199
 Pulmonary lymphangioleiomyomatosis, **200**
 Pulmonary lymphangitic carcinomatosis, 487
 Pulmonary mycotoxicosis, 83
 Pulmonary nodules, 36
 Pulmonary parenchyma, 5
 blood from, 17
 examination, 11
 MRI and, 37
 Pulmonary parenchymal disease, 28–29
 Pulmonary physiology, laboratory test values, 511t
 Pulmonary receptors, 9
 Pulmonary rehabilitation programs, 11, 187
 Pulmonary sarcoidosis, 6
 Pulmonary secretions, CF lung and, 176
 Pulmonary tests, results, 514, 533–534
 Pulmonary thromboembolism (PE)
 acute management of, 210f
 imaging and, 38
 Pulmonary thromboembolism-related shock, 212
 Pulmonary thromboendarterectomy, 213
 Pulmonary vascular disease, 226
 Pulmonary vascular malformations, secondary to hepatic cirrhosis, 35
 Pulmonary vascular pressures, measurement of, methods of, 29–30
 Pulmonary vascular resistance (PVR), 29, 205
 abnormal function, 30
 Pulmonary vasculature, 29
 function of, clinical correlations with, 30
 Pulmonary venous obstruction, lung transplantation and, 236
 Pulmonary vessels, diseases affecting, 30
 Pulse oximetry, 32–33, 252
 Pulse rate, atropine and, 351
 Pulseless electrical activity (PEA), 307, 311
 Pulseless sustained ventricular tachycardia, 307
 Pulseless ventricular tachycardia, algorithm of, 313
 Pulsus paradoxus, 75
 Pupillary changes, 357
 Pupillary constriction, 527–528, 548
 Pupillary reactions, 347–348
 Pupillary reactivity, 344
 Purified protein derivative skin testing, 239
 Purple toes, 375
 Purpura fulminans, 432, 433
 Pyogenic bacterial osteomyelitis, 124
 Pyrazinamide
 chronic renal failure and, 134
 recommended dosage, 130t
 tuberculosis and, 129
 Pyridoxine, vitamin B₆ and, 130
 Pyroglutamic acidemia, 414
 Pyuria, 379
 QO₂. *See* Oxygen delivery
 Quality of life, lung transplantation and, 235–236
 Quantitative-culture methods, 110
 Quinidine, 338
 Quinolones, 169, 374, **439**, **442**
 Quinupristin, 438
 Quinupristin/dalfopristin, drug interactions of, 450
 Q-wave MI, 326
 Q-waves, 326
 Radiation injury, 487
 Radiation pneumonitis, 487–488
 Radiation therapy, 476
 airway obstruction and, 483
 Radiation therapy plus glucocorticoids, MSCC and, 480–481
 Radiation-derived units, laboratory test values, 512t
 Radiation-induced lung toxicity, 487
 Radicular pain, 479
 Radiocontrast agents, kidney injury and, 373
 Radiography
 COPD and, 185
 M. tuberculosis and, 128
 for respiratory diseases, 36
 Radioisotope scan, lung resection and, 38
 Radiolabeled xenon gas, 37–38
 Radionuclide imaging techniques, 328, 351
 Radon gas, lung cancer and, 96–97
 Rales, 4, 100, 336
 Ramipril, 545
 Randomized SHOCK, 301, 302f
 Rapid shallow breathing index, 519, 538–539
 RAS. *See* Reticular activating system
 Rasburicase, 485
 Rasmussen's aneurysm, 122
 RAST, for asthma, 70
 Raynaud's disease, 11, 23–24, 513, 532
 Reactivation tuberculosis, 121–122
 Reactive oxygen species, 270
 Rebleeding, 367
 Rebound thromboembolism, 211
 β₁-receptor, 535
 H₂-receptor antagonists, mechanical ventilation and, 264
 β receptors, 67
 Recombinant activated protein C (aPC), 287–288
 Recombinant factor VIII, 531, 552
 Recombinant human DNase, 176
 Recombinant tissue plasminogen activator, 514, 533
 Rectal examination, STEMI and, 334
 Rectal tuberculosis, 125
 Red hepatization phase, classic pneumonia and, 100
 Reference values, laboratory tests, 491–512
 Refractory ascites, 382
 Refractory asthma, **75**
 differential diagnosis of, 75
 mechanisms of, 75
 treatment for, 77
 Refractory hypotension, 286–287
 Regional hydrocephalus, 345, 345f
 Reimplantation response, lung transplantation and, 236
 Reinfection, HRSV and, 155
 Relapse, 454
 Renal biopsy, 380
 Renal failure, 345
 dialysis and, 386–392
 hyperchloremic acidosis and, 417
 Renal failure indices, **379**
 Renal function tests, laboratory test values, 508t
 Renal hypoperfusion, 370
 Renal prostaglandin biosynthesis inhibitors, 371
 Renal salt retention, 371
 Renal tuberculosis, 124f
 Renal water excretion, 395
 Renal water retention, 371
 Renal-free water excretion, impairment of, 397
 Renin, 268, 404, 408
 Renin-angiotensin-aldosterone system, 370
 inhibition of, 336
 Reperfusion, cardiogenic shock, 337
 Reperfusion edema, lung transplantation and, 236

- Reperfusion therapy, 297, 328, 330
STEMI and, 331f
- Rerupture, SAH and, 365
- Rescue PCI, 333
- Resent osmostat, 398
- Residual volume (RV), 25
- Resistant mutants, 447
- Resistant nosocomial organisms, 447
- Respirator, brain death and, 351
- Respiratory acid-base disorders, 421t
- Respiratory acidosis, 421, 524, 545
treatment of, 422
- Respiratory alkalosis, 14, 422, 530, 551
- Respiratory arrest, 528, 548–549
- Respiratory bronchiolitis, 193
- Respiratory diseases
by diagnostic categories, 29t
diagnostic procedures in, 36–40
- Respiratory distress, 253, 258
- Respiratory drive, 225, 226
SIMV and, 261
ventilator weaning and, 264
- Respiratory epithelium, influenza and, 142–143
- Respiratory failure, 21, 250, 259
CF lung and, 176
ICU and, 252–254
impending, NIV and, 262
type II, 250
type III, 251
type IV, 251
- Respiratory function, 25
disturbances of, 25–35
- Respiratory function screening, mechanical ventilation and, 251
- Respiratory hypoxia, 21
- Respiratory infections
antiviral drugs against, 461–463
in COPD, 179
- Respiratory muscular disorders, 517, 536–537
- Respiratory neuromuscular disorders, 224
- Respiratory neuromuscular system, defects in, 223
- Respiratory response, occupational exposures and, categories of, 88t
- Respiratory support, 285–286
- Respiratory symptoms, 3
- Respiratory syncytial virus (RSVs), 62, 101, 150
ribavirin for, 463
- Respiratory system, 25
compliance, 253
functions of, 30
mechanics, 252–253
- Respiratory system disease, 2, 37
approach to patient with, 2–6
clinical presentation
chest radiography, 4–5, 5f
diagnostic evaluation, 14
patient history, 2–3
physical examination, 3–4
common types, 4, 5t
diagnostic studies and, clinical presentation with, 5–6
- Respiratory system dyspnea, 9
cardiovascular disease v., 11
- Respiratory tract, cystic fibrosis and, 174–175
- Respiratory tract infections, bronchodilators and, 16
- Respiratory viruses, 101
illnesses associated with, 150, 150t
- Respiratory-bronchiolitis-associated interstitial lung disease (RB-ILD), 199
- Rest ischemia, 317
- Resting hypoxemia, 31
- Resting volume, 26, 26f
- Restrictive lung disease, 258
- Restrictive pattern (of ventilatory function), 28–29
- Reticular activating system (RAS), 344
- Retroperitoneal hemorrhages, 433
- Retrosternal clear space, normal, 41f
- Revascularization, 301–302, 302f
- Reversible hematopoietic toxicity, 463
- Review and self-assessment
answers, 532–554
questions, 513–532
- Rewarming, shock and, 276
- Reye's syndrome, 144, 145
- Rhabdomyolysis, 144, 374, 381, 405, 406, 415
- Rheumatoid arthritis, 199
- Rheumatoid factor, HP and, 81
- Rheumatoid factors, ILDs and, 194
- Rhinoviruses, 150, 150, 468–469
clinical manifestations of, 151
diagnosis and treatment, 152
epidemiology of, 151
etiologic agent, 150–151
pathogenesis of, 151
prevention, 152
- Rhizopus* spp., 470
- Rhonchi, 4, 12
- Ribavirin, 463
adenovirus infections, 160
HRSV and, 156
SARS-CoV and, 154
- Rifabutin, 134
- Rifampin, 374, 439, 442, 443
adverse reactions, 452
M. tuberculosis and, 127
recommended dosage, tuberculosis and, 130t
SOT and, 242
tuberculosis and, 129
- Rifampin-resistant organisms, 134
- Right atrium, normal, 41f
- Right coronary artery occlusion, 527, 548
- Right hemi-diaphragm, normal, 41f
- Right mainstream bronchus, chest tomogram of, normal, 42f
- Right middle lobe opacity, 49f
- Right upper lobe collapse, chest x-ray, 43f
- Right ventricle, normal, 41f
- Right ventricular dysfunction, PE and, 205
- Right ventricular infarction
shock secondary to, 302
treatment, 337–338
- Right-to-left shunts, central cyanosis and, 23
- Rimantadine, 462
influenza and, 146, 146t
- Ringer's lactate, hypovolemic shock and, 274
- Rituximab, 428, 489
- RNA segment, 141
- RSV Ig, HRSV and, 156
- Ruptured aneurysm, 364
- RV. *See* Residual volume
- S. aureus*, 169, 533
- S. aureus* pneumonia
influenza infection and, 101
methicillin resistance in, 105
- S. pneumoniae*, 103, 455, 533
- S. pneumoniae* resistance, 104–105
- S. apiospermum* infection, 472
- SABAs. *See* Short-acting β_2 -agonists
- Saccular aneurysms, 363–364
clinical manifestations, 364–365
pathophysiology of, 364
- Saccular bronchiectasis, 166
- SAH. *See* Subarachnoid hemorrhage
- Salicylate-induced acidosis, 415, 551
- Salicylates, influenza and, 145
- Saline, 526, 546–547
- Salt restriction with diuretics, 529, 550–551
- Salt-wasting syndrome, 379, 382, 397
- Sandblasting, silicosis and, 90
- SAPS scoring system, 247
- Sarcoid, 47f
stage I of, 47f
stage II of, 48f
stage III of, 48f
stage IV of, 49f
- Sarcoidosis, 190, 191
CBD v., 92
- SARS. *See* Severe acute respiratory syndrome
- SARS-CoV. *See* Severe acute respiratory syndrome-associated coronavirus
- SCD. *See* Sudden cardiac death
- Scedosporium*, 472
- Scleroderma, 90
- Sclerotherapy, pericardial tamponade and, 476
- Scrofula, 122
- Secondary brain injury, 358
- Secondary brain insults, 354, 355
- Secondary hyperaldosteronism, metabolic alkalosis and, 420
- Secondary influenza viral pneumonia, 144
- Secondary pneumothorax, 219
- Secondary tuberculosis, 118, 121–122
- Secretory antibodies, infection and, 142
- Sedatives
acute severe asthma and, 75
mechanical ventilation and, 251
PAH and, 224
- Seizures, 256, 345, 356, 367, 462
cancer and, 482
- Self-expanding metal stents, 478
- Self-extubation, 113
- Self-inoculation, HRSV and, 155
- Semicoma, 343
- Sensory afferents, 7
- Sensory loss, 479
- Sentinel bleeds, 364–365
- Sepsis, 109, 252, 360–361, 362, 363, 522, 523, 542, 543. *See also* Severe sepsis
in critical care unit, 254
definitions, 278, 279t
genetic factors in, 283
- Sepsis-induced hypotension, 284
- Sepsis-related incidence and mortality rates, age and, 278, 280
- Septic encephalopathy, 360
diagnosis of, 360–361
- Septic myopathy, 363
- Septic response, 278, 280, 284
- Septic shock, 249, 278
definitions, 278
mortality and, 523–524, 543–544
treatment, 285–288
- Serial laboratory analysis, 552, 553
- Serology, CAP and, 104
- Serum albumin levels, 283
- Serum antibody responses, measurement of, 142
- Serum brain injury biomarker, 361
- Serum cardiac biomarkers, 327
- Serum creatinine measurements, 379
- Serum immunoglobulins, 81
- Serum magnesium, 336
- Serum potassium levels, 382
- Serum precipitins, 81
- Serum testing, for fungal infection, 531, 553
- Serum troponin, 526, 547
- Serum uric acid, 379

- Severe acute respiratory syndrome (SARS), 101, 150, 153, 154f
- Severe acute respiratory syndrome-associated coronavirus (SARS-CoV), 152, 152f, 153
- diagnosis, 154
- prevention, 155
- Severe anemia, 22
- Severe central nervous system dysfunction, approach to patient, 355–356
- Severe cerebral edema, 365
- Severe inflammatory conditions, 252
- Severe interstitial lung disease, 95
- Severe liver disease, 552, 553
- Severe lung disease, 532
- Severe obstructive lung disease, 258
- Severe pulmonary hypertension, 57f
- Severe rhinosinusitis, 76
- Severe sepsis, **278**
- cardiopulmonary complications, 283–284
- clinical manifestations of, 283
- definitions, 278, 279t
- diagnosis, 284–285
- epidemiology, 278, 280
- etiology, 278
- general support in, 287
- laboratory findings, 284
- microorganisms involved, 278, 279t
- neurologic complications, 284
- pathophysiology of, 280–283
- prevention of, 289
- prognosis, 288
- renal complications, 284
- single pathogenesis to, 282–283
- treatment, 285–288
- Severity-of-illness scoring systems, 247
- Shallow breathing, 292
- Shock, **247**, 252, 537
- adjunctive therapies, 275–276
- approach to patient, 270–271
- cardiovascular response, 268–269
- cellular responses to, 268
- classification of, 267t
- EGDT and, 249f
- forms of, 271–275
- physiologic characteristics of, 272t
- hyperperfusion in, 251
- inflammatory responses, 269–270
- initial evaluation of, 247, 248
- mechanical ventilation and, 249
- metabolic derangements, 269
- neuroendocrine response to, 268
- organ dysfunction and, 282
- pathogenesis and organ response to, 266–271
- patient in, approach to, 266–276
- patient monitoring, 270–271
- patient resuscitation from, 273f
- pulmonary response, 269
- renal response, 269
- right ventricular infarction and, 302
- Shock-induced tachypnea, 269
- Shock-induced vicious circle, 266, 267f
- Shohl's solution, 417
- Short-acting β_2 -agonists (SABAs), 71, 72
- acute severe asthma and, 75
- Short-course chemotherapy, tuberculosis control, 136
- Short-course therapy, antibiotics, 455
- Shortness of breath, 8t
- subacute v. chronic, 2
- Shunting (of blood), hypoxemia and, 34, 34f
- SI. *See* System of international units
- Signal transduction pathways, 74
- Silhouette sign, 49f
- Silica, 90
- Silicates, 91
- Silicosis, **90**
- Silicotic nodules, 90
- Silicotuberculosis, 134
- Simple acid-base disorders, **411**
- compensatory responses in, 411t
- Simple Coal worker's pneumoconiosis (CWP), 91
- Simple silicosis, 90
- SIMV. *See* Synchronized intermittent mandatory ventilation
- Sinus bradycardia, 339, 340
- Sinus tachycardia, 304
- SIRS. *See* Systemic inflammatory response syndrome
- Situs inversus, 515, 534
- Sjögren's syndrome, 200
- Skeletal tuberculosis, 124, 124f
- Skin lesions, 283
- Skin prick tests
- for allergens, 70
- BPA and, 78
- toxic exposure and, 87
- Skin testing. *See also* Tuberculin skin test
- for asthma, 70
- reactivity, *Mycobacterium tuberculosis* and, 121
- SOT and, 241
- SLE. *See* Systemic lupus erythematosus
- SLED (Slow, low-efficiency dialysis), 386
- Sleep
- hypoventilation and, 222
- sleep apnea and, 230
- small-volume aspiration in, 99
- Sleep apnea, **228**, 262
- Sleep disturbance, cough and, 17
- Sleepy patient, clinical indicators in, 229t
- Small airway
- COPD and, 182
- fatal asthma and, histopathology of, 63f
- Small bowel resection, melanoma and, 478
- Small-cell lung cancer, 56f, 478, 532, 553
- Small-particle aerosol, 142
- Small-volume aspiration, 99
- Smoke inhalation, 95
- Smoking, 3, 15. *See also* Cigarette smoke
- asthma and, 61
- Smoking cessation, COPD and, 186
- Smooth muscle cells, β_2 -agonists and, 71
- Smooth muscle hyperplasia, 197
- Sodium
- excretion, 395
- intake, 394–395
- modeling, 388
- Sodium balance, **394**
- Sodium bicarbonate, 381, 383, 486, 528, 549
- lactic acidosis and, 484
- Sodium citrate, 417
- Sodium polystyrene sulfonate, 409
- Sodium/water balance, in brain, 345
- Solid organ transplantation (SOT)
- recipients, vaccination for, 242t
- tuberculosis and, 241–242
- Solitary pulmonary nodules, 38, 55f, 128
- Somatosensory evoked potentials (SSEPs), 358
- Sorbitol-induced colonic necrosis, 409
- SOT. *See* Solid organ transplantation
- Speech therapy, 76
- Spider hemangiomas, 35
- Spinal tuberculosis, 124, 124f
- Spine sign, 50f
- Spirometry, 28–29, 195
- ARDS and, 296
- Spontaneous breathing trials, 251, 519, 538–539
- Spontaneous central sleep syndrome, **232**
- Spontaneous expectoration, 38
- Spontaneous pneumothorax, 3
- Spontaneous reperfusion of coronary artery, 330
- Sputum, 15, 17
- blood in, 16
- collection, 38
- culture, 103
- tuberculosis and, 130
- induction, 38
- M. tuberculosis* and, 117–118, 128
- production, primary influenza viral pneumonia, 143–144
- purulent, 15–16, 122
- sample, squamous epithelial cells in, 38
- smear
- HIV-associated tuberculosis, 126
- miliary tuberculosis and, 126
- Squamous cell carcinoma, 55f
- Squamous epithelial cells, in sputum sample, 38
- SSEPs. *See* Somatosensory evoked potentials
- ST elevation MI. *See* STEMI
- Staphylococcal chromosomal cassette types, 105
- Staphylococcus aureus*, 264, 391
- in cystic fibrosis, 173
- lung allograft and, 237
- vancomycin and, 441
- Staphylococcus epidermidis*, vancomycin-resistant, 441
- Starling's law of capillary–interstitial liquid exchange, 267, 393
- Static lung volumes, 28–29
- Statins, 321
- Status epilepticus, 256
- STEMI (ST elevation MI), 297, 302, **324**, 329f, 333, 335f
- ACE inhibitors and, 335, 336
- arrhythmias after, 338
- clinical presentation, 325–326
- complications of, management, 336–341
- elderly, 324
- emergency department, 328–329
- hospital phase management, 333–334
- initial management, 328–333
- discomfort control, 329–330
- laboratory findings, 326
- pathophysiology of, acute plaque rupture and, 324–325
- patient transportation options, 331f
- pharmacotherapy, 334–336
- physical findings, 326
- pre-hospital care, 328
- reinfarction and death, preventing, 341
- reperfusion therapy, 331f
- return to work, 341
- secondary prevention, 341–342
- sedation and, 334
- Stenotrophomonas maltophilia*, antibiotic resistance, 111
- Stepwise therapy, chronic asthma, 74–75, 74f
- Stereotactic radiosurgery, 481
- Steroid-sparing therapies
- asthma and, 74
- refractory asthma, 77
- Stiff lungs, 249
- Stiff-man syndrome, 533
- Stimulant drugs, sleep apnea and, 230
- Stool analysis, laboratory test values, 507t
- Streptococcus pneumoniae*, 101
- COPD and, acute exacerbations of, 189
- macrolide resistant, 441
- Streptogramins, **438**
- resistant bacteria, 441

- Streptokinase, 331, 332, 334
allergic reactions to, 333
- Streptomycin, tuberculosis and, 129
- Stress, asthma triggers and, 69
- Stress ulcer prophylaxis, 287
histamine receptor antagonists and, 287
- Stress ulcers, 283
ICU and, 254
mechanical ventilation, 264
- Stridor, asthma and, 76
- Stroke, 255, 351
- Stroke volume, shock and, 268
- Structural cells, asthma and, 65
- Structural lesion, 355, 356
- Structural lung disease, 533
- ST-segment elevation, 330, 552, 553
- Stupor, 343, 345f
- Subacute hypersensitivity pneumonitis (HP), 81
- Subarachnoid blood, 368
- Subarachnoid hemorrhage (SAH), 256, 356, **363**
delayed neurologic deficits of, 365–366
laboratory evaluation and imaging, 366–367, 366f
treatment, 367–368
- Subcutaneous emphysema, 53f
- Subcutaneous nodules, 375
- Sublingual nitroglycerin, 329
- Subpleural atelectasis, 54f
- Subxiphoid pericardiotomy, 476
- Succinylcholine chloride, 406
neuromuscular paralysis and, 259
- Sudden cardiac death (SCD), 306, 526, 547
age factors, 307, 309f
bradyarrhythmias and, 340
causes, 308t
etiology, initiating events, clinical epidemiology, 307–308
forms of, 307
pathology, 308
population subsets/risk predictors, 310f
prediction of, 308–309
prevention of, 309, 315
- Sudden collapse, 312
- Sudden coma, 350–351
- Sudden deaths, 306
- Sudden infant death syndrome, 307
- Sudden loss of consciousness, 364
- Sudden natural death, 307
- Sudden nocturnal deaths, OSAHS and, 229–230
- Sufentanil, 259
- Sulconazole, 473
- Sulfhemoglobin, central cyanosis and, 23
- Sulfonamides, 374, **439**, 442
adverse reactions, 451
eosinophilic pneumonias and, 84
resistance, 164, 164t
- Sulfur dioxide, asthma and, 62
- Superior vena cava, normal, 42f
- Superior vena cava syndrome (SVCS), **475**, 532, 553
treatment, 476
- Supportive therapy
adenovirus infections, 160
bronchiectasis and, 169
coronaviruses and, 154
- Suppressive therapy, with valacyclovir, 464
- Suprapubic cystostomy, 478
- Suprasternal mediastinoscopy, 40
- Supraventricular arrhythmias, 339
- Surfactant replacement therapy, 294–295
- Surgery
asthma and, 77–78
lung abscess and, 170
obstructive sleep apnea and, 230
- Surgery, oral, hemophilia and, 426
- Surgical repair, SAH, 367
- Survival
ARDs, 296
lung transplantation and, 235
malignant pericardial disease and, **477**
of out-of-hospital cardiac arrest, long-term management, 314–315
primary ventricular fibrillation and, 338
recipient, by pretransplantation diagnosis, 236t
- Survival after sudden death. *See* Sudden cardiac death
- Surviving sepsis guidelines, 543
- Survivors, tuberculosis, 118
- Susceptibility, infecting organism, 444
- SVCS. *See* Superior vena cava syndrome
- SVR. *See* Systemic vascular resistance
- Swan-Ganz catheter, 303, 337
- Sweat acinus, 174
- Sweat chloride test, 521, 541
- Sweat gland, in cystic fibrosis, 174
- Sweat test, CF and, 175
- Sweating, 404
- Swine influenza vaccine, Guillain-Barré syndrome and, 147
- Sympathetic nervous system, 370
- Synchronized intermittent mandatory ventilation (SIMV), 261
weaning by, 265
- Syndrome of acute hydrocephalus, 351
- Syndrome of inappropriate antidiuretic hormone secretion (SIADH), 397, **484**, 551
causes, 397–398
subtypes, 398
- Syndromes of interstitial lung disease with diffuse alveolar hemorrhage, 201
- Synercid, 438
- Synergistic activity, 447
- System of international units (SI), 491
- Systemic anticoagulation, 368
- Systemic arterial pH, 410
- Systemic corticosteroids, 73
- Systemic diseases, 325
pulmonary complications with, 4
- Systemic host response, 281
- Systemic inflammatory response syndrome (SIRS), 100, 278, 360, 362, 363, 523, 543
multiorgan system failure syndrome and, 252
- Systemic lupus erythematosus (SLE), 199–200, 520, 540
- Systemic vascular resistance (SVR), 266–267, 284, 300
- Systemic wasting, COPD and, 185
- T cell lymphoma, 85
- T cell-mediated hypersensitivity reaction, 81
- T helper 2 cells, asthma and, 62
- T lymphocytes, 81
asthma and, 63, 65
Mycobacterium tuberculosis and, 120
- Tachyarrhythmias, 304
- Tachycardia, acute severe asthma and, 75
- Tachypnea, 194, 292
ACMV and, 261
- Tacrolimus
kidney injury and, 373
renal injury and, 381
- TACTICS-TIMI, 318
- Talc dusts, 91, 95
- TARC. *See* Thymus and activation-regulated chemokine
- Target-site modification, macrolides and, 105
- Task Force on Ethics, withdrawing care and, 256
- Taxanes, 482, 489
- TBI. *See* Traumatic brain injury
- T-cell mediated immunity, parainfluenza virus and, 158
- Teicoplanin, 437
- Telbivudine, **468**
- Telithromycin, 441
pneumococci resistance and, 106
- Temporary electrical pacing, 339–340
- Tenecteplase (TNK), 331
- Tenofovir, **468**
- Tension pneumothorax, 219
- Teratomatous neoplasms, 220
- Terbinafine, 473, **473**
- Terbutaline, 71
- Terconazole, 473
- Tetanus/diphtheria/pertussis vaccine, transplant recipients and, 242
- Tetracyclines, 101, **441**
drug interactions with, 450–450
- TFPI. *See* Tissue factor pathway inhibitor
- Thalamic hemorrhage, 351
- Theophylline, 72, 75
clearance of, 72t
contrast nephropathy, 381
COPD and, 187
plasma concentrations of, 72
refractory asthma and, 77
side effects, 72
- Therapeutic drug monitoring, laboratory test values, 501t–503t
- Therapy duration, for bacterial infections, 454t
- Thermodilution technique, cardiac output and, 271
- Thermophilic actinomycetes, 93
- Thermophilic antigens, 79
- Thermophilic bacteria, 85
- Thermoregulation, 395
- Thiamine, 361, 362
Wernicke disease and, 351
- Thiazides, 84, 402, 513, 533
- Thienopyridine clopidogrel, 319
- Thiotepa, 482
- Third nerve palsy, 345f, 549
- Third space, fluid sequestration in, 396
- Thirst, 375, 394, 395–396, 400
- Thoracentesis, **39**, 521–522, 534, 537, 541
for parapneumonic effusion, 216
pleural effusions and, 216
- Thoracic radiation therapy, 487
- Thoracoscopy, metastatic disease and, 217
- Thoracotomy, 40
- Thorax infections, digital clubbing and, 4
- Thrombin, 325
- Thrombocytopenia, 284, 432
- Thromboembolism, 340
- Thrombolysis in Myocardial Infarction Risk Score (TIMI risk score), 318, 318f, 331–332
- Thrombosis, 322f
- Thrombotic thrombocytopenic purpura (TTP), 486
- Thromboxane A₂, 267
- Thunderclap headache, 364
- Thymus and activation-regulated chemokine (TARC), 66, 66f
- Thyroid masses, 220
- Tigecycline, **441**
- Time cycling, 259
- Time to initial defibrillation, 526, 547
- TIMI risk score. *See* Thrombolysis in Myocardial Infarction Risk Score
- Tinzaparin, 211
- Tioconazole, 473

- Tipifarnib, 482
 Tirofiban, 319, 527, 548
 Tissue
 examination, ILDs and, 195–196
 oxygenation, 282
 perfusion, 414
 samples, flexible fiberoptic bronchoscopy and, **39**
 Tissue factor pathway inhibitor (TFPI), 288f
 Tissue plasminogen activator (tPA), 255, 331
 TLC. *See* Total lung capacity
 TLRs. *See* Toll-like receptors
 TLS. *See* Tumor lysis syndrome
 TMP-SMX. *See* Trimethoprim-sulfamethoxazole
 TNF- α . *See* Tumor necrosis factor- α
 TNK. *See* Tenecteplase
 Tobacco smoke, 96–97, 521–522, 541
 secondhand, 522, 542
 Tobramycin, 176
 Toll-like receptors (TLRs), 280
 shock and, 270
 Tolnaftate, 473
 Topical acyclovir, 464
 Topical antifungal agents, **473**
 Torsades des pointes, 338
 Torsemide, 303
 Total body sodium, 393
 Total body water, 393, 399
 Total dead space ventilation, 30
 Total disability, 95–96
 Total lipoprotein cholesterol, classification of,
 laboratory test values, 504t
 Total lung capacity (TLC), 25, 514, 533–534
 Toxic agents, 86–87, 93, 94t, 95
 portal of entry, 97
 Toxic chemicals, **93**
 Toxic drug-induced coma, 345
 Toxic gas, bronchiectasis and, 167
 Toxic injury, shock and, 269
 Toxic substances
 blood-brain barrier and, 345
 bronchiectasis and, 167
 Toxicology, laboratory test values, 501t–503t
 Toxin-induced acidosis, 415
Toxoplasma gondii, transplantation and, 239
 tPA. *See* Tissue plasminogen activator
 T-piece weaning, 264–265
 Trace minerals, laboratory test values, 504t
 Trachea
 chest tomogram of, normal, 42f
 cough and, 14
 normal, 41f
 Tracheal intubation, 351–352
 Tracheal obstruction, 476
 Tracheobronchial tree, blood from, 17
 Tracheostomy
 obstructive sleep apnea and, 230
 in ventilated patients, 259
 Traction bronchiectasis, 47f
 Transbronchial biopsy, 39
 Transcription factors, asthma and, 66
 Transesophageal echocardiography, PE and, 209
 Transforming growth factor β (TGF β), 81
 Transgenic knockout mice, *Mycobacterium tuberculosis*
 and, 120
 Transient ischemia, 308
 Transmural myocardial infarction, 326
 Trispeptidation, 437
 Transplant recipients, infections in, 239–243
 Transplantation. *See* Organ transplantation
 Transplanted stem cells, bacterial infection of, 239
 Transpulmonary pressure, 25, 26f
 Transtentorial herniations, 344, 344f
 coma v., 344f, 355
 Transthoracic echocardiography, PE and, 209
 Transtracheal aspiration, lung abscess with, 170
 Transtubular K concentration gradient
 (TTKG), 408
 Transudative pleural effusions, 215
 differential diagnosis of, 218t
 Trauma patients, 113, 353
 Trauma-induced hypovolemia, 274
 Traumatic brain injury (TBI), 354, 355
 Traumatic pneumothorax, 219
 Traumatic shock, **274**
 Treatment failure, therapy duration and, 454
 “Tree in bud” opacities, and bronchiectasis, 53f
 Trendelenburg position, for shock, 275–276
 Tretinoin, 483
 Tricyclic antidepressants, 513, 533
 Trifluridine, **467**
 Trigger-induced asthma, 74
 Trimethoprim, **439, 442**
 Trimethoprim-plus dapson and clindamycin
 plus primaquine, pneumocystosis and,
 163, 163t
 Trimethoprim-sulfamethoxazole (TMP-SMX), 488
 bioavailability of, 442
 bronchiectasis and, 169
 pneumocystosis and, 163, 163t
 “Triple H,” 368
 Triple-drug regimen, 111t, 112
 Tropical eosinophilia, 84
 Troponin elevation, 367
Trypanosoma cruzi, transplantation and, 239
 TST. *See* Tuberculin skin test
 TTKG. *See* Transtubular K concentration gradient
 TTP. *See* Thrombotic thrombocytopenic purpura
 Tube thoracostomy
 metastatic disease and, 217
 secondary pneumothorax, 219
 Tuberculin purified protein derivative (PDD), 128,
 129
 Tuberculin skin test (TST), 118
 Bacille Calmette-Guérin vaccination and, 135
 HIV-associated tuberculosis, 126
 latent *M. tuberculosis* infection, diagnosis of,
 128–129
 LTBI and, 135–136
 miliary tuberculosis and, 126
 Tuberculoma, 124, 125, 167
 Tuberculosis, 17, 43f, 90, **115**, 518, 538. *See also*
 Tuberculosis treatment
 alternative treatment regimens, 131, 131t
 cavities (in lungs), 121–122, 122f
 chest radiography and, 521, 541
 clinical manifestations of, 122–127
 control, 136–138
 cutaneous forms, 126
 death from, 117f
 diagnosis of, 127–129
 diseases and conditions favoring, 118, 118t
 epidemiology of, 116–117, 116f, 117f
 ethambutol, 129, 130t
 ethionamide, 129
 as etiologic agent, 115–116
 Europe and, 117
 extrapulmonary, 118
 HIV co-infection and, 118
 incidence rates, 116f
 natural history of, 118
 pathogenesis and immunity, 119–121
 prevention, 134–135
 serologic tests, 128
 SOT and, 241–242
 spontaneous remission, 118
 Tuberculosis of central nervous system, 124
 Tuberculosis of upper airways, **123**
 Tuberculosis resistant to first line drugs, second-line
 drugs, 129–130
 Tuberculosis treatment, 129–134, 131–131t
 breastfeeding and, 134
 clinical situations, 134
 drug toxicity, monitoring, 131–132
 drug-resistant strains, 132
 drugs, 129–130
 failure and relapse, 132
 regimens, 130–131
 response, monitoring, 131–132
 Tuberculous empyema, 123
 Tuberculous lymphadenitis. *See* Lymph
 node tuberculosis
 Tuberculous meningitis, **124**, 124–125
 Tuberculous otitis, 126
 Tuberculous pericarditis. *See* Pericardial tuberculosis
 Tuberculous peritonitis, 125
 Tuberculous pleuritis, 217
 Tubuloglomerular feedback, 373
 Tumor(s), 355, 404, 478
 airway obstruction and, 483, 484f
 DIC and, 429
 insulin-like growth factor II and, 484
 masses, pain and, 478
 SVCS and, 475
 Tumor lysis syndrome (TLS), 374, 406, **485**
 treatment, 485–486, 486f
 Tumor necrosis factor (TNF), 100, 280
 Tumor necrosis factor- α (TNF- α), 76, 282, 486
 asthma and, 64, 66, 66f
 CBD and, 92
 COPD and, 184, 185
 host defense and, 281
 Mycobacterium tuberculosis and, 120
 shock and, 270
 Tungsten carbide exposures, 92
 Tunnel infections, 391
 Tunneled dialysis catheter, 389
 Two-dimensional echocardiography
 left ventricular aneurysm, 340
 right ventricular infarction and, 337
 Type 1 brittle asthma, 76
 Type 2 brittle asthma, 76
 Type II fiber atrophy, 363
 Tyrosine kinases, 487
 UA/NSTEMI (Unstable angina/non-ST-elevation
 myocardial infarction), **316**, 527,
 547–548
 clinical presentation, 317
 definitions, 316
 diagnostic evaluation and, 317–318, 318f
 long-term management, 321
 pathophysiology, 316–317
 risk stratification and prognosis, 318
 treatment, 319–321
 drugs in, 319, 320t, 321t
 invasive v. conservative, 321
 UFH. *See* Unfractionated heparin
 UIP. *See* Interstitial pneumonitis
 Ultrafiltration, 388, 389
 Ultrasonography, lung disease and, 38
 Ultraviolet radiation, tuberculosis control, 136
 Uncal transtentorial herniation, 344, 344f, 549
 Undecylenic acid, 473
 Unfractionated heparin (UFH), **210**, 319,
 334, 368, 517–518, 537
 UNICEF, 128
 United States, tuberculosis and, 117
 Unstable angina, 527, 548
 with myocardial oxygen demand, 316–317

- Upper airway
 function, ventilator weaning and, 264
 obstruction, 476
 secretions, cough and, 14
- Upper airway cough syndrome, 15
- Upper respiratory infection, 15
- Uranium miners, cancers and, 95
- Urate oxidase, 485
- Uremic acidosis, 418
 oral alkali replacement and, 417
- Uremic bleeding, 384
- Uremic syndrome, 380
- Ureteral stents, 478
- Uretic obstruction, 382
- Urgent PCI, 333
- Uric acid, 381
- Uric acid crystals, 379, 381
- Uricosuria, 374
- Urinalysis, **375**
 genitourinary tuberculosis and, 123
 HUS and, 486
- Urinary tract imaging, 380
- Urinary tract infections (UTIs), 446
- Urinary tract obstruction, 374, **375**, 478
- Urine
 electrolytes, 419
 gap, 418
 heavy metal concentrations in, 87
 osmolality, 401
 output, hyponatremia and, 399
 sediment, 379
- Urine sodium concentration. *See* Fractional excretion of chloride
- Urine to plasma osmolality ratio, 406
- Urine analysis, laboratory test values, 506t
- Ursodeoxycholic acid, cholestatic liver disease and, 177
- Usual interstitial pneumonitis, CT scan of, 47f
- UTIs. *See* Urinary tract infections
- Vaccination
 CAP and, 108
 transplant recipients and, 242–243, 242t
- Vaccines, 434
 adenovirus infections, 160
 influenza, 146–147
 SARS and, 155
- Vaginal candidiasis, 473
- Valacyclovir, 463, **463**
 suppressive therapy with, 464
- Valganciclovir, **465**
- Valproate, 360
- Valsartan, 525, 545–546
- Vancomycin, 437, 523, 543
 CA-MRSA ad, 107
 MRSA and, 112
- Vancomycin-resistant bacteria, **441**
- Vancomycin-resistant enterococci (VRE), 441
- VAP. *See* Ventilator-associated pneumonia
- Varicella-zoster (VZV), 466
 acyclovir and, 464
- Varicella-zoster immune globulin, 243
- Varicella-zoster virus, 144, 239
- Vascular responses, asthma and, 67
- Vascular structures, CT scanning and, 36–37
- Vasoconstrictors, 414–415
- Vasodepressor syncope, 307
- Vasodilation, shock and, 267
- Vasodilators, 337
 circulating, shock and, 267
 renal injury and, 381
- Vasogenic edema, 353
- Vasopressin, 313
 hypovolemic shock and, 274
 shock and, 267
- Vasopressin infusion, 286
- Vasopressors
 cardiovascular system and, 515–516, 535
 MI and, 300–301
- Vasospasm, 365, 366, 367
- Vasospastic disorder, 322
- VATS. *See* Video-assisted thoracic surgery
- VC. *See* Vital capacity
- Vegetative state, 343
- Venous obstruction, peripheral cyanosis and, 23–24
- Venous oxygen saturation, 254
- Venous system, shock and, 268
- Venous thromboembolism (VTE), **204**, 517–518, 537
 diagnosis of, 205–206
 epidemiology of, 204–205
 pathophysiology of, 205
 prevention, 213–214, 231t
- Ventilation, 25, 30
 acute severe asthma and, 75
 interventions used with, 263
 nonconventional strategies, 263
- Ventilation disorders, **221**
- Ventilation scans, 208
- Ventilation-perfusion lung scanning, 37
- Ventilation-perfusion matching, 30, 31
- Ventilation-perfusion mismatch, 12, 12t, 21
 hypoxemia and, 35
 severe sepsis, 283
- Ventilation-perfusion (V/Q) ratios, 31
- Ventilator, 524, 544–545
 ET and, 259
 management principles, 263
 operation, terminology for, 259, 261–263
 weaning, 264
- Ventilator-associated pneumonia (VAP), 99, **108**, 264
 clinical manifestations of, 109–110
 complications of, 112
 diagnosis, 110–111
 clinical approach, 110–111
 differential diagnosis of, 110
 empirical therapy, 111–112, 111t
 epidemiology of, 108–109
 etiology of, 108
 failure to improve, 112
 follow-up, 112–113
 microbiologic causes of, 108t
 pathogenic mechanisms for, 109t
 prevention strategies for, 109t, 113
 prognosis, 113
 treatment, 111–112
- Ventilator-dependent respiratory failure, lung transplantation and, 233
- Ventilator-induced lung injury, 293–294, 293f
- Ventilator-induced volutrauma, 250
- Ventilatory function, **25**
 abnormal, patterns of, 28–29
 alterations in, 29t
 disturbances in, 25–29
 physiologic features, 25–27
 measurement of, 27–28
- Ventilatory pump, respiratory system dyspnea and, 8, 9
- Ventricular dysfunction, 326, 336
- Ventricular fibrillation (VF), 307, 338
- Ventricular pacing, 339–340
- Ventricular premature beats, 338
- Ventricular remodeling, 336
- Ventricular septal rupture, 302
- Ventricular tachycardia, 338
- Ventricular tachycardia and fibrillation, STEMI and, 338–339
- Ventriculostomy, 367, 481
- Verapamil, 339, 368
- Vertebral column, metastatic tumor and, 479
- VF. *See* Ventricular fibrillation
- Vidarabine, **467**
- Video-assisted thoracic surgery (VATS),
 parenchymal lung disease and, 40
- Video-assisted thoracoscopy, mediastinal masses and, 220
- Vigorous diuresis, 381
- Viral bronchitis, 14
- Viral DNA, 465
 acyclovir and, 463
- Viral infections
 asthma and, 62
 exudative pleural effusions, 217–218
 inflammatory reaction and, 68
- Viral neuraminidase enzyme, 461
- Viral pathogens, 108
- Viral respiratory infections, **149**, 155–156
 adenovirus, 158–160
 coronavirus, 152–155
 general considerations, 149–150
 human metapneumovirus, 156
 parainfluenza virus, 156–158
 rhinovirus, 150–152
- Viral RNA, HRSV and, 155
- Virtual bronchoscopy, 37
- Virus load, 456
- Virus shedding, interferons and, 143
- Virus-coded thymidine kinase, 463
- Viruses, 456
 acute respiratory illness and, 149
- Virus-like particle vaccines (VLP vaccines),
 transplantation and, 243
- Vital capacity (VC), 25, 26f, 514, 533–534
 PNS disorders and, 362
- Vitamin B₆, pyridoxine and, 130
- Vitamin K
 CF lung and, 176
 cycle, 429, 429f
 deficiency, 432
- Vitamin K-dependent coagulation factors, 531, 551–552
 multiple deficiencies of, 429
- Vitamins, laboratory test values, 504t
- VLP vaccines. *See* Virus-like particle vaccines
- Vocal cord dysfunction, 76
- Vole bacillus, 115
- Volume depletion, 417
- Volume resuscitation, hypoadrenal shock and, 275
- Volume-controlled ventilation, 252
- Volume-cycled ventilation, 259
- Vomiting, 364, 396, 405, 419, 461, 531, 551
 intestinal obstruction and, 478
- Voriconazole, 472, 531, 552–553
- VRE. *See* Vancomycin-resistant enterococci
- VTE. *See* Venous thromboembolism
- VZV. *See* Varicella-zoster
- Waiting list, for lung transplantation, 234
- Warfarin, 211, 335, 341, 517–518, 537
- Warfarin dosing, 211
- Warfarin-induced skin necrosis, 211
- Warning arrhythmias, 338
- Washing, flexible fiberoptic bronchoscopy and, 39
- Water, **393**
 dialysis and, 388
 replacement, 402
 transport, in cystic fibrosis, 173

- Water balance, **394**
- Water balloon-shaped
 - heart, 534
- Water excretion, 394
- Water intake, 394
- Water loss, 400
 - correction of, 402
 - renal v. nonrenal, 400
- Watershed infarcts, 359
- Water-soluble gases, environmental
 - exposure to, 87–90
- Watery diarrhea, 488
- Wegener's granulomatosis, 18,
201, 533
- Weight gain, 392
- Weight loss, 122, 194, 396

- Wernicke's disease, 360, **361**
 - pathogenesis of, 362
 - pathology of, 361–362
 - thiamine and, 351
 - treatment of, 362
- West Nile virus, transplantation
 - and, 239
- Wheezes, 4, 12
- Whispered pectoriloquy, 4
- White blood cell casts, 379
- WHO (World Health Organization), 128
 - tuberculosis and, 116, 117f
 - tuberculosis control, 136–137
- Whole-brain radiation therapy, 481, 483
- Whole-lung saline lavage, 516, 536
- Winking owl sign, 480

- Withdrawing care, 256
- Withholding care, 256
- Work of breathing, 259
- Workers' compensation systems, 95–96
- World Federation of Neurosurgical Societies Scale,
365, 365t
- World Health Organization. *See* WHO
- World Trade Center (WTC) disaster, environmental
 - dust and, 95
- Wuchereria bancrofti*, 84

- Yellow nail syndrome, 167

- Zanamivir, 108, **461**, 546
 - influenza and, 145, 146, 146t, 147
 - resistance to, 462