Third Edition

The Brigham Intensive Review of Internal Medicine

Ajay K. Singh & Joseph Loscalzo

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The Brigham Intensive Review *of* Internal Medicine

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The Brigham Intensive Review *of* Internal Medicine

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THE BRIGHAM INTENSIVE REVIEW OF INTERNAL MEDICINE,
THIRD EDITION ISBN: 978-0-323-47670-6

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Library of Congress Cataloging-in-Publication Data
Names: Singh, Ajay, 1960- editor. | Loscalzo, Joseph, editor.
Title: The Brigham intensive review of internal medicine / [edited by] Ajay K. Singh, Joseph Loscalzo.
Other titles: Intensive review of internal medicine
Description: Third edition. | Philadelphia, PA : Elsevier, [2019] | Includes bibliographical references and index.
Identifiers: LCCN 2017024812 | ISBN 9780323476706 (pbk. : alk. paper)
Subjects: | MESH: Internal Medicine--methods | Physical Examination--methods
Classification: LCC RC46 | NLM WB 115 | DDC 616--dc23 LC record available at https://lccn.loc.gov/2017024812

Executive Content Strategist: Kate Dimock
Senior Content Development Specialist: Joan Ryan
Publishing Services Manager: Catherine Jackson
Book Production Specialist: Kristine Feeherty
Design Direction: Patrick Ferguson

Printed in China

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

To my wife, Ritu; my children, Anika, Vikrum, and Nikita; my mother, Gita; and my sister, Anjali
In remembrance of my father, JJ, and my brother, Sanjay (AKS)
To Charlotte, Nicholas, and Ellie (JL)

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Foreword

We are witnessing rapid change in all aspects of internal medicine. Within each specialty there is a deeper understanding of the mechanism of disease, how it should be treated, and the consequences of treatment. This breathtaking progress has been spanned by a course at the Brigham and Women's Hospital and Harvard Medical School that I founded in 1977 titled "The Intensive Review of Internal Medicine." The objectives of the course were to provide an in-depth review of the major areas of internal medicine both for practicing internists and for physicians preparing for the certifying examination for the American Board in Internal Medicine. Of course, more recently, physicians are expected to recertify every 10 years to update their knowledge, and this course serves this purpose as well. Our goal also included correlating pathophysiology with clinical presentation, something that I view as one of our strengths, because at Harvard Medical School we sit at the interface between practice and cutting-edge clinical science. Forty years later, I could hardly have envisioned that the IRIM course, as our course affectionately became known, would still be going strong and that there would be demand for a companion text. Its success has much to do with the outstanding faculty and my successors as chairs in the Department of Medicine, Victor Dzau and Joseph Loscalzo, who have strongly supported it.

The third edition of *The Brigham Intensive Review of Internal Medicine* builds on the success of the first edition. It is amazing to see how rapidly internal medicine is advancing. This edition is again edited very capably by Drs. Singh and Loscalzo. They have selected outstanding authors, many drawn from the faculty at Harvard Medical School and its affiliated hospitals, in particular the Brigham and Women's Hospital. Each author is an authority in the particular area he or she covers. The book is superbly written and illustrated. It elegantly weaves together the many separate strands of internal medicine to provide a thorough understanding of the field. The editors have skillfully incorporated over 500 board-simulated questions and their answers into the book so that it is a "must have" for anyone preparing for board certification or recertification in internal medicine. In addition, the book will be a valuable resource for physicians who are in training and for practicing clinicians alike.

I am, therefore, very pleased to welcome the third edition of *The Brigham Intensive Review of Internal Medicine* and anticipate that this text will become the standard in internal medicine board review.

Eugene Braunwald, MD
Eugene Braunwald, MD, is the Distinguished Hersey Professor of Medicine at Harvard Medical School and Founding Chairman of the TIMI Study Group at the Brigham and Women's Hospital.

Preface

Passing the boards for many readers of this book represents a "rite of passage." In Lakota Sioux culture, *hembleciya* (ham-blay-che-ya) represents a Native American rite of passage. The word *hembleciya* translates to "crying for a dream." The ceremony is frequently referred to as "going up on the hill," because people often go to a nearby mountain for their rite of passage.

The certification by the American Board of Internal Medicine (ABIM), which was established in 1936, has become a rite of passage and is a "going up the hill" of sorts since years are spent acquiring knowledge, skill, and professionalism to achieve this goal. For many, however, preparing for the examination itself is a hard slog. Still, the many hours attending one or more courses tailored toward the boards and reading thick books like this one are worth the effort because of the validation ABIM certification provides. We hope that this book continues to make a useful contribution in this endeavor.

Our book, now in its third edition, has been thoroughly updated, and new material has been added. Faculties from across Harvard Medical School have again participated, and we owe our deepest gratitude to them. A debt of gratitude and many thanks are also owed to Joan Ryan at Elsevier and to Michelle Deraney and Stephanie Tran at the Brigham and Women's Hospital. Our understanding families remain, of course, our most steadfast supporters.

We hope that using this book to navigate the boards successfully is not where learning ends but, like the Native American ritual of *hembleciya,* represents a cry for a dream—one of lifelong learning.

Ajay K. Singh, MBBS, FRCP, MBA
Joseph Loscalzo, MD, PhD

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The Brigham Intensive Review *of* Internal Medicine

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SECTION 1

Infectious Disease

1

Pneumonia and Respiratory Infections

MARY W. MONTGOMERY AND JOEL T. KATZ

Respiratory symptoms are among the most frequent reasons for patients to seek medical attention. Seventy percent of patients presenting with a new cough will be diagnosed with acute bronchitis. Other common causes of a new cough include pneumonia, cough-variant asthma, congestive heart failure, postnasal drip, rhinosinusitis, and aspiration of oral contents. Among patients presenting to their primary care provider with a cough, clinical predictors of the 10% to 15% who will have pneumonia are advanced patient age (odds ratio [OR] 4.6), shortness of breath (2.4), fever (5.5), tachycardia (3.8), and localizing chest auscultation findings such as focal respiratory crackles (23.8) or rhonchi (14.6). The etiology, treatment, and prognosis of upper and lower respiratory tract infections are highly varied and are reviewed in this chapter.

Acute Bronchitis

Acute bronchitis (AB) is a common seasonal (winter peak) infection of the upper respiratory tract that is generally viral in origin and does not require antibiotic therapy. The incidence of AB is 30 to 170 cases per 1000 persons per year. The most common causes are rhinoviruses, respiratory syncytial virus, influenza, parainfluenza, and adenovirus. These are highly contagious pathogens that spread rapidly through exposure to respiratory secretions or indirectly through shared environmental fomites. AB is generally a self-limited condition that lasts no more than 1 to 2 weeks. Over half the patients have purulent sputum, which is caused by sloughing of the tracheobronchial epithelial cells and is not indicative of a bacterial infection. When symptoms last more than 2 weeks, one should consider "atypical" bacteria, such as *Bordetella pertussis* or *Mycoplasma pneumoniae* infections, or alternative diagnoses such as postnasal drip syndrome from conditions of the nose and sinuses, asthma, gastroesophageal reflux disease, chronic bronchitis caused by cigarette smoking or other irritants, bronchiectasis, eosinophilic bronchitis, or the use of an angiotensin-converting enzyme inhibitor. At least nine randomized trials and a number of subsequent metaanalyses have addressed the benefit of antibiotics in AB. There is modest or no benefit to prescribing antibiotics in AB, and this must be weighed against the significant cost and adverse consequences of these medications. Overtreatment of AB leads directly to increasing rates of antimicrobial resistance in the general population. Each year in the United States there are over 2 million illnesses and 23,000 deaths related to antibiotic resistant infections, which result in medical costs in excess of $30 billion.

A small subset of patients with AB merit treatment, including those with episodes that occur during documented *B. pertussis* outbreaks or individuals with underlying lung disease (chronic obstructive pulmonary disease, asthma, or heavy tobacco use). The incidence of pertussis (whooping cough) and a clinically indistinguishable parapertussis have risen recently in the United States. In such settings, a second-generation macrolide, such as azithromycin or clarithromycin, is the ideal agent.

Community-Acquired Pneumonia

Despite major advances in understanding its pathophysiology and management over the century since Sir William Osler declared it the "[c]aptain of the men of death," pneumonia remains the leading infectious cause of death in the United States and in the world. Three major incremental reductions in community-acquired pneumonia (CAP) mortality have resulted from the introduction of antipneumococcal serum therapy (discovered in 1895, widely adopted by the 1920s), antibiotics (discovered in 1928, widely adopted by the 1940s), and mechanical ventilation (discovered in 1952, widely adopted in the 1960s). Pneumococcal vaccination has added only marginal survival benefit compared with these other advances. Annually, about 4 million cases of CAP are reported in the United States (approximately 6 cases per 1000 persons per year), leading to 1 million hospitalizations and 45,000 to 50,000 deaths. Mortality in all hospitalized patients with CAP ranges from 2% to 30%, and those patients who are assigned to the intensive care unit (ICU) for their initial care have a mortality as high as 40%. In contrast, mortality in outpatients ranges from <1% to 3%.

CAP is defined as an acute infection of the lung parenchyma accompanied by a new infiltrate on chest radiography or compatible auscultatory findings in a patient who is not hospitalized or living in a long-term facility for at least 2 weeks before the onset of symptoms. CAP symptoms

usually include at least two of the following features: fever or hypothermia, sweats, rigors, pleurisy, and new cough with or without sputum production or change in color of respiratory secretions. The absence of mucoid sputum production is associated with "atypical" pathogens (*M. pneumoniae, Chlamydophila pneumoniae, Legionella* species, *B. pertussis*).

As was the case in Osler's day, *Streptococcus pneumoniae* is still a leading identifiable cause of CAP although the incidence has declined likely in part because of pneumococcal vaccination (Table 1.1). "Atypical" pathogens are increasingly recognized as the cause of both outpatient and inpatient CAP, and these pathogens should be covered with empiric antibiotics in all cases. In clinical practice, the etiologic cause of CAP is not identified in most cases. One review of over 17,000 cases of CAP admitted to the hospital identified the pathogen in less than 10% of cases (see Barlett, 2011). Recent studies using specialized tests including broad range polymerase chain reaction (PCR) assays to detect pathogens increase the rate of microbiologic diagnosis to 38% to 87% of patients. In these studies, viruses were the most frequently detected pathogens and were found in approximately one-third of cases. The high rate of culture-negative CAP may be attributed to antibiotic pretreatment, inability to produce sputum for analysis, viral causes, or emerging pathogens that remain to be elucidated.

Epidemiologic clues can also help to determine less frequent causes of pneumonia, such as *Mycobacterium tuberculosis*, *Coxiella burnetii,* and endemic fungi (*Coccidioides* species, *Histoplasma capsulatum,* and *Blastomyces dermatitidis*) (see Table 1.5).

In the appropriate clinical situation, the diagnosis of CAP is established by demonstration of focal pulmonary findings, either by lung auscultation or by chest radiograph. Chest radiographs should be done in all patients with suspected CAP, because this test is useful in excluding complications (e.g., pleural effusions) and because associated findings may predict the pathogen (e.g., lymphadenopathy) or suggest alternative diagnoses (e.g., lung mass, lung abscess). When examined in a blinded fashion, the radiographic pattern does not reliably differentiate specific pathogens. This is particularly true among the elderly and immunocompromised patients, who may have unusual or no infiltrate in the setting of CAP. Radiographic improvement lags behind clinical response, and routine serial chest radiographs are not recommended unless the patient is not improving; however, all tobacco smokers and patients over the age of 65 years should have follow-up chest radiographs 3 to 6 months after an episode of pneumonia to exclude an underlying malignancy.

There are limited data to guide when patients should have a thorough microbiologic evaluation for the etiologic agent. It is currently advised when patients are immunocompromised, are admitted to the hospital or ICU, or have failed recent treatment. Hospitalized patients should have at least blood cultures and sputum Gram stain and culture. Any patients requiring an ICU admission will also require further diagnostic testing including *Legionella* and pneumococcus urinary antigen tests and multiplex PCR testing if available. If an etiologic agent is not discovered or there is clinical worsening, then many patients with

TABLE 1.1 Etiology of Community-Acquired Pneumonia by Site of Initial Triage

	Outpatient (*n* = 507 + 514)	Inpatient (*n* = 2521 + 585)	Intensive Care (*n* = 488 + 145)
Unknown	52%–69%	59%–79%	47%–61%
S. pneumoniae	6%–11%	7%–18%	15%–22%
H. influenzae	2%–5%	2%–3%	1%–2%
M. pneumoniae	5%–17%	1%	1%
C. pneumoniae	2%–14%	1%	2%
Legionella spp.	2%	4%	4%
S. aureus	<1%	1%–4%	1%–8%
GN enteric bacilli	<1%	1%–3%	1%–3%
P. aeruginosa	<1%	1%–2%	2%–6%
Respiratory viruses	3%	5%	2%
Polymicrobial	3%	1%–5%	5%–12%

GN, Gram-negative.

Modified from Marrie TJ, Poulin-Costello M, Beecroft MD, et al. Etiology of community-acquired pneumonia treated in an ambulatory setting. *Respir Med*. 2005;99:60–65; Cillóniz C, Ewig S, Polverino E, et al. Microbial aetiology of community-acquired pneumonia and its relation to severity. *Thorax* 2011;66:340–346; and Restrepo MI, Mortensen EM, Velez JA, et al. A comparative study of community-acquired pneumonia patients admitted to the ward and the ICU. *Chest* 2008;133:610–617.

severe pneumonia will undergo a bronchoalveolar lavage, which can be sent for bacterial, fungal, mycobacterial, and viral testing.

Various risk-stratification methods have been developed and validated to predict which patients are at sufficiently low mortality risk to justify home therapy, which costs 20-fold less than an inpatient stay. The easy-to-use CURB-65 risk score can be calculated based on five simple features, including the presence of confusion (1 point), blood urea nitrogen >30 mg/dL (1 point), respiratory rate ≥30 breaths per minute (1 point), systolic blood pressure <90 mm Hg or diastolic blood pressure <60 mm Hg (1 point), and patient age 65 years or older (1 point). The risk of death or ICU admission increases with increasing CURB-65 scores (Table 1.2).

The pneumonia severity index is a validated risk stratification method that considers the risk contributions of patient demographic features (age having the greatest influence) and key physical examination and laboratory findings (Table 1.3). Of note, other than a measurement of arterial oxygenation, all laboratory testing is left up to the discretion of the health care provider. Patients in risk class I or II can be safely cared for at home. Risk class III can generally be cared for at home, but an inpatient observation is reasonable. Patients in risk classes IV and V should be admitted to the hospital (Table 1.4). All CAP patients with unexplained or a high degree of hypoxemia should be admitted to the hospital. Clinical judgment should supersede the recommendations of clinical prediction rules.

Key principles of pharmacotherapy for CAP include the following: (1) once the diagnosis is established, delays in administering antibiotics are associated with increased mortality; (2) all patients with CAP should be covered for "atypical" pathogens; and (3) recent antibiotic exposure should be considered when choosing empiric antibiotics. Clinicians should seek specific environmental exposures that may suggest an unusual pathogen (Table 1.5).

A summary of the Infectious Diseases Society of America (IDSA) and American Thoracic Society combined

TABLE 1.2 Mortality and ICU Admission Based on CURB-65 Score

Points	Mortality/ICU
0	0.7
1	3.2
2	13
3	17
4	41.5
5	57

ICU, Intensive care unit.
Modified from Lim WS, Macfarlane JT, Boswell TC, et al. Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines. *Thorax*, 2001;56:296–301.

TABLE 1.3 Pneumonia Severity Index Point Assignments

Characteristic or Demographic Factor	Points Assigned
Age	
Men	Age (years)
Women	Age (years) – 10
Nursing home resident	10
Coexisting Illness	
Cancer	30
Liver disease	20
Congestive heart failure	10
Cerebrovascular disease	10
Renal disease	10
Physical Examination Findings	
Altered mental status	20
Respiratory rate >30 breaths/min	20
Systolic blood pressure <90 mm Hg	20
Temperature <35°C or ≥40°C	15
Pulse >125 beats/min	10
Laboratory and Radiographic Findings	
Arterial pH <7.35	30
BUN >30 mg/dL	20
Sodium <130 mmol/L	30
Glucose >250 mg/dL	10
Hematocrit <30%	10
Partial pressure of arterial oxygen <60 mm Hg	10
Pleural effusion	10

BUN, Blood urea nitrogen.
From Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med*. 1997;336:243–250.

TABLE 1.4 Pneumonia Severity Index Risk Classification and Recommendation

Class	Points	Mortality (%)	Recommendation[a]
I	[b]	0.1	Home antibiotics
II	<70	0.6	Home antibiotics
III	71–90	0.9	Consider short hospitalization
IV	91–130	9.3	Hospitalize
V	>130	27	Hospitalize

[a]If the patient can be cared for at home (social).
[b]Risk class I requires age <50 years, lacking pneumonia severity index comorbidities and abnormal vital signs (see Table 1.3).
From Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med*. 1997;336:243–250.

recommendations is given in Table 1.6. Once a specific organism has been identified, antibiotics should be narrowed to cover this agent with the least overlap in spectrum and additional cost. Treatment duration is on average 5 to 7 days, although a longer duration is recommended for pneumonia caused by certain pathogens including *Staphylococcus aureus, Legionella* species, and *Pseudomonas aeruginosa*. The IDSA guidelines recommend switching patients from intravenous to oral therapy when they are clinically improving, hemodynamically stable, and able to take and absorb oral medications. Antibiotics should then be stopped once patients have been clinically stable for 48 hours. Clinical stability is defined as a temperature ≤37.8°C, heart rate ≤100 beats per minute, respiratory rate ≤24 breaths per minute, systolic blood pressure ≥90 mm Hg, and arterial oxygen saturation ≥90% on pO_2 on room air. Chest radiography is not used to define treatment duration because the radiographic resolution of pneumonia lags behind clinical improvement.

Most patients with pneumonia will improve in 3 to 5 days after starting treatment. A nonresolving pneumonia can be caused by an atypical pathogen that was not covered by the standard therapy (i.e., *M. tuberculosis, Coccidioidomycosis*), an antibiotic resistant organism, the development of a loculated infection such an empyema, an underlying malignancy, or a noninfectious cause such as cryptogenic organizing pneumonia. Certain factors have been identified that increase the overall risk of not responding to antibiotics. The risk factors include liver disease, leukopenia, and the presence of pleural effusions, multilobar infiltrates, or cavitations on chest imaging. The risk factors for *S. pneumoniae* drug resistance are listed in Table 1.7. Further imaging and microbiologic analyses are required for all patients with persistent or worsening symptoms after antibiotic therapy.

Increasingly, health care providers and facilities are being graded publicly on prespecified performance and outcome measures for certain diseases. The current Centers for Medicare and Medicaid Services performance measure for CAP is the use of a guideline-compliant antibiotic. The two outcome measures are 30-day mortality and 30-day readmission rate.

Finally, several vaccines are available for the prevention of *S. pneumoniae* and influenza virus infections. Every fall, all patients should be offered the influenza

TABLE 1.5 Epidemiologic Conditions Related to Specific Pathogens in Patients With Selected Community-Acquired Pneumonia

Condition	Commonly Encountered Pathogen(s)
Alcoholism	*Streptococcus pneumoniae* and anaerobes
COPD and/or smoking	*S. pneumoniae, Haemophilus influenzae, Moraxella catarrhalis,* and *Legionella* species
Nursing home residency	*S. pneumoniae,* gram-negative bacilli, *H. influenzae, Staphylococcus aureus,* anaerobes, and *Chlamydia pneumoniae*
Poor dental hygiene	Anaerobes
Epidemic legionnaires disease	*Legionella* species
Exposure to bats or soil enriched with bird droppings	*Histoplasma capsulatum*
Exposure to birds	*Chlamydia psittaci*
Exposure to rabbits	*Francisella tularensis*
HIV infection (early stage)	*S. pneumoniae, H. influenzae,* and *Mycobacterium tuberculosis*
HIV infection (late stage)	Above plus *Pneumocystis jiroveci, Cryptococcus*, and *Histoplasma* species
Travel to southwestern United States	*Coccidioides* species
Exposure to farm animals or parturient cats	*Coxiella burnetii* (Q fever)
Influenza active in community	Influenza, *S. pneumoniae, S. aureus, Streptococcus pyogenes*, and *H. influenzae*
Suspected large-volume aspiration	Anaerobes (chemical pneumonitis, obstruction)
Structural disease of lung (bronchiectasis, cystic fibrosis, etc.)	*Pseudomonas aeruginosa, Burkholderia (Pseudomonas) cepacia*, and *S. aureus*
Injection drug use	*S. aureus,* anaerobes, *M. tuberculosis*, and *S. pneumoniae*
Airway obstruction	Anaerobes, *S. pneumoniae, H. influenzae*, and *S. aureus*
From TB endemic part of world, history of incarceration or homeless	*M. tuberculosis*

COPD, Chronic obstructive pulmonary disease; *HIV,* human immunodeficiency virus; *TB,* tuberculosis.

TABLE 1.6 Infectious Diseases Society of America/American Thoracic Society Treatment Guidelines for Community-Acquired Pneumonia

Initial Triage	Treatment
Outpatients	Macrolides or doxycycline Fluoroquinolones may be preferred for older patients or in individuals with underlying chronic illnesses (heart, liver, renal, diabetes, alcoholism, malignancy, immunosuppressive medications) In general, avoid antibiotic classes that have been administered in the past 3 months
Hospitalized (general medical ward)	Extended-spectrum cephalosporin or beta-lactam/beta-lactamase inhibitor plus a macrolide; or fluoroquinolone (alone)
Hospitalized (ICU)	Extended-spectrum cephalosporin or a beta-lactam/beta-lactamase inhibitor plus either a macrolide or fluoroquinolone
Special considerations Individuals with structural lung disease	Antipseudomonal agents (piperacillin, piperacillin tazobactam, carbapenem, or cefepime) plus a fluoroquinolone
Beta-lactam allergy	Fluoroquinolone +/– clindamycin
Suspected community-associated MRSA	Add vancomycin or linezolid
Suspected aspiration	Fluoroquinolone +/– clindamycin, metronidazole, or a beta-lactam/beta lactamase inhibitor

ICU, Intensive care unit*; MRSA,* methicillin-resistant *Staphylococcus aureus*.
From Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44:S27–S72. Also available online at: http://cid.oxfordjournals.org/content/44/Supplement_2/S27.full.

TABLE 1.7 Risk Factors for Drug Resistance to *Streptococcus pneumoniae* Age >65 Years

Antibiotic therapy in the last 3 months (beta-lactams, macrolides, fluoroquinolones)
Alcoholism
Immunosuppressive illness (including treatment with corticosteroids)
Multiple medical comorbidities
Exposure to child in a day care center

From Ramsdell J, Narsavage GL, Fink JB, et al. Management of community-acquired pneumonia in the home: an American College of Chest Physicians clinical position statement. *Chest*. 2005;127(5):1752–1763.

vaccination. As of 2014, the Advisory Committee on Immunization Practices (ACIP) recommends all adults ≥65 years of age should receive the pneumococcal conjugate vaccine (PCV13) followed by the pneumococcal polysaccharide vaccine (PCV23). The ACIP also recommends PCV13 and PCV23 for patients with a cerebrospinal fluid leak, a cochlear implant, functional or anatomic asplenia, or an underlying immunodeficiency such as HIV or cancer. One adult pertussis vaccine dose (Tdap) is recommended by the Centers for Disease Control and Prevention for all adults, effective 2013. Hospitalization for other problems should not be overlooked as an opportunity to protect unvaccinated patients by administering these vaccines.

Chapter Review

Questions

1. A 45-year-old woman with hypertension and hyperlipidemia presents to an urgent care clinic with 10 days of fatigue and a productive cough with green sputum. On physical examination, she is afebrile with a respiratory rate of 12 breaths per minute and an oxygen saturation of 99% on room air. Auscultation of her lungs reveals few scattered wheezes bilaterally. Which of the following is the appropriate treatment of this patient?
A. Prescribe azithromycin
B. Prescribe amoxicillin-clavulanic acid
C. Withhold antibiotics at this time
D. Prescribe levofloxacin

2. A 63-year-old man with well-controlled diabetes, hypertension, and obesity presents to a clinic with 6 days of fevers, a productive cough, pleuritic chest pain, and dyspnea. On physical examination, he has a fever of 101.9°F, heart rate 99 beats per minute, blood pressure 140/80 mm Hg, respiratory rate 18 breaths per minute, and oxygen saturation 96% on room air. On lung examination, crackles are heard in the right lung base. Basic laboratory testing reveals normal electrolytes, creatinine, and liver function tests. The white blood cell count is elevated to 14,000 cells per microliter with a neutrophilic predominance. The hematocrit and platelets are normal. Chest x-ray reveals a right lower lobe

infiltrate with no pleural effusion. Should this patient be admitted to the hospital?
A. Yes
B. No
C. Depends on the arterial blood gas result
D. Need more information

3. A 28-year-old male presents to the emergency room with fever, shortness of breath, and a dry cough. In the past 6 months he has lost 20 lbs of weight. His past medical history is significant for syphilis, which was treated with intramuscular penicillin 2 years ago. He has had multiple sexual partners and rarely uses protection. On physical examination, he is cachectic and chronically ill appearing. Temperature is 101°F, heart rate 100 beats per minute, blood pressure 100/60 mm Hg, respiratory rate 26 breaths per minute, and oxygen saturation 92% on room air and 83% with ambulation. He has multiple white plaques on his tongue and upper palate. Lung examination reveals bilateral and diffuse crackles. Chest radiography demonstrates diffuse interstitial infiltrates. A rapid screen for HIV is positive. What is the most likely pathogen causing his pneumonia?
A. *Chlamydia psittaci*
B. *Streptococcus pneumoniae*
C. *Pneumocystis jiroveci*
D. *Coccidioides* species

4. An 82-year-old woman is brought by ambulance to the emergency room because of fever, a cough, and worsening confusion. She has known dementia, osteoporosis, and giant cell arteritis treated with 10 mg of prednisone daily. She also has frequent urinary tract infections treated with antibiotics. She resides in a nursing home. On physical examination, she has a fever of 102°F, heart rate 120 beats per minute, blood pressure 90/60 mm Hg, respiratory rate 26 breaths per minute, and oxygen saturation 92% on room air. Lung examination reveals crackles in the left lower lobe, and egophony is noted. Serum electrolytes, creatinine, liver function tests, complete blood count, blood cultures, and sputum Gram stain and culture are sent and are pending. Which empiric antibiotic regimen would be appropriate to start at this time?
A. Azithromycin
B. Vancomycin + cefepime + levofloxacin
C. Clindamycin
D. Doxycycline

Answers

1. C
2. B
3. C
4. B

Additional Reading

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2

HIV Infection and AIDS

JENNIFER A. JOHNSON AND DANIEL R. KURITZKES

According to the Centers for Disease Control and Prevention (CDC), more than 1.2 million persons with HIV infection were estimated to be living in the United States by 2012, 13% of whom were unaware of their HIV diagnosis. Internists often provide medical care both to patients with as-yet undiagnosed HIV infection and to those with known infection. Without appropriate treatment, patients may develop a variety of potentially fatal infectious and noninfectious complications of HIV infection. Through early diagnosis and prompt initiation of antiretroviral therapy (ART), patients with HIV can live long and healthy lives, with life expectancy approaching that of the general population. Early diagnosis and appropriate management of patients with HIV is also an important public health measure because those with known HIV infection can take highly effective measures to avoid transmitting the virus to others. In recent years, our resources for HIV prevention have expanded significantly; many of these tools are best implemented by internists in primary care and other settings.

History and Epidemiology

HIV and AIDS first entered public consciousness with the CDC's *Morbidity and Mortality Weekly Report* (MMWR) published on June 5, 1981, discussing five cases of *Pneumocystis carinii* (now known as *P. jiroveci*) pneumonia (PCP) among previously healthy gay men living in Los Angeles.

By the late 1980s it appeared that the initial education efforts and activism focusing on disease awareness among men who have sex with men (MSM) were having an appreciable impact on curbing AIDS incidence within this high-risk group. By the end of the 1990s, however, the trend toward decreasing incidence among MSM had reversed and has since been rising steadily.

In 2014 there were more than 44,000 new HIV diagnoses in the United States; approximately 67% of these were among MSM. Incidence among MSM is uneven by race/ethnicity. HIV incidence declined significantly from 2005 to 2014 in most risk groups, except among African-American MSM; new diagnoses among African-American MSM have increased 22% over the past decade. Only 24% of new infections in 2014 were attributed to heterosexual contact and only 6% to injection drug use. Among other risk groups incidence is also uneven by race/ethnicity. There were more than four times more new HIV infections among African-American women than among white women in 2014. Hispanic/Latina men and women are also disproportionately affected by HIV.

Signs and Symptoms

Primary HIV infection typically presents as a mononucleosis-like syndrome with nonspecific symptoms that can be confused for many other infections. In one series, approximately 75% of persons acutely infected with HIV experienced symptoms attributable to an acute retroviral syndrome. Symptoms can occur from a few days to 10 weeks after exposure. The severity of the illness can range from a mild flu-like illness that resolves promptly to a severe multisystem disease requiring hospitalization. The most common symptoms of acute HIV infection include fever, maculopapular rash, mucocutaneous ulcers, lymphadenopathy, arthralgias, pharyngitis, malaise, weight loss, aseptic meningitis, and myalgias (Table 2.1). The symptoms of fever, rash (especially in combination), oral ulcers, and pharyngitis are highly predictive for the diagnosis of acute HIV infection.

Because of a precipitous drop in CD4 lymphocytes that may occur during acute HIV infection, some individuals can present during this phase with opportunistic infections, such as PCP or thrush.

After the acute retroviral syndrome resolves, patients may be asymptomatic during a plateau period in the infection, which can last for years. Later symptoms vary depending on disease stage and the degree of immunologic dysfunction. Table 2.2 lists AIDS-defining clinical conditions associated with significant immune suppression.

Conditions commonly seen by internists in the outpatient setting that are not AIDS-defining but should prompt consideration of HIV testing include herpes zoster virus reactivation (shingles), seborrheic dermatitis, thrush, and recurrent vaginal candidiasis; all occur commonly in those without HIV infection but with higher incidence and increased severity among patients with HIV. Any new testing, diagnosis, or treatment of other sexually transmitted

infections (genital herpes simplex, syphilis, gonorrhea, chlamydia) should also prompt HIV testing given mutual risk factors. Tuberculosis can present in HIV-infected individuals even with a relatively high CD4 count, and all persons diagnosed with tuberculosis should be tested for HIV. Many HIV-infected persons will be asymptomatic, however, underscoring the need for routine screening.

TABLE 2.1 Signs and Symptoms of Acute HIV Retroviral Syndrome

Sign/Symptom	Frequency (in 209 Cases)
Fever	96%
Adenopathy	74%
Pharyngitis	70%
Rash	70%
Myalgia/arthralgia	54%
Thrombocytopenia	45%
Leukopenia	38%
Diarrhea	32%
Headache	32%
Nausea/vomiting	27%
Transaminitis	~20%
Thrush	12%
Neuropathy	6%
Encephalitis/meningitis	6%

Modified from Niu MT, Stein DS, Schnittman SM. Primary human immunodeficiency virus type 1 infection: review of pathogenesis and early treatment intervention in humans and animal retrovirus infections. *J Infect Dis*. 1993;168(6):1490-1501.

Establishing the Diagnosis

The CDC guidelines for HIV testing published in the September 2006 MMWR recommend one-time routine opt-out testing for patients age 13 to 64 years in all health care settings unless the patient declines. CDC guidelines also recommend annual testing among those who engage in high-risk behavior. It is important to recognize that the notion of high-risk groups has been replaced by that of high-risk behavior and that many people who engage in high-risk behaviors do not disclose these behaviors. A study of MSM in New York City found that about 40% of those engaging in high-risk behaviors had not disclosed attraction to or having had sex with men to their health care providers.

In 2014 the CDC updated their guidelines for HIV diagnostic testing. Current guidelines recommend initial testing with a US Food and Drug Administration (FDA)-approved antigen/antibody combination (fourth generation) immunoassay that detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen to screen for established infection with HIV-1 or HIV-2. The inclusion of the p24 antigen capture allows for diagnosis before seroconversion, shortening the "window" period (recent infection but negative serology) to approximately 10 to 13 days after the appearance of viral RNA (Fig. 2.1). Samples that are nonreactive on initial screening immunoassay are determined to be negative. Samples that are reactive on initial screen undergo differentiation HIV-1/HIV-2 antibody immunoassay, and subsequently HIV-1 nucleic acid testing if necessary to confirm. This new testing algorithm provides the most sensitive and specific HIV testing, detects HIV infection earlier than previous algorithms and resolves some of the confusion with indeterminate HIV-1 Western blot results. Although this testing algorithm shortens the

TABLE 2.2 AIDS-Defining Conditions in HIV-Infected Persons

Infectious	Oncologic	Other
Candidiasis of bronchi, trachea, lungs, esophagus	Cervical cancer, invasive	Encephalopathy, HIV-related
Coccidioidomycosis, disseminated or extrapulmonary	Kaposi sarcoma	HIV-attributed wasting syndrome
Cryptococcosis, extrapulmonary	Lymphoma, Burkitt (or equivalent)	
Cryptosporidiosis, chronic intestinal	Lymphoma, immunoblastic (or equivalent)	
Cytomegalovirus other than liver, spleen, or nodes including retinitis	Lymphoma, primary, of brain	
Herpes: chronic ulcers or bronchitis, pneumonitis, esophagitis		
Histoplasmosis, disseminated or extrapulmonary		
Isosporiasis, chronic intestinal		
Mycobacterium spp. (*M. avium* complex or *M. kansasii, M. tuberculosis*, or other) disseminated or extrapulmonary		
Pneumocystis jiroveci pneumonia		
Pneumonia, recurrent		
Progressive multifocal leukoencephalopathy		
Salmonella septicemia, recurrent		
Brain toxoplasmosis		

Modified from http://www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm.

window period, some patients with acute retroviral syndrome may still have negative serology even with the combination antigen/antibody immunoassay. A high suspicion for acute HIV infection based on signs and symptoms should prompt HIV-1 RNA polymerase chain reaction (viral load) testing concurrent with the antigen/antibody combination immunoassay.

The CDC no longer recommends use of the previous HIV testing algorithm of initial screening for HIV-1/HIV-2 antibody by enzyme-linked immunosorbent assay (ELISA) followed by confirmatory Western blot assay for those with reactive ELISA, although this may be the only serologic test available at some practice sites.

Rapid HIV testing can be performed on both blood specimens and oral secretions. A negative test carries the same implications as a negative ELISA; a positive rapid test must be confirmed with standard serologic testing, preferably by the recommended combination antigen/antibody immunoassay.

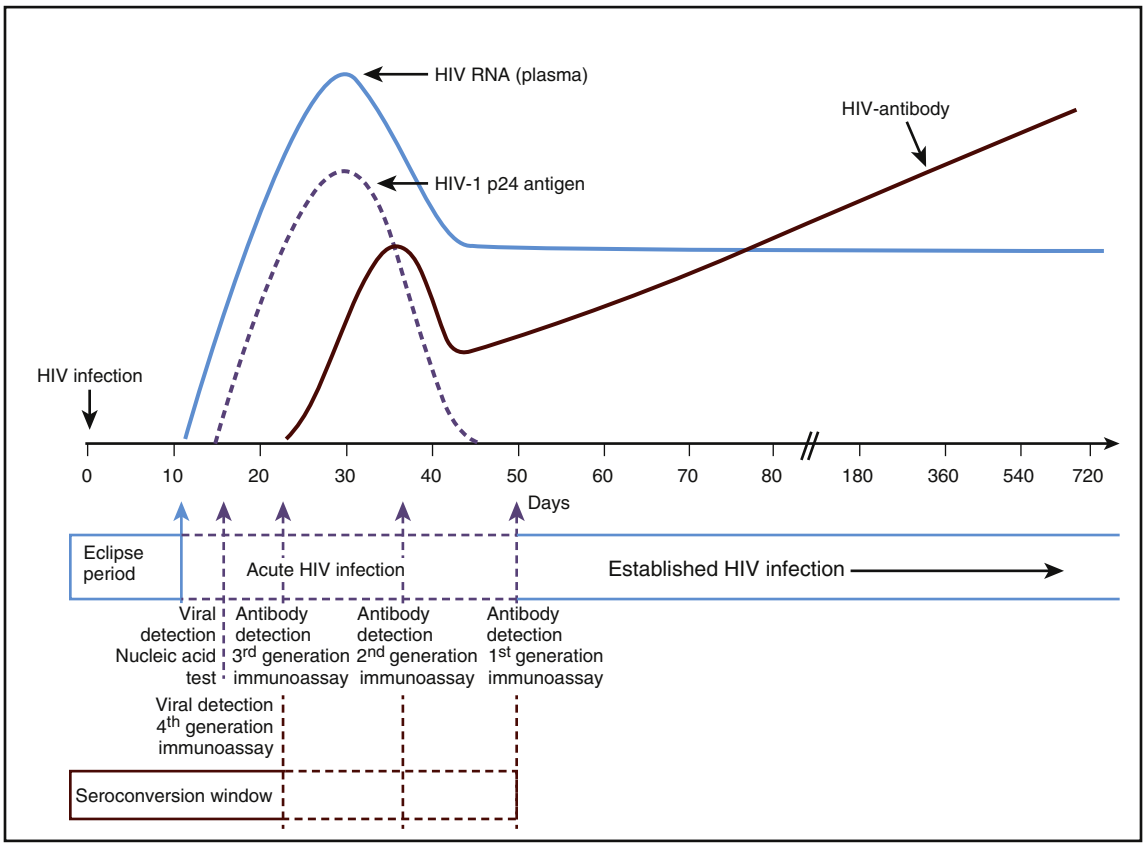
Rapid testing has been associated with a relatively high number of false-positive results when performed in low-prevalence settings. Hence reactive results should be communicated as "preliminary" or "inconclusive" with a need for confirmatory testing. Despite this drawback, rapid point-of-care HIV testing may be advantageous in some patient care settings.

The CDC recommends opt-out HIV screening as a part of the routine panel of prenatal screening tests for all pregnant women without a special written consent being required. Repeat screening in the third trimester should be performed in geographic areas with an elevated HIV incidence.

Initial Evaluation

The initial evaluation of an individual with HIV infection should consist of a complete history including a detailed social history, physical examination, and laboratory evaluation. In addition to making the diagnosis, the stage of HIV illness should be determined, and the presence of other possible concurrent infections should be determined.

Initial laboratory evaluation should include HIV antigen/antibody testing (if the original laboratory test is not available for review), CD4 count, plasma HIV RNA (viral load), and genotypic HIV resistance testing. Basic blood work including complete blood count with differential, chemistry, and liver function tests should be obtained. Fasting glucose and fasting lipid panel are also recommended



Note. Units for vertical axis are not noted because their magnitude differs for RNA, p24 antigen, and antibody.

• **Fig. 2.1** Laboratory testing for HIV infection. (Modified from *Centers for Disease Control and Prevention and Association of Public Health Laboratories.* Laboratory testing for the diagnosis of HIV infection: updated recommendations. http://dx.doi.org/10.15620/cdc.23447; June 27, 2014.)

at baseline. A urinalysis should be obtained (to evaluate for HIV-associated nephropathy).

Initial evaluation should also include screening tests for syphilis (by treponemal test if available), toxoplasmosis IgG, cytomegalovirus IgG, and viral hepatitis serologies (hepatitis A antibody, hepatitis B surface antigen and antibody, hepatitis B core antibody, and hepatitis C antibody). In addition, a tuberculin skin test (TST) or interferon-γ release assay (IGRA) (unless there is a history of prior tuberculosis or positive TST or IGRA) should be obtained. If a TST is performed when the patient's CD4 is <200 cells/mm^3, it should be repeated when the CD4 rises to >200 cells/mm^3 after initiation of ART. If the TST or IGRA is positive or there are pulmonary symptoms, a chest x-ray (CXR) should be obtained. Women should undergo a Papanicolaou (Pap) smear, and one should consider baseline testing for gonorrhea and chlamydia. Although there are no formal CDC recommendations for performing annual anal Pap smears for MSM, many experts in the field support this practice. New York State has issued formal guidelines for anal dysplasia screening that include baseline and annual anal Pap smear testing for HIV-positive MSM and women, and high-resolution anoscopy for patients with evidence of dysplasia on Pap smear.

Many factors can powerfully affect the outcome of treatment by influencing adherence and access to care, including substance use, mental illness, social support, economic stressors, ongoing high-risk behaviors, and family-planning issues; all should be assessed during initial evaluation and regularly during care. Given the stigma that still surrounds the diagnosis of HIV, it is important to discuss disclosure and family support with patients with newly diagnosed HIV. Education about HIV risk behaviors and prevention of HIV transmission to others should be provided initially and then subsequently at each patient visit.

Initiation of Therapy

Mounting evidence of the benefits of early initiation of ART from multiple large clinical trials has led to the most recent the Department of Health and Human Services (DHHS) recommendations for timing of initiation of ART. Since 2012 the DHHS guidelines in HIV-infected adults and adolescents have recommended initiation of ART for all persons with HIV infection, regardless of CD4 count. Early initiation of ART has been shown to decrease morbidity and mortality for persons with HIV infection. Recently two large clinical trials, START (Strategic Timing of Antiretroviral Therapy) and TEMPRANO, documented a significant decrease in morbidity and mortality with immediate initiation of ART even at CD4 cell count ≥500 cells/mm^3. In addition, ART for persons with HIV infection effectively prevents transmission of infection to others. Prior concerns about long-term toxicities of ART and potential for drug resistance have diminished with newer less-toxic antiretroviral agents, coformulated tablets with increased ease of dosing, and medications with high barriers to drug resistance. Currently, the benefits of early ART clearly outweigh any potential risks. In 2016 the World Health Organization updated its HIV treatment guidelines and now also recommends initiation of ART for all persons with HIV infection regardless of CD4 count or stage of HIV infection.

ART is most successful as continuous lifelong treatment, so adherence is essential. Deferred initiation of ART may be considered on a case-by-case basis if clinical or psychosocial factors warrant management before initiation. Conversely, ART should be initiated urgently for persons with opportunistic infections, pregnancy, coinfections with hepatitis B or C, HIV neurocognitive disorders, or HIV nephropathy.

Hepatitis Coinfection

Those at risk for HIV infection are also at risk for other chronic infections with similar modes of transmission. Coinfections of particular clinical interest in the HIV-infected person include hepatitis B virus (HBV), hepatitis C virus (HCV), and syphilis.

Chronic HBV infection develops more frequently in HIV-coinfected patients than in those with HBV alone. Although HIV infection affects the natural course of HBV infection, HBV coinfection does not appear to have an effect on CD4 depletion or progression to AIDS. Many agents used to treat HBV are also active against HIV. Treating only HBV may lead to drug-resistant HIV. For this reason, coinfected patients requiring treatment for HBV should be started on a standard ART regimen that includes two agents active against both HIV and HBV (such as tenofovir and emtricitabine [FTC]).

HIV and HCV coinfection can accelerate the clinical course of both infections. Immunologic decline from HIV may be more rapid, and HCV RNA levels are increased in these patients; patients with HIV and HCV are more likely to develop cirrhosis or decompensated liver disease. Previously, management of chronic HCV infection with interferon-based therapy was difficult and often unsuccessful. However, current treatments with directly acting agents for chronic HCV are well tolerated and result in cure of HCV in >90% to 95% of cases.

Regimens for Initial Antiretroviral Therapy

Preferred initial ART consists of a three-drug regimen: two nucleos(t)ide reverse transcriptase inhibitors (NRTIs) and a third drug from one of two classes: an integrase strand transfer inhibitor (INSTI) or a protease inhibitor (PI) combined with a pharmacokinetic booster (either ritonavir [RTV] or cobicistat). Regimens that include a nonnucleoside reverse transcriptase inhibitor (NNRTI) may be considered as an alternative. All of the preferred regimens for initial ART are dosed once daily, and many are available as coformulated single-tablet once-daily regimens. Medication regimens with low pill burden and low dosing frequency have been associated with increased medication adherence, decreased pharmacy costs, and decreased rates of complications including

hospitalizations. Other regimen options may be appropriate on a case-by-case basis. The preferred and alternative regimens for initial ART are outlined in Box 2.1. The recommended regimens for initial ART are updated frequently; updated guidelines and additional information regarding ART for special populations (including children and pregnant women) are available at http://aidsinfo.nih.gov.

Nucleos(t)ide Reverse Transcriptase Inhibitors

All preferred and alternative initial ART regimens include either tenofovir with FTC or abacavir (ABC) with lamivudine (3TC). Tenofovir disoproxil fumarate (TDF) can cause renal dysfunction and bone demineralization. The recent advent of tenofovir alafenamide (TAF), which offers the same antiviral efficacy as TDF with lower risk of nephrotoxicity and bone demineralization, has led to expanded recommendations for initial ART. Both TDF and TAF are available coformulated with FTC and as components of single-tablet ART regimens. ABC does not carry a risk of nephrotoxicity, but ABC use has been associated with increased risk of cardiovascular events in some studies so it may not be the optimal choice for persons with preexisting cardiovascular disease or risk factors. ABC may cause life-threatening hypersensitivity in persons who carry the human leukocyte antigen (HLA)-B*5701 allele; as such, all patients should be tested for HLA-B*5701 before receiving this medication, and ABC allergy should be listed in a patient's medical record if he or she tests positive. ABC is available coformulated with 3TC in a once-daily tablet; both are also coformulated into a single-tablet ART regimen with dolutegravir (DTG). Other NRTIs, including zidovudine (AZT), didanosine (ddI), and stavudine (d4T) are no longer recommended because of toxicities.

• BOX 2.1 Preferred and Alternative Regimens for Initial Antiretroviral Therapy

Preferred Initial Antiretroviral Therapy Regimens

INSTI-Based Regimens

- Dolutegravir/abacavir/lamivudine[a]
- Dolutegravir plus tenofovir alafenamide/emtricitabine or tenofovir disoproxil fumarate/emtricitabine
- Elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine or elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine
- Raltegravir plus tenofovir alafenamide/emtricitabine or tenofovir disoproxil fumarate/emtricitabine

Protease Inhibitor–Based Regimen

- Darunavir/ritonavir plus tenofovir alafenamide/emtricitabine or tenofovir disoproxil fumarate/emtricitabine

Alternative Initial Antiretroviral Therapy Regimens

NNRTI-Based Regimens

- Efavirenz/tenofovir disoproxil fumarate/emtricitabine
- Efavirenz plus tenofovir alafenamide/emtricitabine
- Rilpivirine/tenofovir alafenamide/emtricitabine or rilpivirine/tenofovir disoproxil fumarate/emtricitabine[b]

Protease Inhibitor–Based Regimens

- Atazanavir/cobicistat or atazanavir/ritonavir plus tenofovir alafenamide/emtricitabine or tenofovir disoproxil fumarate/emtricitabine
- Darunavir/cobicistat or darunavir/ritonavir plus tenofovir alafenamide/emtricitabine or tenofovir disoproxil fumarate/emtricitabine
- Darunavir/cobicistat or darunavir/ritonavir plus abacavir/lamivudine[a]

[a]Abacavir-containing regimens only for patients who are human leukocyte antigen–B*5701 negative.

[b]Only when HIV viral load <100,000 c/mL and CD4 count >200 cells/mm^3.

INSTI, Integrase strand transfer inhibitor; *NNRTI*, nonnucleoside reverse transcriptase inhibitor.

From *Panel on Antiretroviral Guidelines for Adults and Adolescents*. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf; updated July 2016.

Nonnucleoside Reverse Transcriptase Inhibitors

Efavirenz (EFV) was coformulated with TDF and FTC into the first single-tablet once-daily regimen for HIV treatment, which became available in 2006. EFV use is associated with a number of side effects including rash and central nervous system symptoms such as dizziness, somnolence, depressed mood, and vivid dreams. EFV was previously thought to be a teratogen, but recent data suggest there is no increased risk of teratogenicity; most treatment guidelines no longer proscribe EFV use during pregnancy. Rilpivirine (RPV) is an alternative NNRTI that is available as a coformulated single-tablet regimen together with TAF and FTC, and one with TDF and FTC. RPV should not be used in those with a baseline viral load >100,000 copies/mL or baseline CD4 count <200 cells/mm^3 because of higher rates of virologic failure in this population. Absorption of RPV is dependent on simultaneous consumption of a high-fat meal and can be diminished by concurrent use of antacids. Nevirapine is no longer recommended in the United States because of significant toxicities, including hepatotoxicity.

Protease Inhibitors

All currently recommended PIs require pharmacologic boosting with a CYP3A4 inhibitor, either RTV or cobicistat. Of the many PIs, only boosted darunavir is currently recommended as part of a preferred initial ART regimen; boosted atazanavir is now considered an alternative for initial ART. Darunavir has slightly fewer toxicities in some clinical trials and slightly increased efficacy in some populations. Atazanavir absorption can be diminished by concurrent use of antacids, similar to RPV. Atazanavir use is also associated with indirect hyperbilirubinemia and rare nephrolithiasis. PIs afford a high barrier to resistance even in patients with nonadherence and virologic failure. Although RTV is also a PI, its side effects are dose-limiting, and it is now used exclusively as a booster for other PIs. The boosting effect comes from the potent inhibitory effect of RTV

on the cytochrome P450 system, which is advantageous for increasing the levels of other PIs but a potential problem for the dosing of many other medications. For this reason, providers must carefully screen for drug-drug interactions with RTV. Some of the most commonly prescribed medications that interact with RTV are statins, warfarin, amiodarone, oral contraceptives, methadone, benzodiazepines, and corticosteroids. RTV use concurrent with use of peripherally administered corticosteroids (such as joint injections and inhalers) can cause systemic corticosteroid effects, in some cases resulting in iatrogenic Cushing syndrome and subsequent adrenal insufficiency. Cobicistat is a newer CYP3A4 inhibitor that was first approved as part of a single-tablet ART regimen in 2012. Cobicistat is currently used to boost PIs (darunavir and atazanavir) and the integrase inhibitor elvitegravir. The drug-drug interactions of cobicistat are similar to those seen with RTV.

Integrase Strand Transfer Inhibitors

Since the FDA approval of the first INSTI (raltegravir [RAL]) in 2007, ART has been transformed by this class of drugs. Integrase inhibitors offer highly potent antiviral activity with low pill burden, minimal adverse events and (for some INSTIs) minimal drug-drug interactions. Twice daily RAL has been replaced in recent years by once-daily elvitegravir (EVG) and DTG. EVG requires boosting with cobicistat; a fixed-dose combination of EVG/cobicistat is available as part of two single-tablet once-daily regimens: one with TAF and FTC, the other with TDF and FTC. Cobicistat inhibits renal excretion of creatinine, resulting in an increase in serum creatinine. Although not itself nephrotoxic, the creatinine increase associated with cobicistat administration results in an artifactual decrease in estimated glomerular filtration rate, which is challenging to distinguish from true nephrotoxicity in certain clinical settings. For this reason, it is not recommended for persons with significant renal disease. DTG is a once-daily highly potent antiretroviral agent with a high barrier to the development of drug resistance. DTG does not require pharmacologic boosting for once-daily dosing and is available in a small tablet that can be taken with TAF/FTC or TDF/FTC for a full regimen. A single-tablet once-daily regimen of DTG with ABC and 3TC is also available.

Goals of Therapy

The goal of HIV therapy is to suppress the replication of HIV as demonstrated by an undetectable viral load from serum. CD4 cell count recovery will be variable and dependent on many factors. Once begun, treatment should not be interrupted without a compelling reason because those on intermittent therapy have been shown to have a poorer prognosis. Frequency of monitoring (CD4 and HIV viral load) depends in part on the clinical course, but generally it is performed every 3 to 4 months and every 6 to 12 months in stable patients with long-term virologic suppression. In this era of highly effective and often coformulated ART, nonadherence is by far the most common cause of virologic failure (detectable viral load despite prescribed ART). Still, genotypic resistance testing should be performed in most instances of virologic failure to rule out the development of new drug resistance (see Box 2.1).

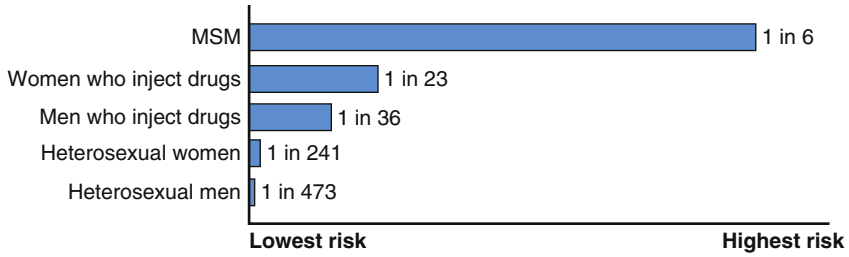
Monitoring and Routine Follow-Up Care

After patients enter care and begin ART, ongoing clinical and laboratory monitoring depends on the clinical scenario. Patients with adherence difficulties, ongoing viremia, adverse reactions to medications, opportunistic infections, or other complications require close clinical and laboratory monitoring. Patients who are stable on ART with successful virologic suppression for a prolonged period of time may only require clinical and laboratory monitoring every 6 to 12 months. Primary preventive care is critically important for patients with HIV because HIV infection is associated with increased risk of non–AIDS-defining malignancies and cardiovascular disease. Age-appropriate cancer screening (e.g., cervical and breast cancer screening, colon cancer screening) and cardiovascular risk evaluation/modification (e.g., smoking cessation, lipid and glucose monitoring, diet and exercise programs) are important facets of primary care for patients with HIV.

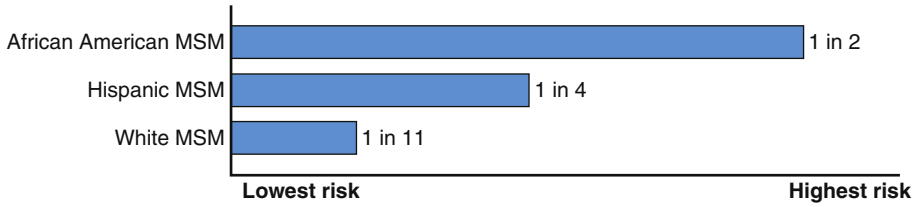
HIV Prevention

Despite the declining incidence of HIV infection in the United States over the past decade, incidence has declined more slowly in recent years; more than 44,000 new HIV infections were diagnosed in the United States in 2014. There is still a great need and opportunity for advances in HIV prevention and implementation of prevention techniques to curtail the epidemic within the United States and throughout the world. Certain populations have a startlingly high incidence of HIV in the United States. In 2016 the CDC calculated the estimated lifetime risk of HIV for many risk groups and race/ethnicity groups. Most notably at current infection rates an estimated one in six MSM and one in two African-American MSM will be diagnosed with HIV infection within their lifetime. Comprehensive HIV prevention strategies should target these high-risk vulnerable populations (Figs. 2.2 and 2.3).

Many methods of HIV prevention are currently in use, and many more are currently under investigation. Risk reduction education and traditional barrier methods, such as male and female condoms, are important tools for HIV prevention but may not be sufficient in some settings. Needle exchange testing/treating programs have been effective at decreasing HIV incidence among injection drug users. Male circumcision decreases sexual HIV transmission from women to the circumcised male partner by approximately 60% and does not require ongoing patient adherence to any drug or behavior, but efficacy in preventing transmission among MSM has not been tested. Perinatal transmission can



• **Fig. 2.2** Lifetime risk of HIV diagnosis by transmission group. *MSM*, Men who have sex with men. (From Centers for Disease Control and Prevention. http://www.cdc.gov/nchhstp/newsroom/2016/croi-2016.html#Graphics.)



• **Fig. 2.3** Lifetime risk of HIV diagnosis among men who have sex with men *(MSM)* by race/ethnicity. (From Centers for Disease Control and Prevention. http://www.cdc.gov/nchhstp/newsroom/2016/croi-2016.html#Graphics.)

be lowered to <1% to 2% with the implementation of prevention of mother-to-child transmission programs, which include fully suppressive combination ART to the mother during pregnancy and postnatal ART for the newborn, as well as exclusive formula feeding in developed countries.

Patients who have had a recent (within 72 hours) occupational or nonoccupational exposure that carries the possibility of HIV transmission (e.g., needlestick, occupational mucosal exposure, unprotected anal intercourse, sexual assault) should be screened for and offered antiretroviral postexposure prophylaxis (PEP). PEP consists of a combination ART regimen (usually tenofovir and FTC with either RAL or DTG) taken for a 28-day course. The limited available data on PEP suggests that this treatment decreases the risk of HIV transmission by at least 80%.

In 2014 the CDC published guidelines for the use of preexposure prophylaxis (PrEP) for prevention of HIV transmission. These guidelines were developed from review of a number of clinical trials of use of antiretroviral agents among HIV-negative individuals at high risk for HIV acquisition caused by a variety of risk factors (most commonly MSM but also heterosexual persons and injection drug use) for prevention of HIV acquisition. PrEP is now recommended as one option for HIV prevention for MSM and heterosexual men and women at substantial risk of HIV infection and should be considered for persons with injection drug use and for decreasing potential for HIV transmission in serodiscordant couples during conception. PrEP consists of daily treatment with fixed-dose combination tenofovir and FTC; episodic dosing around times of sexual activity has also been shown to be effective in some populations. Baseline evaluation includes screening for HIV infection, anemia, renal/hepatic dysfunction, hepatitis B and C infections, and sexually transmitted infection (STI) screening (gonorrhea, chlamydia, and syphilis). PrEP is then prescribed for 3-month intervals punctuated by in-clinic visits for risk reduction counseling, laboratory monitoring, and screening for HIV and other STIs. Efficacy of PrEP has been closely linked to adherence, which has been low in some studies.

Multiple studies have now demonstrated that treatment of HIV-infected persons effectively prevents transmission to others, with efficacy approaching 100%. This concept, known as *treatment as prevention,* can be optimized by early diagnosis of HIV via increased routine testing and universal treatment of all HIV-infected persons.

Chapter Review

Questions

1. A 42-year-old man presents to primary care physician with complaint of progressive cough and shortness of breath over the past few weeks. Upon further questioning he reports weight loss, malaise, and diarrhea over the past 6 to 12 months. On examination, he is mildly tachycardic and tachypneic, oxygen saturation is 90% on room air, and he has scattered rales on lung auscultation and seborrheic dermatitis on the face. CXR shows patchy bilateral infiltrates. Sputum culture is negative for bacteria. Serum lactate dehydrogenase is 295 U/L, and serum 1,3-beta glucan is >500 pg/mL. HIV Ag/Ab test is screen positive, and differentiation is positive for HIV-1. The most likely explanation for the current clinical situation is:

A. Acute retroviral syndrome complicated by pneumonia

B. Acute retroviral syndrome complicated by tuberculosis
C. Established HIV infection, now AIDS, complicated by PCP
D. Atypical pneumonia with false-positive HIV test

2. Additional testing reveals HIV viral load >1 million copies/mL, CD4 count 98. The patient is admitted to the hospital and initiates high-dose sulfamethoxazole/trimethoprim for PCP. The most appropriate plan for initiation of ART is:
A. Start TAF/FTC plus DTG during hospitalization, and then schedule for follow-up in the clinic within 1 to 2 weeks of hospital discharge for close monitoring.
B. Complete 21-day course of sulfamethoxazole/trimethoprim, and then initiate TAF/FTC plus DTG in outpatient follow-up after hospital discharge.
C. Complete 21-day course of sulfamethoxazole/trimethoprim, and then continue on once-daily prophylactic sulfamethoxazole/trimethoprim for 3 months to demonstrate adherence to medications and clinic visits before initiation of ART.
D. Start TAF/FTC plus DTG during hospitalization, and then schedule for follow-up in clinic at 6 months after hospital discharge for monitoring on stable ART.

3. Before beginning ART, which of the tests following is not indicated?
A. Serum creatinine
B. Urine toxicology
C. Genotypic HIV resistance test
D. Hepatitis B surface antigen

4. A 23-year-old man presents to primary care clinic with new penile discharge and dysuria for the past 7 to 10 days. Urethral gonorrhea is diagnosed by urine nucleic acid amplification test. The patient is treated with intramuscular ceftriaxone injection and oral azithromycin. Which of the following is the most appropriate next step for HIV prevention?
A. Initiation of tenofovir/FTC plus RAL for 28-day course for PEP
B. Initiation of daily tenofovir/FTC for PrEP at that visit, without further laboratory testing
C. Baseline HIV Ag/Ab screening, give condoms, follow up annually for HIV screening and risk reduction counseling
D. Baseline HIV Ag/Ab screening, discussion of risks and benefits of PrEP and initiation of tenofovir/FTC for PrEP if HIV screening negative and patient amenable

Answers

1. C
2. A
3. B
4. D

Additional Reading

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3

Infective Endocarditis

ANJU NOHRIA

Infective endocarditis (IE) is an infection of the endocardial surface of the heart. It is characterized by one or more vegetations comprising a mass of platelets, fibrin, microorganisms, and inflammatory cells. IE primarily involves the heart valves (native or prosthetic). Other structures may also be involved, including the interventricular septum, the chordae tendineae, the mural endocardium, or intracardiac devices such as a pacemaker. The most common infective causes are bacterial; however, fungal endocarditis can be seen in patients who are immunocompromised (Table 3.1). Valvular involvement in IE may lead to congestive heart failure (CHF), conduction abnormalities, and myocardial abscesses. Systemic complications in IE include embolization of both sterile and infected emboli, abscess formation, and mycotic aneurysms.

IE should be distinguished from nonbacterial endocarditis or marantic endocarditis. The latter is most commonly found on previously undamaged valves, and, unlike IE, the vegetations are usually small and sterile. Nonbacterial endocarditis does not cause a systemic illness, but systemic embolization may occur. Causes of nonbacterial endocarditis include a hypercoagulable state, cancer (usually mucinous adenocarcinoma), Libman-Sacks endocarditis, or pregnancy.

The incidence of IE based on hospital admissions in the United States is approximately 15 cases per 100,000 persons per year and is increasing by 2.4% annually. The mean age of patients with IE in the United States is 60.8 years of age, with more than one-third being 70 years of age or older. IE is more than twice as common in males than in females. There is no racial predilection. Untreated, IE has a very high morbidity and mortality. Antibiotic therapy is the mainstay of treatment. Surgery may be required under certain circumstances.

Pathophysiology

IE develops because of local adherence and invasion of bacteria onto the valvular leaflet. Normal endothelium is resistant to colonization and infection by circulating bacteria. Disruption of the endothelium exposes the underlying matrix and promotes the production of tissue factor and the deposition of fibrin and platelets as part of the normal healing process. Such nonbacterial thrombotic endocarditis facilitates bacterial adherence and infection. Endothelial damage can result from mechanical lesions provoked by turbulent flow, catheters, electrodes, inflammation (such as in rheumatic heart disease), or degenerative changes.

Endothelial inflammation without valvular lesions can also promote IE. In these circumstances, local inflammation leads to the expression of beta-1 integrins that bind circulating fibronectin. Pathogens such as *Staphylococcus aureus* contain fibronectin binding proteins on their surface, allowing them to be internalized by the endothelial cell where they can hide from host defenses, multiply, and spread to distant organs. IE develops most commonly on the mitral valve, closely followed in descending order of frequency by the aortic valve, the combined mitral and aortic valve, the tricuspid valve, and, rarely, the pulmonic valve. Mechanical prosthetic and bioprosthetic valves exhibit equal rates of infection.

Bacteremia may occur during dental treatment as well as invasive procedures involving the gastrointestinal (GI) and genitourinary (GU) tracts. However, there are other potential causes for bacteremia including the presence of colon cancer, urinary tract infections, and intravenous drug abuse (IVDA).

Predisposing Factors for Infective Endocarditis

Risk factors for IE are shown in Box 3.1. Whereas in the past, rheumatic fever was the most common predisposing factor for native valve IE, degenerative valve disease (significant mitral and/or aortic regurgitation) currently represents the most common underlying abnormality. Mitral valve prolapse (MVP) is the most common lesion, and the risk of IE is increased in the presence of thickened mitral leaflets or mitral regurgitation. Although rheumatic heart disease remains a major cause of IE in the developing world, it constitutes <5% of IE cases in the Western hemisphere.

TABLE 3.1 Microbiologic Causes by Type of Infective Endocarditis Among 2781 Patients With Definite Infective Endocarditis

	% Patients			
	Native Valve IE		Intracardiac Device IE	
Causative Organism	IVDA	Non-IVDA	PVE	Other Devices
Staphylococcus aureus	68	28	23	35
Coagulase-negative *Staphylococcus*	3	9	17	26
Viridans group streptococci	10	21	12	8
Streptococcus bovis	1	7	5	3
Other streptococci	2	7	5	4
Enterococcus	5	11	12	6
HACEK	0	2	2	0.5
Fungi/yeast	1	1	4	1
Polymicrobial	3	1	0.8	0
Negative cultures	5	9	12	11
Other	3	4	7	6

IVDA; Intravenous drug abuse; *HACEK, Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella,* and *Kingella* species; *IE*, infective endocarditis; *PVE*, prosthetic valve endocarditis.
Modified from Murdoch DR, Corey GR, Hoen B, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: The International Collaboration on Endocarditis-Prospective Cohort Study. *Arch Intern Med*. 2009;169(5):463-473.

Approximately 12% of patients have congenital heart disease as a predisposing factor for IE, with bicuspid aortic valve being the most common abnormality. Other contributing congenital abnormalities include ventricular septal defect, patent ductus arteriosus, transposition of the great arteries, and tetralogy of Fallot. Atrial septal defect (secundum variety) is rarely associated with IE.

Prosthetic valves continue to be an important predisposing factor for IE and are present in approximately 20% of cases. It is estimated that 5% of mechanical and bioprosthetic valves become infected, with valves in the mitral position being more susceptible than those in the aortic position. Mechanical valves are more likely to be infected within the first 3 months of implantation and bioprosthetic valves after 1 year.

The proportion of IE patients with chronic intravenous access (9%) and intracardiac devices (11%) is rising. Devices commonly become infected within a few months of implantation. Infection of pacemakers includes that of the generator pocket (the most common), the proximal leads, and the portions of the leads in direct contact with the endocardium.

IVDA remains an important risk factor in approximately 10% of patients with IE. The majority of patients with IVDA IE have no underlying valvular abnormality, and one-half of IVDA-associated IE cases involve the tricuspid valve.

Patients with conditions such as diabetes mellitus, chronic hemodialysis, and immunocompromised states as a result of cancer and HIV also demonstrate an increased susceptibility for IE.

Clinical Features

IE can present as a rapidly progressive acute febrile illness or as an indolent subacute illness with low-grade fever, malaise, anorexia, and weight loss. Fever is the most common sign and symptom of IE and is present in 96% of patients. Valvular involvement can give rise to a new murmur (48%) or worsening of a preexisting murmur (20%). Other clinical manifestations relate either to intracardiac extension of infection or to extracardiac consequences of systemic infection or embolic disease (Box 3.2).

CHF is the most common complication of IE (32%). The clinical features can include dyspnea, pulmonary edema, and cardiogenic shock. Acute regurgitation caused by native valve IE is the most common cause of CHF and can occur because of mitral chordal rupture, flail leaflet, leaflet perforation, or interference of leaflet closure by the vegetation. Perivalvular extension in prosthetic valve IE can lead to valvular dehiscence and CHF.

Perivalvular extension can also lead to abscess formation (14%), pseudoaneurysms, and fistulae. These should be suspected in cases of persistent fevers despite antibiotics or new atrioventricular block. These are most commonly seen with IE involving the aortic valve and are more frequent in patients with prosthetic valve infection.