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CHAPTER 16

Infectious Diseases

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Chapter contents

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BRONCHITIS

David R. McBride

Key Points

- Acute bronchitis is part of the continuum of "acute respiratory tract infection" most often caused by viruses.
- Antibiotics are not routinely recommended for the treatment of bronchitis.
- The cough of bronchitis may last up to 4 weeks.
- Beta-adrenergic agonists are not helpful unless patients have signs of bronchospasm associated with the infection.
- Acute exacerbations of chronic bronchitis with increased sputum production should be treated with antibiotics to decrease mortality.

Infections of the upper respiratory tract accounted for more than 36 million ambulatory medical visits in 2005, according to the National Ambulatory Medical Care Survey (Cherry et al., 2007). Although a large percentage of these infections are viral in origin, antibiotics are still prescribed for more than 50% of patients with *acute respiratory tract infection* (ARTI). *Acute bronchitis,* in the ARTI category, is defined as a respiratory infection in which cough is the predominant symptom and there is no evidence of pneumonia. Antibiotics are often prescribed despite limited evidence that they shorten the duration of acute bronchitis. With increasing incidence of antibiotic resistance, bronchitis allows physicians to practice "prescriptive restraint" and to provide supportive therapy. Consider using the phrase "chest cold" to help patients understand the viral and benign nature of this infection.

Chronic bronchitis is one of the manifestations of *chronic obstructive pulmonary disease* (COPD) and is defined clinically as cough and sputum production on most days for 3 months annually for 2 years. Chronic bronchitis is thought to be primarily inflammatory in origin, although infection may be associated with acute exacerbations; with increased sputum production and worsening dyspnea, antibiotics have proved effective in acute episodes. However, systemic corticosteroids are the mainstay of COPD exacerbation management.

The patient with acute bronchitis presents with cough, often productive. Patients may report clear or colored mucus in association with the presumed diagnosis of acute bronchitis. Despite what many patients believe, the color of sputum, even purulent sputum, is not predictive of bacterial infection. The cough of bronchitis can last up to 4 weeks, sometimes even longer. Typically, acute bronchitis is associated with other manifestations of infection, such as malaise and fever.

Respiratory viruses are thought to cause the majority of cases of acute bronchitis. Influenza A and B, parainfluenza, respiratory syncytial virus (RSV), coronavirus, adenovirus, and rhinovirus are common pathogens in the viral category. Clues to a specific virus may be found in the patient history; for example, RSV might be considered when there is household exposure to infected children. Influenza typically presents with sudden onset of symptoms, including fever, myalgias, cough, and sore throat.

Neuraminidase inhibitors are modestly effective in shortening the duration of influenza in ambulatory and healthy patients (by about 1 day), if initiated in the first 48 hours of illness. The resistance patterns of influenza A and B have shifted in the last several years and may vary based on yearly viral strains. Influenza B has remained, as of 2010, sensitive to zanamivir (Relenza) and oseltamivir (Tamiflu). Currently circulating strains of influenza A, both H1N1 and H3N2, and influenza B have generally remained sensitive to both oseltamivir and zanamivir (Fiore et al., 2011). Family physicians are advised to consider restraint in the prescribing of these agents, since resistance is of great concern. Yearly influenza immunization and cough etiquette and hygiene are likely the most useful techniques for influenza management.

Studies have identified other pathogens, such as *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae,* in a small minority of cases of clinical acute upper respiratory illness with cough as the predominant symptom. No significant benefit has been found in treating these infections with antibiotics. An exception in the treatment of acute bronchitis-like illness with antibiotics is when confirmed or probable *Bordetella pertussis* is present. Early treatment with a macrolide antibiotic and patient isolation will likely decrease coughing paroxysms and limit spread of disease (Braman, 2006). Although common upper respiratory bacterial pathogens, such as *Moraxella (Branhamella) catarrhalis, Streptococcus pneumoniae,* and *Haemophilus influenzae,* may be isolated from patients with acute bronchitis, their relevance is questionable because these bacteria can be present in the respiratory tract of healthy individuals. Obtaining sputum for culture when bronchitis is the diagnosis generally is not useful.

Antibiotics may offer a modest benefit in the treatment of acute bronchitis, with many studies showing no statistical significance in the outcome of treated versus not-treated groups. Measures of function, such as duration of illness, loss of work, and limitation of activity, have not shown clinically significant improvement in those with acute bronchitis taking antibiotics. Coupled with cost and the potential for side effects, the use of antibiotics for acute bronchitis is not recommended. If a provider decides to use an antibiotic in a specific patient situation, narrow-spectrum respiratory agents are preferred, such as a first-generation macrolide or doxycycline.

Treating the symptom of cough in acute bronchitis is an important concern for patients. In adults with acute bronchitis with signs of airway obstruction, evidenced by wheezing on examination or decreased peak expiratory flow rate, beta-2 agonists may be helpful in alleviating cough. These agents are not helpful for children with acute cough or adults with cough and no evidence of airway obstruction. Side effects of tremor and an anxious feeling must be weighed against this benefit.

Patients often are primarily interested in alleviating symptoms caused by respiratory illness. Unfortunately, there is mixed evidence for the use of over-the-counter (OTC) and prescription cough medications. Dextromethorphan and codeine may be somewhat effective, although they have not been evaluated in randomized, double-blinded, placebo-controlled trials for acute bronchitis. Combination first-generation antihistamine-decongestant products may be effective for the cough associated with colds. Naproxen showed efficacy against cough in one upper respiratory model study (Sperber et al., 1992). Guaifenesin acts as an expectorant and may have some effect on cough by its mucus-thinning properties.

Chronic Bronchitis: Acute Exacerbation

Acute exacerbations of chronic bronchitis may be triggered by bacterial or viral infection or may be noninfectious. *H. influenzae* accounts for 50% of bacterial exacerbations with *S. pneumoniae* and *M. catarrhalis* causing an additional third (Moussaoui et al., 2008). For acute exacerbation of COPD associated with purulent sputum and increased shortness of breath, antibiotic therapy decreases mortality by 77% and treatment failure by 53% (Ram et al., 2009). This finding was true regardless of the antibiotic choice, although coverage for the organisms just noted seems rationale. Consideration of the frequency of beta-lactamase production within these organisms in a community is important. More recent meta-analysis shows that a shorter course, no longer than 5 days, is as effective as longer treatment with antibiotic (Moussaoui et al., 2008).

Other features of the management of acute exacerbation of chronic bronchitis include systemic corticosteroids, inhaled beta agonists and anticholinergics (e.g., ipratropium), and support for oxygenation status and ventilation. Patients with chronic bronchitis may have multiple hospital admissions and may remain colonized with both community-acquired and hospital-acquired organisms. It is advisable to reserve the use of antibiotics, unless absolutely necessary to prevent the development of resistant organisms.

KEY TREATMENT

Antibiotics for the treatment of bronchitis is not recommended because of the cost, potential for side effects, and lack of clinical benefit (Braman, 2006; Smith et al., 2009) (SOR: A).

In the treatment of *Bordetella pertussis*, early administration of a macrolide antibiotic and patient isolation will likely decrease coughing paroxysms and limit spread of disease (Braman, 2006) (SOR: A).

In adults with acute bronchitis with signs of airway obstruction, as evidenced by wheezing on examination or decreased peak expiratory flow rate, beta-2 agonists may be helpful in alleviating cough (Braman, 2006) (SOR: B).

For acute exacerbation of COPD associated with purulent sputum and increased shortness of breath, treatment with antibiotics decreases mortality by 77% and treatment failure by 53% (Ram et al., 2009) (SOR: A).

PNEUMONIA

Anthony Zeimet

Key Points

- Assessment tools for pneumonia severity (e.g., CURB-65) can help determine the treatment approach.
- The therapy of pneumonia is often empiric because the infecting organism is not readily isolated in more than 50% of cases.
- Chest radiography is one of the most useful diagnostic tools in pneumonia.

Community-acquired pneumonia (CAP) is defined as an acute infection of the pulmonary parenchyma and, along with influenza, is the seventh leading cause of death in the United States. Fever, cough, sputum production, pleuritic chest pain, and dyspnea are common symptoms of CAP. Nausea, vomiting, and diarrhea also may occur, and in elderly patients, CAP may present with mental status changes. Although its absence usually makes pneumonia less likely, fever can be absent in the elderly patient. Other physical examination findings include an elevated respiratory rate, conversational dyspnea, tachycardia, and rales. Egophony and dullness to percussion may be noted with focal consolidation. Typical laboratory findings include leukocytosis. The diagnosis of pneumonia is based on the presence of symptoms *and* the presence of an infiltrate on chest radiograph. If infiltrate is not present, consider obtaining a chest tomography scan (which has higher sensitivity) to rule in or rule out CAP. If negative, other diagnoses should be considered.

The most common microbiologic agent of pneumonia is often not isolated (Table 16-1). Furthermore, studies have shown that bacteriologic causes of pneumonia cannot be determined by radiographic appearance (i.e., "typical" vs. "atypical"). In the proper clinical setting, certain clinical microbes should be considered because they can affect treatment considerations and epidemiologic studies. These include *Legionella* spp., influenza A and B, and community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA).

Certain diagnostic tests are performed based on clinical setting. Blood cultures are not routinely done in the outpatient setting but should always be done if the patient is being admitted to the hospital, ideally before antibiotics are given. The use of Gram stain and sputum culture remains controversial but can provide more evidence of a bacterial cause (e.g., many PMNs). If sputum cultures are being obtained, it is recommended that the physician have the patient expectorate directly into a specimen cup and have it sent immediately for processing. This can increase the yield of isolating *Streptococcus pneumoniae* among

Table 16-1 Most Common Etiologies of Community-Acquired Pneumonia

Patient Type	Etiology
Outpatient	*Streptococcus pneumoniae* *Mycoplasma pneumoniae* *Haemophilus influenzae* *Chlamydophila pneumoniae* Respiratory viruses*
Inpatient (non-ICU)	*S. pneumoniae* *M. pneumoniae* *C. pneumoniae* *H. influenzae* *Legionella* spp. Aspiration Respiratory viruses*
Inpatient (ICU)	*S. pneumoniae* *Staphylococcus aureus* *Legionella* spp. Gram-negative bacilli *H. influenzae*

Modified from Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society–American Thoracic Society Consensus Guidelines on Management of Community-Acquired Pneumonia in Adults. Clin Infect Dis 2007;44:S27-S72.
ICU, Intensive care unit.
*Influenza A and B, adenovirus, respiratory syncytial virus, and parainfluenza.

other respiratory pathogens. Other tests include urine antigen tests for *S. pneumoniae*, *Legionella pneumophila* serogroup 1, and nasal swab for influenza A and B. In young children, RSV, adenovirus, and parainfluenza in addition to influenza are common causes. Nasal swab for RSV and influenza can be rapidly done, but the other causes can be determined with viral cultures, serology, enzyme-linked immunosorbent assay (ELISA), and polymerase chain reaction (PCR), although results usually are received after resolution of the acute symptoms.

Perhaps the most important decision for clinicians is to determine the location of treatment. The American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) recommend use of the *pneumonia severity index* (PSI), which uses 20 variables to risk-stratify the patient into five mortality classes, or the *CURB-65*, which measures five clinical variables in this decision making. The CURB-65 may be the easiest and most convenient to use at the site of decision making. A score of 0 or 1 indicates treatment as an outpatient; a score of 2 requires hospital admission to the general medical ward; and a score of 3 or more indicates admission to an intensive care unit (ICU) (Box 16-1).

Treatment of CAP should be targeted toward the most likely etiology (Table 16-2). Outpatient therapy for patients who have no comorbidities and have not received antibiotics within the last 3 months includes doxycycline or a macrolide antibiotic. Use of a fluoroquinolone antibiotic (levofloxacin or moxifloxacin) should be reserved for patients with more complicated pneumonia and those requiring hospitalization. Patients who have comorbid conditions or recent antibiotic exposure, or who will be hospitalized, should receive a respiratory fluoroquinolone or combination therapy with a beta-lactam drug plus a macrolide, for 48 to 72 hours after fever abates (usually 5-7 days' total therapy). If an organism is isolated, therapy may be narrowed to cover the causative agent. The clinician should consider longer therapy and appropriate antibiotics to cover for infection by less common organisms such as *Staphylococcus aureus* or *Pseudomonas aeruginosa*. If the patient has no more than one abnormal value (temperature <37.8° C, heart rate <100, respiratory rate <24, SBP >90, O_2 saturation >90%, Po_2 >60 on room air) *and* the patient is able to maintain oral intake and has a normal mental status, the clinician can safely switch to oral therapy and discharge the patient from the hospital. Unless the etiology of the pneumonia is known, the physician should switch to oral antibiotics in the same class as the intravenous antibiotics used.

Box 16-1 CURB-65 Criteria

Assign a value of 1 for each variable:
- Confusion: Is the patient disoriented to person, place, or time?
- BUN >20 mg/dl
- Respiratory rate > 30 breaths/min
- Blood pressure: systolic <90 or diastolic <60 mm Hg
- Age >65 years

Interpretation
- Score 0 or 1: outpatient treatment
- Score 2 : inpatient treatment on a general medical floor
- Score >3: inpatient treatment in an intensive care unit

BUN, Blood urea nitrogen.

The U.S. Preventive Services Task Force (USPSTF) along with IDSA and ATS recommend annual influenza vaccinations to those over 50 years of age, those who are (or who reside with those who are) at high risk for influenza complications, and all health care workers. Furthermore, the pneumococcal vaccine should be given to all those over age 65. Smoking cessation is also important and should be discussed at each clinic visit.

KEY TREATMENT

Locally adapted guidelines should be implemented to improve the processing of care variables and relevant clinical outcomes in pneumonia (Mandell et al., 2007) (SOR: B).
Objective criteria or scores should always be supplemented with physician determination of subjective factors, including the patient's ability to take oral medication safely and reliably and the availability of outpatient support resources (Mandell et al., 2007) (SOR: B).
For patients with CURB-65 score of 2 or higher, more intensive treatment (i.e., hospitalization or, where appropriate and available, intensive in-home health care services) is usually warranted (Mandell et al., 2007) (SOR: C).

INFLUENZA

Anthony Zeimet

Key Points

- Concerns about development of resistant seasonal and H1N1 swine-derived influenza virus should be considered in the decision to administer antiviral medications to healthy patients with these infections.
- The abrupt onset of fever with chills, headache, malaise, myalgias, arthralgias, and rigors during "flu season" is sufficient to diagnose influenza.
- Prevention of influenza is generally with vaccination.

Influenza deserves special mention because it is an important cause of pneumonitis and can precede a bacterial pneumonia. Influenza viruses are medium-sized enveloped ribonucleic acid (RNA) viruses that consist of a lipid bilayer with matrix proteins with spiked surface projections of glycoproteins (hemagglutinins, neuraminidase) on the outer surface (Figure 16-1). Both influenza A and influenza B have eight segmented pieces of single-stranded RNA. The only difference between influenza A and B is that B does not have an M2 ion channel. *Hemagglutinins,* three types of which typically infect humans (H1, H2, H3), bind to respiratory epithelial cells and allow fusion with the host cell. *Neuraminidase,* consisting of two types (N1, N2), allows release of virus from the infected cells.

A unique aspect of influenza is that antigenic variation occurs annually. Antigenic shift is caused by a genetic reassortment between animal and human influenza strains, producing a novel virus that generally causes the worldwide pandemics. Influenza viruses circulate mostly among humans, birds, and swine. Sometimes; a human strain and an animal strain can intermingle and create a new, unique virus. This is what happened during spring 2009, heralding the most recent pandemic and creating "Novel H1N1 Influenza" (swine influenza). Genotype analysis

Table 16-2 Guide to Empiric Choice of Antimicrobial Agent for Treating Patients with Community-Acquired Pneumonia (CAP)

Patient Characteristics	Preferred Treatment Options
Outpatient	
Previously Healthy	
No recent antibiotic therapy	Oral-based β-lactam, macrolide,* or doxycycline
Recent antibiotic therapy†	A respiratory fluoroquinolone‡ alone, an advanced macrolide* plus high-dose amoxicillin,§ or an advanced macrolide plus high-dose amoxicillin-clavulanate.¶
Comorbidities (COPD, diabetes, renal failure or congestive heart failure, or malignancy)	
No recent antibiotic therapy	An advanced macrolide* plus β-lactam or a respiratory fluoroquinolone
Recent antibiotic therapy	A respiratory fluoroquinolone‡ alone or an advanced macrolide plus a β-lactam**
Suspected aspiration with infection	Amoxicillin-clavulanate or clindamycin
Influenza with bacterial superinfection	Vancomycin, linezolid, or other coverage for MRSA or community-acquired MRSA
Inpatient	
Medical Ward	
No recent antibiotic therapy	A respiratory fluoroquinolone alone or an advanced macrolide plus a β-lactam††
Recent antibiotic therapy	An advanced macrolide plus a β-lactam, or a respiratory fluoroquinolone alone (regimen selected will depend on nature of recent antibiotic therapy)
Intensive Care Unit (ICU)	
Pseudomonas infection is not an issue	A β-lactam††† plus either an advanced macrolide or a respiratory fluoroquinolone
Pseudomonas infection is not an issue but patient has a β-lactam allergy	A respiratory fluoroquinolone, with or without clindamycin
Pseudomonas infection is an issue‡‡‡ (cystic fibrosis, impaired host defenses)	Either (1) an antipseudomonal β-lactam§§ plus ciprofloxacin, or (2) an antipseudomonal agent plus an aminoglycoside## plus a respiratory fluoroquinolone or a macrolide
Pseudomonas infection is an issue but the patient has a β-lactam allergy. Health care–associated exposure	Aztreonam plus aminoglycoside plus levofloxacin¶¶ or other respiratory quinolone Anti-*Pseudomonas* cephalosporin, carbapenem (not ertapenem) or β-lactam/β-lactamase inhibitor with anti-*Pseudomonas* activity plus vancomycin (for MRSA coverage) ± quinolone or aminoglycoside
Nursing Home	
Receiving treatment in nursing home	A respiratory fluoroquinolone alone or vancomycin (for *S. aureus* including MRSA) plus a β-lactam (cefepime or piperacillin/tazobactam if *Pseudomonas* is suspected; ceftriaxone if *Pseudomonas* is not suspected)
Hospitalized	Same as for medical ward and ICU

Data from Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44:S27-S72.

COPD, Chronic obstructive pulmonary disease; *MRSA,* methicillin-resistant *Staphylococcus aureus*.

*Azithromycin or clarithromycin.

†That is, the patient was given a course of antibiotic(s) for treatment of any infection within the past 3 months, excluding the current episode of infection. Such treatment is a risk factor for drug-resistant *Streptococcus pneumoniae* and possibly for infection with gram-negative bacilli. Depending on the class of antibiotics recently given, one or another of the suggested options may be selected. Recent use of a fluoroquinolone should dictate selection of a nonfluoroquinolone regimen, and vice versa.

‡Moxifloxacin, levofloxacin, or gemifloxacin.

§Dosage: 1 g orally (PO) three times daily (tid).

¶Dosage: 2 g PO twice daily (bid).

**High-dose amoxicillin (1 g tid), high-dose amoxicillin-clavulanate (2 g bid), cefpodoxime, cefprozil, or cefuroxime.

††Cefotaxime, ceftriaxone, ampicillin-sulbactam, or ertapenem.

‡‡The antipseudomonal agents chosen reflect this concern. Risk factors for *Pseudomonas* infection include severe structural lung disease (e.g., bronchiectasis) and recent antibiotic therapy, health care–associated exposures or stay in hospital (especially in the ICU). For patients with CAP in the ICU, coverage for *S. pneumoniae* and *Legionella* species must always be considered. Piperacillin-tazobactam, imipenem, meropenem, and cefepime are excellent β-lactams and are adequate for most *S. pneumoniae* and *H. influenzae* infections. They may be preferred when there is concern for relatively unusual CAP pathogens, such as *P. aeruginosa, Klebsiella* spp., and other gram-negative bacteria.

§§Piperacillin, piperacillin-tazobactam, imipenem, meropenem, or cefepime.

##Data suggest that older adults receiving aminoglycosides have worse outcomes.

¶¶Dosage for hospitalized patients, 750 mg/day.

of this strain determined that components came from an influenza virus circulating among swine herds in North America that combined with a virus circulating among ill swine in Eurasia, creating a new influenza strain capable of causing disease in humans. Because this virus had not previously infected humans, it had the potential to cause widespread morbidity and mortality worldwide. During pandemics, the U.S. Centers for Disease Control and Prevention (CDC) estimates an additional 10,000 to 40,000 deaths caused by influenza. Although higher than in nonpandemic years, mortality was significantly less than initially predicted in 2009.

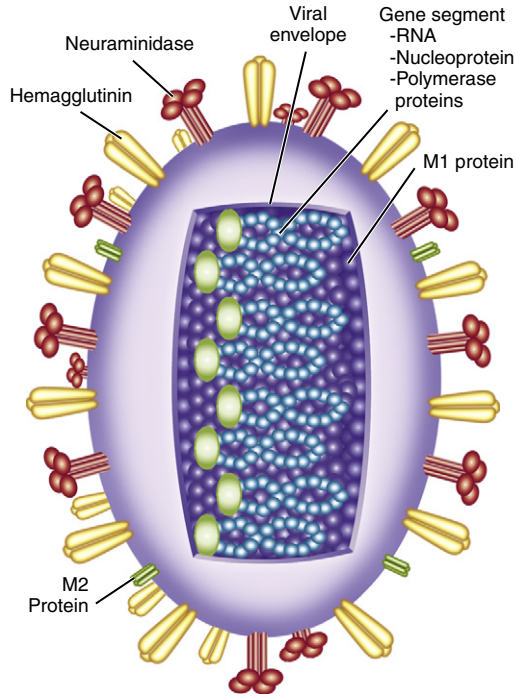


Figure 16-1 Schematic model of influenza A virus.
(From Treanor JJ: Influenza viruses, including avian influenza and swine influenza. In Mandell GL, Bennett JE, Dolin RD (eds). Mandell, Douglas, and Bennett's Principles and Practices of Infectious Diseases, 7th ed. Philadelphia, Churchill Livingstone, 2010, p 2266.)

The abrupt onset of fever, along with chills, headache, malaise, myalgias, arthralgias, and rigors during "flu season," is sufficient to diagnose influenza. As the fever resolves, a dry cough and nasal discharge predominate. A rapid nasal swab or viral cultures can be used to confirm the diagnosis of influenza but is rarely needed. In fact, the sensitivity of these rapid tests can range from 50% to 70%, so a negative test does not rule out influenza. The primary care physician needs to determine if the patient has influenza or the common cold, because symptoms of both illnesses generally overlap (Table 16-3).

Treatment of influenza is generally not necessary because it is usually a self-limiting condition. Treatment should be reserved for those with comorbidities who present within 48 hours of symptom onset. Neuraminidase inhibitors (zanamivir and oseltamivir) prevent the release of virus from the respiratory epithelium and are approved for both influenza A and influenza B. The M2 inhibitors (amantadine and rimantadine) are approved by the U.S. Food and Drug Administration (FDA) for the treatment of influenza A because these drugs block the M2 ion protein channel, preventing fusion of the virus to host cell membrane (influenza B has no M2 ion channel). The use of M2 inhibitors is limited because of increasing resistance among influenza A viruses, as well as causing central nervous system (CNS) problems that are usually exacerbated in elderly persons, who are more likely to seek treatment for influenza (Table 16-4).

The major complication of influenza is a secondary bacterial pneumonia or exacerbation of underlying COPD. Initial improvement in clinical symptoms followed by deterioration usually suggests a secondary bacterial pneumonia, which can usually be confirmed with a chest radiograph showing an infiltrate. Other, less common complications of influenza include myositis, myocarditis, pericarditis, transverse myelitis, encephalitis, and Guillain-Barré syndrome.

Table 16-3 Common Cold versus Influenza Symptoms

Symptom	Common Cold	Influenza
Fever	Rare	Abrupt onset
Cough	Frequent, usually hacking	Frequent, usually severe
Sore throat	Frequent	Rare
Nasal congestion	Frequent	Rare
Sneezing	Frequent	Rare
Myalgia	Rare	Frequent
Headache	Rare	Frequent
Fatigue	Mild	Severe

Prevention of influenza is generally with vaccination. Box 16-2 outlines patients at risk for influenza complications who should be vaccinated yearly. Although anyone wanting an influenza vaccine should be vaccinated, during periods of vaccine shortage, high-risk groups have priority. A well-matched vaccine can prevent influenza among 70% to 90% of adults and decrease work absenteeism. Conversely, a poorly matched vaccine only prevents influenza in 50% of healthy adults. Proper hand hygiene and covering one's cough are two additional important components in preventing the spread of influenza virus.

KEY TREATMENT

Early treatment (within 48 hours of onset of symptoms) with oseltamivir or zanamivir is recommended for influenza A (Jefferson et al., 2006) (SOR: A).
Use of oseltamivir and zanamivir is not recommended for patients with uncomplicated influenza with symptoms for more than 48 hours (Kaiser and Hayden, 1999) (SOR: A).
Oseltamivir and zanamivir may be used to reduce viral shedding in hospitalized patients or to treat influenza pneumonia (Mandell et al., 2007) (SOR: C).

SYSTEMIC VIRAL INFECTIONS

Anthony Zeimet

Key Points

- Population-based vaccination programs have been highly effective in decreasing the incidence of many viral infections.
- Acyclovir can be used in adults and children with varicella to decrease symptoms if given in the first 48 hours after rash onset, but its benefit must be weighed against its cost and the possibility of development of viral resistance.
- Antiviral medications should be considered to decrease the incidence of postherpetic neuralgia, particularly in older patients.

Table 16-4 Treatment and Chemoprophylaxis Recommendations for Influenza

Agent/ Group	Treatment	Chemoprophylaxis
Neuraminidase Inhibitors		
Oseltamivir		
Adults	75-mg capsule twice daily (bid) for 5 days	75-mg capsule once daily (qd)
Children (age >12 mo)		
<15 kg	60 mg/day divided into 2 doses	30 mg qd
15-23 kg	90 mg/day in 2 doses	45 mg qd
24-40 kg	120 mg/day in 2 doses	60 mg qd
>40 kg	160 mg/day in 2 doses	75 mg qd
Zanamivir		
Adults	Two 5-mg inhalations (10 mg bid)	Two 5-mg inhalations (10 mg qd)
Children	Two 5-mg inhalations (10 mg bid)(age >7 yr)	Twp 5-mg inhalations (10 mg qd)(age >5 yr)
M2 Inhibitors (Adamantadines)*		
Rimantadine†		
Adults	200 mg/day as either a single daily dose or divided into 2 doses	200 mg/day as either a single daily dose or divided into 2 doses
Children		
1-9 yr	6.6 mg/kg/day (max, 150 mg/day) divided in 2 doses	5 mg/kg qd, not to exceed 150 mg
>10 yr	200 mg/day as either a single daily dose or divided into 2 doses	200 mg/day as either a single daily dose or divided into 2 doses
Amantadine		
Adults	200 mg/day as either a single daily dose or divided into 2 doses	200 mg/day as either a single daily dose or divided into 2 doses
Children		
1-9 yr	5-8 mg/kg/day divided into 2 doses or as a single daily dose (max, 150 mg/day)	5-8 mg/kg/day divided into 2 doses or as a single daily dose (max, 150 mg/day)
9-12 yr	200 mg/day divided into 2 doses	200 mg/day divided into 2 doses

Modified from Harper SA, Bradley JS, Englund JA, et al. Seasonal influenza in adults and children: diagnosis, treatment, chemoprophylaxis, and institutional outbreak management. Clinical Practice Guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2009;48:1003-1032.
*The amantadines should be used only when influenza A (H1N1) infection or exposure is suspected. The amantadines should not be used for infection or exposure to influenza A (H2N3) or influenza B.
†Rimantadine has not been approved by the U.S. Food and Drug Administration for treatment of children, although published data exist on safety and efficacy in the pediatric population.

Box 16-2 Groups at risk for Influenza Complications*

Unvaccinated infants age 12 to 24 months
Persons with asthma or other chronic pulmonary disease, such as cystic fibrosis in children or chronic obstructive pulmonary disease in adults
Patients with hemodynamically significant cardiac disease
Patients with immunosuppressive disorders or receiving immunosuppressive therapy
Patient with human immunodeficiency virus (HIV) infection
Patients with sickle cell anemia and other hemoglobinopathies
Patients with disease requiring long-term aspirin therapy (e.g., rheumatoid arthritis, Kawasaki disease)
Patients with chronic renal obstruction
Patients with cancer
Patients with chronic metabolic disease, such as diabetes mellitus
Patient with neuromuscular disorders, seizure disorders, or cognitive dysfunction that may compromise the handling of respiratory secretions
Adults older than 66 years
Residents of any age of nursing homes or other long-term care facilities

Modified from Harper SA, Bradley JS, Englund JA, et al. Seasonal influenza in adults and children: diagnosis, treatment, chemoprophylaxis, and institutional outbreak management. Clinical Practice Guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2009;48:1003-1032.
*Data suggest that the highest risk of both mortality and serious morbidity (e.g., hospitalization) occurs in severely immunocompromised patients (e.g., hematopoietic stem cell transplant patients) and very elderly (>85 years) residents of nursing homes; infants under age 24 months also have high hospitalization rates but lower case-fatality rates than the other two groups.

- Measles has had a resurgence in recent years and should be suspected when a patient presents with cough, coryza, conjunctivitis, and head-to-toe rash.
- Epstein-Barr virus and cytomegalovirus infections are generally not clinically distinguishable, and their treatment is primarily supportive.

Vaccinations have dramatically decreased the incidence of a number of historically common viral infections; smallpox has been eradicated through widespread vaccination. However, recent outbreaks of measles and mumps on college campuses underscore the need to remain vigilant in administering vaccines at the population level, even though no vaccine is available for many common viruses.

Varicella and Herpes Zoster

Varicella is one of the classic viral exanthems of childhood. Before routine vaccination, having chickenpox was one of childhood's "rites of passage." The virus, a herpesvirus (human herpesvirus 3), is effectively transmitted, causing outbreaks in schools and households.

Patients with primary varicella present with fever, headache, and sore throat. Generally within 1 to 2 days of onset of symptoms, a papulovesicular rash erupts diffusely. The classic description of the chickenpox lesion is "a dewdrop on a rose petal," suggesting a central vesicle on an erythematous base. Lesions continue to appear for 5 to 7 days. All lesions going from papule to vesicle to crusted lesion takes about

2 weeks. Patients are considered to be infectious, primarily through respiratory secretions, during the 2 days before symptoms appear and until all lesions are crusted.

Treatment of varicella is generally supportive. Control of spread may be a concern in group-living environments such as schools or residence halls. Isolation of the infected patient away from those susceptible to varicella infection is standard practice. Acyclovir can be started within the first 24 hours after rash eruption to achieve an attenuation of the infectious course. In children, this means a decrease in the duration of fever by about 1 day and a decrease in the number of lesions (Swingler, 2010). In adults, acyclovir decreases rash duration and the number of lesions, although the results are less significant than for children. Adult dosing of acyclovir for varicella is 800 mg five times daily. The marginal benefit must be weighed against the possible development of resistance at a population level and the cost of the medication. Complications of varicella can include secondary infection of skin lesions, pneumonitis, encephalitis, and dehydration from vomiting and diarrhea.

Varicella is prevented primarily through administration of vaccine. The vaccine is highly effective in children, with recommended dosing at 12 to 15 months with a second dose at 4 to 6 years. Varicella is now included in a measles-mumps-rubella (MMR) vaccine, which can be given between 12 months and 12 years of age. The varicella vaccine is a live, attenuated virus and should not be given to certain immunocompromised patients. The vaccine can also be administered to exposed immunocompetent contacts, although the benefit is clearer for children than adults. Severely immunocompromised patients exposed to varicella (particularly those with advanced HIV disease) may be given high-dose acyclovir to prevent development of disease.

Herpes zoster is a reactivation of the neurotropic varicella virus, typically in a dermatomal distribution. This is more common in elderly or immunocompromised patients but can occur in healthy people as well. Patients with zoster may note generalized malaise, hyperesthesia, numbness, tingling, and pain in the skin before development of a rash. The appearance of the rash is the same as for chickenpox, although most often isolated to a unilateral dermatome. The diagnosis of herpes zoster is clinical based on the history and the classic appearance of the rash. In immunocompromised patients, however, the rash may not be dermatomally isolated. When the diagnosis is unclear, viral culture can be obtained from the base of a lesion.

Antiviral medications are likely to decrease the incidence of *postherpetic neuralgia* and are recommended, particularly in elderly patients (Wareham, 2010). Valacyclovir (1 g three times daily) or famciclovir (500 mg every 8 hours) for 7 days is likely more effective than acyclovir in achieving this result. Either drug should be started as soon after the diagnosis as possible, preferably within 48 to 72 hours of rash onset. When patients have established postherpetic neuralgia, gabapentin and tricyclic antidepressants are helpful in alleviating the pain.

The rash of zoster is infectious to the touch. Patients should be advised to keep the rash covered until all the lesions have crusted. Zoster of the trigeminal nerve can extend to the eye and warrants immediate ophthalmologic intervention.

A vaccine to prevent herpes zoster in adults was released in 2006. The zoster vaccine differs from the varicella vaccine in that the amount of attenuated virus is 14 times higher in the zoster vaccine. The vaccine decreases the incidence of zoster by 50%. It is recommended for administration by the American Academy of Family Physicians (AAFP) to adults over age 60, regardless of prior varicella or zoster history. Although generally well tolerated, the vaccine is somewhat costly.

Measles

In 2008, more measles cases were reported than in any other year since 1997 (CDC, 2010). Measles is the "first disease" of childhood from the history of medicine. In adults, measles infection may be acquired in the face of waning immunity from remote immunization. A booster dose of MMR vaccine is recommended before college entry.

Clinically, measles presents with cough, coryza (nasal irritation and congestion), and conjunctivitis. Fever is common several days before the onset of the rash. The rash of measles typically spreads from head to toe and has an erythematous, papular appearance with a "sandpaper" feeling. Koplik's spots are erythematous papules with a bluish center on the oral mucosa and appear early in measles. Measles is highly contagious through droplets.

Lymphopenia and neutropenia are common laboratory findings with measles infection. Complications of measles include primary infections such as pneumonia, gastroenteritis, encephalitis, and the rare subacute sclerosing panencephalitis. Secondary infections such as otitis media, pneumonia, and adenitis may also occur.

Treatment is supportive, and the implications of measles infection are primarily in the public health realm. Patients with measles should be isolated for at least 4 days after the appearance of the rash. It is important to recognize that patients are contagious for 2 days before the development of symptoms. Careful verification of immunization status for close contacts is essential.

Epstein-Barr Virus and Cytomegalovirus

Clinical *infectious mononucleosis* is a common infection in adolescents and early adults. The clinical syndrome is most often caused by Epstein-Barr virus (EBV), although cytomegalovirus (CMV) may also be the source in this clinical syndrome, which includes fever, exudative tonsillitis, adenopathy (often including posterior cervical or occipital nodes), and fatigue. EBV is transmitted in oral secretions and may be transmitted sexually as well. B cells are infected with EBV either directly or after contact with epithelial cells, resulting in diffuse lymphoid enlargement.

The diagnosis of infectious mononucleosis is made by recognizing the clinical symptoms of fever, pharyngitis, and adenopathy along with the laboratory findings of greater than 50% lymphocytes with 10% or more atypical lymphocytes (Hoagland, 1952). Also, a positive serologic test for heterophile antibody assists the family physician in the diagnosis. To differentiate EBV from CMV mononucleosis, serology (IgG and IgM) may be obtained. Results of these tests are generally not available in time to have a significant benefit clinically.

Splenic enlargement as part of this lymphoid hypertrophy can lead to splenic rupture (0.1% risk) (Dommerby

et al., 1986). Athletes with infectious mononucleosis must be managed carefully to avoid their participation in sports that could result in abdominal trauma. Other risks associated with infectious mononucleosis include upper airway obstruction, asymptomatic transaminase elevation, thrombocytopenia, and rash after the administration of ampicillin or amoxicillin. Routinely obtaining transaminase levels in patients without clinical hepatitis is of little value and can increase the overall cost of management.

Treatment of infectious mononucleosis is largely supportive. Patients should be instructed to treat fever with antipyretics, rest, and expect symptom duration of 2 to 4 weeks, although symptoms can last for several months. The use of steroids, such as prednisone, has shown limited benefit. Data suggest an initial benefit 12 hours after steroid administration, although this is lost within several days (Candy and Hotopf, 2006). Combination of steroid and an antiviral (valacyclovir) may have some positive effect on fatigue.

KEY TREATMENT

Acyclovir started within the first 24 hours after varicella rash eruption can attenuate the infectious course, decreasing duration of fever by 1 day and reducing the number of lesions (SOR: A).
Administration of varicella vaccine to a susceptible child within 3 days of exposure will likely modify or prevent disease (Macartney and McIntyre, 2008) (SOR: A).
Antiviral medications decrease the incidence of postherpetic neuralgia (Wareham, 2010) (SOR: B).

TUBERCULOSIS

David McCrary

Key Points

- The most common presentation of tuberculosis is pulmonary disease.
- Tuberculosis is diagnosed by acid-fast bacilli smears and cultures.
- Standard first-line agents to treat TB are isoniazid, rifampin, pyrazinamide, and ethambutol.
- High-risk patients with a positive purified protein derivative skin test or Quantiferon-TB Gold test should be treated for latent TB infection.
- The current recommendation for first-line treatment for latent TB is 9 months of oral isoniazid.

Tuberculosis skin testing should be interpreted without regard to bacille Calmette-Guérin (BCG) history, because BCG is administered in areas where TB is endemic and BCG does not provide complete protection from TB infection.

Tuberculosis (TB) is a disease that has plagued humans since antiquity, with evidence of spinal TB in neolithic and early Egyptian remains. At present, TB affects approximately one third of the world's population. TB is the world's second most common cause of death from infectious disease after human immunodeficiency virus or acquired immunodeficiency syndrome (HIV/AIDS). Tuberculosis is caused by *Mycobacterium tuberculosis*, an acid-fast bacillus. TB is acquired by inhalation of respiratory droplets. These respiratory droplets are spread by coughing. Brief contact carries little risk for acquiring TB, and infection generally does not occur in open air; open-air sanatoriums were the cornerstone of TB treatment before antimicrobial therapy.

Epidemiology

In the United States, TB incidence rates have been on the decline since 1992, coinciding with the control of HIV-induced AIDS by antiretroviral therapy. However, TB remains prevalent in certain high-risk groups (i.e. immigrants, IV drug use, homeless persons). Most cases of TB are in people age 15 to 49 years. TB in elderly persons is generally caused by a reactivation of latent infection acquired in the remote past, whereas TB in young children indicates ongoing active transmission in the community. Infection in children is more likely to progress to active TB and disseminated disease. Persons with HIV infection have a disproportionately higher risk for acquiring TB than the general population.

Presentation

Tuberculosis is most frequently manifested clinically as pulmonary disease, but it can involve any organ. Extrapulmonary TB accounts for about 20% of disease in HIV-seronegative persons but is more common in HIV-seropositive persons. Pulmonary TB typically manifest with fever, night sweats, chronic cough, sputum production, hemoptysis, anorexia, and weight loss. Chest radiographs in patients with pulmonary TB typically reveal upper-lobe cavitary lesions and can reveal infiltrates or nodular lesions, as well as lymphadenopathy (Figure 16-2). TB in the setting of advanced HIV co-infection does not generally manifest in the typical manner (Table 16-5).

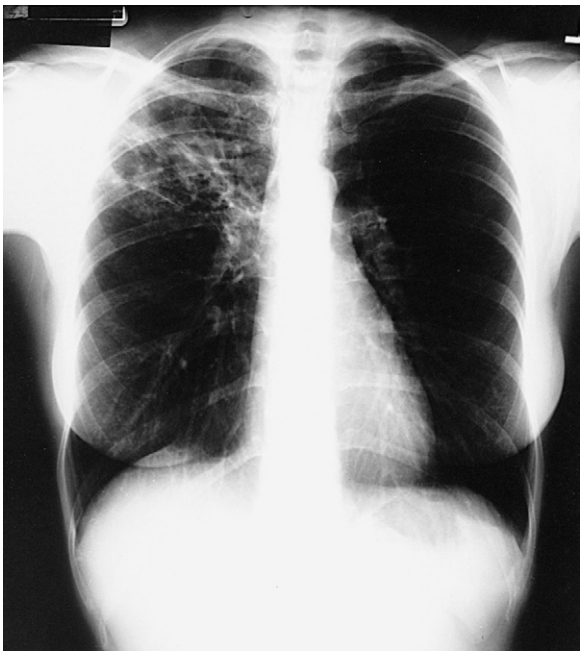


Figure 16-2 Chest radiograph showing right apical infiltrate typical of a patient with primary tuberculosis.
(From Fitzgerald D, Sterling T, Haas D. Mycobacterium tuberculosis. In Mandell GL, Bennett JE, Dolin R (eds). Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 7th ed. Philadelphia, Churchill Livingstone, 2010, p 3141.)

Diagnosis

The diagnosis of pulmonary TB is made by the demonstration of acid-fast bacilli (AFB) in sputum and the growth of *M. tuberculosis* in culture. These patients typically have an abnormal chest radiograph, as previously described. *M. tuberculosis* is a slow-growing bacterium, and cultures can take up to 6 weeks to grow. A PCR assay developed for *M. tuberculosis* can be run on AFB smear–positive sputum to hasten the diagnosis of pulmonary TB. A positive PCR on AFB-positive sputum is diagnostic of pulmonary TB, but a negative test does not rule out the diagnosis.

Table 16-5 Clinical Manifestations of Active Tuberculosis in Early verus Late* Human Immunodeficiency Virus Infection

Sign	Early	Late
Tuberculin test	Usually positive	Usually negative
Adenopathy	Unusual	Common
Pulmonary distribution	Upper lobe	Lower and middle lobes
Cavitation	Often present	Typically absent
Extrapulmonary disease	10%-15% of cases	50% of cases

Modified from Murray JF. Cursed duet: HIV infection and tuberculosis. Respiration 1990;57:210-220.
*For practical purposes, "early" and "late" may be defined as CD4+ cell counts >300 cells/mm^3 and <200 cells/mm^3, respectively.

Treatment

Patients with AFB positive smears from sputum samples should be started on anti-TB therapy while awaiting results of PCR and cultures. The treatment of TB always uses multiple agents with anti-TB activity. Single agents should never be used. The standard first-line agents are isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) (Figure 16-3 and Table 16-6). If administered, INH should be given with pyridoxine (vitamin B_6; 25-50 mg orally daily) to prevent neuropathy. Treatment of active pulmonary TB is generally for 6 months regardless of HIV status, but treatment may need to be extended in certain situations.

Directly observed therapy (DOT) is the preferred mechanism of administration to ensure compliance. Many local county and state health departments have systems for DOT. Treatment of HIV-seropositive patients with TB who are receiving an antiretroviral (ARV) regimen that contains a protease inhibitor is complicated by the latter's interaction with rifamycins (particularly rifampin). Management of such patients should be coordinated with an infectious diseases specialist, who also should manage drug-resistant TB treatment.

Latent Tuberculosis Infection and Purified Protein Derivative

In the United States, latent tuberculosis infection (LTBI) is the most prevalent form of tuberculosis. LTBI is the term given to patients with a positive purified protein derivative (PPD) skin test without evidence of active TB. PPD has been used for more than 100 years and relies on delayed-type hypersensitivity (DTH) to *M. tuberculosis* cellular proteins.

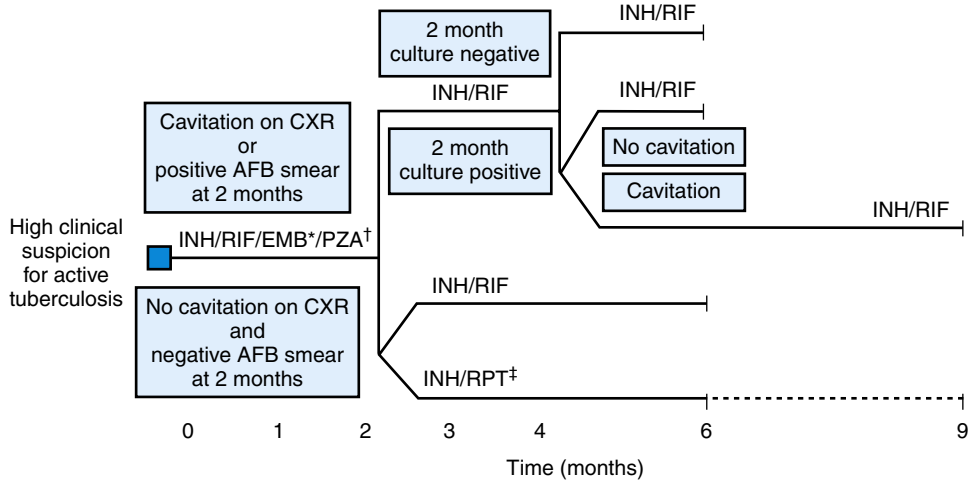


Figure 16-3 Treatment algorithm for tuberculosis. Patients in whom TB is proved or strongly suspected should have treatment initiated with isoniazid, rifampin, pyrazinamide, and ethambutol for the initial 2 months. A repeat smear and culture should be performed when 2 months of treatment has been completed. If cavities were seen on the initial chest radiograph or the acid-fast smear is positive at completion of 2 months of treatment, the continuation phase of treatment should consist of isoniazid and rifampin daily or twice weekly for 4 months to complete a total of 6 months of treatment. If cavitation was present on the initial chest radiograph and the culture at completion of 2 months' therapy is positive, the continuation phase should be lengthened to 7 months (total of 9 months of treatment). If the patient has HIV infection and the CD4+ cell count is less than 100/mm^3, the continuation phase should consist of daily or three-times-weekly isoniazid and rifampin. In HIV-uninfected patients having no cavitation on chest radiograph and negative acid-fast smears at completion of 2 months of treatment, the continuation phase may consist of either once-weekly isoniazid and rifapentine, or daily or twice-weekly isoniazid and rifampin, to complete a total of 6 months *(bottom)*. Patients receiving isoniazid and rifapentine, and whose 2-month cultures are positive, should have treatment extended by an additional 3 months (total of 9 months).
*EMB may be discontinued when results of drug susceptibility testing indicate no drug resistance. †PZA may be discontinued after it has been taken for 2 months (56 doses).
‡RPT should not be used in HIV-infected patients with TB or in patients with extrapulmonary TB. Therapy should be extended to 9 months if 2-month culture is positive.
AFB, Acid-fast bacilli; *CXR,* chest radiograph (x-ray); *EMB,* ethambutol; *INH,* isoniazid; *PZA,* pyrazinamide; *RIF,* rifampin; *RPT,* rifapentine.
From Centers for Disease Control and Prevention (CDC). Treatment of tuberculosis. American Thoracic Society, CDC, and Infectious Diseases Society of America. MMWR 2003;52(RR-11):1-88.

Because PPD relies on DTH, any factor that reduces the DTH affects the host response to PPD. The most common clinical example is use of corticosteroids, which blunt the DTH response and can complicate PPD interpretation. Therefore, PPD testing should not be performed while a patient is taking corticosteroids. Also, TB testing should be targeted to those with higher risk of infection and should not routinely be done in those with low risk (ATS/CDC, 2000).

The PPD can also give false-positive results in patients with previous bacille Calmette-Guérin (BCG) vaccination or with infection by other mycobacterial infections. In the United States, this may cause difficulties in testing immigrants from countries who routinely use BCG vaccination programs. However, previous BCG vaccination should not change the interpretation of the PPD or willingness to treat such individuals accordingly.

Table 16-6 Recommended Treatment Regimens for Pulmonary Tuberculosis

Initial Phase			Continuation Phase			Rating* (Evidence)†	
Drugs	Interval and doses‡ (minimal duration)	Regimen	Drugs	Interval and doses‡ § (minimal duration)	Range of total doses (minimal duration)	HIV Positive	HIV Negative
Regimen 1							
INH RIF PZA EMB	7 days per week for 55 doses (8 wk) or 5 d/wk for 40 doses (8 wk)¶¶	1a	INH/RIF	7 d/wk for 126 doses (18 wk) or 5 d/wk for 90 doses (18 wk)¶	182-130(26 wk)	A (I)	A (II)
		1b	INH/RIF	Twice weekly for 36 doses(18 wk)	92-76(26 wk)	A (I)	A (II)¶
		1c**	INH/RPT	Once weekly for 18 doses(18 wk)	74-58(26 wk)	B (I)	E (I)
Regimen 2							
INH RIF PZA EMB	7 days per week for 14 doses (2 wk), then twice weekly for 12 doses (6 wk) or 5 d/wk for 10 doses (2 wk),¶ then twice weekly for 12 doses (6 wk)	2a	INH/RIF	Twice weekly for 36 doses (18 wk)	62-58(26 wk)	A (II)	B (II)¶
		2b**	INH/RPT	Once weekly for 18 doses(18 wk)	44-40(26 wk)	B (I)	E(I)
Regimen 3							
INH RIF PZA EMB	Three times weekly for 24 doses (8wk)	3	INH/RIF	Three times weekly for 54 doses (18wk)	78 (26 wk)	B (I)	B(II)
Regimen 4							
INH RIF EMB	7 days per week for 56 doses (8wk) or 5d/wk for 40 doses (8wk) ¶	4a	INH/RIF	7 days per week for 217 doses (31wk) or 5d/wk for 155 doses (31 wk)¶¶	273-195(39 wk)	C (I)	C (III)
		4b	INH/RIF	Twice weekly for 62 doses (31wk)	118-102(39 wk)	C (I)	C (III)

From American Thoracic Society, CDC, Infectious Diseases Society of America. Treatment of tuberculosis. MMWR 2003;52:1-77.
DOT, Directly observed therapy; *EMB,* ethambutol, *INH,* isoniazid; *PZA,* pyrazinamide; *RIF,* rifampin; *RPT,* rifapentine.
*Definitions of evidence ratings: *A,* preferred; *B,* acceptable alternative; *C,* offer when A and B cannot be given; *E,* should never be given.
†Definition of evidence ratings: *I,* randomized clinical trial; *II,* data from clinical trials that were not randomized or were conducted in other populations; *III,* expert opinion.
‡When DOT is used, drugs may be given 5 days per week and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicates this would be an effective practice.
§Patients with cavitation on initial chest radiograph and positive cultures on completion of 2 months of therapy should receive a 7-month (31 weeks, either 217 doses [daily] or 62 doses [twice weekly]) continuation phase.
¶Five-days-a-week administration is always given by DOT. Rating for 5 day per week regimens is AIII.
¶¶Not recommended for HIV-infected patients with CD4+ cell counts <100 cells/μL.
**Options 1c and 2b should be used only in HIV-negative patients who have negative sputum smears at completion of 2 months of therapy and who do not have cavitation on initial chest radiograph. For patients started on this regimen and found to have a positive culture from the 2-month specimen, treatment should be extended an extra 3 months.

The DTH response can wane over time. To overcome this problem, nonreacting patients may undergo repeat PPD 1 week after their initial PPD. The diagnosis of LTBI is made by interpretation of a PPD and by ascertaining the patient's risk factors for progression to active TB if left untreated (Box 16-3). Interpretation of the PPD should be based on the area of induration and not the area of surrounding erythema. Persons whose PPDs have converted from negative to positive within 2 years are presumed to have been infected recently. The decision to use PPD means treating the patient for LTBI if the PPD test is positive.

Patients at increased risk for progression to active TB include those who have been recently infected (recent PPD converters); patients who are HIV seropositive; patients who have silicosis, diabetes, or chronic renal failure (including those receiving hemodialysis); solid-organ transplant recipients; patients with gastrectomy or jejunoileal bypass or head and neck cancer; injection drug users; patients with chest radiograph evidence of prior TB; and patients who weigh at least 5% less than ideal body weight. Patients taking chronic corticosteroid therapy and those who are to receive tumor necrosis factor alpha (TNF-α) blockers (e.g., infliximab) are also at risk. Patients taking corticosteroids also have higher risk of progression to active TB with larger doses and longer courses of corticosteroids.

Standard therapy for LTBI is INH, 300 mg orally daily for 9 months, regardless of HIV status. Again, INH should always be administered with pyridoxine to prevent neuropathy.

Interferon-γ Release Assays

To overcome the false-positive results and confusion of PPD testing in certain populations, newer interferon-gamma (IFN-γ) release assays such as the Quantiferon-TB Gold (QFT-G) test have been developed to detect latent *M. tuberculosis*. QFT-G quantifies the release of IFN-γ from lymphocytes of the host's blood in response to three *M. tuberculosis* target antigens that are absent from BCG and most other nontuberculous *Mycobacterium* spp. The advantages of using QFT-G include one-time blood testing without the need for follow-up visit, no triggering of amnestic responses, and possibly more specific response to *M. tuberculosis*. However, QTF-G use in immunocompromised or anergic patients is limited, with indeterminate results. Some studies also show discordant results in individuals tested with both PPD and QTF-G. In general, QTF-G may be used in all circumstances in which the PPD is used. However, whether the QTF-G is truly more specific or sensitive than the PPD in latent or active TB is yet to be determined.

Box 16-3 Criteria for Tuberculin Positivity by Risk Group

Reaction ≥5mm of Induration

HIV-positive persons

Recent contacts of tuberculosis patients

Fibrotic changes on chest radiography consistent with prior tuberculosis

Patients with organ transplants and other immunosuppressed patients (receiving equivalent of ≥15 mg/day of prednisone for at least 1 month)

Reaction ≥10 mm of Induration

Recent immigrants (within 5 years) from high-prevalence countries

Injection drug users

Residents and employees of high-risk congregate settings (prisons and jails, nursing homes, hospitals and other health care facilities, residential facilities for patients with AIDS, and homeless shelters)

Children less than 4 years of age, or infants, children, and adolescents exposed to adults at high risk.

Reaction ≥15 mm of Induration

Person with no risk factors for tuberculosis

Modified from Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. MMWR 2000;49(RR-6):1-51.

KEY TREATMENT

The treatment of choice for latent TB infection is daily isoniazid (INH) for 9 months (ATS/CDC, 2000) (SOR: A).

Short-course rifampin (Rifadin) plus INH (3 months) is equivalent to standard INH therapy and may increase compliance in patients with latent TB infection (Ena and Valls, 2005) (SOR: B).

Although uncommon in the United States, drug-resistant TB and multidrug-resistant TB underscore the need for combination drug therapy and directly observed therapy in patients with tuberculosis (CDC, 2007) (SOR: C).

SEXUALLY TRANSMITTED INFECTIONS

David R. McBride

Key Points

- The U.S. Preventive Services Task Force recommends "high-intensity" behavioral counseling to at-risk adults and adolescents to prevent sexually transmitted infections.
- Be specific in addressing patients' sexual practices so as to provide appropriate prevention advice.
- Regular screening for *Chlamydia* infection is recommended for all sexually active women under age 24, all pregnant women under 24, and at-risk pregnant and nonpregnant women over 24.
- The presence of STIs such as gonorrhea, *Chlamydia,* and herpes increases the likelihood of HIV transmission.
- Testing for HIV should be offered on an "opt out" basis in all health care settings.
- The majority of patients with herpes simplex virus infection will not show recognizable symptoms. Screening for HSV immunity is of questionable value.
- Urine is an acceptable specimen to test for gonorrhea and *Chlamydia* in both men and women.
- The human papillomavirus vaccine is effective in reducing incidence of HPV infection, and physicians should discuss the vaccine with young women and men and their families.
- Routine screening for the mere presence of HPV is not recommended outside the context of cervical cancer screening.

The CDC estimates that 19 million new cases of *sexually transmitted infections* (STIs) occur each year. More than half are in young people age 15 to 24 years. The most important

development in the primary prevention of STIs is immunization against human papillomavirus (HPV). The vaccine can prevent infection with certain strains of HPV that cause cervical cancer and genital warts. Trials are ongoing to determine the effectiveness of daily ARV therapy in preventing transmission of HIV. Vaccination investigation is ongoing for herpes simplex, *Chlamydia trachomatis,* and HIV. This breadth of research effort holds promise for the future in the prevention of STIs.

Prevention

The USPSTF recommends "high-intensity" behavioral counseling to at-risk adults and adolescents to prevent STIs. High-intensity counseling involves multiple sessions and often is delivered to groups of patients. Unfortunately, this type of intervention has limitations in its practicality for population-based delivery. No risk of harm was discovered in the delivery of counseling for STI prevention.

Vaccination is the most important form of primary prevention of common infectious diseases. Two vaccines are currently on the market for HPV prevention—one that protects against four viral subtypes (6,11,16,18) and is licensed for use in males and females 9 to 26 years of age, and the other against two subtypes (16,18), licensed for females 10 to 25 years of age. Hepatitis B is a sexually transmitted infection, and immunization is recommended for adolescents who have not been previously inoculated. This is a requirement in many states for school entry. Hepatitis A can be transmitted by oro-anal sexual contact, and vaccination should be offered to patients who are contemplating engaging in this sexual practice.

Recommendations surrounding the use of barrier methods for STI prevention should be tailored to the sex practices of the client. For example, a percentage of women use anal sex as a method of birth control but may not consider the need for condom use with this practice. The question, "Do you regularly use condoms?" has little relevance to infection control for many sexual practices. Evidence supports the advice to use barrier methods of latex or other approved material in a manner that prevents the exchange of blood and body fluids in decreasing STIs. Condoms confer a 30% risk reduction for herpes simplex and up to an 80% risk reduction for HIV, when used correctly (Weller and Davis-Beaty, 2002; Martin et al., 2009).

The secondary prevention of STIs is achieved through direct and nonjudgmental patient assessment and screening and avoiding assumptions about patient sexual practices. Screening is a tool to prevent the inadvertent spread of infection as well as the sequelae of undetected disease. Table 16-7 summarizes USPSTF and CDC recommendations for screening of STIs.

Table 16-7 Recommendations for the Screening of Sexually Transmitted Infections (STIs)

STI	Who to Screen?	Recommending Body
Chlamydia	All sexually active women under age 24. Women over 24 at increased risk. All pregnant women under 24 and those over 24 at increased risk. Insufficient evidence for or against screening men.	USPSTF
Gonorrhea	All sexually active women at increased risk. Insufficient evidence for screening women not at increased risk. Insufficient evidence for or against screening men at increased risk.	USPSTF
Syphilis	Strongly recommended for pregnant women and all patients at increased risk.	USPSTF
HIV	All individuals as a routine part of health care in all settings after informing the patient. Pregnant women as standard prenatal testing.	CDC
Herpes	Recommendation against screening for asymptomatic individuals.	USPSTF
Hepatitis B	Strongly recommended for pregnant women at their first prenatal visit.	USPSTF

Modified from US Preventive Services Task Force (USPSTF). Guide to Clinical Preventive Services, 2009. http://www.ahrq.gov/clinic/pocketgd09/pocketgd09.pdf; and Branson B et al. Revised recommendations for HIV testing of adults, adolescents and pregnant women in health-care settings. MMWR 2006;55(RR-14):1-17.

Genital Ulcers

Infectious genital ulcers are associated with herpes simplex virus (HSV), syphilis, chancroid, lymphogranuloma venereum, and granuloma inguinale. HSV is by far the most common, affecting 50 million people in the United States. HSV-1 and HSV-2 are chronic, neurotropic viral infections that enter through epithelium and come to rest in the dorsal root ganglia. Therefore, infection leads to lifetime presence of the virus, but the clinical manifestation of this condition is variable. A small percentage of those with serologic evidence of HSV-2 (10%-25%) have had symptoms of clinical herpes infection. In addition, patients with HSV infection can shed the virus in the absence of symptoms, creating a prime opportunity for spread.

Herpes Simplex

Herpes simplex outbreak may be followed by a prodrome of malaise, fever, and regional lymphadenopathy before the appearance of grouped vesicles on an erythematous base. The vesicles are typically quickly broken and become ulcerated in appearance, with each vesicle usually less than several millimeters in size. True first-time infections tend to present more severely than secondary presentations of previously infected individuals, with a prodrome present in 80% of cases.

The lesions can be in any location around the genitals or rectum, on the proximal thighs and buttocks, inside the vagina, and in and around the mouth. The lesions are most

often painful, particularly when on mucosal surfaces, or itchy. In women, herpes simplex can present with cervicitis-like symptoms with bleeding and discharge and cervical ulcerations on examination, or simply mucopurulent cervicitis. Herpetic lesions around the urethra tend to be extremely painful and can make urination difficult. Rectal HSV can be confused with irritation, perianal fissure, and even candidiasis because of its often beefy-red appearance and itching.

Vesicles typically appear 6 days after infection and can last up to 2 weeks in an initial infection. Subsequent outbreaks tend to have a shorter duration and to be less uncomfortable for patients. Confirmation of infection is helpful, but the diagnosis can be made primarily on the clinical appearance of the exanthema. Vigorous sample collection from an ulcer (which the patient may not appreciate) to be sent for PCR identification and typing is the most readily available method of laboratory diagnosis. Serum antibody testing is not useful in the initial HSV diagnosis because antibody levels will not be appreciable early in infection. The appearance of convalescent immunoglobulin G (IgG) and IgM levels several weeks after a suspected outbreak might help to support the diagnosis of HSV infection.

The value of screening for HSV immunity is debatable and should generally not be recommended for asymptomatic individuals. In addition, the USPSTF recommends against screening asymptomatic pregnant women for HSV to prevent transmission to the newborn. Given that many patients with HSV infection never manifest symptoms, the value of knowing that one is HSV seropositive is questionable. In addition, HSV-1 and HSV-2, although classically oral and genital, respectively, can "mix and match" based on sexual practices. It is often confusing for asymptomatic individuals to know that they have HSV antibody (Do I have cold sores? Do I have genital herpes? How should this change the way I live my life?). In monogamous couples with one partner known to be HSV positive and the other with unknown status, testing of the latter may indicate suppressive therapy in the seropositive partner if the other is found to be negative.

Regular barrier method use decreases transmission of herpes in both men and women, with patients using condoms 100% of the time having a 30% reduction in HSV acquisition from those who never use condoms (Martin et al., 2009). Serodiscordant couples may also decrease transmission through antiviral suppressive therapy to the HSV-positive partner (Table 16-8).

Syphilis

Syphilis is a spirochetal infection that has resurged since 2001, the nadir year since 1996. Syphilis infection rates are highest in men who have sex with men. Syphilis is much less common than the other STIs, with an infection rate of 5.6 per 100,000 population in the United States (vs. 496 per 100,000 for *Chlamydia*).

Syphilis presents in several stages. The *primary* phase of syphilis is a painless ulcer called a *chancre* (Figure 16-4). The chancre may be visible on the genitals, although it can also be inside the vagina, mouth, or rectum, making it difficult to find. This lesion will appear within 3 weeks of transmission and will last for several weeks untreated. The *secondary* phase of infection is disseminated and involves a diffuse macular rash, typically with palm and sole lesions, generalized lymphadenopathy, fever, and condyloma latum (smooth, moist lesions on genitals without cauliflower appearance of condyloma acuminatum). *Tertiary* syphilis is often asymptomatic but affects the heart, eyes, and auditory system and can be associated with gumma formation. *Gummas* are soft, granulomatous growths in organs that can cause mechanical obstruction and weakening of blood vessel walls. Latent infection often involves the CNS.

Diagnosis of primary syphilis is challenging. The test of choice is darkfield microscopy, which is not readily available. Direct fluorescent (monoclonal) antibody (DFA) testing may be available. Antibody tests for syphilis, such as the rapid plasma reagin (RPR) and the less frequently used Venereal

Table 16-8 Treatment Guidelines for Herpes Simplex Infection

Drug	Initial Outbreak	Suppression	Recurrence
Acyclovir	400 mg tid for 7-10 days	400 mg bid	400 mg tid for 5 days 800 mg bid for 5 days 800 mg tid for 2 days
Valacyclovir	1.0 g bid for 7-10 days	500 mg once daily 1.0 g once daily	500 mg bid for 3 days 1.0 g once daily for 5 days
Famciclovir	250 mg tid for 7-10 days	250 mg bid	125 mg bid for 5 days 1.0 g bid for 1 day

Data from Centers for Disease Control and Prevention. Sexually transmitted disease treatment guidelines, 2010. MMWR 2010;59(No. RR-12).
tid, Three times daily; *bid*, twice daily.

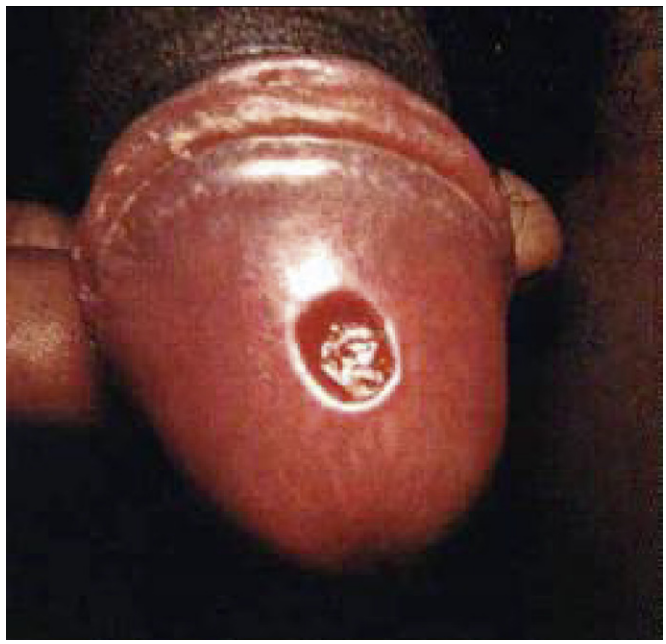


Figure 16-4 Primary chancre of syphilis.
(From http://www.stdptc.uc.edu/system/files/images/syphilisprimary%20chancre%20of%20glans.thumbnail.jpg.)

Disease Research Laboratories (VDRL), are often not positive early in infection and thus cannot be used to rule out primary syphilis based on a single reading. Treponemal antigen testing (EIA) may be available in some laboratories. The fluorescent treponemal antibody absorption (FTA-ABS) test may also be negative in the early infection. Direct PCR for primary syphilis lesions has been tested but is not yet FDA approved. A physician may choose to treat presumptively if a painless chancre and risk factors are present and may then do a convalescent RPR test in 1 to 2 weeks to confirm the infection by the appearance of a positive reaction. One would expect a fourfold change in titer of either test to indicate the presence of disease.

Primary and secondary syphilis are treated with a single injection of penicillin G, 2.5 million units. Other regimens do not have proven effectiveness but can be used in the penicillin-allergic patient, including doxycycline, 100 mg twice daily for 14 days; ceftriaxone, 500 mg to 1 g intramuscularly (IM) daily for 8 to 10 days; or azithromycin, 2 g as a single oral dose, although resistance to azithromycin has been observed. Patients treated for primary syphilis should have periodic clinical follow-up and serologic testing to determine a fourfold decrease in RPR reactivity within 6 months.

Latent syphilis can be either *early,* meaning infection within the last year, or *late,* meaning infection beyond a year. Early latent syphilis is treated with a single injection of penicillin G, 2.4 million units. Syphilis of late latency or unknown duration is treated with three injections of penicillin G, 2.4 million units, in 3 consecutive weeks. For penicillin-allergic patients, doxycycline, 100 mg twice daily for 28 days, is required. Those with latent syphilis should have ophthalmic examination as well as evaluation for vascular gumma formation. Suspected neurologic involvement of latent syphilis must be evaluated with cerebrospinal fluid (CSF) examination and treatment with aqueous penicillin G, 3-4 million units intravenously (IV) every 4 hours for 10 to 14 days.

Partners of patients with newly diagnosed syphilis are at risk for infection. Partners within 90 days of a diagnosis of primary syphilis should be tested, but treated presumptively even if serologic testing is negative. For partners prior to 90 days before diagnosis, serology is generally reliable in detecting presence of infection and may guide treatment. Patients with secondary syphilis should inform partners within 6 months before diagnosis, or 12 months for those diagnosed with tertiary syphilis (Table 16-9).

Table 16-9 Diagnosis and Treatment of Syphilis

Stage	Clinical Manifestations	Diagnosis (Sensitivity)	Treatment
Primary syphilis	Chancre	Darkfield microscopy of skin lesion (80%) Nontreponemal tests (78%-86%) Treponemal-specific tests (76%-84%)	Penicillin G benzathine, 2.4 million units IM (single dose) Alternatives in nonpregnant patients with penicillin allergy: doxycycline (Vibramycin), 100 mg PO bid for 2 weeks; tetracycline, 500 mg PO four times daily for 2 weeks; ceftriaxone (Rocephin), 1 g IM or IV once daily for 8-10 days; *or* azithromycin (Zithromax), 2 g PO (single dose)
Secondary syphilis	Skin and mucous membranes: diffuse rash, condyloma latum, other lesions Renal system: glomerulonephritis, nephrotic syndrome Liver: hepatitis CNS: headache, meningismus, cranial neuropathy, iritis, uveitis Constitutional symptoms: fever, malaise, generalized lymphadenopathy, arthralgias, weight loss, others	Darkfield microscopy of skin lesion (80%) Nontreponemal tests (100%) Treponemal-specific tests (100%)	Same treatments as for primary syphilis
Latent syphilis	None	Nontreponemal tests (95%-100%) Treponemal-specific tests (97%-100%)	Early latent syphilis: same treatments as for primary and secondary syphilis Late latent syphilis: penicillin G benzathine, 2.4 million units IM once weekly for 3 weeks Alternatives in nonpregnant patients with penicillin allergy: doxycycline, 100 mg PO bid for 4 weeks, *or* tetracycline, 500 mg PO four times daily for 4 weeks
Tertiary (late) syphilis	Gummatous disease, cardiovascular disease	Nontreponemal tests (71%-73%) Treponemal-specific tests (94%-96%)	Same treatment as for late latent syphilis
Neurosyphilis	Seizures, ataxia, aphasia, paresis, hyperreflexia, personality changes, cognitive disturbance, visual changes, hearing loss, neuropathy, loss of bowel or bladder function, others	Cerebrospinal fluid examination	Aqueous crystalline penicillin G, 3-4 million units IV q4h for 10-14 days, *or* penicillin G procaine, 2.4 million units IM once daily, plus probenecid, 500 mg PO four times daily, both drugs given for 10-14 days

Data from Brown DL, Frank JE. Diagnosis and management of syphilis. Am Fam Physician , 2003;68:283-290.
IM, Intramuscularly; *IV,* intravenously, *PO,* orally; *q4h,* every 4 hours; *CNS,* central nervous system.

Chancroid

Chancroid may occur in regional outbreaks and presents with a painful genital ulcer and suppurative regional adenopathy. Herpes and syphilis should both be ruled out in the patient suspected of having chancroid infection. Chancroid is caused by *Haemophilus ducreyi* and there is currently no FDA approved test to directly detect this organism. Treatment with azithromycin (1 g as single dose), ceftriaxone (250 mg IM as a single dose), ciprofloxacin (500 mg twice daily for 3 days), or erythromycin (500 mg three times daily for 7 days) are all alternatives (Table 16-10). It may be necessary to perform incision and drainage on fluctuant inguinal nodes. Patients should be reexamined in 1 to 2 weeks to ensure healing of the primary ulcer(s) and resolution of the adenopathy. Partners who had contact with the infected patient starting 10 days before development of the patient's symptoms should be treated, regardless of the presence of symptoms.

Table 16-10 Treatment of Chancroid, Lymphogranuloma Venereum, and Granuloma Inguinale

Infection	Recommended Treatment	Alternate Treatment
Chancroid	Azithromycin, 1 g PO × 1 *or* Ceftriaxone, 250 mg IM single dose *or* Ciprofloxacin, 500 mg bid for 3 days *or* Erythromycin base, 500 mg tid for 7 days	—
Lymphogranuloma venereum	Doxycycline, 100 mg bid for 21 days	Erythromycin base, 500 mg PO four times daily for 21 days
Granuloma inguinale	Doxycycline, 100 mg bid for at least 3 weeks until all lesions have completely healed	Azithromycin, 1 g PO once weekly for 3 weeks until all lesions have completely healed *or* Ciprofloxacin, 750 mg PO four times daily for at least 3 weeks until all lesions have completely healed *or* Erythromycin base, 500 mg four times daily for at least 3 weeks until all lesions have completely healed *or* TMP/SMX, 1 DS bid for at least 3 weeks *or* until all lesions have completely healed

PO, Orally; *IM,* intramuscularly; *bid,* twice daily; *tid,* three times daily; *qid,* four times daily; *TMP-SMX,* trimethoprim-sulfamethoxazole; *DS,* double-strength tablet.

Lymphogranuloma Venereum and Granuloma Inguinale

Less common ulcerating STIs include lymphogranuloma venereum (LGV) and granuloma inguinale (Figure 16-5). LGV causes regional adenopathy and often an ulcer at the point of entry. Rectal LGV may cause a proctocolitis with anal pain, discharge, bleeding, and diarrhea. LGV is caused by *Chlamydia trachomatis* serotypes and can be detected by testing swabbed material from open lesions or aspirates from lymph nodes with culture, DFA, or nucleic acid detection. Treatment is noted above (Table 16-10). Granuloma inguinale, caused by *Klebsiella granulomatis,* is rare in the United States and causes progressive ulcerative disease of the genitals.

Urethritis and Cervicitis

A second STI category includes those causing the clinical presentation of vaginal discharge, pelvic pain, dyspareunia, and dysuria in women and penile discharge and dysuria in men, as well as possible rectal pain and discharge in men and women. Of this group, *Chlamydia trachomatis* is the most common, causing 1.2 million infections in the United States in 2008 (CDC, 2009). In fact, *Chlamydia* is the most frequently reported reportable infection.

Chlamydia trachomatis

The majority of women with *Chlamydia* infection are without symptoms. Many men are asymptomatic as well. Regular screening for *Chlamydia,* as recommended by the USPSTF, can significantly reduce the incidence of pelvic inflammatory disease (PID), one of the most serious sequelae of untreated infection. In women with untreated *Chlamydia* infection, in addition to PID, tubo-ovarian abscess, tubal scarring and ectopic pregnancy, and infertility can all result.

As previously mentioned, regular screening is currently recommended for all sexually active women under age 24, all pregnant women under 24, and at-risk pregnant and nonpregnant women over 24. *Chlamydia* testing can be performed on several liquid-based Papanicolaou (Pap) tests.

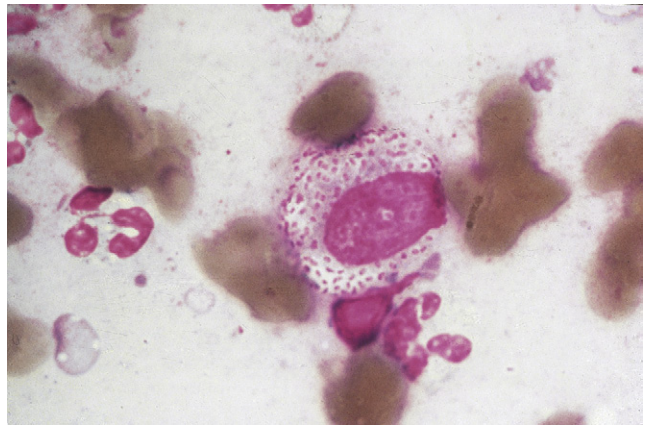


Figure 16-5 Biopsy of granuloma inguinale lesion revealing "Donovan bodies" consistent with *Klebsiella granulomatis.*
(From Mandell GL, Bennett JE, Dolin R (eds). Mandell, Douglas, and Bennett's Principles and Practices of Infectious Diseases, 7th ed. Philadelphia, Churchill Livingstone, 2010.)

Endocervical swabs for nucleic acid amplification are acceptable when a conventional Pap smear is being used. Given the recent liberalization of recommendations about Pap testing for women under 21 years of age, urine nucleic acid amplification is a readily available alternative for *Chlamydia* testing. This can easily be done at a contraceptive counseling clinic. Urine testing is also an acceptable method of testing for men, in addition to a urethral swab. Rectal *Chlamydia* infection can occur in individuals who practice receptive anal intercourse. An FDA-approved method of testing should be used for screening and diagnosis of this infection.

Asymptomatic *Chlamydia* infection is treated with either a single dose of azithromycin, 1 g orally, the drug of choice, or doxycycline, 100 mg twice daily, for 7 days (Table 16-11). *Patient-delivered partner therapy* (PDPT), the practice of dispensing treatment to diagnosed patients to treat their partner(s), has proved effective in reducing reinfection rates and further spread of infection. EPT is legally allowable in 21 states and potentially allowable in another 21.

Chlamydia infection may present symptomatically in men or women with symptoms of dysuria and with discharge and with pelvic pain and dyspareunia in women. The discharge of *C. trachomatis*, versus that of *Neisseria gonorrhoeae*, is said to be more mucoid than purulent, although this characteristic is not specific enough to provide diagnostic accuracy. Symptomatic *Chlamydia*, without evidence of PID, is treated the same as asymptomatic infection. Many practitioners will treat presumptively for *Chlamydia* and gonorrhea in patients who present with the symptoms previously mentioned while they wait for confirmatory testing.

Table 16-11 Treatment of Urethritis and Cervicitis

Infection	Recommended Treatment	Alternate Treatment
Chlamydia trachomatis	Azithromycin, 1 g PO × 1 *or* Doxycycline, 100 mg bid for 7 days	Erythromycin base, 500 mg PO four times daily for 7 days *or* Ofloxacin, 300 mg PO bid for 7 days *or* Levofloxacin, 500 mg PO once daily for 7 days
Neisseria gonorrhoeae: urethral, cervical, or rectal	Ceftriaxone, 125 mg IM × 1 Treat for *C. trachomatis* concurrently if this has not been ruled out.	Cefixime, 400 mg PO single dose
Neisseria gonorrhoeae: pharynx	Ceftriaxone, 125 mg IM × 1 *or* Treat for *C. trachomatis* concurrently if this has not been ruled out.	—
Nongonococcal urethritis	Azithromycin, 1 g PO single dose *or* Doxycycline, 100 mg PO bid for 7 days	Erythromycin base, 500 mg PO qid for 7 days *or* Ofloxacin, 300 mg PO bid for 7 days *or* Levofloxacin, 500 mg PO daily for 7 days
Trichomonas vaginalis	Metronidazole, 1 g PO × 1 *or* Tinidazole, 2 g PO × 1	—

Modified from Centers for Disease Control and Prevention. Sexually transmitted disease treatment guidelines, 2010. MMWR 2010;59(No. RR-12).

Neisseria gonorrhoeae

Neisseria gonorrhoeae infection may be asymptomatic in both men and women. The current USPSTF recommendation is for screening women at risk. Men with penile gonorrhea typically present with purulent penile discharge and dysuria with *N. gonorrhoeae* infection. Mucopurulent discharge, dysuria, pelvic pain, and dyspareunia are typical symptoms in women. In patients who engage in anal intercourse, anal discharge, rectal pain, and bleeding can be presenting symptoms. Gonococcal pharyngitis is within the differential of exudative pharyngitis in sexually active patients. When symptomatic, throat pain, tonsillar exudates, and anterior cervical adenopathy may be present.

Testing for gonorrhea can be done using liquid-based Pap technologies, cervical or urethral swabs, or urine for nucleic acid amplification. In men with visible discharge, a Gram stain with white blood cells (WBCs) and gram-positive intracellular diplococci has a high degree of sensitivity. Culture testing may be preferred for suspected pharyngeal and rectal specimens pending FDA approval of other methods.

Again, physicians may opt to treat patients with mucopurulent cervicitis or urethritis presumptively for gonorrhea and *Chlamydia* while waiting for confirmatory testing. Fluoroquinolone therapy is no longer recommended because of widespread resistance (Table 16-11).

Because reinfection with gonorrhea is common for several months after treatment, it may be advisable to retest patients with confirmed gonorrhea in the 3 months after treatment. Similarly, STIs may be an indicator of risk behavior, and a complete risk history and testing for other STIs is advisable if not completed at the initial visit.

Nongonococcal Urethritis

In male patients with symptomatic urethritis, a causative agent may not be identified, a situation often referred to as nongonococcal urethritis (NGU). Technically, *Chlamydia* is included in this category. Organisms such as *Ureaplasma urealyticum* and *Mycoplasma genitalium* may be the cause and may be difficult to detect. Treatment for these infections is the same as for symptomatic *Chlamydia*, with azithromycin or doxycycline (Table 16-11). It is recommended that partners of patients with NGU should be evaluated and treated. In some cases, testing of partners may detect a specific organism as the cause of infection (e.g., *Chlamydia*).

Trichomonas vaginalis

Trichomonas vaginalis causes vaginitis in women, who may have a stereotypic frothy, green, and foul-smelling discharge. Many women are asymptomatic with trichomoniasis. In addition to causing asymptomatic infection in men, *T. vaginalis* may cause urethritis. This organism may be suspected in men when patients have repeated treatment failures and

no other explanation for symptoms. Microscopic examination of vaginal discharge is 60% to 70% sensitive in women. A first voided urine specimen or urethral swab for microscopic exam may be helpful in identifying the protozoa. Culture for *Trichomonas,* which requires a special medium, may be necessary to identify this infection accurately in men. *Trichomonas* is effectively treated with a single 2-g dose of metronidazole (Table 16-11).

For non-STI causes of vaginal discharge, see the online discussion at www.expertconsult.com.

Pelvic Inflammatory Disease

Pelvic inflammatory disease can be caused by a number of organisms, including *Chlamydia,* and presents with pelvic pain and discharge. Findings that contribute to the diagnosis of PID include fever greater than 101° F, cervical or vaginal mucopurulent discharge, abundant WBCs on saline preparation of vaginal discharge, elevated erythrocyte sedimentation rate (ESR), elevated C-reactive protein (CRP), and evidence of *N. gonorrhoeae* or *C. trachomatis* infection. Hospitalization with parenteral antibiotics may be necessary in pregnant patients, patients in whom surgical emergency cannot be ruled out, those who do not respond to oral treatment, those who cannot tolerate oral treatment, and patients who have severe illness or tubo-ovarian abscess. When treating PID parenterally, improvement of symptoms for 24 hours may prompt a change to oral therapy (Table 16-12). Conversely, if oral therapy is not producing significant improvement within 2 to 3 days, admission for parenteral therapy may be necessary.

Human Papillomavirus

Patient awareness of human papillomavirus infection has greatly increased in recent years, in large part related to the patient-directed advertising of the HPV vaccine. HPV is likely the most common STI. Thirty types of HPV can infect the genital area, some causing genital warts, some causing malignancies of the genital organs, and most being asymptomatic. The gross categories most often used are "high risk" (most often types 16 and 18) and "low risk" (types 6 and 11) HPV infection, the former more often associated with genital cancer.

Prevention of HPV infection and cervical cancer was revolutionized with the release of the HPV vaccine, which is effective in reducing the incidence of HPV-associated disease. Currently, two vaccines are licensed in the United States. Gardasil (Merck), released in 2006, includes protection against viral types 6, 11, 16, and 18. It is approved for the prevention of vulvar and vaginal cancer and for the prevention of cervical cancer, cervical dysplasia, and genital warts in females age 9 to 26. The vaccine was recently approved for males of the same age range for the prevention of genital warts. More recently, Cervarix (GlaxoSmithKline) was approved for the prevention of cervical cancer and cervical dysplasia from HPV types 16 and 18 in women age 10 to 25. Ideally, the vaccine should be administered before initiation of sexual activity to prevent initial acquisition of these HPV types. Patients who are already sexually active may also receive the vaccine.

The transmission of HPV to men decreases with consistent condom use, from 53.9% in men who never use condoms to 37.9% in men who "always" use them. Unfortunately, HPV can infect skin that is not covered by the use of traditional barrier methods (Nielson et al., 2010). Male circumcision may decrease the transmission of HPV.

Patients have many questions about HPV, in particular about screening for asymptomatic infection. HPV infection occurs with high frequency in the sexually active population; up to 50% or more of sexually active individuals have HPV at some point in their life. In addition, HPV is effectively transmitted, even if contact does not involve genital-to-genital touching (i.e., manual stimulation can transmit the virus). Again, most HPV infections are without symptoms and resolve spontaneously through eradication by the intact immune system. For all these reasons, screening for the mere presence of HPV infection has minimal utility. There is no treatment for asymptomatic HPV infection.

The most common presentation of HPV infection is in the context of an abnormal Pap smear. HPV is directly linked to cervical dysplasia. For women over age 21 and under 35, HPV testing with high-risk viral detection is common. The presence of high-risk HPV informs further management of the Pap result. It is currently recommended that women over 35 be automatically tested for high-risk HPV infection at the Pap smear.

Patients may present with visible warts, or these may be detected at routine or STI screening. Genital warts are often cosmetically unacceptable to patients, even though they are infrequently functionally problematic. In some circumstances, wart burden can be high enough to cause physical discomfort or relative obstruction of the vagina or rectum.

Table 16-12 Treatment of Pelvic Inflammatory Disease (PID)

Route	Recommended Treatment	Alternate Treatment
Parenteral	Cefotetan, 2 g IV q12h *or* Cefoxitin 2 g IV q6h *plus* Doxycycline, 100 mg PO or IV q12h *or* Clindamycin, 900 mg IV q8h *plus* Gentamicin loading dose IV or IM (2 mg/kg) followed by maintenance dose (1.5 mg/kg) q8h; may use once-daily gentamicin dosing.	Ampicillin/sulbactam, 3 g IV q6h *plus* Doxycycline, 100 mg PO or IV q12h
Intramuscular	Ceftriaxone, 250 mg IM single dose, *plus* doxycycline, 100 mg bid for 14 days, with or without metronidazole, 500 mg bid for 14 days	Cefoxitin 2 g IM single dose plus probenecid 1 g orally concurrently administered plus doxycycline 100 mg bid for 14 days with or without metronidazole 500 mg bid for 14 days.

Data from Centers for Disease Control and Prevention. Sexually transmitted disease treatment guidelines, 2010. MMWR 2010;59(No. RR-12).
IV, Intravenously; PO, orally; IM, intramuscularly; *q6h, q8h, q12h,* every 6, 8, or 12 hours; *bid,* twice daily.

Non-STI Causes of Vaginal Discharge

Vulvovaginal candidiasis and bacterial vaginosis are generally not thought to be sexually transmitted, although they are often in the differential diagnosis of sexually transmitted infection (STI). Both these infections likely are related to changes in the vaginal pH and the normal flora distribution. It is not always clear which of these factors is primary and which is secondary, because at diagnosis, both pH and normal vaginal flora will often be abnormal.

Vulvovaginal candidiasis is a common infection causing typically white, curdlike discharge, itching, and sometimes dysuria. The causative organism is usually *Candida albicans* but can be other *Candida* spp. Antibiotics can alter normal vaginal flora, so the recent use of antibiotics may predispose women to candidiasis. Physical examination may reveal erythematous external genitalia as well as external and internal white, clumping discharge. Usually, no distinctive odor is associated with vaginal yeast. Wet preparation of vaginal specimen or treatment with potassium hydroxide (KOH) may reveal branching pseudohyphae and yeast. When pH is performed, it should be directly on the vaginal discharge and not on the saline-diluted specimen because the saline will alter the pH of the specimen. Typically, the pH of yeast discharge is less than 4.5 (normal vaginal pH,3.8-4.5).

Bacterial vaginosis (BV) is the most common cause of infectious vaginal discharge (Spence and Melville, 2007). Many different organisms are associated with the diagnosis of BV, including *Gardnerella vaginalis* and *Mycoplasma hominis*. Women with BV may report discharge, vaginal irritation, vaginal odor, and at times, dysuria. Findings of BV are often detected during a normal screening Pap smear or pelvic examination. Physical findings may reveal signs of vaginal irritation. The discharge is usually thin and gray. An amine (fishy) odor may be produced with the application of KOH. The finding of clue cells, or epithelial cells with adherent bacteria, under saline preparation microscopy and a decrease in normal lactobacilli are common findings. The Amsel criteria are useful in BV diagnosis; other scoring systems (e.g., Nugent criteria) have been used but require Gram staining. The specific Amsel criteria are (1) milky, homogeneous, adherent discharge; (2) discharge pH greater than 4.5; (3) positive whiff test (fishy smell with addition of KOH); and (4) at least 20% clue cells on microscopic examination. If three of the four criteria are present, the likelihood of BV is 90%.

In routine vaginal examination and bimanual examination for patients with vaginal discharge, signs and symptoms of vaginitis are poor predictors of the microbiologic cause of infection (Schaaf et al., 1990). The clinical examination and office testing, in fact, are fair predictors of the true cause of infection (Lowe et al., 2009). Many patients with vaginal discharge will use over-the-counter preparations before consulting a physician, which can delay correct diagnosis of the etiology of symptoms. Patient-collected, low vaginal swabs may be as useful as provider-collected specimen in making a diagnosis for the patient with vaginal discharge. The purpose of bimanual examination is to evaluate for signs of pelvic inflammatory disease and is not necessary in the low-risk patient with vaginal discharge.

Treatment of asymptomatic BV or vaginal yeast is not necessary in the nonpregnant patient or usually is not needed to test or treat partners of patients with isolated yeast or BV. When infection is recurrent, particularly when a woman's male partner is uncircumcised, treatment of the male partner for carriage of either infection may be warranted. Options for treatment of recurrent infections are presented in **eTable 16-1.**

eTable 16-1 Treatment options for Vulvovaginal Candidiasis and bacterial vaginosis

Infection	Preferred treatment	Alternative Treatment
Vulvovaginal candidiasis	Butoconazole 2% cream, 5 g intravaginally for 3 days, *or* Butoconazole 2% cream, 5 g (sustained release), single intravaginal application, *or* Clotrimazole 1% cream, 5 g intravaginally daily for 7-14 days, *or* Clotrimazole, 100 mg vaginal tablets daily for 7 days, *or* Miconazole 2% cream, 5 g intravaginally daily for 7 days, *or* Terconazole 0.8% cream, 5 g intravaginally for 3 days, *or* Fluconazole, 150 mg orally, single dose	
Vulvovaginal candidiasis, recurrent	7-14 days of topical therapy *or* Fluconazole, 150 mg orally every third day for three doses, followed by fluconazole, 150 mg orally once weekly for 6 months	Initial treatment as noted, followed by topical clotrimazole, 200 mg twice weekly for 6 months
Bacterial vaginosis	Metronidazole, 500 mg orally twice daily for 7 days, *or* Metronidazole gel 0.75%, one applicator intravaginally once daily for 5 days, *or* Clindamycin cream 2%, one applicator intravaginally at bedtime for 7 days	Clindamycin, 300 mg orally twice daily for 7 days, *or* Clindamycin ovules, 100 mg intravaginally once at bedtime for 3 days
Bacterial vaginosis, recurrent	Initial treatment followed by metronidazole gel 0.75% on applicator twice weekly for 6 months	

Data from Workowski KA, Berman SM. Sexually transmitted disease treatment guidelines. MMWR 2006;55(RR-11).

The treatment of warts is destructive and may serve to stimulate an immune response to the HPV-infected cells, which are typically "above" the surveillance mechanisms of the immune system in the epidermis. Office methods of treatment include cryotherapy and trichloroacetic acid or podophyllin resin application. Patients may apply podofilox 0.5% solution or gel or imiquimod 5% cream (Table 16-13). For more extensive cases of warts or intra-anal or intravaginal infections that are difficult to treat using the previous methods, surgical techniques may be necessary to achieve resolution. Untreated, warts may resolve spontaneously, remain the same, or worsen.

Ectoparasites

Patients with *pediculosis pubis,* or pubic lice, most often present with pruritus or with visible nits. Pubic lice are visible on inspection of the pubic area, as are nits, which are adherent to the hair shaft. Partners of patients with pubic lice should also be treated to prevent reinfection. Linens and clothing should be laundered or dry-cleaned or kept in a closed plastic container or bag for 72 hours.

Table 16-13 Treatment of Genital Warts

Provider applied
Cryotherapy Trichloroacetic acid (TCA): small amount applied until wart whitens Podophyllin resin, 10% to 25% All these may be repeated every 1 to 2 weeks until warts are resolved.
Patient applied
Podofilox 0.5% solution or gel applied twice daily for 3 days, followed by 4 days of no therapy. Imiquimod 5% cream applied once daily at bedtime three times a week for up to 16 weeks; washed off 6 to 10 hours after application.

Table 16-14 Treatment for Ectoparasites

Infestation	Recommended Treatment	Alternate Treatment
Pediculosis pubis	Permethrin 1% cream applied to affected area and washed off after 10 minutes *or* Pyrethrins with piperonyl butoxide applied to affected area and washed off after 10 minutes	Malathion 0.5% lotion applied for 8-12 hours and washed off *or* Ivermectin, 250 μg/kg orally once, repeated in 2 weeks
Scabies	Permethrin cream 5% applied to whole body, neck to soles of feet, and washed off in 8-14 hours, *or* Ivermectin, 200 μg/kg orally once, repeated in 2 weeks	Lindane 1% applied to whole body, neck to soles of feet, and washed off in 8 hours

Data from Workowshi KA, Berman SM. Sexually transmitted disease treatment guidelines. MMWR 2006;55(RR-11).

Scabies diagnosis can be challenging. Again, patients present with itching that can be anywhere on the body, although often in the genital area or on the buttocks when infection is sexual in origin. The pruritus associated with *Sarcoptes scabiei* is a result of sensitization to the mite droppings underneath the skin as the mite burrows. The classic "burrow" or linear papular eruption is not always present. Scraping of lesions with microscopic examination may be performed to identify the mite. As with pediculosis, close contacts should be treated. Linens and clothing should be laundered or dry-cleaned or isolated in plastic containers for 72 hours. The pruritus-associated with scabies can take several weeks to resolve after treatment. Patients living in group settings (dormitories or apartments) may reinfect one another as a result of inadequate primary treatment of all contacts (Table 16-14).

KEY TREATMENT

Regular barrier method use decreases transmission of herpes simplex virus in both men and women, with patients using condoms 100% of the time having a 30% reduction in HSV acquisition compared with those who never use condoms (Martin et al., 2009) (SOR: A).
For STIs other than syphilis, expedited partner therapy, the practice of administering medication to diagnosed patients to treat their partner(s), has proved effective in reducing reinfection rates and further spread of infection (CDC, 2006) (SOR: B).
Human papillomavirus vaccine is effective in reducing the incidence of HPV infection (Sundar et al., 2010) (SOR: A).
Imiquimod 1% or 5% increases wart clearance compared with placebo in people without HIV infection (Buck, 2010) (SOR: A).
Podofilox (Condylox) is more effective than placebo at clearing genital warts after 16 weeks (SOR: A).
The most common outpatient treatment for PID is ceftriaxone (250 mg IM) plus doxycycline (100 mg) twice daily for 14 days.

GENITOURINARY INFECTIONS

William E. Roland

Key Points

- Symptomatic urinary tract infections (UTIs) should be treated.
- Uncomplicated cystitis in women can be treated safely and effectively through telephone treatment protocols.
- Asymptomatic UTIs should be treated in pregnant women and in men about to undergo urologic surgery.
- Young children with UTIs might benefit from an etiologic workup (renal ultrasound, voiding cystourethrogram) if they are:
  - Boys of any age
  - Children of any age with a febrile UTI
  - Girls younger than 3 years with first UTI (difficulty verbalizing symptoms)
  - Children with recurrent UTI who have not been imaged previously
  - First UTI in children with a family history or with renal disease, abnormal voiding, poor growth, urinary tract abnormalities, or hypertension
- Acute prostatitis is usually caused by *Escherichia coli.*

Urinary tract infection (UTI) is defined as significant bacteriuria in the presence of symptoms. UTI accounts for a significant number of emergency department visits; an estimated 20% of women experience a UTI in their lifetime. The urinary tract is normally sterile. *Uncomplicated* UTI involves the urinary bladder in a host without underlying renal or neurologic disease. The bladder mucosa is invaded, most often by enteric coliform bacteria (e.g., *E. coli*) that ascend into the bladder via the urethra. Sexual intercourse can promote this migration, and cystitis is common in otherwise healthy young women. Frequent and complete voiding has been associated with a reduction in the incidence of UTI. *Complicated* UTI occurs in the setting of underlying structural, medical, or neurologic disease.

Signs and symptoms of a UTI include dysuria, frequency, urgency, nocturia, enuresis, incontinence, urethral pain, suprapubic pain, low back pain, and hematuria. Fever is unusual. Up to 30% of patients with symptoms of cystitis have a smoldering *pyelonephritis,* especially when symptoms have been present for more than 1 week. A patient with pyelonephritis usually appears ill, with fever, sweating, and prostration, along with costovertebral angle (flank) tenderness in most cases. The differential diagnosis of uncomplicated UTI includes use of diuretics or caffeine, interstitial cystitis, vaginitis, pregnancy, pelvic mass, PID, and benign prostatic hypertrophy (BPH).

If a UTI is suspected, the initial test of choice is urinalysis, although with classic signs and symptoms of infection in women, this test is not always necessary. Pyuria, as indicated by a positive result on the leukocyte esterase dip test, is found in the majority of patients with UTI. The presence of urinary nitrites is fairly specific for UTI. The combination of positive leukocyte esterase and nitrites improves sensitivity. On urine microscopy, levels of pyuria as low as two to five leukocytes per high-power field (2-5 WBCs/hpf) in a centrifuged specimen are significant in the female patient with appropriate symptoms, as is the presence of bacteriuria. Urine culture and sensitivity are not needed in simple UTIs. Cultures should be done in patients with recurrent UTIs, patients with pyelonephritis, and pregnant patients.

Antibiotic therapy can be given in a 3-day regimen for young, sexually active women. A 7- to 10-day course of antibiotics should be used in pregnant patients and patients with complicated UTIs. All the drugs listed in Table 16-15 can be used in a 3-day or 7- to 10-day course. Clinical practice guidelines that include telephone assessment and treatment have shown a decrease in unnecessary laboratory utilization while maintaining quality of care (Saint et al., 1999). Trimethoprim-sulfamethoxazole (TMP-SMX) has been a mainstay of UTI therapy, but in some localities, resistance of *E. coli* to TMP-SMX is 20% (Mehnert-Kay, 2005).

If a urine culture is done and the organism is resistant to the drug prescribed, a change in antibiotics is indicated only if the patient is still symptomatic. For symptomatic treatment, a bladder anesthetic can be used, such as phenazopyridine (Pyridium), 200 mg three times daily for 2 days. Patients should be warned that this produces an orange tinge in tears and urine. Patients should also be instructed to increase fluid intake.

Pyelonephritis is suggested by a failure of a short course of antibiotics. Signs and symptoms of pyelonephritis include shaking chills and fever higher than 38.5° C (101.3° F), flank pain, malaise, urinary frequency and burning, and costovertebral angle tenderness. The infection can produce septic shock. A patient who is unable to tolerate oral intake should be hospitalized and given empiric IV antibiotics aimed at broad-spectrum gram-negative coverage, such as third-generation cephalosporins, fluoroquinolones, or aminoglycosides, while awaiting results of blood and urine cultures. A 14-day course of antibiotic therapy (IV or PO) is recommended.

Table 16-15 Treatment Regimens for Acute Uncomplicated Cystitis*

Otherwise Healthy Women†
3-Day Regimens
TMP-SMX, 160/800 mg q12h Trimethoprim, 100 mg q12h Fluoroquinolones‡ Ciprofloxacin, 100-250 mg q12h Ciprofloxacin XR, 500 mg qd Gatifloxacin, 200 mg qd Levofloxacin, 250 mg qd
5-Day to 7-Day Regimens
Nitrofurantoin monohydrate/macrocrystals, 100 mg q12h Nitrofurantoin macrocrystals, 50-100 mg qid Amoxicillin, 250 mg q8h or 500 mg q12h Cephalexin, 250 mg q6h, or other cephalosporin Consider 7-day regimen.
Pregnant Women
Amoxicillin, 250 mg q8h or 500 mg q12h Nitrofurantoin monohydrate/macrocrystals, 100 mg q12h Nitrofurantoin macrocrystals, 50-100 mg qid Cephalexin, 250 mg q6h, or other cephalosporin TMP-SMX, 160/800 mg q12h
Other Patients
Male gender, diabetes, symptoms for 7 days, recent antimicrobial use, age > 65 TMP-SMX,§ 160/800 mg q12h Fluoroquinolones, as per 3-day regimens Cephalexin, 250 mg q6h, or other cephalosporin Consider 7-day regimen.

From Hooton TM, Stamm WE. Diagnosis and treatment of uncomplicated urinary tract infection. Infect Dis North Am 1997;11:551.
TMP-SMX, Trimethoprim-sulfamethoxazole; *qd,* every day; *q12h,* every 12 hours; *q6h,* every 6 hours; *q8h,* every 8 hours; *qid;* four times daily.
*Treatments listed to be prescribed before etiologic agent is known (Gram stain may help); therapy can be modified when cause is identified.
†Characteristic pathogens are *Escherichia coli* (85%-90%) and *Staphylococcus saprophyticus* (5%-15%); other organisms account for less than 5% of cases and include *Proteus mirabilis, Klebsiella pneumoniae,* and *Enterococcus* spp.
‡Fluoroquinolones should not be used in pregnancy.
§Although classified as pregnancy category C, TMP-SMX is widely used; however, avoid its use in the first and second trimesters.

Urinary Tract Infection in Pregnancy

Although the most common bacterial infection during pregnancy, the incidence of UTI in pregnancy is similar to that reported in sexually active nonpregnant women of childbearing age. Up to 40% of pregnant women with

untreated bacteriuria in the first trimester develop acute pyelonephritis later in pregnancy. Premature births and perinatal mortality are increased in pregnancies complicated by UTI. Therefore, in pregnant women, asymptomatic bacteriuria should be actively sought and aggressively treated with at least one urinalysis, preferably toward the end of the first trimester.

Nitrofurantoin, ampicillin, and the cephalosporins have been used most extensively in pregnancy and are the regimens of choice for treating asymptomatic or minimally symptomatic UTI. TMP-SMX should be avoided in the first trimester because of possible teratogenic effects and should be avoided near term because of a possible role in the development of kernicterus. Fluoroquinolones are avoided because of possible adverse effects on fetal cartilage development. For pregnant women with overt pyelonephritis, admission to the hospital for parenteral therapy should be the standard of care; beta-lactam agents with or without aminoglycosides are the cornerstone of therapy. Prevention of UTI, including pyelonephritis, can be accomplished during pregnancy with nitrofurantoin or cephalexin taken prophylactically after coitus or at bedtime without relation to coitus. Such prophylaxis should be considered for patients who have had acute pyelonephritis during pregnancy, patients with bacteriuria during pregnancy who have had a recurrence after a course of treatment, and patients who had recurrent UTI before pregnancy that required prophylaxis.

Catheter-Associated Urinary Tract Infection

Catheter-associated UTIs are associated with increased mortality and costs. Risk factors for catheter-associated UTIs include the duration of catheterization, lack of systemic antibiotic therapy, female gender, age older than 50 years, and azotemia. To help prevent infection, urinary catheters should be avoided when possible and used only as long as needed. The catheter should be inserted with strict aseptic technique by trained persons, and a closed system should be used at all times. Treatment of catheter-associated UTI depends on the clinical circumstances. Symptomatic patients (e.g., those with fever, chills, dyspnea, and hypotension) require immediate antibiotic therapy along with removal and replacement of the urinary catheter if it has been in place for a week or longer. In an asymptomatic patient, therapy should be postponed until the catheter can be removed. Patients with long-term indwelling catheters seldom become symptomatic unless the catheter is obstructed or is eroding through the bladder mucosa. In patients who do become symptomatic, appropriate antibiotics should be administered and the catheter changed. Therapy for asymptomatic catheterized patients leads to the selection of increasingly antibiotic-resistant bacteria.

Recurrent Urinary Tract Infection

Recurrence of uncomplicated cystitis in reproductive-age women is common, and some form of preventive strategy is indicated if three or more symptomatic episodes occur in 1 year. However, risk factors specific to women with recurrent cystitis have received little study (Sen, 2008). Several antimicrobial strategies are available, but before initiating therapy, the patient should try such simple interventions as voiding immediately after sexual intercourse and using a contraceptive method other than a diaphragm and spermicide. Ingestion of cranberry juice has been shown to be effective in decreasing bacteriuria with pyuria, but not bacteriuria alone or symptomatic UTI, in an elderly population. Cranberry juice may be effective for preventing UTI in young, otherwise healthy women.

If simple nondrug measures are ineffective, continuous or postcoital—if the infections are temporally related to intercourse—low-dose antimicrobial prophylaxis with TMP-SMX, a fluoroquinolone, or nitrofurantoin should be considered. Typically, a prophylactic regimen is initially prescribed for 6 months and then discontinued. If the infections recur, the prophylactic program can be instituted for a longer period. An alternative approach to antimicrobial prophylaxis for women with less frequent recurrences (<4 a year) is to supply TMP-SMX or a fluoroquinolone and allow the patient to self-medicate with short-course therapy at the first symptoms of infection.

A minority of patients have *relapsing* UTI, as evidenced by finding the same bacterial strain within 2 weeks after completion of antimicrobial therapy. Two factors can contribute to the pathogenesis of relapsing infection in women: (1) deep tissue infection of the kidney that is suppressed but not eradicated by a 14-day course of antibiotics and (2) structural abnormality of the urinary tract, particularly calculi. Patients with true relapsing UTIs should undergo renal ultrasound, intravenous pyelogram (IVP), or voiding cystourethrogram, and longer-term therapy should be considered.

Urinary Tract Infections in Children

Urinary tract infection is one of the most common infections of childhood. Factors predisposing to UTI include taking broad-spectrum antibiotics (e.g., amoxicillin, cephalexin), which are likely to alter gastrointestinal and periurethral flora; incomplete bladder emptying or infrequent voiding; voiding dysfunction; and constipation. UTI in young children serves as a marker for abnormalities of the urinary tract. Imaging of the urinary tract is recommended in every febrile infant or young child with a first UTI to identify children with abnormalities that predispose to renal damage. Imaging should consist of urinary tract ultrasonography to detect dilation of the renal parenchyma. Voiding cystourethrography is often ordered but does not appear to improve clinical outcomes in uncomplicated UTIs (Alper and Curry, 2005).

Prostatitis

A common complication of UTI in men is prostatitis. Bacterial prostatitis is usually caused by the same gram-negative bacilli that cause UTI in female patients; 80% or more of such infections are caused by *Escherichia coli*. The pathogenesis of this condition is poorly understood. Antibacterial substances in prostatic secretions probably protect against such infections. A National Institutes of Health (NIH) expert consensus panel has recommended classifying prostatitis into three syndromes: acute bacterial prostatitis, chronic bacterial prostatitis, and *chronic pelvic pain syndrome* (CPPS). *Acute bacterial prostatitis* is a febrile illness characterized by chills, dysuria,

urinary frequency and urgency, and pain in the perineum, back, or pelvis. The bladder outlet can be obstructed. On physical examination, the prostate is found to be enlarged, tender, and indurated. Pyuria is present, and urine cultures generally grow *E. coli* or another typical uropathogen.

Chronic bacterial prostatitis is a clinically more occult disease and may be manifested only as recurrent bacteriuria or variable low-grade fever with back or pelvic discomfort. Urinary symptoms usually relate to the reintroduction of infection into the bladder, with both pyuria and bacteriuria. A chronic prostatic focus is the most common cause of recurrent UTI in men. CPPS is the diagnosis for the large group of men who present with minimal signs on physical examination but have a variety of irritative or obstructive voiding symptoms; perineal, pelvic, or back pain; and sexual dysfunction. These men can be divided into those with and those without inflammation (defined as >10 WBCs/hpf in expressed prostatic secretions). The etiology and appropriate management in these patients, regardless of inflammatory status, is unknown.

KEY TREATMENT

Pregnant women should be screened for asymptomatic bacteriuria in the first trimester of pregnancy (Wadland and Plante, 1989) (SOR: A).

Pregnant women who have asymptomatic bacteriuria should be treated with antimicrobial therapy for 3 to 7 days (Nicolle et al., 2005) (SOR: B).

Pyuria accompanying asymptomatic bacteriuria should not be treated with antimicrobial therapy (Nicolle, 2003) (SOR: C1).

A 3-day course of TMP-SMX (Bactrim, Septra) is recommended as empiric therapy of uncomplicated UTIs in women, in regions where the rate of resistant *E. coli* is less than 20% (Warren et al., 1999) (SOR: C).

Fluoroquinolones are not recommended as first-line treatment of uncomplicated UTIs, to preserve their effectiveness for complicated UTIs (Warren et al., 1999) (SOR: C).

A randomized, placebo-controlled trial of 150 women over 12 months found that cranberry juice and cranberry extract tablets significantly decreased the number of patients having at least one symptomatic UTI per year (Stothers, 2002) (SOR: B).

TICK-BORNE INFECTIONS

William E. Roland

Key Points

- Laboratory findings in acute tick-borne infection often include a normal or low WBC count, thrombocytopenia, hyponatremia, and elevated liver enzymes.
- Doxycycline is the drug of choice for patients with RMSF.
- Appropriate antibiotic treatment should be initiated immediately with strong suspicion of ehrlichiosis.
- If left untreated, Lyme disease can progress to cognitive disorders, sleep disturbance, fatigue, and personality changes.

In the United States, more vector-borne diseases are transmitted by ticks than by any other agent. Tick-borne diseases can result from infection with pathogens that include bacteria, rickettsiae, viruses, and protozoa. Most tick-borne diseases are transmitted during the spring and summer months when ticks are active. A knowledge of which species of tick is endemic in an area can help narrow the diagnosis (Table 16-16).

Rocky Mountain Spotted Fever

Rocky Mountain spotted fever (RMSF) is the most severe and most often reported rickettsial illness in the United States. It is caused by *Rickettsia rickettsii,* a species of bacteria that is spread to humans by ixodid (hard) ticks (Figure 16-6).

Initial signs and symptoms include sudden onset of fever, headache, and muscle pain, followed by development of rash. The disease can be difficult to diagnose in the early stage. RMSF is most common among males and children. Risk factors are frequent exposure to dogs and living near wooded areas or areas with high grass. The presentation of RSMF is nonspecific, following an incubation of about 5 to 10 days after a tick bite. Initial symptoms can include fever, nausea, vomiting, severe headache, muscle pain, and lack of appetite. Later signs and symptoms include rash, abdominal pain, joint pain, and diarrhea. The rash first appears 2 to 5 days after the onset of fever. Most often it begins as small, flat, pink, nonitchy spots on the wrists, forearms, and ankles. The characteristic red spotted rash of RMSF is usually not seen until the sixth day or later after onset of symptoms. As many as 10% to 15% of patients never develop a rash (Figure 16-7). No widely available laboratory assay provides rapid confirmation of early RMSF, although commercial PCR testing is available. Therefore, treatment decisions should be based on epidemiologic and clinical clues. Treatment should never be delayed while waiting for confirmation by laboratory results. Routine clinical laboratory findings suggestive of RMSF include normal WBC count, thrombocytopenia, hyponatremia, and elevated liver enzyme levels. Serologic assays are the most often used methods for confirming cases of RMSF.

Doxycycline is the drug of choice for patients with RMSF. Therapy is continued for at least 3 days after fever subsides and until there is unequivocal evidence of clinical improvement, generally for a minimum total course of 5 to 10 days. Tetracyclines are usually not the preferred drug for use in pregnant women. Whereas chloramphenicol is typically the preferred treatment for RMSF during pregnancy, care must be used when administering chloramphenicol late during the third trimester of pregnancy because of risks associated with gray baby syndrome.

Ehrlichiosis

Three species of *Ehrlichia* in the United States are known to cause disease in humans. *Ehrlichia chaffeensis,* the cause of human monocytic ehrlichiosis, occurs primarily in southeastern and south-central regions and is primarily transmitted by the lone star tick, *Amblyomma americanum* (Figure 16-8). Human granulocytic ehrlichiosis is caused by *Anaplasma phagocytophila* or *Anaplasma equi* and is transmitted by *Ixodes* ticks. *Ehrlichia ewingii* is the most recently recognized human pathogen, with cases reported in immunocompromised patients in Missouri, Oklahoma, and Tennessee.

After an incubation period of about 5 to 10 days following the tick bite, initial symptoms generally include fever,

Table 16-16 Features of Common Tick-Borne Diseases in the United States*

Disease (Causative Agent)	Primary Vector(s)	Approx. Distribution	Incubation Period (Days)	Common Initial Signs and Symptoms	Common Laboratory Abnormalities	Rash	Fatality Rate (%)
Rocky Mountain Spotted fever *(Rickettsia rickettsii)*	American dog tick *(Dermacentor variabilis)*, Rocky Mountain wood tick *(D. andersoni)*; brown dog tick (*Rhipicephalus sanguineus)* in Arizona	Widespread in United States, especially in south Atlantic and south-central states	2 to 14	Fever, nausea, vomiting, myalgia, anorexia, headache	Thrombocytopenia, mild hyponatremia, mildly elevated hepatic transaminase levels	Maculopapular rash ; appears about 2 to 4 days after fever onset in 50% to 80% of adults and more than 90% of children; may involve palms and soles	5 to 10
Human monocytic ehrlichiosis *(Ehrlichia chaffeensis)*	Lone star tick *(Amblyomma americanum)*	Southern, south-central, mid-Atlantic, and northern states; isolated areas of New England	5 to 14	Fever, headache, malaise, myalgia	Leukopenia, thrombocytopenia, elevated serum transaminase levels	Rash appears in more than 30% of adults and in about 60% of children	2 to 3
Human granulocytic anaplasmosis *(Anaplasma phagocytophilum)*	Black-legged tick (*Ixodes scapularis* and *I. pacificus*) in United States	North central and Pacific states; New England	5 to 21	Fever, headache, malaise, nausea, vomiting	Leukopenia, thrombocytopenia, elevated serum transaminase levels	Rare	<1
Ehrlichia ewingii infection	Lone star tick	South Atlantic and south-central states; isolated areas of New England	5 to 14	Fever, headache, myalgia, nausea, vomiting	Leukopenia, thrombocytopenia, elevated serum transaminase levels	Rare	None documented

Modified from Chapman AS, Bakken JS, Folk SM, et al. Diagnosis and management of tick-borne rickettsial diseases: Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis—United States. A practical guide for physicians and other health-care and public health professionals. MMWR 2006;55(RR-4):3.
*Treatment for these diseases is the same: adults should receive 100 mg of doxycycline (Vibramycin) orally or intravenously twice a day, and children who weigh less than 100 lb (45.4 kg) should receive 2.2 mg/kg of doxycycline orally or intravenously twice a day.

Figure 16-6 Ixodid tick

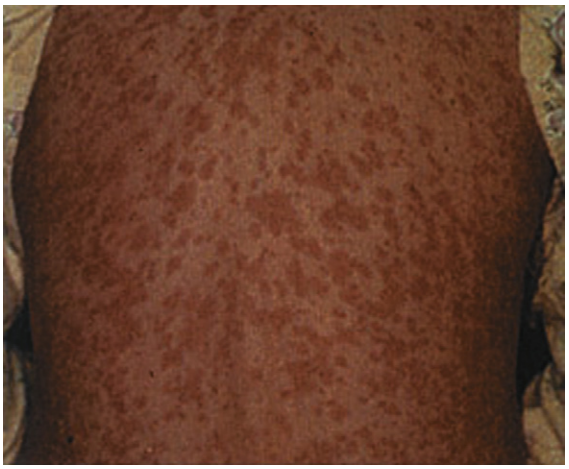


Figure 16-7 Image of a patient with Rocky Mountain spotted fever; note late rash on trunk.
(From Bratton R, Corey G. Tick-borne diseases. Am Fam Physician 2005;71:2323-2332.)

Figure 16-8 Lone star tick, *Amblyomma americanum.*
(From http://www.cdc.gov/ncidod/dvbid/stari/lone-star-tick-image.htm.)

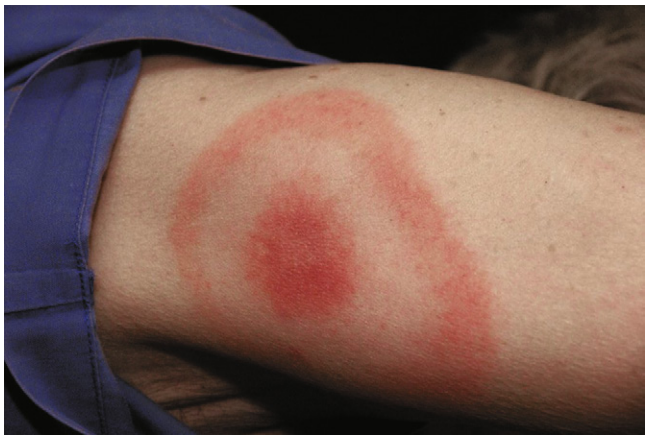


Figure 16-9 Target rash of erythema migrans in Lyme disease.
(From http://phil.cdc.gov/PHIL_Images/9875/9875_lores.jpg.)

headache, malaise, and muscle aches. Other signs and symptoms can include nausea, vomiting, diarrhea, cough, joint pains, confusion, and occasionally rash. Laboratory findings indicating ehrlichiosis include leukopenia, thrombocytopenia, and elevated liver enzymes. Ehrlichiosis can be a severe illness, especially if untreated, and as many as half of all patients require hospitalization. Laboratory confirmation of ehrlichiosis requires serologic, molecular (PCR), or culture-based methods.

Appropriate antibiotic treatment should be initiated immediately when there is a strong suspicion of ehrlichiosis on the basis of clinical and epidemiologic findings. The treatment recommendations are the same as for Rocky Mountain spotted fever. Rifampin has been used successfully in a limited number of pregnant women with documented ehrlichiosis.

Babesiosis

Babesiosis is caused by hemoprotozoan parasites of the genus *Babesia*. The white-footed deer mouse is the main reservoir in the United States, and the vector is *Ixodes* ticks. Most infections are probably asymptomatic. Manifestations of disease include fever, chills, sweating, myalgias, fatigue, hepatosplenomegaly, and hemolytic anemia. Symptoms typically occur after an incubation period of 1 to 4 weeks and can last several weeks. The disease is more severe in immunosuppressed, splenectomized, or elderly patients. Diagnosis can be made by microscopic examination of thick and thin blood smears stained with Giemsa, looking for the parasite in red blood cells (RBCs). Options for treatment include clindamycin plus quinine or atovaquone plus azithromycin.

Lyme Disease

Lyme disease is caused by the spirochetal bacterium *Borrelia burgdorferi*. *Ixodes* ticks are responsible for transmitting Lyme disease bacteria to humans. In the United States, Lyme disease is mostly localized to states in the northeastern, mid-Atlantic, and upper north-central regions, as well as northwestern California. Lyme disease most often manifests with a characteristic bull's-eye rash (erythema migrans) accompanied by nonspecific symptoms such as fever, malaise, fatigue, headache, muscle aches, and joint aches (Figure 16-9).

Lyme disease spirochetes disseminate from the site of the tick bite, causing multiple (secondary) erythema migrans lesions. Other manifestations of dissemination include lymphocytic meningitis, cranial neuropathy (especially facial nerve palsy), radiculoneuritis, migratory joint and muscle pains, myocarditis, and transient atrioventricular blocks of varying degree. If left untreated, the disease can progress to intermittent swelling and pain of one or a few joints (usually large weight-bearing joints such as the knee), cognitive disorders, sleep disturbance, fatigue, and personality changes. The diagnosis is based primarily on clinical findings, and it is often appropriate to treat patients with early disease solely on the basis of objective signs and a known exposure. Serologic testing may provide valuable supportive diagnostic information in patients with endemic exposure and objective clinical findings that suggest later-stage disseminated Lyme disease.

Treatment for 3 to 4 weeks with doxycycline or amoxicillin is generally effective in early disease. Cefuroxime axetil or erythromycin can be used for persons allergic to penicillin or who cannot take tetracyclines. Later disease, particularly with objective neurologic manifestations, can require treatment with intravenous ceftriaxone or penicillin for 4 weeks or more, depending on disease severity.

Tularemia

Tularemia is caused by *Francisella tularensis*, one of the most infectious pathogenic bacteria known. Most cases in the United States occur in south-central and western states. Humans can become infected through diverse environmental exposures, including bites by infected arthropods; handling infectious animal tissues or fluids; direct contact with or ingestion of contaminated food, water, or soil; and inhalation of infective aerosols. Inhaled *F. tularensis* causes pleuropneumonitis. Some exposures contaminate the eye, resulting in ocular tularemia; penetrate broken skin, result-

Figure 16-10 *Dermacentor andersoni* tick.
(From http://www.cdc.gov/ticks/images/rocky_mountain_wood_tick.jpg.)

ing in ulceroglandular or glandular disease; or cause oropharyngeal disease with cervical lymphadenitis. Untreated, bacilli inoculated into skin or mucous membranes multiply, spread to regional lymph nodes, multiply further, and then can disseminate to organs throughout the body.

The onset of tularemia is usually abrupt, with fever, headache, chills and rigors, generalized body aches, coryza, and sore throat. A dry or slightly productive cough and substernal pain or tightness often occur with or without objective signs of pneumonia. Nausea, vomiting, and diarrhea can occur. Sweats, fever, chills, progressive weakness, malaise, anorexia, and weight loss characterize continuing illness. Rapid diagnostic testing for tularemia is not widely available. Respiratory secretions and blood for culture should be collected in suspected patients and the laboratory alerted to the need for special diagnostic and safety procedures. Streptomycin (1 g IM bid for 10 days) is the drug of choice, and gentamicin is an acceptable alternative. Tetracyclines and chloramphenicol can also be used.

Colorado Tick Fever

Colorado tick fever is an acute viral infection transmitted by the bite of the *Dermacentor andersoni* tick (Figure 16-10). The disease is limited to the western United States and is most prevalent from March to September. Symptoms start about 3 to 6 days after the tick bite. Fever continues for 3 days, stops, and then recurs 1 to 3 days later for another few days. Other symptoms include excessive sweating, muscle aches, joint stiffness, headache, photophobia, nausea, vomiting, weakness, and an occasional faint rash. Routine blood tests might show a low WBC count, mildly elevated liver function, and mildly elevated creatine phosphokinase (CPK). Diagnosis is confirmed by testing blood for complement fixation immunofluorescent antibody staining to Colorado tick virus. Treatment is removal of the tick and treatment of symptoms.

Prevention of Tick-Borne Disease

Physicians should advise patients who walk or hike in tick-infested areas to tuck long pants into socks to protect the legs and wear shoes and long-sleeved shirts. Ticks show up on white or light colors better than dark colors, making them easier to remove from clothing. If attached, ticks should be removed immediately by using a tweezers, pulling carefully and steadily. Insect repellents such as DEET, alone or in combination with permethrin, may be helpful.

KEY TREATMENT

Appropriate antibiotic therapy should be initiated immediately when there is suspicion of Rocky Mountain spotted fever, ehrlichiosis, or relapsing fever rather than waiting for laboratory confirmation (Bratton and Corey, 2005; Spach et al., 1993) (SOR: C).
Treatment with doxycycline (Vibramycin) or tetracycline is recommended for RMSF, Lyme disease, ehrlichiosis, and relapsing fever (Bratton and Corey, 2005; Spach et al., 1993) (SOR: C).
Recommended actions to prevent tick-borne disease include avoidance of tick-infested areas; wearing long pants and tucking the pant legs into socks; applying diethyltoluamide (DEET) insect repellents; using bed nets when camping; and carefully inspecting oneself frequently while in an at-risk area (Bratton and Corey, 2005; Spach et al., 1993) (SOR: C).
Antibiotic prophylaxis is not routinely recommended for a tick bite to prevent Lyme disease, unless the risk of infection is high (Wormser et al., 2006) (SOR: B).
Recommended treatment for suspected tularemia is streptomycin or gentamicin given empirically before evidence of laboratory confirmation (Bratton and Corey, 2005; Spach et al., 1993) (SOR: C).

CELLULITIS

William E. Roland

Key Points

- Most cases of cellulitis are caused by staphylococci or streptococci, but other causes should be considered by clinical situation.
- Physicians must rule out more ominous causes of skin inflammation, such as necrotizing fasciitis and pyomyositis, when considering cellulitis.
- Edema-associated cellulitis is best treated by mobilizing edema fluid.

Cellulitis is an acute, spreading inflammation of the derma and subcutaneous issue. Patients complain of tenderness, warmth, swelling, and spreading erythema. In contrast to *erysipelas,* cellulitis usually lacks sharp demarcation at the border. Factors that predispose to cellulitis include trauma, an underlying skin lesion (furuncle, ulcer), or a complication arising from a wound, ulcer, or dermatosis. Occasionally, cellulitis results from a blood-borne infection that metastasizes to the skin.

Pain and erythema usually develop within several days and are often associated with malaise, fever, and chills. The area involved is often extensive, red, hot, and swollen. Patchy involvement with skip lesions can be seen. Regional lymphadenopathy is common, and bacteremia can occur. Several clinical entities resemble cellulitis, including pyoderma gangrenosum, gout, and insect bites. Necrotizing fasciitis and gas gangrene are surgical emergencies. Given that the predominant organism involved in most cases of cellulitis is a gram-positive coccus, clinical history and morphology on physical examination usually suffice in the diagnosis and treatment of cellulitis. A history of freshwater exposure may implicate *Aeromonas hydrophila* as the causative organism; saltwater

exposure suggests *Vibrio* spp. Cellulitis in a patient with liver disease and shellfish ingestion moves *Vibrio vulnificans* to the top of the differential.

Patients with soft tissue infection should have blood drawn for laboratory testing if signs and symptoms of systemic toxicity are present (e.g., fever or hypothermia, tachycardia, hypotension). Laboratory testing should include blood culture and drug susceptibility tests; WBC count with differential; and measurement of creatinine, bicarbonate, CPK, and CRP levels. Hospitalization should be considered for patients with hypotension or an elevated creatinine level, low serum bicarbonate level, elevated CPK level (i.e., 2-3 times upper limit of normal), marked left shift, or CRP level greater than 13 mg/L (123.8 nmol/L). Gram stain with culture and culture of needle aspiration or punch biopsy specimens should be performed to determine a definitive etiology, and a surgical consult should be considered for inspection, exploration, and drainage. Findings that may signal potentially severe, deep, soft tissue infection and that may require emergent surgical evaluation include cutaneous hemorrhage, gas in the tissue, pain disproportionate to physical findings, rapid progression, skin anesthesia, skin sloughing, and violaceous bullae.

Radiologic studies may be helpful if abscess or osteomyelitis is a possibility. Ultrasonography is helpful in detecting a subcutaneous collection of fluid. Magnetic resonance imaging (MRI) is also useful in differentiating cellulitis from necrotizing fasciitis. The diagnosis of necrotizing cellulitis is by direct surgical examination or by frozen pathology sections.

Empiric antibiotics for immunocompetent patients with cellulitis should be targeted toward gram-positive cocci (Table 16-17). Broader coverage should be initiated for diabetic patients to include gram-positive aerobes, gram-negative aerobes, and anaerobes. Patients who present with severe infection or whose infection is progressing despite empiric antibiotic therapy should be treated more aggressively; the treatment strategy should be based on results of appropriate Gram stain, culture, and drug susceptibility analysis. In the case of *Staphylococcus aureus,* the physician should assume that the organism is resistant, and agents effective against MRSA, such as vancomycin, linezolid (Zyvox), or daptomycin (Cubicin), should be used.

The antibiotic may be switched from an intravenous drug to an oral drug when fever has subsided and the skin lesion begins to resolve, usually in 3 to 5 days. The total duration of therapy should be 7 to 14 days. Longer duration may be required if the response is slow or is associated with abscess, tissue necrosis, or underlying skin processes (infected ulcers or wounds). Treatment of cellulitis should include elevation and immobilization to decrease swelling. Patients with interdigital dermatophytic infections should be treated with a concomitant topical antifungal applied once or twice daily. Topical antifungals can also help reduce the risk of recurrence of the cellulitis. Support stockings, good skin hygiene, and prompt treatment of tinea pedis helps with prevention of cellulitis in patients with peripheral edema, who are predisposed to recurrence. In patients who continue to have frequent episodes of cellulitis or erysipelas, prophylactic treatment with penicillin V, 250 mg or 500 mg orally twice daily, or erythromycin, 250 mg once or twice daily (for penicillin-allergic patients), may be indicated.

KEY TREATMENT

Penicillin, given parenterally or orally depending on clinical severity, is the treatment of choice for erysipelas (Stevens et al., 2005) (SOR: A).
For cellulitis, a penicillinase-resistant semisynthetic penicillin (amoxicillin/clavulanate) or a first-generation cephalosporin should be selected, unless streptococci or staphylococci resistant to these agents are common in the community (Stevens et al., 2005) (SOR: A).
For suspected MRSA skin infections, oral treatment options include trimethoprim-sulfamethoxazole, clindamycin, and doxycycline (Stevens et al., 2005) (SOR: C).

FURUNCLES AND CARBUNCLES

David R. McBride

KEY POINTS

- The majority of furuncles and carbuncles are caused by *Staphylococcus* spp., increasingly, community-acquired methicillin-resistant *S. aureus*.
- Drainage of pus is of primary importance in treating skin and soft tissue infections.
- Culture of SSTIs is important in guiding antibiotic treatment when initial measures of drainage are not effective.
- For recurrent boils, consider referral to Infectious disease specialist, possibly to eradicate carriage state.

Furuncles, or boils, are infections of the skin and soft tissue usually associated with a hair follicle. *Carbuncles* are an extension of this skin and soft tissue infection continuum and involve more of the surrounding and subcutaneous tissue. The broad category *skin and soft tissue infections* (SSTIs) is used to describe this continuum that includes furuncles and carbuncles. SSTIs are common in both healthy and immunocompromised patients and likely initiate with some breach of the skin integrity, such as irritation of hair follicles from friction or microscopic trauma to the skin.

Up to 74% of furuncles and carbuncles are caused by community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) (CDC, 2010). Other potential causative organisms include nonresistant *Staphylococcus* spp. and *Streptococcus* spp. It has become increasingly important to obtain culture of a lesion to direct antibiotic coverage given the increase in CA-MRSA.

There is no reliable historical or examination element that will distinguish a CA-MRSA from a methicillin-sensitive staphylococcal skin lesion. Stereotypically, patients report CA-MRSA lesions starting like a spider bite. Furuncles and carbuncles can occur anywhere on the body, although the axillae, groin, and buttocks are particularly common sites. In addition, practices that cause skin trauma (e.g., shaving, waxing) are often noted in patients with these SSTIs. Fever and malaise are uncommon with milder lesions but become more frequent with the increasing scope of localized infection.

Of primary importance in the management of carbuncles and furuncles is facilitation of drainage of any purulent material. With smaller lesions, this may be accomplished by heat application by the patient at home. As lesions increase in size and fluctuance, surgical drainage is essential to facilitate resolution of an SSTI. It is important to consider culture

Table 16-17 Antimicrobial Therapy for Impetigo and for Skin and Soft Tissue Infections (SSTIs)

	Dosage		
Antibiotic	**Adults**	**Children***	**Comments**
Impetigo†			
Dicloxacillin	250 mg qid PO	12 mg/kg/day in 4 divided doses PO	—
Cephalexin	250 mg qid PO	25 mg/kg/day in 4 divided doses PO	—
Erythromycin	250 mg qid PO‡	40 mg/kg/day in 4 divided doses PO	Some strains of *Staphylococcus aureus* and *Streptococcus pyogenes* may be resistant.
Clindamycin	300-400 mg tid PO	10-20 mg/kg/day in 3 divided doses PO	—
Amoxicillin/ clavulanate	975/125 mg bid PO	25 mg/kg/day of amoxicillin component in 2 divided doses PO	—
Mupirocin ointment	Apply to lesions tid.	Apply to lesions tid.	For patients with limited lesions
MSSA SSTIs			
Nafcillin or oxacillin	1-2 g q4h IV	100-150 mg/kg/day in 4 divided dose	Parenteral drug of choice; inactive against MRSA
Cefazolin	1 g q8h IV	50 mg/kg/day in 3 divided doses	For penicillin-allergic patients, except those with immediate hypersensitivity reactions
Clindamycin	600 mg/kg q8h IV *or*300-450 mg tid PO	25-40 mg/kg/day in 3 divided doses IV *or* 10-20 mg/kg/day in 3 divided doses PO	Bacteriostatic; potential for cross-resistance and emergence of resistance in erythromycin-resistant strains; inducible resistance in MRSA
Dicloxacillin	500 mg qid PO	25 mg/kg/day in 4 divided doses PO	Oral agent of choice for methicillin-susceptible strains
Cephalexin	500 mg qid PO	25 mg/kg/day in 4 divided doses PO	For penicillin-allergic patients, except those with immediate hypersensitivity reactions
Doxycycline, minocycline	100 mg bid PO	Not recommended for children <8 yr	Bacteriostatic; limited clinical experience
TMP-SMZ	1 or 2 double-strength tablets bid PO	9-12 mg/kg (based on TMP component) in either 4 divided doses IV or 2 divided doses PO	Bacteriostatic; efficacy poorly documented
MRSA SSTIs			
Vancomycin	30 mg/kg/day in 2 divided doses IV	40 mg/kg/day in 4 divided doses IV	For penicillin-allergic patients; parenteral drug of choice for MRSA infections
Linezolid	600 mg q12h IV *or* 600 mg bid PO	10 mg/kg q12h IV or PO	Bacteriostatic; limited clinical experience; no cross-resistance with other antibiotic classes; expensive; may replace other second-line agents as preferred oral drug for MRSA infections
Clindamycin	600 mg/kg q8h IV *or* 300-450 mg tid PO	25-40 mg/kg/day in 2 divided doses IV *or*10-20 mg/kg/day in 3 divided doses PO	Bacteriostatic; potential for cross-resistance and emergence of resistance in erythromycin-resistant strains; inducible resistance in MRSA
Daptomycin	4 mg/kg every 24 hours IV	Not applicable	Bactericidal; possible myopathy
Doxycycline, minocycline	100 mg bid PO	Not recommended for children <8 yr	Bacteriostatic; limited clinical experience
TMP-SMZ	1 or 2 double-strength tablets bid PO	9-12 mg/kg (based on TMP component) in either 4 divided doses IV or 2 divided doses PO	Bactericidal; limited efficacy data

Modified from Stevens D et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis 2005;41:1373-1406.
MSSA, Methicillin-susceptible *Staphylococcus aureus; MRSA,* methicillin-resistant *S. aureus; TMP-SMZ,* trimethoprim-sulfamethoxazole; *PO,* orally; *IV,* intravenously; *qid,* four times daily; *tid,* three times daily; *bid,* twice daily; *q4h,* every 4 hours; *q8h,* every 8 hours; *q12h,* every 12 hours.
*Doses listed not appropriate for neonates.
†Infection caused by *Staphylococcus* and *Streptococcus* spp. Duration of therapy is about 7 days, depending on clinical response.
‡Adult dosage of erythromycin ethylsuccinate is 400 mg qid PO.

of purulent material when performing incision and drainage in the event that the patient fails to improve and antibiotic coverage becomes necessary. Cure rates of lesions with drainage alone exceed 90%. Careful follow-up after drainage is essential to ensure clinical improvement; daily dressing changes in the office after surgical drainage is effective. The addition of postdrainage antibiotics has not shown much added benefit.

To prevent the spread of infection to others who come into contact with the patient recovering from an SSTI, an occlusive dressing to prevent leakage of lesion fluid and careful hygiene are indicated. There is no evidence that extensive cleaning of common spaces (e.g., locker rooms) prevents the spread of SSTI-causing bacteria more than routine cleaning measures. Towels and soiled clothing should be laundered in hot water, and any common equipment should be cleaned per manufacturer recommendations.

When lesions do not respond to heat, or when lesions are larger yet not amenable to drainage, antibiotics may be used. Reasonable first-line antibiotic coverage for nonfluctuant lesions may include dicloxacillin, first- or second-generation cephalosporins, macrolides, or clindamycin. In patients with suspected CA-MRSA, better choices include TMP-SMX, tetracycline, or clindamycin. It is important to note that up to 50% of CA-MRSA species will be resistant to clindamycin, particularly if the patient has been treated with other antibiotics in the previous weeks to months (Stevens et al., 2005). Oral administration of these antibiotics is acceptable in the nontoxic patient. Patient signs and symptoms that would warrant hospital admission include fever or hypothermia, tachycardia, or hypotension as signs of sepsis and lesions greater than 5 cm in size (Table 16-18).

For patients with recurrent SSTIs, evaluation for the presence of nasal carriage with a nasal culture is indicated. The value of eradication of bacterial carriage is unclear. Referral for infectious disease specialist evaluation may be indicated to guide decision making in the patient with recurrent furuncles and carbuncles.

Table 16-18 Proposed Strategy for Management of Patients with Skin and Soft Tissue Infection (SSTI)

Class	Patient Criteria	Management	Antibiotic
1	Afebrile and healthy, other than cellulitis	Treat with common first-line antibiotics for SSTI if no drainable abscess. Surgical drainage with or without antibiotics.	Semisynthetic penicillin, Oral 1st/2nd-generation cephalosporin, macrolide, or clindamycin
2	Febrile and ill appearing, but no unstable comorbidities; lesion <5 cm	Surgical drainage of abscess if possible. Treat presumptively for MRSA and monitor closely for response. Inpatient management may be indicated.	Trimethoprim-sulfamethoxazole (TMP-SMX), tetracycline (TTC), or clindamycin
3	Toxic appearance or at least one unstable comorbidity or a limb-threatening infection	Hospital admission with broad-spectrum antibiotics with MRSA coverage; infectious disease (ID) consultation.	Broad-spectrum coverage, including vancomycin
4	Sepsis syndrome or life-threatening infection (necrotizing fasciitis)	Same as above, plus aggressive surgical debridement.	Same as above, with ID specialist guidance

Modified from McBride D. CA-MRSA lesions: what works, what doesn't. J Fam Pract 2008;57:588-592.

KEY TREATMENT

Cure rates of fluctuant skin lesions with drainage alone is over 90%. Postdrainage antibiotics do not significantly improve outcomes (Stevens et al., 2005; Rajendran et al., 2007) (SOR: A). Trimethoprim-sulfamethoxazole (TMP-SMX), clindamycin, and tetracycline are first-choice antibiotics when CA-MRSA is suspected. Up to 50% of CA-MRSA species will be resistant to clindamycin, particularly in the patient previously treated with other antibiotics (Stevens et al., 2005) (SOR: C).

DIABETIC ULCERS

William E. Roland

Key Points

- The existence, severity, and extent of infection, as well as vascular status, neuropathy, and glycemic control, should be assessed in patients with a diabetic foot infection.
- Visible bone and palpable bone on probing suggest underlying osteomyelitis in patients with a diabetic foot infection.
- Before an infected wound of a diabetic foot infection is cultured, any overlying necrotic debris should be removed to eliminate surface contamination and to provide more accurate results.

Patients with diabetes are prone to skin ulcers caused by neuropathy, vascular insufficiency, and diminished neutrophil function. Minor wounds can be secondarily infected, leading to ulcer formation. These ulcers often have extensive undermining with necrotic tissues and are often close to the anus, thus promoting an environment suitable for multiple species of microorganisms, including anaerobes. Diabetic foot infections range in severity from superficial paronychia to deep infection involving bone. Non–limb-threatening infections involve superficial ulcers with minimal cellulitis (<2 cm from portal of entry), no signs of systemic toxicity, and no significant ischemia in the limb.

Common causes of infections are aerobic gram-positive bacteria, particularly *Staphylococcus aureus* and beta-hemolytic streptococci. Limb-threatening infections have extensive cellulitis, lymphangitis, ulcers extending to the

subcutaneous tissues, and prominent ischemia. Infection in patients who have recently received antibiotics or who have deep, limb-threatening infection or chronic wounds are usually caused by a mixture of aerobic gram-positive, aerobic gram-negative (e.g., *Escherichia coli*, *Proteus* spp., *Klebsiella* spp.), and anaerobic organisms (e.g., *Bacteroides*, *Clostridium*, *Peptococcus*, and *Peptostreptococcus* spp.). Surgery is necessary to unroof encrusted areas, and the wounds need to be examined and probed to determine the extent of the infection and check for bone involvement (Dinh et al., 2008). Debridement or drainage should be promptly performed. Deep wound cultures should be obtained if possible. If deep culture is not feasible, Gram stain and culture from the curettage of the base of the ulcer or from purulent exudates may be needed to guide antibiotic therapy (Figure 16-11).

Plain radiography of the foot is indicated for detection of osteomyelitis, foreign bodies, and soft tissue gas. When plain radiography is negative but osteomyelitis is clinically suspected, radionuclide scan or MRI should be performed. MRI provides more accurate information regarding the extent of the infectious process. The presence of peripheral artery disease and neuropathy should be assessed.

The antibiotic regimen should be based on meaningful bacteriologic data. However, the initial regimen for a previously untreated patient with non–limb-threatening infection should focus on *S. aureus* and streptococci. Mild infections may be treated with dicloxacillin or cephalexin for 2 weeks. Amoxicillin/clavulanate may be used if polymicrobial infection is suspected. If MSRA is suspected, oral treatment options include TMP-SMX or doxycycline. For limb-threatening infections, broad-spectrum antibiotics are recommended for coverage of group B streptococci, other streptococci, Enterobacteriaceae, anaerobic gram-positive cocci, and *Bacteroides* spp. Treatment regimens include ampicillin-sulbactam or ertapenem (Invanz), clindamycin plus a third-generation cephalosporin, and clindamycin plus ciprofloxacin. Intravenous vancomycin should be added if MRSA infection is suspected. Ciprofloxacin as a single agent is not recommended.

In addition to antibiotic treatment, good glycemic control should be obtained and open wounds gently packed with sterile gauze moistened with ¼-strength povidone-iodine (Betadine) solution. Edema should be reduced by bed rest, elevation, and diuretic therapy as indicated. For prevention of diabetic foot ulcers, all patients with diabetes should have an annual foot examination that includes assessment for anatomic deformities, skin breaks, nail disorders, loss of protection sensation, diminished arterial supply, and inappropriate footwear.

KEY TREATMENT

Routine wound swabs and cultures of material from sinus tracts are unreliable and strongly discouraged in the management of diabetic foot infection (Pellizzer et al., 2001; Senneville et al., 2006) (SOR: B).

The empiric antibiotic regimen for diabetic foot infection should always include an agent active against *Staphylococcus aureus*, including MRSA if necessary, and streptococci (Abdulrazak et al., 2005; Lipsky et al., 2004). (SOR: A)

BITE INFECTIONS

David McCrary

Key Points

- The use of prophylactic antibiotics may be necessary in the initial management of bite wounds, particularly if the bite is on the hand or face or from a cat.
- First-generation cephalosporins (e.g., cephalexin) are not effective as monotherapy for bite wounds because of resistance issues.
- Avoid primary wound closure in the management of bite wounds.

It is estimated that bites account for 800,000 medical visits annually in the United States, making up 1% of emergency department visits. Bite wounds consist of lacerations, evulsions, punctures, and scratches. The microbiology of bite wounds is generally polymicrobial, with an array of potential bacteria from the environment, the victim's skin flora, and the biter's oral flora.

Animal Bites

Dog bites account for approximately 80% of all animal bites requiring medical attention, in which 85% are provoked attacks. Most dog bites occur on the distal extremities, but children tend to sustain facial bites. Patients who present for medical attention are often concerned about the care of disfiguring wounds or the need for appropriate vaccination (i.e., tetanus, rabies). However, up to 30% of medically treated wounds may become infected. These wounds are often contaminated with multiple strains of aerobic and anaerobic bacteria. Local signs of infection with erythema, edema, pain, and purulent drainage are common with animal bite wounds.

Although the most frequently isolated pathogen related to dog and cat bite wounds is *Pasteurella multocida*, the array of potential organisms is much greater. Anaerobes such as *Bacteroides tectum*, *Prevotella* spp., fusobacteria, and peptostreptococci can be isolated from animal bite wounds 75% of the time, mostly from wounds with abscess formation. *Capnocytophaga canimorsus* has also been associated with fatal infection from fulminant sepsis in asplenic patients. Wounds inflicted by cats are often scratches or tiny punctures located on the extremity and are likely to become infected and lead to abscess formation.

In the United States, venomous snakes bite approximately 8000 people yearly. Envenomation in such snakebites account for the majority of morbidity and mortality associated with such bites. However, infection of soft tissue structures may also occur as a result of oral flora from the snake, which tends to be fecal in nature because live prey usually defecate in the snake's mouth with their ingestion.

Human Bites

Human bites are not uncommon, especially in children. Human bites have a higher complication and infection rate than do animal bites. Human bite wounds most often affect the hand and fingers and in some cases may present as "love

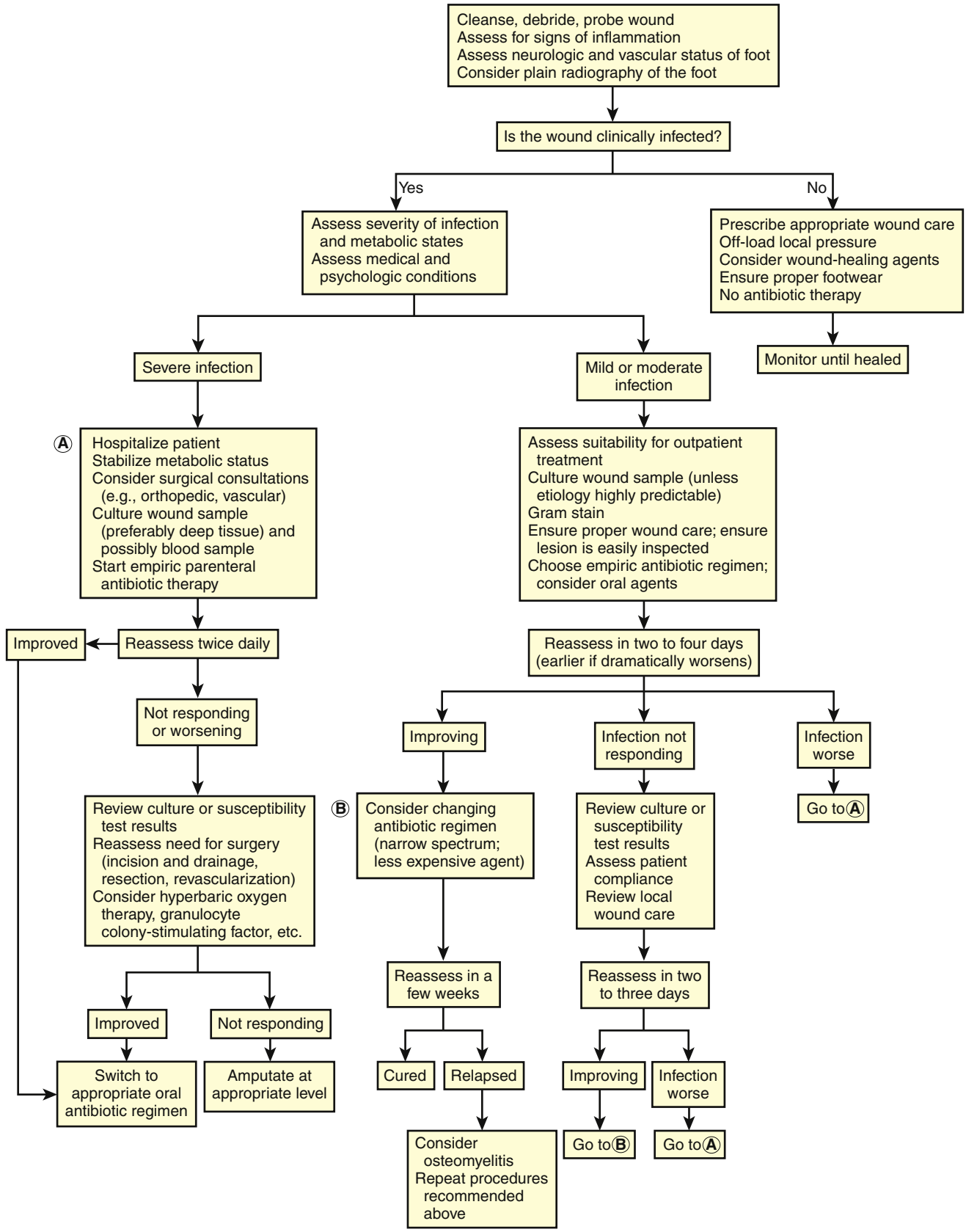


Figure 16-11 Algorithm for the evaluation and treatment of diabetic foot infection.
(Modified from Lipsky BA. Medical treatment of diabetic foot infections. Clin Infect Dis 2004;39(suppl 2):S110.

nips" to the breast and genital areas. Self-inflicted bites often include wounds of the lip and tissues surrounding the nail, such as paronychia. Also included in this are clenched-fist injuries or "fight bites," which result in small lacerations to the knuckles when striking a person in the mouth. Normal human oral flora, rather than skin flora, is the source of most bacteria isolated from human bite wound cultures (viridans streptococci, *Eikenella corrodens*).

Treatment

Management of bite wounds is the same as for any other wound: good wound care in the form of adequate irrigation and debridement of nonviable tissue as needed (Table 16-19). Bite wounds in general do not require primary closure, but after adequate irrigation and debridement, wounds may be approximated and closed by delayed primary or secondary intention. An exception to this rule may include bite wounds to the face. General wound management measures such as tetanus toxoid administration should also be employed. Bite wounds involving the hands should be evaluated by a hand surgeon, given the risk of adjacent tendon sheath, bone, or joint involvement and the dire consequences if such structures are involved.

The transmission of *rabies* through the bites of domestic pets in the United States and developed countries is rare. In fact, the dog strain of rabies is considered eliminated in the U.S. dog population, and cat bites are often managed through observation of the animal, without the immediate need for rabies *postexposure treatment* (PET). However, wild mammal exposure, especially bat, skunk, or raccoon, often warrants PET, which involves thorough cleaning of the bite wound, ideally with povidone-iodine solution, along with rabies immune globulin given at the wound site and rabies vaccine given on days 0, 3, 7, and 14.

Bite wounds should be considered contaminated wounds from presentation, given the oral microbial flora of humans and animals, and most patients should probably receive antibiotics early. Empiric antibiotics are used to eradicate oral flora inoculated from the mouth of the biter, whether human or animal, into the wound. All moderate to severe animal bite wounds, or wounds that have an associated crush injury or that are close to a bone or joint, should be considered contaminated with potential pathogens, and these patients should receive 3 to 5 days of "prophylactic" antimicrobial therapy. Gram stains with culture of bite wounds are specific but not sensitive indicators of bacterial growth. Nonetheless, Gram stain can be used to help guide initial empiric antibiotic therapy.

Amoxicillin–clavulanic acid (amoxicillin-clavulanate; Augmentin) or penicillin plus a penicillinase-resistant penicillin are normally first-line agents for empiric therapy directed at bite wounds. First-generation cephalosporins (e.g., cephalexin) are not effective as monotherapy because of resistance of some anaerobic bacteria and *E. corrodens*. A 5- to 10-day course of antibiotics is usually adequate for infections limited to the soft tissue, and a minimum of 3 weeks of therapy is required for infections involving joints or bones. Close follow-up is required in all bites to ensure adequate healing.

Of special consideration in human bite wounds is the potential for spread of viral pathogens, most notably *hepatitis B virus* (HBV) and HIV, if the source person is positive. HBV exposure in this setting should be handled in the same manner as other exposures, with administration of HBIG and HBV vaccination. With regard to HIV, CDC guidelines for managing nonoccupational HIV exposure recommend handling each case individually in consultation with an infectious diseases specialist.

KEY TREATMENT

Use of antibiotic prophylactic after bites of the hand reduces the incidence of infection (Medeiros and Saconato, 2005) (SOR: B). Antibiotic prophylaxis after bites by humans reduces incidence of infection (SOR: C).

BONE AND JOINT INFECTIONS

Anthony Zeimet

Key Points

- The diagnosis of osteomyelitis is based on radiographic findings (plain radiograph or MRI) showing bony destruction along with histologic analysis and culture results.
- Chronic osteomyelitis is not an emergency, and antibiotics can be safely withheld until an etiologic diagnosis is established.
- Diabetic foot infections require a careful evaluation to assess perfusion and vascular supply, and corrective measures should be undertaken to reestablish adequate perfusion if necessary.
- In diabetic foot ulcers, if one can probe to bone, the patient most likely has osteomyelitis.
- Orthopedic hardware infections are best managed in conjunction with an infectious diseases specialist and orthopedic surgeon.

Osteomyelitis

Osteomyelitis is defined as progressive, inflammation leading to destruction of the bone, usually secondary to an infectious agent. Bacteria can enter bone through hematogenous seeding or a contiguous focus after trauma, implantation of a foreign device, or a local soft tissue infection. Acute osteomyelitis is defined as infection that evolves over a few weeks. Chronic osteomyelitis implies persistent infection of several weeks to months.

Hematogenous osteomyelitis occurs primarily in children within the metaphyses of long bones (tibia and femur) and vertebrae in adults. In addition to local signs of inflammation and infection, patients generally have various systemic signs, including fever, irritability, and lethargy. Physical findings include tenderness over involved area and decreased range of motion in adjacent joints. Chronic osteomyelitis usually occurs in adults, caused by an open injury to bone and surrounding soft tissue. Erythema, drainage around area, and bone pain are usually present on physical examination. Systemic symptoms occur less frequently.

The diagnosis of osteomyelitis is based on the clinical picture and supporting laboratory and radiologic findings. Leukocytosis and elevations in CRP and ESR may

Table 16-19 Management of Bite Wounds

History
Animal bite: Ascertain the type of animal, whether the bite was provoked or unprovoked, and the situation/environment in which the bite occurred. If the species can be rabid, locate the animal for 10 days' observation or sacrifice. *Patient:* Obtain information on antimicrobial allergies, current medications, splenectomy, mastectomy, liver disease, and immunosuppression.
Physical Examination
Record a diagram of the wound with the location, type, and depth of injury; range of motion; possibility of joint penetration; presence of edema or crush injury; nerve and tendon function; signs of infection; and odor of exudate.
Culture
Infected wounds should be cultured and a Gram stain performed. Anaerobic cultures should be obtained in the presence of abscesses, sepsis, serious cellulitis, devitalized tissue, or foul odor of the exudate. Small tears and infected punctures should be cultured with a minitipped (nasopharyngeal) swab.
Irrigation
Copious amounts of normal saline should be used for irrigation. Puncture wounds should be irrigated with a "high-pressure jet" from a 20-mL syringe and an 18-gauge needle or catheter tip.
Debridement
Devitalized or necrotic tissue should be cautiously debrided. Debris and foreign bodies should be removed.
Radiographs
Radiographs should be obtained if fracture or bone penetration is possible to provide a baseline for future osteomyelitis.
Wound Closure
Wound closure may be necessary for selected, fresh, uninfected wounds, especially facial wounds, but primary wound closure is not usually indicated. Wound edges should be approximated with adhesive strips in selected cases.
Antimicrobial Therapy
Prophylaxis: Consider prophylaxis (1) for moderate to severe injury less than 8 hours old, especially if edema or crush injury is present; (2) if bone or joint penetration is possible; (3) for hand wounds; (4) for immunocompromised patients (including those with mastectomy, liver disease, or steroid therapy); (5) if the wound is adjacent to prosthetic joint; and (6) if the wound is in the genital area. Coverage should include *Pasteurella multocida, Staphylococcus aureus,* and anaerobes. *Treatment:* Cover *P. multocida, S. aureus,* and anaerobes. Use oral medication if the patient is seen early after a bite and only mild to moderate signs of infection are present. The following can be considered for cat or dog bites in adults: • *First choice:* Amoxicillin/clavulanic acid, 875/125 mg bid or 500/125 mg tid with food. • *Penicillin allergy:* No alternative treatment for animal bites has been established for penicillin-allergic patients. The following regimens can be considered for adults: 1. Clindamycin (300 mg PO qid) plus either levofloxacin (500 mg PO daily) or trimethoprim-sulfamethoxazole (2 double-strength tablets PO bid). 2. Doxycycline, 100 mg PO bid. 3. Moxifloxacin, 400 mg PO daily. 4. In the highly penicillin-allergic pregnant patient, macrolides have been used, but the wounds must be watched carefully. On emergency department discharge, a single starting dose of parenteral antibiotic, such as ertapenem (1 g), may be useful in selected cases. If hospitalization or closely monitored outpatient follow-up is required, intravenous agents should be used. Current choices include ampicillin/sulbactam and cefoxitin. The rising incidence of community-acquired *S. aureus* isolates that are methicillin resistant and therefore resistant to the drugs recommended here emphasizes the importance of susceptibility-testing any *S. aureus* isolates.
Hospitalization
Indications include fever, sepsis, spread of cellulitis, significant edema or crush injury, loss of function, a compromised host, and patient noncompliance.
Immunizations
Give tetanus booster (Td; tetanus and diphtheria toxoids for adults) if original three-dose series has been given but none in the past 5 years. Adults who have not received acellular pertussis vaccine (Tdap), should be given this instead of Td. Give a primary series and tetanus immune globulin if the patient was never immunized. Rabies vaccine (on days 0, 3, 7, 14, and 28) with hyperimmune globulin may be required, depending on the type of animal, ability to observe the animal, and locality.
Elevation
Elevation may be required if any edema is present. Lack of elevation is a common cause of therapeutic failure.

Table 16-19 Management of Bite Wounds—cont'd

Immobilization
Immobilize the extremity, especially hands, with a splint.
Follow-up
Follow-up should occur at 24 hours and perhaps 48 hours for outpatients.
Reporting
Reporting the incident to a local health department may be required.

From Goldstein EJC. Bites. In Mandell GL, Bennett JE, Dolin RD (eds). Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 7th ed. Philadelphia, Churchill Livingstone-– Elsevier, 2010.
PO, Orally; *bid,* twice daily; *tid,* three times daily; *qid,* four times daily.

be seen but can also be normal. Blood cultures may be positive in up to half of children with acute osteomyelitis. If plain radiographs show bone destruction and inflammation; the diagnosis of osteomyelitis is confirmed. Typical findings on plain-radiographs will include osteolysis, periosteal reaction, and sequestra (segments of necrotic bone separated from living bone by granulation tissue). Findings seen on plain radiographs usually denote a process that has been ongoing for at least 2 weeks. Bone scintigraphy (bone scan) is often performed on patients with suspected osteomyelitis; however, sensitivity is quite low, and a negative result can offer false reassurance to the physician, so its routine use is not recommended. If the plain-radiographs are negative but the suspicion for osteomyelitis is still high, an MRI scan should be considered.

Once the diagnosis of osteomyelitis has been made, the next step is to obtain an etiologic diagnosis. Histopathologic and microbiologic examination of bone is the "gold standard." Cultures of sinus tracts are not reliable for identifying the causative organism. Common causative bacteriologic organisms in neonates include *Staphylococcus aureus,* group B streptococci, and *Escherichia coli.* Later in life, *S. aureus* is most common, and in elderly persons, gram-negative organisms such as *Pseudomonas aeruginosa* and *Serratia* spp. have increased incidence.

Empiric antibiotics are rarely required for chronic disease but are often necessary for acute osteomyelitis. Ideally, surgical debridement of all necrotic tissue and inflammatory debris (pus) should be undertaken and multiple surgical cultures with bone histology samples obtained. Antimicrobial therapy will be dictated by test results. Generally, treatment is for 4 to 6 weeks. With the exception of the fluoroquinolone class of antibiotics, which achieve high serum levels with oral administration, bone antibiotic levels cannot exceed the minimum inhibitory concentration (MIC) for the infecting organism; therefore, antibiotics must be given intravenously. This underscores the importance in obtaining a bacterial diagnosis so that the appropriate antibiotic can be used for the duration of treatment. Acute osteomyelitis is usually readily curable; however, chronic osteomyelitis is generally more refractory to therapy and requires repeat debridement and antibiotic courses.

Diabetic Foot Osteomyelitis

Patients with uncontrolled diabetes are at increased risk for development of osteomyelitis, especially in the presence of neuropathy or venous or arterial insufficiency. *S. aureus* and beta-hemolytic streptococci are the predominant organisms, although other gram-positive or gram-negative aerobic or anaerobic bacteria may also be seen. Plain radiographs should be the initial test to evaluate for the presence of osteomyelitis, followed by MRI if negative. If there is a draining sinus, the "probe to bone" test should be performed with a sterile probe; if bone is palpated, the diagnosis of osteomyelitis is highly likely. Further evaluation of the diabetic patient should be to assess for vascular insufficiency with the use of ankle-brachial indices and transcutaneous oximetry. If significant compromise is found, arteriography followed by revascularization should be undertaken. Surgical debridement is again the cornerstone of treatment, along with antibiotics directed toward the causative microorganism.

Orthopedic Hardware Infections

Infections secondary to orthopedic hardware devices have become common problems with the increasing incidence of hip, knee, and shoulder replacement surgeries. Also, patients with traumatic injury resulting in a fracture often have hardware implanted to stabilize the bone. These patients present in one of the three following ways:

1. *Early:* Symptoms develop less than 3 months after surgery and have an acute presentation with pain, erythema, and warmth, usually caused by *S. aureus* and gram-negative bacilli.
2. *Delayed:* Symptoms develop 3 to 24 months after surgery, generally with subtle signs of infection, including implant loosening and persistent pain, and usually caused by less virulent organisms such as coagulase-negative staphylococci and *Propionibacterium acnes.*
3. *Late:* Symptoms develop 24 months after surgery and are usually caused by hematogenous seeding from skin, dental, respiratory, and urinary infections.

Treatment requires debridement of the surrounding tissue and hardware removal, although this cannot always be done in patients with bone instability. It is recommended that treatment

of these infections be done in conjunction with an infectious diseases specialist working with the orthopedic surgeon.

Septic Arthritis

Septic arthritis is defined as infection within the joint space of two bones. The major causative organisms include *S. aureus* and in the sexually promiscuous individual, *Neisseria gonorrhoeae.* Intravenous drug users are likely to develop septic arthritis within unusual joints (e.g., sternoclavicular, sacroiliac). Rheumatoid arthritis, presence of joint prostheses, and steroid use are predisposing factors for development of septic arthritis.

Diagnosis is usually based on clinical presentation of a warm, swollen joint with limitation in range of motion. A joint aspiration should be completed and the synovial fluid sent for Gram stain with culture, WBC count with differential, and crystal analysis to rule out gout and pseudogout. Blood cultures should also be drawn before initiation of antibiotics.

Gonococcal arthritis usually presents as an acute arthritis involving one or more joints in a sexually active individual. Two thirds of patients have dermatitis with one or multiple, usually asymptomatic, lesions that progress from macular to papular and finally vesicular or pustular. Joint fluid, urethral, and rectal cultures should also be obtained. Treatment is generally with a third-generation cephalosporin intravenously until improvement, followed by oral therapy to complete a 1-week course of therapy.

Treatment of nongonococcal arthritis requires proper draining of the infected joint. This is often done surgically, although repeat needle drainage may also be successful if the joint is easily accessible. Treatment generally depends on the Gram stain and includes a third-generation cephalosporin, with the addition of vancomycin if gram-positive cocci in clusters are seen. Duration of therapy is 3 to 4 weeks.

KEY TREATMENT

Treatment of osteomyelitis requires surgical debridement followed by a 4- to 6-week course of intravenous antibiotic therapy (SOR: C).
Septic arthritis is usually caused by a gonococcus in a sexually active adult, and use of a third-generation cephalosporin is the mainstay of therapy (Workowski and Berman, 2006) (SOR: A).
Nongonococcal arthritis should be treated with surgical debridement or repeated needle aspirations, with a third-generation cephalosporin and vancomycin if gram-positive cocci are seen (Goldenberg, 1998) (SOR: B).

FEVER OF UNKNOWN ORIGIN

Anthony Zeimet

Key Points

- A comprehensive history and physical examination with laboratory and radiologic evaluation are important in the workup for fever of unknown origin (FUO).
- If routine information is unrevealing, more specific testing for FUO is undertaken based on the patient's age, travel history, and disease process to develop a differential diagnosis.
- The serum ferritin level (often elevated with malignancy) and naproxen test (reduces fever with malignancy) may be helpful in determining an underlying malignant process.
- Initiation of empiric antibiotics should be done only in specific FUO situations to prevent skewing culture results, thus maximizing isolation of the causative organism.

Patients who have a persistent fever despite workup are generally classified as having a "fever of unknown origin" (FUO). In 1961, Petersdorf and Beeson described 100 patients with persistent fever, otherwise known as fever of unknown origin. They introduced the standard, classic definition of FUO: fever higher than 38.3° C (101° F) on several occasions, persisting without diagnosis for at least 3 weeks, with 1 week of investigational study in the hospital setting. With advancing technology, this definition has been revised to allow for more than two outpatient visits, or 3 days if investigation is in the hospital setting. Most patients with FUO have chronic or subacute symptoms and can be safely evaluated in the outpatient setting, with a median time to diagnosis of 40 days.

The differential diagnosis of FUO is quite broad and extensive. Determining an etiologic diagnosis of an FUO depends on generating a differential diagnosis compatible with the patient's history and physical examination. The principal disease categories for FUO include infection (30% overall), neoplasms (18%), collagen vascular diseases (12%), and miscellaneous (14%) (Box 16-5). Because of this broad differential, a newer classification system divides FUO into four groups: classic, nosocomial, neutropenic, and HIV associated, which helps narrow the differential diagnosis. Furthermore, classic FUO can be broken down into three subgroups: infants and children, elderly, and travelers. Despite an extensive workup, the etiologic diagnosis usually remains elusive in 7% to 30% of patients (Box 16-4).

The diagnostic workup of FUO should begin with a thorough history and physical examination, including documentation of the fever. The patient may provide a diary noting the date and time of fever. Routine noninvasive investigations are recommended in all patients before diagnosing FUO (Box 16-6). Acute febrile illness is never called an FUO. The patient's medication profile is reviewed because numerous drugs can be the cause. If unrevealing, a workup is initiated based on the differential diagnosis for the patient's age, travel history, geographic location, and disease process. Dukes criteria for infective endocarditis have 99% specificity in patients with FUO. When the initial investigations are not helpful in identifying a cause, imaging should be considered, such as computed tomography (CT) scans of the chest, abdomen, and pelvis; CT may reveal an abscess or suggest an underlying malignancy. An elevated serum ferritin level can suggest a neoplasm or myeloproliferative disorder and, if normal, greatly decreases the chance that the patient has an underlying malignancy. Lower-extremity Doppler ultrasound should be considered in the sedentary or obese patient to rule out deep venous thrombosis. A temporal artery biopsy should be considered in the elderly patient to rule out temporal arteritis. Liver biopsy has a high diagnostic yield with minimal toxicity, whereas bone marrow cultures usually have a low yield and should be considered only in special situations.

Empiric therapy with antibiotics is rarely appropriate for the patient with FUO. A diagnosis is essential to guide

Box 16-4 Differential Diagnosis for Fever of Unknown Origin (FUO)

Classic

Infections: Abscesses, endocarditis, tuberculosis (TB), complicated urinary tract infection (UTI).

Geographic location: Leishmaniasis (Spain), melioidosis (Southeast Asia, Australia), Kikuchi-Fujimoto disease (form of necrotizing lymphadenitis, Japan).

Connective tissue diseases: Juvenile rheumatoid arthritis (JRA, Still's disease), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), temporal arteritis, polymyalgia rheumatica (PMR).

Neoplasms: malignant neoplasm, lymphoma, leukemia.

Other: Familial Mediterranean fever in Ashkenazi Jews.

Infants and Children

Respiratory infections predominate if <12 years.

Kawasaki disease if <5 years.

JRA, (Still's disease) in the older child/young adult.

Elderly

Connective tissue diseases are more prominent.

Travelers

Infections: Malaria, hepatitis, pneumonia/bronchitis, UTI/pyelonephritis, dysentery, dengue fever, enteric fever, TB, rickettsial infection, acute human immunodeficiency virus (HIV) infection, amebic liver abscess.

Nosocomial

Postoperative urinary and respiratory tract instrumentation; use of intravascular devices; drug therapy; immobilization.

Septic thrombophlebitis, pulmonary embolus, *Clostridium difficile* colitis, drug fever.

Neutropenic

Fungal: 40% susceptible to empiric antifungals, 5% will be resistant to empiric therapy.

Bacterial: 10% not responding to empiric antimicrobial therapy and usually with cryptic focus.

Unusual pathogens: 5% will be toxoplasmosis *(Toxoplasma gondii)* reactivation, atypical mycobacterial, TB, fastidious pathogens *(Legionella, Mycoplasma, Chlamydophila).*

Viral: 5% of causes (HSV, CMV, EBV, HHV-6, VZV, RSV, influenza, parainfluenza).

Other: 10% will be transplant related (e.g., GVHD) following stem cell transplant, 25% will be undefined.

HIV Associated

Infections: Mycobacterium avium complex (MAC), *Pneumocystis carinii* pneumonia (PCP), cytomegalovirus (CMV), histoplasmosis, viral (HCV, HBV, adenovirus, HSV esophagitis, VZV encephalitis), TB, other fungi, cerebral toxoplasmosis, disseminated cryptosporidiosis.

Neoplasms: Lymphoma, Kaposi's sarcoma.

Other: Drug fever, Castleman's disease.

HSV, Herpes simplex virus; *EBV,* Epstein-Barr virus; *HHV,* human herpesvirus; *VZV,* varicella-zoster virus; *RSV,* respiratory syncytial virus; *GVHD,* graft-versus-host disease; *HCV,* hepatitis C virus; *HBV,* hepatitis B virus.

Box 16-5 Causes of Fever of Unknown Origin

Infections

Abscesses: Hepatic, subhepatic, gallbladder, subphrenic, splenic, periappendiceal, perinephric, pelvic, and other sites.

Granulomatous: Extrapulmonary and miliary tuberculosis, atypical mycobacterial infection, fungal infection.

Intravascular: Catheter-related endocarditis, meningococcemia, gonococcemia, *Listeria, Brucella,* rat-bite fever, relapsing fever.

Viral, rickettsial, and chlamydial: Infectious mononucleosis, cytomegalovirus, human immunodeficiency virus, hepatitis, Q fever, psittacosis.

Parasitic: Extraintestinal amebiasis, malaria, toxoplasmosis.

Noninfectious Inflammatory Disorders

Collagen vascular diseases: Rheumatic fever, systemic lupus erythematosus, rheumatoid arthritis (particularly Still's disease), vasculitis (all types).

Granulomatous: Sarcoidosis, granulomatous hepatitis, Crohn's disease.

Tissue injury: Pulmonary emboli, sickle cell disease, hemolytic anemia.

Neoplastic Diseases

Lymphoma/leukemia: Hodgkin's and non-Hodgkin's lymphoma, acute leukemia, myelodysplastic syndrome

Carcinoma: Kidney, pancreas, liver, gastrointestinal tract, lung, especially when metastatic

Atrial myxomas

Central nervous system tumors

Drugs

Sulfonamides

Penicillins

Thiouracils

Barbiturates

Quinidine

Laxatives (especially with phenolphthalein)

Factitious Illnesses

Injections of toxic material

Manipulation or exchange of thermometers

Other Causes

Familial Mediterranean fever

Fabry's disease

Cyclic neutropenia

From Dale DC. The febrile patient. In Goldman L, Ausiello D (eds). Cecil Textbook of Medicine, 22nd ed. Philadelphia, Saunders, 2004, p 1730.

treatment, and use of antibiotics may delay determining a causative infectious agent. The naproxen test (Naprosyn; 375 mg PO every 12 hours for 3 days) is helpful in determining if the fever is secondary to infection or malignancy. A dramatic decrease in the patient's temperature during the test generally indicates a malignant focus, whereas minimal or no response indicates an infectious etiology.

The prognosis of FUO depends on the etiologic category. Undiagnosed FUO has a very favorable outcome. Patients in whom diagnostic investigations fail to identify an etiology should be followed clinically with serial history reviews and physical examinations until the fever resolves or new diagnostic clues are found.

KEY TREATMENT

Diagnosis of FUO may be assisted by the Dukes criteria for endocarditis, CT scan of the abdomen, nuclear scanning with a technetium-based isotope, and liver biopsy (Mourad et al., 2003) (SOR: B).
Routine bone marrow cultures are not recommended in the FUO workup (Mourad et al., 2003) (SOR: B).
Empiric antibiotics should be initiated only in specific situations, to avoid skewing culture results and thus maximizing potential isolation of the causative organism (Mourad et al., 2003) (SOR: B).

Box 16-6 Minimal Diagnostic Workup to Qualify as Fever of Unknown Origin

Comprehensive history
Physical examination
Complete blood cell count plus differential
Blood film reviewed by hematopathologist
Routine blood chemistry (including lactate dehydrogenase, bilirubin, and liver enzymes)
Urinalysis and microscopy
Blood (×3) and urine cultures
Antinuclear antibodies, rheumatoid factor
Human immunodeficiency virus antibody
Cytomegalovirus IgM antibodies; heterophil antibody test (if consistent with mononucleosis-like syndrome)
Q-fever serology (if exposure risk factors exist)
Chest radiography
Hepatitis serology (if abnormal liver enzyme test result)

From Mourad O, Palda V, Detsky A. A comprehensive evidence-based approach to fever of unknown origin. Arch Intern Med 2003;163:545-551.

COMPLICATED INTRA-ABDOMINAL INFECTIONS

Richard Basilan

Intra-abdominal infections may either be *uncomplicated* (limited to the gut lumen, such as gastroenteritis or colitis) or *complicated* (extending through to the peritoneum) (Solomkin et al., 2010). The clinical presentation of complicated intra-abdominal infections can range from mild symptoms such as nausea, mild abdominal pain, and cramping to life-threatening septic shock.

Clinical findings result from local or diffuse inflammation with or without abscess formation. Fever and abdominal pain are typically present, with additional symptoms depending on the organ involved. Elderly and immunocompromised patients present with atypical, usually milder symptoms. Imaging studies form an important adjunct to diagnosis. Management involves empiric antibiotic coverage for bowel flora—mainly streptococci, enterococci, enteric gram-negative rods, and anaerobes—as well as controlling the source of infection, usually through surgery.

SPONTANEOUS BACTERIAL PERITONITIS

Richard Basilan

Key Points

- Spontaneous bacterial peritonitis usually occurs in the setting of ascites and chronic liver disease.
- Spontaneous bacterial peritonitis is a diagnosis of exclusion.
- Ascitic fluid culture yield improves with inoculation into blood culture bottles at bedside.

Spontaneous bacterial peritonitis (SBP) is a form of infectious peritonitis without a surgically correctable cause and is therefore a diagnosis of exclusion. The route of infection in SBP is usually not apparent and is often presumed to be hematogenous, lymphogenous, by transmural migration through an intact gut wall from the intestinal lumen, or in women, from the vagina via the fallopian tubes (Levison and Bush, 2010). SBP occurs in the setting of ascites in most cases, and it is particularly common in patients with cirrhosis. In pediatric populations, those with postnecrotic cirrhosis or nephrotic syndrome are more often affected. In adults, almost 70% of patients who develop SBP have Child-Pugh class C liver disease, and 10% to 30% of hospitalized patients with cirrhosis and ascites have SBP (Mowat and Stanley, 2001). SBP is almost always caused by a single organism, typically enteric gram-negative rods, most often *E. coli*, followed by *Klebsiella pneumoniae.* Gram-positive cocci account for about 25% of episodes of SBP, and streptococci are isolated most often. SBP caused by anaerobes is rare. Growth of more than one organism should raise the suspicion of secondary peritonitis.

Signs and symptoms of SBP are subtle and require a high index of suspicion. Fever greater than 100° F (38° C) is the most common presenting sign, occurring in 50% to 80% of cases. Abdominal pain, nausea, vomiting, and diarrhea are usually present. Peritoneal signs (abdominal tenderness or rebound tenderness) are common but may be absent in patients with ascites. In adults, mental status changes may also occur. SBP is often confused with acute appendicitis in children. In adults, SBP should be suspected in any patient with previously stable chronic liver disease who undergoes acute decompensation in clinical status.

Spontaneous bacterial peritonitis is diagnosed by analysis of ascitic fluid obtained by abdominal paracentesis. Infection has been typically defined as an ascitic fluid WBC count higher than 250 cells/mm^3, which is considered diagnostic even when the culture of the ascitic fluid is negative. In cases where bloody fluid is obtained ("traumatic paracentesis"), the WBC count should be corrected by 1 WBC per 250 RBCs/mm^3. The use of bedside dipstick for leukocyte esterase has a high false-negative rate and is not recommended (Nguyen-Khac et al., 2008). Ascitic fluid culture yield can be increased by inoculating blood culture bottles with 10 mL of ascitic fluid at the bedside. Blood cultures should also be obtained as part of the workup.

After the diagnosis of peritonitis is established, secondary peritonitis should be ruled out. CT of the abdomen with oral and intravenous contrast can help direct the surgeon to a particular source of infection, as opposed to doing a full exploratory laparotomy. A high ascitic fluid total protein (>1 g/dL) or amylase level is suggestive of secondary peritonitis. The treatment of choice is generally a third-generation cephalosporin such as cefotaxime (2 g IV every 8-12 hours) or ceftriaxone (2 g IV once daily). Patients who have an ascitic fluid WBC count higher than 250 cells/mm^3 should be given empiric intravenous antibiotics without delay. Oral amoxicillin–clavulanic acid can be used for mild, uncomplicated cases (Navasa et al., 1996). Duration of treatment varies

from 5 to 14 days depending on clinical response. Patients usually respond to appropriate antibiotic therapy within 48 to 72 hours; otherwise, a repeat paracentesis should be performed. If the ascitic fluid WBC count does not decrease by more than 25%, alternative diagnoses should be considered. Prophylaxis with a fluoroquinolone or trimethoprim-sulfamethoxazole should be considered, particularly in high-risk patients (Garcia-Tsao and Lim, 2009).

KEY TREATMENT

Spontaneous bacterial peritonitis is treated with third-generation cephalosporins (cefotaxime or ceftriaxone), with ampicillin-sulbactam, fluoroquinolones, or carbapenems as alternative agents (Solomkin et al., 2010) (SOR: B).
Patients with diffuse peritonitis should undergo an emergency surgical procedure as soon as possible, even if ongoing measures to restore physiologic stability need to be continued during the procedure (Solomkin et al., 2010) (SOR: B).

Discussions of the following infections can be found online at www.expertconsult.com:

- Secondary bacterial peritonitis and intra-abdominal abscesses
- Cholecystitis
- Cholangitis
- Appendicitis
- Diverticulitis

CENTRAL NERVOUS SYSTEM INFECTIONS

Richard Basilan

Key Points

- Bacterial meningitis is life threatening and requires urgent medical attention and treatment.
- Viral encephalitis should be treated with acyclovir until herpes simplex virus is ruled out.
- Most brain abscesses are caused by streptococci and *Staphylococcus aureus.*
- The CNS infections most likely to be encountered in clinical practice include meningitis, encephalitis, and abscess.
- All CNS infections can be difficult to diagnose, and a high index of suspicion by the health care provider is sometimes indicated to ensure patient survival.
- MRI is the most sensitive neuroimaging test for encephalitis.
- Acyclovir should be started immediately and continued until HSV PCR testing is obtained.

Bacterial Meningitis

Meningitis can be acute, subacute, or chronic. In otherwise healthy children, the three most common organisms causing acute bacterial meningitis are *Streptococcus pneumoniae, Neisseria meningitidis*, and *Haemophilus influenzae* type b (Hib). Isolation of an organism other than these three organisms from the CSF of a child older than 2 months always requires an explanation or evaluation for unusual host susceptibility. Children with cochlear implants, asplenia, HIV infection, or CSF leak from basilar skull or cribriform fracture are at greater risk for pneumococcal meningitis. Deficiencies in terminal components of complement lead to greater risk for meningococcal infection (Saez-Llorens and McCracken, 2008). In adults, the common etiologic agents of acute meningitis include *S. pneumoniae, N. meningitidis,* and *Listeria monocytogenes*.

Patients with acute meningitis most often present with fever, headache, meningismus, and altered mental status. Infants can present with nonspecific symptoms such as inconsolable crying, irritability, nausea, vomiting, and diarrhea. Lethargy, anorexia, and grunting respirations indicate a critically ill infant. Older children may complain of headache, vomiting, back pain, myalgia, and photophobia; may be confused or disoriented; and may verbalize specifically that the neck is stiff or sore. Seizures are noted in up to 20% to 30% of children before hospital admission or early in the course of the illness.

In contrast, patients with subacute or chronic meningitis may have the same symptoms with a much more gradual onset, lower fever, and associated lethargy and disability. *Mycobacterium tuberculosis, Treponema pallidum* (syphilis), *Borrelia burgdorferi* (Lyme disease), and fungi (e.g., *Cryptococcus neoformans, Coccidioides* spp.) are the most common agents (Tunkel et al., 2010).

Physical examination should look for papilledema, middle ear and sinus infections, petechiae (common with *N. meningitidis*), nuchal rigidity, and in infants, a bulging fontanel. Blood cultures should be taken. A lumbar puncture (LP) for CSF analysis should be done as soon as possible. A brain CT scan before LP is not necessary if the patient has no evidence of immunocompromise, CNS disease, new seizure, papilledema, altered consciousness, or focal neurologic deficit, and if a subarachnoid hemorrhage is not suspected. If neuroimaging is necessary, blood cultures should be taken and antibiotics given before the study; a delay in administration of antibiotics leads to a worse outcome. CSF should be sent for cell count, WBC differential, glucose, protein, and Gram stain with culture. Acid-fast bacilli stain and cryptococcal antigen may be obtained when indicated.

Empiric antibiotics for the initial treatment of bacterial meningitis are listed in Table 16-20, but these should be tailored to the isolated organisms whenever possible. Adjunctive dexamethasone is recommended for children and infants with Hib meningitis, but not if they have already received antibiotics. In adults, adjunctive dexamethasone is recommended for pneumococcal meningitis (Tunkel et al., 2004). Close contacts of patients with *N. meningitidis* should receive rifampin, 20 mg/kg (not to exceed 600 mg) twice daily for 2 days, or ciprofloxacin, 500 mg as a single dose, or ceftriaxone, 250 mg IM as a single dose. Unimmunized persons exposed to *H. influenzae* meningitis should receive rifampin (Turkel et al., 2010). Pregnant women should not receive rifampin or doxycycline.

A repeat LP should be done if no clinical response is seen after 48 hours of appropriate antibiotic therapy, particularly for patients with resistant pneumococcal disease and those who received dexamethasone. Neonates with gram-negative bacilli and patients with ventriculoperitoneal (VP) shunts require documentation of CSF sterility. The duration of antimicrobial therapy is 7 days for patients with *N. meningitidis* or Hib, 10 to 14 days for pneumococcal meningitis, and 14 to 21 days for *Streptococcus agalactiae.*

Table 16-20 Empiric Antibiotics for Initial Treatment of Bacterial Meningitis

Age/Risk Factors	Empiric Antibiotic Therapy
<1 month	Ampicillin + cefotaxime *or* amp + aminoglycoside
1 month to 2 years	Vancomycin + ceftriaxone *or* cefotaxime*
2 to 50 years	Vancomycin + ceftriaxone *or* cefotaxime*
>50 years	Ampicillin + vancomycin + ceftriaxone or cefotaxime*
Basilar skull fracture	Vancomycin + ceftriaxone *or* cefotaxime
Penetrating head trauma	Vancomycin + ceftazidime, cefepime, *or* meropenem†
Postneurosurgery status	Vancomycin + ceftazidime, cefepime, *or* meropenem
Cerebrospinal fluid (CSF) shunt	Vancomycin + ceftazidime, cefepime, *or* meropenem

Modified from Practice Guidelines for Bacterial Meningitis, CID 2004:39.
*Consider adding rifampin if dexamethasone is also given.
†Imipenem should be avoided because it increases the risk of seizures.

KEY TREATMENT

Adjunctive dexamethasone is recommended for children and infants with *H. influenzae* type b meningitis, but not if they have already received antibiotics (Tunkel et al., 2004) (SOR: A).
In adults, adjunctive dexamethasone is recommended for pneumococcal meningitis (Tunkel et al., 2004) (SOR: B).

Viral Meningitis Viral meningitis manifests similar to bacterial meningitis, although its course is rarely aggressive. The diagnostic process and examination are similar to those for bacterial meningitis. Viral meningitis is usually caused by enteroviruses, HSV, mumps virus, and HIV. Along with the signs of meningitis, signs that suggest a viral etiology include genital lesions (HSV-2), diarrhea, or a maculopapular rash (enteroviruses). Diagnosis is made by the history, examination, and CSF results. Early in the course, the CSF might show predominantly neutrophils that can resemble bacterial meningitis. Treatment is symptomatic. Suppressive therapy should be offered to patients with recurrent HSV meningitis.

Viral Encephalitis

Although encephalitis can also be caused by bacteria and fungi, the great majority of cases are caused by viruses. Herpes simplex accounts for 10% of cases. Patients present with fever, acute decreased level of consciousness, and occasionally, seizures and language, memory, or behavior disturbances. MRI is the most sensitive neuroimaging test for encephalitis and might show temporal lobe inflammation in early HSV encephalitis. CSF studies and electroencephalography (EEG) are also recommended for all patients with encephalitis. Herpes simplex PCR should be done, and acyclovir should be given immediately until HSV encephalitis is ruled out. During late summer and early fall, doxycycline should be considered to cover for tick-borne illnesses, and testing should include the mosquito-borne encephalitides such as West Nile, St. Louis, Eastern equine, and Western equine. Treatment depends on the suspected etiologic agent but is generally supportive (Tunkel et al., 2008).

Brain Abscess

A brain abscess is a focal, intracerebral infection that develops into a collection of pus surrounded by a well-vascularized capsule. Although fungi and protozoa (particularly *Toxoplasma*) can also cause brain abscesses, bacterial causes are much more common. Streptococci are found in 70% of bacterial abscesses and are usually from oropharyngeal infection or infective endocarditis, whereas *Staphylococcus aureus* accounts for 10% to 20% of isolates and is more often found after trauma. Community-associated MRSA strains have been increasing. Enteric gram-negative bacilli (e.g., *E. coli; Proteus, Klebsiella,* and *Pseudomonas* spp.) are isolated in 23% to 33% of patients, often in patients with ear infection, septicemia, or immunocompromise and those who have had neurosurgical procedures.

Most clinical symptoms are caused by the size and location of the abscess rather than the systemic signs of an infection. Headache is the most common complaint and may be accompanied by fever, mental status changes, evidence of increased intracranial pressure (nausea, vomiting, papilledema), or focal neurologic deficits. Diagnosis is usually made by CT scan with IV contrast showing the characteristic hypodense center with a peripheral uniform ring enhancement, with or without a surrounding area of brain edema. MRI is becoming the preferred imaging modality because of increased sensitivity, particularly for detecting satellite lesions. Additional testing depends on risk factors and the likely underlying source of infection and may include blood cultures, chest imaging, testing for HIV and antibodies to *Toxoplasma,* and transesophageal echogram. Empiric therapy typically involves vancomycin, ceftriaxone, and metronidazole. Optimal management also includes surgical drainage for most abscesses, both to find an etiologic microorganism and to improve chances of cure (Turkel, 2010).

INFECTIOUS DIARRHEA

Hoonmo Koo

Key Point

- Most acute diarrheal illness is viral and can be managed symptomatically and with appropriate attention to hydration.
- Travelers' diarrhea is usually caused by diarrheogenic *Escherichia coli.*
- The infection in travelers' diarrhea is usually self-limited.
- Antibiotics may shorten the duration of diarrhea by 1 to 3 days.
- The most common cause of antibiotic-associated diarrhea is *Clostridium difficile.*
- Treatment of antibiotic-associated diarrhea involves discontinuing the offending agent, if possible.

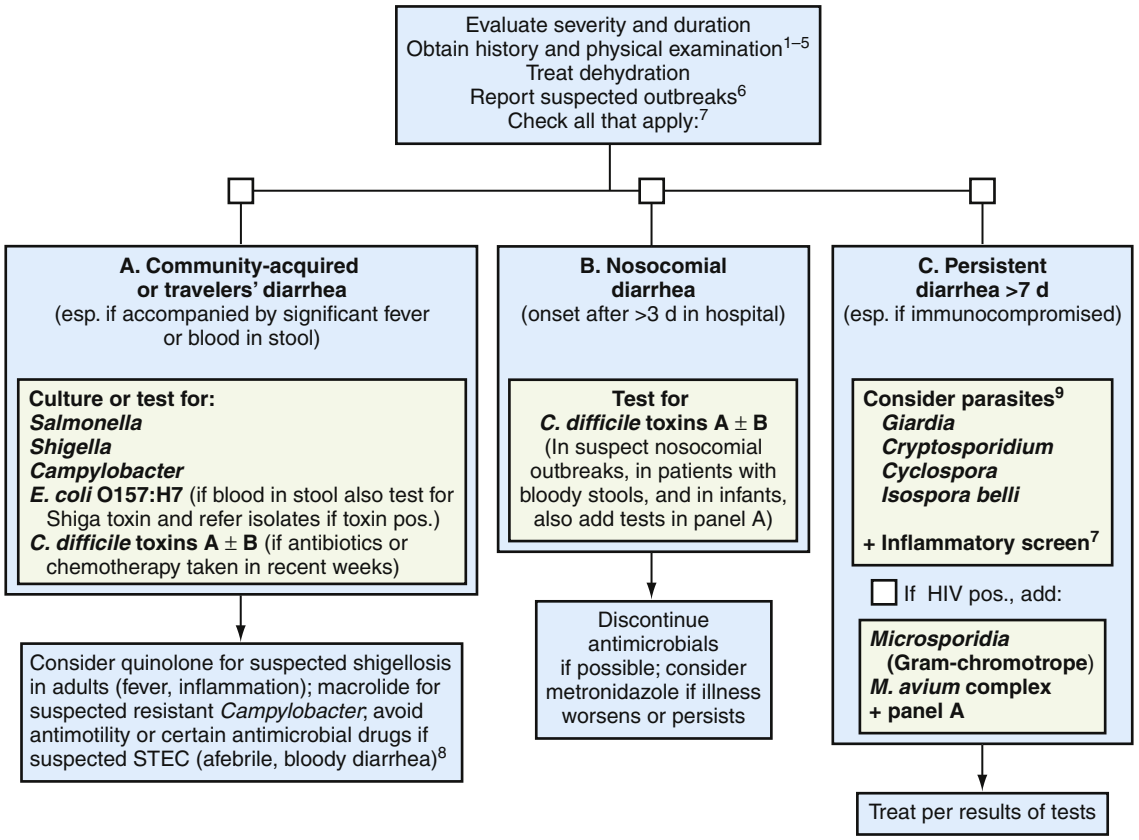


Figure 16-12 Recommendations for diagnosis and management of diarrheal illnesses. *HIV,* Human immunodeficiency virus; *Pos.,* positive. [1]Seafood or seacoast exposure should prompt culture for *Vibrio* spp. [2]Travelers'diarrhea that has not responded to empiric therapy with rifaximin, a quinolone, or azithromycin should be managed with the above approach. [3]Persistent abdominal pain and fever should prompt culture for *Yersinia enterocolitica* and cold enrichment. Right-side abdominal pain without high fever but with bloody or nonbloody diarrhea should prompt culture for Shiga toxin producing *E. coli* (STEC) O157. [4]Proctitis in symptomatic homosexual men can be diagnosed with sigmoidoscopy. Involvement in only the distal 15 cm suggests herpesvirus, gonococcal, chlamydial, or syphilitic infection; colitis extending more proximally suggests *Campylobacter*, *Shigella*, *Clostridium difficile*, or chlamydial (LGV serotype) infection, and noninflammatory diarrhea suggests giardiasis. [5]Postdiarrheal hemolytic uremic syndrome (HUS) should prompt testing of stools for STEC O157 and for Shiga toxin (send isolates to reference laboratory if toxin-positive but STEC-negative). [6]Outbreaks should prompt reporting to the health department. Consider saving culture plates and isolates and freeze whole stools or swabs at −70° C. [7]Fecal lactoferrin testing or microscopy for leukocytes can help document inflammation, which may be present in invasive colitis with *Salmonella*, *Shigella*, *Campylobacter*, or *C. difficile* colitis, and with inflammatory bowel disease. [8]Some experts recommend avoiding administration of antimicrobial agents to persons in the United States who have bloody diarrhea. [9]Commonly used tests for parasitic causes of diarrhea include fluorescence and EIA for *Giardia* and *Cryptosporidium*; acid-fast stains for *Cryptosporidium*, *Cyclospora*, *Isospora*, or *Mycobacterium* spp. (as well as culture for *Mycobacterium avium* complex); and special chromatrope or other stains for *Microsporidia.*
From Guerrant RL, Van Gilder T, Steiner TS, et al. Practice guidelines for the management of infectious diarrhea. Clin Infect Dis 2001;32:334.

Diarrhea is a common presenting complaint in the primary care physician's office. Not all causes of diarrhea are infectious, and not all infectious causes of diarrhea require specific antibiotic therapy. Diarrhea remains a major cause of morbidity and mortality, particularly for children in the developing world. Diarrhea is an alteration of normal bowel function, characterized by an increase in the water content, volume, or frequency of stools. *Acute* diarrhea is typically defined as present less than 14 days, and diarrhea is considered *chronic* when symptoms persist longer than 30 days (Figure 16-12).

Viral Gastroenteritis

Infectious diarrhea seen in the primary care physician's office is most frequently caused by viruses. A number of viral agents can cause diarrheal illness (Box 16-7). Rotaviruses are the principal enteric pathogens in children less than 5 years of age and the most important cause of hospitalization and infant mortality related to diarrheal illnesses. Noroviruses

Box 16-7 Viral Pathogens Causing Gastroenteritis

Established Pathogens

Adenoviruses (enteric types)
Astroviruses
Caliciviruses (Noroviruses)
Rotaviruses groups A, B, C
Cytomegalovirus

Likely and Emerging Pathogens

Coronaviruses
Enteroviruses
Picobirnaviruses, picotrirnaviruses
Pestiviruses
Toroviruses

From Guerrant RL, Bobak DA. Nausea, vomiting, and noninflammatory diarrhea. In Mandell GL, Bennett JE, Dolin R (eds). Principles and Practice of Infectious Diseases, 6th ed. Philadelphia, Churchill Livingstone, 2005, pp 1236-1249.

are the most common cause of food-borne disease worldwide.

Viral gastroenteritis is usually an acute self-limited illness, referred to as the "stomach flu." Enteric viruses are easily spread by fecal-oral transmission, through contamination of food and water, fomites, and person-to-person spread. Secondary attack rates can be high. Nausea and vomiting are the most prominent symptoms of viral gastroenteritis. Diarrhea, fever, headache, and constitutional symptoms may also be experienced. These viral infections can occur at any time during the year, but tend to occur more often in the winter. There is no specific therapy. Treatment is supportive, with particular emphasis on adequate replacement of fluids and electrolytes. If rehydration can be accomplished enterally, it is preferred.

Both the pentavalent bovine-human reassortment (RV5) and the oral, live-attenuated monovalent (RV1) rotavirus vaccines are effective for prevention of severe gastroenteritis. The RV5 vaccine series is recommended for children at ages 2, 4, and 6 months, whereas the RV1 vaccine should be administered to children 2 and 4 months of age.

Travelers' Diarrhea

Approximately 40% of travelers to developing regions of the world will develop diarrhea. Bacteria are responsible for approximately 80% of diarrhea acquired by travelers. Other important causes include viruses and parasites. The onset of the majority of cases of travelers' diarrhea is usually within 5 to 15 days after arrival. The presentation is typically a noninflammatory, nonbloody diarrhea associated with abdominal discomfort, fever, nausea, or vomiting. The duration is usually 1 to 5 days.

Enterotoxigenic *E. coli* is responsible for approximately 30% of travelers' diarrhea. Enteroaggregative *E. coli* is the second most common bacterial agent and causes 20% of cases. *Salmonella*, *Shigella*, and *Campylobacter* spp. are less often detected but are important causes of dysentery, particularly in Asia and Africa. *Dysentery* is severe inflammatory diarrhea manifested by fever and bloody stools. Most cases of travelers' diarrhea are self-limited, but chronic postinfectious irritable bowel syndrome may occur in up to 10% of those who experience diarrhea.

Prevention of travelers' diarrhea is an important component of pretravel counseling for high-risk countries. Food should be boiled, cooked, or peeled and water boiled to avoid consumption of fecal contamination. If a person develops travelers' diarrhea, a short course of antibiotics with rifaximin, ciprofloxacin, or azithromycin can shorten the duration of illness by 1 to 3 days. Antibiotic therapy is recommended for persons with bloody diarrhea or fever. Rifaximin, a nonabsorbed antibiotic, is not effective against invasive pathogens and should not be administered for dysentery. Ciprofloxacin or azithromycin should be used for dysenteric symptoms based on local antimicrobial susceptibilities.

KEY TREATMENT

In travelers' diarrhea, in which enterotoxigenic *E. coli* or other bacterial pathogens are likely causes, prompt treatment with a fluoroquinolone, azithromycin, or rifaximin or, in children, azithromycin 10 mg/kg/day once daily can reduce the duration of an illness from 3 to 5 days to 1 to 2 days (DuPont, 2010) (SOR: A).

Antibiotic-Associated Diarrhea

Antibiotics are frequently prescribed in the primary care physician's office for a variety of infections. Unfortunately, antibiotics can alter the normal host microflora that can be protective against other infections. Antibiotic effects on the normal gastrointestinal tract microbiome can lead to antibiotic-associated diarrhea, which causes significant morbidity and mortality. Administration of antibiotics usually precedes symptoms of antibiotic-associated diarrhea by about 1 week but can be as distant as 2 or 3 months. Strong associations with clindamycin (Cleocin), cephalosporins, penicillins, and fluoroquinolones have been demonstrated, but any antibiotic can lead to antibiotic-associated diarrhea.

The most important cause of antibiotic-associated diarrhea is *Clostridium difficile*, an anaerobic, gram-positive, spore-forming rod. *C. difficile* is implicated as the cause in up to 25% of antibiotic-associated diarrhea cases, in 50% to 75% of antibiotic-associated colitis cases, and in more than 90% of antibiotic-associated pseudomembranous colitis cases. Risk factors for *C. difficile* diarrhea include antibiotics, health care exposure (recent stay in hospitals or long-term care facilities), older age (>60), and comorbid conditions.

The clinical presentation of *C. difficile* colitis is usually diarrhea, abdominal pain or cramping, and fever in a patient who recently received antibiotics. Leukocytosis is common and may be profound; levels can be consistent with leukemoid reaction. A rare but potentially fatal complication is toxic megacolon. *Toxic megacolon* manifests as acute colonic dilation to a diameter greater than 6 cm, associated with systemic toxicity and the absence of mechanical obstruction. With its high associated mortality, any patient who develops toxic megacolon requires immediate surgical evaluation for possible colectomy.

Diagnosis of *C. difficile* diarrhea is achieved by demonstration of *C. difficile* toxin A or B in the stool by enzyme immunoassay (EIA) or cell culture cytotoxicity assay in a symptomatic patient with a previous history of antibiotic use. Asymptomatic patients should not be tested. With the improved sensitivities of these diagnostic assays, one stool sample is usually sufficient to test for *C. difficile*, unless symptoms recur. Test of cure after therapy with repeat stool for *C. difficile* toxin is not recommended because stools may remain positive for *C. difficile* toxin despite clinical resolution. Endoscopy can demonstrate pseudomembranes in the colon. Pseudomembranes are diagnostic of *C. difficile* infection, but are often not present. Endoscopy may only reveal the presence of nonspecific colitis.

Clostridium difficile colitis is treated by discontinuing the offending agent(s) if possible and initiating antibiotic therapy (Box 16-8). Antimotility agents should be avoided. Oral metronidazole (Flagyl), 500 mg three times daily for 10 to 14 days, is recommended for mild-moderate *C. difficile* diarrhea. Severe diarrhea should be treated with oral vancomycin. Oral vancomycin is currently not recommended for all patients with *C. difficile* diarrhea because of concerns for the promotion of vancomycin-resistant enterococci (VRE) and its expense. About 10% to 20% of patients experience relapse

Box 16-8 Classification of *Clostridium difficile* Disease Severity and Treatment Recommendations

Severity Scoring

1 point

Requiring care in the ICU
T_{max} >38.3° C (100.9° F)
Albumin <2.5 mg/dL
WBC >15,000 cells/mm3
Age >60 years

2 points

Endoscopic or CT evidence of pseudomembranous colitis

Recommendations

For mild-moderate *C. difficile* diarrhea (≤1 point), treat with metronidazole (Flagyl) PO 500 mg tid.

For severe disease (≥2 points), use vancomycin 125 mg PO qid.

For patients who cannot receive oral medications, IV metronidazole 500 mg qid and vancomycin by nasogastric tube ± rectal enema should be administered.

ICU, Intensive care unit; *CT,* computed tomography; *PO,* by mouth; *IV,* intravenous; *qid,* four times daily; *tid,* three times daily; *WBCs,* white blood cells.

Modified from Zar FA, Bakkanagari FR, KMLST, et al. A comparison of vancomycin and metronidazole for the treatment of ***Clostridium difficile***–associated diarrhea, stratified by disease severity. Clin Infect Dis 2007;45:302-307.

KEY TREATMENT

Treat mild-moderate *C. difficile* diarrhea with metronidazole (Zar et al., 2007) (SOR: B).
Vancomycin should be administered for severe *C. difficile* diarrhea (Zar et al., 2007) (SOR: B).

after therapy. For relapse, a repeat course of the original *C. difficile* treatment should be administered. Patients who have mild to moderate cases without volume depletion or systemic toxicity can be treated as outpatients.

Discussions of the following infections can be found online at www.expertconsult.com:

- Infectious viral hepatitis
- Endocarditis

References

The complete reference list is available online at www.expertconsult.com.

Web Resources

Standards, Practice Guidelines, and Statements Developed and/or Endorsed by Infectious Diseases Society of America. Systematically developed statements to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances.

www.cdc.gov/std/
Up-to-date information on sexually transmitted diseases (STDs) and their treatment.

www.cdc.gov/tb/
Up-to-date information on tuberculosis and its treatment.

www.cdc.gov/ticks/-
Up-to-date information on tick-borne diseases and their treatment.

www.tripprep.com/scripts/main/default.asp
Information for travelers by destination and illness and an extensive listing of Travel Medicine providers throughout the world; requires free registration.

http://chestjournal.chestpubs.org/content/129/1_suppl
Evidence-based clinical practice guidelines from the American College of Chest Physicians.

www.mrw.interscience.wiley.com/cochrane/cochrane_clsysrev_subjects_fs.html
Comprehensive analyses of evidence related to bronchitis and many other conditions.

http://clinicalevidence.bmj.com/ceweb/index.jsp
Evidence-based reviews of the diagnosis and treatment of many common clinical problems.

www.mdcalc.com/curb-65-severity-score-community-acquired-pneumonia
CURB-65 score calculator to determine the severity of community-acquired pneumonia and need for hospitalization.

Infectious Viral Hepatitis

Anthony Zeimet

Key Points

- All types of hepatitis can cause marked inflammation and necrosis of the liver, which results in elevation of transaminases and bilirubin.
- Consider hepatitis A virus infection in a traveler returning from an endemic area with acute hepatitis.
- Hepatitis B virus is spread by parenteral and sexual exposure.
- Hepatitis C virus causes acute and chronic infections, but it is generally seen clinically only as chronic infection.
- Consider hepatitis D virus infection in patients with underlying hepatitis B who develop acute hepatitis.
- Hepatitis E virus has a high mortality in pregnancy.

Hepatitis is defined as inflammation of the liver that is commonly induced by viruses that include the hepatitis viruses A through E, which will be the focus of this discussion. Other viruses that can induce hepatitis include Epstein-Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV), varicella zoster virus (VZV), adenovirus, and coxsackievirus. Various medications and alcohol abuse are two important nonviral causes. Most infectious causes of hepatitis are self-limiting; however, hepatitis B and C viruses can cause a chronic infection that may lead to cirrhosis and eventual liver failure, as well as hepatocellular carcinoma. Hepatitis A virus (HAV) and hepatitis E virus (HEV) are spread by the fecal-oral route and only cause an acute infection. Hepatitis B, C, and D viruses (HBV, HCV, HDV) are spread through the blood and have an acute form of disease that sometimes can become chronic.

The clinical presentation of hepatitis is clinically indistinguishable. Asymptomatic infections are more common than symptomatic infection. Symptoms generally include right upper quadrant (RUQ) abdominal pain, anorexia, nausea, vomiting, diarrhea, dark-colored urine, pale stools, and generalized malaise; patients may notice a yellow hue to their skin or eyes. Pruritus is common, caused by deposition of bilirubin in the skin. The physical examination generally reveals jaundice and sclera icterus in addition to RUQ pain. Hepatomegaly is seen in 85% and splenomegaly in 15% of patients with hepatitis. Liver function tests reveal elevated levels of aspartate transaminase (AST), alanine transaminase (ALT), and bilirubin, and to a lesser extent, alkaline phosphatase (ALP).

Hepatitis A Virus

Hepatitis A virus is the most common cause of viral hepatitis worldwide. Poor hygiene practices in both the industrial and the developing world account for its prevalence. In the United States, HAV is common among lower socioeconomic groups, daycare attendants and workers, men who have sex with men (MSM), and illicit drug users. Hepatitis A is often acquired by travelers to endemic areas. The incubation period is 15 to 45 days (mean, 30 days). HAV is highly contagious, and peak fecal shedding generally occurs at the onset of illness in most infected patients. Viremia averages 30 to 90 days. HAV infection manifests as an acute, self-limited illness, with the prodromal symptoms lasting about a week before the onset of jaundice. Jaundice generally resolves after 2 weeks, and most patients recover. Fulminant hepatic failure is possible but extremely rare.

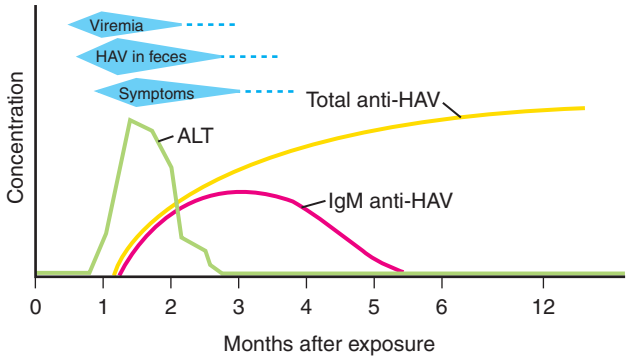
Diagnosis of acute HAV infection is made by demonstration of anti-HAV immunoglobulin M (IgM) in the patient's serum. This may be negative if the patient presents early, and repeat testing may be necessary if HAV is strongly suspected. Anti-HAV IgG in the serum indicates remote infection or immunization **(eFig 16-1).** Treatment is primarily supportive, except in patients with fulminant liver failure, who may require a liver transplant.

Vaccination should be administered to all patients who are seronegative and to persons at increased risk for acquiring HAV, including those about to travel to endemic areas, patients with chronic liver disease or receiving clotting factor concentrates, MSM, HIV-positive patients, and illicit drug users. Certain areas of the United States now require mandatory vaccination of children as well as those who work in the restaurant industry. The vaccine is safe and highly efficacious and is given as a two-dose series at 0 and at 6 to 12 months. Passive immunization with immune globulin is recommended for those exposed to the virus by a known contact, including household and sexual contacts, and those who are traveling to an endemic area for less than 4 weeks but never vaccinated. Any person who receives immune globulin should also start the vaccination series.

Hepatitis B Virus

Hepatitis B virus infection can be acute or chronic. About 40,000 people die from acute HBV infection annually, and 500,000 die of cirrhosis and hepatocellular carcinoma caused by chronic infection. About 400 million people worldwide are living with chronic HBV infection. In the United States, an estimated 1.25 million residents have chronic HBV infection, with 4000 to 5500 deaths each year. Significant burdens of disease are seen in Asia, Pacific islands, sub-Saharan Africa, Amazon basin, and Eastern Europe.

Most adults with acute HBV will clear the virus, with less than 5% progressing to chronic infection. Chronic infection will develop in almost all children infected perinatally and in 50% of those who become infected at 1 to 5 years of age.



eFigure 16-1 Clinical, virologic, and serologic events associated with hepatitis A virus (HAV) infection. *ALT,* Alanine transaminase; *IgM,* immunoglobulin M. *(From Mandell GL, Bennett JE, Dolin R (eds). Principles and Practice of Infectious Diseases, 6th ed. Philadelphia, Churchill Livingstone, 2005.)*

HBV is transmitted through exchange of body fluids, sexually and perinatally. In the United States, most HBV cases are acquired during adolescence and early adulthood with onset of sexual activity, experimentation with drug use, and sometimes occupational exposure. Fever, polyarthralgia, rash, and a serum sickness–like illness are features of HBV infection in addition to jaundice and may be seen in association with polyarteritis nodosa.

Clinicians have the most difficulty in interpreting the various serologic tests for diagnosis of hepatitis B **(eTable 16-3).** The mean incubation period is 60 to 70 days, with a range of 30 of 180 days after infection. Diagnosis of acute infection can be detected by obtaining HBV surface antigen (HBsAg), which can appear as early as 1 week after exposure but generally by day 50. In a patient strongly suspected to have HBV infection, the clinician can consider checking the HBV DNA viral load; which can be detected as early as 1 week after exposure. Eventually the patient will develop an anti-HBV surface antibody, which indicates recovery from the illness. The other viral serologies for HBV are rarely obtained in acute illness.

In chronic HBV infection, there are three major phases of infection:

1. *Immune tolerant.* Active viral replication in the liver with high levels of HBV DNA levels but essentially normal or minimal elevation of AST and ALT. Most patients eventually progress to the next stage.
2. *Immune active.* More robust liver inflammation with ALT elevation, and liver biopsy shows inflammation with or without fibrosis. HBV early antigen (HBeAg) is detected along with HBsAg.
3. *Inactive carrier state.* As patients enter this phase, they clear the HBeAg and develop anti-HBe antibody and have undetectable or low levels of HBV DNA, with normalization of ALT and liver inflammation. If patients become HBsAg negative, they then develop anti-HBs and have resolved their infection; otherwise, they are considered a chronic carrier.

Treatment of acute HBV is primarily supportive. In the last decade, however, there have been significant advances in the treatment of chronic HBV infection. The use of interferon has long been the mainstay of treatment and has a defined, limited course but is generally poorly tolerated. With the advent of the HIV/AIDS epidemic and research into treatment of HIV disease, antiviral medications are now starting to replace interferon as the preferred treatment option for HBV patients. Nucleoside/nucleotide analogs such as lamivudine, adefovir, entecavir, tenofovir, and telbivudine are generally given for long-term, indefinite therapy to prevent progression of liver disease and development of hepatocellular carcinoma. Any patient with chronic HBV infection should be referred to an infectious diseases specialist or a hepatologist to determine the appropriate treatment course.

Universal vaccination of newborns and infants is routine in the United States since 1991, and the incidence of HBV infection has declined. During primary care visits, the vaccination status of any adult or adolescent born before 1991 should be reviewed and the vaccine offered. The vaccine requires three doses given at 0, 1, and 6 months. An unvaccinated person or neonate who is exposed to the body fluids of a HBV-infected individual should start the vaccination series in addition to receiving the hepatitis B immune globulin (HBIG).

Hepatitis C Virus

Hepatitis C virus infection is the most common cause of chronic viral hepatitis in the United States. HCV does have an acute form of infection but is usually subclinical and rarely diagnosed. The CDC estimates that there are more than 2.7 million people with HCV infection. HCV is generally transmitted parenterally, as in injection drug users who share needles. Before 1992, those who received a blood transfusion may have contracted HCV. Sexual transmission

eTable 16-3 Interpretation of Serologic Tests in Hepatitis B Virus (HBV) Infection

Test	Acute HBV	Immunity through Infection*	Immunity through Vaccination	Chronic HBV	Chronic Infection with Precore Mutant	Healthy Carrier
HBsAg	+	–	+	+	+	+
Anti-HBs	–	+	–	–	–	–
HBcAg	+		–	+	–	–
Anti-HBc		±	–	–	+	+
Anti-HBc	+	+	–	+	+	+
IgM anti-HBe	+	–	–	–	–	–
HBV DNA†	+	–	–	±	+	–
ALT	Elevated	Normal	Normal	Elevated	Elevated	Normal

Modified from Mandell GL, Bennett JE, Dolin R (eds). Principles and Practice of Infectious Diseases, 6th ed. Philadelphia, Churchill Livingstone, 2005.
*Occasionally, patients with past infection have isolated anti-HBc only. Presence of an isolated IgM and HBc may indicate a window during acute infection or remote prior infection with loss of HBsAg or anti-HBs. In such patients, HBV DNA testing may prove useful.
†Presence of HBV DNA depends on the sensitivity of the test used.
HBsAg, Hepatitis B surface antigen; *HBcAg,* hepatitis B core antigen; *IgM,* immunoglobulin M; *DNA,* deoxyribonucleic acid; *ALT,* alanine transaminase.

has been reported in monogamous couples, with one partner who has HCV infection and the other without infection who eventually acquires the virus. This occurs in 3% to 5% of couples and represents a rare mode of transmission. Because the most common mode of acquisition is sharing needles, any patient who is HCV positive should be screened for HIV because these two infections often occur together **(eBox 16-1)**.

The diagnosis of acute HCV infection can be made by obtaining a HCV RNA viral load; although this is rarely done because the initial infection is subclinical. Chronic disease is generally discovered by a positive anti-HCV antibody along with an elevated HCV RNA viral load. HCV genotype should also be obtained in any positive individual, because this has important prognostic factors with regard to therapy, with genotype 1a and 1b the predominant type in the United States and unfortunately having a poor response to therapy. As with HBV, chronic HCV infection can lead to cirrhosis and the development of hepatocellular carcinoma. Treatment consists of 24 to 48 weeks of interferon and ribavirin therapy. Any patient being considered for therapy should be referred to an infectious diseases specialist or hepatologist. A liver biopsy is often needed to determine appropriate treatment candidates.

Hepatitis D Virus

Also known as the hepatitis *delta antigen* virus, HDV is a defective virus that requires the presence of HBV to be infectious. HDV should be suspected in any patient with chronic HBV who develops acute hepatitis. Hepatitis D is endemic in the Mediterranean, Balkans, Africa, Middle East, and Amazon basin. Diagnosis is made through an anti-HDV antibody in the presence of someone with positive HBsAg or anti-HB core antibody IgM or IgG. Treatment is supportive. Any person vaccinated against HBV cannot become infected with HDV.

eBox 16-1 Persons for whom Hepatitis C Virus (HCV) Screening is Recommended

Persons who have injected illicit drugs in the recent and remote past, including those who injected only once and do not consider themselves to be drug users.

Persons with conditions associated with a high prevalence of HCV infection, including:

- Persons with human immunodeficiency virus (HIV) infection
- Persons with hemophilia who received clotting factor concentrates before 1987
- Persons who have ever received hemodialysis
- Persons with unexplained abnormal transaminase (aminotransferase) levels

Prior recipients of transfusions or organ transplants before July 1992, including:

- Persons who were notified that they had received blood from a donor who later tested positive for HCV infection
- Persons who received a transfusion of blood or blood products
- Persons who received an organ transplant

Children born to HCV-infected mothers

Health care, emergency medical, and public safety workers after a needle stick injury or mucosal exposure to HCV-positive blood

Current sexual partners of HCV-infected persons*

Modified from Centers for Disease Control and Prevention. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. MMWR 1998;47(RR):1-39.

*Although the prevalence of infection is low, a negative test in the partner provides reassurance, making testing of sexual partners of benefit in clinical practice.

Hepatitis E Virus

Similar to HAV infection, HEV is spread by the fecal-oral route. HEV only has an acute form and does not progress to chronic infection. Most reported epidemics have been related to consumption of contaminated drinking water. HEV is endemic to Southeast and Central Asia, North Africa, Middle East, Mexico, Brazil, Venezuela, and Cuba. Hepatitis E can be considered a cause of infectious hepatitis in the United States in the traveler returning from an endemic area. The incubation period is 40 days. Infection is of major concern during pregnancy, which can cause death in late pregnancy. Diagnosis is made by demonstration of anti-HEV antibody in serum. Treatment is supportive.

KEY TREATMENT

- Universal vaccination of infants with hepatitis B vaccine reduces the risk of acute hepatitis, chronic carrier state, and complications of chronic infection and may be more effective than selective vaccination of high-risk individuals (Lee et al., 2006) (SOR: A).
- As part of a comprehensive health evaluation, all persons should be screened for behaviors that place them at high risk for hepatitis C infection (Ghany et al., 2009) (SOR: B).
- Liver biopsy may be considered in patients with chronic HCV infection to determine fibrosis stage for prognostic purposes or to make a treatment decision (Ghany et al., 2009) (SOR: B).

Endocarditis

David McBride

Key Points

- Endocarditis prophylaxis is now recommended solely for patients at high risk of a complicated course with a more narrow range of cardiac conditions.
- Routine prophylaxis for GI and GU procedures is no longer recommended.
- The Duke criteria represent a reliable scoring system for diagnosing endocarditis.
- Echocardiography is indicated to confirm suspected endocarditis.

Bacterial endocarditis is one of the most feared infections; although uncommon, it carries high morbidity and mortality. Increase in antibiotic resistance among bacteria causing this infection has created challenges for effective treatment. The fundamental view of the American Heart Association (AHA) in preventing infective endocarditis has shifted in recent years. Views on pathophysiology have not changed substantially, but it is now recognized

that cumulative daily episodes of bacteremia likely carry more risk than the transient bacteremia caused by dental procedures.

Infective endocarditis likely begins with turbulent flow and damaged endothelium around heart valves, which allow platelet aggregation and thrombus formation, causing a "nonbacterial thrombotic endocarditis" (Wilson et al., 2007). The presence of bacteremia then allows this vegetation to become seeded with infection. Bacterial "adhesins" are present to a greater degree in some species and allow for more effective attachment to the injured area of endothelium. With high concentrations of bacteria in the mouth, vagina, GI tract, and perhaps GU system, antibiotic prophylaxis was initiated when these anatomic locations were manipulated.

Prevention

Recommendations for infective endocarditis prevention changed in 2007–2008, with AHA recognizing more likely benefit from providing adequate population-based dental care and good oral hygiene, and thus less significant ongoing bacteremia at home in brushing, flossing, and "toothpicking," than in providing antibiotic prophylaxis to patients undergoing a dental procedure. No prospective RCT has shown that dental prophylaxis prevents infective endocarditis. With recognition of the risk associated with administration of antibiotics (GI upset, diarrhea, rash, anaphylaxis) and the risk of contributing to increasing antibiotic resistance, versus the likely negligible benefit, AHA has substantially changed its advice on this long-held practice.

A preexisting cardiac condition produces a predisposition to the development of infective endocarditis **(eBox 16-2).** For example, those who have valve replacement for infection of an infected native valve carry a lifetime risk of 630 per 100,000 patient-years. The risk in the general population without known heart disease is 5 per 100,000 patient-years. More concerning, however, is the risk to a given patient of poor outcome if the patient develops endocarditis, which drives current AHA recommendations. Those with an infected mechanical valve have a mortality rate of about 20%, versus 5% or less for patients with an infected native valve (Wilson et al., 2007).

A summary of current recommendations for endocarditis prophylaxis is provided in **eTable 16-4.** Of note, GI and GU procedures have been removed from those for which antibiotics are recommended, unless those systems are actively infected at the time of the procedure. The same is true for skin and soft tissue procedures, in that only infected tissue would warrant antibiotics to prevent infective endocarditis. It is still recommended to provide prophylaxis for respiratory tract procedures, if the respiratory wall will be invaded through biopsy or the procedure. In addition, respiratory procedures to treat infections (e.g., empyema) should be combined with antibiotic administration (Nishimura et al., 2008).

Antibiotic regimens for prophylaxis for dental procedures are still based primarily on synthetic penicillins as their cornerstone. This is with recognition that *Streptococcus viridans* is both a mouth floral inhabitant and a common agent causing infective endocarditis. With other procedures, antibiotics should be targeted to bacterial pathogens causing any active infection in the system being manipulated.

eBox 16-2 Cardiac Conditions Associated with the Highest Risk of Adverse Outcome from Endocarditis for Which Prophylaxis with Dental Procedures is Reasonable

- Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
- Previous IE
- Congenital heart disease (CHD)*
  - Unrepaired cyanotic CHD, including palliative shunts and conduits
  - Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months of the procedure†
  - Repaired congenital heart defect with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
- Cardiac transplantation recipients who develop cardiac valvulopathy

From Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis. Guidelines from the American Heart Association. Circulation 2007;116:1736-1754.

*Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD.

†Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 months after the procedure

eTable 16-4 Recommendations for Endocarditis Prophylaxis

Procedure	Oral Antibiotic	IV/IM Alternative
Dental	Amoxicillin, 2 g orally, *or* *If penicillin allergic:* Cephalexin, 2 g orally, *or* Clindamycin, 600 mg orally, *or* Azithromycin or clarithromycin, 500 mg orally.	Ampicillin, 2 g, *or* *If penicillin allergic:* Cefazolin or ceftriaxone, 1 g, *or* Clindamycin, 600 mg
Gastrointestinal/ Genitourinary	Not routinely recommended.	
Respiratory with invasion of mucosa	As for Dental.	As for Dental.
Respiratory with active infection	Coverage for the active infection plus coverage for *Streptococcus viridans.*	Same.
Manipulation of infected skin and soft tissue	Coverage for staphylococci and beta-hemolytic streptococci (penicillin, cephalosporin), *or* Vancomycin or clindamycin if intolerant to above.	Same.

Modified from Nishimura RA et al. ACC/AHA 2008 guideline update on valvular heart disease: focused update on infective endocarditis. Circulation 2008;118;887-896.
IV/IM, Intravenous or intramuscular.

Diagnosis

William Osler discussed "malignant endocarditis" in 1885 and its great diagnostic challenge. In 2009 the modified Duke criteria remains a reliable tool for assessing patients with endocarditis. Endocarditis is suspected in febrile patients without an obvious source, in those with recent bacteremia (including IV drug use), in those with underlying cardiac predisposition, and perhaps in patients with the clinical finding of a new cardiac murmur.

In establishing a diagnosis of infective endocarditis, a patient is considered to have definite disease if two major or one major and three minor or five minor criteria are present. Possible disease is defined as one major and one minor or three minor criteria **(eBox 16-3).** Pathologic specimens showing changes consistent with endocarditis would make a definitive diagnosis.

Echocardiography is indicated in making the diagnosis of infective endocarditis. Transthoracic echocardiography (TTE) is helpful if vegetations are seen, although size of the patient and other disease (e.g., COPD) may limit the ability of TTE to view the cardiac valves adequately. If TTE is negative and suspicion remains, transesophageal echocardiography (TEE) is indicated. TTE may be more widely available, depending on regional and institutional variation, and should be used rather than delaying this diagnostic test.

Treatment

Bacteria present within valvular vegetations are often less metabolically active, which partly explains the requirement for longer courses of antibiotics for this type of infection. Clearly, therapy for endocarditis should be targeted at the organism identified on blood culture, if any. The counting of antibiotic days should begin when the blood culture becomes negative and not at the start of the particular agent.

Recommendations for antibiotic use in infectious endocarditis are highly variable and based on the presence or absence of synthetic valvular material and the infectious agent **(eTable 16-5).** Generally speaking, a minimum of 4 weeks of IV antibiotics is indicated. In cases of resistant organisms, up to 8 weeks may be required. In either case, synergistic use of agents such as gentamicin may be indicated for the first several weeks of treatment, which then can be discontinued. The ability of a given patient to complete this course at home versus in a health care facility is dependent on the dosing frequency of the antibiotic, availability of in-home nursing services, and the type of intravenous access through which the antibiotic will be delivered.

At the completion of endocarditis therapy, echocardiography should be repeated to re-assess the function of the valve(s) in question. Valvular dysfunction at the completion of therapy is a good indication that the patient will need valve replacement in the future. There are circumstances, like the development of congestive heart failure in the face of endocarditis, in which primary surgery is indicated.

eBox 16-3 Definition of Terms in Modified Duke Criteria for Diagnosis of Infective Endocarditis (IE)

Major Criteria

Blood Culture Positive for IE

Typical microorganisms consistent with IE from 2 separate blood cultures: viridans streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus*; or community-acquired enterococci in the absence of a primary focus; *or*

Microorganisms consistent with IE from persistently positive blood cultures, defined as follows: At least 2 positive cultures of blood samples drawn >12 hours apart; or all of 3 or a majority of ≥4 separate cultures of blood (with first and last sample drawn at least 1 hour apart).

Single positive blood culture for *Coxiella burnetii* or anti–phase 1 IgG antibody titer >1:800

Evidence of Endocardial Involvement

Echocardiogram positive for IE (TEE recommended for patients with prosthetic valves, rated at least "possible IE" by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients) defined as follows: oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or abscess; or new partial dehiscence of prosthetic valve; new valvular regurgitation (worsening or changing or preexisting murmur not sufficient)

Minor Criteria

Predisposition, predisposing heart condition, or IDU

Fever, temperature >38° C

Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions

Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor

Microbiologic evidence: positive blood culture but does not meet a major criterion as noted above* or serological evidence of active infection with organism consistent with IE

Echocardiographic minor criteria eliminated

Modified from Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30:637.

Modifications shown in **boldface**.

*Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis.

TEE indicates transesophageal echocardiography; TTE, transthoracic echocardiography

KEY TREATMENT

Echocardiography should be performed in all patients with suspected infective endocarditis (Baddour et al., 2005) (SOR: A). There is no evidence that antibiotic prophylaxis is effective or ineffective for preventing infectious endocarditis after dental procedures in patients at risk (Chung, 2009) (SOR: C).

eTable 16-5 Therapy of Native Valve Endocarditis Caused by Highly Penicillin-Susceptible Viridans Group Streptococci and *Streptococcus bovis*

Regimen	Dosage* and Route	Duration (wk)	SOR	Comments
Aqueous crystalline penicillin G sodium, *or*	12-18 million U/24 hr IV either continuously or in 4 or 6 equally divided doses	4	IA	Preferred in most patients >65 yr or patients with impairment of 8th cranial nerve function or renal function
Ceftriaxone sodium	2 g/24 hr IV/IM in 1 dose	4	IA	
	Pediatric dose†: penicillin, 200,000 U/kg/24 hr IV in 4-6 equally divided doses; *or* Ceftriaxone, 100 mg/kg/24 hr IV/IM in 1 dose			
Aqueous crystalline penicillin G sodium, *or*	12-18 million U/24 hr IV either continuously or in 6 equally divided doses	2	IB	2-wk regimen not intended for patients with known cardiac or extracardiac abscess or for those with creatinine clearance of <20 mL/min, impaired 8th cranial nerve function, or *Abiotrophia, Granulicatella,* or *Gemella* spp. infection; gentamicin dosage should be adjusted to achieve peak serum concentration of 3-4 μg/mL and trough serum concentration of <1 μg/mL when 3 divided doses are used; nomogram used for single daily dosing§
Ceftriaxone sodium, *plus*	2 g/24 hr IV/IM in 1 dose	2	IB	
Gentamicin sulfate‡	3 mg/kg/24 hr IV/IM in 1 dose	2		
	Pediatric dose: penicillin, 200,000 U/kg/24 hr IV in 4-6 equally divided doses; *or* Ceftriaxone, 100 mg/kg/24 hr IV/IM in 1 dose; *or* Gentamicin, 3 mg/kg/24 hr IV/IM in 1 dose or 3 equally divided doses‖			
Vancomycin hydrochloride¶	30 mg/kg/24 hr IV in 2 equally divided doses not to exceed 2 g/24 hr unless concentrations in serum are inappropriately low	4	IB	Recommended only for patients unable to tolerate penicillin or ceftriaxone; vancomycin dosage should be adjusted to obtain peak (1 hr after infusion completed) serum concentration of 30-45 μg/mL and trough concentration range of 10-15 μg/mL
	Pediatric dose: 40 mg/kg/24 hr IV in 2 or 3 equally divided doses			

From Baddour LM et al. Infective endocarditis: diagnosis, antimicrobial therapy, and complications. Circulation 2005:111;e394-e434.
Minimum inhibitory concentration ≤0.12 μg/mL.
*Dosages recommended are for patients with normal renal function.
†Pediatric dose should not exceed that of a normal adult.
‡Other potentially nephrotoxic drugs (e.g., nonsteroidal antiinflammatory drugs) should be used with caution in patients receiving gentamicin therapy. Although it is preferred that gentamicin (3 mg/kg) be given as a single daily dose to adult patients with endocarditis caused by viridans group streptococci, as a second option, gentamicin can be administered daily in 3 equally divided doses.
§See Nicolau et al., 1995. Although this reference outlines dosing for gentamicin use at 7 mg/kg/dose for treatment in other types of infection syndromes, the nomogram was selected as an example for use with gentamicin dosing of 3 mg/kg/dose in this table to direct dosing in patients with underlying renal dysfunction. Currently, there is no other formal address of drug concentration monitoring with this gentamicin dosage.
‖Data for once-daily dosing of aminoglycosides for children exist, but no data for treatment of IE exist.
¶Vancomycin dosages should be infused during course of at least 1 hour to reduce risk of histamine-release "red man" syndrome.
SOR, Strength of recommendation; *IV,* intravenously; *IM,* intramuscularly.

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