INFECTIOUS DISEASES
| 1  | ANTI-INFECTIVE THERAPY          |
| 2  | SEPSIS SYNDROME                |
| 3  | THE FEBRILE PATIENT            |
| 4  | PULMONARY INFECTIONS           |
| 5  | MEASLES (RUBEOLA)              |
| 6  | CENTRAL NERVOUS SYSTEM INFECTIONS |
| 7  | MUMPS                         |
| 8  | GASTROINTESTINAL AND HEPATOBIARY INFECTIONS |
| 9  | SCARLET FEVER                 |
| 10 | STREPTOCOCCUS PYOGENES (GROUP A STREPTOCOCCUS) |
| 11 | DIPHTHERIA (CORYNEBACTERIUM DIPHTHERIAE) |
| 12 | PARASITIC INFECTIONS           |
| 13 | ZOONOTIC INFECTIONS            |
| 14 | BIOTERRORISM                   |
| 15 | SERIOUS VIRAL ILLNESS IN THE ADULT PATIENT |
| 16 | PERTUSSIS (BORDETELLA PERTUSSIS AND BORDETELLA |
| 17 | HIV INFECTION                  |
| 18 | VARICELLA (CHICKENPOX)         |
| 19 | TYPHOID FEVER                  |
Despite dire warnings that we are approaching the end of the antibiotic era, the incidence of antibiotic-resistant bacteria continues to rise. The proportions of penicillin-resistant *Streptococcus pneumoniae*, hospital-acquired meticillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant *Enterococcus* (VRE) strains continue to increase. Community-acquired MRSA (cMRSA) is now common throughout the world. Multiresistant *Acinetobacter* and *Pseudomonas* are everyday realities in many of our hospitals. The press is now warning the lay public of the existence of “dirty hospitals.” As never before, it is critical that health care providers understand the principles of proper anti-infective therapy and use anti-infective agents judiciously. These agents need to be reserved for treatable infections—not used to calm the patient or the patient’s family. Too often, patients with viral infections that do not warrant anti-infective therapy arrive at the physician’s office expecting to be treated with an antibiotic. And health care workers too often prescribe antibiotics to fulfill those expectations.

Physicians unschooled in the principles of microbiology utilize anti-infective agents just as they would more conventional medications, such as anti-inflammatory agents, anti-hypertensive medications, and cardiac drugs. They use one or two broad-spectrum antibiotics to treat all patients with suspected infections.

Many excellent broad-spectrum antibiotics can effectively treat most bacterial infections without requiring a specific causative diagnosis. However, overuse of empiric broad-spectrum antibiotics has resulted in the selection of highly resistant pathogens. A simplistic approach to anti-infective therapy and establishment of a fixed series of simple rules concerning the use of these agents is unwise and has proved harmful to patients. Such an approach ignores the remarkable adaptability of bacteria, fungi, and viruses. It is no coincidence that these more primitive life forms have survived for millions of years, far longer than the human race.

The rules for the use of anti-infective therapy are dynamic and must take into account the ability of these pathogens to adapt to the selective pressures exerted by the overuse of antibiotic, antifungal, and antiviral agents. The days of the “shotgun” approach to infectious diseases must end, or more and more patients will become infected with multiresistant organisms that cannot be treated. Only through the judicious use of anti-infective therapy can we hope to slow the arrival of the end of the antibiotic era.
**KEY POINTS**

About Anti-Infective Therapy

1. Too often, antibiotics are prescribed to fulfill the patient’s expectations, rather than to treat a true bacterial infection.
2. A single antibiotic cannot meet all infectious disease needs.
3. Physicians ignore the remarkable adaptability of bacteria, fungi, and viruses at their patient’s peril.
4. Anti-infective therapy is dynamic and requires a basic understanding of microbiology.
5. The “shotgun” approach to infectious diseases must end, or we may truly experience the end of the antibiotic era.

### ANTIBIOTIC RESISTANCE

#### GENETIC MODIFICATIONS LEADING TO ANTIMICROBIAL RESISTANCE

To understand why antibiotics must be used judiciously, the physician needs to understand how bacteria are able to adapt to their environment. Point mutations can develop in the DNA of bacteria as they replicate. These mutations occur in the natural environment, but are of no survival advantage unless the bacteria are placed under selective pressures. In the case of a mutation that renders a bacterium resistant to a specific antibiotic, exposure to the specific antibiotic allows the bacterial clone that possesses the antibiotic resistance mutation to grow, while bacteria without the mutation die and no longer compete for nutrients. Thus the resistant strain becomes the dominant bacterial flora. In addition to point mutations bacteria can also use three major mechanisms to transfer genetic material among themselves:

1. **Conjugation.** Bacteria often contain circular, double-stranded DNA structures called plasmids. These circular DNA structures lie outside the bacterial genome (Figure 1.1). Plasmids often carry resistance (“R”) genes. Through a mechanism called “conjugation,” plasmids can be transferred from one bacterium to another. The plasmid encodes for the formation of a pilus on the donor bacteria’s outer surface. The pilus attaches to a second bacterium and serves as bridge for the transfer of the plasmid DNA from the donor to the recipient bacterium. Using this mechanism, a single resistant bacterium can transfer resistance to other bacteria.

2. **Transduction.** Bacteriophages are protein-coated DNA segments that attach to the bacterial wall and inject DNA in a process called “transduction.” These infective particles can readily transfer resistance genes to multiple bacteria.

3. **Transformation.** Donor bacteria can also release linear segments of chromosomal DNA, which is then taken up by recipient bacteria and incorporated into the recipient’s genome. This process is called “transformation,” and the naked DNA capable of incorporating into the genome of recipient bacteria is called a transposon (Figure 1.1). Natural transformation most commonly occurs in *Streptococcus, Haemophilus*, and *Neisseria* species. Transposons can transfer multiple antibiotic resistance genes in a single event and have been shown to be responsible for high-level vancomycin resistance in enterococci.

*Figure 1–1.* Mechanisms by which bacteria transfer antibiotic resistance genes.
Thus bacteria possess multiple ways to transfer their DNA, and they promiscuously share genetic information. This promiscuity provides a survival advantage, allowing bacteria to quickly adapt to their environment.

**BIOCHEMICAL MECHANISMS FOR ANTIMICROBIAL RESISTANCE**

What are some of the proteins that these resistant genes encode for, and how do they work?

The mechanisms by which bacteria resist antibiotics can be classified into three major groups:

- Degradation or modification of the antibiotic
- Reduction of the bacterial antibiotic concentration by inhibiting entry or by efflux pumps
- Modification of the antibiotic target

Under the selection pressure of antibiotics, the question is not whether, but when resistant bacteria will take over.

**Degradation or Modification of the Antibiotic**

**β-LACTAMASES**

Many bacteria synthesize one or more enzymes called β-lactamases that inactivate antibiotics by breaking the amide bond on the β-lactam ring. Transfer of β-lactamase activity occurs primarily through plasmids and transposons.

Multiple classes of β-lactamases exist. Some preferentially break down penicillins; others preferentially destroy specific cephalosporins or carbenicillin. Extended-spectrum β-lactamases (ESBLs) readily destroy most cephalosporins. Another class of β-lactamase is resistant to clavulanate, an agent added to numerous antibiotics to inhibit β-lactamase activity. Some bacteria are able to produce β-lactamases called carbapenemases that are capable of inactivating imipenem and meropenem.

Gram-negative bacilli produce a broader spectrum of β-lactamases than do gram-positive organisms, and therefore infections with gram-negative organisms more commonly arise in patients treated for prolonged periods with broad-spectrum antibiotics. In some instances, β-lactamase activity is low before the bacterium is exposed to antibiotics; however, following exposure, β-lactamase activity is induced. *Enterobacter* is a prime example. This gram-negative bacterium may appear sensitive to cephalosporins on initial testing. Following cephalosporin treatment, β-lactamase activity increases, resistance develops, and the patient’s infection relapses. For this reason, third-generation cephalosporins are not recommended for serious *Enterobacter* infections.

**OTHER ENZYME MODIFICATIONS OF ANTIBIOTICS**

Erythromycin is readily inactivated by an esterase that hydrolyzes the lactone ring of the antibiotic. This esterase has been identified in *Escherichia coli*. Other plasmid-mediated erythromycin inactivating enzymes have been discovered in *Streptococcus* species and *S. aureus*. Chloramphenicol is inactivated by chloramphenicol acetyltransferase, which has been isolated from both gram-positive and gram-negative bacteria. Similarly, aminoglycosides can be inactivated by acetyltransferases. Bacteria also inactivate this class of antibiotics by phosphorylation and adenylation.

These resistance enzymes are found in many gram-negative strains and are increasingly detected in enterococci, *S. aureus* and *S. epidermidis*.

**Reduction of the Bacterial Antibiotic Concentration**

**INTERFERENCE WITH ANTIBIOTIC ENTRY**

For an antibiotic to work, it must be able to penetrate the bacterium and reach its biochemical target. Gram-negative bacteria contain an outer lipid coat that impedes penetration by hydrophobic reagents (such as most antibiotics). The passage of hydrophobic antibiotics is facilitated by the presence of porins—small channels in the cell walls of gram-negative bacteria that allow the passage of charged molecules. Mutations

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**KEY POINTS**

**About Antibiotic Resistance**

1. Bacteria can quickly alter their genetic makeup by
   a) point mutation.
   b) transfer of DNA by plasmid conjugation.
   c) transfer of DNA by bacteriophage transduction.
   d) transfer of naked DNA by transposon transformation.
2. The ability of bacteria to share DNA provides a survival advantage, allowing them to quickly adapt to antibiotic exposure.
3. Biochemical alterations leading to antibiotic resistance include
   a) degradation or modification of the antibiotic.
   b) reduction of the bacterial antibiotic concentration by inhibiting entry or by efflux pumps.
   c) modification of the antibiotic target.
4. Under the selection pressure of antibiotics, the question is not whether, but when resistant bacteria will take over.
leaving to the loss of porins can reduce antibiotic penetration and lead to antibiotic resistance.

**Production of Efflux Pumps**

Transposons have been found that encode for an energy-dependent pump that can actively pump tetracycline out of bacteria. Active efflux of antibiotics has been observed in many enteric gram-negative bacteria, and this mechanism is used to resist tetracycline, macrolide, and fluoroquinolone antibiotic treatment. S. aureus, S. epidermidis, S. pyogenes, group B streptococci, and S. pneumoniae also can utilize energy-dependent efflux pumps to resist antibiotics.

**Modification of the Antibiotic Target**

**Alterations of Cell Wall Precursors**

Alteration of cell wall precursors is the basis for VRE. Vancomycin and teicoplanin binding requires that D-alanine-D-alanine be at the end of the peptidoglycan cell wall precursors of gram-positive bacteria. Resistant strains of Enterococcus faecium and Enterococcus faecalis contain the vanA plasmid, which encodes a protein that synthesizes D-alanine-D-lactate instead of D-alanine-D-alanine at the end of the peptidoglycan precursor. Loss of the terminal D-alanine markedly reduces vancomycin and teicoplanin binding, allowing the mutant bacteria to survive and grow in the presence of these antibiotics.

**Changes in Target Enzymes**

Penicillins and cephalosporins bind to specific proteins called penicillin-binding proteins (PBPs) in the bacterial cell wall. Penicillin-resistant S. pneumoniae demonstrate decreased numbers of PBPs or PBPs that bind penicillin with lower affinity, or both. Decreased penicillin binding reduces the ability of the antibiotic to kill the targeted bacteria.

The basis for antibiotic resistance in MRSA is production of a low affinity PBP encoded by the mecA gene. Mutations in the target enzymes dihydropteroate synthetase and dihydrofolate reductase cause sulfonamide and trimethoprim resistance respectively. Single amino-acid mutations that alter DNA gyrase function can result in resistance to fluoroquinolones.

**Alterations in Ribosomal Binding Site**

Tetracyclines, macrolides, lincosamides, and aminoglycosides all act by binding to and disrupting the function of bacterial ribosomes (see the descriptions of individual antibiotics later in this chapter). A number of resistance genes encode for enzymes that demethylate adenine residues on bacterial ribosomal RNA, inhibiting antibiotic binding to the ribosome. Ribosomal resistance to gentamicin, tobramycin, and amikacin is less common because these aminoglycosides have several binding sites on the bacterial ribosome and require multiple bacterial mutations before their binding is blocked.

**Conclusions**

Bacteria can readily transfer antibiotic resistance genes. Bacteria have multiple mechanisms to destroy antibiotics, lower the antibiotic concentration, and interfere with antibiotic binding. Under the selective pressures of prolonged antibiotic treatment, the question is not whether, but when resistant bacteria will take over.

**Anti-Infective Agent Dosing**

The characteristics that need to be considered when administering antibiotics include absorption (when dealing with oral antibiotics), volume of distribution, metabolism, and excretion. These factors determine the dose of each drug and the time interval of administration. To effectively clear a bacterial infection, serum levels of the antibiotic need to be maintained above the minimum inhibitory concentration (MIC) for a significant period. For each pathogen, the MIC is determined by serially diluting the antibiotic into liquid medium containing \(10^4\) bacteria per milliliter. Inoculated tubes are incubated overnight until broth without added antibiotic has become cloudy or turbid as a result of bacterial growth. The lowest concentration of antibiotic that prevents active bacterial growth—that is, the liquid media remains clear—constitutes the MIC (Figure 1.2). Automated analyzers can now quickly determine, for individual pathogens, the MICs for multiple antibiotics, and these data serve to guide the physician's choice of antibiotics.

The mean bactericidal concentration (MBC) is determined by taking each clear tube and inoculating a plate of solid medium with the solution. Plates are then incubated to allow colonies to form. The lowest concentration of antibiotic that prevents all growth of bacteria—that is, no colonies on solid medium—represents the MBC.

Successful cure of an infection depends on multiple host factors in addition to serum antibiotic concentration. However, investigators have attempted to predict successful treatment by plotting serum antibiotic levels against time. Three parameters can be assessed (Figure 1.3): time above the MIC (T>MIC), ratio of the peak antibiotic concentration to the MIC (Cmax/MIC), and the ratio of the area under the curve (AUC) to the MIC (AUC/MIC).

Cure rates for β-lactam antibiotics are maximized by maintaining serum levels above the MIC for >50% of the time. Peak antibiotic concentrations are of less
importance for these antibiotics, and serum concentrations above 8 times the MIC are of no benefit other than to enhance penetration into less permeable body sites. Unlike β-lactam antibiotics, aminoglycosides and fluoroquinolones demonstrate concentration-dependent killing. In vitro studies show that these antibiotics demonstrate greater killing the more their concentrations exceed the MIC. High peak levels of these antibiotics may be more effective than low peak levels at curing infections. Therefore, for treatment with aminoglycosides and fluoroquinolones Cmax/MIC and AUC/MIC are more helpful for maximizing effectiveness. In the treatment of gram-negative bacteria, aminoglycosides have been suggested to achieve maximal effectiveness when Cmax/MIC is 10 to 12. For fluoroquinolones, best outcomes in community-acquired pneumonia may be achieved when the AUC/MIC is >34. To prevent the development of fluoroquinolone resistance to S. pneumoniae, in vitro studies have suggested that AUC/MIC should be >50. For P. aeruginosa, an AUC/MIC of >200 is required.

In vitro studies also demonstrate that aminoglycosides and fluoroquinolones demonstrate a post-antibiotic effect: when the antibiotic is removed, a delay in the recovery of bacterial growth occurs. Gram-negative bacteria demonstrate a delay of 2 to 6 hours in the recovery of active growth after aminoglycosides and fluoroquinolones, but no delay after penicillins and cephalosporins. But penicillins and cephalosporins generally cause a 2-hour delay in the recovery of gram-positive organisms. Investigators suggest that antibiotics with a significant post-antibiotic effect can be dosed less frequently; those with no post-antibiotic effect should be administered by constant infusion. Although these in vitro effects suggest certain therapeutic approaches, it must be kept in mind that concentration-dependent killing and post-antibiotic effect are both in vitro phenomena, and treatment strategies based on these effects have not been substantiated by controlled human clinical trials.

**KEY POINTS**

**About Antibiotic Dosing**

1. Absorption, volume of distribution, metabolism, and excretion all affect serum antibiotic levels.
2. Mean inhibitory concentration (MIC) is helpful in guiding antibiotic choice.
3. To maximize success with β-lactam antibiotics, serum antibiotic levels should be above the MIC for at least 50% of the time (T>MIC > 50%).
4. To maximize success with aminoglycosides and fluoroquinolones, high peak concentration, Cmax/MIC, and high AUC/MIC ratio are recommended.
5. The clinical importance of concentration-dependent killing and post-antibiotic effect for aminoglycosides and fluoroquinolones remain to be proven by clinical trials.
BASIC STRATEGIES FOR ANTIBIOTIC THERAPY

The choice of antibiotics should be carefully considered. A step-by-step logical approach is helpful (Figure 1.4).

1. Decide Whether The Patient Has a Bacterial Infection

One test that has traditionally been used to differentiate an acute systemic bacterial infection from a viral illness is the peripheral white blood cell (WBC) count. In patients with serious systemic bacterial infections, the peripheral WBC count may be elevated and may demonstrate an increased percentage of neutrophils. On occasion, less mature neutrophils such as band forms and, less commonly, metamyelocytes are observed on peripheral blood smear. Most viral infections fail to induce a neutrophil response. Viral infections, particularly Epstein–Barr virus, induce an increase in lymphocytes or monocytes (or both) and may induce the formation of atypical monocytes. Unfortunately, the peripheral WBC count is only a rough guideline, lacking both sensitivity and specificity. Recently, serum procalcitonin concentration has been found to be a far more accurate test for differentiating bacterial from viral infection. In response to bacterial infection, this precursor of calcitonin is synthesized and released into the serum by many organs of the body; production of interferon in response to viral infection inhibits its synthesis. The serum procalcitonin test may also be of prognostic value, serum procalcitonin levels being particularly high in severe sepsis (see Chapter 2).

2. Make a Reasonable Statistical Guess as to the Possible Pathogens

Based on the patient’s symptoms and signs, as well as on laboratory tests, the anatomic site of the possible infection can often be determined. For example, burning on urination, associated with pyuria on urinalysis, suggests a urinary tract infection. The organisms that cause uncomplicated urinary tract infection usually arise from the bowel flora. They include *E. coli*, *Klebsiella*, and *Proteus*. Antibiotic treatment needs to cover these potential pathogens. Later chapters review the pathogens commonly associated with infections at specific anatomic sites and the recommended antibiotic coverage for those pathogens.

3. Be aware of the Antibiotic Susceptibility Patterns in Your Hospital and Community

In patients that develop infection while in hospital (“nosocomial infection”), empiric therapy needs to take into account the antibiotic susceptibility patterns of the flora associated with the hospital and the floor where the patient became ill. Many hospitals have a high incidence of MRSA and therefore empiric antibiotic treatment for a possible staphylococcal infection must include vancomycin, pending culture results. Other hospitals have a large percentage of *Pseudomonas* strains that are resistant to gentamicin, eliminating that antibiotic from consideration as empiric treatment of possible gram-negative sepsis. In many communities, individuals who have never been hospitalized are today presenting with soft-tissue infections caused by cMRSA, and physicians in these communities must adjust their empiric antibiotic selection (see Chapter 10).
4. Take into Account Previous Antibiotic Treatment

The remarkable adaptability of bacteria makes it highly likely that a new pathogen will be resistant to previously administered antibiotics. If the onset of the new infection was preceded by a significant interval when antibiotics were not given, the resident flora may have recolonized with less resistant flora. However, the re-establishment of normal flora can take weeks, and patients in hospital are likely to recolonize with highly resistant hospital flora.

5. Take into Consideration Important Host Factors

a. **Penetration into the site of infection.** For example, patients with bacterial meningitis should not be treated with antibiotics that fail to cross the blood–brain barrier (examples include 1st-generation cephalosporins, gentamicin, and clindamycin).

b. **Peripheral WBC count.** Patients with neutropenia have a high mortality rate from sepsis. Immediate broad-spectrum, high-dose intravenous antibiotic treatment is recommended as empiric therapy for these patients.

c. **Age and underlying diseases (hepatic and renal dysfunction).** Elderly patients tend to metabolize and excrete antibiotics more slowly; longer dosing intervals are therefore often required. Agents with significant toxicity (such as aminoglycosides) should generally be avoided in elderly patients because they exhibit greater toxicity. Antibiotics metabolized primarily by the liver should generally be avoided or reduced in patients with significant cirrhosis. In patients with significant renal dysfunction, antibiotic doses need to be modified.

d. **Duration of hospitalization.** Patients who have just arrived in the hospital tend to be colonized with community-acquired pathogens; patients who have been in the hospital for prolonged periods and have received several courses of antibiotics tend to be colonized with highly resistant bacteria and with fungi.

e. **Severity of the patient’s illness.** The severely ill patient who is toxic and hypotensive requires broad-spectrum antibiotics; the patient who simply has a new fever without other serious systemic complaints can usually be observed off antibiotics.

6. Use the Fewest Drugs Possible

a. **Multiple drugs may lead to antagonism rather than synergy.** Some regimens, such as penicillin and an aminoglycoside for *Enterococcus*, have been shown to result in synergy—that is, the combined effects are greater than simple addition of the MBCs of the two agents would suggest. In other instances, certain combinations have proved to be antagonistic. The use of rifampin combined with oxacillin is antagonistic in some strains of *S. aureus*, for example. Many combination regimens have not been completely studied, and the natural assumption that more antibiotics lead to more killing power often does not apply.

b. **Use of multiple antibiotics increases the risk of adverse reactions.** Drug allergies are common. When a patient on more than one antibiotic develops an allergic reaction, all antibiotics become potential offenders, and these agents can no longer be used. In some instances, combination therapy can increase the risk of toxicity. The combination of gentamicin and vancomycin increases the risk of nephrotoxicity, for example.

c. **Use of multiple antibiotics often increases costs and the risk of administration errors.** Administration of two or more intravenous antibiotics requires multiple intravenous reservoirs, lines, and pumps. Nurses and pharmacists must dispense each antibiotic dose, increasing labor costs. The more drugs a patient receives, the higher the probability of an administration error. Use of two or more drugs usually increases the acquisition costs.

d. **Use of multiple antibiotics increases the risk of infection with highly resistant organisms.** Prolonged use of broad-spectrum antibiotic coverage increases the risk of infection with MRSA, VRE, multiresistant gram-negative bacilli, and fungi. When multiple antibiotics are used, the spectrum of bacteria killed increases. Killing most of the normal flora in the pharynx and gastrointestinal tract is harmful to the host. The normal flora compete for nutrients, occupy binding sites that could otherwise be used by pathogenic bacteria, and produce agents that inhibit the growth of competitors. Loss of the normal flora allows resistant pathogens to overgrow.

7. Switch to Narrow-Spectrum Antibiotic Coverage Within 3 Days

(Table 1.1, Figure 1.5). Within 3 days following the administration of antibiotics, sequential cultures of mouth flora reveal that the numbers and types of bacteria begin to change significantly. The normal flora die, and resistant gram-negative rods, gram-positive cocci, and fungi begin to predominate. The more quickly the selective pressures of broad-spectrum antibiotic coverage can be discontinued, the lower the risk of selecting for highly resistant pathogens. Broad coverage is reasonable as initial empiric therapy until cultures are available. By the 3rd day, the microbiology laboratory can generally identify the pathogen or pathogens, and a narrower-spectrum, specific antibiotic
regimen can be initiated. Despite the availability of culture results, clinicians too often continue the same empiric broad-spectrum antibiotic regimen, and that behavior is a critical factor in explaining subsequent infections with highly resistant superbugs. Figure 1.5 graphically illustrates the spectrum of available antibiotics as a guide to the antibiotic choice.

**Obey the 3-day rule.** Continuing broad-spectrum antibiotics beyond 3 days drastically alters the host’s resident flora and selects for resistant organisms. After 3 days, streamline antibiotic coverage. Use narrower-spectrum antibiotics to treat the specific pathogens identified by culture and Gram stain.

**8. All Else Being Equal, Choose The Least Expensive Drug**

As is discussed in later chapters, more than one antibiotic regimen can often be used to successfully treat a specific infection. Given the strong economic forces driving medicine today, the physician needs to consider the cost of therapy whenever possible. Too often, new, more expensive antibiotics are chosen over older generic antibiotics that are equally effective. In this book, the review of each specific antibiotic tries to classify that antibiotic’s cost range to assist the clinician in making cost-effective decisions.

However, in assessing cost, factoring in toxicity is also important. For example, the acquisition cost of gentamicin is low, but when blood-level monitoring, the requirement to closely follow blood urea nitrogen

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**Table 1.1. Classification of Antibiotics by Spectrum of Activity**

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<th>Moderately Broad</th>
<th>Broad</th>
<th>Very Broad</th>
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**KEY POINTS**

**About the Steps Required to Design an Antibiotic Regimen**

1. Assess the probability of bacterial infection. (Antibiotics should be avoided in viral infections.)
2. Be familiar with the pathogens primarily responsible for infection at each anatomic site.
3. Be familiar with the bacterial flora in the local hospital and community.
4. Take into account previous antibiotic treatment.
5. Take into account the specific host factors (age, immune status, hepatic and renal function, duration of hospitalization, severity of illness).
6. Use the minimum number and narrowest spectrum of antibiotics possible.
7. Switch to a narrower-spectrum antibiotic regimen based on culture results.
8. Take into account acquisition cost and the costs of toxicity.
Figure 1–5. Antibiotogram of all major antibiotics.

<table>
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<tr>
<th>Antibiotic</th>
<th>MSSA</th>
<th>MRSA</th>
<th>MRSE</th>
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<td>Tetracycline</td>
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<tr>
<td>Doxycycline</td>
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<tr>
<td>Ofloxacin</td>
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<tr>
<td>Ciprofloxacin</td>
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<tr>
<td>Vancocin</td>
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<tr>
<td>Daptomycin</td>
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<tr>
<td>Teicoplanin</td>
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<tr>
<td>Vancomycin</td>
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<tr>
<td>Quinupristin/Dalfopristin</td>
<td></td>
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</tr>
</tbody>
</table>

Blank = not recommended
Light gray = < 30% susceptibility
Darker gray = 30-60% susceptibility
Black = 61-90% susceptibility
and serum creatinine, and the potential for an extended hospital stay because of nephrotoxicity are factored into the cost equation, gentamicin is often not cost-effective.

Obey the 3-day rule. Continuing broad-spectrum antibiotics beyond 3 days drastically alters the host’s normal flora and selects for resistant organisms. After 3 days streamline the antibiotics. Use narrower-spectrum antibiotics to treat the specific pathogens identified by culture and Gram stain.

**COLONIZATION VERSUS INFECTION**

**CASE 1.1**

Following a motor vehicle accident, a 40-year-old man was admitted to the intensive care unit with 4 fractured ribs and a severe lung contusion on the right side. Chest X-ray (CXR) demonstrated an infiltrate in the right lower lobe. Because of depressed mental status, this man required respiratory support.

Initially, Gram stain of the sputum demonstrated few polymorphonuclear leukocytes (PMNs) and no organisms. On the third hospital day, this patient developed a fever to 103°F (39.5°C), and his peripheral WBC increased to 17,500 from 8000 (80% PMNs, 15% band forms). A new CXR demonstrated extension of the right lower lobe infiltrate. Gram stain of sputum revealed abundant PMNs and 20 to 30 gram-positive cocci in clusters per high-power field. His sputum culture grew methicillin-sensitive *S. aureus*. Intravenous cefazolin (1.5 g every 8 hours) was initiated. He defervesced, and secretions from his endotracheal tube decreased over the next 3 days. On the fourth day, a repeat sputum sample was obtained. Gram stain revealed a moderate number of PMNs and no organisms; however, culture grew *E. coli* resistant to cefazolin. The physician changed the antibiotic to intravenous cefepime (1 g every 8 hours).

Case 1.1 represents a very typical example of how antibiotics are misused. The initial therapy for a probable early *S. aureus* pneumonia was appropriate, and the patient responded (fever resolved, sputum production decreased, gram-positive cocci disappeared from the Gram stain, and *S. aureus* no longer grew on culture). However, because the sputum culture was positive for a resistant *E. coli*, the physician switched to a broader-spectrum antibiotic. The correct decision should have been to continue cefazolin.

One of the most difficult and confusing issues for many physicians is the interpretation of culture results. Wound cultures and sputum cultures are often misinterpreted. Once a patient has been started on an antibiotic, the bacterial flora on the skin and in the mouth and sputum will change. Often these new organisms do not invade the host, but simply represent new flora that have colonized these anatomic sites. Too often, physicians try to eradicate the new flora by adding new more-powerful antibiotics. The result of this strategy is to select for organisms that are multiresistant. The eventual outcome can be the selection of a bacterium that is resistant to all antibiotics.

No definitive method exists for differentiating between colonization and true infection. However, several clinical findings are helpful in guiding the physician. Evidence supporting the onset of a new infection include a new fever or a change in fever pattern, a rise in the peripheral WBC with an increase in the percentage of PMNs and band forms (left shift), Gram stain demonstrating an increased number of PMNs in association with predominance of bacteria that are morphologically consistent with the culture results. In the absence of these findings, colonization is more likely, and the current antibiotic regimen should be continued.

**KEY POINTS**

**About Differentiating Colonization from Infection**

1. Growth of resistant organisms is the rule in the patient on antibiotics.
2. Antibiotics should be switched only on evidence of a new infection.
3. Evidence for a new superinfection includes
   a) new fever or a worsening fever pattern,
   b) increased peripheral leukocyte count with left shift,
   c) increased inflammatory exudate at the original site of infection,
   d) increased polymorphonuclear leukocytes on Gram stain, and
   e) correlation between bacterial morphology and culture on Gram stain.
SPECIFIC ANTI-INFECTIVE AGENTS

ANTIBIOTICS

Before prescribing a specific antibiotic, clinicians should be able to answer these questions:

• How does the antibiotic kill or inhibit bacterial growth?
• What are the antibiotic’s toxicities and how should they be monitored?
• How is the drug metabolized, and what are the dosing recommendations? Does the dosing schedule need to be modified in patients with renal dysfunction?
• What are the indications for using each specific antibiotic?
• How broad is the antibiotic’s antimicrobial spectrum?
• How much does the antibiotic cost?

Clinicians should be familiar with the general classes of antibiotics, their mechanisms of action, and their major toxicities. The differences between the specific antibiotics in each class can be subtle, often requiring the expertise of an infectious disease specialist to design the optimal anti-infective regimen. The general internist or physician-in-training should not attempt to memorize all the facts outlined here, but rather should read the pages that follow as an overview of anti-infectives. The chemistry, mechanisms of action, major toxicities, spectrum of activity, treatment indications, pharmacokinetics, dosing regimens, and cost are reviewed. The specific indications for each anti-infective are briefly covered here. A more complete discussion of specific regimens is included in the later chapters that cover infections of specific anatomic sites.

Upon prescribing a specific antibiotic, physicians should reread the specific sections on toxicity, spectrum of activity, pharmacokinetics, dosing, and cost. Because new anti-infectives are frequently being introduced, prescribing physicians should also take advantage of hand-held devices, online pharmacology databases, and antibiotic manuals so as to provide up-to-date treatment (see Further Reading at the end of the current chapter). When the proper therapeutic choice is unclear, on-the-job training can be obtained by requesting a consultation with an infectious disease specialist. Anti-infective agents are often considered to be safe; however, the multiple potential toxicities outlined below, combined with the likelihood of selecting for resistant organisms, emphasize the dangers of over-prescribing antibiotics.

β-Lactam Antibiotics

CHEMISTRY AND MECHANISMS OF ACTION

The β-Lactam antibiotics have a common central structure (Figure 1.6) consisting of a β-lactam ring and a thiazolidine ring [in the penicillins and carbapenems, Figure 1.6(A)] or a β-lactam ring and a dihydrothiazine ring [in the cephalosporins, Figure 1.6(B)]. The side chain attached to the β-lactam ring (R₁) determines many of the antibacterial characteristics of the specific antibiotic, and the structure of the side chain attached to the dihydrothiazine ring (R₂) determines the pharmacokinetics and metabolism.

The β-lactam antibiotics bind to various PBPs. The PBPs represent a family of enzymes important for bacterial cell wall synthesis, including the carboxypeptidases, endopeptidases, transglycolases, and transpeptidases. Strong binding to PBP-1, a cell wall transpeptidase and transglycolase causes rapid bacterial death. Inhibition of this transpeptidase prevents the cross-linking of the cell wall peptidoglycans, resulting in a loss of integrity of the bacterial cell wall. Without its protective outer coat, the hyperosmolar intracellular contents swell, and the bacterial cell membrane lyses. Inhibition of PBP-3, a

---

Figure 1.6. Basic structure of the A penicillins and B the cephalosporins.
transpeptidase and transglycolase that acts at the septum of the dividing bacterium, causes the formation of long filamentous chains of non-dividing bacteria and bacterial death. Inhibition of other PBPs blocks cell wall synthesis in other ways, and activates bacterial lysis.

The activity of all β-lactam antibiotics requires active bacterial growth and active cell wall synthesis. Therefore, bacteria in a dormant or static phase will not be killed, but those in an active log phase of growth are quickly lysed. Bacteriostatic agents slow bacterial growth and antagonize β-lactam antibiotics, and therefore, in most cases, bacteriostatic antibiotics should not be combined with β-lactam antibiotics.

**TOXICITY**

Table 1.2 summarizes the toxicities of the β-lactam antibiotics.

Hypersensitivity reactions are the most common side effects associated with the β-lactam antibiotics. Penicillins are the agents that most commonly cause allergic reactions, at rates ranging from 0.7% to 10%. Allergic reactions to cephalosporins have been reported in 1% to 3% of patients, and similar percentages have been reported with carbapenems. However,

**Table 1.2. Toxicities of β-Lactam Antibiotics**

<table>
<thead>
<tr>
<th>Clinical symptom</th>
<th>Penicillins</th>
<th>Cefazolin</th>
<th>Cefotetan</th>
<th>Ceftriaxone</th>
<th>Cefepime</th>
<th>Aztreonam</th>
<th>Imipenem</th>
<th>Meropenem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic skin rash</td>
<td>Black</td>
<td>DarkGray</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
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<tr>
<td>Steven–Johnson</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
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<tr>
<td>Seizures</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
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<tr>
<td>Encephalopathy</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
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<tr>
<td>Diarrhea (Clostridium difficile)</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
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<tr>
<td>Cholelithiasis</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
<td>LightGray</td>
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<td>LightGray</td>
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<tr>
<td>Phlebitis</td>
<td>LightGray</td>
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<tr>
<td>Laboratory tests:</td>
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<tr>
<td>Coagulation</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Creatinine↑</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytopenias</td>
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<td></td>
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<tr>
<td>Eosinophilia</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST/ALT↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Encephalopathy associated with myoclonus has been reported in elderly patients.

Black = principal side effect; dark gray = less common side effect; light gray = rare side effect; white = not reported or very rare; ↑ = rise; AST/ALT = aspartate aminotransferase/alanine transaminase.
the incidence of serious, immediate immunoglobulin E (IgE)–mediated hypersensitivity reactions is much lower with cephalosporins than with penicillins. Approximately 1% to 7% of patients with penicillin allergies also prove to be allergic to cephalosporins and carbapenems.

Penicillins are the most allergenic of the β-lactam antibiotics because their breakdown products, particularly penicilloyl and penicillanic acid, are able to form amide bonds with serum proteins. The resulting antigens increase the probability of a host immune response. Patients who have been sensitized by previous exposure to penicillin may develop an immediate IgE-mediated hypersensitivity reaction that can result in anaphylaxis and urticaria. In the United States, penicillin-induced allergic reactions result in 400 to 800 fatalities annually. Because of the potential danger, patients with a history of an immediate hypersensitivity reaction to penicillin should never be given any β-lactam antibiotic, including a cephalosporin or carbapenem. High levels of immunoglobulin G anti-penicillin antibodies can cause serum sickness, a syndrome resulting in fever, arthritis, and arthralgias, urticaria, and diffuse edema.

Other less common toxicities are associated with individual β-lactam antibiotics. Natural penicillins and imipenem lower the seizure threshold and can result in grand mal seizures. Ceftriaxone is excreted in high concentrations in the bile and can crystallize, causing biliary sludging and cholecystitis. Antibiotics containing a specific methylthiotetrazole ring (cefamandole, cefoperazone, cefotetan) can induce hypoprothrombinemia and, in combination with poor nutrition, may increase postoperative bleeding. Cefepime has been associated with encephalopathy and myoclonus in elderly individuals. All broad-spectrum antibiotics increase the risk of pseudomembranous colitis (see Chapter 8). In combination with aminoglycosides, cephalosporins demonstrate increased nephrotoxicity.

**Penicillins**

Tables 1.3 and 1.4, together with Figure 1.5, summarize the characteristics of the various penicillins.

Penicillins vary in their spectrum of activity. Natural penicillins have a narrow spectrum. The aminopenicillins have an intermediate spectrum, and combined with β-lactamase inhibitors, the carboxy/ureidopenicillins have a very broad spectrum of activity.

**NATURAL PENICILLINS**

Pharmacokinetics—All natural penicillins are rapidly excreted by the kidneys, resulting in short half-lives (Table 1.3). As a consequence, the penicillins must be dosed frequently, and dosing must be adjusted in patients with renal dysfunction. Probenecid slows renal excretion, and this agent can be used to sustain higher serum levels.
Depending on the specific drug, penicillins can be given intravenously or intramuscularly. Some penicillins have been formulated to withstand the acidity of the stomach and are absorbed orally. Penicillins are well distributed in the body and are able to penetrate most inflamed body cavities. However, their ability to cross the blood–brain barrier in the absence of inflammation is poor. In the presence of inflammation, therapeutic levels are generally achievable in the cerebrospinal fluid.

### Spectrum of Activity and Treatment Recommendations

#### Pencillin G (Table 1.4) remains the treatment of choice for *S. pyogenes* ("group A strep") and the *S. viridans* group. It also remains the most effective agent for the treatment of infections caused by mouth flora. Penicillin G is also primarily recommended for *Clostridium perfringens*, *C. tetani*, *Erysipelothrix rhusiopathiae*, *Pasteurella multocida*, and spirochetes including syphilis and *Leptospira*. This antibiotic also remains the primary recommended therapy for *S. pneumoniae* sensitive to penicillin (MIC < 0.1 μg/mL). However, in many areas of the United States, more than 30% of strains are moderately resistant to penicillin (MIC = 0.1–1 μg/mL). In these cases, ceftriaxone, cefotaxime, or high-dose penicillin (≥12 million units daily) can be used. Moderately resistant strains of *S. pneumoniae* possess a lower-affinity PBP, and this defect in binding can be overcome through the addition of β-lactamase inhibitors such as clavulanate.

#### Table 1.3. Penicillins: Half-Life, Dosing, Renal Dosing, Cost, and Spectrum

<table>
<thead>
<tr>
<th>Antibiotic (trade name)</th>
<th>Half-life (h)</th>
<th>Dose</th>
<th>Dose for reduced creatinine clearance (mL/min)</th>
<th>Costa</th>
<th>Spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Natural penicillins (PCNs)</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>PCN G</td>
<td>0.5</td>
<td>2–4 × 10⁶ U IV q4h</td>
<td>&lt;10: Half dose</td>
<td>$</td>
<td>Narrow</td>
</tr>
<tr>
<td>Procaine PCN G</td>
<td></td>
<td>0.6–1.2 × 10⁶ U IM q24h</td>
<td></td>
<td>$</td>
<td>Narrow</td>
</tr>
<tr>
<td>Benzathine PCN G</td>
<td></td>
<td>2.4 × 10⁶ U IM weekly</td>
<td></td>
<td>$</td>
<td>Narrow</td>
</tr>
<tr>
<td>PCN V–K</td>
<td>0.5</td>
<td>250–500 mg PO q6–8h</td>
<td></td>
<td>$</td>
<td>Narrow</td>
</tr>
<tr>
<td><strong>Aminopenicillins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin (Omnipen)</td>
<td>1</td>
<td>Up to 14 g IV daily, given q4–6h</td>
<td>30–50: q8h</td>
<td>$</td>
<td>Moderate</td>
</tr>
<tr>
<td>Amoxicillin (Amoxil)</td>
<td>1</td>
<td>500 mg PO q8h or 875 mg q12h</td>
<td>&lt;10: q24h</td>
<td>$</td>
<td>Moderate</td>
</tr>
<tr>
<td>Amoxicillin–clavulanate (Augmentin)</td>
<td></td>
<td>Same as amoxicillin PO</td>
<td>Same as amoxicillin</td>
<td>$$$</td>
<td>Broad</td>
</tr>
<tr>
<td>Ampicillin–subactam (Unasyn)</td>
<td>1</td>
<td>1.5–2 g q6h IV</td>
<td>30–50: q8h</td>
<td>$$$</td>
<td>Broad</td>
</tr>
<tr>
<td><strong>Penicillinase-resistant PCNs</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Oxacillin (Prostaphlin)</td>
<td>0.5</td>
<td>1–2 g q4h IV</td>
<td>None</td>
<td>$</td>
<td>Narrow</td>
</tr>
<tr>
<td>Nafcillin (Unipen)</td>
<td>0.5</td>
<td>0.5–2 g q4h IV</td>
<td>None</td>
<td>$$$</td>
<td>Narrow</td>
</tr>
<tr>
<td>Cloxacillin/dicloxacillin (Dynapen)</td>
<td>0.5</td>
<td>0.25–1 g q6h</td>
<td>None</td>
<td>$</td>
<td>Narrow</td>
</tr>
<tr>
<td><strong>Carboxy/ureido–PCNs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ticarcillin–clavulanate (Timentin)</td>
<td>1</td>
<td>3.1 g q4–6h IV</td>
<td>10–50: 3.1 g q6–8h</td>
<td>$</td>
<td>Very broad</td>
</tr>
<tr>
<td>Piperacillin–tazobactam (Zosyn)</td>
<td>1</td>
<td>3.375 g q6h or 4.5 g q8h</td>
<td>10–50: 2.25 g q6h</td>
<td>$</td>
<td>Very broad</td>
</tr>
</tbody>
</table>

* Intravenous preparations (daily cost dollars): $ = 20 to 60; $ = 61 to 100; $$$ = 101 to 140; $$$$ = 140 to 180; $$$$$ = more than 180; oral preparations (10-day course cost dollars): $ = 10 to 40; $ = 41 to 80; $$$ = 81 to 120; $$$$ = 121 to 160; $$$$$ ≥ 160.
by high serum levels of penicillin in the treatment of pneumonia, but not of meningitis. Infections with high-level penicillin-resistant \textit{S. pneumoniae} (MIC > 2 \textmu g/mL) require treatment with vancomycin or another alternative antibiotic.

\textbf{Aminopenicillins}

Pharmacokinetics—In aminopenicillins, a chemical modification of penicillin increases resistance to stomach acid, allowing these products to be given orally (Table 1.3). They can also be given intramuscularly or intravenously. Amoxicillin has excellent oral absorption: 75\% compared with 40\% for ampicillin. Absorption is not impaired by food. The higher peak levels achievable with aminopenicillins allow for a longer dosing interval, making them a more convenient oral antibiotic than ampicillin. The half-life is short (1 hour) and these drugs are primarily excreted unmodified in the urine.

Spectrum of Activity and Treatment Recommendations—The spectrum of activity in the aminopenicillins is slightly broader than in the natural penicillins (Table 1.4). Intravenous ampicillin is recommended for treatment of \textit{Listeria monocytogenes}, sensitive enterococci, \textit{Proteus mirabilis}, and non-\beta-lactamase-producing \textit{Haemophilus influenzae}. Aminopenicillins are also effective against \textit{Shigella flexneri} and sensitive strains of nontyphoidal \textit{Salmonella}. Amoxicillin can be used to treat otitis media and air sinus infections. When combined with a \beta-lactamase inhibitor (clavulanate or sulbactam), aminopenicillins are also effective against methicillin-sensitive \textit{S. aureus} (MSSA), \beta-lactamase-producing strains of \textit{H. influenzae}, and \textit{Moraxella catarrhalis}. The latter two organisms are commonly cultured from middle ear and air sinus infections (see Chapter 5). However, the superiority of amoxicillin–clavulanate over amoxicillin for middle ear and air sinus infections has not been proven.

\textbf{Penicillinase-Resistant Penicillins}

Pharmacokinetics—The penicillinase-resistant penicillins have the same half-life as penicillin (30 minutes) and require dosing at 4-hour intervals or constant intravenous infusion (Table 1.3). Unlike the natural penicillins, these agents are cleared hepatically, and doses of nafcillin and oxacillin usually do not need to be adjusted for renal dysfunction. But the efficient hepatic excretion of nafcillin means that the dose needs to be adjusted in patients with significant hepatic dysfunction. The liver excretes oxacillin less than penicillin.
efficiently, and so dose adjustment is usually not required in liver disease.

Spectrum of Activity and Treatment Recommendations—The synthetic modification of penicillin to render it resistant to the β-lactamases produced by S. aureus reduces the ability of these agents to kill anaerobic mouth flora and Neisseria species (Table 1.4). These antibiotics are strictly recommended for the treatment of MSSA. They are also used to treat cellulitis when the most probable pathogens are S. aureus and S. pyogenes. Because oral preparations result in considerably lower serum concentration levels, cloxacillin or dicloxacillin should not be used to treat S. aureus bacteremia. These oral agents are used primarily for mild soft-tissue infections or to complete therapy of a resolving cellulitis.

**CARBOXYPENICILLINS AND UREIDOPENICILLINS**

Pharmacokinetics—The half-lives of ticarcillin and piperacillin are short, and they require frequent dosing (Table 1.3). Sale of ticarcillin and piperacillin alone has been discontinued in favor of ticarcillin–clavulanate and piperacillin–tazobactam.

Dosing every 6 hours is recommended for piperacillin–tazobactam to prevent accumulation of tazobactam. In P. aeruginosa pneumonia, the dose of piperacillin–tazobactam should be increased from 3.375 g Q6h to 4.5 g Q8h to achieve cidal levels of piperacillin in the sputum. In combination with an aminoglycoside, piperacillin–tazobactam often demonstrates synergy against P. aeruginosa. However, the administration of the piperacillin–tazobactam needs to be separated from the administration of the aminoglycoside by 30 to 60 minutes.

Spectrum of Activity and Treatment Recommendations—Ticarcillin and piperacillin are able to resist β-lactamases produced by Pseudomonas, Enterobacter, Morganella, and Proteus–Providencia species. At high doses, ticarcillin and piperacillin can also kill many strains of Bacteroides fragilis and provide effective anaerobic coverage. These antibiotics can be used for empiric coverage of moderate to severe intra-abdominal infections. They have been combined with a β-lactamase inhibitor (clavulanate or tazobactam) to provide effective killing of MSSA. These agents are reasonable alternatives to nafcillin or oxacillin when gram-negative coverage is also
### Table 1.5. Cephalosporins: Half-Life, Dosing, Renal Dosing, Cost, and Spectrum

<table>
<thead>
<tr>
<th>Antibiotic (trade name)</th>
<th>Half-life (h)</th>
<th>Dose</th>
<th>Dose for reduced creatinine clearance (mL/min)</th>
<th>Cost*</th>
<th>Spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefazolin (Ancef)</td>
<td>1.8</td>
<td>1–1.5 g IV or IM q6–8h</td>
<td>10–50: 0.5–1 g q8–12h</td>
<td>$</td>
<td>Narrow</td>
</tr>
<tr>
<td>Cephalexin (Keflex)</td>
<td>0.9</td>
<td>0.25–1 g PO q6–8h</td>
<td>&lt;10: 0.25–0.75 g q18–24h</td>
<td>$</td>
<td>Narrow</td>
</tr>
<tr>
<td>Cephradine (Veloce)</td>
<td>0.7</td>
<td>0.25–1 g PO q6h</td>
<td></td>
<td>$–$$</td>
<td></td>
</tr>
<tr>
<td>Cefadroxil (Duricef)</td>
<td>1.2</td>
<td>0.5–1 g PO q12h</td>
<td></td>
<td>$$–$$ $$</td>
<td>Narrow</td>
</tr>
<tr>
<td><strong>2nd generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefoxitin (Mefoxin)</td>
<td>0.8</td>
<td>1–2 g IV or IM q4–6h,</td>
<td>50–80: q8–12h</td>
<td>$$</td>
<td>Moderately broad</td>
</tr>
<tr>
<td></td>
<td></td>
<td>not to exceed 12 g daily</td>
<td>10–50: q12–24h</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;10: q48h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotetan (Ceftan)</td>
<td>3.5</td>
<td>1–2 g IV or IM q12h</td>
<td>10–50: q24h</td>
<td>$</td>
<td>Moderately broad</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;10: q48h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefuroxime (Zinacef)</td>
<td>1.3</td>
<td>0.75–1.5 g IV q8h</td>
<td>10–50: q12h</td>
<td>$</td>
<td>Moderately broad</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;10: 0.75 g q24h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefuroxime–axetil (Ceftin)</td>
<td>1.5</td>
<td>0.25–0.5 g PO q12h</td>
<td>10–50: q12h</td>
<td>$$$</td>
<td>Moderately broad</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;10: 0.25 g q12h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefaclor (Ceclor)</td>
<td>0.8</td>
<td>0.25–0.5 g PO q8h</td>
<td>No change required</td>
<td>$$$</td>
<td>Moderately broad</td>
</tr>
<tr>
<td><strong>3rd generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone (Rocephin)</td>
<td>8</td>
<td>1–2 g IV q12–24h</td>
<td>No change required</td>
<td>$</td>
<td>Broad</td>
</tr>
<tr>
<td>Cefotaxime (Claforin)</td>
<td>1.5</td>
<td>2 g IV q4–8h (maximum 12 g daily)</td>
<td>10–30: q8–12h</td>
<td>$</td>
<td>Broad</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;10: q12–24h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefizoxime (Cefizox)</td>
<td>1.7</td>
<td>1–4 g IV q8–12h (maximum 12 g daily)</td>
<td>10–30: q12h</td>
<td>$</td>
<td>Broad</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;10: q24h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftazidime (Fortaz)</td>
<td>1.9</td>
<td>1–3 g IV or IM q8h, up to 8 g daily</td>
<td>10–50: 1 g q12–24h</td>
<td>$</td>
<td>Broad</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;10: 0.5 q24–48h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefixime (Suprax)</td>
<td>3.7</td>
<td>400 mg PO q12h or q24h</td>
<td>10–30: 300 mg q24h</td>
<td>$$$</td>
<td>Broad</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;10: 200 mg q24h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefpodoxime proxetil (Vantin)</td>
<td>2.2</td>
<td>200–400 g PO q12h</td>
<td>10–30: ×3 weekly</td>
<td>$$</td>
<td>Broad</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;10: ×1 weekly</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>4th generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefepime (Maxipime)</td>
<td>2.1</td>
<td>0.5–2 g IV q12h</td>
<td>10–30: 0.5–1 g q24h</td>
<td>$$–$$ $</td>
<td>Very broad</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;10: 250–500 mg q24h q12h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefpirome (IV–Cef)</td>
<td>2</td>
<td>1–2 g IV q12h</td>
<td>Same as cefepime</td>
<td>$</td>
<td>Very broad</td>
</tr>
<tr>
<td><strong>Monobactams</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aztreonam (Azactam)</td>
<td>2</td>
<td>1–2 g IV q6h</td>
<td>10–30: q12–18h</td>
<td>$$–$$ $$</td>
<td>Narrow</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;10: q24h</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Intravenous preparations (daily cost dollars): $ = 20–70; $$ = 71–110; $$$ = 111–150; $$$$ = 150–200; $$$$$ = ≥ 200; oral preparations (10-day course cost dollars): $ = 10–50; $$ = 51–100; $$$ = 101–140; $$$$ = 141–180; $$$$$ = ≥ 180.
required. Both agents can be used for in-hospital aspiration pneumonia to cover for mouth flora and gram-negative rods alike, and they can also be used for serious intra-abdominal, gynecologic, and acute prostate infections. They have been used for skin and bone infections thought to be caused by a combination of gram-negative and gram-positive organisms.

**Cephalosporins**

Tables 1.5 and 1.6, together with Figure 1.5, summarize the characteristics of the various cephalosporins.

In an attempt to create some semblance of order, the cephalosporins have been classified into generations based on spectrum of activity (Table 1.5). First-generation cephalosporins are predominantly effective against gram-positive cocci. Second-generation cephalosporins demonstrate increased activity against aerobic and anaerobic gram-negative bacilli, but have variable activity against gram-positive cocci. The third-generation cephalosporins demonstrate even greater activity against gram-negative bacilli, but only limited activity against gram-positive cocci. Finally, the fourth-generation cephalosporins demonstrate the broadest spectrum of activity, being effective against both gram-positive cocci and gram-negative bacilli.

Classification of the cephalosporins by generation naturally leads to the assumption that newer, later-generation cephalosporins are better than the older cephalosporins. However, it is important to keep in mind that, for many infections, earlier-generation, narrower-spectrum cephalosporins are preferred to the more recently developed broader-spectrum cephalosporins.

**First-Generation Cephalosporins**

Pharmacokinetics—Cefazolin, the preferred parenteral first-generation cephalosporin, has a longer half-life than penicillin, and it is primarily excreted by the kidneys (Table 1.5). The first-generation cephalosporins penetrate most body cavities, but they fail to cross the blood–brain barrier. Oral preparations (cephalexin, cefradine, cefadroxil) are very well absorbed, achieving excellent peak serum concentrations (0.5 g cephalexin results in a 18 \mu g/mL peak). Absorption is not affected by food.

**Table 1.6.** Organisms That May Be Susceptible to Cephalosporins

<table>
<thead>
<tr>
<th>1st generation (cefa-zolin)</th>
<th>2nd generation (cefoxitin, cefotetan)</th>
<th>3rd generation (ceftriaxone, cefotaxime)</th>
<th>4th generation (cefe-pime)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methicillin-sensitive</td>
<td>Covers same organisms</td>
<td>Covers same organisms</td>
<td>Covers same organisms</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>as cefazolin, but weaker gram-positive activity.</td>
<td>as cefazolin, but often weaker gram-positive and stronger gram-negative activity.</td>
<td>as cefazolin and ceftriaxone. Excellent gram-positive and gram-negative activity.</td>
</tr>
<tr>
<td>(best activity)</td>
<td></td>
<td>Also covers: <em>Haemophilus influenzae</em></td>
<td>Also covers: <em>S. pneumoniae</em></td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td></td>
<td><em>Moraxella catarrhalis</em></td>
<td>Intermediate</td>
</tr>
<tr>
<td>Penicillin (PCN)–sensitive</td>
<td></td>
<td><em>Neisseria gonorrhoeae</em></td>
<td><em>Enterobacter spp.</em></td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td></td>
<td><em>N. meningitidis</em></td>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td></td>
<td><em>Bacteroides fragilis</em></td>
<td><em>Serratia spp.</em></td>
</tr>
<tr>
<td>(some species)</td>
<td></td>
<td>(some species)</td>
<td></td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(some species)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(some species)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**KEY POINTS**

**About First-Generation Cephalosporins**

1. Excellent gram-positive coverage, some gram-negative coverage.
2. Do not cross the blood–brain barrier.
3. Inexpensive.
4. Useful for treating soft-tissue infections and for surgical prophylaxis. Can often be used as an alternative to oxacillin or nafcillin.
by food. The half-lives of cephalxin and cephadrine are short, requiring frequent administration. These agents need to be corrected for renal dysfunction.

Spectrum of Activity and Treatment Recommendations—The first-generation cephalosporins are very active against gram-positive cocci, including MSSA, and they also have moderate activity against some community-acquired gram-negative bacilli (Table 1.6). They are active against oral cavity anaerobes, but are ineffective for treating B. fragilis, H. influenzae, L. monocytogenes, MRSA, penicillin-resistant S. pneumoniae, and Enterococcus.

First-generation cephalosporins are an effective alternative to nafcillin or oxacillin for soft-tissue infections thought to be caused by MSSA or S. pyogenes. Cefazolin is also the antibiotic of choice for surgical prophylaxis. Because of its inability to cross the blood–brain barrier, cefazolin should never be used to treat bacterial meningitis. Oral preparations are commonly used to treat less severe soft-tissue infections, including impetigo, early cellulitis, and mild diabetic foot ulcers.

SECOND-GENERATION CEPHALOSPORINS
Pharmacokinetics—The second-generation cephalosporins are cleared primarily by the kidney (Table 1.5). They have half-lives that range from 0.8 to 3.5 hours, and they penetrate all body cavities.

Spectrum of Activity and Treatment Recommendations—The second-generation cephalosporins possess increased activity against some gram-negative strains, and they effectively treat MSSA and non-enterococcal streptococci (Table 1.6). Given the availability of the first-, third-, and fourth-generation cephalosporins and the newer penicillins, second-generation cephalosporins are rarely recommended as primary therapy.

Because cefoxitin and cefotetan demonstrate increased anaerobic coverage, including many strains of B. fragilis, and also cover gonococcus, these two agents are used as part of first-line therapy in pelvic inflammatory disease. They are also used for the treatment of moderately severe intra-abdominal infections and mixed aerobic–anaerobic soft-tissue infections, including diabetic foot infections. The oral preparation cefuroxime achieves serum levels that are approximately one tenth that of intravenous preparations, and this agent is recommended for the outpatient treatment of uncomplicated urinary tract infections and otitis media. Other less costly oral antibiotics effectively cover the same pathogens.

Cefaclor, the other second-generation oral preparation, is inactivated by β-lactamases produced by H. influenzae and M. catarrhalis. Although cefaclor has been recommended for otitis media, other oral antibiotics are generally preferred.

THIRD-GENERATION CEPHALOSPORINS
Pharmacokinetics—With the exception of ceftriaxone, the third-generation cephalosporins are excreted by the kidneys (Table 1.5). Ceftriaxone is cleared primarily by the liver, but high concentrations of the drug are also excreted in the biliary system. The half-lives of these agents vary, being as short as 1.5 hours (cefotaxime) and as long as 8 hours (ceftriaxone). They penetrate most body sites effectively.

Spectrum of Activity and Treatment Recommendations—As compared with the first- and second-generation, third-generation cephalosporins have enhanced activity against many aerobic gram-negative bacilli, but they do not cover Serratia marcescens, Acinetobacter, and Enterobacter cloacae. With the exceptions of ceftazidime and cefoperazone, third-generation cephalosporins are ineffective against P. aeruginosa.

These agents have excellent cidal activity against S. pneumoniae (including moderately penicillin-resistant strains), S. pyogenes, and other streptococci. All members of this generation are ineffective for treating Enterococcus, MRSA, highly penicillin-resistant pneumococcus, and L. monocytogenes.

The ESBLs are increasing in frequency, and they promise to reduce the effectiveness of the third- and fourth-generation cephalosporins. A large number of third-generation cephalosporins are available, all with similar indications. Small deficiencies in coverage and less-desirable pharmacokinetics have affected the popularity of a number of these drugs.

Ceftriaxone and cefotaxime are recommended for empirical treatment of community-acquired pneumonia and community-acquired bacterial meningitis (see Chapters 4 and 6). Third-generation cephalosporins can be used
in combination with other antibiotics to empirically treat the septic patient. Ceftriaxone is recommended for treatment of *N. gonorrhoeae*. Cefotaxime is cleared renally and does not form sludge in the gallbladder. For this reason, this agent is preferred over ceftriaxone by some pediatricians, particularly for the treatment of bacterial meningitis in children—where high-dose therapy has been associated with symptomatic biliary sludging. Ceftazidime is the only third-generation cephalosporin that has excellent activity against *P. aeruginosa*; however, the fourth-generation cephalosporin cefepime (and the monobactam aztreonam) are now more commonly utilized for anti-*Pseudomonas* therapy in many institutions.

The oral third-generation cephalosporin cefixime has a long half-life, allowing for once-daily dosing. Cefixime provides effective coverage for *S. pneumoniae* (penicillin-sensitive), *S. pyogenes*, *H. influenzae*, *M. catarrhalis*, *Neisseria* species, and many gram-negative bacilli, but it is ineffective against *S. aureus*. Its absorption is not affected by food. This agent is a potential second-line therapy for community-acquired pneumonia, and it is an alternative to penicillin for the treatment of bacterial pharyngitis. The other oral preparation, cefpodoxime proxetil, has an antimicrobial spectrum similar to that of cefixime. In addition, it has moderate activity against *S. aureus*. The indications for use are similar to those for cefixime, and cefpodoxime proxetil has also been recommended as an alternative treatment for acute sinusitis.

**KEY POINTS**

### About the Third-Generation Cephalosporins

1. Improved gram-negative coverage.
2. Excellent activity against *Neisseria gonorrhoeae*, *N. meningitidis*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.
3. Ceftriaxone has a long half-life that allows for once-daily dosing. In children, acalculous cholecystitis can occur with large doses.
4. Cefotaxime has a shorter half-life but activity identical to that of ceftriaxone; does not cause biliary sludging.
5. Ceftazidime has excellent activity against most *Pseudomonas aeruginosa* strains, but reduced activity against *Staphylococcus aureus*.
6. Extended spectrum β-lactamases are increasing in frequency and endangering the effectiveness of third-generation cephalosporins.
7. Recommended for community-acquired pneumonia and bacterial meningitis

### About Fourth-Generation Cephalosporins

1. Zwitterionic properties allow for excellent penetration of the bacterial cell wall and of human tissues and fluids.
2. Weakly induce β-lactamases.
4. Excellent gram-positive (including penicillin-sensitive *Staphylococcus aureus*) and gram-negative coverage (including *Pseudomonas aeruginosa*).
5. Excellent broad-spectrum empiric therapy. Useful in nosocomial infections.

**FOURTH-GENERATION CEPHALOSPORINS**

Pharmacokinetics—Clearance of the fourth-generation cephalosporins is renal, and the half-lives of these agents are similar to the renally cleared third-generation cephalosporins (Table 1.5). The R₂ substitution of the fourth-generation cephalosporins contains both a positively and negatively charged group that, together, have zwitterionic properties that permit these antibiotics to penetrate the outer wall of gram-negative bacteria and concentrate in the periplasmic space. This characteristic also allows for excellent penetration of all body compartments, including the cerebrospinal fluid.

**Spectrum of Activity and Treatment Recommendations**—The fourth-generation cephalosporins are resistant to most β-lactamases, and they only weakly induce β-lactamase activity (Table 1.6, Figure 1.5). These agents also bind gram-positive PBPs with high affinity.

The only agent currently available in the United States is cefepime. In addition to having broad antimicrobial activity against gram-negative bacilli, including *P. aeruginosa*, cefepime provides excellent coverage for *S. pneumoniae* (including strains moderately resistant to penicillin), *S. pyogenes*, and MSSA. Cefepime and ceftazidime provide comparable coverage for *P. aeruginosa*. To maximize the likelihood of cure of serious *P. aeruginosa* infection, more frequent dosing (q8h) has been recommended.

Cefepime is not effective against *L. monocytogenes*, MRSA, or *B. fragilis*. As compared with third-generation cephalosporins, cefepime is more resistant to β-lactamases, including the ESBLs. It has been effectively used to treat gram-negative meningitis. Cefepime is effective as a single agent in the febrile neutropenic
patient, and it is an excellent agent for initial empiric coverage of nosocomial infections.

Cefpirome is available in Europe. It has an antimicrobial spectrum similar to that of cefepime, although it is somewhat less active against *P. aeruginosa*.

**Monobactams**

**AZTREONAM**

Chemistry and Pharmacokinetics—Aztreonam was originally isolated from *Chromobacterium violaceum* and subsequently modified. This antibiotic has a distinctly different structure from the cephalosporins, and it is the only available antibiotic in its class. Rather than a central double ring, aztreonam has a single ring (“monocyclic β-lactam structure”), and has been classified as a monobactam.

Because of its unique structure, aztreonam exhibits no cross-reactivity with other β-lactam antibiotics. It can be used safely in the penicillin-allergic patient. The drug penetrates body tissue well and crosses the blood–brain barrier of inflamed meninges. Aztreonam is renally cleared and has a half-life similar to that of the renally cleared third- and fourth-generation cephalosporins.

**Spectrum of Activity and Treatment Recommendations**—Aztreonam does not bind to the PBPs of gram-positive organisms or anaerobes; rather, it binds with high affinity to PBPs, particularly PBP-3 (responsible for septum formation during bacterial division), of gram-negative bacilli including *P. aeruginosa*. Gram-negative organisms exposed to aztreonam form long filamentous structures and are killed.

Aztreonam is effective against most gram-negative bacilli, and this agent has been marketed as a non-nephrotoxic replacement for aminoglycosides. However, unlike aminoglycosides, aztreonam does not provide synergy with penicillins for *Enterococcus*. A major advantage of aztreonam is its restricted antimicrobial spectrum, which allows for survival of the normal gram-positive and anaerobic flora that can compete with more resistant pathogens.

Aztreonam can be used for the treatment of most infections attributable to gram-negative bacilli. It has been used effectively in pyelonephritis, nosocomial gram-negative pneumonia, gram-negative bacteremia, and gram-negative intra-abdominal infections. Importantly, though, aztreonam provides no gram-positive or anaerobic coverage. Therefore, when it is used for empiric treatment of potential gram-positive pathogens in the seriously ill patient,

**Table 1.7.** Carbapenems: Half-Life, Dosing, Renal Dosing, Cost, and Spectrum

<table>
<thead>
<tr>
<th>Antibiotic (trade name)</th>
<th>Half-life (h)</th>
<th>Dose</th>
<th>Dose for reduced creatinine clearance (mL/min)</th>
<th>Cost*</th>
<th>Spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem–cilastin</td>
<td>1</td>
<td>0.5–1 g IV q6h</td>
<td>50–80: 0.5 g q6–8h 10–50: 0.5 g q8–12h &lt;10: 0.25–0.5 g q12h</td>
<td>$$$–$$$$</td>
<td>Very broad</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1</td>
<td>1 g IV q8h</td>
<td>10–50: 0.5 g q8h  &lt;10: 0.5 g q24h</td>
<td>$$$</td>
<td>Very broad</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>4</td>
<td>1 g IV or IM q24h</td>
<td>&lt;30: 500 mg q24h</td>
<td>$</td>
<td>Very broad</td>
</tr>
</tbody>
</table>

aztreonam should be combined with vancomycin, clindamycin, erythromycin, or a penicillin.

**Carbapenems**

Table 1.7, together with Figure 1.5, summarizes the characteristics of the various carbapenems.

**CHEMISTRY AND PHARMACOKINETICS**

The carbapenems have both a modified thiazolidine ring and a change in the configuration of the side chain that renders the β-lactam ring highly resistant to cleavage. Their hydroxyethyl side chain is in a trans rather than cis conformation, and this configuration is thought to be responsible for the group’s remarkable resistance to β-lactamase breakdown. At physiologic pH, these agents have zwitterionic characteristics that allow them to readily penetrate tissues. The carbapenems bind with high affinity to the high molecular weight PBPs of both gram-positive and gram-negative bacteria.

Imipenem is combined in a 1:1 ratio with cilastatin to block rapid breakdown by renal dehydropeptidase I. Meropenem and ertapenem are not significantly degraded by this enzyme and do not require co-administration with cilastatin. These drugs are all primarily cleared by the kidneys.

**SPECTRUM OF ACTIVITY AND TREATMENT RECOMMENDATIONS**

The carbapenems have a very broad spectrum of activity, effectively killing most strains of gram-positive and gram-negative bacteria, including anaerobes. Overall, imipenem has slightly better activity against gram-positive organisms. Meropenem and ertapenem have somewhat better activity against gram-negative pathogens (except *Pseudomonas*, as described later in this subsection).

These agents are cidal not only against *S. pneumoniae*, *S. pyogenes*, and MSSA, but also against organisms that are not covered by the cephalosporins, including *Listeria*, *Nocardia*, *Legionella*, and *Mycobacterium avium intracellulare* (MAI). They have static activity against penicillin-sensitive enterococci; however, many penicillin-resistant strains are also resistant to carbapenems. MRSA, some penicillin-resistant strains of *S. pneumoniae*, *C. difficile*, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia* are also resistant. Resistance in gram-negative bacilli is most often secondary to loss of an outer membrane protein called D2 that is required for intracellular penetration of the carbapenems. Increasing numbers of gram-negative strains can also produce β-lactamases called carbapenemases that can hydrolyze these drugs.

Imipenem and meropenem can be used as empiric therapy for sepsis, and they are particularly useful if polymicrobial bacteremia is a strong possibility. They can also be used to treat severe intra-abdominal infections and complicated pyelonephritis. Infections attributable to gram-negative bacilli resistant to cephalosporins and aminoglycosides may be sensitive to imipenem or meropenem. Imipenem or meropenem are recommended as primary therapy for *Serratia*. Meropenem can be used for meningitis, achieving therapeutic levels in the cerebrospinal fluid. Imipenem is not recommended for this purpose because of its propensity to cause seizures. In general, imipenem and meropenem should be reserved for the seriously ill patient or the patient infected with a highly resistant bacterium that is sensitive only to this antibiotic.

Ertapenem has a longer half-life and can be given just once daily, making it a useful agent for home intravenous therapy. This agent is not effective against *P. aeruginosa*, but otherwise it has a spectrum similar to that of meropenem. It is recommended for complicated intra-abdominal infections, postpartum and postoperative acute pelvic infections, and complicated soft-tissue infections.

Because the carbapenems are extremely broad-spectrum agents, they kill nearly all normal flora. The loss of normal flora increases the risk of nosocomial infections with resistant pathogens including MRSA, *Pseudomonas*, and *Candida*. 

**KEY POINTS**

**About the Carbapenems**

1. β-Lactam ring is highly resistant to cleavage.
2. Have zwitterionic characteristics, and penetrate all tissues.
3. Frequent cross-reactivity in penicillin-allergic patients (7%).
4. Imipenem causes seizures at high doses; be cautious in renal failure patients. Meropenem is less epileptogenic.
5. Bind penicillin binding proteins of all bacteria with high affinity.
6. Very broad cidal activity for aerobic and anaerobic gram-positive and gram-negative bacteria. Also covers *Listeria monocytogenes* and *Nocardia*.
7. Imipenem and meropenem are useful for empiric therapy of suspected mixed aerobic and anaerobic infection or a severe nosocomial infection, pending culture results. Reserve for the severely ill patient.
8. Ertapenem can be given once daily. Lacks *Pseudomonas aeruginosa* coverage.
9. Treatment markedly alters the normal bacterial flora.
Aminoglycosides

Tables 1.8 and 1.9, together with Figure 1.5, summarize the characteristics of the various aminoglycosides.

Chemistry and Mechanism of Action

Aminoglycosides were originally derived from Streptomyces species. These agents have a characteristic 6-member ring with amino-group substitutions, and they are highly soluble in water. At neutral pH, they are positively charged, and this positive charge contributes to their antibacterial activity. At a low pH, the charge is reduced, impairing antimicrobial activity. Their positive charge also causes aminoglycosides to bind to and become inactivated by β-lactam antibiotics. Therefore aminoglycosides should never be in the same solution with β-lactam antibiotics.

Upon entering the bacterium, the antibiotic molecules interact with and precipitate DNA and other anionic components. Aminoglycosides also bind to the 30S sub-unit of bacterial 16S ribosomal RNA and interfere with translation. These combined effects are bactericidal.

Toxicity

The aminoglycosides have a narrow ratio of therapeutic effect to toxic side effect, and monitoring serum levels is generally required to prevent toxicity. These agents are among the most toxic drugs prescribed today, and they should be avoided whenever safer alternative antibiotics are available (Table 1.10).

Two major toxicities are observed:

1. Nephrotoxicity. Injury to the proximal convoluted tubules of the kidney leads to a reduction in creatinine clearance. The brush border cells of the proximal tubule take up aminoglycosides by endocytosis, and intracellular entry is associated with cell necrosis. Aminoglycosides cause significant reductions of glomerular filtration in 5% to 25% of patients. Patient characteristics associated with an increased risk of nephrotoxicity include older age, pre-existing renal disease, hepatic dysfunction, volume depletion, and hypotension. Re-exposure to aminoglycosides increases risk, as do the use of larger doses, more frequent dosing intervals, and treatment for more than 3 days. The risk of renal failure is also associated with co-administration of vancomycin, amphotericin B, clindamycin, piperacillin, cephalosporins, fosfomycin, or furosemide. Because renal tubular cells have regenerative power, renal dysfunction usually reverses on discontinuation of the aminoglycoside. Because aminoglycosides are primarily renally cleared, aminoglycoside serum levels are useful for detecting worsening renal function. Trough aminoglycoside serum levels often rise before a significant rise in serum creatinine can be detected.

2. Ototoxicity. Aminoglycosides enter the inner ear fluid and damage outer hair cells important to the detection of high-frequency sound. Loss of high-frequency hearing occurs in 3% to 14% of patients treated with aminoglycosides. The risk of hearing loss is greater after prolonged treatment, with most cases developing after 9 or more days of therapy. Hearing loss is irreversible and can occur weeks after therapy has been discontinued. A genetic predisposition has been observed, with certain families having a high incidence of deafness after receiving aminoglycosides. The risk of hearing loss depends on the specific aminoglycoside. Neomycin has the highest risk of toxicity, followed in order of decreasing frequency by gentamicin, tobramycin, amikacin, and netilmicin. Concomitant use of furosemide or vancomycin, and exposure to loud noises increases the risk. As compared with dosing at 8-hour intervals, once-daily dosing reduces the toxic risk.

Less commonly, aminoglycosides can cause neuromuscular blockade; they should be avoided in myasthenia gravis. Given the high risk of toxicity, aminoglycosides should be used only when alternative antibiotics are unavailable. When aminoglycosides are required, the duration of therapy should be as brief as possible. Pretreatment and periodic testing of high-frequency hearing should be performed, and serum creatinine and aminoglycoside serum levels should be monitored.

Pharmacokinetics

Following intravenous infusion, aminoglycosides take 15 to 30 minutes to distribute throughout the body. Therefore, to determine peak serum level, blood samples should be drawn 30 minutes after completion of the intravenous infusion. The half-life of aminoglycosides is 2 to 5 hours, and these agents are cleared by the kidneys.

Proper dosing of aminoglycosides is more complicated than for most other antibiotics, and these agents require close monitoring. In many hospitals, a pharmacist is consulted to assist in dose management. For daily multiple-dose therapy, a loading dose is first given to rapidly achieve a therapeutic serum level; maintenance doses are then administered. Doses are calculated based on ideal body weight. In the setting of renal dysfunction, dosing must be carefully adjusted, and peak and trough serum levels monitored. As renal impairment worsens, the dosage interval should be extended.

Once-daily aminoglycoside dosing is now the preferred therapy in nearly all instances. As compared with multidose therapy, once-daily administration reduces
### Table 1.8. Aminoglycosides: Half-Life, Dosing, Renal Dosing, Cost, and Spectrum

<table>
<thead>
<tr>
<th>Antibiotic (trade name)</th>
<th>Half-life (h)</th>
<th>Dose</th>
<th>Dose for reduced creatinine clearance (mL/min)</th>
<th>Cost*</th>
<th>Spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin and tobramycin (Garamycin and Nebcin)</td>
<td>2</td>
<td>2 mg/kg load, then 1.7–2 mg/kg q8h; or 5 mg/kg q24h</td>
<td>0.03 mg/kg × CrCl q8h, adjusting peak to 5–10 μg/mL and trough 1–2 μg/mL; or 60–79: 4 mg/kg q24h 50: 3.5 mg/kg q24h 40: 2.5 mg/kg q24h &lt;30: Conventional dosing, adjusting trough to &lt;0.5 μg/mL</td>
<td>$$$– Narrow</td>
<td></td>
</tr>
<tr>
<td>Amikacin (Amikin)</td>
<td>2</td>
<td>8 mg/kg load, then 7.5–8 mg/kg q8h, or 15 mg/kg daily</td>
<td>0.12 mg/kg × CrCl q8h, adjusting peak to 20–40 μg/mL, and trough 5–10 μg/mL; or 60–79: 12 mg/kg q24h 50: 7.5 mg/kg q24h 40: 4.0 mg/kg q24h &lt;30: Conventional dosing, adjusting trough to &lt;5 μg/mL</td>
<td>$$$– Narrow</td>
<td></td>
</tr>
<tr>
<td>Netilmicin</td>
<td>2.5</td>
<td>2 mg/kg load, then 2 mg/kg q8h</td>
<td>Same as gentamicin and tobramycin</td>
<td>$$$– Narrow</td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>2–5</td>
<td>7.5 mg/kg load, then 7.5 mg/kg q12h</td>
<td>50–80: 15 mg/kg q24–72h 10–40: 15 mg/kg q72–96h &lt;10: 7.5 mg/kg q72–96h, adjusting peak to 15–25 μg/mL and trough to 5–10 μg/mL</td>
<td>$$$– Narrow</td>
<td></td>
</tr>
</tbody>
</table>

Intravenous preparations (daily cost dollars): $ = 20–70; $$ = 71–110; $$$ = 111–150; $$$$ = 150–200; $$$$$ ≥ 200. Includes costs of monitoring and toxicity.

### Table 1.9. Organisms That May Be Susceptible to Aminoglycosides

<table>
<thead>
<tr>
<th>Gentamicin</th>
<th>Tobramycin</th>
<th>Amikacin</th>
<th>Streptomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most Enterobacteriaceae (see Figure 1.5)</td>
<td>Most Enterobacteriaceae (see Figure 1.5)</td>
<td>Most Enterobacteriaceae (see Figure 1.5)</td>
<td>Yersinia pestis Francisella tularensis</td>
</tr>
<tr>
<td>Francisella tularensis Brucella spp. (combined with doxycycline)</td>
<td>Pseudomonas aeruginosa (synergy with anti-Pseudomonas penicillin or cephalosporins)</td>
<td>Mycobacterium avium complex</td>
<td>Brucella spp. (combined with doxycycline)</td>
</tr>
<tr>
<td>Synergy with penicillins, vancomycin, and ceftriaxone for S. viridans</td>
<td></td>
<td></td>
<td>M. tuberculosis</td>
</tr>
<tr>
<td>Synergy with penicillins and vancomycin for Enterococcus</td>
<td></td>
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</tr>
</tbody>
</table>
### Table 1.10. Toxicities of Miscellaneous Antibiotics

<table>
<thead>
<tr>
<th>Clinical symptom</th>
<th>Antibiotic</th>
<th>Aminoglycosides</th>
<th>Vancomycin</th>
<th>Macrolides</th>
<th>Clindamycin</th>
<th>Tetracyclines</th>
<th>Chloramphenicol</th>
<th>Quinolons</th>
<th>Linezolid</th>
<th>Quinupristin/dalfopristin</th>
<th>Daptomycin</th>
<th>Meronidazole</th>
<th>Sulfas</th>
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</thead>
<tbody>
<tr>
<td>Allergic skin rash</td>
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<td>a</td>
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<td>Steven–Johnson</td>
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<td>Diarrhea (Clostr. difficile)</td>
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<td>Gastrointestinal intolerance</td>
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<td>Hearing loss</td>
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<td>Dizziness</td>
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<td>Neurotoxicity</td>
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<td>Seizure</td>
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<td>Phlebitis</td>
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<td>Cytopenias</td>
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</table>

* "Red man syndrome" common, but not a true allergic reaction (see text).
* Also photosensitivity.
* Gemifloxacin is associated with frequent skin rash in women under 40 years of age.
* Severe and occasionally fatal hepatitis associated with talithromycin.

Black = principle side effect; dark gray = less common side effect; light gray = rare side effect; white = not reported or very rare; ↑ = rise; AST/ALT = aspartate aminotransferase/alanine transaminase.

The concentration of the aminoglycoside that accumulates in the renal cortex and lowers the incidence of nephrotoxicity. Because aminoglycosides demonstrate concentration-dependent killing, the high peak levels achieved with this regimen increase the bactericidal rate and prolong the post-antibiotic effect. In addition, a once-daily regimen is simpler and less expensive to administer. This regimen has not been associated with a higher incidence of neuromuscular dysfunction. To adjust for renal impairment, the daily dose should be reduced.

Monitoring of serum levels is recommended for both multidose and once-daily regimens. With multidose therapy, blood for a peak level determination should be drawn 30 minutes after intravenous infusion is complete, and for a trough level, 30 minutes before the next dose. Blood for peak and trough determinations should be drawn after the third dose of
antibiotic to assure full equilibration within the distribution volume. In the critically ill patient, blood for a peak level determination should be drawn after the first dose to assure achievement of an adequate therapeutic level.

For once-daily dosing, trough levels need to be monitored to assure adequate clearance. Serum level at 18 hours should be <1 µg/mL. Alternatively, blood for a level determination can be drawn between 6 and 14 hours, and the value applied to a nomogram to help decide on subsequent doses. In the seriously ill patient, blood for a peak level determination should also be drawn 30 minutes after completion of the infusion to assure that a therapeutic level is being achieved (for gentamicin–tobramycin, a target concentration of 16 to 24 µg/mL should be achieved). Once-daily dosing is not recommended for the treatment of enterococcal endocarditis and has not been sufficiently studied in pregnancy or in patients with osteomyelitis or cystic fibrosis.

**Spectrum of Activity and Treatment Recommendations**

The aminoglycosides are cidal for most aerobic gram-negative bacilli, including *Pseudomonas* species. These agents kill rapidly, and the killing is concentration-dependent—that is, the rate increases as the concentration of the antibiotic increases. Once-daily dosing takes advantage of this characteristic. Aminoglycosides also demonstrate persistent suppression of bacterial growth for 1 to 3 hours after the antibiotic is no longer present. The higher the concentration of the aminoglycoside, the longer the post-antibiotic effect. Aminoglycosides also demonstrate synergy with antibiotics that act on the cell wall (*β*-lactam antibiotics and glycopeptides). The effect of these combinations is greater than the sum of the anti-microbial effects of each individual agent. Synergy has been achieved in the treatment of enterococci, *S. viridans*, *S. aureus*, coagulase-negative staphylococci, *P. aeruginosa*, *L. monocytogenes*, and JK corynebacteria.

An aminoglycoside in combination with other antibiotics is generally recommended for treatment of the severely ill patients with sepsis syndrome to assure broad coverage for gram-negative bacilli. An aminoglycoside combined with penicillin is recommended for empiric coverage of bacterial endocarditis. Tobramycin combined with an anti-pseudomonal penicillin or an anti-pseudomonal cephalosporin is recommended as primary treatment of *P. aeruginosa*. Streptomycin or gentamicin is the treatment of choice for tularemia and *Yersinia pestis*, and either agent can

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**KEY POINTS**

**About Dosing and Serum Monitoring of Aminoglycosides**

1. Aminoglycosides take 15 to 30 minutes to equilibrate in the body.
2. For multidose therapy, blood for a peak serum level determination should be drawn 30 minutes after infusion.
3. Blood for trough serum level determinations should be drawn just before the next dose.
4. Conventionally, aminoglycosides are given 3 times daily. Dosing should be based on lean body weight.
5. Once-daily dosing takes advantage of concentration-dependent killing and the post-antibiotic effects of aminoglycosides.
6. Once-daily dosing reduces, but does not eliminate, nephrotoxicity.
7. In most cases, trough serum levels need to be monitored only during once-daily dosing. Toxicity correlates with high trough levels.
8. Once-daily dosing is not recommended for enterococcal endocarditis or pregnant women.
also be used to treat *Brucella*. Gentamicin combined with penicillin is the treatment of choice for both *S. viridans* and *Enterococcus faecalis*.

**Glycopeptide Antibiotics**

Table 1.11, together with Figure 1.5, summarizes the characteristics of the glycopeptide antibiotics.

**CHEMISTRY AND MECHANISM OF ACTION**

Vancomycin and teicoplanin are complex glycopeptides of approximately 1500 Da molecular weight. These agents act primarily at the cell wall of gram-positive organisms by binding to the D-alanine–D-alanine peptidoglycan precursor and preventing it from being incorporated into the peptidoglycan. The binding of vancomycin to this cell wall precursor blocks the transpeptidase and transglycolase enzymes, interfering with cell wall formation and increasing permeability of the cell. These agents may also interfere with RNA synthesis. They bind rapidly and tightly to bacteria and rapidly kill actively growing organisms. They also have a 2-hour post-antibiotic effect.

**TOXICITY**

The most common side effect of the glycopeptide antibiotics is “red man syndrome,” which occurs most often when vancomycin is infused rapidly (Table 1.10). The patient experiences flushing of the face, neck, and upper thorax. This reaction is thought to be caused by sudden histamine release secondary to local hyperosmolality and not to be a true hypersensitivity reaction. Infusing vancomycin over a 1-hour period usually prevents this reaction. There is less experience with teicoplanin; however, this agent does not cause significant thrombophlebitis, and skin flushing after rapid infusion is uncommon. Ototoxicity has been reported.

**PHARMACOKINETICS**

The half-lives of vancomycin (4 to 6 hours) and teicoplanin (40 to 70 hours) are prolonged (Table 1.11). Both drugs are excreted primarily by the kidneys, and in the anuric patient, the half-life of vancomycin increases to 7 to 9 days. For vancomycin, peak levels should reach 20 to 50 μg/mL, with trough levels being maintained at 10 to 12 μg/mL. Vancomycin penetrates most tissue spaces, but does not cross the blood–brain barrier in the absence of inflammation. Therapeutic cerebrospinal levels are achieved in patients with meningitis. Unlike vancomycin, which is minimally bound to protein, teicoplanin is 90% protein-bound, accounting for its slow renal clearance. Tissue penetration has not been extensively studied, and little data are available on penetration of bone, peritoneal, or cerebrospinal fluid.
### Table 1.11. Glycopeptides, Macrolides, Clindamycin, Tetracyclines, and Chloramphenicol: Half-Life, Dosing, Renal Dosing, Cost, and Spectrum

<table>
<thead>
<tr>
<th>Antibiotic (trade name)</th>
<th>Half-life (h)</th>
<th>Dose</th>
<th>Dose for reduced creatinine clearance (mL/min)</th>
<th>Cost&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin (Vancocin)</td>
<td>4–6</td>
<td>15 mg/kg IV q12h (usual dose: 1 g q12h)</td>
<td>40–60: 1 g q12–24h 20–40: q24–48h 10–20: q48–72h &lt;10: q3–7d Exact dose based on levels: peak: 25–50 μg/mL; trough: 10–12 μg/mL</td>
<td>$</td>
<td>Narrow</td>
</tr>
<tr>
<td>Teicoplanin (Targocid)</td>
<td>40–70</td>
<td>6 mg/kg IV or IM followed by 3 mg/kg q24h</td>
<td>10–50: Half the dose &lt;10: One third the dose</td>
<td>Not sold in United States</td>
<td>Narrow</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>1.2–1.6</td>
<td>250–500 mg PO q6h 1 g IV q6h</td>
<td>No change required</td>
<td>$</td>
<td>Narrow</td>
</tr>
<tr>
<td>Clarithromycin (Biaxin, Biaxin XL)</td>
<td>4</td>
<td>250–500 mg PO q12h 1 g PO q24h</td>
<td>&lt;10: 250–500 mg q24h</td>
<td>$–$$</td>
<td>Narrow</td>
</tr>
<tr>
<td>Azithromycin (Zithromax)</td>
<td>68</td>
<td>500 mg PO, followed by 250 mg PO q24h, or 500 mg IV q24h</td>
<td>Probably no change required &lt;10: Not studied</td>
<td>$</td>
<td>Narrow</td>
</tr>
<tr>
<td>Talithromycin (Ketek)</td>
<td>10</td>
<td>800 mg PO q24h</td>
<td>&lt;30: 600 mg q24h</td>
<td>$$</td>
<td>Narrow</td>
</tr>
<tr>
<td>Clindamycin (Cleocin)</td>
<td>2.5</td>
<td>150–300 mg PO q6h 300–900 mg IV q6–8h</td>
<td>No change required</td>
<td>PO: $$$$$ IV: $</td>
<td>Narrow</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>8</td>
<td>250–500 mg PO twice daily</td>
<td>50–80: q12h 10–50: q12–24h &lt;10: q24h</td>
<td>$</td>
<td>Broad</td>
</tr>
<tr>
<td>Doxycycline (Vibramycin, Doxy)</td>
<td>18</td>
<td>100 mg PO twice daily</td>
<td>No change required</td>
<td>$</td>
<td>Broad</td>
</tr>
<tr>
<td>Minocycline (Minocin, Dynacin)</td>
<td>16</td>
<td>200 mg PO twice daily</td>
<td>No change required</td>
<td>$</td>
<td>Broad</td>
</tr>
<tr>
<td>Tigecycline (Tygecil)</td>
<td>42</td>
<td>100 mg IV, followed by 50 mg IV q12h</td>
<td>No change required. For severe hepatic dysfunction, maintenance dose: 25 mg IV q12h</td>
<td>$$</td>
<td>Very broad</td>
</tr>
<tr>
<td>Chloramphenicol (Chloromycetin)</td>
<td>4</td>
<td>0.25–1 g IV q6h</td>
<td>No change required. Serum levels should be monitored in hepatic failure.</td>
<td>$</td>
<td>Broad</td>
</tr>
</tbody>
</table>

<sup>a</sup> Intravenous preparations (daily cost dollars): $ = 20–70; $$ 5 71–110; $$$ = 111–150; $$$$ = 150–200; $$$$$ ≥ 200; oral preparations (10-day course cost dollars): $ = 10–50; $$ = 51–100; $$$ = 101–140; $$$$ = 141–180; $$$$$ ≥ 180.
Vancomycin and teicoplanin both cover MRSA and MSSA, and they are the recommended treatment for MRSA. These agents also kill most strains of coagulase-negative staphylococci (*S. epidermidis*), which are usually methicillin-resistant. They are recommended for the treatment of coagulase-negative staphylococcal line sepsis and bacterial endocarditis. For the latter infection, the glycopeptide antibiotic should be combined with one or more additional antibiotics (see Chapter 7). Vancomycin-intermediately-resistant strains of *S. aureus* were first discovered in Japan and have also been identified in Europe and the United States. These strains have MICs of 8 to 16 μg/mL and are cross-resistant to teicoplanin. The increasing use of vancomycin has selected for these strains and warns us that the indiscriminant use of the glycopeptide antibiotics must be avoided.

Vancomycin and teicoplanin not only have excellent activity against *Staphylococcus*, but also against penicillin-resistant and susceptible strains of *S. pneumoniae*, and they are recommended for empiric treatment of the seriously ill patient with pneumococcal meningitis to cover for highly penicillin-resistant strains. The glycopeptide antibiotics also effectively treat *S. pyogenes*, GpB streptococci, *S. viridans*, and *S. bovis*, and they are recommended for treatment of these infections in the penicillin-allergic patient. Corynebacterium jeikeium (previously called JK diphtheroids) is sensitive to vancomycin, and that antibiotic is recommended for its treatment. Oral vancomycin clears *C. difficile* from the bowel, and in the past it was recommended for *C. difficile* toxin–associated diarrhea. However, because of the increased risk of developing VRE following oral vancomycin, this regimen is recommended only for cases that are refractory to metronidazole or for patients who are very seriously ill.

Vancomycin is frequently used to treat *Enterococcus faecalis* and *faecium*; however, an increasing number of strains have become resistant. Three gene complexes transfer resistance. The van A gene cluster directs peptidoglycan cell wall synthesis and converts D-alanine–D-alanine (the site of vancomycin action) to D-alanine–D-lactate, markedly reducing vancomycin and teicoplanin binding. The other two resistance gene clusters, van B and van C, result in vancomycin resistance, but do not impair teicoplanin activity.

### Macrolides and Ketolides

Tables 1.11 and 1.12, together with Figure 1.5, summarizes the characteristics of the macrolides and ketolides.

### KEY POINTS

#### About the Treatment Recommendations for Vancomycin

1. Treatment of choice for methicillin-resistant *Staphylococcus aureus*; vancomycin-tolerant strains have been reported.
2. Treatment of choice for coagulase-negative staphylococci.
3. Excellent activity against high-level penicillin-resistant *Streptococcus pneumoniae*.
4. In the penicillin-allergic patient, vancomycin is recommended for *Strep. pyogenes*, Gp B streptococci, *Strep. viridans*, and *Strep. bovis*.
5. Excellent activity against some strains of *Enterococcus*; however, van A gene–mediated vancomycin-resistant enterococci (VRE) are increasing in frequency.
6. Vancomycin use must be restricted to reduce the likelihood of selecting for VRE and vancomycin-tolerant *Staph. aureus*.

### Chemistry and Mechanism of Action

The founding member of the macrolide family, erythromycin, was originally purified from a soil bacterium. It has a complex 14-member macrocyclic lactone ring (which gives rise to the class name “macrolides”) attached to two sugars. Azithromycin has a 15-member lactone ring and a nitrogen substitution. Clarithromycin has a methoxy group modification at carbon 6 of the erythromycin molecule. These modifications enhance oral absorption and broaden the antimicrobial spectrum.

The newest class of macrolide-like agents are the semisynthetic derivatives of erythromycin called ketolides. The ketolides, represented by talithromycin, have a 14-member macrolactone ring with a keto group at position 3, with the hydroxyls at positions 11 and 12 replaced by a cyclic carbamate. These agents all inhibit protein biosynthesis by blocking the passage of nascent proteins through the ribosome exit tunnel. In the case of conventional macrolides, inhibition is accomplished by binding to a single domain of the 50S ribosomal subunit (domain V of the 23 rRNA molecule). As compared
with the macro-lides, talithromycin binds to the 50S subunit with higher affinity, binding to two regions of the 23S rRNA molecule (domains II and V) rather than one region. This unique binding mode explains the enhanced antimicrobial activity of ketolides against macrolide-resistant pathogens.

**TOXICITY**

Macrolides and ketolides are among the safer classes of antibiotics (Table 1.10). The primary adverse reactions are related to these agents’ ability to stimulate bowel motility. In fact, erythromycin can be used to treat gastric paresis. Particularly in younger patients, abdominal cramps, nausea, vomiting, diarrhea, and gas are common with erythromycin. These symptoms are dose-related and are more common with oral preparations, but can also occur with intravenous administration. Gastrointestinal toxicity can be debilitating, forcing the drug to be discontinued. Azithromycin and clarithromycin at the usual recommended doses are much less likely to cause these adverse reactions.

Talithromycin administration has been accompanied by difficulty with accommodation, resulting in blurred vision. Patients have also experienced diplopia following administration of this agent. Talithromycin treatment has also resulted in the sudden onset of severe and occasionally fatal hepatitis. All patients receiving this agent should therefore be warned of this potential side effect, and the drug should be prescribed only for cases of pneumonia in which the incidence of penicillin-resistant *S. pneumoniae* is high. Under these circumstances a fluoroquinolone with gram-positive coverage may be preferred.

Macrolides and ketolides may exacerbate myasthenia gravis and should be avoided in patients with that illness. Macrolides prolong the QT interval, and erythromycin administration has, on rare occasions, been associated with ventricular tachycardia.

These agents are metabolized by the cytochrome P450 3A4 system, and they cause an increase in serum levels of other drugs metabolized by that system, including many of the statins, short-acting benzodiazepines, such as midazolam (Versed), cisapride (Propulsid), ritonavir (Norvir), and tacrolimus (Prograf).

**PHARMACOKINETICS**

The stearate, ethylsuccinate, and estolate forms of erythromycin are reasonably well absorbed on an empty stomach, reaching peak serum levels 3 hours after ingestion. Clarithromycin, azithromycin, and talithromycin are better absorbed orally than erythromycin is, resulting in peak concentrations within 1 hour. Erythromycin and azithromycin should be taken on an empty stomach. If cost is not a primary issue, the improved

<table>
<thead>
<tr>
<th>Erythromycin</th>
<th>Clarithromycin</th>
<th>Azithromycin</th>
<th>Talithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td>More active against <em>S. pyogenes</em></td>
<td>Less active against <em>S. pyogenes</em></td>
<td>Most active against <em>S. pyogenes</em></td>
</tr>
<tr>
<td>Penicillin (PCN)–sensitive</td>
<td>More active against PCN-sensitive <em>S. pneumoniae</em></td>
<td>Less active against PCN-sensitive <em>S. pneumoniae</em></td>
<td>Active against some erythromycin-resistant strains</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>All pathogens covered by erythromycin, plus: <em>Haemophilus influenzae</em></td>
<td>All pathogens covered by erythromycin, plus: more active against <em>H. influenzae</em></td>
<td>Active against multiresistant <em>S. pneumoniae</em></td>
</tr>
<tr>
<td>Mouth flora including anaerobes, but not <em>Bacteroides fragilis</em></td>
<td><em>Moraxella catarrhalis</em></td>
<td><em>Moraxella catarrhalis</em></td>
<td>All pathogens covered by erythromycin, plus:</td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td><em>Borrelia burgdorferi</em></td>
<td>Most active against <em>Borrelia burgdorferi</em></td>
<td>Most active against erythromycin-sensitive <em>S. aureus</em></td>
</tr>
<tr>
<td><em>Neisseria meningitides</em></td>
<td><em>Mycoplasma leprae</em></td>
<td>Good activity against <em>Enterococcus faecalis</em>, but not <em>Enterococcus faecium</em></td>
<td></td>
</tr>
<tr>
<td><em>Campylobacter jejuni</em></td>
<td><em>Mycobacterium avium</em> complex</td>
<td><em>Legionella pneumophilia</em></td>
<td></td>
</tr>
<tr>
<td><em>Bordetella pertussis</em></td>
<td><em>Toxoplasma gondii</em></td>
<td><em>M. avium complex</em></td>
<td></td>
</tr>
<tr>
<td><em>Legionella pneumophilia</em></td>
<td><em>Helicobacter pylori</em></td>
<td><em>Helicobacter pylori</em></td>
<td></td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
<td><em>Plasmodium falciparum</em></td>
<td><em>Plasmodium falciparum</em></td>
<td></td>
</tr>
<tr>
<td><em>Ureaplasma urealyticum</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Chlamydia trachomatis</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Chlamydophila pneumoniae</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Corynebacterium diphtheriae</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Bartonella quintana</em></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 1.12.** Organisms That May Be Susceptible to Macrolides and Ketolides
absorption and lower incidence of gastrointestinal toxicity make the three newer agents preferable to erythromycin in most instances (Table 1.11).

Most of the macrolides and ketolides are metabolized and cleared primarily by the liver. Azithromycin is not metabolized, being excreted unchanged in the bile. Small percentages of these drugs are also excreted in the urine. These agents are widely distributed in tissues, achieving concentrations that are several times the peak concentration achieved in serum in most areas the body, including the prostate and middle ear. Clarithromycin levels in middle ear fluid have been shown to be nearly 10 times serum levels. Azithromycin concentrations in tissue exceed serum levels by a factor of 10 to 100, and its average half-life in tissues is 2 to 4 days. Therapeutic levels of azithromycin have been estimated to persist for 5 days after the completion of a 5-day treatment course. With the exception of intravenous erythromycin, these agents fail to achieve significant levels in the cerebrospinal fluid.

**Spectrum of Activity and Treatment Recommendations**

Macrolides demonstrate excellent activity against most gram-positive organisms and some gram-negative bacteria. Erythromycin can be bacteriostatic or bactericidal. Cidal activity increases when antibiotic concentrations are high and bacteria are growing rapidly.

These drugs are recommended for the treatment of community-acquired pneumonia (see Chapter 4). However, S. pneumoniae resistance to macrolides has steadily increased and now ranges between 10% and 15%. Resistance is more likely in intermediate penicillin-resistant strains (40% macrole resistant) and highly penicillin-resistant strains (60% macrole resistance). Multiresistant S. pneumoniae can be treated with talithromycin as a consequence of that agent’s different ribosomal binding sites.

In most countries, including the United States, 95% of S. pyogenes are sensitive to macrolides. However, in Japan, where macrolides are commonly used, 60% are resistant. Because S. aureus can develop resistance after a single mutation, macrolides are generally not recommended in their treatment. The macrolides and ketolides are effective against mouth flora, including anaerobes, but they do not cover the bowel anaerobe B. fragilis. The macrolides are also the treatment of choice for Legionella pneumophilia, with talithromycin, azithromycin, and clarithromycin being more potent than erythromycin.

Macrolides are the primary antibiotics used to treat the two major pathogens associated with atypical pneumonia: Mycoplasma pneumoniae and Chlamydia pneumoniae (see Chapter 4). Talithromycin is also approved for acute bacterial sinusitis. In many instances the erythromycins can be used as an alternative to penicillin in the penicillin-allergic patient.

Clarithromycin is one of the primary antibiotics used for the treatment of atypical mycobacterial infections, particularly MAI complex. Azithromycin in combination with other antibiotics is also recommended for the treatment of MAI complex, and it can be used alone for MAI prophylaxis in HIV-infected patients with CD4 cell counts below 100 cells/mL.

In combination with antacid therapy, effective regimens for curing peptic ulcer disease caused by Helicobacter pylori include azithromycin or clarithromycin combined with bismuth salts and either amoxicillin, metronidazole, or tetracycline. Single high-dose azithromycin (1 g) effectively treats chancroid, as well as Chlamydia trachomatis urethritis and cervicitis. Single-dose therapy also cures male Ureaplasma urealyticum urethritis.

**Clindamycin**

**Chemistry and Mechanism of Action**

Although clindamycin is structurally different from erythromycin, many of its biologic characteristics are similar. Clindamycin consists of an amino acid linked
to an amino sugar, and it was derived by modifying lincomycin. It binds to the same 50S ribosomal binding site used by the macrolides, blocking bacterial protein synthesis.

**TOXICITY**

Diarrhea is a major problem seen in 20% of patients taking clindamycin (Table 1.10). The incidence is highest with oral administration. In up to half of the affected patients, the cause of diarrhea is pseudomembranous colitis, a disease caused by overgrowth of the anaerobic bacteria *C. difficile* (see Chapter 8).

**PHARMACOKINETICS**

Clindamycin is well absorbed orally; however, the drug can also be administered intravenously and the intravenous route can achieve higher peak serum levels. Clindamycin penetrates most tissues, but it does not enter the cerebrospinal fluid. Clindamycin is metabolized primarily by the liver and is excreted in the bile. Therapeutic concentrations of clindamycin persist in the stool for 5 or more days after the antibiotic is discontinued, and the reduction of clindamycin-sensitive flora persists for up to 14 days. Small percentages of clindamycin metabolites are also excreted in the urine.

**ANTIMICROBIAL SPECTRUM AND TREATMENT RECOMMENDATIONS**

Clindamycin is similar to erythromycin in its activity against streptococci and staphylococci (Figure 1.5). Moderately penicillin-resistant *S. pneumoniae* are often sensitive to clindamycin. In the penicillin-allergic patient, clindamycin is a reasonable alternative for *S. pyogenes* pharyngitis. Because its activity against *H. influenzae* is limited, clindamycin is not recommended for the treatment of otitis media.

Clindamycin distinguishes itself from the macrolides by possessing excellent activity against most anaerobic bacteria. It is used effectively in combination with an aminoglycoside, aztreonam, or a third-generation cephalosporin to treat fecal soilage of the peritoneum. However, other less-toxic regimens have proved to be equally effective. Clindamycin in combination with a first-generation cephalosporin can be used to block toxin production in severe cellulitis and necrotizing fasciitis caused by MSSA or *S. pyogenes*. It is also effective for the treatment of anaerobic pulmonary and pleural infections. Clindamycin also has significant activity against *Toxoplasma gondii* and is recommended as alternative therapy in the sulfa-allergic patient.

**Tetracyclines**

**CHEMISTRY AND MECHANISMS OF ACTION**

The tetracyclines consist of four 6-member rings with substitutions at the 4, 5, 6, and 7 positions that alter...
the pharmacokinetics of the various preparations; however, with the exception of tigecycline, these changes have no effect on the antimicrobial spectrum. The tetracyclines enter gram-negative bacteria by passively diffusing through porins. They bind to the 30S ribosomal subunit and block tRNA binding to the mRNA ribosome complex. This blockade primarily inhibits protein synthesis in bacteria, but to a lesser extent, it also affects mammalian cell protein synthesis, particularly mitochondria. The inhibition of bacterial protein synthesis stops bacterial growth, but does not kill the bacterium. Therefore, tetracycline is termed a bacteriostatic agent.

**TOXICITY**

Photosensitivity reactions consisting of a red rash over sun-exposed areas can develop (Table 1.10). Hypersensitivity reactions are less common than with the penicillins, but they do occur. Tetracyclines interfere with enamel formation, and in children, teeth often become permanently discolored. Therefore these agents are not recommended for children 8 years of age or younger, or for pregnant women. Because the tetracyclines inhibit protein synthesis, they increase azotemia in renal failure patients. Minocycline can cause vertigo, and that side effect has limited its use. Benign intracranial hypertension (pseudotumor cerebri) is another rare neurologic side effect.

**PHARMACOKINETICS**

Tetracycline is reasonably well absorbed (70% to 80%) by the gastrointestinal tract (see Table 1.11). Food interferes with its absorption. Doxycycline is nearly completely absorbed in the gastrointestinal tract. Calcium- or magnesium-containing antacids, milk, or multivitamins markedly impair absorption of all tetracycline preparations, and simultaneous ingestion of these products should be avoided. Tigecycline can be administered only intravenously. Tetracycline is cleared primarily by the kidneys; other agents, including doxycycline and tigecycline are cleared primarily by the liver.

**ANTIMICROBIAL SPECTRUM AND TREATMENT RECOMMENDATIONS**

The tetracyclines are able to inhibit the growth of a broad spectrum of bacteria (Table 1.13, Figure 1.5). However, for most conventional pathogens, other agents are more effective. High concentrations of tetracycline are achieved in the urine, and this agent can be used for uncomplicated urinary tract infections. Doxycycline combined with gentamicin is the treatment of choice for brucellosis. Tetracyclines are also recommended for the treatment of Lyme disease (*Borrelia burgdorferi*), and chlamydia infections (including *Chlamydia pneumonia*, psittacosis, epididymitis, urethritis, and endocervical infections). Tetracyclines are the treatment of choice for rickettsial infections (including Rocky Mountain spotted fever, ehrlichiosis, Q fever, and typhus fever). They are also often used in combination with other antibiotics for the treatment of pelvic inflammatory disease.

The most recently developed member of this family, tigecycline, was derived from minocycline. Tigecycline has a broader spectrum of activity. It effectively inhibits the growth of many resistant gram-positive bacteria (Table 1.13). This agent also

<table>
<thead>
<tr>
<th>Tetra-, Doxy-, and Minocycline</th>
<th>Tigecycline</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Vibrio</em> spp.</td>
<td>Methicillin-resistant</td>
</tr>
<tr>
<td><em>Mycobacterium marinum</em></td>
<td><em>Staphylococcus aureus</em> (MRSA)</td>
</tr>
<tr>
<td><em>Borrelia burgdorferi</em></td>
<td>Vancomycin intermediate-resistant</td>
</tr>
<tr>
<td><em>Leptospira</em></td>
<td><em>S. aureus</em> (VISA)</td>
</tr>
<tr>
<td><em>Chlamydia</em> spp.</td>
<td>Vancomycin-resistant enterococci (VRE)</td>
</tr>
<tr>
<td><em>Rickettsia</em> spp.</td>
<td>Penicillin-resistant <em>S. pneumoniae</em></td>
</tr>
<tr>
<td><em>Brucella</em></td>
<td><em>Acinetobacter baumannii</em></td>
</tr>
<tr>
<td></td>
<td><em>Stenotrophomonas maltophilia</em></td>
</tr>
<tr>
<td></td>
<td>Enterobacteriaceae, including those with extended-spectrum β-lactamases</td>
</tr>
<tr>
<td></td>
<td><em>Bacteroides fragilis</em></td>
</tr>
<tr>
<td></td>
<td><em>Clostridium perfringens</em> and <em>difficile</em></td>
</tr>
</tbody>
</table>
demonstrates improved activity against many highly resistant nosocomial gram-negative bacteria, but it does not effectively cover *P. aeruginosa* or *Proteus* species. Tigecycline is approved for complicated intra-abdominal and soft-tissue infections.

**Chloramphenicol**

**CHEMISTRY AND MECHANISMS OF ACTION**

Chloramphenicol consists of a nitro group on a benzene ring and a side chain containing five carbons. Chloramphenicol uses an energy-dependent mechanism to enter bacteria, and once in the cell, binds to the larger 50S subunit of the 70S ribosome, blocking attachment of tRNA. It inhibits bacterial protein synthesis, making it bacteriostatic for most bacteria; however, chloramphenicol is cidal for *H. influenzae*, *S. pneumoniae*, and *N. meningitidis*.

**TOXICITY**

Probably as result of its binding to human mitochondrial ribosomes, this agent has significant bone marrow toxicity (see Table 1.10). Two forms are observed.

The first form is dose-related and is commonly observed in patients receiving chloramphenicol 4 g or more daily. The reticulocyte count decreases, and anemia develops in association with elevated serum iron. Leukopenia and thrombocytopenia are also commonly encountered. These changes reverse when the antibiotic is discontinued. The second form of marrow toxicity, irreversible aplastic anemia, is rare, but usually fatal. This complication can occur weeks or months after the antibiotic is discontinued. Any patient receiving chloramphenicol requires twice-weekly monitoring of peripheral blood counts. If the WBC drops below 2500/mm\(^3\), the drug should be discontinued.

**PHARMACOKINETICS**

As a result of the much higher incidence of idiosyncratic aplastic anemia associated with oral administration as compared with intravenous administration, oral preparations of chloramphenicol are no longer available in the United States. The drug is well absorbed, and therapeutic serum levels can be achieved orally (Table 1.11). Chloramphenicol is metabolized by the liver. It diffuses well into tissues and crosses the blood–brain barrier in uninflamed as well as inflamed meninges. A serum assay is available, and serum levels should be monitored in patients with hepatic disease, maintaining the serum concentration between 10 and 25 μg/mL.

**ANTIMICROBIAL SPECTRUM AND TREATMENT RECOMMENDATIONS**

Chloramphenicol has excellent activity against most gram-positive organisms with the exception of enterococci and *S. aureus*, as well as many gram-negative organisms.
pathogens (Figure 1.5). Chloramphenicol also is very active against spirochetes, as well as Rickettsiae, Chlamydiae, and mycoplasmas.

Because of its bone marrow toxicity, chloramphenicol is not considered the treatment of choice for any infection. Alternative, less-toxic agents are available for each indication. For the penicillin-allergic patient, chloramphenicol can be used for bacterial meningitis. Chloramphenicol can also be used as alternative therapy for brain abscess, C. perfringens, psittacosis, rickettsial infections including Rocky Mountain spotted fever, Vibrio vulnificus, and typhoid fever.

Quinolones

Tables 1.14 and 1.15, together with Figure 1.5, summarize the characteristics of the quinolone antibiotics.

**CHEMICAL STRUCTURE AND MECHANISMS OF ACTION**

The quinolones all contain two 6-member rings (see Figure 1.7) with a nitrogen at position 1, a carbonyl group at position 4, and a carbonyl group attached to the carbon at position 3. Potency of the quinolones is greatly enhanced by adding fluorine at position 6, and gram-negative activity is enhanced by addition of a nitrogen-containing piperazine ring at position 7.

The quinolones inhibit two enzymes critical for DNA synthesis: DNA gyrase, which is important for regulating the superhelical twists of bacterial DNA, and topoisomerase IV, which is responsible for segregating newly formed DNA into daughter cells. The loss of these activities blocks DNA synthesis and results in rapid bacterial death. Killing is concentration-dependent.

**TOXICITY**

The most common side effects are mild anorexia, nausea, vomiting, and abdominal discomfort (Table 1.10). Quinolones can result in arthropathy because of cartilage damage and tendonitis. Although rare, this complication can be debilitating, but it usually reverses weeks to months after the quinolone is discontinued. Because of concerns about cartilage damage in children, quinolones are not recommended for routine administration in pediatric patients. Gatifloxacin administration can be associated with severe dysregulation of glucose homeostasis and can result in either severe hypo- or hyperglycemia. Fluoroquinolones are associated with a concentration-dependent delay in cardiac repolarization, causing a prolongation of the QT interval—a condition that can predispose to ventricular tachycardia. In combination with other agents that effect repolarization, moxifloxacin has occasionally been associated with life-threatening cardiac arrhythmias.

**PHARMACOKINETICS**

The quinolones are readily absorbed orally, but can also be given intravenously. Ciprofloxacin, levofloxacin, and gatifloxacin are cleared primarily by the kidneys. Moxifloxacin is also partially metabolized by the liver, and gemifloxacin is metabolized primarily by the liver. All quinolones demonstrate similar tissue penetration, being concentrated in prostate tissue, feces, bile, and lung tissue. These drugs tend to be very highly concentrated in macrophages and neutrophils.

**SPECTRUM OF ACTIVITY AND TREATMENT RECOMMENDATIONS**

Ciprofloxacin—Ciprofloxacin is the most potent quinolone for *P. aeruginosa* (Table 1.15, Figure 1.5). As a
Table 1.14. Quinolones, Linezolid, Quinupristin/Dalfopristin, Daptomycin, Metronidazole, and Sulfonamides: Half-Life, Dosing, Renal Dosing, Cost, and Spectrum

<table>
<thead>
<tr>
<th>Antibiotic (trade name)</th>
<th>Half-life (h)</th>
<th>Dose (loading/maintenance)</th>
<th>Dose for reduced creatinine clearance (mL/min)</th>
<th>Cost&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin (Cipro)</td>
<td>4</td>
<td>250–750 mg PO q12h, or 200–400 mg IV q12h</td>
<td>10–50: q18h PO; 10: q24h IV</td>
<td>PO: $$$</td>
<td>Moderately broad</td>
</tr>
<tr>
<td>Levofloxacin (Levoquin)</td>
<td>6–8</td>
<td>500 mg PO or IV q24h</td>
<td>10–50: 250 mg q24h PO; 10: 250 mg q48h IV</td>
<td>PO: $$$</td>
<td>Broad</td>
</tr>
<tr>
<td>Gatifloxacin (Tequin)</td>
<td>6–8</td>
<td>400 mg PO or IV q24h</td>
<td>10–50: 200 mg q24h PO; 10: 200 mg q24h IV</td>
<td>PO: $$</td>
<td>Very broad</td>
</tr>
<tr>
<td>Moxifloxacin (Avelox)</td>
<td>6–8</td>
<td>400 mg PO q24h</td>
<td>No change required PO; 10: 200 mg q24h IV</td>
<td>PO: $</td>
<td>Very broad</td>
</tr>
<tr>
<td>Gemifloxacin (Factive)</td>
<td>7</td>
<td>320 mg PO q24h</td>
<td>10–50: 160 mg q24h PO; 10: 160 mg q24h IV</td>
<td>$$$$$</td>
<td>Broad</td>
</tr>
<tr>
<td>Linezolid (Zyvox)</td>
<td>5</td>
<td>600 mg PO or IV q12h</td>
<td>No change required PO; 10: 160 mg q24h IV</td>
<td>PO: $$$$</td>
<td>Narrow</td>
</tr>
<tr>
<td>Quinupristin/dalfopristin (Synercid)</td>
<td>1.5</td>
<td>7.5 mg/kg IV q8–12h</td>
<td>No change required</td>
<td>$$$$$</td>
<td>Narrow</td>
</tr>
<tr>
<td>Daptomycin (Cubicin)</td>
<td>8–9</td>
<td>4 mg/kg IV q24h (soft-tissue infection) 6 mg/kg IV q24h (Staphylococcus aureus bacteremia)</td>
<td>&lt;10: q48h</td>
<td>$ $$$–$$ $$$</td>
<td>Narrow</td>
</tr>
<tr>
<td>Metronidazole (Flagyl, Protostat, Metronid)</td>
<td>6–14</td>
<td>500 mg PO q8h, or 500 mg–1 g PO q12h 15 mg/kg followed by 7.5 mg/kg IV q6h or 15 mg/kg q12h (not to exceed 4 g)</td>
<td>No change required. In severe hepatic failure, half the dose.</td>
<td>$</td>
<td>Narrow</td>
</tr>
<tr>
<td>Sulfisoxazole</td>
<td>1–2 g PO q6h</td>
<td>10–50: 1 g q8–12h</td>
<td>&lt;10: 1 g q12–24h</td>
<td>$</td>
<td>Moderately Broad</td>
</tr>
<tr>
<td>Sulfadiazine</td>
<td>0.5–1.5 g PO q4–6h</td>
<td>10–50: 0.5–1.5 g q8–12h</td>
<td>&lt;10: 0.5–1.5 g q12–24h</td>
<td>$</td>
<td>Moderately Broad</td>
</tr>
<tr>
<td>Trimethoprim–sulfamethoxazole</td>
<td>2–4 tablets q24h or 1–2 DS PO q24h Trimethoprim: 3–5 mg/kg IV q6–12h</td>
<td>Half the oral dose, and reduce the IV dose to 10–50: 3–5 mg/kg q12–24h &lt;10: Don’t give</td>
<td>$</td>
<td>Moderately Broad</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Intravenous preparations (daily cost dollars): $ = 20–70; $$ = 71–110; $$$ = 111–150; $$$$$ = 150–200; $$$$$$ ≥ 200; oral preparations (10-day course cost dollars): $ = 10–50; $$ = 51–100; $$$ = 101–140; $$$$$ = 141–180; $$$$$$ ≥ 180.
result of an excellent gram-negative spectrum, ciprofloxacin is one of the primary antibiotics recommended for treatment of urinary tract infections. It concentrates in the prostate and is recommended for treatment of prostatitis. For gonococcal urethritis, it is a useful alternative to ceftriaxone. Ciprofloxacin has been used effectively for traveler’s diarrhea most commonly caused by enterotoxigenic *E. coli* and *Shigella*. It is the drug of choice for *Salmonella typhi* (typhoid fever), and it also is recommended for treatment of *Salmonella* gastroenteritis when antibiotic treatment is necessary. Ciprofloxacin is the recommended treatment for cat scratch disease caused by *Bartonella henselae*.

Levofloxacin, Moxifloxacin, Gatifloxacin, and Gemifloxacin—These agents all demonstrate improved gram-positive coverage (Table 1.15, Figure 1.5) and have been recommended as one of the first-line treatments for community-acquired pneumonia in the otherwise healthy adult who does not require hospitalization. With the exception of gemifloxacin, these agents can also be used in soft-tissue infection in which a combination of gram-positive and gram-negative organisms is suspected. Given the worse toxicity profiles of the three newer agents (moxifloxacin, gatifloxacin, and gemifloxacin), levofloxacin should probably be the fluoroquinolone of choice for those infections. Gatifloxacin and moxifloxacin demonstrate moderate in vitro activity against anaerobes and may be considered for the treatment of mixed infections thought to include anaerobes. The exact indications for these agents are currently evolving. Fear of selecting for resistant pathogens has led to their use being restricted in some hospitals.

**Oxazolidones (Linezolid)**

**CHEMISTRY AND MECHANISMS OF ACTION**

The oxazolidones have a unique ring structure consisting of a 5-member ring containing an oxygen and a nitrogen. The nitrogen connects to a 6-member ring, and each specific compound has side chains added to both rings at positions A and B (Figure 1.8). These agents bind to the 50S ribosome at a site similar to that used by chloramphenicol. However, unlike chloramphenicol, they do not inhibit the attachment of tRNA, but instead block the initiation of protein synthesis by preventing the nearby 30S subunit from

---

**Table 1.15. Organisms That May Be Susceptible to the Quinolones**

<table>
<thead>
<tr>
<th>Ciprofloxacin</th>
<th>Levofloxacin, Gemifloxacin, Gatifloxacin, Moxifloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Same as ciprofloxacin, plus:</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>Methicillin-sensitive</td>
</tr>
<tr>
<td><em>Enterobacter cloacae</em></td>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td><em>Proteus spp.</em></td>
<td><em>Streptococcus pneumoniae</em></td>
</tr>
<tr>
<td><em>Providencia</em></td>
<td>Vancomycin-sensitive <em>Enterococcus</em></td>
</tr>
<tr>
<td><em>Salmonella, including Sal. typhi</em></td>
<td><em>Strep. pyogenes</em></td>
</tr>
<tr>
<td><em>Shigella spp.</em></td>
<td>Gatifloxacin and moxifloxacin: anaerobes</td>
</tr>
<tr>
<td><em>Yersinia spp.</em></td>
<td></td>
</tr>
<tr>
<td><em>Campylobacter spp.</em></td>
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</tr>
<tr>
<td><em>Bacillus anthracis</em></td>
<td></td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
<td></td>
</tr>
<tr>
<td><em>Chlamydia spp.</em></td>
<td></td>
</tr>
<tr>
<td><em>Ureaplasma urealyticum</em></td>
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<tr>
<td><em>Bartonella henselae</em></td>
<td></td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td></td>
</tr>
</tbody>
</table>

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![Figure 1–8. Basic structure of the oxazolidones.](image-url)
KEY POINTS
About the Specific Quinolones

1. Ciprofloxacin:
   a) Excellent coverage of *Pseudomonas*. Also covers many other gram-negative organisms including *Esch. coli*, *Salmonella*, *Shigella*, *Neisseria*, and *Legionella*.
   b) Kills *Mycoplasma*, *Chlamydia*, and *Ureaplasma*.
   c) Recommended for urinary tract infections and prostatitis, gonococcal urethritis, traveler’s diarrhea, typhoid fever, and *Salmonella* gastroenteritis; used for cat scratch disease.

2. Levofoxacin, gatifloxacin, moxifloxacin, gemifloxacin
   a) Greater activity against *Streptococcus pneumoniae*, covers highly penicillin-resistant strains.
   b) Also cover methicillin-sensitive *Staphylococcus aureus*.
   c) Recommended for community-acquired pneumonia (levofloxacin preferred).
   d) Levofoxacin, gatifloxacin, and moxifloxacin recommended for mixed skin infections.
   e) Gatifloxacin and moxifloxacin have somewhat improved anaerobic coverage.
   f) Gatifloxacin and moxifloxacin recommended for mixed skin infections.

KEY POINTS
About Linezolid

1. Like chloramphenicol, binds to the 50S ribosome subunit; inhibits the initiation of protein synthesis.
2. Thrombocytopenia common with treatment exceeding 2 weeks; inhibitor of monoamine oxidase; avoid tyramine, pseudoephedrine, serotonin uptake inhibitors.
3. Strictly gram-positive activity; bacteriostatic activity for vancomycin-resistant enterococci (VRE), and methicillin-resistant *Staphylococcus aureus*. Also has activity against penicillin-resistant *Streptococcus pneumoniae*.
4. Recommended for the treatment of VRE.

Toxicity

Linezolid is the only agent in this class released for use. Reversible thrombocytopenia has been reported in association with prolonged therapy, and monitoring of platelet count is recommended for patients receiving two or more weeks of linezolid. Leukopenia and hepatic enzyme elevations have also been reported. Because this agent is a weak inhibitor of monoamine oxidase, hypertension has been reported in association with ingestion of large amounts of tyramine. Pseudoephedrine and selective serotonin reuptake inhibitors should be prescribed with caution.

Pharmacokinetics

Linezolid is well-absorbed orally, and peak serum levels are achieved in 1 to 2 hours. Food slows absorption, but does not lower peak levels. An intravenous preparation is also available. Linezolid achieves excellent penetration of all tissue spaces, including the cerebrospinal fluid. The drug is partly metabolized by the liver and excreted in the urine.

Antimicrobial Activity and Treatment Recommendations

Linezolid demonstrates activity only against gram-positive organisms. It has bacteriostatic activity against both vancomycin-resistant *Enterococcus faecium* and *Enterococcus faecalis* (VRE). This agent is also active against MSSA and MRSA, and has activity against penicillin-resistant *S. pneumoniae*. Linezolid is recommended primarily for the treatment of VRE.

Streptogramins

Chemical Structure and Mechanism of Action

The streptogramins belong to the macrolide family. They are derived from pristinamycin. Quinupristin is a peptide derived from pristinamycin IA and dalfopristin is derived from pristinamycin IIB. A combination of 30:70 quinupristin:dalfopristin has synergistic activity and has been named Synercid. These two agents inhibit bacterial protein synthesis by binding to the 50S bacterial ribosome. Quinupristin inhibits peptide chain elongation, and dalfopristin interferes with peptidyl transferase activity.

Toxicity

Myalgias and arthralgias are the most common and severe adverse reaction, and they can force discontinuation of
the drug (Table 1.10). Administration has also been associated with hyperbilirubinemia.

**PHARMACOKINETICS**
The streptogramins are administered intravenously, and they are metabolized primarily in the liver (Table 1.14).

**ANTIMICROBIAL ACTIVITY AND TREATMENT INDICATIONS**
Synercid is active primarily against gram-positive organisms (Figure 5.1). It has proved to be efficacious in the treatment of VRE and MRSA. Synercid or linezolid are the treatments of choice for VRE.

**Daptomycin**

**CHEMICAL STRUCTURE AND MECHANISM OF ACTION**
Daptomycin is a large cyclic lipopeptide (C\(_{72}\)H\(_{101}\)N\(_{17}\)O\(_{26}\)) with a molecular weight of 1620 that was derived from *Streptomyces roseosporus*. Daptomycin has a mechanism of action that is distinctly different from that of other antibiotics. It binds to bacterial membranes and causes rapid depolarization of the membrane potential. As a result, protein, DNA, and RNA synthesis is inhibited. This antibiotic is cidal and causes rapid concentration-dependent killing, but it does not result in the systemic release of cell membrane or cell wall contents. It also demonstrates significant post-antibiotic effect. Synergy with aminoglycosides, β-lactam antibiotics, and rifampin has been observed.

**TOXICITY**
Muscle pain and weakness are reported in less than 5% of patients. This drug is also associated with a rise in creatine phosphokinase (CPK; Table 1.10). The patient’s CPK levels should be monitored weekly, and the drug should be discontinued if CPK exceeds 1000 in association with symptoms of myopathy, or if CPK exceeds 2000 in the absence of symptoms. Other drugs associated with rhabdomyolysis, specifically HMG-CoA reductase inhibitors (statins), should not be administered with daptomycin. Less commonly, daptomycin administration has resulted in neuropathy associated with a slowing of nerve conduction velocity. The peripheral or cranial nerves can be affected. Patients may experience paresthesia or Bell’s palsy. This rare toxicity has also been observed in animal studies.

**PHARMACOKINETICS**
Daptomycin is given intravenously, and a 4-mg/kg dose achieves peak serum levels of 58 μg/mL (Table 1.14). Daptomycin is 92% protein-bound and is excreted by the kidneys. Its ability penetrate various tissue compartments including the cerebrospinal fluid has not been extensively studied.

**SPECTRUM OF ACTIVITY AND TREATMENT RECOMMENDATIONS**
Daptomycin kills aerobic and facultative gram-positive organisms, including *Enterococcus faecium* and *faecalis* (including VREs), *S. aureus* (including MRSA), *S. epidermidis* (including methicillin-resistant strains),...
S. pyogenes, and Corynebacterium jeikeium (Figure 1.5). It is approved for the treatment of complicated skin and soft-tissue infections by susceptible strains and for S. aureus (including MRSA) bacteremia and right-sided endocarditis. It is not currently approved for VRE, because of insufficient clinical data. Daptomycin is inactivated by surfactant and should not be used for the treatment of pneumonia.

**Metronidazole**

**CHEMICAL STRUCTURE AND MECHANISM OF ACTION**

Metronidazole is a nitroimidazole with a low molecular weight that allows it to readily diffuse into tissues. Within a bacterium, this antibiotic acts as an electron acceptor and is quickly reduced. The resulting free radicals are toxic to the bacterium, producing damage to DNA and to other macromolecules. Metronidazole has significant activity against anaerobes.

**TOXICITY**

Metronidazole is usually well tolerated, but it can result in a disulfiram (Antabuse-like) reaction with alcohol consumption (Table 1.10). Concern about the mutagenic potential of this agent has resulted in multiple mammalian studies that, overall, have failed to demonstrate significant DNA abnormalities. Metronidazole is not recommended in pregnancy, and it should usually be avoided in patients on Coumadin, because it impairs metabolism of that drug.

**PHARMACOKINETICS**

This agent is rapidly and completely absorbed orally, but it can also be given intravenously. Therapeutic levels are achieved in all body fluids, including the cerebrospinal fluid and brain abscess contents. Metronidazole is metabolized primarily in the liver.

**SPECTRUM OF ACTIVITY AND TREATMENT RECOMMENDATIONS**

Metronidazole was originally used primarily for Trichomonas vaginitis, being effective both topically and orally. It is also effective for treating amoebic abscesses and giardiasis. Metronidazole is cidal for most anaerobic bacteria, and it is the antibiotic of choice for covering anaerobes. Because metronidazole has no significant activity against aerobes, it is usually administered in combination with a cephalosporin for aerobic coverage. Metronidazole is the drug of choice for treatment of pseudomembranous colitis attributable to overgrowth of C. difficile. Metronidazole is also recommended as part of the regime for Helicobacter pylori gastric and duodenal infection.

**Sulfonamides and Trimethoprim**

**CHEMICAL STRUCTURE AND MECHANISMS OF ACTION**

The sulfonamides all have a structure similar to para-aminobenzoic acid (PABA), a substrate required for bacterial folic acid synthesis (Figure 1.9). All sulfonamides inhibit bacterial folic acid synthesis by competitively inhibiting PABA incorporation into tetrahydropteroyl acid. These agents are bacteriostatic.

A sulfonyl radical is attached to carbon 1 of the 6-member ring, increasing PABA inhibition. Alterations in the sulfonyl radical determine many of the pharmacokinetic properties of the compounds. Trimethoprim consists of two 6-member rings, one of which has two nitrogens and two amino groups, the other having three methoxybenzyl groups. This agent strongly inhibits dihydrofolate reductase and complements sulfonamide inhibition of folate metabolism (Figure 1.9). Inhibition of bacterial dihydrofolate reductase by trimethoprim is 100,000 times that of the agent’s inhibition of the mammalian enzyme, minimizing toxicity to the patient.

---

**Sulfonamides**

\[\text{PAGA} \rightarrow \text{Dihydrofolate} \rightarrow \text{Tetrahydrofolate}\]

**Trimethoprim**

\[\text{Sulfonamides} \rightarrow \text{Trimethoprim} \rightarrow \text{Purines}\]

**Figure 1-9.** Effects of sulfonamides and trimethoprim on the bacterial folate pathway.
**TOXICITY**

Hypersensitivity reactions represent the most severe toxicity (Table 1.10). Maculopapular drug rashes, erythema multiforme, Steven–Johnson syndrome, vasculitis (including drug-induced lupus), serum sickness-like syndrome, and anaphylaxis have been reported. Hemolytic anemia can be associated with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Sulfonamides should be avoided in the last month of pregnancy because they displace bilirubin bound to plasma albumin and increase fetal blood levels of unconjugated bilirubin.

**PHARMACOKINETICS**

Sulfonamides are classified as short-, medium-, or long-acting, depending on half-life. Sulfisoxazole is in the short-acting class, having a half-life of 5 to 6 hours. Sulfamethoxazole and sulfadiazine are medium-acting. All of these agents are generally well absorbed orally. Intravenous preparations are available for some agents. All are metabolized by the liver, undergoing acetylation and glucuronidation, with the metabolites being excreted in the urine. Trimethoprim is excreted primarily by the renal tubules, and very high concentrations of active drug are found in the urine. Some trimethoprim is also excreted in bile. The half-life of trimethoprim is 9 to 11 hours matching the half-life of sulfamethoxazole. The ratio of trimethoprim to sulfamethoxazole supplied is 1:5.

**SPECTRUM OF ACTIVITY AND TREATMENT RECOMMENDATIONS**

The sulfonamides demonstrate activity against gram-positive and gram-negative organisms; however, resistance in both community and nosocomial strains is widespread (Table 1., Figure 1.5). Sulfonamides have proved to be effective for the empiric treatment of uncomplicated urinary tract infections; however, because of widespread resistance, they are seldom used as empiric therapy in other infections. Sulfonamides are the treatment of choice for Nocardia asteroides, and are useful in combination with other agents for the treatment of M. kansasii.

Trimethoprim is generally administered in combination with sulfamethoxazole. This combination often

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**Table 1.16. Organisms That May Be Susceptible to Trimethoprim/Sulfamethoxazole**

<table>
<thead>
<tr>
<th>Usually susceptible</th>
<th>Some susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pyogenes</td>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>(including community-acquired methicillin-resistant strains)</td>
</tr>
<tr>
<td>Bacillus anthracis</td>
<td>Strepococcus pneumoniae</td>
</tr>
<tr>
<td>Shigella spp.</td>
<td>Proteus mirabilis</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>Klebsiella spp.</td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>Salmonella</td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td>Neisseria gonorrhoeae</td>
</tr>
<tr>
<td>Burkholderia cepacia</td>
<td></td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td></td>
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<tr>
<td>Yersinia enterocolitica</td>
<td></td>
</tr>
<tr>
<td>Nocardia spp.</td>
<td></td>
</tr>
</tbody>
</table>

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**KEY POINTS**

**About Sulfonamides**

1. Competitively inhibit para-aminobenzoic acid incorporation, blocking folic acid synthesis; trimethoprim inhibits dihydrofolate reductase, potentiating sulfonamide activity.
2. Hypersensitivity reactions (including Steven–Johnson syndrome) are common; hemolytic anemia seen in G6PD-deficient patients. Agranulocytosis and thrombocytopenia are less common.
3. Broad spectrum of activity for gram-positive and gram-negative organisms, but resistance is common.
5. Trimethoprim–sulfamethoxazole combination is the drug of choice for Pneumocystis prophylaxis and treatment.
results in significantly improved activity. Trimethoprim-sulfamethoxazole (TMP-SMX) demonstrates excellent activity against *Listeria monocytogenes*, and it is the antibiotic of choice in the penicillin-allergic patient with listeriosis. It can be used to treat a number of other gram-positive and gram-negative pathogens. However, plasmid-mediated resistance is common, and treatment for most pathogens should be initiated only after sensitivity is confirmed by microbiologic testing. This combination is highly effective for killing *Pneumocystis carinii*, and TMP-SMX is the drug of choice for treatment or prophylaxis of that infection in immunocompromised hosts, including patients with AIDS.

**ANTIFUNGAL AGENTS**

Fungi are eukaryotes, and they share many of the structural and metabolic characteristics of human cells. As a result, designing agents that affect fungi without harming human cells has proved difficult. One major difference between the two cell types is the primary sterol building block used to form the plasma membrane. The fungal plasma membrane consists of ergosterols; the major sterol component of the human plasma membrane is cholesterol. This difference has been exploited in the development of two classes of drugs. The polyenes act by binding to ergosterol and disrupting the fungal membrane. These agents are fungicidal. The azoles inhibit ergosterol synthesis, and lowered ergosterol levels results in fungal membrane breakdown. These agents are usually fungistatic.

### Key Points

1. Polyene compound forms rod-like structures that bind to ergosterol in the fungal membrane, forming pores that result in a leak of intracellular potassium.
2. Rapidly cidal; does not require active growth.

---

**Agents for Treatment of Systemic Fungal Infections**

**Amphotericin B**

*Chemical Structure, Mechanism of Action, and Spectrum of Activity*—Amphotericin B is a long, cyclic polyene compound that forms a large rod-like structure. Multiple molecules bind to ergosterol in the fungal membrane, forming pores that result in leakage of intracellular potassium and in fungal cell death. This fungicidal action is rapid and does not require active growth.

*Toxicity—Nephrotoxicity* is the major complication associated with the conventional deoxycholate form of amphotericin B. This agent causes vasoconstriction of renal arterioles, resulting in a reduction in glomerular filtration rate. Vasoconstriction also impairs proximal and distal tubular reabsorption, causing potassium, magnesium, and bicarbonate wasting. These effects are reversible. However, permanent loss of nephrons and permanent damage to tubular basement membranes are also observed and correlate with the total dose administered. Renal dysfunction is observed in virtually all patients receiving this drug, and serum creatinine levels of 2 to 3 mg/dL are to be expected. Hydration with normal saline before infusion reduces nephrotoxicity.

Fever is commonly associated with administration of amphotericin B, and fever can be associated with chills and tachypnea, particularly if the drug is infused too rapidly. This agent should be infused slowly [2 to 3 hours for the deoxycholate form (ABD) and under 2 hours for the lipid preparations]. Fever and chills usually diminish with each subsequent dose. However, if those reactions persist, the patient can be premedicated with acetaminophen or 25 to 50 mg hydrocortisone can be added to the solution. This febrile reaction does not represent an allergic reaction and should not be misinterpreted as anaphylaxis. A 1 mg test dose preceding administration of the full dose has not proved to be helpful, and use of a test dose delays achievement of therapeutic antifungal serum and tissue levels. Because of a high incidence of phlebitis, amphotericin B should be administered through a centrally placed intravenous line.

*Pharmacokinetics*—At physiologic pH, ABD is insoluble in water (Table 1.17). It is stored as a powder that is dispersed as colloidal suspension in a 5% dextrose solution. Following intravenous infusion, amphotericin B is bound to lipoproteins in the serum and then leaves the circulation. The drug is stored in the

---

**THE MAJOR DIFFERENCE BETWEEN MAMMALIAN AND FUNGAL CELLS**

*Like mammals, fungi are eukaryotes. Drug therapy takes advantage of fact that fungi use ergosterols rather than cholesterol as the major building block of their plasma membrane.*
### Table 1.17. Toxicities of Systemic Antifungal Agents

<table>
<thead>
<tr>
<th>Clinical symptom</th>
<th>Amphotericin B</th>
<th>Amphotericin B lipid</th>
<th>Fluconazole</th>
<th>Itraconazole</th>
<th>Ketoconazole</th>
<th>Voriconazole</th>
<th>Posaconazole</th>
<th>Caspofungin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic skin rash</td>
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<tr>
<td>Anaphylaxis</td>
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<td>Stevens–Johnson</td>
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<td>Pruritus</td>
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<td>Hypotension</td>
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<tr>
<td>Fever and chills</td>
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<td>Nausea and vomiting</td>
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<td>Diarrhea</td>
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<td>Headache</td>
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<td>Seizures</td>
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<td>Visual disturbances</td>
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<tr>
<td>Other neurotoxicity</td>
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<tr>
<td>Phlebitis</td>
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<tr>
<td>Alopecia (reversible)</td>
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<td>Adrenal insufficiency</td>
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<tr>
<td>Gynecomastia</td>
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<td>Impotence</td>
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<td>Laboratory tests:</td>
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<td>Renal tubular acidosis</td>
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<td>Hypokalemia</td>
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<td>ALP↑</td>
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</table>

Black = principle side effect; dark gray = less common side effect; light gray = rare side effect; white = not reported or very rare; ↑ = rise; AST/ALT = aspartate aminotransferase/alanine transaminase; ALP = alkaline phosphatase.
liver and other organs and subsequently released into the circulation.

Lipid-associated amphotericin B is ingested by macrophages, resulting in high intracellular levels in that cell type. This drug shows poor penetration of the blood–brain barrier and brain. Therapeutic levels are detectable in inflamed pleural fluid, peritoneum, and joint fluid. Amphotericin B is degraded slowly, and degradation is not affected by hepatic or renal dysfunction. Serum concentrations of the drug are detectable 7 weeks after therapy is discontinued.

Spectrum of Activity—Amphotericin B is effective against most fungal infections and remains the most effective agent for systemic fungal infections. Clinical resistance to amphotericin B has been demonstrated among Candida lusitaniae, Fusarium species, and Pseudallescheria boydii. C. lusitaniae initially is susceptible to amphotericin B, but develops resistance during treatment. The alterations in sterol structure required for amphotericin B resistance often reduce tissue invasiveness, such strains being capable of growing only on mucosal surfaces or in the urine.

Efficacy of Various Amphotericin B Preparations—Lipid-associated preparations of amphotericin B are preferred because of their lower nephrotoxicity. However, these preparations are very expensive (Table 1.18) and

<table>
<thead>
<tr>
<th>Antifungal (trade name)</th>
<th>Half-life (h)</th>
<th>Dose</th>
<th>Dose for reduced creatinine clearance (mL/min)</th>
<th>Cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B deoxycholate (Fungizone)</td>
<td>15 d</td>
<td>0.3–1.0 mg/kg IV q24h (infuse over 4–6 h)</td>
<td>No change required</td>
<td>$</td>
</tr>
<tr>
<td>Amphotericin B lipid preparations (Abelcet, Amphotec, AmBisome)</td>
<td>7 d</td>
<td>3–5 mg/kg IV q24h</td>
<td>No change required</td>
<td>$$$$$</td>
</tr>
<tr>
<td>Fluconazole (Diflucan)</td>
<td>20–50</td>
<td>100–200 mg PO q12–24h</td>
<td>10–50: Half the dose; &lt;10: One quarter to half the dose</td>
<td>$–$$–$$–$$–$$</td>
</tr>
<tr>
<td>Ketoconazole (Nizoral)</td>
<td>1–4</td>
<td>200–400 mg PO q12–24h</td>
<td>No change required</td>
<td>$–$$–$$–$$–$$</td>
</tr>
<tr>
<td>Itraconazole (Sporanox)</td>
<td>20–60</td>
<td>100–200 mg PO q12–24h</td>
<td>&lt;30: Contraindicated</td>
<td>$$$$$–$$$$$$</td>
</tr>
<tr>
<td>Posaconazole (Noxfail)</td>
<td>35</td>
<td>200 mg PO q6h, or 400 mg PO q12h</td>
<td>No change required</td>
<td>$$$$$</td>
</tr>
<tr>
<td>Voriconazole (Vfend)</td>
<td>Nonlinear kinetics</td>
<td>200 mg PO q12h</td>
<td>&lt;50: IV not recommended; switch to oral</td>
<td>$$$$$</td>
</tr>
<tr>
<td>Anidulafungin (Eraxis)</td>
<td>10–15</td>
<td>200 mg IV, then 100 mg q24h</td>
<td>No change required</td>
<td>$$$$$</td>
</tr>
<tr>
<td>Caspofungin (Cancidas)</td>
<td>9–11</td>
<td>70 mg IV, then 50 mg q24h</td>
<td>No change required</td>
<td>$$$$$</td>
</tr>
<tr>
<td>Micafungin (Mycamine)</td>
<td>14–17</td>
<td>150 mg IV q24h</td>
<td>No change required</td>
<td>$$$$$</td>
</tr>
<tr>
<td>Fluconosine (Ancobon)</td>
<td>3–6</td>
<td>25–33 mg/kg PO q6h</td>
<td>10–50: 25 mg/kg q12–24h; 25 mg/kg q24h (&lt;10)</td>
<td>$$$$$</td>
</tr>
</tbody>
</table>

*a Intravenous preparations (daily cost dollars): $ = 20–70; $$ = 71–110; $$$ = 111–150; $$$$ = 150–200; $$$$$ = ≥200; oral preparations (10-day course cost dollars): $ = 10–50; $$ = 51–100; $$$ = 101–140; $$$$ = 141–180; $$$$$ = ≥180.
in most clinical trials have comparable efficacy to amphotericin-B deoxycholate. Liposomal amphotericin B was shown to be superior to ABD for the treatment of pulmonary histoplasmosis. The lipid-associated preparations are recommended in patients with significant preexisting renal dysfunction or in patients who develop progressive renal failure (serum creatinine above 2.5 mg/dl) while being treated ABD. Clinicians also need to be aware of the observation that ABD-related renal dysfunction (50% increase in baseline creatinine to a minimum of 2 mg/ml) is associated with a 6.6-fold increased risk of death.

**AZOLES**

Chemical Structure and Mechanism of Action—The azoles are chemically synthesized agents that come in two classes. The first to be synthesized were the imidazoles (miconazole and ketoconazole). Those compounds are now seldom used for systemic infections, being primarily reserved for topical treatment of superficial fungal infections. The second class, the triazoles, are preferred for systemic fungal infection; they are well absorbed orally and have excellent toxicity profiles.

All azoles inhibit a cytochrome P450–dependent demethylation system that results in decreased production of ergosterol and accumulation of intermediate sterols. The loss of ergosterol results in altered fungal membrane permeability, disturbed activity of membrane surface enzymes, and retention of metabolites. These agents have broad antifungal activity, but they demonstrate fungistatic rather than fungicidal activity. Itraconazole can antagonize amphotericin B activity by reducing its binding target, ergosterol.

Toxicity—Ketoconazole not only interferes with fungal sterol metabolism, but at higher doses it also interferes with testosterone and cortisone production (Table 1.17). Gynecomastia and loss of libido are commonly observed. Severe hepatitis can develop during treatment with this agent. As a result of its many toxicities, ketoconazole is rarely prescribed today.

The triazoles (fluconazole, itraconazole, posaconazole, voriconazole) demonstrate minimal toxicity. Side effects include headache, gastrointestinal intolerance, and asymptomatic increases in serum transaminase levels. Voriconazole infusion can be associated with transient loss of light perception. This symptom resolves with subsequent doses. Visual hallucinations less commonly occur.

**KEY POINTS**

About the Toxicity of Amphotericin B

1. Nephrotoxicity is observed with virtually all patients receiving amphotericin B deoxycholate (ABD); reduced by hydration using normal saline. Reversible in most cases. Permanent damage with prolonged therapy.
2. Fever is common with all preparations. Slow infusion (2 to 3 hours with ABD, less than 2 hours with liposomal preparations) reduces severity. Premedication with corticosteroids or acetaminophen, or both, often reduce fever.
3. Phlebitis is common, requiring administration by central intravenous line.

About Amphotericin Spectrum of Activity and Preparations

1. Preferred antifungal agent for severe systemic fungal infections.
2. Effective against most fungi except Candida lusitaniae, Fusarium, and Pseudallescheria boydii.
3. Lipid-associated preparations reduce nephrotoxicity, but similar incidence of fever, with efficacy comparable to conventional amphotericin B deoxycholate (ABD).
4. Higher doses of lipid-associated preparations required: 3 to 5 mg/kg daily as compared with 0.3 to 1.4 mg/kg for ABD.
5. Very high cost. Recommended for patients with significant pre-existing renal dysfunction or those who develop progressive renal dysfunction on ABD (serum creatinine >2.5 mg/dL).

About the Mechanism of Action of the Azoles

1. Inhibit cytochrome P450–dependent demethylation, resulting in decreased ergosterol production and altered fungal membrane permeability.
2. Azoles are usually fungistatic.
3. Itraconazole can antagonize amphotericin B activity by reducing its binding target.
1. No activity against *Aspergillus*. Active against *Candida albicans*, but natural resistance in *C. glabrata* and *C. krusei* is common. Active against Cryptococcus neoformans.

2. With prolonged treatment, drug resistance can develop in *Candida* species.

3. Treatment of choice for oral candidiasis and *Candida* vulvovaginitis.

4. Can be used for uncomplicated *C. albicans* fungemia in the non-immunocompromised patient.

5. Can be used to complete therapy of cryptococcal meningitis in HIV patients after an initial course of amphotericin B.

6. Prophylaxis reduces *Candida* infections in neutropenic patients. The role of prophylaxis in other settings remains controversial because of the risk of selecting for resistant strains.

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**Pharmacokinetics**—Fluconazole is well absorbed orally, and serum levels after ingestion of the oral preparation are comparable to those with intravenous administration. Penetration into tissues and body fluids, including the cerebrospinal fluid, is excellent. Itraconazole is more variable in its oral absorption and requires stomach acidity for adequate absorption. Capsule absorption is enhanced by food and reduced by agents that reduce stomach acidity. Itraconazole penetrates most tissues, but does not cross the blood–brain barrier and enters ocular fluids only minimally. Posaconazole oral absorption is enhanced by food, particularly high-fat meals or liquid nutritional supplements. Voriconazole is well absorbed orally, demonstrating 96% bioavailability, and also can be given intravenously.

All of the azoles are metabolized by the liver via the cytochrome P450 system, and as a consequence, drug–drug interactions are common with these agents. Rifampin, rifabutin, long-acting barbiturates, carbamazepine, and cisapride usually lower azole levels. The azoles slow the metabolism of Coumadin, warfarin, phenytoin, tacrolimus, cyclosporine, certain antihistamines, benzodiazepines, calcium channel blockers, sulfonlureas, prednisolone, digoxin, statins, and anti-HIV protease inhibitors. The doses of these agents usually need to be lowered in the presence of azoles. Drug–drug interactions have proven to be the most problematic with voriconazole. Voriconazole is metabolized primarily by the P450 enzyme CYP2C19, and that enzyme has variable activity depending on the patient’s genetic background. As a consequence, serum levels can vary by up to a factor of 4 in individuals with rapid as opposed to slow metabolism. In the United States, the co-administration of rifabutin and voriconazole is contraindicated because rifabutin levels may increase by a factor of 3, while voriconazole levels drop below therapeutic levels. Rifampin, carbamazepines, and long-acting barbiturates can also markedly reduce voriconazole levels, and these drugs should probably be discontinued when voriconazole is being administered.

**Spectrum of Activity and Treatment Recommendations**—Fluconazole—Fluconazole has no activity against *Aspergillus* species, and some strains of *Candida*, including *C. glabrata* and *C. krusei*, demonstrate natural resistance. Because of increased production of demethylase and increased drug efflux, any *Candida* species can develop resistance.

Fluconazole is recommended for the treatment of oropharyngeal and vulvovaginal candidiasis. Intravenous fluconazole has proved therapeutically equivalent to amphotericin B in uncomplicated candidemia in the non-immunocompromised host. However, for the immunocompromised (including neutropenia) host, and for seriously ill patients with deep tissue *Candida* infection, amphotericin B or caspofungin should be used. Fluconazole is also effective for
completed the treatment of cryptococcal meningitis in patients with AIDS. After initial therapy with amphotericin B, with or without flucytosine, for 2 weeks, fluconazole (400 mg daily) treatment for 2 months, followed by daily fluconazole maintenance therapy (200 mg daily), is recommended. The role of fluconazole in patients with non-AIDS-related cryptococcal infection has not been defined.

The use of fluconazole for prevention of fungal infections has been explored in neutropenic allogeneic bone marrow transplant patients and was found to reduce mortality and the incidence of invasive Candida infections, but no effect on the incidence of Aspergillus infections was observed. Fluconazole prophylaxis of leukemia patients also reduced the incidence of invasive Candida infections, but had no effect on mortality. Fluconazole is frequently used in the surgical intensive care unit in the hopes of preventing candidemia in patients. To date, such prophylaxis has not been proved to significantly reduce Candida infections, and this practice increases the prevalence of fluconazole-resistant fungi, including C. krusei and C. glabrata. Because of the risk of selecting for resistant fungi, fluconazole prophylaxis is not recommended in patients infected with HIV.

Itraconazole—As compared with fluconazole, itraconazole has demonstrated improved activity against histoplasmosis, coccidiomycosis, blastomycosis, and sporotrichosis. Itraconazole can be used for acute and chronic vaginal candidiasis and HIV-associated oral and esophageal candidiasis, and for consolidation and maintenance therapy for cryptococcal meningitis in patients with AIDS. Itraconazole is the preferred agent for the treatment of lymphocutaneous sporotrichosis and of non-meningeal, non-life-threatening histoplasmosis, blastomycosis, and coccidiomycosis. For disseminated histoplasmosis and coccidiomycosis, amphotericin B remains the treatment of choice. Itraconazole is recommended as primary prophylaxis and for the prevention of relapse of histoplasmosis in patients with AIDS.

Voriconazole and Posaconazole—As compared with amphotericin B deoxycholate, voriconazole demonstrates increased activity against Aspergillus and has proven to be superior for the treatment of invasive aspergillosis. Voriconazole is also approved for the treatment of Fusarium and Scedosporium. Clinical trials exploring the efficacy of voriconazole for invasive candidiasis are currently under way.

The newestazole, posaconazole, has the broadest spectrum in the class. In addition to being effective against Aspergillus, this agent has activity against many of the Zygomycetes. Posaconazole is currently approved as salvage therapy for mucormycosis.

**CASPOFUNGIN/ANIDULAFUNGIN/MICAFUNGIN**

Chemical Structure and Mechanism of Action—The echinocandins are all derived from echinocandin B, a
semisynthetic lipopeptide that blocks synthesis of β-(1,3)-D-glucan. That polysaccharide is a critical component of the cell wall in many pathogenic fungi.

Toxicity—The echinocandins have proven to be very safe, provoking only the occasional fever, rash, or flushing of the face during infusion (Table 1.17). Serum levels are increased by co-administration of cyclosporin. Agents that may reduce serum levels including efavirenz, nelfinavir, Dilantin, Tegretol, rifampin, and dexamethasone. The echinocandins can reduce serum levels of tacrolimus.

Pharmacokinetics—The echinocandins are not absorbed by the gastrointestinal tract and must be administered intravenously (Table 1.18). They are metabolized by the liver.

Spectrum of Activity and Treatment Indications—The echinocandins are active against *Aspergillus* and *Candida*, including isolates that are resistant to other antifungal agents. They are less effective against *C. parapsilosis* in vitro, and are not active against *Cryptococcus*. They are approved for the treatment of invasive aspergillosis in patients who fail on, or are unable to tolerate, amphotericin B or itraconazole.

Caspofungin can also be used to treat oral candidiasis that is refractory to azole or amphotericin B therapy.

**FLUCYTOSINE**

Chemical Structure and Mechanism of Action—Flucytosine, or 5-fluorocytosine (5-FC), is a fluorine analog of cytosine. After a multi-step conversion requiring deamination and phosphorylation, the resulting product, 5-fluorouracil (5-FU) acts as an inhibitor of thymidylate synthetase, impairing DNA and RNA synthesis. In humans, 5-FC is not toxic because of a lack of the deaminase required for conversion to 5-FU.

Toxicity—The major toxicity of flucytosine is bone marrow suppression leading to neutropenia, anemia, and thrombocytopenia (Table 1.17). This side effect is dose-related and usually occurs when serum levels exceed 125 μg/mL. Patients with diminished bone marrow reserve such as those with AIDS and those receiving cancer chemotherapy are more likely to suffer this complication. Commonly, 5-FC is administered in combination with amphotericin B. As discussed earlier in this chapter, amphotericin B impairs renal function, and reductions in renal function reduce the clearance of 5-FC. In patients

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**Table 1.19. Spectrum of the Systemic Antifungals**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Aspergillus</th>
<th>Blastomyces</th>
<th>Candida albicans</th>
<th>Candida krusei</th>
<th>Candida guillermondii</th>
<th>Candida lusitaniae</th>
<th>Coccidiomyces</th>
<th>Cryptococcus</th>
<th>Histoplasma</th>
<th>Zygomycetes</th>
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</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
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<td>Deoxycholate</td>
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<tr>
<td>Lipid preparation</td>
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<td>Flucytosine</td>
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<td>Fluconazole</td>
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<td>Itraconazole</td>
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<td>Ketoconazole</td>
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<td>Posaconazole</td>
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<td>Voriconazole</td>
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<td>Caspofungin</td>
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<tr>
<td>Micafungin</td>
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<tr>
<td>Anidulafungin</td>
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Dark gray = usually susceptible; white = not recommended.
with renal dysfunction, monitoring of peak (2 hours after oral administration) and trough levels (just before the next dose) is recommended. Doses should be adjusted, and serum levels should be monitored.

4. Never use as monotherapy. In cryptococcal meningitis, the combination of amphotericin B and flucytosine sterilize the cerebrospinal fluid faster than does amphotericin B alone. In animal studies, combination therapy is beneficial for Candida infections, but efficacy has not been proven in humans.

Antiviral therapy can be used to control viral infections in a variety of ways. First, antiviral agents can be designed to block viral nucleic acid synthesis. These agents tend to act at a single step in viral replication, resistance may develop during treatment. The development of resistance is favored by a high viral load, a high intrinsic viral mutation rate (more common in RNA than DNA viruses), and a high degree of selective pressure—that is, prolonged antiviral therapy or repeated courses of treatment. A second method for controlling viral infection is to modify the host immune response. Infusions of antibody preparations and treatment with interferon have proved efficacious in several viral infections.

**Antiviral Drugs (Other Than Antiretroviral Agents)**

Most antiviral agents target viral nucleic acid synthesis. Because these agents tend to act at a single step in viral replication, resistance may develop during treatment. The development of resistance is favored by a high viral load, a high intrinsic viral mutation rate (more common in RNA than DNA viruses), and a high degree of selective pressure—that is, prolonged antiviral therapy or repeated courses of treatment. A second method for controlling viral infection is to modify the host immune response. Infusions of antibody preparations and treatment with interferon have proved efficacious in several viral infections.

### Antiviral drugs that block DNA transcription

**Acyclovir, Valacyclovir, Famciclovir**

**Chemical Structure and Mechanisms of Action**—Acyclovir and valacyclovir are synthetic analogs of guanine in which a side chain has been substituted for a sugar moiety. Famciclovir is a acyclic guanosine analog derived from penciclovir, and this prodrug is quickly converted to penciclovir following oral absorption. These antiviral agents are phosphorylated in virus-infected cells by viral thymidine kinase, forming a monophosphate compound. Host cell kinases then add two additional phosphates, allowing the triphosphate to add to replicating DNA. The acyclic side chain of acyclovir prevents the addition of subsequent nucleic acids to DNA causing premature termination.

Penciclovir is not a DNA chain terminator; it acts primarily as a viral DNA polymerase inhibitor. Acyclovir also selectively inhibits viral DNA polymerase. Because these agents require viral thymidine kinase for their initial phosphorylation step, the concentrations of the triphosphate compounds are 40 to 100 times higher in infected than uninfected cells. Acyclovir and penciclovir resistance are most commonly caused by a reduction in viral thymidine kinase. The loss or reduction in viral thymidine kinase activity impairs acyclovir

### Table: Key Points

**About Flucytosine**

1. Impairs fungal DNA and RNA synthesis; fungistatic.
2. Cleared by the kidneys; penetrates all tissues and fluids, including the cerebrospinal fluid.
3. High levels cause bone marrow suppression. In patients with renal failure, doses should be adjusted, and serum levels should be monitored.
4. Never use as monotherapy. In cryptococcal meningitis, the combination of amphotericin B and flucytosine sterilize the cerebrospinal fluid faster than does amphotericin B alone. In animal studies, combination therapy is beneficial for Candida infections, but efficacy has not been proven in humans.

**About Antiviral Therapy**

1. Usually target viral nucleic acid synthesis.
2. Development of resistance is common and is favored by
   a) high viral load,
   b) high intrinsic viral mutation rate (RNA viruses more than DNA viruses), and
   c) prolonged or intermittent antiviral therapy.
phosphorylation and also renders the virus resistant to ganciclovir, because that agent also requires activation by viral thymidine kinase.

Toxicity—Toxicity related to these drugs is generally minimal (Table 1.20). Rarely patients develop rash, hematuria, headache and nausea. Neurotoxicity may occur in 1–4% receiving intravenous acyclovir and can result in lethargy, obtundation, coma, hallucinations, seizures, and autonomic instability. Most patients who suffer these complications have renal dysfunction resulting in high acyclovir serum levels. Co-administration of zidovudine and acyclovir increases the risk of developing

<table>
<thead>
<tr>
<th>Clinical symptom</th>
<th>Antiviral agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic skin rash</td>
<td>Acyclovir/valacyclovir, penciclovir/famciclovir, ganciclovir/valganciclovir, cidofovir, foscarnet, ribavirin, interferon-α, oseltamivir, zanamivir, rimantadine</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Acyclovir/valacyclovir</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Acyclovir/valacyclovir, penciclovir/famciclovir</td>
</tr>
<tr>
<td>Fever and chills</td>
<td>Penciclovir/famciclovir, ganciclovir/valganciclovir</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>Acyclovir/valacyclovir, penciclovir/famciclovir, ganciclovir/valganciclovir, cidofovir, foscarnet, ribavirin, interferon-α, oseltamivir, zanamivir, rimantadine</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Acyclovir/valacyclovir, penciclovir/famciclovir, ganciclovir/valganciclovir, cidofovir, foscarnet, ribavirin, interferon-α, oseltamivir, zanamivir, rimantadine</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Acyclovir/valacyclovir, penciclovir/famciclovir</td>
</tr>
<tr>
<td>Headache</td>
<td>Acyclovir/valacyclovi, penciclovir/famciclovir, ganciclovir/valganciclovir, cidofovir, foscarnet, ribavirin, interferon-α, oseltamivir, zanamivir, rimantadine</td>
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<tr>
<td>Dizziness</td>
<td>Acyclovir/valacyclovi, penciclovir/famciclovir, ganciclovir/valganciclovir, cidofovir, foscarnet, ribavirin, interferon-α, oseltamivir, zanamivir, rimantadine</td>
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<tr>
<td>Seizures</td>
<td>Acyclovir/valacyclovi, penciclovir/famciclovir, ganciclovir/valganciclovir, cidofovir, foscarnet, ribavirin, interferon-α, oseltamivir, zanamivir, rimantadine</td>
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<tr>
<td>Other neurotoxicity</td>
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<tr>
<td>Uveitis or retinitis</td>
<td>Acyclovir/valacyclovi, penciclovir/famciclovir, ganciclovir/valganciclovir, cidofovir, foscarnet, ribavirin, interferon-α, oseltamivir, zanamivir, rimantadine</td>
</tr>
<tr>
<td>Respiratory problems</td>
<td>Acyclovir/valacyclovi, penciclovir/famciclovir, ganciclovir/valganciclovir, cidofovir, foscarnet, ribavirin, interferon-α, oseltamivir, zanamivir, rimantadine</td>
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<tr>
<td>Phlebitis</td>
<td>Acyclovir/valacyclovi, penciclovir/famciclovir, ganciclovir/valganciclovir, cidofovir, foscarnet, ribavirin, interferon-α, oseltamivir, zanamivir, rimantadine</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Acyclovir/valacyclovi, penciclovir/famciclovir, ganciclovir/valganciclovir, cidofovir, foscarnet, ribavirin, interferon-α, oseltamivir, zanamivir, rimantadine</td>
</tr>
</tbody>
</table>

Laboratory tests:

- Abnormal electrolytes
- Creatinine↑
- Anemia
- Other cytopenias
- AST/ALT↑
- Lactic acidosis
- Arrhythmias

Drug–drug interactions

Black = principle side effect; dark gray = less common side effect; light gray = rare side effect; white = not reported or very rare; ↑ = rise; AST/ALT = aspartate aminotransferase/alanine transaminase.
### Table 1.21. Systemic Antiviral Agents: Half-Life, Dosing, Renal Dosing, and Cost

<table>
<thead>
<tr>
<th>Antibiotic (trade name)</th>
<th>Half-life (h)</th>
<th>Dose</th>
<th>Dose for reduced creatinine clearance (mL/min)</th>
<th>Cost*</th>
</tr>
</thead>
</table>
| **Acyclovir (Zovirax)** | 2–2.5        | 200–800 mg PO × 3–5 daily, 5–10 mg/kg IV q8h | 10–50: 800 mg PO q8h, 5–12 mg/kg IV q12–24h | $–$$$
|                         |              | 10–50: 800 mg PO q12h, 2.5–6 mg/kg IV q24h |                                 |       |
| **Valacyclovir (Valtrex)** | 2.5–3.3     | 500 mg PO q12h to 1000 mg PO q8h | 10–50: 1 g q12–24h | $$–$$$$$–$$$$$
|                         |              | 5–12 mg/kg IV q12–24h |                                 |       |
| **Famciclovir (Famvir)** | 2.3          | 125 mg PO q12h to 500 mg PO q8h | 10–50: 2.5 mg/kg q24h | $$–$$$$$–$$$$$
|                         |              | 5–12 mg/kg IV q12–24h |                                 |       |
| **Ganciclovir (Cytovene)** | 2.5–3.6     | 5 mg/kg IV q12h induction, 5 mg/kg q24h maintenance | 50–80: Half the dose, same intervals 10–50: 2.5 mg/kg q24h, or 1.2 mg/kg q24h maintenance | $–$$$
|                         |              | <10: 1.2 mg/kg × 3 weekly, or 0.6 mg/kg × 3 weekly maintenance |                                 |       |
| **Valganciclovir (Valcyte)** | 4           | 900 mg PO q12h × 3 weeks, then 900 mg q24h | 10–50: Half the dose <10: 450 mg q48h × 3 weeks, then twice weekly | $$–$$$$$
|                         |              | 5–12 mg/kg IV q24h |                                 |       |
| **Cidofovir (Vistide)** | 17–65        | 5 mg/kg IV twice weekly | 50–80: Usual dose <50: Contraindicated | $–$$$
|                         |              | 900 mg q24h |                                 |       |
| **Foscarnet (Foscavir)** | 3            | 40–60 mg/kg IV q8h induction, 90–120 mg/kg q24h maintenance | 50–80: 40–50 mg/kg q8h induction, 60–70 mg/kg q24h maintenance 10–50: 20–30 mg/kg q8h induction, 50–70 mg/kg q24h maintenance <10: Contraindicated | $$–$$$$$
|                         |              | 60–70 mg/kg q24h maintenance |                                 |       |
| **Ribavirin (Copegus, Rebetol)** | 0.5–2      | <75 kg: 400 mg AM, and 600 mg PO PM >75 kg: 600 mg PO q12h | <50: Not recommended | $$–$$$$$
|                         |              | <50: Not recommended |                                 |       |
| **Interferon α-2B (PEG-Intron, Pegasys)** | 0.5–2       | PEG-Intron: 1.5 μg/kg SC weekly Pegasys: 180 mg SC weekly | No changes required | $$–$$$$$
|                         |              | No changes required |                                 |       |
| **Oseltamivir (Tamiflu)** | 6–10        | Treatment: 75 mg PO q12h Prophylaxis: 75 mg PO q24h | 10–50: 75 mg q24h <10: Not recommended | $$–$$$$$
|                         |              | 10–50: 75 mg q24h |                                 |       |
| **Zanamivir (Relenza)** | 3            | 5 mg inhalation, 2 inhalations q12h × 5 days | 50–80: Usual dose <50: No data | $–$$$
|                         |              | 50–80: Usual dose <50: No data |                                 |       |

(Continued)
**Table 1.21.** (Continued)

<table>
<thead>
<tr>
<th>Antibiotic (trade name)</th>
<th>Half-life (h)</th>
<th>Dose</th>
<th>Dose for reduced creatinine clearance (mL/min)</th>
<th>Cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine (Symmetrel, Symadine)</td>
<td>15–20</td>
<td>&lt;65 years: 100 mg q12h &gt;65 years: 100 mg PO q24h</td>
<td>50–80: 100–150 q24h 10–50: 100 mg × 2–3 weekly</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;10: 100–200 mg weekly</td>
<td></td>
</tr>
<tr>
<td>Rimantadine (Flumadine, Rimantid)</td>
<td>24–30</td>
<td>&lt;65 years: 100 mg PO q12h &gt;65 years: 100–200 mg PO q24h</td>
<td>&lt;10: 100 mg q24h</td>
<td>$</td>
</tr>
</tbody>
</table>


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**KEY POINTS**

**About Acyclovir, Valacyclovir, and Famiclovir**

1. All require viral thymidine kinase phosphorylation for activity.
2. Acyclovir binds to the replicating viral DNA, causing premature chain termination; acyclovir and famciclovir both inhibit viral DNA polymerase.
3. Resistance is most commonly mediated by a reduction in viral thymidine kinase.
4. Toxicity is minimal. Intravenous administration of acyclovir can cause lethargy, obtundation, hallucinations, and seizures.
5. Valacyclovir is rapidly converted to acyclovir; resulting acyclovir levels are higher than those achieved with oral preparations of acyclovir. Famiclovir is rapidly converted to penciclovir.
6. Excellent activity against herpes simplex 1 and 2. Oral preparations recommended for treatment and prophylaxis of genital herpes and ocular herpes. Intravenous acyclovir recommended for herpes simplex encephalitis.
7. Moderate activity against varicella (intravenous acyclovir recommended for the immunocompromised host), and varicella pneumonia or encephalitis in the normal host. High doses of oral valacyclovir and famciclovir can be used to treat less severe disease.
8. Famiclovir can also be used to treat hepatitis B virus.

lethargy. Intravenous administration can also cause crystalluria and crystalline nephropathy, particularly if the patient is dehydrated. Cyclosporin increases the risk of nephrotoxicity.

Pharmacokinetics—The oral absorption of acyclovir is limited, only 15% to 20% of the drug being bioavailable (Table 1.21). Absorption tends to be even poorer in transplant patients, necessitating higher oral dosing. The prodrug preparation valacyclovir is rapidly and completely converted to acyclovir by hepatic and intestinal valacyclovir hydrolase. Oral valacyclovir achieves acyclovir serum levels that are 3 to 5 times higher than those achieved by oral acyclovir. Similarly, famciclovir is well absorbed orally, and in the liver and intestine, its purine is quickly deacetylated and oxidized to form penciclovir.

Acyclovir and penciclovir are widely distributed in tissues and fluids. Therapeutic levels can be achieved in cerebrospinal fluid, saliva, vaginal secretions, and the aqueous humor. Both drugs are excreted unchanged primarily in the urine. Probenecid reduces renal clearance and increases the half life.

Antiviral Activity and Therapeutic Indications—Acyclovir and famciclovir have excellent activity against herpes simplex viruses 1 and 2. Topical administration of these drugs is of minimal efficacy against herpes simplex labialis, and topical preparations are rarely used. Oral acyclovir and famciclovir are recommended for treatment of genital herpes and are used to prevent recurrent herpes genitalis. Acyclovir is also recommended for the treatment and prevention of recurrent ocular herpes simplex. Intravenous acyclovir has reduced the mortality from herpes simplex encephalitis and is the treatment of choice for that disorder. Acyclovir and famciclovir also have significant activity against varicella; however, higher drug
concentrations are required to kill that virus. Intravenous acyclovir is recommended for the treatment of varicella and herpes zoster in the immunocompromised host, and for treatment of varicella pneumonia or encephalitis in the previously healthy adult. Acyclovir demonstrates some activity against Epstein–Barr virus, but is generally not recommended for therapy. This agent also demonstrates modest protection against cytomegalovirus (CMV) when used for prophylaxis in allogeneic bone marrow, renal, and liver transplant recipients; however, ganciclovir has proved to be more efficacious. Famiciclovir can reduce levels of hepatitis B viral DNA and serum transaminase in patients with chronic hepatitis B. Its effects are additive when combined with interferon. Famiciclovir has also been used to treat recurrent hepatitis B following liver transplantation.

**Ganciclovir and Valganciclovir**

Chemical Structure and Mechanisms of Action—Like acyclovir, ganciclovir is a guanine analog. Ganciclovir has an additional hydroxymethyl group on the acyclic side chain. Viral thymidine kinase converts this analog to the monophosphate form, after which host cell kinase phosphorylation produces the active triphosphate form. Ganciclovir triphosphate competitively inhibits viral DNA polymerase incorporation of guanosine triphosphate into elongating DNA, but does not act as a chain terminator.

In infected cells, intracellular concentrations of ganciclovir triphosphate reach levels that are 10 times that of acyclovir triphosphate, and once in the cell, ganciclovir triphosphate persists, having an intracellular half life of 16 to 24 hours. The resulting higher intracellular concentrations may account for the greater activity of ganciclovir against CMV. Ganciclovir is also active against herpes simplex, varicella, and Epstein–Barr virus. Because ganciclovir requires viral thymidine kinase activity for conversion to the active triphosphate form, acyclovir-resistant viral strains with reduced thymidine kinase activity are also less sensitive to ganciclovir. Mutations that alter the structure of the viral DNA polymerase also confer ganciclovir resistance, and these mutants often demonstrate reduced sensitivity to foscarin and cidofovir.

Toxicity—Significant concentrations of ganciclovir triphosphate accumulate in uninfected cells (Table 1.20). Bone marrow progenitor cells are particularly sensitive to this agent. The triphosphate form can incorporate into cellular DNA and block host cell DNA replication. Neutropenia and thrombocytopenia are commonly observed in patients with AIDS who are receiving ganciclovir, and these patients require close monitoring for WBC and platelet counts during therapy. The risk is lower, but significant, in transplant patients. Co-administration of zidovudine increases the risk of bone marrow suppression. Discontinuation of treatment is recommended if the absolute neutrophil count drops below 500 cells/mm3. Central nervous system (CNS) side effects (including headache, confusion, psychosis, coma, and seizures) are also common.

Pharmacokinetics—Valganciclovir is a prodrug that is well absorbed orally and quickly converts to ganciclovir (Table 1.21). With oral administration, excellent serum levels that are nearly comparable to intravenous ganciclovir can be achieved. Ganciclovir readily penetrates all tissues and fluids including the brain and cerebrospinal fluid. The drug is primarily excreted unmodified in the urine.

**Spectrum of Activity and Treatment Indications**—Of the guanine analogs, ganciclovir has the highest activity against CMV. Ganciclovir is the treatment of choice for CMV infections including retinitis, pneumonia, and colitis. Ganciclovir is also used for prophylaxis of immunocompromised transplant patients. Following treatment of active infection in AIDS patients with low CD4 counts, oral valganciclovir is given to prevent relapse.

**Cidofovir**

Chemical Structure, Mechanisms of Action, and Pharmacokinetics—Cidofovir (Tables 1.20, 1.21) is an analog...
of deoxycytidine monophosphate that inhibits viral DNA synthesis. This agent does not require viral kinase for activity, being converted by cellular enzymes to its active diphosphate form. It acts as a competitive inhibitor of viral DNA polymerase and also adds to DNA, substituting for deoxycytidine triphosphate (dCTP), causing premature chain termination. Viral thymidine kinase mutations do not impair cidofovir activity.

Resistance is conferred through viral DNA polymerase mutations. Such mutations can result in cross-resistance to ganciclovir and, less commonly, to foscarnet. Cidofovir is cleared by the kidneys.

Toxicity—Cidofovir is highly nephrotoxic, causing proteinuria in half of treated patients, and azotemia and metabolic acidosis in a significant number. Vigorous saline hydration and co-administration of probenecid reduces nephrotoxicity. The drug should be discontinued if 3+ proteinuria or higher develops, or if serum creatinine increases by more than 0.4 mg/dL. Neutropenia is also commonly encountered.

Spectrum of Activity and Treatment Indications—Cidofovir has activity against many DNA viruses: CMV; herpes simplex; herpesvirus 6 and 8; varicella; pox viruses, including smallpox; papilloma viruses; polyoma viruses; and adenoviruses. This agent is approved only for the treatment of CMV retinitis in patients with AIDS. Given its highly toxic profile, parenteral use of this drug in other viral infections is likely to be limited. Topical therapy may prove efficacious in acyclovir-resistant herpes simplex infections in patients with AIDS, and it is being studied for the treatment of anogenital warts.

**Foscarnet**

Chemical Structure and Mechanism of Action—Foscarnet is an inorganic pyrophosphate analog, trisodium phosphonoformate, which reversibly blocks the pyrophosphate binding site of viral DNA polymerase. Foscarnet binding inhibits the polymerase from binding deoxynucleotidyl triphosphates. Mutations to the viral DNA polymerase are primarily responsible for viral resistance; however, resistance among clinical isolates is rare.

Toxicity. Nephrotoxicity is the most common serious side effect of foscarnet, resulting in azotemia, proteinuria, and occasionally acute tubular necrosis (Table 1.20). Renal dysfunction usually develops during the second week of therapy and in most cases reverses when the drug is discontinued. Dehydration increases the incidence of nephrotoxicity, and saline loading is of benefit in reducing this complication. Metabolic abnormalities are frequent. Hypocalcemia is the most common, being the result of chelation by foscarnet. Reductions in ionized calcium can cause CNS disturbances, tetany, paresthesias, and seizures. Other metabolic abnormalities include hypophosphatemia, hypomagnesemia, hypokalemia, hypercalcemia, and hyperphosphatemia. To minimize these metabolic derangements, intravenous infusion should not exceed 1 mg/kg per minute. Electrolytes, magnesium, phosphate, and calcium should be closely monitored. Other common side effects include fever,

<table>
<thead>
<tr>
<th>KEY POINTS About Cidofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. An analog of deoxycytidine monophosphate, it causes premature chain termination of viral DNA and also inhibits viral DNA polymerase.</td>
</tr>
<tr>
<td>2. Does not require viral thymidine kinase for conversion to its active form. Acyclovir-resistant strains are usually not resistant to cidofovir.</td>
</tr>
<tr>
<td>3. Highly nephrotoxic; causes proteinuria, azotemia, and metabolic acidosis in nearly half of patients. Saline hydration and probenecid reduce nephrotoxicity. Neutropenia also is common.</td>
</tr>
<tr>
<td>4. Broad spectrum of antiviral activity including cytomegalovirus (CMV), herpes simplex, herpesvirus 6 and 8, varicella, pox viruses, papilloma virus, polyoma viruses, and adenoviruses.</td>
</tr>
<tr>
<td>5. Approved for CMV retinitis in patients with AIDS. Other indications are currently being explored. However, the usefulness of cidofovir is likely to be limited because of renal and bone marrow toxicity.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>KEY POINTS About Foscarnet</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Blocks binding of deoxynucleotidyl triphosphates to viral DNA polymerase.</td>
</tr>
<tr>
<td>2. Nephrotoxicity is common, usually developing during the second week of therapy. Can be reduced by saline hydration. Usually reversible.</td>
</tr>
<tr>
<td>3. Also causes abnormalities in serum calcium, magnesium, and phosphate.</td>
</tr>
<tr>
<td>4. Active against cytomegalovirus (CMV), herpes simplex, varicella, Epstein-Barr virus, and herpesvirus 8.</td>
</tr>
<tr>
<td>5. Approved for the treatment of CMV retinitis and acyclovir-resistant mucocutaneous herpes simplex.</td>
</tr>
</tbody>
</table>
headache, nausea, vomiting, and abnormal liver function tests.

Pharmacokinetics—Foscarnet is poorly absorbed orally and is administered intravenously. This drug penetrates all tissues and fluids, achieving excellent levels in the cerebrospinal fluid and vitreous humor. Foscarnet is excreted unmodified, primarily by the kidneys.

Spectrum of Activity and Treatment Indications. Foscarnet is active against CMV, herpes simplex, varicella, Epstein–Barr virus, and herpesvirus 8. It is approved for the treatment of CMV retinitis and for acyclovir-resistant mucocutaneous herpes simplex.

Other Antiviral Agents

RIBAVIRIN

Chemical Structure and Mechanism of Action—Ribavirin is a guanosine analog that contains the d-ribose side chain. It inhibits DNA and RNA viruses alike. The mechanisms of inhibition are complex and not completely understood. Ribavirin is phosphorylated to the triphosphate form by host cell enzymes, and the triphosphate form interferes with viral messenger RNA formation. The monophosphate form interferes with guanosine triphosphate synthesis, lowering nucleic acid pools in the cell.

Toxicity—Systemic ribavirin results in dose-related red blood cell hemolysis; at high doses, it suppresses the bone marrow (Table 1.20). The resulting anemia reverses when the drug is discontinued. Intravenous administration is not approved in the United States, but is available for patients with Lhasa fever and some other forms of hemorrhagic fever. Aerosolized ribavirin is associated with conjunctivitis and with bronchospasm that can result in deterioration of pulmonary function. A major concern for health care workers exposed to aerosolized ribavirin are teratogenic and embryotoxic effects noted in some animal studies. Pregnant health care workers should not administer this drug.

Pharmacokinetics—Approximately one third of orally administered ribavirin is absorbed. The drug penetrates all tissues and body fluids. Ribavirin triphosphate becomes highly concentrated in erythrocytes (40 times plasma levels) and persists for prolonged periods with red blood cells. The drug is cleared both by the kidneys and by the liver. Aerosolized ribavirin produces high drug levels that have a half life of up to 2.5 h in respiratory secretions. A special aerosol generator is required for proper administration.

Spectrum of Activity and Treatment Recommendations.—Ribavirin is active against a broad spectrum of DNA and RNA viruses including respiratory syncytial virus (RSV), influenza and parainfluenza virus, herpes, adenovirus, pox viruses, Bunyavirus, and arenaviruses. It is approved in the United States for the aerosol treatment of RSV bronchiolitis and pneumonia in hospitalized patients. Oral ribavirin in combination with interferon is approved for the treatment of chronic hepatitis C.

INTERFERONS

Chemical Structure and Mechanism of Action—The interferons (IFNs) are proteins of 16 to 27,000 Da molecular weight, synthesized by eukaryotic cells in response to viral infections. These cytokines in turn stimulate host antiviral responses. Interferon receptors regulate approximately 100 genes, and in response to INF binding, cells rapidly produce dozens of proteins. A wide variety of RNA viruses are susceptible to the antiviral actions of IFNs; most DNA viruses are only minimally affected.

Toxicity—Side effects tend to mild when doses of less than 5 million units are administered (Table 1.20). Doses of 1 to 2 million units given subcutaneously or intramuscularly are associated with an influenza-like syndrome that is particularly severe during the first week of therapy. This febrile response can be reduced by pre-medication with antipyretics such as aspirin, ibuprofen, and acetaminophen. Local irritation at injection sites is also frequently reported. Higher doses of INF result in bone marrow suppression, causing granulocytopenia and thrombocytopenia. Neurotoxicity resulting in confusion, somnolence, and behavior disturbances is also common when high doses are administered.
KEY POINTS

About Interferon for Treatment of Viral Infections

1. Binds to host cell interferon receptors, upregulating many genes responsible for the production of proteins with antiviral activity.
2. RNA viruses are more susceptible to the antiviral actions of IFNs.
3. The most common side effect is an influenza-like syndrome. At doses above 5 million units, bone marrow suppression and neurotoxicity may develop. Hepatoxicity and retinopathy are commonly associated with high doses.

Toxicity—Amantadine causes moderate CNS side effects, especially in the elderly (Table 1.20). Insomnia, inability to concentrate, and dizziness are most commonly reported. Amantadine also increases the risk of seizures in patients with a past history of epilepsy. Rimantadine causes CNS side effects less frequently, and this agent is now preferred over amantadine.

Treatment Recommendations—To be effective, treatment must be instituted within 48 hours of the onset of symptoms (Table 1.21). Efficacy has been proven in healthy adults, but trials have not been performed in high-risk patients.

Neuraminidase Inhibitors

Mechanism of Action—The neuraminidase inhibitors have activity against both influenza A and B.

Toxicity—Zanamivir is given by inhaler and commonly causes bronchospasm, limiting its usefulness.

Treatment—To be effective, neuraminidase inhibitors must be given within 48 hours of the onset of symptoms.

Amantadine, rimantadine, or oseltamivir can be given for a longer duration as prophylaxis in patients at risk of serious complications from influenza during an epidemic. Influenza vaccine is preferred for prophylaxis.

FURTHER READING

Antibiotic Handbooks


Electronic Sources

ePocrates and ePocrates ID [software]. San Mateo, Calif: Epocrates, Inc. [Web address: www.epocrates.com; cited:]
The Johns Hopkins University, Division of Infectious Diseases. ABX Guide [Web resource]. Baltimore, Md: The Johns Hopkins University. [Web address: www.hopkins-abxguide.org; cited:]

Other


Sepsis Syndrome

Time Recommended to complete: 1 day

Reuben Ramphal, M.D.

GUIDING QUESTIONS

1. How is sepsis syndrome defined, and what is SIRS?
2. Do all episodes of bacteremia cause sepsis syndrome, and are all sepsis syndromes the result of bacteremia?
3. Which bacterial products can produce sepsis syndrome?
4. What is a “superantigen,” and which bacteria produce them?
5. Which host cells are most important in sepsis syndrome, and how do they mediate it?
6. What are the clinical clues that suggest pre-shock, and why is pre-shock important to recognize?
7. What are the therapeutic measures that need to be instituted in patients with sepsis syndrome?

PREVALENCE

Sepsis—severe infection leading to organ dysfunction—is a problem of increasing magnitude in the United States. Estimates of the occurrence of this syndrome range from 300,000 to 500,000 cases per year. Mortality associated with the syndrome has been reported to be between 15% and 60%, governed by factors such as underlying diseases, age, infecting organism, and the appropriateness of empiric anti-infective therapy. Most cases of sepsis syndrome are the result of bacterial infection, but it should be appreciated that the syndrome is also seen in viral infections (for example, dengue fever), fungal infections (for example, candidemia), and certain noninfectious diseases (for example, pancreatitis). For

KEY POINTS

About the Prevalence and Definitions of Sepsis Syndrome

1. Prevalence is 300,000–500,000 cases per year in the United States.
2. Mortality ranges from 15% to 60%.
3. Sepsis syndrome is systemic inflammatory response syndrome (SIRS) caused by microbial products.
4. Viruses (dengue fever), fungi (Candida), and noninfectious diseases (pancreatitis, tissue ischemia, severe trauma) can also cause SIRS.
5. Severe sepsis is defined as SIRS caused by microbial products that is associated with organ dysfunction.
6. Septic shock is shock associated with sepsis that is unresponsive to volume replacement.
7. Bacteremia does not always cause sepsis syndrome, and sepsis syndrome is not always caused by bacteremia.
the purposes of this chapter, sepsis is presumed to be a result of bacterial agents and their products.

DEFINITIONS

Sepsis represents a continuum that progresses from localized infection to severe sepsis (Figure 2.1). “Sepsis” is best defined as the systemic inflammatory response syndrome (SIRS) caused by microbial products. This definition acknowledges that SIRS may be produced by entities other than infection and that, in the absence of viable organisms, microbial products are capable of producing this clinical picture. “Severe sepsis” is defined as sepsis with organ dysfunction, and it represents progression of SIRS with more severe pathophysiologic disturbances. “Septic shock” is hypotension due to sepsis that has become unresponsive to initial attempts at volume expansion. “Infection,” often colloquially called “sepsis,” indicates the presence of infection and should not be considered synonymous with sepsis syndrome. Bacteremia is often called sepsis, and although some bacteremias result in sepsis syndrome, not all sepsis syndromes are caused by bacteremia. In fact, in earlier clinical trials of biologic agents in sepsis syndrome, using the best possible definitions and available laboratory studies, fewer than 40% of patients have had proven infection.

PATHOGENESIS

SIRS results from the activation of cellular pathways that lead to a triggering of innate immune responses and coagulation mechanisms. The pathways are linked to ancient mechanisms that defend the host by responding to tissue injury or the presence of microbial products. This innate immune response eventually leads to a classic adaptive immune response characterized by the production of antibodies, activated T cells and memory of antigens.

Much is now known about the microbial triggers of this system, with most of the information having been obtained using a portion of the gram-negative cell wall, the lipopolysaccharide molecule (LPS) or endotoxin. It is clear, however, that gram-positive cell wall material—specifically peptidoglycans and lipoteichoic acid, toxins produced by gram-positive bacteria, and fungal cell walls—is also recognized by a family of molecules on the surfaces of target cells. This recognition leads to the synthesis of molecules that trigger inflammation and coagulation pathways.

Cell Wall Factors

In gram-negative bacteria, the cytoplasmic bilayer is covered with a layer of peptidoglycan. Overlying the peptidoglycan layer is an outer membrane, into which endotoxin is inserted. Endotoxin is the most carefully studied microbial substance implicated in sepsis syndrome and shock. There is compelling evidence that endotoxin plays a key role in the pathogenesis of gram-negative sepsis. Its structural organization is common across all gram-negative bacteria. From the outside going inward, it consists of an “O” side chain that is joined to a core, which is in turn connected to the “business” end of the molecule, the lipid A portion.

Lipid A is anchored into the outer membrane. The triggering of the inflammatory and coagulation systems is believed to begin with the interaction of LPS with cellular receptors on macrophages and mononuclear leukocytes. The structure of lipid A is remarkably well conserved in most common gram-negative bacteria, irrespective of the species from which it is obtained. Indeed, the clinical features of sepsis caused by *Escherichia coli* are similar to those caused by *Klebsiella* or *Enterobacter* species.

The infusion of LPS or lipid A into animals results in a sepsis-like picture. Endotoxin can be found in the blood of patients with gram-negative sepsis. In some cases, such as meningococcemia, there is a good correlation between the plasma level of endotoxin and the outcome; even in more “general” types of gram-negative infection, the presence of endotoxemia correlates with more severe physiologic variables.

In addition to LPS, fungal cells walls, gram-positive cell walls and possibly bacterial flagellins are also capable of interacting with macrophages to trigger the sequence of events leading to sepsis and shock. Endotoxin is not present in gram-positive bacteria. Instead, the cell wall contains a thick layer of peptidoglycan on its surface. In capsular strains the peptidoglycan lies directly beneath the capsule. Embedded in the peptidoglycan are molecules of lipoteichoic acid. Several in vitro studies have demonstrated that these structural components of gram-positive cell walls are able to mimic some of the properties of endotoxin—for example, their ability to induce proinflammatory cytokines from mononuclear cells.

Secreted Factors

In addition to factors that are integral parts of the cell wall, secreted factors from gram-positive bacteria are
believed to cause septic shock. The prototypical factor is toxic shock syndrome toxin 1 (TSST-1), produced by some strains of *Staphylococcus aureus*.

Toxic shock syndrome was first described in menstruation-associated staphylococcal infection of young women. Fever and profound shock were often followed by conjunctival and palmar hyperemia and desquamation. This condition proved to be associated with the production of an exotoxin, TSST-1.

Another secreted factor responsible for shock was discovered in strains of the gram-positive bacteria *Streptococcus pyogenes*. It is called streptococcal pyrogenic exotoxin A (SPEA). Clinically, the action of SPEA has been identified in necrotizing fascitis due to *Strep. pyogenes* associated with shock. Infection is hypothesized to lead to local or systemic release of toxins, massive lymphocyte activation, and release of cytokines, resulting in cellular injury and organ failure. This mechanism bypasses the macrophage, and the cytokine cascade is triggered at the level of the T cells. This bypassing of the macrophage has given rise to the term “superantigen” to describe toxins that, unlike conventional antigens that require processing by macrophages and dendritic cells are able to directly activate lymphocytes.

### Host Cell Receptors for Bacterial Products

A detailed discussion of the physiologic host responses to bacteria is beyond the scope of this chapter. Good evidence suggests that, in gram-negative infections, monocyte–macrophage or dendritic cells are the first cells to respond to endotoxin. Endotoxin first binds to LPS-binding protein, an acute-phase protein produced by the liver. The LPS–protein complex acts as the ligand for CD14 (a cell-surface receptor on mononuclear cells) and to toll-like receptor (TLR) 2 or 4 on these cells. There are a number of TLRs that recognize different substances regardless of microbial origin. For example, TLR2 recognizes peptidoglycans, mannans, lipoteichoic acids, and some LPS molecules; TLR4 recognizes LPS; and TLR5 recognizes bacterial flagellin. TLR receptors and co-receptors bind the foreign stimulant and internalize it. Internalization results in signal transduction and cell activation, leading to cytokine release.

### Cytokine and Other Inflammatory Mediator Cascades

The activation of monocytes leads to the production of the proinflammatory cytokines (that is, the cytokines that stimulate inflammation), particularly tumor necrosis factor α (TNF-α) and interleukin 1 (IL-1). Infection also activates other host pathways, including the complement and coagulation pathways and the production of reactive oxygen intermediates. Many studies have been conducted in animals in which cytokines have been measured in response to both purified bacterial components and, perhaps more informatively, live bacterial infection. Intravenous injection of live *E. coli* into mice, rabbits, or baboons results in a consistent picture in which proinflammatory cytokines such as IL-1, IL-6, IL-8, and TNF-α, are released in a well-ordered sequence, followed by interferon gamma and then counterregulatory cytokines such as IL-10. This picture is similar to that seen when endotoxin is injected into humans.

### How Infection Leads to Septic Shock

Figure 2.2 shows a simple diagram of the pathways leading to septic shock. It must be realized that these events represent a continuum, and they progress at speeds that have not been characterized. However, the general belief is that the larger the inoculum of the challenge molecule, LPS or gram-positive toxins, the more likely the process is to progress rapidly. Additionally the various cell-wall products are likely to differ in their intrinsic potency to stimulate the innate immune system. For example, clinical observation suggests that endotoxin is a more powerful stimulant than are the cells walls of enterococci or coagulase-negative staphylococci, because...
humans demonstrate a remarkable tolerance for bacteremia attributable to those organisms.

**KEY POINTS**

**About the Roles of Host Cells in Sepsis Syndrome**

1. Monocyte–macrophages or dendritic cells are the first cells to respond to endotoxin (LPS).
2. Endotoxin binds to LPS–protein in serum, and this complex binds to CD14 receptors and to toll-like receptor 4 (TLR4) on mononuclear cells.
3. TLR2 binds peptidoglycans, lipoteichoic acids found in gram-positive bacteria, and mannans found on fungi. It also binds to some forms of LPS. TLR-5 bind bacterial flagellin.
4. Receptor binding stimulates monocyte–macrophages to release
   a) proinflammatory cytokines tumor necrosis factor α and interleukin-1, stimulating inflammation.
   b) toxic oxygen byproducts.
   c) products that activate the complement and coagulation cascades.

**CLINICAL MANIFESTATIONS**

**CASE 2.1**

A 66-year-old white woman underwent elective thoracoabdominal aneurysm repair. Three days after surgery, she became confused and developed a new fever. She had no cough, no dysuria, and no abdominal pain. A surgical drain was noted to be leaking increasing amounts of serous fluid. She was receiving vancomycin for operative prophylaxis.

On physical exam, her temperature was 39°C, her pulse was 143 per minute, and her blood pressure was 110/70 mm Hg. She was intubated and on a respirator. She appeared toxic and somewhat lethargic. No skin lesions were noted, and her respiratory, cardiac, and abdominal exams were unremarkable. Her extremities were warm to the touch. Chest X-ray revealed no infiltrates.

Laboratory workup showed that the patient’s peripheral white blood cell (WBC) count had dropped to 1400/mm³ from 22,600/mm³ the day before, with 24% polymorphonuclear leukocytes, 37% bands, and 9% metamyelocytes. Her hematocrit was 30%; blood urea nitrogen, 41 mg/dL; serum creatinine, 1.0 mg/dL; and HCO₃ 26 mEq/L. Blood cultures and culture of the surgical drain subsequently grew Escherichia coli. Computed
tomography scan of the abdomen failed to reveal an abscess. She was initially treated with intravenous cefepime and subsequently switched to ceftriaxone. Except for a brief bout of hypotension requiring intravenous saline and dopamine, she fully recovered and was subsequently discharged from the hospital.

Fever

As noted in case 2.1, fever is usually the first and most common manifestation of sepsis. In general, the higher the temperature, the more likely a patient is to be bacteremic. However, it should be emphasized that hypothermia and normal body temperature are seen in patients who are bacteremic. In fact, there is good reason to believe that hypothermia is a poor prognostic indicator in bacteremic patients, indicating an inability to mount an adequate inflammatory response.

Hemodynamic Changes

Tachycardia is a concomitant finding with fever and is to be expected. Case 2.1 had marked sinus tachycardia associated with her bacteremia. Bradycardia, on the other hand, is unusual, and has been reported in patients with specific bacterial infections, such as typhoid fever and brucellosis. Of the easily measurable hemodynamic changes, hypotension is the most important in determining outcome. Failure to reverse hypotension in its early stages results in serious end-organ damage that may not be reversed by antibiotics or other therapy. The stage at which hypotension is reversible is called pre-shock. The pre-shock stage is often characterized by warm skin, diminished mentation (often worse in the elderly), and oliguria. Persistent hypotension leads to the well-recognized septic shock findings of cool skin, acute renal failure, and, on occasion, hepatic injury.

Acid–Base Disturbances

Reduced tissue perfusion requires a change from aerobic to anaerobic metabolism and causes lactic acid accumulation. Lactic acid and elevated cytokine levels stimulate the respiratory center, resulting in hyperventilation, which initially produces a respiratory alkalosis. This is the first pronounced change that is seen in impending shock. It is diagnostic, and it is usually seen at a time when the hemodynamic changes are reversible with fluid resuscitation. Recognition of this early stage is thus vital to making improvements in the management of a patient with sepsis syndrome. Metabolic acidosis can develop just before or can accompany hypotension, and it signals the beginning of a fatal downward spiral. Case 2.1 was recognized and treated before the development of acidosis, which explains the patient’s rapid recovery.

Respiratory Changes

Tachypnea is a common feature of sepsis, generated by cytokine stimulation of the central nervous system, elevated body temperature, and the accumulation of lactic acid. In addition to hyperventilation, severe depression of oxygenation is often seen. The adult respiratory distress syndrome (ARDS) commonly develops in septic shock and can be experimentally induced by endotoxin. Endotoxin is thought to activate neutrophils that become trapped in the small vessels of the lungs and cause vessel-wall damage and leakage of fluid into the alveoli.

ARDS is diagnosed by chest X-ray changes that mimic cardiac pulmonary edema, and it is accompanied
by severe hypoxemia. However, patients with sepsis may also demonstrate pneumonia on chest X-ray, and infection of the lungs can be accompanied by bacteremia and sepsis syndrome (see Chapter 4).

**DIAGNOSIS**

Diagnosis of sepsis syndrome is perhaps the greatest challenge encountered in designing clinical trials for new therapeutic agents. If fever, tachycardia, and tachypnea with or without leukocytosis are used to define SIRS, then this definition includes other causes in addition to infection. Therefore evidence of actual infection must be sought.

The most prevalent sites of infection are the lungs, bloodstream, abdomen, and wounds. Even with a positive bacterial culture from any of these sites, sepsis in patients fitting the broad definitions of SIRS remains an uncertainty. In fact, most patients with pneumonia would fit this definition of sepsis syndrome, although they rarely require intensive care. The strictest criteria should include the presence of a positive blood culture, preferably two, and should exclude most cases of coagulase-negative staphylococci that are common skin contaminants. Exceptions to a positive blood culture would have to be made in patients presenting clear clinical evidence of an intra-abdominal infection such as peritonitis. Adjunctive information should also include the presence of hypotension that is not a result of hypovolemia or a recent cardiac event.

Critical diagnostic tools that are not currently available include a means to rapidly diagnose the presence of bacteria in the blood and a method to rapidly quantify the inflammatory response. (Infection produces more inflammation than does a noninfectious cause.) Such tests would guide a decision to initiate or not to initiate antibiotics and activated protein C (see “Drotrecogin α” under “Treatment”). A method for detecting early organ damage would also be helpful for determining the severity of SIRS. Currently, reliance must be placed on clinical assessment of illness severity and supportive bacteriologic studies that usually do not become available for 24–48 hours.

The presence of other abnormalities such as thrombocytopenia, evidence of fibrinogen consumption, and clot lysis are helpful, and when accompanied by hypotension, increased cardiac output and changes in peripheral vascular resistance may serve to define infection as the cause of SIRS. However, these findings are more likely to be seen in the more severe cases, where the diagnosis of infection is already clinically apparent.

Case 2.1 had a marked drop in peripheral WBC, with a marked shift to the left and a high percentage of immature granulocyte forms indicating marked consumption of granulocytes. That finding served as a useful warning that sepsis had developed, and it precipitated the administration of broad spectrum antibiotic coverage.

These common clinical and laboratory findings are indicative of sepsis:

1. Temperature: <36°C or >38°C
2. Pulse rate: >90/min
3. Respiratory rate: >20 per minute
4. PaCO₂: <32, with pH >7.45 (early sepsis)
5. WBC count: <4000/mm³ or >12,000/mm³ with a band count >10%
6. Chills, lethargy, hemorrhagic skin lesions

These laboratory studies are recommended in patients with suspected sepsis syndrome:

1. Two blood cultures, urine culture, and sputum culture if the patient has chest X-ray abnormalities
2. Complete blood count with differential and platelets
3. Coagulation studies to include international normalized ratio, fibrinogen, and D-dimers or fibrin split products
4. Blood gases and metabolic panels

**TREATMENT**

**Antibiotic Therapy**

The outcome of patients with sepsis, in particular those with bacteremia, is governed by host and microbial factors alike. In some studies, certain organisms, including *Pseudomonas aeruginosa* and *Candida* species have

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**KEY POINTS**

**About the Diagnosis of Sepsis Syndrome**

1. Early diagnosis is difficult and is based on clinical findings.
2. Fever, tachycardia, and hypotension need to be accompanied by documented bacteremia.
3. Tests to quickly demonstrate bacteremia, to accurately assess the extent of inflammation, and to assess organ ischemia are not currently available.
4. Thrombocytopenia and evidence of fibrinogen consumption and clot lysis combined with hypotension, increased cardiac output, and reduced peripheral vascular resistance suggest the diagnosis.
been suggested to carry a higher mortality rate. Polymicrobial bacteremia also carries an increased mortality risk. Therefore, if the clinical situation is epidemiologically consistent with the isolation of more risky pathogens, consideration must be given to covering these possibilities empirically.

The other microbial factor of significance is the susceptibility of the pathogen to empiric therapy. Patients with gram-negative bacteremia treated empirically with antibiotics to which their organism(131,375),(945,603)
expansion, initially with normal saline. The duration of hypotension before the administration of effective antibiotics has been found to be extremely important in the survival of hypotensive patients. Each hour of delay up to 6 hours resulted in an increase in mortality of 7.9%.

If there is a drainable site of infection in the abdomen or pelvis, or if those locations are the possible sources of infection, immediate surgical consultation must be sought. (See Chapter 8, “Gastrointestinal and Hepatobiliary Infections.”) Similarly the presence of gas in soft tissues or clinical evidence of a necrotizing infection mandates surgical consultation and possibly intervention. (See Chapter 10, “Skin and Soft-Tissue Infections.”) Any intravascular catheter in place must be removed and cultured. (See Chapter 7, “Cardiovascular Infections.”)

The following measurements are suggested in patients who are initially stable and kept on a conventional ward:

1. Hourly measurement of vital signs and urine output
2. Two-hourly measurement of arterial blood pH, PaCO$_2$, and PaO$_2$
3. Blood lactate and coagulation parameters initially, and perhaps every 4–6 hours until a clear sense develops of how the patient is progressing

Failure of the patient to respond to fluids and antibiotics—as indicated by a persistent fall in blood pressure, accumulation of lactate, increasing hypoxemia, and laboratory signs suggesting a coagulopathy—dictate that the patient be moved to an intensive care unit for closer monitoring and more aggressive hemodynamic support. There are no proven superior therapies at this time. Judicious use of vasopressors is generally recommended, beginning with dopamine and progressing to norepinephrine. Aggressive fluid resuscitation should be continued with specific attention to central venous pressures and pulmonary vascular congestion. Further management needs to be deferred to the intensive care specialists.

### Adjunctive Therapies

Many different substances have been used to reverse the persistent hypotension and associated end-organ damage associated with sepsis syndrome. Most of these adjunctive measures have failed to improve mortality in large studies. Given current knowledge of the pathogenesis of sepsis, additional trials are likely to be undertaken in the future. These are some of potential therapies that have not proved beneficial to date:

1. Anti-inflammatory agents such as ibuprofen and even narcotic antagonists have not proven to be of value in large scale studies.
2. Monoclonal antibody against the core of the endotoxin molecule has not been conclusively shown to be beneficial.
3. Antibody against TNF-α and the TNF-α receptor have failed.
4. Studies utilizing IL-1 receptor antagonists have been inconclusive.
5. Platelet activating factor antagonists have failed.

### Corticosteroids

The use of corticosteroids in septic shock has been under debate for decades. It is known that some of these patients have or develop adrenal insufficiency. Recent studies have re-examined this question with the startling revelation that, as compared with high doses, low physiological doses of corticosteroids for 7 days are associated with improved survival. However, debate continues regarding whether only patients with adrenal insufficiency should receive these agents or whether all patients should be so treated. Further studies will be required to clarify the efficacy of low-dose steroid;
however, pending these studies, treatment with 200–300 mg of hydrocortisone or its equivalent daily for 7 days should be strongly considered.

**Drotrecogin α**

Investigations of sepsis have shown that protein C levels are low and that septic patients are unable to activate this substance. Protein C plays a key role in inhibiting coagulation, and it may be an important inhibitor of monocyte activation. Animal studies have shown that infusion of activated protein C reduces mortality in lethal *E. coli* infections. Clinical trials in humans have subsequently shown a modest reduction of mortality in septic shock when patients are treated with activated protein C. This agent, now called drotrecogin α, has now been approved by the U.S. Food and Drug Administration as an adjunct to standard therapy for the treatment of severe sepsis. Drotrecogin α reduced mortality to 24.7% from 30.8% in placebo-treated patients over 28 days, a statistically significant reduction. Because of the complexity of patient inclusion criteria, very high costs, and potential for bleeding complications, this agent is reserved for use by intensive care and infectious disease specialists. Its major contraindication is recent surgery, the risk of bleeding complications being prohibitively high in the postoperative patient population.

**CONCLUSION**

The physician first needs to make an immediate decision about severity of the illness, and with clinical experience, most physicians become skilled at recognizing the sickest patients. Among the severely ill, patients with sepsis syndrome have the highest mortality and morbidity. Early recognition of sepsis and efforts to remove the precipitating cause and to deliver aggressive fluid and vasopressor therapy, optimal supportive care for organ dysfunction, and empiric antimicrobial therapy for the most likely microbial pathogens remain the standard of care.

It is important that the physician reassess empiric antibiotic coverage in 48 hours when culture results have returned. The organisms grown on blood culture can help to identify the site of primary infection. They also often allow the spectrum of antibiotic coverage to be narrowed, reducing the likelihood of patient colonization with highly resistant bacterial flora. (See Chapter 1, “Anti-infective Therapy.”) Activated protein C is of modest benefit, but not all patients are candidates for this agent. However, agents of this type that will be more effective are likely to be developed in the future, as more is learned about the mechanisms involved in the progression of sepsis.

**FURTHER READING**


TEMPERATURE REGULATION

Body temperature is regulated by the anterior hypothalamus in combination with many other neural structures, including the brain stem, spinal cord, and sympathetic ganglia. The region of the hypothalamus near the optic chiasm is thought to be primarily responsible for maintaining the body’s core temperature. A distinct temperature set point is established, and when body core temperature drops below that set point, the nervous system increases body metabolism and stimulates shivering and chills. When core temperature exceeds that set point, the nervous system increases peripheral blood flow and sweating. “Normal” body temperature is 37°C, but it varies from individual to individual, following a normal distribution. Some individuals therefore have a lower set point, and others have a higher set point than the mean “normal” temperature. Furthermore, in each individual’s core temperature varies during the day, being lower in the morning and increasing in the evening. Before deciding that a patient has a fever, the physician must be familiar with that patient’s normal set point and diurnal core temperature variation.

MECHANISMS UNDERLYING THE FEBRILE RESPONSE

Fever is a consequence of the anterior hypothalamus responding to inflammatory mediators. Among the mediators thought to stimulate a rise in the normal core temperature set point are interleukin 1 (IL-1), tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), and interferon γ (IFN-γ). These cytokines are released primarily by monocytes and macrophages in response to invasion by various pathogens and by other inflammatory stimuli. Investigators speculate that these cytokines stimulate the circumventricular organs near the optic chiasm, activating phospholipase A2, which in turn stimulates the cyclo-oxygenase pathway to produce increased levels of prostaglandin E2. This small molecule crosses the blood–brain barrier and stimulates the neurons within the anterior hypothalamus and brain stem responsible for thermal regulation.

BENEFITS AND HARMFUL EFFECTS OF FEVER

In addition to serving as a warning sign for the onset of infection, fever is thought to be beneficial. The growth of some viruses, bacteria, fungi, and parasites is inhibited by a rise in temperature above 37°C. Fever has also been shown to enhance the ability of macrophages and neutrophils to kill foreign pathogens and to improve cell-mediated immune function.

Depending on the individual patient, fever may also have harmful effects. Patients with heart disease may suffer cardiac ischemia because of the increase in heart rate and the oxygen demands associated with fever. Patients with severe pulmonary disease may similarly be
unusual to compensate for the increased oxygen demands associated with fever. Elderly patients with limited mental capacity may develop confusion and lethargy in response to fever, complicating their care. Children can suffer from seizures in association with high fever—although, to date, there is no proof that reducing fever prevents febrile seizures.

**TREATMENT OF FEVER**

The primary treatment for fever is to treat the underlying cause. The role of lowering body temperature while trying to determine the primary cause of fever remains controversial.

Based on current understanding of thermal regulation, direct cooling of the body using ice, cold water, or a cooling blanket should be considered only in conjunction with medicines that reset the thermal set point. Otherwise, the central nervous system will respond to such measures by inducing chills and shivering, increasing the patient's discomfort. Use of antipyretics is probably warranted in patients with heart disease, pulmonary disease, and in elderly patients with mental dysfunction in association with fever.

The pharmacologic agents used to reset the thermal set point all inhibit prostaglandin synthetase activity and reduce prostaglandin $E_2$ production. Acetylsalicylic acid (ASA), nonsteroidal anti-inflammatory drugs (NSAIDs), and acetaminophen are all effective. In children, ASA should probably be avoided because of the increased risk of Reyes syndrome (a deadly syndrome consisting of fatal hepatic and renal failure), and acetaminophen should be avoided in patients with serious underlying liver disease. Coronary artery vasoconstriction has been associated with NSAIDs, and therefore those drugs probably should not be used in patients with ischemic heart disease. To avoid repeated shifting of the thermal set point and recurrent shivering and chills, antipyretic agents must be administered on a regular schedule until the primary cause of fever has been treated.

### FEVER OF UNDETERMINED ORIGIN

#### GUIDING QUESTIONS

1. What are the criteria used to define FUO?
2. Which diseases are most commonly associated with FUO?
3. Which diseases are most commonly associated with FUO in the elderly?
4. Which basic diagnostic tests should be ordered in cases of FUO?
5. What is Sutton's law, and how is this law applied to FUO?
6. Should empiric antibiotics be started in cases of FUO?
7. What is the prognosis in patients with FUO?
1. an illness that has lasted least 3 weeks,
2. fever of more than 38.3°C on several occasions, and
3. no diagnosis after routine work up for 3 days in hospital or after 3 or more outpatient visits.

A duration of 3 weeks or longer was chosen to eliminate self-limiting viral illnesses that are generally difficult to diagnose and that resolve within that time period. A temperature of more than 38°C was chosen to eliminate those individuals at the far right of the normal temperature distribution curve who normally may have a slightly higher core temperature set point and an exaggerated diurnal temperature variation. Recognizing that, in the present era of managed care, most patients with FUO are now diagnosed and managed as outpatients, the third criterion has been modified to include outpatient diagnostic testing as well as that conducted in hospital.

Before launching a complex and expensive series of diagnostic tests, the physician must carefully document that the patient fulfills the criteria for FUO. Most important is the documentation of true fever. The patient should be instructed to measure both 6 A.M. and 6 P.M. temperature to rule out an exaggerated circadian rhythm. Secondly, an electronic thermometer should always be used to exclude the possibility of factitious fever (discussed in the next subsection). The exact pattern of fever generally is not helpful in identifying the fever’s cause.

### CAUSES OF FUO

Many diseases can initially present with the primary manifestation of prolonged fever (Table 3.1). The possible causes can be classified into three major categories (“the big three”): infections, neoplasms, and autoimmune disorders. The miscellaneous causes are numerous, the most common being six diseases (“the little six”): granulomatous diseases, regional enteritis, familial Mediterranean fever (FMF), drug fever, pulmonary emboli, and factitious fever.

### Table 3.1. Major Causes of Fever of Unknown Origin

<table>
<thead>
<tr>
<th>Big 3</th>
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<tbody>
<tr>
<td>1. Infection</td>
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<tr>
<td>2. Neoplasm</td>
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<tr>
<td>3. Autoimmune disease</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Little 6</th>
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</thead>
<tbody>
<tr>
<td>1. Granulomatous disease</td>
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<tr>
<td>2. Regional enteritis</td>
</tr>
<tr>
<td>3. Familial Mediterranean fever</td>
</tr>
<tr>
<td>4. Drug fever</td>
</tr>
<tr>
<td>5. Pulmonary emboli</td>
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<tr>
<td>6. Factitious fever</td>
</tr>
</tbody>
</table>

**CASE 3.1**

A 19-year-old white male, university sophomore, presented with a 3-week history of fevers to 40°C, fatigue, and anorexia. He was evaluated in the school infirmary and was given intravenous fluids for dehydration. He was treated empirically with penicillin and clarithromycin. Despite this treatment, his fevers persisted.

Epidemiology indicated no recent travel. A review of systems was negative, other than 1 to 2 loose bowel movements daily for the week before admission.

Vital signs included a temperature of 39.2°C, pulse 88 per minute, respirations 20 per minute, blood pressure 122/60 mm Hg. The patient appeared mildly ill. His physical exam was completely normal, including absence of palpable lymph nodes, no skin rashes, no cardiac murmurs, a benign abdominal exam without organomegaly, and a normal joint and extremity exam.

Laboratory workup showed a white blood cell (WBC) count of 11,600/mm³, with 93% polymorphonuclear leukocytes. Hematocrit was 35%; platelets, 228,000/mm³; blood urea nitrogen, 6 mg/dL; serum albumin, 3.0 g/dL; total protein, 6.2 g/dL; alkaline phosphatase (ALP), 327 IU/L; alanine transaminase (ALT), 107 IU/L; and erythrocyte sedimentation rate (ESR), 105 mm/h. Blood cultures were twice negative, and a chest X-ray (CXR) was within normal limits.

Because of the persistent fever and anorexia, the patient underwent an abdominal computed tomography (CT) scan that demonstrated an hepatic abscess 9 cm in diameter in the right lower lobe of the liver. Echinococcal serum titer was negative. Cutaneous
aspiration demonstrated thick pus, and culture grew Staphylococcus aureus, methicillin-sensitive.

Comment

Other than a mildly elevated ALP level, no clinical clues indicative of liver abscess were seen. On further review of past medical history, the patient reported having intermittent furunculosis. His skin was likely the initial portal of entry, resulting in transient bacteremia and seeding of the liver.

Infection

In patients under the age of 65 years, infection remains the most common cause of FUO (Table 3.2). Common infectious causes of FUO include abscesses, particularly abdominal abscesses that may persist for prolonged periods before being diagnosed. Improvements in imaging techniques have improved on the ability to locate and drain occult pyogenic collections. Osteomyelitis—particularly of the vertebral bodies, mandible, and air sinuses—can also present as FUO. Bone scan is particularly helpful in identifying such infections.

In earlier series, subacute bacterial endocarditis (SBE) was a major cause of FUO. However, improved culture techniques, including prolonged incubation of blood cultures to identify more fastidious slow-growing pathogens such as the HACEK organisms (see Chapter 7 on bacterial endocarditis), and drawing large volumes of blood for culture have improved the sensitivity of blood cultures and reduced the number of undiagnosed cases of SBE. Transesophageal cardiac echo has also improved identification of vegetations. As a result of those advances, SBE has become a less common cause of FUO in recent reports. In almost every case, patients with SBE have an audible murmur, emphasizing the importance of a careful physical exam during the initial evaluation of the patient with FUO.

The physician must also keep in mind that, if the patient has received antibiotics, the utility of blood cultures is markedly reduced. Administration of antibiotics temporarily sterilizes the bloodstream. Antibiotics must be discontinued for 7 to 10 days before blood cultures become positive.

Biliary system infections also can present as FUO. Such patients often have no right upper quadrant pain and no right upper quadrant tenderness. Subacute pyelonephritis can also present with a prolonged fever in the absence of dysuria, frequency, or flank pain.

In cases of FUO, miliary tuberculosis (TB) must always be considered. This potentially lethal disease is most common in elderly and immunocompromised patients, particularly patients with HIV and patients on high-dose glucocorticoids or a TNF inhibitor. Bone marrow culture is particularly helpful in making this diagnosis. A CXR may demonstrate micronodular (“millet seed”) interstitial changes; however, this radiologic finding may be absent in elderly individuals. If appropriate antituberculosis therapy is not initiated promptly, these patients usually deteriorate over 2 to 3 weeks and die.

Leptospirosis can cause persistent fever and is difficult to diagnose. A combination of appropriate epidemiology (animal or contaminated soil or water exposure), conjunctival suffusion, aseptic meningitis, liver enzyme abnormalities, and renal dysfunction should alert the clinician to this possibility. Other spirochetal diseases reported to cause persistent fever include Lyme disease and relapsing fever. Animal exposure, particularly the skinning of wild boar, should raise the possibility of brucellosis. Brucellosis can also be contracted by eating unpasteurized cheese.

Rickettsial infections can also cause FUO. Epidemiology plays a critical role in alerting the clinician to this group of pathogens. A history of camping, hunting, or other outdoor activities in areas endemic for these infections should raise the possibility. Rickettsia are tick-borne; however, a history of tick bite is not always obtained.

Rickettsial infections can also cause FUO. Epidemiology plays a critical role in alerting the clinician to this group of pathogens. A history of camping, hunting, or other outdoor activities in areas endemic for these infections should raise the possibility. Rickettsia are tick-borne; however, a history of tick bite is not always obtained.

Chlamydia is another intracellular pathogen that on occasion can cause prolonged fever. Chlamydia psittaci in particular can result in a mononucleosis-like syndrome. This organism is usually contracted from birds, including

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**Table 3.2. Infectious Causes of Fever of Unknown Origin**

| 1. | Abscesses |
| 2. | Osteomyelitis (vertebrae, mandible, sinuses) |
| 3. | Subacute bacterial endocarditis (murmur usually present, beware of previous antibiotics) |
| 4. | Biliary system infections (may have no right upper quadrant tenderness) |
| 5. | Urinary tract infections (in absence of related symptoms) |
| 6. | Tuberculosis (especially miliary disease) |
| 7. | Spirochetal infection (leptospirosis, Borrelia) |
| 8. | Brucellosis (animal exposure, unpasteurized cheese) |
| 9. | Rickettsial infection |
| 10. | Chlamydia |
| 11. | Epstein–Barr virus, cytomegalovirus |
| 12. | Fungal infection (Cryptococcus, histoplasmosis) |
| 13. | Parasites (malaria, toxoplasmosis, trypanosomiasis) |

Infection in patients under the age of 65 years, infection remains the most common cause of FUO (Table 3.2). Common infectious causes of FUO include abscesses, particularly abdominal abscesses that may persist for prolonged periods before being diagnosed. Improvements in imaging techniques have improved on the ability to locate and drain occult pyogenic collections. Osteomyelitis—particularly of the vertebral bodies, mandible, and air sinuses—can also present as FUO. Bone scan is particularly helpful in identifying such infections.
KEY POINTS

About Infectious Causes of Fever of Unknown Origin

1. Infection is the most common cause of FUO in patients under 65 years of age.
2. Epidemiology (animal exposure, insect bites, outdoor camping, travel, exposure to infected humans) is helpful.
3. Physical exam may provide useful clues, particularly inspection of skin, nail beds, and fundi, and cardiac auscultation.
4. Abdominal abscess, miliary tuberculosis, and disseminated fungal infections can be fatal.
5. Prior antibiotic administration interferes with diagnosis.

Table 3.3. Neoplastic Causes of Fever of Unknown Origin

1. Lymphoma (especially Hodgkin, Pel–Ebstein fever)
2. Leukemia (aleukemic or preleukemic phase)
3. Hypernephroma (high sedimentation rate)
4. Hepatoma (generally not metastatic liver disease)
5. Atrial myxoma

CASE 3.2

A 27-year-old Asian man presented with a chief complaint of fevers of 2 weeks’ duration. Two weeks earlier, he had begun to experience fever associated with weakness, malaise, shoulder and neck weakness, and muscle tenderness. He also noted a sore throat. He was admitted to a hospital in Puerto Rico where a CXR
Autoimmune Disease

Autoimmune disease is the third major category of diseases that cause FUO (Table 3.4). In early series of FUO cases, systemic lupus erythematosus (SLE) was a frequent cause. However, with improvements in antinuclear and anti-DNA markers, these sensitive tests readily identify cases of SLE. The diagnosis is now usually made within 3 weeks.

Still's disease (adult-onset juvenile rheumatoid arthritis) is one of the most frequent autoimmune diseases resulting in FUO in younger patients. Key clinical features of this disease include an evanescent macular rash, arthralgias, and a sore throat. Patients with parasites were thrice negative. Hepatitis B surface antibody was positive (Ab+), core was Ab+, and surface antigen was negative. He had a 1:185, antinuclear antibodies (ANAs) and rheumatoid factor were negative, and the rapid plasma reagin was also negative. Eight separate blood cultures were negative, and a monospot test was negative. Repeat transaminase values registered ALT 94 IU/L, AST 64 IU/L, ALP 403 IU/L, and GGT 180 IU/L.

The patient continued to have fevers. A liver biopsy demonstrated nonspecific inflammation. Weight loss continued, and the patient’s ESR and WBC remained elevated. After 8 days in the hospital, he developed a swollen left wrist and swollen right elbow. He was treated with high-dose oral salicylates. Within 24 hours of initiation of therapy, he defervesced. Over the next 2 weeks, his symptoms completely resolved. Based on past medical history, clinical presentation, and response to salicylates, he was discharged with a diagnosis of Still's disease.

**Table 3.4. Autoimmune Diseases That Cause Fever of Unknown Origin**

| 1. | Systemic lupus erythematosus |
| 2. | Still's disease |
| 3. | Hypersensitivity angiitis |
| 4. | Polymyalgia rheumatica, combined with temporal arteritis |
| 5. | Polyarteritis nodosa |
| 6. | Mixed connective tissue disease |
| 7. | Subacute thyroiditis |
Still’s disease often have high fevers associated with a high peripheral WBC counts, and this combination frequently causes the physician to begin antibiotic therapy for a presumed bacterial infection. However, the fever fails to subside after initiation of antibiotics. No specific test is available for Still’s disease. Serum ferritin levels are generally markedly elevated, as is the ESR. In elderly patients, polymyalgia rheumatica is the most common autoimmune disorder to cause FUO. This disease results in proximal muscle weakness, visual symptoms, and a high ESR. T emporal headaches and visual complaints are present, as is temporal arteritis, a vasculitis commonly associated with polymyalgia rheumatica.

Other autoimmune diseases reported to cause FUO include polyarteritis nodosa, hypersensitivity angiitis, and mixed connective tissue disease. Subacute thyroiditis may present with prolonged fever. On examination, the thyroid is often tender and serum antithyroid antibodies are elevated. Recently, Kikuchi’s disease, also called histiocytic necrotizing lymphadenitis, has been reported to cause prolonged fever. This self-limiting autoimmune disorder occurs in young Asian females and is associated with generalized lymphadenopathy. Diagnosis is made by lymph node biopsy.

**Other Causes of FUO**

In addition to the “big 3” categories, clinicians must also consider the “little 6.”

1. Regional enteritis can present with fever in the absence of gastrointestinal symptoms.
2. Pulmonary emboli can present with fever in the absence of respiratory symptoms.
3. Discontinue all medications in the patient with FUO.
4. Consider factitious fever in the female health care worker with a medical textbook at the bedside and recurrent polymeric bacterial infection.
5. No diagnosis is made in an increasing percentage of modern cases.

**Table 3.5. Drugs That Cause Fever of Unknown Origin**

<table>
<thead>
<tr>
<th>Antihistamines</th>
<th>Isoniazid</th>
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<tbody>
<tr>
<td>Barbiturates</td>
<td>Nitrofurantoin</td>
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<tr>
<td>Chlorambucil</td>
<td>Penicillins</td>
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<tr>
<td>Dilantin</td>
<td>Procaine amide</td>
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<tr>
<td>Hydralazine</td>
<td>Quinidine</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Salicyclates</td>
</tr>
<tr>
<td>Iodides</td>
<td>Thiouracil</td>
</tr>
<tr>
<td>Aldomet</td>
<td>Mercaptopurine</td>
</tr>
</tbody>
</table>

KEY POINTS

- **About Autoimmune Causes of Fever of Unknown Origin**
  1. Still’s disease is associated with high fevers, evanescent skin rash, leukocytosis, high serum ferritin, and elevated erythrocyte sedimentation rate (ESR). A diagnosis by exclusion.
  2. Polymyalgia rheumatica and temporal arteritis are found in elderly patients and cause proximal muscle weakness, visual symptoms, and a high ESR.
  3. Subacute thyroiditis should be considered if the thyroid is tender.
  4. Kikuchi’s disease often presents with fever and lymphadenopathy.

- **About Other Causes of Fever of Unknown Origin**
  1. Regional enteritis can present with fever in the absence of gastrointestinal symptoms.
  2. Pulmonary emboli can present with fever in the absence of respiratory symptoms.
  3. Discontinue all medications in the patient with FUO.
  4. Consider factitious fever in the female health care worker with a medical textbook at the bedside and recurrent polymeric bacterial infection.
  5. No diagnosis is made in an increasing percentage of modern cases.
penicillins are other major offenders. When a patient presents with FUO, all medications should be discontinued or switched to exclude this possibility.

Fifth of the “little 6” diseases is pulmonary emboli. Prolonged bed rest increases the risk of thrombus formation in the calves. When emboli are small, they may not result in respiratory complaints and may simply present as fever. In all patients at risk for thrombophlebitis who present with FUO, pulmonary emboli need to be excluded.

The final disorder in this list is factitious fever. In earlier series, patients often manipulated the mercury thermometer to fool the physician; the advent of the electronic thermometer has made this maneuver impossible. Today, patients usually inject themselves with saliva or stool, causing polymicrobial bacteremia and fever. This disorder occurs almost exclusively in women. A medical background is also the rule. In the absence of any clear cause for fever, a history of health care training should raise the clinician’s suspicion, particularly if the patient takes great interest in her illness and has a medical textbook at the bedside. The diagnostic test of choice is often a search of the patient’s room seeking a syringe used for self injection.

Finally, in a recent series, a high proportion of patients (30%) had no explanation for their FUO. In many of these cases, fever spontaneously resolved over 3 to 6 months without harmful consequences.

**HISTORY IN FUO**

History can play a critical role in narrowing the differential diagnosis and in deciding on the most appropriate diagnostic tests. A review of all symptoms associated with the illness needs to be periodically updated. Symptoms often are transient and are recalled by the patient only after repeated questioning. A patient’s past medical history often provides useful clues. History of tuberculosis, tuberculosis exposure, or a positive PPD should be included. Family history must also be thoroughly reviewed to exclude genetic disorders such as cyclic neutropenia and familial Mediterranean fever. Social history needs to include animal exposure (pets, and other domestic or wild animals), home environment, and occupational exposure. Travel history should explore travel to areas endemic for malaria and other parasites, typhoid, coccidiomycosis, histoplasmosis, and tick-borne illnesses. A list of all medications, including over-the-counter and natural organic remedies, must be compiled to exclude the possibility of drug fever.

**PHYSICAL EXAM IN FUO**

In addition to a careful history, careful repeat physical examination is frequently helpful. Particular attention should be paid to the skin exam, looking for embolic or vasculitic lesions or evidence of physical manipulation. Particular attention should be paid to the nail beds, where small emboli can become trapped in the distal capillaries of the fingers and toes, resulting in small splinter-shaped infarcts. Joint motion and the presence of effusions should be looked for. Careful eye exam should be repeated looking for conjunctival petechiae, conjunctivitis, punctate corneal lesions, uveitis, optic nerve changes, retinal or choroidal abnormalities. Thorough palpation of all lymph nodes needs to be repeatedly performed, documenting the consistency, size, and tenderness. Cardiac exam should be repeated daily, listening for cardiac murmurs and pericardial rubs. The abdomen also should be palpated daily to detect new masses, areas of localized tenderness, and hepatosplenomegaly.
All patients with FUO should receive a series of basic diagnostic tests (Table 3.6). However, because each case is different, a series of yes-or-no branch points are not possible for guiding the subsequent diagnostic approach to FUO.

In recent years, rather than insufficient studies being the norm, clinicians have erred on the side of excessive and uninformative testing. Each patient’s diagnostic workup must be tailored to personal history and physical findings. A cookbook approach subjects the patient to undue costly testing and stress. “Tincture of time” and repeated history and physical exam often allow the physician to apply Sutton’s law.

Willy Sutton was a famous bank robber, who, when finally captured, was asked by newspaper reporters, “Willy, why do you rob banks?” Willy replied, “That’s where the money is.” Clinicians need to focus on diagnostic tests that are likely to have a high yield. They need to “go where the money is.”

### Classes of Diagnostic Tests

#### Skin Tests

An intermediate-strength PPD should be performed in all patients with FUO who do not have a previously documented positive PPD. The use of skin tests to detect histoplasmosis and coccidiomycosis is not generally recommended.

#### Cultures

Blood cultures should be part of the initial workup of all patients with significant prolonged fever. Yield for subacute bacterial endocarditis is usually maximized by drawing blood for three cultures (see Chapter 7). In general no more than six blood cultures should be drawn. They may be repeated periodically or if a significant change occurs in the fever pattern. Because of the possibility of fastidious slow-growing bacteria, all blood cultures should be held for 3 weeks.

Multiple urine samples should be obtained and cultured for tuberculosis in addition to more conventional bacteria. In patients with respiratory complaints or CXR abnormalities, sputum should be cultured, and in patients undergoing bone marrow biopsy, culture is an important component of the marrow analysis. All biopsy specimens need to be cultured. Aerobic, anaerobic, mycobacterial, and fungal cultures should be ordered on virtually all samples. Viral cultures or quantitative polymerase chain reaction (PCR) may also be considered in specific cases in which cytomegalovirus or Epstein–Barr virus is suspected.

#### Smears

Peripheral blood smears with Giemsa and Wright stains are critical for making the diagnosis of malaria, trypanosomiasis, or relapsing fever. In addition to a peripheral WBC count, Wright stain with differential cell count is often helpful in determining the nature of the inflammatory response associated with fever, and it should be performed in all patients with FUO. Stool smears for ova and parasites are usually less helpful, being that gastrointestinal parasites seldom present as FUO.

### Other Peripheral Blood Tests

Antibody titers should be considered when specific pathogens are part of the differential diagnosis. To prove active infection, rising antibody titers are required. A single titer simply demonstrates a past history of exposure; a rising titer indicates recent infection. Therefore, two samples separated by 3 to 4 weeks need to be drawn. Antibody titers are particularly useful in cytomegalovirus,
Epstein–Barr virus, *Toxoplasma, Rickettsia, Chlamydia*, and *Brucella* infections. If liver functions are abnormal, hepatitis serology should also be ordered (see Chapter 8). An HIV antibody test should be performed in all patients with potential risk factors (see Chapter 17).

Tests that should be considered to diagnose connective tissue disease in most cases of FUO are antibody titers to human tissue, including ANAs, anti-DNA antibodies, rheumatoid factor, and immune complexes. An ESR assay should be performed in all cases of FUO. A very high ESR is seen in the polymyalgia rheumatica—temporal arthritis combination and in Still’s disease. A normal ESR virtually excludes these diagnoses, as well as subacute bacterial endocarditis.

**IMAGING STUDIES**

Tests That Should Be Ordered in All Patients with FUO—As part of the preliminary workup, a chest CT scan should be ordered. Results to look for are mediastinal enlargement (suggestive of lymphoma), micronodular interstitial changes (“millet seed” pattern, suggestive of miliary tuberculosis), or nodular lesions or infiltrates (can be seen in many infectious diseases, connective tissue diseases, and neoplasms). Abdominal CT scan should also be performed to identify abdominal abscesses, mesenteric nodes, and tumors. Imaging of the chest and abdomen by CT have an approximately 10% yield in patients with FUO who lack specific localizing symptoms.

Tests That Should Be Ordered Depending on the Patient’s Symptoms and Signs—In patients who are suspected of having a chronic infection, radionuclide scans may be helpful in localizing the site. Gallium scan may be useful in patients with chronic infection because this agent accumulates in areas of inflammation; however, indium white blood cell scan tends to be more specific. The indium white blood cell scan also has a higher positive yield than abdominal CT scan does for identifying occult intra-abdominal infection.

Another tracer molecule that accumulates in areas of inflammation and in malignant tumors is 18F fluorodeoxyglucose. Unlike other scans, which require that the patient be scanned during a period of 24 to 36 hours, positron emission tomography with 18F fluorodeoxyglucose is completed within a few hours. In preliminary studies, this test has proved more sensitive and specific than gallium scan. For the assessment of osteomyelitis or tumor metastasis to bone (with the exception of prostate cancer and multiple myeloma), technetium scan is the most sensitive and specific technique.

Air sinus films or sinus CT scan can be performed to exclude occult sinus infection and tooth abscess. In patients with a heart murmur and persistent fever, cardiac echo should be considered. Transesophageal echo is the test of choice; it has a greater than 90% sensitivity for detecting cardiac vegetations, and it is also helpful in detecting myocardial abscess and atrial myxoma.

Ultrasound of the lower abdomen may be helpful in cases in which pelvic lesions are suspected. Abdominal CT is not as sensitive in that region because of reflection artifacts generated by the pelvic bones. When other tests are unrevealing, upper gastrointestinal barium study with small bowel follow-through should be ordered to exclude regional enteritis. Barium enema should be considered in older patients; however, yield from this procedure is likely to be low in FUO. Radiographs of all joints should be ordered in any patient with persistent joint complaints to document anatomic defects.

Invasive Procedures—If all noninvasive tests prove to be negative, liver biopsy is recommended to exclude the possibility of granulomatous hepatitis. Laparoscopic guided biopsy improves the yield by allowing biopsies to be taken in areas where abnormalities in the external capsule are seen.

Bone marrow aspiration and biopsy is also recommended as a routine invasive test if all noninvasive studies are negative. Leukemia in its early stages may be detected, as may stage IV lymphoma. It is critical that the bone marrow be appropriately cultured (see the earlier subsection titled “Cultures”), because disseminated tuberculosis, histoplasmosis, coccidiomycosis, and other fungal and mycobacterial infections often seed the bone marrow.

Use of other invasive procedures will depend on the diagnostic findings, history, and physical findings to that point. In elderly patients with a high ESR and persistent fever, temporal artery biopsy is generally recommended. It should be kept in mind that, because skip lesions are common in temporal arteritis, a long sample of the temporal artery should be obtained and multiple arterial sections examined.

In early series of FUO, diagnostic laparotomy was frequently recommended. With the advent of new abdominal imaging techniques, this invasive procedure is now seldom performed; however, it may be considered in selected cases.

In addition to a complete series of cultures, all biopsy specimens should undergo Brown–Brenn, Ziehl–Neelsen, methenamine silver, periodic acid Schiff, and Dieterle silver staining in addition to routine hematoxylin and eosin. Frozen sections should be obtained for immunofluorescence staining, and the remaining tissue block should be saved for additional future studies.

It should be emphasized that, when symptoms, signs, or a specific diagnostic abnormality is found, all other scheduled diagnostic tests should be delayed, and Sutton’s law applied. For example, if an abnormal fluid collection is found on abdominal CT, then all other diagnostic procedures can be halted while a needle aspiration of the potential abscess performed. If the result
proves to be positive, additional investigations are unnecessary. The “money” has been found.

Ordering tests for completeness’ sake is unnecessary. When in doubt about performing additional tests, the wisest course of action is to wait. Over time, the patient’s fever may spontaneously resolve, or new manifestations may develop, helping to identify the cause.

**TREATMENT OF FUO**

In the past, many clinicians discouraged the use of antipyretics in FUO, because these agents mask the pattern of fever. However, as noted earlier in this chapter, with rare exceptions, the pattern of fever has not proved to be helpful in determining the cause of FUO.

Fever is commonly associated with chills, sweating, fatigue, and loss of appetite. Therefore, once true fever has been documented, antipyretics can be administered in most cases of FUO to relieve some of the patient’s symptoms while the diagnostic workup is pursued. To avoid repeated shifting of the thermal set point and recurrent shivering and chills, ASA, NSAIDs, or acetaminophen must be administered at the proper time intervals to maintain therapeutic levels. Otherwise, these antipyretics will exacerbate rather than reduce the symptoms of fever.

As was discussed in Chapter 1, physicians often over-prescribe antibiotics. In cases of FUO, the temptation to institute an empiric trial of antibiotics is great. This temptation should be avoided. Antibiotics are contraindicated until a specific diagnosis is made. Use of an empiric antibiotic trial often delays diagnosis and is rarely curative. Because infections susceptible to conventional antibiotics represent a small percentage of the diseases that cause FUO, antibiotic treatment will have no effect in most cases. In cases of occult bacterial infection, empiric antibiotics may mask the manifestations of the infection and delay appropriate treatment. Most infections that cause FUO require prolonged antibiotic treatment and surgical drainage. In the absence of a specific diagnosis, clinicians have difficulty justifying a prolonged course of antibiotics, and therefore antibiotics are often discontinued after 1 to 2 weeks, allowing the infection to relapse.

When a connective tissue disorder appears to be the most likely explanation for FUO, empiric use of systemic glucocorticoids is often considered. These agents are very effective in treating temporal arteritis and polymyalgia rheumatica, they may be helpful in Still’s disease, and they are used to treat specific complications in lupus erythematosus. However, because these agents markedly reduce inflammation and impair host defense, administration of glucocorticoids can markedly exacerbate bacterial, mycobacterial, fungal, and parasitic infections. Therefore, before considering an empiric trial of glucocorticoids such as prednisone, dexamethasone, or methylprednisone, infection must be convincingly ruled out. The physician must also keep in mind the many potential side effects of prolonged glucocorticoid use (Cushingoid face, osteoporosis, aseptic necrosis of the hip, diabetes mellitus, and opportunistic infections) before committing the patient with FUO to a prolonged course of systemic steroid treatment.

**PROGNOSIS**

Delay in diagnosis worsens the outcome in cases of intra-abdominal abscess, miliary tuberculosis, disseminated fungal infections, and pulmonary emboli. However, if these diseases are carefully excluded, lack of a diagnosis after an extensive workup is associated with a 5-year mortality of only 3%. The prognosis is somewhat worse in elderly patients because of their increased risk of malignancy. Therefore, once the clinician has completed the FUO diagnostic battery described in this chapter and serious life-threatening diseases have been excluded, additional diagnostic study is not warranted. If fever persists for an additional 4 to 6 months, a complete series of diagnostic studies may then be repeated.

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**Key Points**

**About the Treatment of Fever of Unknown Origin**

1. Once the pattern of fever has been documented, NSAIDS, acetylsalicylic acid, or acetaminophen can be used to lower fever.

2. Empiric antibiotics are contraindicated.

3. Glucocorticoids should be used only when infection has been excluded.

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**FUO in the HIV-Infected Patient**

Primary HIV infection can present with prolonged fever, and in patients with the appropriate risk profile (see Chapter 17), a diagnosis of HIV needs to be considered. Serum markers are negative in the early stages of HIV infection; quantitative PCR for HIV is therefore the diagnostic test of choice.

In the later stages of HIV infection, fever is a common manifestation of opportunistic infection. In order of
chains. In the later postoperative period, *S. aureus* exudate usually demonstrates gram-positive cocci in purulence at the operative site. A Gram stain of serous fluid for septic shock and severe bacteremia with only minimal symptoms is usually positive. After 24 to 48 hours, *Streptococcus pyogenes* can result in a localized edema, and tenderness. In the immediate postoperative period, all surgical wounds need to be carefully examined for purulent discharge, erythema, edema, and tenderness. In the immediate postoperative period (24 to 48 hours), *Streptococcus pyogenes* can result in septic shock and severe bacteremia with only minimal symptoms. A Gram stain of purulent material at the operative site is usually positive. A Gram stain of serous fluid for septic shock and severe bacteremia with only minimal symptoms is usually positive. After 24 to 48 hours, *Streptococcus pyogenes* can result in a localized edema, and tenderness. In the immediate postoperative period, all surgical wounds need to be carefully examined for purulent discharge, erythema, edema, and tenderness. In the immediate postoperative period (24 to 48 hours), *Streptococcus pyogenes* can result in septic shock and severe bacteremia with only minimal symptoms. A Gram stain of purulent material at the operative site is usually positive.

**KEY POINTS**

About Fever of Unknown Origin in HIV-Infected Patients

1. Can be a manifestation of primary HIV infection.
2. Often the first symptom of an opportunistic infection.
3. Mycobacteria are the most common infectious cause.
4. Cytomegalovirus is also common, as are *Cryptococcus* and *Toxoplasma*.
5. Non-Hodgkin lymphoma is the most common noninfectious cause.

Fevers in surgical intensive care and medical intensive care patients

One of the most common problems encountered by the infectious disease consultant is the evaluation of fever in patients residing in the surgical or medical intensive care unit (ICU). These patients are usually severely ill and have multiple potential causes for fever.

In the postoperative patient, wound infection must be excluded. All surgical wounds need to be carefully examined looking for purulent discharge, erythema, edema, and tenderness. In the immediate postoperative period (24 to 48 hours), *Streptococcus pyogenes* can result in septic shock and severe bacteremia with only minimal purulence at the operative site. A Gram stain of serous exudate usually demonstrates gram-positive cocci in chains. In the later postoperative period, *S. aureus* and nosocomial pathogens such as *Pseudomonas*, *Klebsiella*, and *Escherichia coli* are associated with wound infection.

Appropriate antibiotic therapy is generally guided by culture and Gram stain. Empiric antibiotic therapy should include gram-positive and gram-negative coverage. In patients who have suffered bowel perforation, the development of intra-abdominal abscess is a common cause of fever, and an abdominal CT scan should be ordered to exclude this possibility.

Because most ICU patients are intubated, bacteria colonizing the nasopharynx can more readily gain entry to the bronchi and pulmonary parenchyma, causing bronchitis and pneumonia. As is outlined in more detail in Chapter 4, sputum Gram stain is critical for differentiating colonization from true infection. The presence of a single organism on Gram stain, combined with more than 10 neutrophils per high-power field, strongly suggests infection. Sputum culture identifies the offending organism and sensitivities to antibiotics. Other parameters that are helpful in differentiating colonization from true infection are CXR and arterial blood gases. The presence of a new infiltrate supports the diagnosis of pneumonia, as does a reduction in arterial PaO₂.

Patients in the ICU usually have 1 or 2 intravenous catheters in place, plus an arterial line. These lines are always at risk of becoming infected, and line sepsis is a common cause of fever in the ICU setting. At the onset of new fever, all intravenous and arterial lines should be examined for erythema, warmth, and exudate. Particularly in the patient who has developed shock, all lines should be replaced, and appropriate empiric antibiotic coverage instituted.

*S. aureus*, *S. epidermidis*, and gram-negative rods are the primary causes of line sepsis. Initial antibiotic coverage should include vancomycin and a 3rd-generation cephalosporin. Empiric antibiotic coverage must be individualized to take into account the prevailing bacterial flora in each ICU and the history of antibiotic use in the patient. Patients who have been in the hospital for prolonged periods and who have received multiple antibiotics are at risk of candidemia, particularly if two or more peripheral site cultures have grown this organism. These patients should be empirically covered with fluconazole or an echinocandin (caspofungin, anidulafungin, or micafungin) pending blood culture results.

Another major infectious cause of fever in the ICU patient is prolonged bladder catheterization. The bladder catheter bypasses the urethra, and despite the use of closed urinary collecting systems, nearly all patients with bladder catheters develop urinary tract infections within 30 days (see Chapter 9). Urinalysis and urine culture therefore need to be part of the fever workup in all patients with urinary catheters.

In patients with nasogastric tubes or those who have been intubated through the nasal passage, the ostia...
draining the air sinuses can become occluded. This condition can lead to sinusitis and fever. Fever work up in these patients therefore needs to include sinus films. If sinusitis is discovered, the tube must be removed from the nasal passage, and appropriate antibiotic coverage instituted (see Chapter 5).

Noninfectious causes of fever also need to be considered. As noted earlier in this chapter, pulmonary emboli may present with fever. Patients in the ICU are usually receiving a large number of medications, and they are therefore at higher risk of developing drug fever. All medications should be reviewed, and when possible, medications should be discontinued or changed.

Another cause of persistent low-grade fever is undrained collections of blood. These collections can be identified by CT scan. Generally, they do not require drainage, but they take time to fully resorb.

Fever in the ICU patient requires a systematic diagnostic approach and the judicious use of antibiotics. Too often, patients are covered unnecessarily for prolonged periods using broad-spectrum antibiotics. This condition leads to the selection of highly resistant bacterial pathogens, and it also predisposes the patient to candidemia and *Clostridium difficile* colitis.

Empiric antibiotic coverage needs to be streamlined once culture data are available. Close communication between the ICU staff and the infectious disease consultant is critical to achieve the best care for the febrile ICU patient.

### FURTHER READING


POTENTIAL SEVERITY

Acute pneumonia is a potentially life-threatening illness requiring rapid diagnosis and treatment. A delay in antibiotic treatment increases the risk of a fatal outcome.

GENERAL CONSIDERATIONS IN ACUTE PNEUMONIA

Prevalence

Annually, 2 to 3 million cases of pneumonia are reported in the United States. Estimates suggest that pneumonia is responsible for more than 10 million physician visits, 500,000 hospitalizations, and 45,000 deaths annually. Overall, 258 people per 100,000 population require hospitalization for pneumonia, and that number rises to 962 per 100,000 among those over the age of 65 years. It is estimated that, annually, 1 in 50 people over 65 years of age and 1 in 20 over 85 years will develop a pneumonia. Pneumonia occurs most commonly during the winter months.

Causes

Improved diagnostic techniques have shown that the number of pathogens that cause acute pneumonia is ever expanding (Table 4.1).

The leading cause of acute community-acquired pneumonia remains *Streptococcus pneumoniae*, followed by *Haemophilus influenzae*. *Mycoplasma* and *Chlamydia*
pneumoniae also account for a significant percentage of acute pneumonias. Staphylococcus aureus is an unusual community-acquired pathogen, but it can cause ventilator associated pneumonia. Gram-negative bacteria other than H. influenzae are also an uncommon cause of community-acquired pneumonia except in patients with underlying lung disease or alcoholism. Gram-negative pneumonia most commonly develops in hospitals or nursing homes. Legionella species vary in importance, depending on the season and geographic area. Anaerobes such as anaerobic streptococci and bacteroids can cause acute pneumonia following aspiration of mouth contents. Common viral pathogens include influenza, parainfluenza, and respiratory syncytial virus.

**Pathogenesis and Pathology**

Under normal conditions, the tracheobronchial tree is sterile. The respiratory tract has a series of protective mechanisms that prevent pathogens from gaining entry [Figure 4.1(A)]:

1. The nasal passages contain turbinates and hairs that trap foreign particles.
2. The epiglottis covers the trachea and prevents secretions or food from entering the trachea.
3. The tracheobronchial tree contains cells that secrete mucin. Mucin contains a number of antibacterial compounds including immunoglobulin A antibodies, defensins, lysozymes, and lactoferrin. Mucin also is sticky, and it traps bacteria or other foreign particles that manage to pass the epiglottis.
4. Cilia lining the inner walls of the trachea and bronchi beat rapidly, acting as a conveyor belt to move mucin out of the tracheobronchial tree to the larynx.
5. When significant volumes of fluid or large particles gain access to the trachea, the cough reflex is activated, and the unwanted contents are quickly forced out of the tracheobronchial tree.
6. If pathogens are able to bypass all of the above protective mechanisms and gain entry into the alveoli, they encounter a space that, under normal circumstances, is dry and relatively inhospitable. The presence of an invading pathogen induces the entry of neutrophils and alveolar macrophages that ingest and kill infecting organisms. Immunoglobulins and complement are found in this space. Surfactants also have a protective function.
7. The lymphatic channels adjacent to the alveoli serve to drain this space and transport fluid, macrophages, and lymphocytes to the mediastinal lymph nodes.

Bacterial pathogens usually gain entry into the lung by aspiration of mouth flora or by inhalation of small aerosolized droplets (<3 µm in diameter) that can be transported by airflow to the alveoli. Once the pathogen takes hold, a series of inflammatory responses is triggered. These responses have been most carefully studied in pneumonia attributable to S. pneumoniae.

![Figure 4-1. A. Host defense in the respiratory tract. B. Factors that interfere with host defense of the respiratory tract.](image-url)
First, an outpouring of edema fluid into the alveoli occurs, serving as an excellent culture media for further bacterial growth. As fluid accumulates, it spills over to adjacent alveoli through the pores of Kohn and the terminal bronchioles, resulting in a centrifugal spread of infection. Coughing and the physical motion of respiration further enhance spread.

Next, polymorphonuclear leukocytes (PMNs) and some red blood cells begin to accumulate in the alveolar space. Eventually, they fill the region and form a zone of consolidation.

Macrophages then enter the lesions and assist the PMNs in clearing the infection. Histopathology reveals zones of varying age. The most distal regions represent the most recent areas of infection. There, edema fluid, PMNs, and red blood cells predominant. On lower power microscopy, this region has an appearance similar to the architecture of the liver—an effect termed “red hepatization.” Older central regions have more densely packed PMNs and macrophages. This region has a grayer color and forms the zone of “gray hepatization.”

Pulmonary pathogens demonstrate marked differences in their invasiveness and ability to destroy lung parenchyma. *S. pneumoniae* causes minimal tissue necrosis and is associated with little or no scar formation. Full recovery of pulmonary function is the rule. *S. aureus* releases a number of proteases that permanently destroy tissue. Gram-negative rods and anaerobic bacteria also cause permanent tissue destruction.

**Predisposing Factors**

Most bacterial pneumonias are preceded by a viral upper respiratory infection [Figure 4.1(B)]. Influenza virus is well known to predispose to *S. pneumoniae* and *S. aureus* pneumonia. Viral infections of the upper respiratory tract can damage the bronchial epithelium and cilia.

Virus-mediated cell damage also results in the production of serous fluid that can pool in the pulmonary alveoli, serving as an excellent culture media for bacteria. The low viscosity of this fluid, combined with depressed ciliary motility, enables the viral exudate to carry nasopharyngeal bacteria past the epiglottis into the lungs. Smoking also damages the bronchial epithelial cells and impairs mucociliary function. As a consequence, smokers have an increased risk of developing pneumonia. Congenital defects in ciliary function (such as Kartagener’s syndrome) and diseases resulting in highly viscous mucous (such as cystic fibrosis) predispose patients to recurrent pneumonia.

An active cough and normal epiglottal function usually prevent nasopharyngeal contents from gaining access to the tracheobronchial tree. However, drugs such as alcohol, sedatives, and anesthetics can depress the level of consciousness and impair these functions, predisposing the patient to pneumonia. Elderly individuals, particularly after a cerebrovascular accident, often develop impairments in swallowing that predispose them to aspiration. In addition, elderly people demonstrate reduced humoral and cell-mediated immunity, rendering them more susceptible to viral and bacterial pneumonia.
Patients with impairments in immunoglobulin production, T- and B-cell function, and neutrophil and macrophage function are also at greater risk for developing pneumonia. Organ-transplant patients on immunosuppressive agents and AIDS patients have a greater likelihood of developing pneumonia. Chronic diseases, including multiple myeloma, diabetes, chronic renal failure, and sickle cell disease have been associated with an increased risk of pneumonia.

Cold weather is thought to contribute to the development of pneumonia. Cold, dry weather can alter the viscosity of mucous and impair bacterial clearance. Cold weather also encourages people to remain indoors, a situation that enhances person-to-person spread of respiratory infections.

**Symptoms and Signs**

**CASE 4.1**

A 55-year-old woman was first seen in the emergency room in December complaining of a nonproductive cough, nasal stuffiness, and fever. She also noted diffuse severe muscle aches and joint pains and a generalized headache. In her epidemiologic history, she noted that she had recently seen her grandchildren, who all had high fevers and were complaining of muscle aches.

**Figure 4–2.** Pneumococcal pneumonia: A. Chest radiograph demonstrates classical lobar infiltrate (Courtesy of Dr. Pat Abbitt, University of Florida); and B. sputum Gram stain shows *Streptococcus pneumoniae*. Note that the cocci come to a slight point, explaining the term “lancet-shaped.” See color image on color plate 1
and 4% monocytes. Sputum Gram stain showed many gram-positive lancet-shaped diplococci, many PMNs (>10/high-power field), and no squamous epithelial cells. A CXR revealed a dense left lower lobe and lobar infiltrate (Figure 4.2).

In case 4.1, the patient’s initial symptoms suggested a viral illness involving the upper respiratory tract (rhinitis and nonproductive cough); central nervous system (CNS) or air sinuses, or both (headache); and musculoskeletal system (myalgias and arthralgias). Such symptoms are generally attributed to an influenza-like illness. A number of viruses can explain these symptoms, including influenza, parainfluenza, adenovirus, respiratory syncytial virus (more common in children, but also found in elderly individuals and transplant patients), rhinoviruses (usually less severe), and enteroviruses.

Subsequently, within a 24-hour period, this patient experienced the abrupt onset of a new constellation of symptoms. The onset of the new illness can be classified as acute. An illness is termed “acute” when symptoms and signs develop over 24 to 48 hours. Symptoms that develop over 3 days to 1 week are generally classified as subacute, and symptoms that progress more slowly (over 3 weeks to several months) are classified as chronic.

In generating a potential list of causative agents, the infectious disease specialist frequently uses the pace of the illness to narrow the possibilities. Pneumonias are generally classified into two groups: acute and chronic. Most bacterial and viral pneumonias develop quickly; fungal and mycobacterial pulmonary infections tend to develop at a slower pace. Acute pneumonia can be further classified as “typical” or “atypical.” Typical pneumonia is characterized by the more rapid onset of symptoms, more severe symptomatology, a productive cough, and dense consolidation on CXR, as observed in case 4.1. Atypical pneumonia tends to be slower in onset (often subacute), symptoms tend to be less severe, cough is productive of minimal sputum, and CXR usually reveals a patchy or interstitial pattern. Finally, pulmonary infections are separated into community-acquired or nosocomial. “Community-acquired” is defined as an infection developing in a patient who has not recently (>14 days) been hospitalized or resided in a chronic care facility.

Although considerable overlap in symptoms, signs, and CXR findings are observed in cases of acute community-acquired pneumonia, certain key clinical characteristics are helpful in guiding the determination of the most likely causes (Table 4.2). Generation of a logical differential list of potential pathogens guides the choice of diagnostic tests and narrows the possible treatment regimens.

Important symptoms that need to be reviewed include these:

1. **Cough.** Frequency of the cough, production of sputum, and color of the sputum should be documented. A nonproductive cough or a cough productive of scanty sputum suggests an atypical pneumonia; a cough productive of rusty-colored sputum raises the possibility of *S. pneumoniae*. Thick, “red current jelly” sputum has been reported in cases of *Klebsiella pneumoniae*, green-colored sputum is more frequently encountered in patients with *H. influenzae* and *Pseudomonas aeruginosa* pneumonia (typically a nosocomial pathogen, or found in patients cystic fibrosis). Frank hemoptysis is observed in cavitary tuberculosis, lung abscess, and lung carcinoma. It should be emphasized that considerable overlap occurs in the sputum characteristics of the various forms of pneumonia, and these observations cannot be considered specific.

2. **Chest discomfort.** Pleuritic chest pain (pain associated with deep inspiration) is classically described in patients with *S. pneumoniae*. Pain is usually sharp and stabbing. Because the pulmonary parenchyma has no pain-sensing nerves, the presence of chest pain indicates inflammation of the parietal pleura. When the diaphragm becomes inflamed, the pain can mimic cholecystitis or appendicitis, and on occasion this sort of pain has precipitated exploratory laparotomy. Anaerobes, *S. pyogenes*, and *S. aureus* are
other pathogens that can also spread to the pleura and cause chest pain. Pleuritic pain is also characteristic of pleurodynia, a pain syndrome caused by the enteroviruses coxsackievirus and echovirus.

3. **Rigor.** Mild chills are encountered in most febrile illnesses. However, a teeth-chattering, bed-shaking chill indicative of a true rigor is usually associated with bacteremia. This symptom is very prominent, and patients often can report the exact time of their first rigor. A single rigor is the rule in *Streptococcus pneumoniae* infection; multiple rigors are more typical of *S. aureus*, anaerobes, *Klebsiella* species, and *S. pyogenes*. *H. influenzae* seldom causes rigors.

4. **Shortness of breath.** A report of increased shortness of breath suggests poor alveolar oxygen exchange, indicative of severe infection. Some patients experience shortness of breath as a result of pleuritic chest pain that limits the ability to breathe deeply. To avoid pain, patients may breath quickly and shallowly, and this breathing pattern may be interpreted as shortness of breath.

5. **Epidemiology.** A careful epidemiologic history is often helpful. A number of environmental factors predispose to pneumonia. Animal exposure must be carefully reviewed, including contact with wild game, birds, bats, and rodents (see Chapter 13). Exposure to outside air conditioning units or construction sites should be identified (legionnaires’ disease). Travel history may be helpful. For example, travel to the Southwest raises concerns about coccidiomycosis, and travel to the Ohio River valley raises the possibility of histoplasmosis. Because many respiratory illnesses spread from person to person, a history of exposure to family members or friends with illnesses should be ascertained. Occupational and sexual history should also be elicited.

---

Table 4.2. Clinical Characteristics of Acute Community-Acquired Pneumonia Classified by Cause

<table>
<thead>
<tr>
<th>Causative agent</th>
<th>Classical symptoms</th>
<th>Typical radiographic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Rusty-colored sputum, rigor, pleuritic chest pain</td>
<td>Lobar infiltrate, air bronchograms</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>More gradual onset; seen in smokers with COPD</td>
<td>Lobar or patchy infiltrates</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Follows influenza pneumonia, rapidly progressive acute disease</td>
<td>Bronchopneumonia, lung abscess, pneumothorax, and empyema</td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
<td>Follows from loss of consciousness, poor gag reflex, abnormal swallowing; foul-smelling sputum</td>
<td>Dense consolidation (more in the right lower lobe than in the left lower lobe, or in posterior segment of upper lobes); later, lung abscess and empyema</td>
</tr>
<tr>
<td><em>Legionella pneumophila</em></td>
<td>Nonproductive cough, gastrointestinal symptoms, confusion</td>
<td>Lobar pneumonia, cavities in immunocompromised patients</td>
</tr>
<tr>
<td>Atypical pneumonia</td>
<td>Mild-to-moderate symptoms, nonproductive cough, pulmonary exam often normal</td>
<td>Patchy lower lobe bronchopneumonia</td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease.

---

KEY POINTS

**About the History in Pneumonia**

1. **Cough.** Frequency, production of sputum, color and thickness of sputum.
2. **Chest pain.** Pain on deep inspiration, usually sharp, suggests pleural involvement. Seen in *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Streptococcus pyogenes*, anaerobes, and coxsackievirus and echovirus.
3. **Rigor.** Bed-shaking chills, 1 rigor in *S. pneumoniae*, more than 1 in *S. aureus*, *Klebsiella* spp., *S. pyogenes*, and anaerobes.
4. **Shortness of breath.** A worrisome symptom, may be the result of pleuritic chest pain rather than poor gas exchange.
5. **Epidemiology.** Travel history, animal exposure, exposure to people with respiratory illnesses, occupational and sexual history.
KEY POINTS

**About the Physical Exam in Pneumonia**

1. A respiratory rate >30/min, a blood pressure <90 mm Hg, a pulse >125/min, and a temperature <35°C or >40°C are bad prognostic findings.
2. Depressed mental status and stiff neck suggest bacterial meningitis.
3. Pulmonary auscultation often underestimates the extent of pneumonia:
   a) Bronchial breath sounds and egophony suggest consolidation.
   b) Dullness to percussion indicates consolidation or a pleural effusion.
   c) Pleural effusion is accompanied by decreased breath sounds and, in some cases, a friction rub.

A thorough physical examination should be performed during the initial evaluation for possible pneumonia. Vital signs are helpful in determining the severity of illness. A respiratory rate of more than 30 breaths per minute, a systolic blood pressure under 90 mm Hg, a pulse above 125 beats per minute, and a temperature below 35°C (95°F) or above 40°C (104°F) are all bad prognostic signs. Depressed mental status is also associated with a poor prognosis.

Ear, nose, and throat examination may reveal vesicular or crusted lesions consistent with Herpes labialis, an infection that may reactivate as a consequence of the stress of the primary illness. Neck stiffness in association with depressed mental status may indicate the development of bacterial meningitis, a potential complication of pneumococcal pneumonia.

Pulmonary auscultation often fails to detect the extent of infection, and when pneumonia is being considered, the physical exam should be followed by a CXR. Asymmetry of chest movements may be observed, movement being diminished on the side with the pneumonia. When infection has progressed to consolidation, as in case 4.1, filling of the lung parenchyma with exudate alters sound conduction. Air flow from the bronchi is conducted through this fluid to the chest wall, resulting in bronchial or tubular breath sounds. When the patient is asked to say “E,” an “A” is heard on auscultation (egophony). Percussion of the chest wall also demonstrates dullness in the areas of consolidation. Dullness to percussion in association with decreased breath sounds suggests the presence of a pleural effusion. A “leathery” friction rub may be heard over the site of consolidation, indicating pleural inflammation.

### Laboratory Findings

Physical examination is unreliable for making the diagnosis of pneumonia. If pneumonia is a potential diagnosis, CXR must be performed to confirm or exclude the disease. The radiologic pattern can serve as a rough guideline to possible causative agents; however, the use of immunosuppressive agents (resulting in neutropenia, decreased cell-mediated immunity, and depressed macrophage function) can greatly alter the typical radiologic appearance of specific pathogens. Patients with AIDS also present with atypical CXR.

Five classical patterns have been described:

1. **Lobar pneumonia.** “Lobular pneumonia” refers to a homogeneous radiologic density that involves a distinct anatomic segment of the lung (Figure 4.2). Infection originates in the alveoli. As it spreads, this form of infection respects the anatomic boundaries of the lung and does not cross the fissures. Lobar pneumonia is most commonly seen with *S. pneumoniae, H. influenzae, and Legionella.*

2. **Bronchopneumonia.** The bronchopneumonia form of pulmonary infection originates in the small airways and spreads to adjacent areas (Figure 4.3). Infiltrates tend to be patchy, to involve multiple areas of the lung, and to extend along bronchi. Infiltrates are not confined by the pulmonary fissures. Bronchopneumonia is commonly observed with *S. aureus,* gram-negative bacilli, *Mycoplasma, Chlamydia,* and respiratory viruses.

3. **Interstitial pneumonia.** Infections causing inflammation of the lung interstitium result in a fine diffuse granular infiltrate (Figure 17.2). Influenza and cytomegalovirus commonly present with this CXR pattern. In AIDS patients, *Pneumocystis jirovecii* infection results in interstitial inflammation combined with increased alveolar fluid that can mimic cardiogenic pulmonary edema. Miliary tuberculosis commonly presents with micronodular interstitial infiltrates.

4. **Lung abscess.** Anaerobic pulmonary infections often cause extensive tissue necrosis, resulting in loss of lung tissue and formation of cavities filled with inflammatory exudate (Figure 4.4). *S. aureus* also causes tissue necrosis and can form cavitory lesions.

5. **Nodular lesions.** Histoplasmosis, coccidioidomycosis, and cryptococcosis can present as nodular lung lesions (multiple or single) on CXR. Hematogenous pneumonia resulting from right-sided endocarditis commonly presents with “cannonball” lesions that can mimic metastatic carcinoma.
The role of high-resolution chest CT scan is evolving, and this test has proved helpful for more clearly demonstrating interstitial infiltration, pulmonary cavities, nodules, and pleural fluid collections.

Patients with an infiltrate, who are under age 65, have a normal mental status, and normal or only mildly deranged vital signs can be treated as outpatients (Figure 4.5). Sputum Gram stain and culture are optional in these patients, as are any additional tests. In more severely ill patients who are being considered for hospitalization, additional tests to assess the severity of the illness need to be ordered.

A complete and differential blood cell count should be obtained. Patients with bacterial pneumonia usually have an elevated peripheral WBC count and a left shift. When pneumococcal pneumonia is accompanied by a low peripheral WBC count (<6000), a fatal outcome is more likely. The finding of anemia (hematocrit <30%), usually indicative of chronic underlying disease, is also associated with a worse prognosis.

Blood oxygenation also needs to be assessed. The $O_2$ saturation should be determined, and if it is at all depressed, an arterial blood gas should be obtained. Systemic acidosis (pH <7.35) and an arterial partial pressure below 60 mm Hg are bad prognostic signs. A significant depression in oxygenation reflects loss of alveolar function and lack of oxygen transfer to alveolar capillaries. Deoxygenated blood passes from the right side of the heart to the left side, creating a physiologic right-to-left shunt.

Other metabolic parameters also need to be assessed. A blood urea nitrogen level above 30 mg/dL reflects hypoperfusion of the kidneys or dehydration (or both) and is a negative prognostic finding. A serum sodium reading below 130 mEq/L reflects increased antidiuretic hormone secretion in response to decreased intravascular volume in addition to severe pulmonary disease. Such a reading is another negative prognostic finding, as is a serum glucose level exceeding 250 mg/dL. Two blood cultures should be drawn before antibiotics are started. Positive blood cultures definitively identify the cause of the disease. Blood cultures are positive in 1% to 16% of cases of community-acquired pneumonia.

Spumum requires careful analysis and frequently provides helpful clues to the probable diagnosis. Sputum samples often become contaminated with bacteria and cells from the nasopharynx, making interpretation of the cultures difficult. Ideally, acquisition of sputum should be supervised by a physician to ensure that the patient coughs deeply and brings up the sample from the tracheobronchial tree and does not simply expectorate saliva from the mouth. The adequacy of the sample should be determined by low-power microscopic analysis of the sputum Gram stain. The presence of more than 10 squamous epithelial cells per low-power field indicates significant contamination from the nasopharynx.

The CXR should always be performed. Radiographic patterns may be atypical in patients receiving immunosuppressants and in patients with AIDS. Five typical CXR patterns have been described:

a) **Lobar pattern.** *Streptococcus pneumoniae, Haemophilus influenzae, and Legionella.*

b) **Bronchopneumonia pattern.** *Staphylococcus aureus, gram-negative organisms, Mycoplasma, Chlamydia, and viral.*

c) **Interstitial pattern.** *Influenza and cytomegalovirus, Pneumocystis, miliary tuberculosis.*

d) **Lung abscess.** *Anaerobes, S. aureus.*

e) **Nodular lesions.** *Fungal (histoplasmosis, coccidiomycosis, cryptococcosis) and right-sided endocarditis.*

Patterns on chest radiographs are only rough guides. Considerable overlap between the various pathogens has been observed.

1. If pneumonia is being considered, a chest X-ray (CXR) should always be performed.
2. Radiographic patterns may be atypical in patients receiving immunosuppressants and in patients with AIDS.
3. Five typical CXR patterns have been described:
   a) **Lobar pattern.** *Streptococcus pneumoniae, Haemophilus influenzae, and Legionella.*
   b) **Bronchopneumonia pattern.** *Staphylococcus aureus, gram-negative organisms, Mycoplasma, Chlamydia, and viral.*
   c) **Interstitial pattern.** *Influenza and cytomegalovirus, Pneumocystis, miliary tuberculosis.*
   d) **Lung abscess.** *Anaerobes, S. aureus.*
   e) **Nodular lesions.** *Fungal (histoplasmosis, coccidiomycosis, cryptococcosis) and right-sided endocarditis.*
4. Patterns on chest radiographs are only rough guides. Considerable overlap between the various pathogens has been observed.

**KEY POINTS**

**About Chest X-Ray in Pneumonia**

1. With the exception of patients under the age of 50 years, without underlying disease, and with normal vital signs, multiple blood tests are used to assess the severity of disease.
2. A peripheral white blood cell count below 6000/mm³ in *Streptococcus pneumoniae* is a bad prognostic finding.
3. Anemia (hematocrit <30%), blood urea nitrogen above 30 mg/dL, serum sodium below 130 mEq/L, and glucose above 250 mg/dL are associated with a worse prognosis.
4. Arterial blood $O_2$ below 60 mm Hg and pH below 7.35 worsen prognosis.
5. Two blood samples should be drawn before antibiotics are stated; blood cultures are positive in up to 16% of patients.

**KEY POINTS**

**About Blood Tests in Pneumonia**
ynx, and the sample should be discarded. The presence of more than 25 PMNs per low-power field and the presence of bronchial epithelial cells provide strong evidence that the sample originates from the tracheobronchial tree.

Despite originating from deep within the lungs, sputum samples usually become contaminated with some normal throat flora as they pass through the nasopharynx. Gram stain can be helpful in differentiating normal flora (mixed gram-positive and gram-negative rods and cocci) from the offending pathogen. When a single bacterial type predominates, that bacterium is likely to be the primary pathogen. For example, the presence of more than 10 lancet-shaped gram-positive diplococci per high-power field provides strong evidence that *S. pneumoniae* is the cause of the pneumonia (approximately 85% specificity and 65% sensitivity, Figure 4.2).

In reviewing bacterial morphology, the observer must assess the adequacy of decolorization. In ideally stained regions, the nucleus and cytoplasm should be gram-negative, and a mixture of gram-positive and gram-negative organisms should be seen. A gram-positive nucleus indicates underdecolorization, and the presence of gram-negative bacteria only (including cocci) suggests overdecolorization.

Sputum Gram stain is also helpful for assessing the inflammatory response. The presence of many PMNs suggests a bacterial cause for the disease; a predominance of mononuclear cells is more consistent with *Mycoplasma, Chlamydia*, or a viral infection.

Sputum culture is less helpful than Gram stain, because normal flora contaminating the sample frequently overgrow, preventing identification of the true pathogen. To reduce overgrowth, samples should be quickly inoculated onto culture media. Rapid processing has been shown to increase the yield for *S. pneumoniae*. Sputum cultures are falsely negative approximately half the time. Because of the potential problems with sampling error, and the inability to accurately quantify bacteria by standard culture, sputum should never be cultured in the absence of an accompanying Gram stain.

Culture is most helpful in determining the antibiotic sensitivities of potential pathogens. The combination of sputum Gram stain and antibiotic sensitivity testing may allow the clinician to narrow the spectrum of antibiotic coverage, reducing the likelihood of selecting for highly resistant pathogens. In the intubated patient, sputum culture alone should never be the basis for initiating antibiotic therapy. Sputum culture will almost always be positive, a result that often simply represents colonization and not true infection (see Chapter 1).

Additional methods for sputum analysis are being developed. Polymerase chain reaction (PCR) is being used to amplify specific strands of DNA from pathogens. This method will be particularly helpful in identifying organisms that are not normally part of the mouth flora and that are difficult to culture: *L. pneumophila, Mycoplasma pneumoniae, Chlamydia pneumoniae*, and *P. jirovecii*.

When *Legionella* pneumonia is a consideration (see specific discussion later in this chapter), urinary antigen for *L. pneumophila* serogroup 1 (the most common pathogenic serogroup) should be performed. This test is moderately sensitive and highly specific. A positive test is therefore diagnostic; a negative test does not exclude the diagnosis, however. A urinary antigen test for *S. pneumoniae* is also available and is recommended as potentially useful in adults (80% sensitivity for bacteremic pneumonia).
patients, 97% specificity). This test is frequently positive in children colonized with *S. pneumoniae*, and is therefore not recommended for that patient population.

More invasive procedures are usually not required in community-acquired pneumonia, but may be considered in the severely ill patient when an adequate sputum sample cannot be obtained. Invasive procedures such as fiberoptic bronchoscopy with protected brushing or lavage are more commonly required in the immunocompromised patient (see Chapter 16). The sheath surrounding the brush reduces, but does not eliminate, contamination by mouth flora.

Quantitative cultures are required to differentiate infection from contamination, with growth of more than $10^3$ to $10^4$ organisms per milliliter indicating infection. Lavage of a lung segment with sterile fluid samples a larger volume of lung and is particularly useful for diagnosing *P. jirovecii* pneumonia in AIDS patients (see Chapter 17). Bronchoscopy has been shown to be useful in diagnosing not only *P. jirovecii*, but also mycobacterial infections and cytomegalovirus.

The use of bronchial lavage to assist in the diagnosis of ventilator-associated pneumonia (VAP) is controversial. Contamination of samples by organisms colonizing the endotracheal tube can result in misinterpretation of the quantitative cultures. As compared to samples derived from endotracheal suction, samples obtained by bronchoscopy offer no benefit in regard to morbidity, mortality, or reduction in antibiotic use in VAP.

**DECIDING ON HOSPITAL ADMISSION IN ACUTE PNEUMONIA**

The Pneumonia Patient Outcome Research Team developed useful criteria called the pneumonia severity index (PSI) for assessing pneumonia severity; however, that index proved to be complex and difficult to use. A simpler index called the CURB-65 (confusion, urea nitrogen, respiratory rate, blood pressure, age 65 years or older) has been shown to have sensitivity and specificity nearly equal to that of the PSI. Both indexes can be used to guide decisions on admission to a hospital ward or intensive care unit. As shown in Figure 4.5, patients with a score of 0 or 1 can be treated as outpatients; those with a score of 2 or more warrant hospitalization. A patient with a score of 4 to 5 generally requires placement in an intensive care unit.

**Empiric Treatment**

The mainstay of treatment is administration of antibiotics (Table 4.3). Antibiotic treatment should not be delayed because of difficulties with sputum collection. Therapy should be started within 4 hours of diagnosis. Delays beyond this period have been associated with increased mortality.

In patients requiring hospitalization for acute community-acquired pneumonia, cefotaxime or ceftriaxone (covers *S. pneumoniae*, *H. influenzae*, *S. aureus*, *Klebsiella* spp, some gram-negative organisms, and aerobic mouth flora), combined with an advanced macrolide [azithromycin or clarithromycin (covers *Legionella*, *Mycoplasma*, *Chlamydia*)] is recommended for empiric therapy. If aspiration pneumonia is suspected, metronidazole can be added.

In ambulatory patients, either a macrolide in the form of azithromycin or clarithromycin, or a respiratory fluoroquinolone (gatifloxacin, moxifloxacin, or levofloxacin) possessing good gram-positive activity is considered efficacious. Concerns have been raised about the development of resistance to fluoroquinolones, and many experts recommend that this class of antibiotics be reserved for older patients with underlying disease. These patients are not only exposed to the standard causes of community-acquired pneumonia, they also experience an increased incidence of gram-negative bacilli that will be covered by those agents.

The appropriate duration of treatment has not been systematically studied. For *S. pneumoniae*, patients are generally treated for 72 hours after they become afebrile. For infections with bacteria that cause necrosis of lung (*S. aureus*, *Klebsiella*, and anaerobes), therapy should probably be continued for more than 2 weeks. Treatment for 2 weeks is generally recommended for *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* in the immunocompetent patient. Patients on intravenous antibiotics can generally be switched to oral antibiotics when their clinical condition is improving, they are hemodynamically stable, their gastrointestinal tract is functioning normally, and they are capable of taking medications by mouth. In many cases, those criteria are met within 3 days. When possible, the oral antibiotic should be of the same antibiotic class as the intravenous preparation. If staying within the class is not possible, then the oral agent should have a spectrum of activity similar to that of the intravenous agent.

Response to treatment can be assessed by monitoring temperature, respiratory rate, PaO$_2$ and oxygen saturation, peripheral white blood cell count, and frequency of cough. The changes seen on CXR often persist for several weeks despite clinical improvement. Although CXR is not helpful for assessing improvement, conventional films can be combined with pulmonary CT scan to assess the development of complications such as pneumothorax, cavititation, empyema, and adult respiratory distress syndrome (ARDS), and to document continued progression of infiltrates despite therapy.
### Table 4.3. Empiric Treatment of Pneumonia, Infectious Diseases Society of America, 2003

<table>
<thead>
<tr>
<th>Disease characteristics</th>
<th>Drug</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Community-acquired pneumonia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No comorbidity, no previous antibiotics, outpatient</td>
<td>Clarithromycin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>500 mg PO q12h</td>
<td>Low serum levels, high levels in macrophages, preferred for <em>Haemophilus influenzae</em></td>
</tr>
<tr>
<td></td>
<td>Azithromycin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>500 mg PO, followed by 250 mg PO q24h</td>
<td>Gastrointestinal toxicity is common</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td>500 mg q6h</td>
<td>Bacteriostatic agent</td>
</tr>
<tr>
<td></td>
<td>Doxycycline</td>
<td>100 mg PO q12h</td>
<td></td>
</tr>
<tr>
<td>No comorbidity, previous antibiotics, or nursing home resident</td>
<td>Clarithromycin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>500 mg PO q12h</td>
<td>Low serum levels, high levels in macrophages, preferred for <em>Haemophilus influenzae</em></td>
</tr>
<tr>
<td></td>
<td>Azithromycin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>500 mg PO q12h</td>
<td>Gastrointestinal toxicity is common</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td>500 mg q6h</td>
<td>Bacteriostatic agent</td>
</tr>
<tr>
<td></td>
<td>Doxycycline</td>
<td>100 mg PO q12h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gatifloxacin</td>
<td>400 mg PO q24h</td>
<td>Levofoxacin-resistant <em>Streptococcus pneumoniae</em> reported in Canada</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin</td>
<td>500 mg PO q24h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>400 mg PO q24h</td>
<td></td>
</tr>
<tr>
<td>No comorbidity, advanced macrolide, plus β-lactam antibiotic, aspiration suspected</td>
<td>Cefuroxime axetil</td>
<td>500 mg PO q12h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cefpodoxime</td>
<td>400 mg PO q12h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cefprozil</td>
<td>500 mg PO q12h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amoxicillin–clavulanate</td>
<td>2 g PO q12h</td>
<td>If aspiration suspected, amoxicillin or amoxicillin–clavulanate recommended.</td>
</tr>
<tr>
<td><strong>Comorbidity</strong></td>
<td>Advanced macrolide</td>
<td>Doses as above</td>
<td>Regimen depends on the previous antibiotic</td>
</tr>
<tr>
<td>(CHF, COPD, DM, cancer, renal disease)</td>
<td>Respiratory fluoroquinolone</td>
<td>Doses as above</td>
<td></td>
</tr>
<tr>
<td>Inpatient, medical ward</td>
<td>Clarithromycin or azithromycin</td>
<td>500 mg IV q24h</td>
<td></td>
</tr>
<tr>
<td>No recent antibiotics</td>
<td>Ceftriaxone or cefotaxime</td>
<td>1 g IV or IM q24h</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inpatient, medical ward</td>
<td>Advanced macrolide</td>
<td>Doses as above</td>
<td></td>
</tr>
<tr>
<td>Recent antibiotics</td>
<td>Respiratory fluoroquinolone</td>
<td>Doses as above</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Respiratory fluoroquinolone</td>
<td>Doses as above</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clarithromycin or azithromycin, plus ceftriaxone or cefotaxime</td>
<td>1 g IV q8h</td>
<td></td>
</tr>
<tr>
<td>Inpatient, ICU</td>
<td>Advanced macrolide, plus β-lactam antibiotic (preferred) or respiratory fluoroquinolone</td>
<td>Doses as above</td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas</em> not an issue</td>
<td>IV β-lactam antibiotic, plus advanced macrolide or respiratory fluoroquinolone</td>
<td>Doses as above</td>
<td></td>
</tr>
</tbody>
</table>

Continued
CHAPTER 4

Inpatient, ICU

Piperacillin–tazobactam 4 g/0.5 g IV q6h
or
imipenem 0.5–1 g IV q6h
or
meropenem 1 g IV q8h
or
cefepime 1–2 g IV q8h

Aspiration pneumonia

<table>
<thead>
<tr>
<th>Disease characteristics</th>
<th>Drug</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient, ICU</td>
<td>Piperacillin–tazobactam</td>
<td>4 g/0.5 g IV q6h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>imipenem</td>
<td>0.5–1 g IV q6h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>meropenem</td>
<td>1 g IV q8h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>cefepime</td>
<td>1–2 g IV q8h</td>
<td></td>
</tr>
<tr>
<td>Community</td>
<td>Penicillin G</td>
<td>2 ( \times 10^6 ) U IV q4h</td>
<td>Covers usual mouth flora</td>
</tr>
<tr>
<td></td>
<td>Clindamycin</td>
<td>600 mg IV q8h</td>
<td>Slightly more effective than penicillin for lung abscess</td>
</tr>
<tr>
<td>In hospital</td>
<td>Ceftriaxone</td>
<td>1 g IV q24h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>plus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>metronidazole</td>
<td>500 mg IV q8h</td>
<td>Doses as above</td>
</tr>
<tr>
<td></td>
<td>Respiratory fluoroquinolone</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>plus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>metronidazole</td>
<td>500 mg IV q8h</td>
<td>Regimen used by the author</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Piperacillin–tazobactam</td>
<td>3 g/0.375 g IV q6h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ticarcillin–clavulanate</td>
<td>3.1 g IV q4–6h</td>
<td>Requires a large fluid load</td>
</tr>
</tbody>
</table>

\(^a\) Advanced macrolides.

CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; ICU = intensive care unit.

Outcome

In the United States, 45,000 deaths are attributed to pneumonia annually. In hospitalized patients, overall mortality ranges from 2% to 30%. Mortality from pneumonia and influenza is particularly high in individuals over the age of 65 years, causing 150 to 250 deaths per 100,000 population annually. Mortality is also higher in individuals with underlying diseases. Five comorbid illnesses have been identified that result in statistically significant increases in mortality:

- Neoplastic disease
- Cerebrovascular disease
- Liver disease
- Renal disease
- Congestive heart failure

SPECIFIC CAUSES OF ACUTE COMMUNITY-ACQUIRED PNEUMONIA

Great overlap occurs among the clinical manifestations of the pathogens associated with acute community-acquired pneumonia. However, constellations of symptoms, signs, and laboratory findings serve to narrow the possibilities. By developing an ability to focus on a few pathogens or to identify a specific pathogen, clinicians can better predict the clinical course of pneumonia and can narrow antibiotic coverage.

Streptococcus pneumoniae

Pathogenesis

Pathogenic strains of *S. pneumoniae* have a thick capsule that prevents PMN binding and that blocks phagocytosis. Certain capsular types (1, 3, 4, 7, 8, and 12 in adults, and 3, 6, 14, 18, 19, and 23 in children) account for most pneumonia cases. Type 3 has the thickest polysaccharide capsule, and it is the most virulent strain, being associated with the worst prognosis. Immunoglobulins that specifically recognize the capsule are able to link the bacterium to the PMN surface through Fc receptors, enabling PMNs and macrophages (classified as phagocytes) to efficiently ingest and kill the pneumococci. The complement product C3b enhances phagocytosis of the bacteria by the same mechanism. Immunoglobulins and C3b are called “opsonins,” which are products that enhance foreign particle ingestion by phagocytes.

In addition to its polysaccharide capsule, *S. pneumoniae* possesses a number of other virulence factors that enhance adherence to epithelial cells, resist phagocytosis,
and activate complement. *S. pneumoniae* does not produce significant quantities of proteases, and disease manifestations are primarily the consequence of the host’s inflammatory response. As a result, permanent tissue damage is rare, and spread of the disease across anatomic boundaries, such as lung fissures, is uncommon.

### Prevalence and Predisposing Factors

*S. pneumoniae* remains the most common cause of acute community-acquired pneumonia; it represents two thirds of the cases in which a specific pathogen is identified. Because opsonins are required for efficient phagocytosis of the encapsulated organism, patients with hypogammaglobulinemia and multiple myeloma are at increased risk for developing this infection, as are patients with deficiencies in complement (C1, C2, C3, C4). Patients with HIV infection also have defects in antibody production, and they have a higher incidence of pneumococcal infection. Patients with splenic dysfunction increases the risk of fatal pneumococcal bacteremia.

### Key Points

#### About Treatment and Outcome of Pneumonia

1. Treatment must be instituted within 4 hours of diagnosis.
2. Delays are associated with increased mortality.
3. Appropriate triage should be guided by the CURB-65 classification.
4. Empiric therapy depends on the patient and disease characteristics:
   a) **Outpatient with no comorbidity and no previous antibiotics.** Use a macrolide (azithromycin or clarithromycin). If previous antibiotics or elderly nursing home patient, add a β-lactam antibiotic, or use a respiratory fluoroquinolone.
   b) **Hospitalized patient.** Use a 3rd-generation cephalosporin (ceftriaxone or cefotaxime) combined with a macrolide (azithromycin or clarithromycin). If *Pseudomonas* is a concern, use piperacillin–tazobactam, imipenem, or meropenem.
   c) **Aspiration outpatient.** Use penicillin or clindamycin.
   d) **Aspiration inpatient.** Use a 3rd-generation cephalosporin or a respiratory fluoroquinolone plus metronidazole; or use ticarcillin–clavulanate or piperacillin–tazobactam.
5. Using chest radiographs to monitor improvement is not recommended. (They can take several weeks to clear.) They are useful for documenting worsening of disease or development of complications.
6. Mortality ranges from 2% to 30%. Mortality higher with age more than 65 years, neoplastic disease, liver disease, congestive heart failure, cerebrovascular accident, and renal disease.

#### About the Pathogenesis of *Streptococcus pneumoniae*

1. The thick outer capsule blocks phagocytosis. Type 3 has the thickest capsule.
2. Immunoglobulins and complement are important opsonins that allow phagocytes to ingest invading pneumococci.
3. *Strep. pneumoniae* does not produce protease and seldom destroys lung parenchyma.
4. It does not cross anatomic barriers such as lung fissures.
5. Disease manifestations are caused primarily by the host’s inflammatory response to the organism.

#### About *Streptococcus pneumoniae* Prevalence and Predisposing Factors

1. *S. pneumoniae* is the most common form of community-acquired bacterial pneumonia.
2. The risk is higher in patients with deficiencies in opsonin production:
   a) Hypogammaglobulinemia
   b) Complement deficiency
   c) HIV infection
3. Splenic dysfunction increases the risk of fatal pneumococcal bacteremia.
4. Risk is increased in patients with chronic diseases:
   a) Cirrhosis
   b) Alcoholism
   c) Nephrotic syndrome
   d) Congestive heart failure
   e) Chronic obstructive pulmonary disease
dysfunction have a higher risk of overwhelming *S. pneumoniae* sepsis because the spleen plays a vital role in clearing this bacteria from the bloodstream, particularly in the absence of specific anti-pneumococcal capsule antibody. Other chronic diseases, including cirrhosis, nephrotic syndrome, congestive heart failure, chronic obstructive pulmonary disease, and alcoholism, are also associated with greater risk of pneumococcal infection.

**UNIQUE CLINICAL CHARACTERISTICS**

Classically, pneumococcal pneumonia has a very abrupt onset that begins with a single severe rigor. Because *S. pneumoniae* invasion of the lung leads to capillary leakage of blood into the alveolar space, sputum can become rusty in color. Furthermore, pneumococcal infection frequently infects the peripheral lung and spreads quickly to the pleura. As a result, pleuritic chest pain is a common complaint.

**DIAGNOSIS**

Sputum Gram Stain—A careful analysis of the sputum is best performed by a knowledgeable physician. Areas with significant numbers of PMNs per high-power field and a predominance of gram-positive lancet-shaped diplococci suggest the diagnosis [Figure 4.2(B)]. A finding of pneumococci within the cytoplasm of a PMN strongly supports invasive infection.

Sputum Culture—*S. pneumoniae* is catalase negative, bile soluble, and, like *S. viridans*, demonstrates alpha (green) hemolysis on blood agar plates. The propensity of normal mouth flora, in particular *S. viridans*, to overgrow frequently interferes with the identification of *S. pneumoniae*. The optochin disk inhibits growth of *S. pneumoniae*, but not of *S. viridans*, and this test is used to differentiate the two organisms. Another problem with sputum culture arises from the fact that *S. pneumoniae* can be present as normal mouth flora in up to 60% of healthy people. A positive sputum culture in the absence of a positive Gram stain or a positive blood culture may therefore simply represent contamination of the sputum with saliva.

Blood Cultures—Some reports have claimed that 25% of patients with pneumococcal pneumonia develop positive blood cultures; however, the denominator required to calculate this percentage is uncertain. Even in the absence of a positive sputum Gram stain, a positive blood culture in combination with the appropriate symptoms and CXR findings is interpreted as true infection. A urine test for pneumococcal polysaccharide antigen is available and is positive in 80% of adults with bacteremia.

Chest X-Ray—The CXR usually reveals a single area of infiltration involving one or more segments of a single lobe. Involvement of the entire lobe is less common. This organism respects the confining fissures of the lung and rarely extends beyond those boundaries, which explains the classical lobar radiologic pattern [Figure 4.2(A)]. Air bronchograms are found in a few cases. This radiologic finding is the consequence of the alveoli filling with inflammatory fluid and outlining the air-containing bronchi. When found, bronchograms are associated with a higher incidence of bacteremia.

Pleural fluid may be detected in up to 40% of cases. In most instances, the volume of fluid is too small to sample by thoracentesis, and if antibiotic treatment is prompt, only a small percentage go on to develop true empyema.

The radiologic improvement of pneumococcal pneumonia is slow. Despite rapid defervescence and resolution of all symptoms, radiologic changes often persist for 4 to 6 weeks. If the patient is improving clinically, follow-up CXRs are therefore not recommended during this period.

**TREATMENT AND OUTCOME**

In the early antibiotic era, *S. pneumoniae* was highly sensitive to penicillin [minimum inhibitory concentration (MIC)< 0.06 μg/mL]. However, since the late 1990s,
isolates in the United States have become increasingly resistant, with 40% demonstrating intermediate resistance (MIC = 0.1–1 μg/mL), and a small percentage demonstrating high-level resistance (MIC > 2 μg/mL). In some areas of Europe and South Africa, higher percentages of resistant strains have been observed. In the Netherlands and Germany, where strictly limited antibiotic use is the standard of care, the prevalence of resistant strains is lower.

Currently, many intermediate strains remain sensitive to the 3rd-generation cephalosporins ceftriaxone and cefotaxime (MIC < 1 μg/mL); however, resistance to these antibiotics is increasing. For intermediately resistant strains, amoxicillin is more active than is penicillin VK, and amoxicillin is therefore the preferred oral antibiotic. Because penicillin resistance results from a decrease in the affinity of penicillin-binding proteins, intermediate (but not high–level) resistance can be overcome by raising the concentration of penicillin.

With the exception of the CNS, where the blood–brain barrier limits antibiotic penetration, standard doses of penicillin are effective in curing infections attributable to intermediately resistant pneumococci. Penicillin resistance is usually associated with resistance to many other classes of antibiotics, including the tetracyclines, macrolides, and clindamycin. Imipenem is also inactive against highly resistant strains. The respiratory fluoroquinolones that possess good gram-positive activity (levofloxacin, gatifloxacin, moxifloxacin) and vancomycin usually retain excellent activity against all resistant strains. Several cases of pneumonia attributable to levofloxacin-resistant S. pneumoniae have recently been reported; however, the overall percentage of pneumococcal strains that are resistant to fluoroquinolones remains low.

### Treatment Recommendations

For doses of the drugs discussed here, see Table 4.3.

For penicillin-sensitive strains, penicillin G or amoxicillin remain the preferred treatment. Ceftriaxone is also effective. If the patient fails to improve within 48 hours, the possibility of a resistant strain must be considered, and coverage with a respiratory fluoroquinolone is recommended. For cases in which meningitis is suspected, a fluoroquinolone should not be used because of poor penetration of the cerebrospinal fluid, and the patient should be covered with vancomycin. In the penicillin-allergic patient, a respiratory fluoroquinolone can be used.

In the pre-antibiotic era, the mortality rate for pneumococcal pneumonia was 20% to 40%. In the antibiotic era, the mortality rate was reduced to approximately 5%. Prognosis is adversely influenced by

1. Age (patients above 65 years of age and infants have worse outcomes)
2. Delayed treatment
3. Infection with capsular type 2 or 3

### Prevention

Despite the use of antibiotics, mortality during the first 36 hours of hospitalization has not changed. To prevent early mortality and to reduce the incidence of S. pneumoniae infection—the penicillin-sensitive and penicillin-resistant strains alike—vaccination is strongly recommended.
recommended for all patients with chronic illnesses or those over the age of 65 years.

Generation of specific antibodies directed against the bacterial cell wall confer, prevent, or reduce the severity of disease. Polyvalent vaccine containing antigens to 23 capsular types is available and is effective (approximately 60% reduction of bacteremia in immunocompetent adults). Efficacy decreases with age and is not measurable in immunocompromised patients. The vaccine has proved to be safe and inexpensive, and should be widely used.

**Haemophilus influenzae**

Group B and non-typable *H. influenzae* can both cause community-acquired pneumonia. Infection with non-typable *H. influenzae* is more common in elderly individuals and in smokers with chronic obstructive pulmonary disease. The onset of symptoms tends to be more insidious than that seen with *S. pneumoniae*, but the clinical pictures are otherwise indistinguishable. A CXR can demonstrate lobar or patchy infiltrates, and sputum Gram stain reveals small gram-negative pleomorphic coccobacillary organisms.

Because of their small size and their color, which is similar to background material, *H. influenzae* may be missed by an inexperienced diagnostician. For the patient requiring hospitalization, intravenous ceftriaxone or cefotaxime is recommended. For oral antibiotic treatment, amoxicillin–clavulanate is effective. However, a number of other oral antibiotics, including trimethoprim–sulfamethoxazole, the newer macrolides (azithromycin and clarithromycin), the fluoroquinolones, and the extended-spectrum cephalosporins (cefpodoxime, cefixime) are also active against this organism.

**Staphylococcus aureus**

Fortunately, community-acquired pneumonia attributable to *S. aureus* is rare. The most common predisposing factor is a preceding influenza infection. An increase in the incidence of *S. aureus* pneumonia is often a marker for the onset of an influenza epidemic. *S. aureus* pneumonia is also more common in intravenous drug users and in AIDS patients, in association with *P. jirovecii* pneumonia.

In a few communities, community-acquired methicillin-resistant *S. aureus* (cMRSA) pneumonia has been described in addition to methicillin-sensitive *S. aureus* (MSSA). The clinical manifestations of this infection are similar to other forms of bacterial pneumonia. However the illness is often severe, being associated with high fever and a slow response to conventional therapy. A CXR can demonstrate patchy infiltrates or dense diffuse opacifications. *S. aureus* produces multiple proteases that allow this bacterium to readily cross the lung fissures and simultaneously involve multiple lung segments. This broader involvement explains the typical bronchopneumonia pattern on CXR [Figure 4.3(A)]. The rapid spread and aggressive destruction of tissue also explains the greater tendency of *S. aureus* to form lung abscesses and induce a pneumothorax. Spread of this infection to the pleural space can result in empyema (seen in 10% of patients). Sputum Gram stain reveals sheets of PMNs and an abundance of gram-positive cocci in clusters and tetrads [Figure 4.3(B)], and culture readily grows *S. aureus*. Blood cultures may also be positive.

The treatment of choice for MSSA is high-dose intravenous nafcillin or oxacillin. For MRSA

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**KEY POINTS**

**About Haemophilus influenzae Pneumonia**

1. This small, gram-negative, pleomorphic coccobacilli is aerobic. It may be mistaken for the background material on sputum Gram stain.
2. Non-typable strains are more common in elderly people and in smokers with COPD.
3. Clinically, *Haemophilus influenzae* is similar to *S. pneumoniae*, with a somewhat slower onset.
4. Parenteral ceftriaxone or cefotaxime should be used to treat hospitalized patients. Multiple oral regimens—amoxicillin-clavulanate, newer macrolides, fluoroquinolones, and extended-spectrum cephalosporins are useful in outpatients.

**About Staphylococcus aureus Pneumonia**

1. These large gram-positive aerobic cocci form tetrads and clusters.
2. The disease most commonly follows influenza, and is seen in patients with AIDS and in IV drug abusers.
3. Destructive bronchopneumonia is complicated by
   a) lung abscesses,
   b) pneumothorax, and
   c) empyema.
pneumonia, vancomycin is generally recommended. The dose of vancomycin should be adjusted to maintain a trough level of 15 to 20 μg/mL to assure therapeutic levels in the lung. Linezolid is an expensive alternative that has equivalent efficacy.

**Legionella pneumophila**

*Legionella* species are gram-negative bacilli found throughout the environment in standing water and soil. Infection most commonly results from inhalation of water droplets contaminated with *Legionella*. Cooling towers or shower heads are most often responsible for aerosolizing contaminated water. Less commonly, nosocomial infection has resulted from the use of unsterilized tap water in respiratory therapy devices. Outbreaks of *Legionella* pneumonia have also been associated with soil excavation. Immunocompromised patients, smokers, and elderly people are more susceptible to this infection.

Clinically, *Legionella* infection causes symptoms typical of other acute community-acquired pneumonias, including high fever, cough, myalgias, and shortness of breath. As compared with other bacterial pneumonias, cough usually produces only small amounts of sputum. Gastrointestinal symptoms, confusion, and headache are more frequently encountered in patients with *Legionella*. Laboratory findings are similar to other acute pneumonias. The only distinctive finding may be hyponatremia, which is noted in approximately one third of patients. A CXR frequently demonstrates lobar pneumonia. In the immunocompromised host, cavitary lesions may be seen. Small pleural effusions are also commonly found.

Diagnosis requires a high index of suspicion, because sputum Gram stain reveals only acute inflammatory cells. The microbiology laboratory must be alerted to the possibility of *Legionella* species to assure that sputum samples are cultured on buffered-charcoal yeast-extract agar with added suppressive antibiotics. *Legionella* can also be identified by direct fluorescent antibody staining, although the sensitivity of this technique is low (30% to 50%). Amplification of *Legionella* DNA from sputum samples by PCR is available in certain reference laboratories, but not commercially. For *L. pneumophila* serogroup 1, the most common cause of *Legionella* pneumonia in the United States (>80% of cases), a highly sensitive and specific urinary antigen test is commercially available. The antigen is excreted early in the illness and persists for several weeks.

For mild disease, an oral macrolide, fluoroquinolone, or tetracycline may used. However, in more severe disease, high doses of intravenous azithromycin or a fluoroquinolone (ciprofloxacin or levofloxacin) are recommended. In transplant patients, a fluoroquinolone is preferred because the macrolides interfere with cyclosporin or tacrolimus metabolism. In the immunocompetent patient, therapy should be continued for 5 to 10 days with azithromycin and for 10 to 14 days with a fluoroquinolone. In the immunocompromised patient, therapy needs to be prolonged for 14 to 21 days to prevent relapse. Mortality is high in legionnaires’ disease, being
**KEY POINTS**

*About Legionella Pneumonia*

1. These aerobic gram-negative bacteria do not take up Gram stain well.
2. Found in soil and standing water. Aerosolized by cooling towers and shower heads. Also contracted after soil excavation.
3. Elderly people, smokers, and immunocompromised patients are at increased risk.
4. Similar to other acute pneumonias. Somewhat unique characteristics include
   a) minimal sputum production,
   b) confusion and headache,
   c) gastrointestinal symptoms, and
   d) hyponatremia.
5. Diagnostic techniques include
   a) culture on buffered-charcoal yeast-extract agar,
   b) direct fluorescent antibody stain (low sensitivity),
   c) polymerase chain reaction (still experimental), and
   d) urinary antigen to serotype I (causes 80% of infections), which is sensitive and specific, and persists for several weeks.
6. Azithromycin or a fluoroquinolone are the treatments of choice. In transplant patients, fluoroquinolones are preferred. Mortality is high: 16% to 50%.

16% to 30% in community-acquired disease and up to 50% in hospitalized patients.

**Atypical Pneumonia**

The atypical forms of pneumonia tend to be subacute in onset, with patients reporting up to 10 days of symptoms before seeking medical attention. Atypical pneumonia is associated with a nonproductive cough, and clinical manifestations tend to be less severe. It is important to keep in mind that significant overlap occurs in the clinical manifestations of this group of infections and the more typical forms of pneumonia associated with purulent sputum production.

*Mycoplasma pneumoniae* is one of the most frequent causes of “walking pneumonia.” This infection is seen primarily in patients under age 40 years; it is an uncommon cause of pneumonia in elderly individuals. The disease is seasonal, with the highest incidence of *Mycoplasma* being seen in the late summer and early fall. Sore throat is usually a prominent symptom, and bullous myringitis is seen in 5% of cases. Presence of this abnormality is highly suggestive of *Mycoplasma*. Tracheobronchitis results in a hacking cough that is often worse at night and that persists for several weeks. Physical exam may reveal some moist rales, but classically, radiologic abnormalities are more extensive than predicted by the exam. Findings on CXR consist of unilateral or bilateral patchy lower-lobe infiltrates in a bronchial distribution. The clinical course is usually benign. Fever, malaise, and headache usually resolve over 1 to 2 weeks, but cough can persist for 3 to 4 weeks. Peripheral WBC is usually less than 10,000. And sputum Gram stain and culture reveal only normal mouth flora and a moderate inflammatory response.

Diagnosis is made by history and clinical manifestations. Epidemiologic history of contact with a person having similar symptoms is particularly helpful. Currently, no definitive test is available. Sputum PCR has been found to be sensitive and specific, but that test is not commercially available. Cold agglutinin titers in excess of 1:64 support the diagnosis and correlate with severity of pulmonary symptoms, but are not cost effective. Complement fixation antibody titers begin to rise 7 to 10 days after the onset of symptoms.

Because a reliable, rapid diagnostic test is not currently available, therapy is usually empiric. A macrolide or tetracycline is the treatment of choice; alternatively, a fluoroquinolone can be administered. Azithromycin is the preferred agent when *Mycoplasma* is suspected, and a standard 5-day course is effective in most cases.

*Chlamydia pneumoniae* (Taiwan acute respiratory agent) is another important cause of atypical pneumonia. This pathogen is a common cause of community-acquired pneumonia, representing 5% to 15% of cases. The disease occurs sporadically and presents in a manner similar to *Mycoplasma*, with sore throat, hoarseness, and headache in addition to a nonproductive cough. Radiologic findings are also similar to those with *Mycoplasma*. No rapid diagnostic test is widely available, and treatment is empiric. A tetracycline is considered the treatment of choice, but macrolides and fluoroquinolones are also effective.

The final major group of organisms that cause atypical pneumonia is the respiratory viruses: influenza A and B, adenovirus, parainfluenza virus, and respiratory syncytial virus. The respiratory syncytial virus infects primarily young children, elderly people, and the immunocompromised host. These viruses can all present with a nonproductive cough, malaise, and fever.
Auscultatory findings are minimal, and lower lobe infiltrates are generally observed on CXR. The clinical virology laboratory can culture each of these viruses from sputum or a nasopharyngeal swab. Rapid commercial tests (10 to 20 minutes) are available for detection of influenza (Quick View, Flu O1A, and Zstatflu). These tests have a sensitivity of 57% to 77%, and all three can distinguish between types A and B.

If influenza A virus is diagnosed, early treatment of the virus with amantadine or rimantadine is recommended. Neuramidase inhibitors are also available, and these agents have activity against both influenza A and B. The influenza vaccine is safe and efficacious, and should be given annually in October through early November to patients over 65 years of age, individuals with serious underlying diseases, nursing home residents, and health care workers (see Chapter 15).

### Aspiration Pneumonia

**CASE 4.2**

A 35-year-old white man arrived in the emergency room complaining of left-sided chest pain during the preceding 4 days. He had begun drinking large quantities of alcohol 8 days earlier. He vaguely recalled passing out on at least two occasions. He developed a persistent cough, productive of green sputum, 4 days before admission. At that time, he also began experiencing left-sided chest pain on deep inspiration (pleuritic pain). Initially these pains were dull; however, over the next few days, they became increasingly sharp.

Physical exam showed a temperature of 38°C and a respiratory rate of 42 per minute. This was a disheveled man, looking older than his stated age, breathing shallowly and rapidly, in obvious pain.

A check of the throat revealed a good gag reflex, extensive dental caries, several loose teeth, severe gingivitis, and foul-smelling breath and sputum. Decreased excursion of the right lung was noted, and the right lower lung field was dull to percussion. Bronchovesicular breath sounds were heard diffusely (inspiratory and expiratory breath sounds of equal duration); moist, medium rales were heard in the right lower and left lower lung fields. Egophony and whispered pectoriloquy were also heard in these areas.

Laboratory workup showed a hematocrit of 50%; a WBC count of 21,400/mm³, with 79% PMNs, 7% bands, 1% lymphocytes, and 13% monocytes. Blood gases showed a pH of 7.46, Pao₂ of 56 mm Hg, and a Paco₂ of 36 mm Hg. Sputum Gram stain revealed many PMNs and a mixture of gram-positive cocci, gram-positive rods, and gram-negative rods. A CXR demonstrated dense right lower lobe infiltrate.
Aspiration pneumonia should be suspected in patients with a recent history of depressed consciousness and in patients with a poor gag reflex or an abnormal swallowing reflex. The elderly patient who has suffered a stroke is particularly susceptible to aspiration. In case 4.2, the patient’s heavy consumption of alcohol led to depression in consciousness.

Three major syndromes are associated with aspiration:

1. **Chemical burn pneumonitis.** Aspiration of the acidic contents of the stomach can lead to a chemical burn of the pulmonary parenchyma. Aspiration of large quantities of fluid can result in the immediate opacification of large volumes of lung. Acid damage causes pulmonary capillaries to leak fluid, release cytokines, and permit infiltration by PMNs. In some patients, noncardiogenic pulmonary edema or ARDS develops. Onset of symptoms occurs immediately after aspiration.

2. **Bronchial obstruction resulting from aspiration of food particles.** The inhalation of solid particles results in mechanical obstruction and interferes with ventilation. The patient immediately becomes tachypneic.

3. **Pneumonia resulting from a mixture of anaerobic and aerobic mouth flora.** This form of pneumonia develops several days after aspiration of mouth flora. Patients with severe gingivitis have higher bacterial colony counts in the mouth, and they aspirate a higher inoculum of organisms, increasing the likelihood of a symptomatic pneumonia.

   Case 4.2 had poor dental hygiene and severe gingivitis, predisposing him to the latter form of pneumonia. Often, the sputum is putrid-smelling as a result of the high number of anaerobes. Necrosis of tissue is common in this infection, resulting in the formation of lung abscesses. Infection often spreads to the pleura, resulting in pleuritic chest pain as experienced in case 4.2. Pleural effusions filled with bacteria and PMNs can develop as observed in this case. Effusions containing bacteria and large numbers of PMNs are called empyemas. Necrosis of the pleural lining and lung parenchyma can result in formation of a fistula tracking from the bronchus to the pleural space. Development of a bronchopleural fistula prolongs hospitalization and may eventually require surgical repair.

**Diagnosis**

Sputum is often foul-smelling as a result of the high numbers of anaerobic bacteria. Sputum Gram stain reveals many PMNs and a mixture of gram-positive and gram-negative organisms. Sputum culture usually grows normal mouth flora. When aspiration occurs in the hospitalized patient, the mouth often is colonized with more resistant gram-negative organisms plus *S. aureus*. In these patients, a predominance of gram-negative rods or gram-positive cocci in clusters may be seen on Gram stain, and gram-negative rods or *S. aureus* may be cultured from the sputum.

A CXR reveals infiltrates in the dependent pulmonary segments. When aspiration occurs in the upright position, the lower lobes are usually involved, more commonly the right lower lobe than the left. This difference has an anatomic explanation. The right bronchus divides from the trachea at a steeper angle than does the left mainstem bronchus, increasing the likelihood that aspirated material will flow to the right lung. When aspiration

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**KEY POINTS**

**About Aspiration Pneumonia**

1. Can occur in cases of loss of consciousness, poor gag reflex, or difficulty swallowing.

2. Three forms of aspiration:
   - **Aspiration of gastric contents** leads to pulmonary burn and noncardiogenic pulmonary edema.
   - **Aspiration of an obstructing object** causes atelectasis and immediate respiratory distress.
   - **Aspiration of mouth flora**, when associated with poor dental hygiene and mixed mouth aerobes and anaerobes, can lead to foul smelling sputum and eventually lung abscess and empyema. Hospital-acquired aspiration causes gram-negative and *Staphylococcus aureus* pneumonia.

3. Treatment depends on the form of the disease:
   - Penicillin or clindamycin for community-acquired infection.
   - Third-generation cephalosporin and metronidazole for hospital-acquired infection.
   - Bronchoscopy for obstructing foreign bodies.
occurs in the recumbent position, the superior segments of the lower lobes or the posterior segments of the upper lobes usually become opacified.

**TREATMENT**

Clindamycin or penicillin are both effective antibiotic coverage for community-acquired aspiration pneumonia because they kill both aerobic and anaerobic mouth flora (Table 4.3). In cases in which lung abscess has developed, clindamycin has been shown to be slightly superior.

In nosocomial aspiration, broader coverage with a 3rd-generation cephalosporin combined with metronidazole is generally recommended. Alternatively, a semisynthetic penicillin combined with a β-lactamase inhibitor (ticarcillin–clavulanate or piperacillin–tazobactam) or a carbapenem (imipenem or meropenem) can be used.

If aspiration of a foreign body is suspected, bronchoscopy is required to remove the foreign material from the tracheobronchial tree.

**Rarer Causes of Community-Acquired Pneumonia**

**ACTINOMYCOISIS**

*Actinomyces* species are microaerophilic or anaerobic gram-positive rods that can be part of the polymicrobial flora associated with aspiration pneumonia, particularly in patients with poor oral hygiene. Disease is most commonly caused by *Actinomyces israelii*.

Actinomycosis pulmonary infection is often indolent and slowly progressive. Lung parenchymal lesions are usually associated with pleural infection, resulting in a thickened pleura and empyema. This organism can break through fascial planes. Spontaneous drainage of an empyema through the chest wall should strongly suggest the possibility of actinomycosis. “Sulfur granules” are often found in purulent exudate; they consist of clusters of branching *Actinomyces* filaments.

Gram stain reveals branching forms that are weakly gram-positive. These forms can be differentiated from *Nocardia* by modified stain for acid-fast bacilli (AFB), *Actinomyces* being acid-negative and *Nocardia* being acid-positive. The organism should be cultured under anaerobic conditions, and grows slowly, with colonies usually requiring a minimum of 5 to 7 days to be identified. Growth can take up to 4 weeks.

High-dose intravenous penicillin (18 to 24×10⁶ U daily) is recommended for 2 to 6 weeks, followed by oral penicillin therapy for 6 to 12 months. Therapy must be continued until all symptoms and signs of active infection have resolved. Other antibiotics that have been successfully used to treat actinomycosis include erythromycin, tetracyclines, and clindamycin.

**NOCARDIOSIS**

*Nocardia* is an aerobic gram-positive filamentous bacterium that often has to be differentiated from *Actinomyces*. *Nocardia* is ubiquitous in the environment, growing in soil, organic matter, and water. Pneumonia occurs as a consequence of inhaling soil particles. The number of species causing human disease is large and

**KEY POINTS**

**About Actinomycosis**

1. These branching gram-positive bacteria are microaerophilic or anaerobic, slow growing, modified acid-fast negative.
2. Infection is associated with poor oral hygiene.
3. Slowly progressive infection, breaks through fascial planes, causes pleural effusions and fistula tracks, forms “sulfur granules.”
4. Alert clinical microbiology to hold anaerobic cultures.
5. Treatment must be prolonged: high-dose intravenous penicillin for 2 to 6 weeks, followed by 6 to 12 months of oral penicillin.

**About Nocardiosis**

1. *Nocardia* are gram-positive branching bacteria, aerobic, slow growing, modified acid-fast.
2. Ubiquitous organism found in the soil.
3. Inhalation of soil particles leads to pneumonia.
4. The organism infects
   a) immunocompromised patients (causing disseminated disease in AIDS),
   b) normal hosts, and
   c) patients with alveolar proteinosis.
4. Pulmonary infection can lead to bacteremia and brain abscess that can mimic metastatic lung carcinoma.
5. Alert clinical microbiology to use selective media and to hold cultures.
6. Treatment must be prolonged. High-dose parenteral trimethoprim–sulfamethoxazole for at least 6 weeks, followed by oral treatment for 6 to 12 months.

Infection more commonly develops in patients who are immunocompromised; however, 30% of cases occur in otherwise normal individuals. Patients with AIDS, organ transplant, alcoholism, and diabetes are at increased risk of developing nocardiosis. In addition to pulmonary disease, these patients are at increased risk for developing disseminated infection. Patients with chronic pulmonary disorders, in particular patients with alveolar proteinosis, have an increased incidence of pulmonary *Nocardia* infection.

Onset of pulmonary disease is highly variable. In some cases, onset is acute; in others, onset is gradual. Symptoms are similar to other forms of pneumonia. A CXR may reveal cavitary lesions, single or multiple nodules, a reticular nodular pattern, interstitial pattern, or a diffuse parenchymal infiltrate. *Nocardia* pulmonary infection often seeds the bloodstream and forms abscesses in the cerebral cortex. The combination of a lung infiltrate with a CNS lesion or lesions is often mistaken for lung carcinoma with CNS metastasis.

Diagnosis is made by sputum examination or lung or cerebral cortex biopsy. Gram stain demonstrates weakly gram-positive branching filamentous forms that are acid-fast on modified AFB stain. On tissue biopsy, organisms are demonstrated on Brown–Brenn or methenamine silver stain. The organism is slow growing and is frequently overgrown by mouth flora on conventional plates. The clinical laboratory should be alerted to the possibility of *Nocardia* so that they can incubate bacteriologic plates for a prolonged period and use selective media.

Most *Nocardia* are sensitive to sulfonamides and trimethoprim. Trimethoprim–sulfamethoxazole is generally accepted as the treatment of choice, with a daily dose of 2.5 to 10 mg/kg of the trimethoprim component. High-dose therapy should be continued for at least 6 weeks, followed by lower doses for 6 to 12 months. Some *Nocardia* species are resistant to sulfonamides, but they are sensitive to amikacin, imipenem, 3rd-generation cephalosporins, minocycline, dapsone, and linezolid. Whenever possible, culture and antibiotic sensitivities should be used to guide antibiotic therapy.

**Nosocomial (Hospital-Acquired) Pneumonia**

Pneumonia is the second most common form of nosocomial infection. It accounts for 13% to 19% of all nosocomial infections. Hospital-acquired pneumonia is defined as a pneumonia that develops 48 hours or longer after hospitalization and that was not developing at the time of admission. Nosocomial pneumonia is a very serious complication and represents the leading infectious-related cause of death in the hospital, the mortality being roughly 1 of every 3 cases. Development of pneumonia in the hospital prolongs hospitalization by more than 1 week.

The condition that most dramatically increases the risk of nosocomial pneumonia is endotracheal intubation. Endotracheal tubes bypass the normal protective mechanisms of the lung, and they increase the risk of pneumonia by a factor of between 6 and 21. It has been estimated that the risk of pneumonia while on a ventilator is 1% to 3% daily. Other factors that increase the risk of pneumonia include age greater than 70 years; CNS dysfunction, particularly coma, leading to an increased likelihood of aspiration; other severe underlying diseases; malnutrition; and metabolic acidosis. Patients on sedatives and narcotics have depressed epiglottal function and are also at increased risk of aspiration. Corticosteroids and other immunosuppressants reduce normal host defenses and allow bacteria to more readily invade the lung parenchyma.

Aerobic gram-negative bacteria account for more than half the cases of nosocomial pneumonia.

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**KEY POINTS**

**About Nosocomial Pneumonia**

1. Pneumonia is one of the most common nosocomial infections.
2. Risk factors include
   a) endotracheal intubation (20 times the baseline risk, 1% to 3% incidence daily),
   b) age greater than 70 years,
   c) depressed mental status,
   d) underlying disease and malnutrition, and
   e) metabolic acidosis.
3. Primary causes are gram-negative bacilli and *Staphylococcus aureus*.
4. Colonization is difficult to differentiate from infection. Bronchoscopy is not helpful. Factors that favor infection include:
   a) worsening fever and leukocytosis with left shift;
   b) sputum Gram stain with increased PMNs, predominance of one organism;
   c) decreasing *Pao*2 indicative of pulmonary shunting; and
   d) expanding infiltrate on chest radiographs.
5. Broad-spectrum empiric therapy can be initiated after samples are obtained for culture, but coverage should be adjusted based on culture results and clinical response.
When infection is likely or the patient is extremely ill, and when a new pulmonary infection cannot be convincingly ruled out, antibiotics should be quickly started; or, if the patient is receiving antibiotics, the regimen should be changed to cover for antibiotic-resistant bacteria. In the absence of specific findings indicative of infection, colonization is more likely, and the antibiotic regimen should not be changed.

Indiscriminate modifications of antibiotic therapy eventually select for highly resistant pathogens that are difficult—or in some cases impossible—to treat. Switches to broader-spectrum, more powerful antibiotics should be undertaken cautiously, and should be initiated only when convincing evidence for a new infection is present. In the patient who is deteriorating clinically, broader-spectrum coverage can be temporarily instituted once blood, urine, and sputum samples for culture and Gram stain have been obtained. The 3-day rule should then be applied (see Chapter 1), with the antibiotic regimen being modified within 3 days, based on the culture results, so as to prevent colonization with even more highly resistant bacteria.

These regimens (see Table 4.3) are recommended for nosocomial pneumonia:

1. Third-generation cephalosporin (ceftriaxone, cefotaxime, cefizoxime, or ceftazidime)
2. Cefepime
3. Ticarcillin–clavulanate or piperacillin–tazobactam
4. Imipenem or meropenem

An aminoglycoside (gentamicin, tobramycin, or amikacin) may or may not be added. If P. aeruginosa is suspected, ciprofloxacin, piperacillin–tazobactam, ticarcillin–clavulanate, cefepime, aztreonam, imipenem, or meropenem should be used. Many experts recommend administration of two agents from different classes to prevent development of resistance. Aminoglycosides should never be used alone to treat Pseud. aeruginosa because the antibiotic levels achievable in the lung are low. Aerosolized tobramycin (80 mg twice daily) has proven to be useful adjunctive therapy. If Staph. aureus is suspected, vancomycin should be added pending culture and sensitivity results. Specific anaerobic coverage is usually not required in the absence of clear aspiration.

**Empyema**

**Causation**

Infection of the pleural space is most commonly the consequence of spread of pneumonia to the parietal pleura. More than half of empyema cases are associated with pneumonia. The most common pathogens in this setting are S. pneumoniae, S. aureus, S. pyogenes, and anaerobic mouth flora. Empyema is also a complication of trauma and surgery, and when those are the inciting factors,
S. aureus and aerobic gram-negative bacilli predominate. In the immunocompromised patient, fungi and gram-negative bacilli are most commonly encountered.

PATHOPHYSIOLOGY

Pleural effusions occur in approximately half of all pneumonias; however, only 5% of pneumonias develop true empyema. Because pleural fluid is deficient in the opsonins, immunoglobulin G, and complement, bacteria that find a way to this culture medium are only inefficiently phagocytosed by PMNs. As PMNs break down in the closed space, they release lysozyme, bacterial permeability-increasing protein, and cationic proteins. These products slow the growth of bacteria, lengthening doubling times by a factor of 20 to 70. The slow growth of the bacteria renders them less sensitive to the cidal effects of antibiotics. In the empyema cavity, pH is low, impairing WBC function and inactivating some antibiotics—in particular, the aminoglycosides.

CLINICAL MANIFESTATIONS

Persistent fever despite appropriate antibiotic treatment for pneumonia should always raise the possibility of an enclosed pleural infection. Fever is often accompanied by chills and night sweats. Pleuritic chest pain is a common complaint, as is shortness of breath. Physical exam is helpful in detecting large effusions. As noted in case 4.2, the area in which fluid is collecting is dull to percussion, and breath sounds are decreased. At the margin between fluid and aerated lung, egophony and bronchial breath sounds are commonly heard, reflecting areas of pulmonary consolidation or atelectasis.

On CXR, fluid collections as small as 25 mL can alter the appearance of the hemidiaphragm on posterior–anterior view, and on lateral views, 200 mL of fluid is generally required to blunt the posterior costophrenic angle. A lateral decubitus view with the pleural effusion side down can demonstrate layering of 5 to 10 mL of free fluid. Contrast-enhanced chest CT is particularly helpful in differentiating lung abscess from empyema, and it demonstrates the full extent of the effusion and the degree of pleural thickening.

Ultrasound is very useful in determining the dimensions of the effusion, and it is the most effective method for guiding thoracentesis. Septations are readily visualized by this technique and indicate the development of a loculated collection that requires drainage. Ultrasound guidance of thoracentesis is strongly recommended because of the associated decreased incidence of complicating pneumothorax. The fluid should be analyzed for cellular content, and Gram stain, fungal stain, AFB stain, and aerobic and anaerobic cultures should be obtained. If the fluid is frankly purulent, the pleural space should be completely drained. If the fluid is not overtly purulent, the fluid should also be analyzed for pH, glucose, lactate dehydrogenase, and total protein. A pleural fluid pH below 7.2, a glucose level below 40 mg/dL, and a lactate dehydrogenase level above 1000 IU/L are consistent with empyema and justify pleural fluid drainage to prevent loculation, pleural scarring, and restrictive lung disease.

TREATMENT

Antibiotic therapy for the offending pathogen is of primary importance, and antibiotic coverage depends on the pathogen identified by sputum or pleural fluid Gram stain and culture. When a significant pleural fluid collection is apparent, a more prolonged course of antibiotics (2 to 4 weeks) is generally required. Parapneumonic effusions that move freely and that are less than 1 cm in width on lateral decubitus film can be managed medically; thoracentesis is not required. If the collection is larger or does not flow freely, thoracentesis should be performed. If biochemical evidence for empyema is present, drainage by chest tube is recommended. Repeated thoracentesis is rarely successful in completely draining the pleural effusion.
fluid collection unless the fluid has a thin viscosity and is present in small volumes. Drainage by closed chest tube is usually successful with smaller effusions occupying up to 20% of the hemithorax, but it is often ineffective when the volume of fluid occupies more than 40% of the hemithorax. Interventional radiology is required to precisely place French catheters at sites of loculation and to break up areas of adhesion under CT guidance. If tube drainage proves ineffective after 24 hours, intrathoracic urokinase (125,000 U diluted in 50 to 100 mL sterile normal saline) should be instilled to break down intrapleural fibrin and encourage free drainage of infected fluid. If thoracentesis and urokinase are unsuccessful, operative intervention is required.

Empyema is a serious complication, with an associated 8% to 15% mortality in young, previously healthy patients and 40% to 70% mortality in patients who are elderly or have significant underlying disease. Patients with nosocomial pathogens and polymicrobial infection also have a worse prognosis. Delay in diagnosis and appropriate drainage increases the need for surgical resection of the pleura and manual re-expansion of the lung.

**CHRONIC PNEUMONIAS**

**GUIDING QUESTIONS**

1. How is tuberculosis contracted, and how can this disease be prevented?
2. What is primary tuberculosis?
3. What is secondary tuberculosis?
4. Why are the apices of the lung the most common location for tuberculosis?
5. What are the typical symptoms and findings in miliary tuberculosis?
6. How is tuberculosis diagnosed?
7. Why should combination antituberculous therapy always be prescribed in active tuberculosis?
8. What does having a positive PPD mean, and how should an individual with a positive test be treated?
9. In which areas of the country is histoplasmosis most commonly encountered, and why?
10. In which areas of the country is coccidiomycosis most commonly encountered, and why?

**TUBERCULOSIS**

**POTENTIAL SEVERITY**

The miliary form of the tuberculosis can be fatal. Clinicians must maintain a high index of suspicion for tuberculosis in immigrants, indigent and elderly patients, and patients with AIDS.

**CASE 3.3**

A 73-year-old black man, a retired bartender, came to the emergency room complaining of increasing shortness of breath and worsening cough over the preceding 3 weeks. About 5 months earlier, he had begun to notice night sweats that drenched his pajamas. That symptom was followed by development of a nonproductive cough. He began bringing up small quantities of yellow sputum 1 month before presentation at the emergency room. At the time that he noticed the sputum production, he began experiencing increased shortness of breath, even after mild exertion (walking 2 blocks to the grocery store). During the past few months, he felt very tired, and he has lost 10 pounds despite a “good” diet.

Epidemiologic history indicated city residence and visits with a number of old drinking buddies. The patient denied exposure to anyone with tuberculosis, and he had no family history of tuberculosis.

Past medical history revealed an abnormal CXR 20 years earlier and treatment at New York City’s Bellevue Hospital with isoniazid (INH) and para-aminosalicylic acid for 1 year.

Social history indicated that the patient had recently retired after 35 years of tending bar. He lives alone in a 1-bedroom apartment and supports himself on Social Security. He is a former smoker (half a pack daily for 28 years) and drinks half a pint daily.

On physical exam, his temperature was 38°C and his respiratory rate was 18 per minute, presenting a picture of a thin male breathing comfortably. Aside from mild clubbing of his nail beds, the physical findings (including lung exam) were within normal limits.

The laboratory workup showed a hematocrit of 39% and a WBC count of 6000/mm³, with 55% PMNs, 30% lymphocytes, and 15% monocytes.

Sputum Gram stain revealed many PMNs, few gram-positive cocci, and rare gram-negative rods.
Pathogenesis

*Mycobacterium tuberculosis* is an aerobic, nonmotile bacillus with a waxy lipid-rich outer wall containing high concentrations of mycolic acid. This waxy outer wall fails to take up Gram stain. Visualization of mycobacteria requires heating to melt the outer wall, which allows for penetration and binding of the red dye fuchsin. The lipids in the cell wall bind this dye with high affinity and resist acid–alcohol decolorization. This acid-fast bacillus is small in size and appears beaded [Figure 4.5(B)]. Genomic analysis reveals that, as compared with other bacteria, *M. tuberculosis* has a large number of genes encoding for enzymes that regulate lipogenesis and lipolysis. The resulting high lipid content of this pathogen accounts for many of its unique clinical characteristics, including its ability to resist killing by macrophages and PMNs and to survive for many years within the body. Rate of growth in *M. tuberculosis* is very slow, being about 1/20th the growth rate of most conventional bacteria. The slow rate of growth may also be explained by the waxy cell wall, which limits access to nutrients.

Mycobacteria survive and grow in macrophages, and they therefore induce a profound chronic inflammatory response. On gaining entry to the lungs, these organisms are ingested by alveolar macrophages and transported to the hilar lymph nodes. Here macrophages and dendritic cells present tubercular antigens to T cells, inducing a cell-mediated immune response. Helper T cells (CD4+) then activate macrophages to kill the mycobacteria and control the infection. Accumulation of one of the cell wall waxes, cord factor, stimulates the formation of granulomas that contain clusters of epithelioid cells, giant cells, and lymphocytes. Over time, the centers of the

*Figure 4–5.* Cavitory pulmonary tuberculosis: A. Chest radiograph demonstrates bilateral upper lobe cavitory lesions, and B. sputum smear for acid-fast bacilli confirms the presence of those organisms. See color image on color plate 1

Bilateral upper lobe cavitory lesions were observed on CXR [see Figure 4.5(A)]. Acid-fast stain of the sputum revealed multiple acid-fast bacilli per high-power field [see Figure 4.5(B)].
granulomas become necrotic, forming cheesy debris called caseous necrosis. Caseating granulomas are the hallmark lesion of tuberculosis. This pathologic finding is only rarely found in other diseases. If intracellular growth of \textit{M. tuberculosis} continues, increasing numbers of macrophages are activated to produce multiple cytokines. Interleukin 1 stimulates the hypothalamus to raise core body temperature, causing fever. Tumor necrosis factor interferes with lipid metabolism and causes severe weight loss. These cytokines are primarily responsible for the symptoms of fever, night sweats, and weight loss described in case 4.3.

**Epidemiology**

Humans are the only reservoir for \textit{M. tuberculosis}. Person-to-person spread of infection is almost exclusively caused by inhalation of droplet nuclei that have been aerosolized by coughs or sneezes. The likelihood of inhaling infectious droplets is greatly increased in a closed, crowded environment. A single cough has been estimated to form 3000 infectious droplets, with a sneeze producing even higher numbers.

The infectiousness of an individual patient can be estimated by AFB smears. The higher the number of organisms per microscopic field, the greater the infectious potential. Patients with laryngeal tuberculosis are particularly infectious and can release large numbers of organisms while speaking. Patients with AIDS and tuberculosis often harbor a large organism burden. Patients with large pulmonary cavities tend to intermittently release large numbers of infectious particles.

Repeated exposure and close contact are generally required to contract this disease. Respiratory isolation and rapid treatment of infected individuals are the primary ways to prevent spread of infection.

Despite the availability of antituberculous agents, tuberculosis remains a leading cause of death worldwide. Crowded living conditions and the existence of immunologically naive populations continue to allow rapid person-to-person spread, particularly in underdeveloped countries. After a surge in cases in the United States during the mid-1980s because of the AIDS epidemic, the case rate has steadily declined. In 2002, it reached the lowest level ever recorded: 5.2 cases per 100,000. This steady decline among permanent U.S. residents contrasts with the steady increase in the percentage of tuberculosis cases among people immigrating to the United States. Immigrants now account for half of all reported cases in the United States. Individuals immigrating from underdeveloped countries have higher rates of infection. For example, the rate among Vietnamese immigrants is 120 per 100,000.
person–years, and among Haitian immigrants it is 133 per 100,000. Immigrants from established market economies such as those of Western Europe have rates similar to those in the United States.

Tuberculosis occurs more frequently in single men, alcoholics, intravenous drug abusers, the urban poor (particularly homeless people), migrant farm workers, and prison inmates. Elderly people are more likely to develop secondary tuberculosis because cell-mediated immunity wanes with age.

A genetic predisposition to the development of active tuberculosis is known. People with European heritage tend to be more resistant, probably as a consequence of the devastating effects of the tuberculosis epidemic during the Industrial Revolution. At that time, tuberculosis was responsible for one fourth of the deaths in Europe, killing off a significant percentage of the population that had a reduced immune response.

**KEY POINTS**

**About Primary Tuberculosis**

1. Represents the first exposure to inhaled infectious particles.
2. Followed by a flu-like illness.
3. Spread is controlled over 4 to 8 weeks by the development of cell-mediated immunity.
4. Ghon foci are calcified lung lesions at the site of the primary infection.
5. Bacteremia develops and seeds the kidneys, epiphyses of the long bones, and vertebral bodies (areas with high oxygen content). The infection can later reactivate.

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<table>
<thead>
<tr>
<th>CURB-65 score</th>
<th>Treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 or 1</td>
<td>Likely suitable for home treatment</td>
</tr>
<tr>
<td>2</td>
<td>Consider hospital supervised treatment</td>
</tr>
<tr>
<td>3 or more</td>
<td>Manage in hospital as severe pneumonia</td>
</tr>
</tbody>
</table>

*defined as a Glasgow Coma Score of 8 or less, or new disorientation in person, place or time

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<table>
<thead>
<tr>
<th>GROUP 1</th>
<th>Mortality low (1.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 324, died = 5)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GROUP 2</th>
<th>Mortality intermediate (9.2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 184, died = 17)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>GROUP 3</th>
<th>Mortality high (22%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 210, died = 47)</td>
<td></td>
</tr>
</tbody>
</table>
response to mycobacteria. As compared with white people, people who are black or Hispanic, or who are Asia Pacific Islanders or Native Americans experience a 5 to 10 times higher incidence of tuberculosis. Patients with AIDS are particularly susceptible to tuberculosis, and this population has spread the infection to others. Areas and demographic groups in which AIDS is more prevalent therefore have a higher incidence of tuberculosis.

The patient in case 4.3 has a number of epidemiologic characteristics that increase his risk for tuberculosis. He is a single male, black, possibly alcoholic, and elderly.

**Clinical Manifestations**

There are two forms of human tuberculosis infection: primary tuberculosis and secondary tuberculosis.

**Primary Tuberculosis**

Primary disease occurs when a patient inhales infectious *M. tuberculosis* droplets for the first time. A flu-like illness usually follows; however, some people experience no symptoms. Within 4 to 8 weeks of exposure, the human host usually mounts a cell-mediated immune response. Activated macrophages control the spread and growth of the organism. Pulmonary lesions heal spontaneously and form areas of fibrosis or calcification called Ghon lesions or foci. A Ghon lesion in combination with hilar adenopathy is called a Ranke complex.

In addition to transporting organisms to the hilum and mediastinum, infected macrophages may gain access to the thoracic duct, enter the bloodstream, and spread throughout the body. *M. tuberculosis* grows best in regions with high oxygen tension, including the kidneys, long-bone epiphyses, and vertebral bodies. It most commonly infects the apices of the lung, the regions with the highest oxygen content and reduced lymphatic flow.

Although the infection is brought under control, the bacilli are not usually completely eradicated. Organisms can survive for decades, being held in check by the host immune response. But any condition that subsequently depresses cell-mediated immunity can free *M. tuberculosis* to grow and cause symptomatic secondary tuberculosis.

**Miliary Tuberculosis**

In some individuals, initial exposure to *M. tuberculosis* fails to induce cell-mediated immunity, or the immune response is not robust enough to control the infection. Under these conditions, the mycobacteria continue to multiply and disseminate, causing miliary tuberculosis. Very young and very old patients are at higher risk of developing disseminated disease, as are patients receiving immunosuppressants and those with HIV infection. Underlying medical conditions often associated with miliary tuberculosis include alcoholism, malignancy, connective tissue diseases, renal failure, and pregnancy. However, it must be emphasized that absence of an underlying disease does not exclude the possibility of miliary tuberculosis.

Children usually present to the physician with high fever, night sweats, weight loss, hepatosplenomegaly, and lymphadenopathy. However in adults, particularly elderly people, the clinical manifestations may be subtle. Patients usually have nonspecific complaints of fever, malaise, anorexia, weakness, and weight loss. Night sweats are also common.

Physical exam usually reveals a chronically ill patient with no specific findings. In some patients, lymphadenopathy may be detected. In all patients, fundoscopic exam should be carefully performed following pupillary dilation and may reveal choroid tubercles in up to 50% of cases. The diagnosis is often missed, and in up to 20% cases, it is made post-mortem.
The peripheral WBC count is usually normal; however, some patients develop extremely high WBC counts (30,000 to 40,000/mm³), also termed a “leukemoid reaction,” that can be mistaken for leukemia. Pancytopenia can also develop. Liver function abnormalities are common. Elevated alkaline phosphatase and moderate increases in transaminase values are found in most patients. Serum sodium may be low as a consequence of adrenal insufficiency (a well-known complication of miliary tuberculosis) or inappropriate antidiuretic hormone secretion. Morning and evening serum cortisol levels should be measured to exclude adrenal insufficiency. In approximately two thirds of patients, CXR reveals small nodules (0.05 to 1 mm in diameter) that resemble millet seeds (the basis for the designation “miliary”); however, a negative CXR in elderly patients and in patients with HIV does not exclude this diagnosis. In a few patients, ARDS may develop, causing complete opacification of the lungs.

The key to the diagnosis of miliary tuberculosis is a high index of suspicion. Sputum smears are positive in only a few patients. Samples from enlarged lymph nodes, liver biopsy, and bone marrow should therefore be sought for histopathology (seeking granulomas and acid-fast bacilli) and culture. Transbronchial biopsy can yield the diagnosis in many patients. Blood samples for culture should be drawn; in AIDS patients, cultures are commonly positive. If CNS symptoms are noted, a lumbar puncture should also be performed, although the resulting smears are usually negative.

A delay in treatment can have fatal consequences. Therefore, if miliary tuberculosis is high on the differential diagnosis, empiric antituberculous therapy should be initiated as soon as samples for culture have been obtained. A 4-drug combination consisting of INH, rifampin, pyrazinamide, and ethambutol is the preferred regimen. Patients usually defervesce within 7 to 14 days.

**SECONDARY TUBERCULOSIS**

Reactivation of tuberculosis after primary disease occurs in 10% to 15% of patients. In half of these cases the infection reactivates within 2 years of exposure. In past decades, reactivation occurred most commonly in elderly patients, but in the United States today, most secondary cases are now reported in middle-aged adults (30 to 50 years of age). Early in the course of reactivation, patients are often asymptomatic, and evidence of reactivation is found only on CXR. However if the infection is not detected, symptoms slowly develop and worsen over several months. The gradual nature of symptom onset often causes patients to delay seeing a physician. The patient in case 4.3 has the typical symptoms of secondary tuberculosis: a progressively worsening cough with sputum production, low-grade fever, night sweats, fatigue, and weight loss. Symptoms that suggest more advanced disease are hemoptysis (indicating erosion of a tuberculous cavity into an arteriole) and pleuritic chest pain (suggesting pleural involvement and probable tuberculous pleural effusion).

Physical exam is often unrevealing, as observed in case 4.3. Despite the presence of extensive pulmonary disease, auscultation may be normal. Fine rales may be heard in the apices after a short cough and quick inspiration or after full expiration followed by a cough and rapid inspiration (post-tussive rales).

The hallmark of secondary pulmonary disease is the presence of apical cavitory lesions on CXR. Lesions usually develop in posterior segments of the upper lobes just below the clavicle. Less frequently, infiltrates are noted in the apex of the lower lobe (usually obscured by the heart shadow). In addition to routine posterior–anterior and lateral chest films, an apical lordotic view is often helpful in visualizing upper lobe apical lesions. A chest CT scan can be helpful for assessing the extent of disease and for defining the size of the cavities. Unlike conventional lung abscesses, tuberculous cavities

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**KEY POINTS**

**About Secondary Tuberculosis**

1. Reactivation occurs in 10% to 15% of patients, half within 2 years of primary disease.
2. Reactivation is most common in men 30 to 50 years of age.
3. Apical infection is most common. The high oxygen content and reduced lymphatic flow favor *M. tuberculosis* survival in this region.
4. Symptoms progress slowly over several months: worsening cough with sputum production, low-grade fever, night sweats, fatigue, and weight loss.
5. Hemoptysis or pleuritic pain indicate severe disease.
6. Physical exam usually produces minimal findings; post-tussive rales may be seen.
7. Chest radiograph shows apical cavities (without fluid); order apical lordotic. A computed tomography scan is often helpful.
8. Cavitary disease is highly infectious; cavities contain between 10⁸ and 10¹⁰ organisms. Isolate all patients. In HIV infection, the chest radiograph often does not show cavities. All pneumonias in patients with AIDS are considered to involve tuberculosis until proven otherwise.
rarely have air fluid levels. In patients with AIDS, infiltrates may be in any region of the lung and may not cavitate. Any HIV-infected patient with a new pulmonary infiltrate should therefore be considered to have tuberculosis until proven otherwise. In fact, in some instances, HIV-infected patients with active respiratory tuberculosis may have a negative CXR.

Individuals with cavitary disease are potentially highly infectious. Cavities may contain between $10^9$ and $10^{10}$ organisms. Patients should be placed in respiratory isolation while sputum AFB smears and cultures are obtained. The number of organisms seen on smear directly correlates with infectiousness—that is, the higher the number of organisms per microscopic field, the higher the likelihood of disease spread.

**Diagnosis**

The classic test for making the diagnosis of pulmonary tuberculosis is the Ziehl–Nielson acid-fast sputum smear. Morning sputum samples tend to have the highest yield. A single negative smear should not delude the clinician into a false sense of security. Three sputum smears are recommended, because in cavitary disease, the release of infectious droplets is intermittent. Only after three smears are negative should the patient be declared to be at low risk for spreading infection. Negative smears do not definitively exclude tuberculosis.

To be positive, the sputum smear must contain $10^4$ organisms per milliter. A fluorochrome stain using auramine–rhodamine is more sensitive and allows sputum to be examined at low magnification (20x or 40x magnification) as compared with conventional AFB smears that must be examined at high magnification (100x). Sputum smear has only a 60% sensitivity as compared with sputum culture. The PCR technique can effectively detect as few as 10 organisms in a clinical specimen. Two assays, one using mycobacteria RNA as its initial template, and the other using mycobacterial DNA, are commercially available. Sensitivity and specificity are greater than 95% in smear-positive cases, and specificity in smear-negative cases is high. False negative and false positive results are common in less experienced laboratories, and nucleic acid amplification assays are recommended only to complement traditional methods. In patients on antituberculous therapy, PCR cannot differentiate killed from actively growing organisms.

Culture remains the most accurate method for diagnosing *M. tuberculosis*. In patients that fail to produce sputum, aspiration of the gastric contents in the morning before the patient arises from bed is useful for obtaining samples for culture. In patients with suspected disseminated disease, blood samples in which all cells are lysed to release intracellular mycobacteria should be collected. The bacterium grows at about 1/20th the rate of more conventional bacteria, taking 3 to 6 weeks to grow on Lowenstein–Jensen medium. Living mycobacteria can be more quickly detected in blood, sputum, pleural fluid, or CSF using the Bactec radiometric or fluorometric culture system, which is designed to detect mycobacteria metabolism within 9 to 16 days. Drug susceptibilities can also be reliably tested using this method.

**Treatment**

The principal strategies for treating mycobacteria differ somewhat from more conventional bacteria. Because mycobacteria are intracellular and grow very slowly, and because dormant tuberculous organisms found in necrotic cavitary lesions are difficult to kill, antituberculous therapy must be prolonged—a period of months.

Secondly, because the number of mycobacterial organisms in the host is usually high, the potential for selecting for resistant mycobacteria is high. To reduce this risk, treatment with two or more antimycobacterial medications is recommended. Generally, 1 in $10^6$ organisms is resistant to INH. Cavitary lesions often contain between $10^9$ and $10^{10}$ organisms, assuring the survival and replication of resistant organisms. Administration of two drugs reduces the probability of selecting for a resistant organism because only 1 in $10^{12}$ organisms ($10^6 \times 10^6$) would be expected to be resistant to both antimicrobial agents.

A third major consideration is advent of multidrug-resistant *M. tuberculosis* (MDR-TB). These mycobacteria
are resistant to isoniazid and rifampin, and they must be treated with three or more other antimycobacterial agents. In the early 1990s in the United States, MDR-TB was major concern; however, with improved infection control measures, the use of four drug regimens, and directly observed therapy, the incidence of MDR-TB has been reduced to less than 2%, and resistance to INH alone is approximately 8%.

Resistance is classified as either secondary or primary. Primary resistance is defined as infection with a resistant strain in a patient who has never received antituberculous drugs. When a resistant strain is cultured from a patient who were previously treated for drug-sensitive tuberculosis, the infection is said to be secondarily resistant. Secondary resistance is a major problem among homeless people, illicit drug users, and patients with AIDS.
### Table 4.5. Antituberculous Medications: Half-Life, Dosing, Renal Dosing, and Cost

<table>
<thead>
<tr>
<th>Antituberculous agent (trade name)</th>
<th>Half-life (h)</th>
<th>Dose</th>
<th>Dose for reduced creatinine clearance (mL/min)</th>
<th>Cost*</th>
</tr>
</thead>
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<tr>
<td><strong>First line</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid (Tubzid, Nydrazid)</td>
<td>0.5–4</td>
<td>300 mg PO or IM q24h</td>
<td>No change required</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>2–5</td>
<td>No change required</td>
<td></td>
<td>$</td>
</tr>
<tr>
<td>Rifampin (Rifadin, Rimactane)</td>
<td>early</td>
<td>600 mg PO q24h</td>
<td>No change required</td>
<td>$</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>10–16</td>
<td>15–30 mg/kg PO q24h, divided into 2–4 doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethambutol (Myambutol)</td>
<td>3–4</td>
<td>15–25 mg/kg PO q24h</td>
<td>50–80: 15 mg/kg q24h, 10–50: 15 mg/kg q24–36h</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>&lt;10: 15 mg/kg q48h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>2–5</td>
<td>1–2 g IM or IV q24h</td>
<td>50–80: 15 mg/kg q24–48h, 10–50: 15 mg/kg q72–96h</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>&lt;10: 7.5 mg/kg q72–96h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Second line</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin (Cipro)</td>
<td>4</td>
<td>750 mg PO q12h</td>
<td>10–50: q18h/&lt;10: q24h</td>
<td>$$$</td>
</tr>
<tr>
<td>Amikacin (Amikin)</td>
<td>2</td>
<td>7–10 mg/kg IM or IV q24h (not to exceed 1 g), 5 ×/week</td>
<td>Renal dosing based on serum levels</td>
<td>$</td>
</tr>
<tr>
<td>Capreomycin (Capastat)</td>
<td>4–6</td>
<td>1 g IM q24h</td>
<td>10–50: 7.5 mg/kg q24–48h, 10: 7.5 mg/kg ×2 weekly</td>
<td>$$$$</td>
</tr>
<tr>
<td>Cycloserine (Seromycin)</td>
<td>8–12</td>
<td>250–500 mg PO q12h</td>
<td>10–50: 250–500 mg q24h, 10: 250 mg q24h</td>
<td>$$$$</td>
</tr>
<tr>
<td>Para-aminosalicylic acid</td>
<td>2</td>
<td>10–12 g PO q24h</td>
<td>Obtain from the U.S. Centers for Disease Control and Prevention</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>in 3–4 divided doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethionamide (Trecator)</td>
<td>4</td>
<td>0.5–1 g PO q24h</td>
<td>&lt;10: 5 mg/kg q48h</td>
<td>$–$$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>in 1–3 doses</td>
<td></td>
<td>$</td>
</tr>
</tbody>
</table>

*10-Day course cost dollars: $ = 10–50; $$ = 51–100; $$$ = 101–140; $$$$ = 141–180; $$$$$ ≥180.

### Table 4.6. Typical Course of Direct Observed Therapy for Tuberculosis

<table>
<thead>
<tr>
<th>Timing</th>
<th>Frequency</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 1–2</td>
<td>Once daily</td>
<td>Isoniazid 300 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rifampin 600 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pyrazinamide 1.5 g (&lt;50 kg), 2 g (51–74 kg), 2.5 g (&gt;74 kg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Streptomycin 750 mg (&lt;50 kg) or 1 g (&gt;50 kg)</td>
</tr>
<tr>
<td>Weeks 3–8</td>
<td>Twice weekly</td>
<td>Isoniazid 15 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rifampin 600 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pyrazinamide 3 g (&lt;50 kg), 3.5 g (51–74 kg), 4.0 g (&gt;74 kg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Streptomycin 1 g (&lt;50 kg), 1.25g (51–74 kg), 1.5 g (&gt;74 kg)</td>
</tr>
<tr>
<td>Weeks 9–26</td>
<td>Twice weekly</td>
<td>Isoniazid 15 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rifampin 600 mg</td>
</tr>
</tbody>
</table>
Outside of the United States, the percentages of MDR-TB and INH-resistant strains vary widely. The worldwide median frequency of primary INH resistance is estimated to be 7.3%, with higher levels being observed in Asia, Africa, and Latin America, and lower levels in Europe and Oceania. The worldwide incidence of primary MDR-TB is 1.4%; however, rates of MDR-TB as high as 14% have been reported in countries in which tuberculosis control programs have deteriorated (Latvia, South Korea, and Russia, for example). Extensively drug resistant tuberculosis (XDR) has recently been reported in South Africa. XDR TB fails to respond to nearly all drugs. The mortality can exceed 90%.

The various antituberculous agents have been classified as first-line and second-line drugs. First-line medications include INH, rifampin, pyrazinamide, streptomycin, and ethambutol. These agents are more efficacious and less toxic than the second-line drugs. With the exception of ethambutol, first-line agents are also bactericidal. Whenever possible, first-line drugs should be employed for the treatment of \( \text{M. tuberculosis} \). Tables 4.4 and 4.5 summarize the toxicities and recommended doses of each of these agents.

**Prevention**

Tuberculosis is spread strictly from person to person. Identifying and preventing individuals who have been exposed to tuberculosis from developing active disease is a major public health goal. The purified protein derivative (PPD) test is a very helpful skin test that assesses exposure to tuberculosis. The test is produced by acid precipitation of tubercle bacilli proteins, and the 5-tuberculin unit dose has been standardized and is administered as a 0.1-mL subcutaneous injection on the volar aspect of the forearm. Deeper injection is ineffective because tuberculous proteins can be removed by blood flow, producing a false negative result.

The injection should produce a discrete raised blanched wheal. The test is read 48 to 72 hours after injection; however, the reaction usually persists for 1 week. The diameter of induration is measured, and a diameter of more than 10 mm is defined as positive. A positive test indicates high risk for contracting tuberculosis. Of people with a PPD reaction 10 mm in diameter, 90% are infected with tuberculosis. If the reaction measures more than 15 mm, 100% are infected. The 15-mm diameter is defined as a positive reaction in individuals with no risk factors for tuberculosis. In individuals who are immunocompromised (HIV-positive, organ transplant patients receiving more than 15 mg prednisone daily) or who are recent household contacts of a patient with active tuberculosis, more than 5 mm is considered a positive reaction.

A positive test simply indicates that, sometime in the past, the individual was exposed to active tuberculosis; however, this finding does not indicate active

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**KEY POINTS**

**About Antieuberculous Therapy**

1. A four-drug regimen (pending sensitivity testing) is recommended.
   a) Of every \( 10^6 \) organisms, 1 is naturally resistant to one drug.
   b) Cavitary lesions contain between \( 10^9 \) and \( 10^{10} \) organisms.
   c) A minimum of two effective drugs are needed to prevent resistance \( (10^6 \times 10^9 = 10^{15}) \).
   d) Primary isoniazid (INH) resistance is common; to reliably prevent resistance, treat with INH, rifampin, pyrazinamide, and ethambutol (pending sensitivities).

2. INH-resistance is 8% in the United States, 7.3% worldwide. Higher in Asia, Africa, and Latin America.

3. Multidrug resistance is below 2% in the United States, but up to 14% in parts of Eastern Europe.

4. Secondary resistance occurs in patients who don’t reliably take their medications.

5. Directly observed therapy (DOT) is now recommended for unreliable patients, and for patients with INH- or rifampin-resistant strains.
The conversion from negative to positive in an individual who is tested annually indicates exposure to tuberculosis during the time interval between tests. Tuberculin skin tests are useful in otherwise healthy individuals, but cannot be relied upon to determine exposure in HIV patients with low CD4 counts, in patients receiving immunosuppressants, or in patients with severe malnutrition.

Individuals with a positive PPD should have a CXR, and if pulmonary lesions are noted, three sputum samples should be obtained for culture and smear. Prophylaxis should be given only if all sputum samples prove negative for tuberculosis. Because the risk of developing active disease is highest within 2 years of exposure, all individuals who have converted from a negative to a positive test within 2 years should receive INH prophylaxis. Preventive therapy is also warranted when a positive test is associated with other specific risk factors (HIV infection, known recent exposure to tuberculosis, abnormal CXR, intravenous drug abuse, and certain underlying diseases).

In other individuals with a positive PPD, the risk of INH hepatotoxicity must be balanced against the likelihood of preventing the development of active disease. The U.S. Centers for Disease Control and Prevention currently recommends that all individuals with a positive PPD receive prophylaxis. However, in individuals 35 years of age or older, the risk of hepatotoxicity may outweigh the potential benefit of INH prophylaxis. Hepatic enzymes should be monitored at monthly intervals in HIV-positive patients, pregnant women, patients with underlying liver disease, and in those receiving other potentially hepatotoxic drugs or drinking alcohol daily. Prophylaxis should be discontinued if transaminase levels rise exceed 3 times the normal values in association with symptoms consistent with hepatitis.

The recommended prophylactic regimen is INH 300 mg daily for 6 months. For HIV-infected patients, 12 months of INH prophylaxis is recommended.

### Atypical Mycobacteria

Atypical mycobacteria are found throughout the environment in soil and water. These organisms have a low virulence, and they do not usually cause pulmonary disease in otherwise healthy individuals. In patients with underlying pulmonary disease, these organisms can be inhaled and cause pulmonary infection.

_M. avium_ complex is the most common of the atypical mycobacteria to infect the lung. A cavitary upper lobe lesion is the usual manifestation of this disease. The cavities tend to be somewhat smaller and thinner walled than those with _M. tuberculosis_. Pulmonary infection with _M. avium_ complex is seen more commonly in elderly patients without obvious risk factors. Atypical mycobacteria are associated with a chronic cough, hemoptysis, and weight loss. Patients may complain of a nonproductive cough, with or without sputum production. The sputum may be blood-tinged or frankly bloody. Pleuritic chest pain is common. Physical examination typically reveals a posterior pneumothorax, which is usually asymptomatic. The CXR is characteristic, with a cavitary lesion on the upper lobe.

### KEY POINTS

#### About Atypical Mycobacteria

1. Atypical mycobacteria are found in soil and water.
2. Infects males over the age of 50 years, who are also alcoholic, smokers with chronic lung disease. Often presents as upper lobe cavitary disease.
3. Infects women over the age of 60 years without apparent underlying disease. Presents as right middle lobe or lingular disease.
4. _M. avium_ complex is the most common pathogen; _M. kansasii_, _M. fortuitum_, and _M. abscessus_ are rarer.
5. Management is complex and requires a pulmonary or infectious disease specialist.
primarily in male smokers in their early fifties who abuse alcohol. Infection of the lungs is also seen in women 60 year of age or older with no apparent underlying disease, most commonly involving the right middle lobe or lingula.

*M. kansasii*, *M. fortuitum*, and *M. abscessus* can also infect the lungs, causing chronic cavitary disease. Because these organisms are found throughout the environment and may colonize as well as infect patients with chronic lung diseases, elaborate criteria for differentiating colonization from infection have been established. Therapy for atypical mycobacterial infection must be prolonged and is based on sensitivity testing. Often these organisms respond poorly to therapy, and resection of the infected lung segment may be required for cure. Management of these patients is complex and requires the supervision of an experienced pulmonary or infectious disease specialist.

Fungal Pneumonias

The most common forms of fungal pneumonia in the normal host are histoplasmosis and coccidiomycosis. In the immunocompromised host, *Cryptococcus* and *Aspergillus* can also cause pneumonia (see Chapter 15).

**Histoplasmosis**

**Epidemiology.** *Histoplasma capsulatum* is one of the more common causes of chronic pneumonia in the Midwestern and Southeastern United States. This organism survives in moist soil in temperate climates and is most commonly reported in the Ohio and Mississippi River valleys. The development of histoplasmosis is generally associated with construction or excavation of soil contaminated with *H. capsulatum*. Infection is also reported in spelunkers, who contract the infection by disturbing dried bat guano containing high concentrations of infectious particles. Exposure to infectious particles can also occur after the renovation of old buildings previously inhabited by birds or bats.

**Pathogenesis.** *H. capsulatum* is a fungus and exists in two forms: mycelia or yeast. In the moist soil of temperate climates, the organism exists in the mycelial form as macroconidia (8 to 15 µm in size) and microconidia (2 to 5 µm in size). When infected soil is disturbed, microconidia float in the air and can be inhaled into the lung. Once in the lung, microconidia are ingested by alveolar macrophages and neutrophils. In the intracellular environment of these phagocytes, the mycelia transform to rounded, encapsulated yeast cells. During this transformation, multiple genes are upregulated, including a gene that increases production of a calcium-binding protein important for acquiring calcium (an essential ion for yeast survival) from the intracellular environment. The expression of this calcium-binding protein may explain the frequent finding of calcifications in infected tissues.

As is observed in tuberculosis, infected macrophages transport the yeast forms to the hilar lymph nodes where *Histoplasma* antigens are presented to T cells. Within several weeks, cell-mediated immunity develops, and CD4 T cells activate macrophages to produce fungicidal products.

**Clinical Manifestations.** In more than 90% of patients, infection is controlled. In many patients, primary exposure is asymptomatic or results in a mild influenza-like illness. Very young people, elderly people, and patients with compromised immune systems are more likely to develop active disease. Symptoms usually develop within 14 days of exposure and may include high fever, headache, nonproductive cough, and dull nonpleuritic chest pain. This form of chest pain is thought to be the result of mediastinal node enlargement. In other patients, chest pain may be sharper and may worsen upon lying down, reflecting the development of pericarditis (observed in approximately 6% of cases).

On CXR, patchy infiltrates may be seen during acute disease that subsequently calcify producing a “buckshot” appearance. Healed histoplasmosis is also the most common cause of calcified lesions in the liver and spleen. In acute disease, mediastinal lymphadenopathy may be prominent and may mimic lymphoma or sarcoidosis. A history of exposure to a site where soil was excavated is particularly important in trying to
KEY POINTS

About the Clinical Manifestations of Histoplasmosis

1. In 90% of cases, a brief self-limiting flu-like illness occurs or the person remains asymptomatic.
2. Disease can develop in elderly, very young, and immunocompromised individuals.
3. At 14 days post exposure, the individual may have
   a) high fever, headache, nonproductive cough, and dull, nonpleuritic chest pain.
   b) a CXR with patchy infiltrates that later convert to “buckshot” calcifications.
   c) mediastinal lymphadenopathy that may mimic lymphoma or sarcoidosis.
   d) progressive mediastinal fibrosis (a rare complication).
4. Cavitary disease is clinically similar, with men older than 50 years who have chronic obstructive pulmonary disease at higher risk.
5. Disseminated disease occurs in 10% of symptomatic primary disease.
   a) Likelihood of dissemination occurs in people who are very old, very young, or immunosuppressed (because of AIDS or transplantation).
   b) Meningitis with lymphocytosis and low glucose may develop.
   c) Reticulonodular pattern on CXR in most cases, but CXR normal in one third.

Progressive disseminate histoplasmosis occurs in about 10% of symptomatic primary infections. Progressive dissemination also develops as a consequence of reactivation of old disease. In the immunosuppressed individual, reactivation is the most likely pathway for disseminated disease. Onset of symptoms is usually abrupt. Fever and malaise are followed by nonproductive cough, weight loss, and diarrhea. Hepatosplenomegaly usually develops, and lymphadenopathy may be detected. Anemia, thrombocytopenia, and leukopenia are observed in a high proportion of patients. Meningitis may develop, resulting in lymphocytosis and low glucose in the cerebrospinal fluid. A CXR may show a reticulonodular pattern or scattered nodular opacities; however, the CXR is normal in nearly one third of cases. Mortality is high if treatment is not initiated.

Diagnosis. *H. capsulatum* can be readily grown from tissue samples and body fluids using brain–heart infusion media containing antibiotics and cycloheximide (inhibits the growth of saprophytic fungi). Mycelial growth can usually be detected within 7 days and confirmed using a DNA probe. The clinical microbiology

**KEY POINTS**

About the Diagnosis of Histoplasmosis

1. Sputum culture is often positive.
   a) Requires selective media (brain–heart infusion with antibiotics and cycloheximide).
   b) Not a routine method; clinical microbiology must be notified.
   c) Bronchoscopy improves yield (90% in HIV patients).
2. Bone marrow positive in 50% of cases.
3. Lysis–centrifugation method positive in up to 50% of blood samples.
4. Polysaccharide urine and serum antigen test is the most sensitive, being positive for
   a) 90% of disseminated disease,
   b) 40% cavitary disease, and
   c) 20% acute pulmonary disease
5. Method can also be used to test bronchoscopic lavage fluid.
6. Histopathology shows noncaseating or caseating granulomas. Silver stain best for identifying the yeast forms. Hematoxylin–eosin is not useful; periodic acid Schiff may help with identification.
7. Urine antigen test positive in 90% of disseminated histoplasmosis.
lab must be notified that *H. capsulatum* is the possible pathogen, because the necessary culture methods are not employed on routine samples.

A single sputum culture has only a 10% to 15% yield; collection of multiple sputum cultures increases the yield. Bronchoscopy has proved useful for providing good sputum samples yielding positive cultures in 90% of HIV patients with pulmonary histoplasmosis. Bone marrow and blood cultures should also be obtained and are positive in up to 50% of cases. The lysis–centrifugation blood culture technique (also used to culture mycobacteria) is the most sensitive method. The most effective method for detecting progressive disseminated histoplasmosis is the urine and serum polysaccharide antigen test. Antigen is detected in up to 90% of patients with disseminated disease. The antigen test is also positive in 40% of patients with cavitary pulmonary diseases and 20% with acute pulmonary histoplasmosis. Pulmonary lavage fluid can also be tested in this manner. A PCR method is available only on an experimental basis.

Histopathologic examination of infected tissue also allows for rapid diagnosis. Noncaseating or caseating granulomas may be seen. An excessive fibrotic reaction may be seen in some patients. Silver stains are most effective for identifying the typical yeast forms in tissue biopsies. Organisms are poorly visualized by hematoxylin–eosin staining, but can often be seen on periodic acid Schiff stain.

**Treatment.** Itraconazole is the most effective azole for oral treatment. In patients with acute pulmonary histoplasmosis who fail to improve over the first week, itraconazole 200 mg daily for 4 to 6 weeks is recommended. If the patient is unable to tolerate azoles or cannot take oral medications, amphotericin B 0.4 to 0.5 g/kg can be administered intravenously until symptoms subside. In patients with extensive mediastinal involvement, itraconazole 200 mg daily, can be given for 3 to 6 months. If rapid resolution of symptoms is necessary, amphotericin B is preferred.

Patients with severe mediastinal fibrosis may also require surgical intervention to correct vascular and airway obstruction. In cavitary pulmonary disease, progression of lesions over 2 to 3 months or persistent cavities associated with declining respiratory function warrant treatment with itraconazole 200 mg twice daily for a minimum of 6 months. Amphotericin B may be required if lesions fail to improve on itraconazole therapy. In acute, life-threatening progressive disseminated histoplasmosis, amphotericin B should be given in high doses: 0.7 to 1 mg/kg daily. Once the patient has defervesced, the dosage can be lowered to 0.4 to 0.5 mg/kg, or the patient can be switched to itraconazole 200 mg twice daily.

**Coccidiomycosis**

Epidemiology—Like *H. capsulatum*, *Coccidioides immitis* survives and grows in soil. The ideal conditions for survival of *C. immitis* are dry, alkaline soil, hot summers, and winters with few freezes. These conditions exist in central California’s San Joaquin Valley and in the southern regions of Arizona, New Mexico, and Texas. *C. immitis* is also found in Mexico, Central America,
and South America. Infections are most commonly reported in the summer months when dry soil more readily forms dust particles. Epidemics have been associated with disruption of soil by archeological excavation, earthquakes, and dust storms. In recent years, the incidence of coccidiomycosis has increased as a consequence of the increased numbers of people living in endemic areas.

**Pathogenesis.** Also like *H. capsulatum*, *C. immitis* is a dimorphic fungus. It exists in soil as mycelia that can form small arthroconidia (5-μm barrel-shaped structures). Arthroconidia can become airborne, whereupon they are inhaled by humans and become lodged in the terminal bronchioles. In the warm moist environment of the lung, the arthroconidia transform into spherules. As the spherules mature, their outer walls thin, and they release endospores that are ingested by macrophages. As is observed in histoplasmosis and tuberculosis, macrophages transport the infectious particles to the hilar lymph nodes, the lymphatic system, and the bloodstream, resulting in dissemination. Cell-mediated immunity is critical for control of the infection.

**Clinical Manifestations.** Approximately two thirds of patients exposed to arthroconidia experience minimal symptoms. When symptoms are noted, they usually develop 7 to 21 days after exposure. Nonproductive cough and fever are the most frequent symptoms. Pleuritic chest pain, shortness of breath, headache, and fatigue are also commonly reported. Skin manifestations may include erythema nodosum (red, painful nodules on the anterior shins), erythema multiforme (target-like lesions involving the entire body, including the palms and soles) or a nonpruritic papular rash. Arthralgias may develop in association with erythema nodosum. Eosinophilia is commonly observed on peripheral blood smear.

In about half of patients, a CXR is abnormal, most commonly demonstrating unilateral infiltrates, pleural effusions, and hilar adenopathy. In patients with depressed cell-mediated immunity (primarily patients with AIDS and CD4 counts below 100/mm$^3$), the infection can disseminate, causing diffuse opacification of the lungs and severe respiratory failure. Meningitis, skin lesions, bone infection and arthritis may also develop as a consequence of dissemination.

In some patients pulmonary infection can persist, causing progressive destruction of lung parenchyma associated with a productive cough, chest pain, weight loss. A CXR may demonstrate areas of fibrosis, nodules, cavitary lesions, or a combination. An isolated nodule can persist in approximately 4% of pulmonary cases and can be differentiated from neoplasm only by biopsy. These lesions seldom calcify as the lesions of histoplasmosis do. A chronic pleural effusion can result from the rupture of a peripheral cavitary lesion into the pleural space. This complication is most commonly reported in young, otherwise healthy, athletic males.

**Diagnosis.** Travel to, or past residence in, an endemic area should alert the clinician to the possibility of coccidiomycosis. Examination of induced sputum or sputum obtained by bronchoscopy may reveal spherules. The fungus is not seen on Gram stain, but can be detected by silver stain. Biopsies of infected tissue should be obtained; they usually reveal caseating or noncaseating granulomas and spherules. The organism grows readily as a white mold on routine mycology media and on bacterial media under aerobic conditions.

Multiple serologic tests are available. These tests are often required to make the diagnosis, because of unavailability of sputum and biopsy specimens. Immunoglobulin M (IgM) serum titers against *C. immitis* are usually positive within the first week of disease. Immunoglobulin G (IgG) levels are most commonly tested by complement fixation or immunodiffusion. Levels of IgG increase after IgM and often persist for years. A correlation has been observed
between the IgG serum titer and severity of disease. A rising titer that exceeds 1:32 may signal disseminated disease; a falling titer indicates a favorable prognosis. Patients with no detectable lesions can have titers below 1:8 for many years after exposure.

**Treatment.** Most infections with this organism spontaneously resolve. Treatment is reserved for patients with disseminated disease and patients with persistent or progressive coccidioidal pneumonia with hypoxia. Treatment needs to also be considered in patients with pulmonary disease who are at increased risk for dissemination, including people that are black, Philippino, pregnant, diabetic, and immunosuppressed (including patients with AIDS).

Amphotericin B remains the preferred initial therapy for life-threatening disseminated disease or severe pulmonary disease until the infection is under control. High doses of amphotericin B (0.7 to 1 mg/kg daily) are recommended. In less severe disease, fluconazole (400 to 800 mg daily) or itraconazole (200 mg twice daily) are used. These agents are preferred because of their low toxicity and suitability for prolonged therapy. Treatment should be continued until symptoms and signs of infection have resolved. A minimum of 6 months’ therapy is recommended. In patients with meningeal involvement, triazole therapy should be continued indefinitely.

Surgical debridement of large purulent collections is recommended. Resection of rapidly expanding pulmonary cavities should be performed to prevent rupture into the pleural space. Surgical resection is also recommended to prevent bronchopleural fistula formation and to correct life-threatening pulmonary hemorrhage.

**FURTHER READING**

**General**


Pulmonary Infections


**Pneumococcal Pneumonia**


**Haemophilus influenzae Pneumonia**


**Aspiration Pneumonia**


**Legionnaires’ Disease**


**Atypical Pneumonia**


**Actinomycosis and Nocardiosis**


**Tuberculosis**


**Histoplasmosis**


**Coccidiomycosis**


Measles (Rubeola), an acute infection caused by measles virus, is highly contagious and usually seen in children. The illness is characterized by cough, coryza, fever, and a maculopapular rash that begins several days after the initial symptoms appear. Measles in the developed countries has been largely controlled since the introduction of live-attenuated measles vaccine. But measles continues to be a major cause of morbidity and mortality in unvaccinated infants and children, especially those living in developing countries where measles vaccines are not universally available.

**Pathogen**

Measles virus is a member of the Morbillivirus genus of the Paramyxoviridae family. Measles virus contains a single-stranded, negatiesense linear RNA genome. The virus is pleomorphic, ranges in diameter from 100 to 250 nm, and consists of a helical RNA protein core surrounded by a lipid envelope derived from the host cell. Measles virus contains six major structural proteins: two of these, the hemagglutinin (H) protein and the fusion (F) protein, as well as surface envelope glycoproteins, are important in the development of neutralizing antibodies. The H protein, which mediates viral attachment to host cells, is essential for primary infection. The F protein enhances cell-to-cell spread of the virus. Matrix (M) protein, which is located on the inner surface of the virus envelope, is important in viral assembly. Neutralizing antibodies confer lifelong immunity to measles and are primarily directed against the H protein. The nucleoprotein (NP), polymerase phosphoprotein (P), and large protein (L) are internal to the virus. L and P proteins are important in RNA polymerase activity, and NP is a structural nucleocapsid protein. Measles virus infects only humans and primates.

Because measles virus has a lipid envelope, it is inactivated by lipid solvents such as ether and chloroform; the virus is also inactivated by heat (>37°C), cold (<20°C), ultraviolet light, and extremes in pH (<5 and >10). Infectious virus can be maintained for long periods at ~70°C.

**Epidemiology**

Measles is an airborne virus that is spread by direct contact with droplets from respiratory secretions of infected persons. It is one of the most communicable of the infectious diseases, most infectious during the late prodromal phase of the illness, when cough and coryza are at their peak.

Measles is seen in every country in the world. Without a vaccine, epidemics of measles lasting 3 to 4 months could be predicted to occur every 2 to 5 years. Countries in which measles vaccine is widely used have experienced a marked decrease in the incidence of disease.

In China, measles epidemics occurred most often in late winter through early spring, most frequently
in crowded areas. Protective transplacental immunity to measles is conferred to infants whose mothers have either had measles infection or received measles vaccine. However, measles antibody titers are higher after natural infection; infants whose mothers had measles infection have maternally derived passive measles antibody for longer periods, up to 9 to 12 months of age, than do infants whose mothers received measles vaccine. Over time, therefore, more infants will be susceptible to measles infection at younger ages because women born after universal immunization in 1960s will constitute a larger proportion of those giving birth.

Pathogenesis

Measles is transmitted by aerosolized particles from the respiratory secretions of infected individuals directly to susceptible hosts. The particles can also persist in the environment for more than 1 hour and be acquired by inhalation. Individuals with measles are most infectious during the prodromal stage (which occurs 7 to 10 days after exposure) through the fourth day after the onset of rash. Measles is highly contagious, and symptomatic infection develops in virtually all susceptible exposed individuals.

After exposure, measles virus enters the nasopharynx, attaches to and invades the respiratory epithelium, and spreads to the regional lymphatics; cell-associated viremia follows on the second or third day after exposure. Virus continues to replicate in both local and distant reticuloendothelial sites, and secondary viremia occurs between 5 and 7 days after infection. Cell-associated viremia primarily involves leukocytes, especially monocytes. Within 7 to 14 days after exposure active replication of measles virus occurs throughout the body, including the respiratory tract, skin, and other organs. This active replication is clinically manifested as upper respiratory tract symptoms, fever, and rash. The development of both humoral and cellular immunity by 15 to 17 days after exposure aborts further viral replication, and in normal hosts, clinical illness resolves.

Pathologic changes associated with viremia include lymphoid hyperplasia of the adenoids, tonsils, lymph nodes, spleen, and intestinal tract. Multinucleated giant cells are found most commonly during the early stage of measles in the respiratory tract, especially in the nasopharynx and bronchial mucosa. Syncytial epithelial cells can also be demonstrated. Mononuclear infiltration with peribronchial inflammation occurs in the respiratory tract.

Both humoral and cellular responses are important in developing and maintaining normal immunity to measles. Neutralizing antibodies confer lifelong immunity to measles. Neutralizing antibody to H protein, however, appears to confer only partial immunity to measles; individuals vaccinated with killed virus in whom atypical measles developed after exposure to measles virus lacked neutralizing antibody to F protein. By contrast, live-attenuated vaccine provides complete immunity, and vaccine recipients demonstrate neutralizing antibody to both H and F proteins. Whereas humoral immunity is important in preventing measles infection, the cellular immune response appears to be important in aborting clinical symptoms during acute infection. Among children with congenital hypogammaglobulinemia, for example, measles infection follows a normal clinical course in the absence of a specific antibody response, whereas a congenital or acquired deficiency in cellular immunity predisposes children and adults to severe or fatal infection.

A striking feature of the immune response to measles virus is the induction of transient cellular immunosuppression after infection or vaccination. Delayed-type hypersensitivity responses, such as reactivity to purified protein derivative, are transiently suppressed, and defects in lymphocyte proliferation in response to various mitogens are
observed in vitro. Anergy can persist for as long as 2 to 6 weeks after infection. This response is characteristic of cytokine-mediated immune suppression.

Clinical Manifestations

Typical Measles

The incubation period of measles is 10 to 14 days; it is often somewhat longer in adults than in children. A prodromal phase lasting several days begins after the incubation period. It is manifested by malaise, fever, anorexia, conjunctivitis, and respiratory symptoms such as cough and coryza, and may resemble a severe upper respiratory tract infection. Toward the end of the prodrome, just before the appearance of the rash, Koplik’s spots appear. Koplik’s spots are pathognomonic of measles. First noted by Koplik in 1896, they consist of bluish gray specks on a red base. They have been likened to grains of sand and, without examination of the buccal mucosa in good light, may be overlooked. Most often they appear on the mucosa opposite the second molars. However, in severe cases, the entire mucous membrane of the mouth may be involved. This enanthem persists for several days and begins to slough as the rash appears.

The rash of measles usually begins on the face and proceeds down the body to involve the extremities last, including the palms and soles (Fig 1). During the healing phase, the involved areas (except palms and soles) may desquamate. The rash is erythematous and maculopapular; as it progresses, it becomes confluent, especially on the face and the neck. The rash usually lasts about 5 days and starts to clear first on the skin that was initially involved. The patient with measles is usually most ill during the first or second day of the rash. Several days after the appearance of the rash, the fever abates and the patient begins to feel better. The entire uncomplicated illness from late prodrome to resolution of the fever and rash lasts 7 to 10 days; cough may be the last symptom to disappear.

Aptical Measles

Atypical measles occurs in individuals infected with natural virus who had previously received killed measles vaccines. These persons have a sudden onset of high fever accompanied by abdominal pain, cough, vomiting, and pleuritic chest pain.

Koplik’s spots are rarely present, and rash begins distally and progresses in a cephalad direction, with little involvement of the face and upper part of the trunk. The rash is not as generalized and confluent as in typical measles, and although it is erythematous and maculopapular, it often has a vesicular component. Cough and conjunctivitis are not prominent features of atypical measles. Pulmonary symptoms accompanied by radiographic evidence of pneumonia, hilar adenopathy, and pleural effusions are common.
Recovery from atypical measles may take 2 weeks or longer.

**Modified Measles**

An extremely mild form of measles has been observed in persons with some degree of passive immunity to the virus. This includes some babies younger than 1 year who have passively acquired maternal antibody to measles virus and some susceptible persons who received immune globulin after an exposure to measles. The symptoms of modified measles are variable, and certain classic symptoms such as the prodromal period, conjunctivitis, Koplik’s spots, and rash may be absent. The incubation period may be prolonged. At times, the infection is subclinical and, with a great degree of passively acquired immunity, may be prevented completely.

**Complications**

The most common complications of measles involve the respiratory tract and CNS. Involvement of the respiratory tract is part of the virus infection itself. In addition, bacterial superinfection may occur in any area of the respiratory tract, including the middle ear. Superinfection may be secondary to local tissue damage inflicted by the virus and depression of cellular immunity. Pneumonia accompanying measles may be caused by direct viral invasion of the lungs or by bacterial superinfection. Roentgenographic evidence of pneumonia is common, even during apparently uncomplicated measles. In infants who die of measles, pneumonia accounts for about 60% of deaths, whereas in children 10 to 14 years of age, death is more often observed to be from complications of acute encephalitis.

Encephalitis after measles in normal hosts may be acute or chronic (e.g., SSPE). Acute measles encephalitis manifests with a resurgence of fever during convalescence and frequently with headaches, seizures, and changes in the state of consciousness. Up to 50% of patients with measles but no symptoms that suggest cerebral involvement may have abnormalities detected by electroencephalography, so it is believed that viral invasion of the CNS is a common feature of measles. However, only 1 in 1000 to 2000 patients with measles develops clinical signs of encephalitis. Measles ranges encephalitis from mild to severe, and a high proportion of patients who recover are left with neurologic sequelae.

Transient hepatitis has also been reported during acute measles.

**Laboratory Findings**

Laboratory abnormalities during measles infection include leucopenia and marked lymphopenia. Serologic tests that can be used to establish the diagnosis include complement fixation, hemagglutination inhibition, and enzyme immunoassays. Although neutralizing antibody assays are more sensitive than the other tests in diagnosing previous infection, performance is expensive and time-consuming. Antibody levels begin to rise 1 to 3 days after the onset of rash and peak 2 to 4 weeks later. A fourfold or greater rise in antibody titer from paired sera or a single elevated immunoglobulin (Ig) M level is indicative of recent infection. IgM antibody is usually detectable 1 to 2 days after the onset of rash and persists for 30 to 60 days. Measles virus can sometimes be isolated from blood, urine, and nasopharyngeal secretions, but isolation is difficult, and serology is the preferred diagnostic method. Detection of measles virus antigen in respiratory epithelial cells or tissue by immunofluorescent methods and detection of viral genome by polymerase chain reaction have also been described.

**Diagnosis And Differential Diagnosis**

Classic measles with cough, coryza,
conjunctivitis, Koplik’s spots, and a maculopapular rash beginning on the face is easily diagnosed clinically. Often, there is a striking leukopenia, perhaps related to the infection and death of leukocytes. A laboratory diagnosis of measles is helpful when the clinician is unfamiliar with the illness because of the decline in cases of clinical measles since the introduction of measles vaccine. A laboratory diagnosis may also be helpful in cases of possible atypical measles, or when unexplained pneumonia or encephalitis occurs in an immunocompromised patient.

The differential diagnosis of measles includes rubella, Kawasaki syndrome, scarlet fever, roseola, infectious mononucleosis and rickettsial, enteroviral, and adenoviral infections.

**Treatment**

No specific therapy is indicated for measles infection. Although ribavirin is active against measles virus in vitro and has been used to treat immunocompromised patients with measles pneumonia and encephalitis, it has not been evaluated in controlled clinical trials and is not licensed for the treatment of measles.

Patients with measles should be given supportive therapy such as antipyretics and fluids as indicated. Bacterial superinfection should be promptly treated with appropriate antimicrobials, but prophylactic antibiotics to prevent superinfection are of no known value and are therefore not recommended.

Vitamin A, 200,000 IU administered orally to children for 1 day, has been used successfully to decrease the severity of measles, especially in those with vitamin A deficiency (Children, 6 months to 1 year old, should receive 100,000 IU.). Side effects include transient vomiting and headache. This treatment has also been recommended to be considered in the United States for children with measles who are hospitalized and are 6 months to 2 years of age or who are immunodeficient, have malabsorption, or are malnourished. Administration of vitamin A has been reported to reduce seroconversion in vaccinees and should therefore be avoided at or after immunization.

**Prevention**

It is recommended that all healthy children be given live measles vaccine at 8 months. A second is recommended that children be immunized between the ages of 12 and 15 months (usually given as measles-mumps-rubella [MMR] vaccine).

Serious hypersensitivity reactions to measles vaccine in persons allergic to egg protein have been reported. Persons with a history of anaphylactic reactions after the ingestion of eggs should be vaccinated only with extreme caution.

Live measles vaccine is contraindicated in persons with deficits in cell-mediated immunity and in pregnant women. Fatal measles in children with AIDS has been reported. Although the potential risks of measles vaccine in these children are unknown, they are less than the disease itself. It is currently recommended that children with known asymptomatic HIV infection receive measles vaccine after the age of 12 months. The use of measles vaccine should also be considered for children with known HIV infection who manifest symptoms if their CD4 T-cell levels are relatively well preserved. Children who have been treated for malignant disease may be given measles vaccine 3 months after they complete their course of therapy. High-risk children such as those described may be given monovalent measles vaccine or MMR, but they should not be given MMRV vaccine, which contains a significantly higher dose of the varicella component. No safety data for MMR in high-risk children are available.
Central Nervous System Infections

Time Recommended to Complete: 2 days

Frederick Southwick, M.D.

GUIDING QUESTIONS

1. What layers of the brain make up the meninges?
2. Where is the subdural space?
3. What is the blood-brain barrier and why is it important to consider when treating central nervous system infections?

CENTRAL NERVOUS SYSTEM INFECTIONS

Central nervous system (CNS) infections are fortunately rare, but they are extremely serious. The cerebral cortex and spinal cord are confined within the restricted boundaries of the skull and boney spinal canal. Inflammation and edema therefore have devastating consequences, often leading to tissue infarction that in turn results in permanent neurologic sequelae or death.

To understand the pathogenesis and clinical consequences of CNS infections, a working knowledge of basic neuroanatomy and neurophysiology is important.

The cerebral cortex and spinal cord are suspended in and bathed by cerebrospinal fluid (CSF), which is produced by the choroid plexus lining the walls of the cerebral ventricles and resorbed by. The arachnoid villi drain into a large midline vein, the superior sagittal sinus. The cortex and spinal cord are surrounded by three tissue layers called the meninges. The two layers closest to the cortex are called the pia mater (directly overlying the cerebral cortex) and the arachnoid. These layers make up the leptomeninges. The third layer, the dura mater (pachymeninges), serves as the outer layer (Figure 6.1). The CSF flows between the pia mater and arachnoid in the subarachnoid space.

Central nervous system infections are classified by the site of the infection. Infection of the cerebral cortex is called encephalitis, and infection of the meninges is called meningitis. Abscesses usually form in three locations within the central nervous system: the cerebral cortex, where they are termed brain abscesses; between the dura and arachnoid, where they are called subdural abscesses; or immediately outside the dura, where they form epidural abscesses.

The capillaries of the brain and spinal cord differ from those in other regions of the body. The tight junctions linking the endothelial cells of the vessels in this region are less permeable than they are in vessels elsewhere. The limited permeability of the CNS vessels forms a physiologic barrier that is commonly called the blood–brain barrier. This barrier protects the CNS from invading pathogens and toxic substances. However, the impermeability of the CNS capillaries not only confers a protective effect, it also prevents the entry of immunoglobulins, complement, and antibiotics. Therefore, if a pathogen breaches the blood–brain barrier, the host’s initial defense mechanisms are impaired, which partly explains the rapid progression and serious consequences of CNS infections. Antibiotics used to treat central nervous system infections must be capable of penetrating the blood–brain barrier,
and because penetration of all antibiotics is impeded, maximal doses (sometimes termed “meningeal doses”) are required to cure CNS infections.

**MENINGITIS**

**BACTERIAL MENINGITIS**

Bacterial meningitis remains one of the most feared and dangerous infectious diseases that a physician can encounter. This form of meningitis constitutes a true infectious disease emergency. It is important that the physician quickly make the appropriate diagnosis and initiate antibiotic therapy. Minutes can make the difference between life and death in bacterial meningitis. The rapid progression of disease leaves no time to look through textbooks to decide on appropriate management. To assure the best outcome, every clinician needs a basic understanding of bacterial meningitis and its management.

**Epidemiology and Causes**

With the advent of the *Haemophilus influenza B* (HiB) vaccine, the incidence of bacterial meningitis in children declined dramatically in the United States. Bacterial meningitis is now primarily an adult disease. The wider use of pneumococcal vaccine in patients older than 65 years of age and in patients with chronic underlying diseases also promises to reduce the incidence in adults.

Bacterial meningitis is not a reportable disease in the United States, and so an exact incidence is not available, but an estimate places the number at about 3 to 4 per 100,000 population. In underdeveloped countries, the incidence is at least 10 times higher, reflecting crowded conditions, and a lack of vaccination programs as well as other preventive public health measures.

Community-acquired bacterial meningitis in children and adults is caused mainly by four major pathogens (Table 6.1):

1. **Streptococcus pneumoniae.** *S. pneumoniae* is the most common cause of community-acquired meningitis in the United States. In other parts of the world, *Neisseria meningitidis* predominates. *S. pneumoniae* first causes infection of the ear, sinuses, or lungs, and then spreads to the bloodstream, where it seeds the meninges. *S. pneumoniae* is also the most common cause of recurrent meningitis in patients with a CSF leak following head trauma.

2. **Neisseria meningitidis.** *N. meningitidis* can cause isolated, sporadic infection or an epidemic. *N. meningitidis* first infects the nasopharynx, causing sore throat. In individuals lacking anti-pneumococcal antibodies, nasopharyngeal carriage may be followed by bacteremia and seeding of the meninges. Crowded

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**Figure 6–1.** Schematic depiction of the subgaleal, epidural, subdural, and subarachnoid spaces in the central nervous system.
Table 6.1 Causes of Bacterial Meningitis in Adults

<table>
<thead>
<tr>
<th></th>
<th>Community (%)</th>
<th>Nosocomial (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>38</td>
<td>8</td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td>4</td>
<td>38</td>
</tr>
<tr>
<td><em>Neisseria meningitidis</em></td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Listeria spp.</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td><em>Streptococci</em></td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

environments, such as college dormitories or military training facilities, increase the risk of *N. meningitidis* spread. Epidemics usually occur in the winter months when person-to-person transmission by respiratory secretions is most frequent. Patients with defects in terminal complement components are also at increased risk of contracting sporadic meningococcal infection.

3. **Listeria monocytogenes.** *L. monocytogenes* infects primarily individuals with depressed cell-mediated immunity, including pregnant women, neonates, patients on immunosuppressive drugs, or individuals infected with HIV. People over the age of 60 may also have an increased risk of developing *Listeria*. This form of meningitis is contracted by ingesting contaminated food. Heavy contamination with *Listeria* can occur when foods are stored for prolonged periods at 4°C, because the organism can grow in a cool environment. *Listeria* can contaminate unpasteurized soft cheeses and other improperly processed dairy products. High counts of this organism have also been found in defectively processed hot dogs and fish. When *Listeria* enters the gastrointestinal tract, it is able to silently invade the gastrointestinal lining, enter the bloodstream, and infect the meninges.

4. **Haemophilus influenzae.** Before administration of the HIB vaccine became common place, *H. influenzae* was the most common pathogen to cause meningitis in children; however, meningitis resulting from this organism is now rare.

The causes of bacterial meningitis in neonates reflect the organisms with which they come into contact during passage through the birth canal. *Escherichia coli* is the most common cause of neonatal meningitis, followed by group B streptococci.

**KEY POINTS**

About the Epidemiology and Causes of Bacterial Meningitis

1. Primarily a disease of adults.
2. Community-acquired disease is associated with four major pathogens:
   a) *Streptococcus pneumoniae* is the most common. Meningitis follows bacteremia from ear, sinus, or lung infection. Also associated with chronic leaks of cerebrospinal fluid.
   b) *Neisseria meningitidis* begins with colonization of the nasopharynx. Sporadic cases are often associated with terminal complement defects. Epidemics occur in crowded environments such as dormitories and military training camps.
   c) *Listeria monocytogenes* occurs in neonates, pregnant women, and immunocompromised patients. It is contracted by eating contaminated refrigerated foods.
   d) *Haemophilus influenzae* was the most common form of meningitis in children. Following widespread administration of the *H. influenzae* B vaccine, it is now rare.
3. Neonates develop gram-negative and group B streptococcus meningitis.

Nosocomial bacterial meningitis has increased in frequency since the late 1980s. This increased incidence can be explained by the increased numbers of patients undergoing neurosurgical procedures and having hardware placed in the cerebral ventricles. The bacteriology of nosocomial meningitis is very different from that of the community-acquired disease. Gram-negative rods predominate, *E. coli* and *Klebsiella* being the most common. *Staphylococcus aureus* and streptococci are other frequent pathogens (see Table 6.1). Patients undergoing ventricular shunt placement can develop meningitis from contaminated plastic shunt tubing. *S. epidermidis*, *S. aureus*, enterococci, *Bacillus subtilis*, and corynebacteria (previously called diphtheroids) are most commonly encountered.
Pathogenesis

Bacterial meningitis is most commonly blood-borne. Primary infections of the ears, sinuses, throat, lungs, heart, and gastrointestinal tract can all lead to bacteremia and, on rare occasion, the blood-borne bacteria gain entry into the subarachnoid space (Figure 6.2). Blood-borne bacteria may gain entry through the large venous sinuses in the brain. Bacteria can settle along these slow-flowing venous channels, then escape and penetrate the dura and arachnoid, infecting the CSF. Less commonly, bacteria can enter the CSF through a break in the cribiform plate or a defect in the base of the skull following basilar skull fracture. Patients with head trauma can develop CSF leakage at these sites, and bacteria from the nasopharynx or middle ear, primary S. pneumoniae, can track up through the leak into the subarachnoid space. Patients who develop brain abscesses secondary to otitis media and mastoiditis or bacterial sinusitis on rare occasion can develop meningitis because of direct spread of bacteria from the abscess to the subarachnoid space.

Because the blood–brain barrier blocks entry of immunoglobulins and complement, bacteria are able to grow unimpeded by the host's immune system in the early phases of infection. As the number of organisms increases, polymorphonuclear leukocytes (PMNs) are attracted to the site. As they attempt to kill organisms, PMNs often lyse, releasing toxic oxygen products, proteolytic enzymes, and inflammatory cytokines. These products lead to necrosis and edema of the surrounding tissue.

The marked inflammatory response in the subarachnoid space damages the cerebral microvasculature, increasing the permeability of the blood–brain barrier. Leakage of serum from the damaged vessels increases the protein level in the CSF. Inflammation at the surface of the cerebral cortex can induce vasculitis and occlusion of small arteries and cortical veins alike, causing cerebral infarction. Inflammation of the arachnoid and pia matter alters glucose transport into this region, lowering glucose levels in the CSF. Inflammation of the subarachnoid space may impair CSF flow and cause hydrocephalus. Inflammation damages neural cells in the cerebral cortex and causes cerebral edema. The ultimate consequences of intense inflammation and bacterial invasion of the meninges are increased intracranial pressure, decreased cerebral blood flow, and cerebral cortex hypoxia, leading to irreversible ischemic damage.

KEY POINTS

About the Pathogenesis of Bacterial Meningitis

1. Infectious organisms gain entry to the subarachnoid space and cerebrospinal fluid (CSF)
   a) most commonly by bacteremia, gaining entry through the large venous channels;
   b) by nasopharyngeal spread through a CSF leak caused by a cribiform plate defect or basilar skull fracture; or
   c) direct spread from a brain abscess or air sinus infection.
2. Rapid growth occurs in the CSF because the blood–brain barrier blocks entry of immunoglobulins and complement.
3. Inflammation damages the blood–brain barrier, increasing permeability, allowing entry of serum protein, and impairing glucose transport.
4. Progressive cerebral edema, increased CSF pressure, and decreased cerebral blood flow lead to irreversible ischemic damage.
**CASE 6.1**

A 47-year-old sales manager and father of two arrived in the emergency room in deep coma. He had a history of recurrent ear infections since age 12. Three days before admission to the hospital, the patient had complained of a severe left earache. He took the ear drops prescribed by his local physician, and the pain disappeared during the night. The evening before he presented to the emergency room, the patient began complaining of headache and feeling “sort of disoriented.” An hour after onset of the headache, he began vomiting, and he vomited five times during the night. The morning of admission, his wife reported that he appeared drowsy. He stayed home from work, sleeping most of the morning. About noon he awoke, but he did not recognize his wife. He began speaking incoherent sentences and became very restless. By 4 P.M., he was failing to respond when his wife called his name, and he was brought to the emergency room.

A physical examination recorded a temperature of 40°C, a blood pressure of 140/100 mm Hg, a pulse of 140 per minute, and a respiratory rate of 20 per minute. This was a very ill-appearing man who did not respond to his name, and who moved all limbs only in response to deep pain.

The patient’s ears were bilaterally blocked with cerumen. The pupils of his eyes were dilated to 8 mm, but reacted to light. Optic disc margins were flat. The neck was very stiff, with both Kernig’s and Brudzinski’s signs present. Coarse diffuse rhonchi were evident throughout all lung fields. No skin lesions were seen. A neurologic exam showed no cranial nerve abnormalities. Reflexes were symmetrical, and the patient moved all limbs.

Laboratory workup found a peripheral WBC count of 19,500/mm³, with 39% polymorphonuclear leukocytes (PMNs), 50% band forms, 6% lymphocytes, and 5% monocytes. Hematocrit was 35.5%, and chest X-ray (CXR) showed no infiltrates.

A lumbar puncture was performed in the emergency room. Opening CSF pressure was found to be 560 mm H₂O (normal: 70 to 180 mm). A CSF analysis showed a WBC count of 9500/mm³ (95% PMNs), protein 970 mg/dL (normal: 14 to 45 mg/dL), and glucose 25 mg/dL, with a simultaneous serum glucose level of 210 mg/dL (normal: 50 to 75 mg/dL, generally two thirds of serum glucose). Gram-stain of the CSF revealed gram-positive lancet-shaped diplococci. Cultures of CSF and blood grew S. pneumoniae.

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**Clinical Manifestations of Bacterial Meningitis**

Understanding that meningitis is usually the consequence of hematogenous spread from a primary infection, the clinician needs to inquire about antecedent symptoms of ear, nose, and throat infections, as well as about symptoms of pneumonia. The meningitis in case 6.1 was preceded by otitis media.

Case 6.1 had many of the typical symptoms of meningitis. Classically, patients with bacterial meningitis have symptoms of an upper respiratory tract or ear infection that is abruptly interrupted by worsening fever accompanied by one or more “meningeal” symptoms.

Headache is usually severe and unremittting, often being reported as the most severe headache ever experienced. Generalized pain is the rule, reflecting diffuse inflammation of the meninges. Pain may radiate down the neck. Asparin and other over-the-counter pain medications are usually ineffective.

Neck stiffness is frequently noted and is a consequence of meningeal inflammation precipitating muscle spasms in the back of the neck.

As experienced in case 6.1, vomiting is a frequent symptom. The cause of vomiting is unclear, but may be secondary to brain stem irritation and/or elevated intracerebral pressure.

Altered consciousness usually develops within hours of the onset of headache. As noted in case 6.1, the patient may become difficult to rouse and often becomes confused and disoriented. Family members often wait surprisingly long before becoming concerned enough to bring the patient to the hospital. Unfortunately, such delays dramatically worsen the prognosis of bacterial meningitis. In more severe cases, loss of consciousness may be accompanied by grand mal or focal seizures.

Physical examination usually demonstrates high fever or hypothermia. Two maneuvers in addition to a simple test of neck stiffness are commonly used to test for meningeal inflammation:

1. Brudzinski’s nape-of-the-neck sign is elicited by flexing the neck forward. This movement stretches the meninges and is resisted by the patient with meningeal inflammation, because the maneuver causes severe pain.

2. Kernig’s sign requires that the knee be bent at a 45-degree angle as the patient lies supine. As the leg is straightened, the patient with meningeal irritation will resist straightening, complaining of lower back and hamstring pain.

Although emphasized in most textbooks as key physical findings, neck stiffness and Kernig’s and Brudzinski’s signs have not proved to be sensitive indicators of
meningitis. Exacerbation of headache by sudden head movement (head jolt) may be a more sensitive finding.

A careful ear, nose, and throat examination should be performed. Findings of otitis media (dull tympanic membrane, fluid behind the ear drum) may be discovered in cases of *S. pneumoniae* and *H. influenzae* or pharyngeal erythema may be noted in cases of *N. meningitidis*. The nose should be carefully examined looking for a clear nasal discharge suggestive of a CSF leak. Usually, however, meningeal inflammation temporarily closes the CSF leak at the time of presentation, such leakage becoming apparent only after the patient recovers. The nasal passage and posterior pharynx may also reveal a purulent discharge suggestive of sinusitis, an infection that less commonly leads to meningitis.

Auscultation of the heart may reveal a diastolic murmur suggesting aortic insufficiency, which would strongly suggest bacterial endocarditis as the primary infection leading to meningitis. Most cases of endocarditis complicated by meningitis are the result of infection with *S. aureus*.

Lung exam may reveal findings of pneumonia (asymmetrical lung expansion, bronchovesicular breath sounds, rales, egophony, and dullness to percussion), making *S. pneumoniae* the most likely cause. In all patients with meningitis, a CXR should also be performed to exclude pneumonia.

A thorough examination of the skin needs to be performed looking for purpuric lesions. Petechiae and purpura are most commonly encountered in patients with meningococccemia, but they may also be found in *S. aureus* endocarditis and echovirus 9 and rickettsial infections (see Chapter 13). In patients who are asplenic, pneumococcal or *H. influenzae* sepsis is commonly associated with disseminated intravascular coagulation and petechial lesions. The finding of petechiae or purpura is usually a bad prognostic sign.

Finally, and most importantly, a neurologic exam must be performed.

First, mental status must be carefully described. The exact level of neurologic function should be documented by determining a Glasgow score (Table 6.2). The level of consciousness on admission is an important criterion for the use of corticosteroids and is also a useful prognostic indicator. The patient who is unresponsive to deep pain (Glasgow score 3) has a much higher mortality than the patient who responds to voice (Glasgow score 10 to 15).

Next, the cranial nerves should be assessed. Lateral gaze palsy as a result of VIth nerve dysfunction can result from increased intracranial pressure. Focal findings such as hemiparesis, asymmetric pupillary response to light, or other unilateral cranial nerve deficits are uncommon in bacterial meningitis, and they raise the possibility of a space-occupying lesion such as a brain tumor.

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**Table 6.2.** Glasgow Coma Score

<table>
<thead>
<tr>
<th>E: Eye opening</th>
<th>Spontaneous</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Responds to verbal command</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Response to pain</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No eye opening</td>
<td>1</td>
</tr>
<tr>
<td>V: Best verbal response</td>
<td>Oriented</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Confused</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Inappropriate words</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Incomprehensible sounds</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No verbal response</td>
<td>1</td>
</tr>
<tr>
<td>M: Best motor response</td>
<td>Obeys commands</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Localizing response to pain</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Withdrawal response to pain</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Flexion to pain</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Extension to pain</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No motor response</td>
<td>1</td>
</tr>
</tbody>
</table>

\(^a\) Worst possible score is 3; best possible score is 15. Each category should be scored individually—for example, E4V5M6. Interpretation: \(\geq 13\) = mild brain injury; \(9–12\) = moderate brain injury; \(\leq 8\) = severe brain injury.

**KEY POINTS**

About Clinical Manifestations in Bacterial Meningitis

1. Upper respiratory or ear infection interrupted by the abrupt onset of meningeal symptoms:
   a) Generalized, severe headache
   b) Neck stiffness
   c) Vomiting
   d) Depression of mental status

2. Physical findings:
   a) Brudzinski’s (neck flexion) and Kernig’s (straight leg raise) signs are insensitive; “head jolt” maneuver may have higher sensitivity
   b) Abnormal ear exam (*Streptococcus pneumoniae* or *Haemophilus influenzae*), pharyngeal erythema (*Neisseria meningitidis*), or clear nasal discharge resulting from a cerebrospinal fluid leak (*S. pneumoniae*)
   c) Petechial or purpuric skin lesions most common with *N. meningitidis*, also seen with rickettsial infection, echovirus 9, *Staphylococcus aureus*, and asplenic sepsis.
   d) Neurologic exam should look for focal findings (suggests a space-occupying lesion) and assess mental status (Glasgow score is an important prognostic factor).
abscess or tumor. The finding of papilledema on fundoscopic exam is rare in meningitis and usually indicates the presence of a space-occupying lesion.

It is important to keep in mind that meningitis in very young and very old individuals does not present with these classic symptoms and signs. In elderly people, the onset of meningitis is often more insidious. The earliest symptoms are usually fever and alterations in mental status. Meningeal signs are less commonly reported, and many elderly patients have neck stiffness as a consequence of osteoarthritis, an old cerebrovascular accident, or Parkinson's disease. The physician must have a high index of suspicion and must aggressively exclude the possibility of bacterial meningitis in an elderly patient with fever and confusion. In very young patients, neonatal and infant meningitis presents simply as fever and irritability. No history is obtainable, and as a consequence, lumbar puncture should be included in the fever work-up of the very young patient.

**Diagnosis**

The critical test for making a diagnosis of meningitis is the lumbar puncture. If the clinician has included meningitis as part of the differential diagnosis, a lumbar puncture needs to be performed. Too often, clinicians order a computed tomography (CT) scan before performing a lumbar puncture, needlessly delaying the appropriate diagnostic study.

If no focal neurologic deficits are apparent, and if papilledema is not seen on fundoscopic examination, a lumbar puncture can be safely performed (Figure 6.3). The major exception is patients with AIDS or those receiving immunosuppressants. These patients have a higher frequency of cortical space-occupying lesions.

At the time of lumbar puncture, CSF pressure should be documented by manometry. In cases of bacterial meningitis, CSF pressure is almost always elevated, and high elevation suggests severe cerebral edema or defective CSF resorption, or both.

Cellular and biochemical analysis of the CSF is very helpful in deciding on the most likely cause of meningitis (Table 6.3). Patients with bacterial meningitis who have not received prior antibiotics have increased numbers of WBCs with more than 90% PMNs in their CSF. Patients with *L. monocytogenes* can have a lower percentage of PMNs. *Listeria* grows and survives within the cytoplasm of host cells, a condition that can stimulate a monocytic CSF response in some patients. Patients who have received antibiotic therapy before their lumbar puncture may also have a reduced percentage of PMNs.

Because bacterial meningitis causes marked inflammation of the meninges, glucose transport is impaired, and CSF glucose is usually low ("hypoglycorrachia"). Normally, the CSF glucose concentration is about two thirds that of serum glucose; a blood sample for serum glucose should therefore be drawn at the time of the lumbar puncture.

**Figure 6–3.** Initial management of suspected bacterial meningitis

lumbar puncture to more accurately assess the CSF glucose level. In patients with pneumococcal meningitis, a CSF glucose level below 25 mg/dL is associated with worse clinical outcome.

As a consequence of inflammatory damage to blood vessels within the meninges, serum leaks into the cerebrospinal fluid, causing a rise in protein concentration. Concentrations can reach 1000 mg/dL in some cases, and the CSF protein almost always exceeds the normal adult concentration of 50 mg/dL in cases of bacterial meningitis.

The combination of PMNs, low glucose, and high protein in the CSF is almost always caused by bacterial meningitis, and the finding of this CSF formula warrants treatment with antibiotics.

In addition to CSF cell, glucose, and protein levels, Gram stain and culture of the CSF are needed. In more than 75% of bacterial meningitis cases, the Gram stain is positive. The exception is cases involving *L. monocytogenes*. Because this organism usually remains intracellular, Gram stain is positive in only 25% of cases. Latex agglutination tests for *H. influenzae*, *S. pneumoniae*, and *N. meningitidis* are available, and may be ordered in patients with a negative Gram stain. However, it must be emphasized that the sensitivity of these tests is somewhat variable, and a negative latex agglutination test does not exclude the possibility of bacterial meningitis. The CSF culture should be planted immediately after lumbar puncture, and in the absence of prior antibiotics, it remains the most sensitive test for diagnosis. In addition, a positive culture allows for antibiotic sensitivity testing, which is particularly important for guiding treatment of *S. pneumoniae* and enteric pathogens.

### Treatment

Evaluation and institution of antibiotic therapy should occur within 30 minutes if bacterial meningitis is being strongly considered. In cases in which a focal neurologic deficit is evident or papilledema is found, empiric antibiotic therapy should be instituted before sending the patient for CT scan (Figure 6.3). Blood samples for culture should be drawn before antibiotics are started; they often yield the cause of the illness. Empiric antibiotic treatment is also required if Gram stain of the CSF proves negative.

Empiric therapy depends on the age and immune status of the patient and on whether infection is nosocomial.
or community-acquired (Table 6.1). For community-acquired meningitis in patients aged 3 months to 60 years, maximal doses of a third-generation cephalosporin (ceftriaxone or cefotaxime) is recommended. (For doses, see Table 6.4.) If the patient is severely ill, vancomycin should be added to this regimen to cover for the possibility of penicillin-resistant *S. pneumoniae* (see Chapter 4, for a full discussion of penicillin-resistant *S. pneumoniae*). In the patient with an immediate hypersensitivity reaction to penicillin or a history of allergy to cephalosporins, vancomycin is recommended. In patients over the age of 60 years, maximal doses of ampicillin are added to the third-generation cephalosporin to cover for *L. monocytogenes*. This organism is not sensitive to cephalosporins, and penicillin or ampicillin are the treatment of choice. For the immunocompromised host, a third-generation cephalosporin, ampicillin, and vancomycin are recommended for empiric therapy. In patients post neurosurgery or in patients who have a cerebrospinal fluid shunt, vancomycin and ceftazidime or cefepime are recommended.

Once a specific bacterium is identified, the antibiotic regimen can be focused. Table 6.4 outlines the recommended regimens for each major pathogen.

Penicillin-resistant *S. pneumoniae* is a particular concern, given the high prevalence of these strains and the poor penetration of antibiotics across the blood–brain barrier. Intermediately resistant stains (penicillin MIC = 0.1 to 1 µg/mL) may initially improve on penicillin therapy; however, as the integrity of the blood–brain barrier improves, the patient may relapse as a consequence

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### Table 6.4. Antibiotic Treatment for Bacterial Meningitis

<table>
<thead>
<tr>
<th>Organism</th>
<th>Antibiotic</th>
<th>Dose</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Penicillin</td>
<td>$20 - 24 \times 10^6$ U daily, divided q4h</td>
<td>Chloramphenicol, 4–6 g daily, divided q6h</td>
</tr>
<tr>
<td>(penicillin MIC &lt; 0.1 µg/mL)</td>
<td>Ceftriaxone</td>
<td>2–4 g daily, divided q12h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cefotaxime</td>
<td>12 g daily, divided q6h</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Vancomycin, plus rifampin</td>
<td>2 g daily, divided q12h</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>(MIC &gt; 0.1 µg/mL)</td>
<td>300 mg q12h</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Neisseria meningitidis</em></td>
<td>Penicillin</td>
<td>$20 - 24 \times 10^6$ U daily, divided q4h</td>
<td>Ceftriaxone</td>
</tr>
<tr>
<td></td>
<td>Cefotaxime</td>
<td>2–4 g daily, divided q12h</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 g daily, divided q6h</td>
<td></td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td>Ampicillin, with or without gentamicin</td>
<td>12 g daily, divided q4H</td>
<td>Trimethoprim–sulfamethoxazole 15–20 mg/kg daily (trimethoprim, divided q6h)</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>Ceftriaxone</td>
<td>2–4 g daily, divided q12h</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td></td>
<td>Cefotaxime</td>
<td>12 g daily, divided q6h</td>
<td></td>
</tr>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td>Ceftriaxone, with or without gentamicin</td>
<td>2–4 g daily, divided q12h</td>
<td>Aztreonam 6–8 g daily, divided q6h</td>
</tr>
<tr>
<td></td>
<td>4–8 mg intrathecal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cefotaxime, with or without gentamicin</td>
<td>5 mg/kg daily systemic</td>
<td>Trimethoprim–sulfamethoxazole</td>
</tr>
<tr>
<td></td>
<td>12 g daily, divided q6h</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Ceftazidime, plus gentamicin</td>
<td>6–12 g daily, divided q8h</td>
<td>Antipseudomonal penicillin: 18–24 g daily, divided q4h, plus gentamicin</td>
</tr>
<tr>
<td></td>
<td>4–8 mg intrathecal</td>
<td>5 mg/kg daily systemic</td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Nafcillin, or Oxacillin, with or without rifampin</td>
<td>9–12 g daily, divided q4h</td>
<td>Vancomycin, plus rifampin</td>
</tr>
<tr>
<td>(methicillin-sensitive)</td>
<td></td>
<td>9–12 g daily, divided q4h</td>
<td>Trimethoprim–sulfamethoxazole, plus rifampin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>600 mg daily, divided q12h</td>
<td></td>
</tr>
<tr>
<td><em>S. aureus</em> (methicillin-resistant)</td>
<td>Vancomycin, plus rifampin</td>
<td>2 g daily, divided q12h</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>600 mg daily, divided q12h</td>
<td></td>
</tr>
<tr>
<td><em>S. epidermidis</em></td>
<td>Vancomycin, plus rifampin</td>
<td>2 g daily, divided q12h</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>600 mg daily, divided q12h</td>
<td></td>
</tr>
</tbody>
</table>
of reduced levels of penicillin in the CSF. For this reason, high-dose ceftriaxone or cefotaxime is recommended for intermediately penicillin-resistant *S. pneumoniae* meningitis, because these cephalosporins achieve higher levels in CSF.

For infections with highly penicillin-resistant *S. pneumoniae* (penicillin MIC >2 μg/mL), vancomycin needs to be added to the third-generation cephalosporin to assure adequate inhibitory concentrations in the CSF. Vancomycin penetrates the intact blood–brain barrier poorly, and in some patients, therapeutic levels may not be achieved in the CSF without intrathecal administration. Rifampin combined with vancomycin may also be effective for the treatment of highly resistant *S. pneumoniae*. This regimen has been recommended for patients receiving high-dose dexamethasone (see discussion of treatment for inflammation that follows), because corticosteroid therapy reduces meningeal inflammation and improves the integrity of the blood–brain barrier, decreasing vancomycin levels in the CSF. The antibiotic response should be monitored in patients infected with highly penicillin-resistant pneumococci. In these patients, the lumbar puncture should be repeated 24 to 36 hours after the initiation of therapy.

Aminoglycosides, erythromycin, clindamycin, tetracyclines, and first-generation cephalosporins should not be used to treat meningitis, because these drugs do not cross the blood–brain barrier.

Neurologic damage is primarily a consequence of an excessive inflammatory response. Corticosteroids reduce inflammation, and in children with *H. influenzae* bacterial meningitis, dexamethasone (0.15 mg/kg q6h × 4 days) has been shown to reduce CSF pressure, CSF PMNs, and protein, to increase CSF glucose, and to improve cerebral blood perfusion. Dexamethasone also significantly reduces the incidence of deafness. In adults with pneumococcal meningitis and Glasgow coma scores of 8 to 11, dexamethasone administration (10 mg q6h × 4 days) was also found to reduce morbidity and mortality. Dexamethasone should be given just before or simultaneously with antibiotics, because inflammatory mediators are released in response to the lysis of bacteria induced by antibiotic treatment. Other inhibitors of inflammation, such as monoclonal antibodies directed against the adherence receptors of leukocytes, are potentially promising, but remain experimental.

Additional therapeutic measures are primarily directed at reducing cerebral edema and controlling seizures. Administration of hypotonic solutions should be avoided. The airway must be protected, and hypoventilation with associated hypercarbia should be avoided, because elevated PaCO₂ levels cause cerebral vessel dilation and may increase intracranial pressure. Hyperventilation can also be harmful for the opposite reason: reductions in PaCO₂ may reduce cerebral perfusion and increase the risk of infarction. When intracranial pressure is documented by lumbar puncture to be markedly elevated, intravenous 20% mannitol can be administered to remove free water from the cerebral cortex and to quickly reduce cerebral edema. Oral glycerol may also reduce cerebral edema, and its efficacy is presently being investigated. Seizures develop in 20% to 30% of patients with meningitis, but anti-seizure medications (Dilantin and diazepam are most commonly used) are not recommended for prophylaxis. These agents are administered only after the first seizure.

**Complications**

Mortality remains high in patients with bacterial meningitis. *L. monocytogenes* is associated with the highest mortality, 26%; followed by *S. pneumoniae*, 19%; and

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**KEY POINTS**

About the Treatment of Bacterial Meningitis

1. Antibiotics should be given within 30 minutes if bacterial meningitis is suspected.
2. Blood samples for culture should be drawn and antibiotics given before a computed tomography scan is done.
3. Maximal doses of antibiotics must given because of limited passage through the blood–brain barrier.
4. Empiric therapy for
   a) community-acquired disease, patient 3 months to 60 years is ceftriaxone or cefotaxime. If severely ill, add vancomycin. If more than 60 years or immunocompromised, use ceftriaxone or cefotaxime, plus ampicillin and vancomycin.
   b) nosocomial disease, is vancomycin and ceftazidime or cefepime.
5. Give dexamethasone 30 minutes before antibiotics in
   a) children (shown to be efficacious in *Haemophilus influenzae*).
   b) adults (efficacious in *Streptococcus pneumoniae* with Glasgow coma score of 8 to 11).
6. Maintain ventilation, prevent increase in PaCO₂ or decrease in PaO₂.
7. Avoid hypotonic solutions, consider mannitol or glycerol for increased cerebrospinal fluid pressure.
8. Anti-seizure medications after first seizure.
N. meningitidis, 13% mortality. H. influenzae meningitis tends to be less severe, being now associated with an average mortality of 3%. Mortality is higher in very young and elderly individuals. Neurologic sequelae in surviving patients are common. The young patient whose brain is developing often suffers mental retardation, hearing loss, seizure disorders, or cerebral palsy. Older patients may develop hydrocephalus, cerebellar dysfunction, paresis, a seizure disorder, and hearing loss.

**Prevention**

Given the high mortality and high incidence of permanent neurologic sequelae associated with bacterial meningitis, the medical community must strive to reduce the incidence of these devastating infections.

**VACCINES**

Three of the primary pathogens that cause community-acquired bacterial meningitis are encapsulated organisms, and therefore opsonins [immunoglobulin G (IgG) and complement] play a critical role in allowing host macrophages and PMNs to ingest these pathogens and clear them from the bloodstream. Reduced time in the bloodstream reduces the likelihood of seeding the meninges. The remarkable reduction in invasive H. influenzae type B following the widespread administration of the HIB vaccine illustrates the power of this preventive measure. Protective levels of immunoglobulin are achieved when the PedvaxHIB vaccine is administered at 2 and 4 months of age. Two other HIB vaccines are also available that should be administered at 2, 4, and 6 months of age.

A quadrivalent meningococcal vaccine directed against serogroups A, C, Y, and W135 is now available and is recommended for high-risk groups, including military recruits, college students, asplenic patients, and patients with terminal complement deficiencies. This vaccine is also useful for controlling epidemics and should be administered to travelers going to areas where the prevalence of meningococcal disease is high. (Visit www.CDC.gov for current recommendations for travelers.)

A major problem with the current vaccine is the lack of a suitable immunogen against serogroup B. Serogroups B and C are primarily responsible for meningococcal meningitis in the United States. A second problem with the vaccine is the fact that immunity tends to be short-lived, with antibody titer decreasing after 3 years following a single dose of the vaccine. The incidence of meningococcal disease remains low in the United States (approximately 1 in 100,000 population), and therefore this vaccine is not recommended for routine immunization.

A safe, inexpensive, and efficacious 23-valent pneumococcal vaccine is available and has been underutilized. The mortality attributable to pneumococcal infection is higher than that attributable to any other vaccine-preventable disease (approximately 40,000 annually in the United States), and about half of these deaths could be prevented by vaccination. Individuals more than 65 years of age are at higher risk for developing invasive pneumococcal infection including meningitis and should be vaccinated. Other groups that warrant vaccination include patients with chronic cardiovascular, pulmonary, or liver disease, diabetes mellitus, and sickle cell disease, and patients with functional asplenia or those who have had a splenectomy. A single intramuscular or subcutaneous injection is protective for 5 to 10 years. For most patients, revaccination

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### KEY POINTS

**About the Outcome and Prevention of Bacterial Meningitis**

1. **Mortality is high:** 26% for Listeria, 19% for Streptococcus pneumoniae, 13% for Neisseria meningitidis, and 3% for Haemophilus influenzae.

2. **Permanent sequelae are common:**
   - a) In children: mental retardation, hearing loss, seizure disorders, cerebral palsy
   - b) In adults: hydrocephalus, cerebellar dysfunction, paresis, seizure disorder, hearing loss

3. **Efficacious vaccines are available:**
   - a) *S. pneumoniae*: 23-valent vaccine; safe, inexpensive. Recommended in individuals more than 65 years of age; those with chronic cardiovascular, pulmonary, or liver disease, diabetes mellitus, sickle cell disease, and asplenia; heptavalent conjugated vaccine for all children under 2 years of age.
   - b) *H. influenzae*: PedvaxHIB vaccine at age 2 and 4 months; safe, inexpensive.
   - c) *N. meningitidis*: quadrivalent meningococcal vaccine for serogroups A, C, Y, and W135; misses group B. Recommended in military recruits, college students, and individuals with asplenia and terminal complement defects.

4. **Chemoprophylaxis use:**
   - a) *H. influenzae*: Rifampin within 6 days for household contacts with unvaccinated child under 2 years of age, and for children under 2 years of age exposed in a daycare center.
   - b) *N. meningitidis*: Single-dose ciprofloxacin within 5 days for household and daycare contacts, and for those exposed to oral secretions from the index case.
is not recommended. Exceptions are the immunocompromised host and patients over 65 years of age who often develop a more rapid decline in protective antibody levels. Revaccination may considered after at least 5 years have passed since initial vaccination. A heptavalent conjugated vaccine that is immunogenic in children under the age of 2 years is recommended for routine pediatric immunization. This vaccine has significantly reduced invasive pneumococcal disease in children. It is given in four doses at 12 to 15 months, and ages 2, 4, and 6.

**CHEMOPROPHYLAXIS**

Brief antibiotic treatment has been used to prevent secondary cases of *H. influenzae* and *N. meningitidis*. Secondary cases generally occur within 6 days of an index case of *H. influenzae* and within 5 days of an index case of *N. meningitidis* meningitis. Both organisms are carried in the nasopharynx and, in a person lacking specific humoral immunity, these organisms can become invasive. Choice of the individuals to target for prophylaxis has been carefully delineated by epidemiologic data, but fear plays a major role in determining who eventually receives prophylaxis. For *H. influenzae*, household contacts with at least one unvaccinated child under the age of 2 years require prophylaxis. Data on daycare exposure remains controversial; however, most experts agree that children under the age of 2 who may have been exposed in a daycare should receive chemoprophylaxis.

The recommended agent for *H. influenzae* prophylaxis is rifampin 20 mg/kg daily (maximum dose in adults: 600 mg q24h) for 4 days is recommended. Rifampin prophylaxis is not recommended for pregnant woman because of the potential risk of rifampin to the fetus. For *N. meningitidis*, a single dose of ciprofloxacin 500 mg is the preferred prophylactic regimen, and this regimen is recommended for close contacts including household members, daycare contacts, and people who may have been directly exposed to the index patient’s oral secretions (kissing, mouth-to-mouth resuscitation, endotracheal tube intubation). Given the potential severity of this disease and the minimal harm of a single dose of antibiotic, physicians should probably maintain a low threshold for using prophylaxis. This brief treatment may help to alleviate the extreme anxiety associated with meningococcal disease.

**VIRAL MENINGITIS**

**CASE 6.2**

A 45-year-old woman was admitted to the hospital with a chief complaints of severe headache and neck stiffness over 8 days. Ten days prior to admission, she had noted some mild stiffness of the back of her neck, associated with fever and mild shivering. Two days later, she developed a sharp, throbbing bi-temporal headache that radiated to the vertex. Her headache was made worse by sitting up or moving. Bright light bothered her eyes. She also noted some muscle stiffness in other areas in particular her lower back. She felt very tired and lost her appetite. Although she felt lethargic at times, she never lost touch with reality.

An epidemiologic history revealed that during the fall (several weeks before admission), she had administered psychometric tests to a large number of students (ages 10 to 20 years).

Physical examination found a temperature of 38°C. This mildly ill-appearing middle-aged woman was alert but sitting in a dark room complaining of severe headache. Eyes showed mild conjunctival erythema with normal discs. Neck was mildly stiff and negative for Kernig's and Brudzinski's signs. The remainder of the exam, including ear, nose, and throat and neurologic exams, was within normal limits.

Laboratory workup showed a hematocrit of 40%; a WBC count of 6000/mm³, with 45% PMNs, 50% lymphocytes, and 5% monocytes. Lumbar puncture showed an opening pressure (OP) of 100 mm H₂O, and CSF analysis found a WBC count of 180/mm³ (50% PMNs, 48% lymphocytes, 2% monocytes), protein 59 mg/dL, and glucose 61 mg/dL, with simultaneous serum glucose 84 mg/dL. A Gram stain of the CSF was negative for organisms. A repeat lumbar puncture 8 hours later revealed an OP of 100 mm H₂O, and a WBC count of 170/mm³ (2% PMNs, 95% lymphocytes, 3% monocytes), protein 58 mg/dL, and glucose 61 mg/dL. (No blood for serum glucose was drawn at this time.) Gram stain of the CSF remained negative.

During this patient's hospital course, her headache persisted, as did her low-grade fever. She remained alert and continued to have photophobia and a mildly stiff neck. She was discharged on the third hospital day, and her symptoms resolved over the next week.

Viral meningitis is the most common form of meningitis. It is caused primarily by the non-polio enteroviruses, echoviruses, and coxsackieviruses. In temperate climates, infections occur mainly in the warmer months of the year, usually during the summer and early fall. In tropical climates, the infection occurs year round.

Enteroviruses are spread by the fecal–oral route, and small epidemics are frequently reported. Herpes simplex virus type 2 (HSV-2) is the second most common cause, and this form of viral meningitis is often accompanied
by vesicular skin lesions in the genital area. This virus is also the most common cause of recurrent Mollaret’s aseptic meningitis. Varicella virus is the third most common cause, and aseptic meningitis usually is not accompanied by skin lesions.

In the nonimmune patient, mumps virus is often associated with aseptic meningitis that may occur in the absence of salivary gland swelling. The peak incidence of this virus is seen in children 5 to 9 years of age. Less commonly, herpes simplex virus type 1 (HSV-1) causes meningitis. And the mononucleosis syndrome caused by Epstein–Barr virus and cytomegalovirus can be accompanied by meningitis.

Lymphocytic choriomeningitis virus was previously thought to be a common cause of aseptic meningitis, but recent studies have found this virus to be rare. It is transmitted in the urine of rodents, and a diagnosis of lymphocytic choriomeningitis should be considered in individuals who potentially have had contact with rodents or rodent excreta. This infection occurs most commonly in the winter, when rodents are more likely to take up residence in human dwellings.

Finally, at the time of initial HIV infection, 5% to 10% of patients may experience symptoms of aseptic meningitis. In some of these cases, HIV has been isolated from the CSF (see Chapter 17).

As illustrated in case 6.2, severe headache is the most common complaint. Headache is usually generalized, but may localize bilaterally to the frontal, temporal, or occipital regions. Photophobia is another very common complaint, and patients usually request that their room remain darkened. Neck stiffness and diffuse myalgias are also common. On physical examination, the skin should be carefully viewed for maculopapular rashes (found in some strains of echovirus). Eye exam may reveal conjunctivitis, frequently associated with enteroviral infections. Significant nuchal rigidity is found in more than half of all cases of aseptic meningitis. Patients may be slightly lethargic; however, unlike patients with bacterial and fungal meningitis, patients with viral meningitis rarely exhibit significant depression in mental status. Focal neurologic findings should not be observed in this disease.

Lumbar puncture usually reveals a predominance of lymphocytes, a normal glucose level, and mildly elevated CSF protein (Table 6.2). The CSF leukocyte count usually ranges between 100 and 1000 /μL. In some forms of viral meningitis (mumps and lymphocytic choriomeningitis), CSF glucose may be lowered early in the disease. Also early in the disease, PMNs may predominate in the CSF, making it impossible to safely exclude bacterial meningitis. These patients should therefore not be sent home, but covered with empiric antibiotics pending CSF and blood cultures and follow-up lumbar puncture. In most cases, a repeat lumbar puncture 12 to 24 hours later reveals a predominance of lymphocytes, and the patient can be discharged. However, in some patients, PMNs may persist for up to 48 hours, necessitating continued observation in the hospital and antibiotic administration. A negative CSF culture after 48 hours greatly reduces the probability of bacterial meningitis, but the threshold for antibiotic coverage must be low to prevent inadvertent delays in the treatment of a bacterial meningitis.

Polymerase chain reaction (PCR) for HSV-1 and HSV-2 in CSF is sensitive and specific, and available in most hospital laboratories. Enterovirus PCR has also been shown to be sensitive and specific, but the test is not usually available in hospitals. Proof of enterovirus CSF infection would allow the patient to discharged home, because, with the exception of patients with severe immunoglobulin deficiency, viral meningitis is a self-limiting disease that usually resolves spontaneously within 7 to 10 days. In

KEY POINTS

About Viral Meningitis

1. Viral meningitis is most commonly caused by
   a) enteroviruses, echovirus, and coxsackievirus (most frequent, seen in summer and early fall).
   b) mumps in the nonimmune (may be no parotid gland swelling, ages 5 to 9 years).
   c) herpes simplex type 2 (primary disease, also Mollaret’s recurrent meningitis).
   d) Epstein–Barr virus and cytomegalovirus (rare).
   e) lymphocytic choriomeningitis virus (excreted in rodent urine, rare).
   f) HIV (can be the initial presentation of infection).

2. Primary clinical manifestations include
   a) headache and photophobia, stiff neck;
   b) no loss of consciousness; and
   c) conjunctivitis, maculopapular rash, and occasionally with echovirus, petechial rash.
   d) Epstein–Barr virus and cytomegalovirus (rare).

3. The cerebrospinal fluid (CSF) shows a predominance of lymphocytes, early polymorphonuclear leukocytes (PMNs), normal glucose, mild protein increase.

4. Polymerase chain reaction can make the diagnosis of HSV-1 or -2 and enterovirus, but diagnosis is often presumptive.

5. Treatment consists mainly of observation, with antibiotics if CSF contains PMNs; self-limiting disease, lasts 7 to 10 days.
patients with agammaglobulinemia, a chronic enteroviral meningitis (‘meningoencephalitis’) can develop that continues for years. This condition is often fatal. Treatment with systemic and intraventricular pooled IgG preparations has been successful in some of these patients.

TUBERCULOUS MENINGITIS

Tuberculous meningitis arises most commonly in association with miliary tuberculosis. Meningitis can also develop if a tubercle ruptures into the subarachnoid space. About 25% of patients have no evidence of an extracranial site of tuberculous infection.

The symptoms and signs of tuberculous meningitis vary. In some patients, it can mimic other forms of acute bacterial meningitis; in others, the disease is more indolent and presents with a mild headache and malaise. Because tuberculous meningitis involves primarily the basilar meninges, inflammation often involves the pons and optic chiasm, leading to dysfunction of the IIIrd, IVth, and VIth cranial nerves, causing abnormalities in extraocular movements and the pupillary response. Changes in mental status need to be carefully documented; outcome correlates closely with the neurologic findings. Patients who are stuporous or have hemiplegia have a nearly 50% risk of dying or suffering severe neurologic sequelae.

In most children, but in only 50% of adults, a CXR demonstrates changes consistent with tuberculosis. A PPD test is helpful and is usually positive. However, a negative PPD does not exclude the diagnosis.

Lumbar puncture is the key to diagnosis, usually obeying the “500 rule.” That is, the leukocyte count is usually below 500/mm$^3$ (usual range: 100 to 500/mm$^3$), and protein is usually below 500 mg/dL (range: 100 to 500 mg/dL). In addition, a moderate depression in CSF glucose is usually encountered (below 45 mg/dL); however, in a significant number of cases, CSF glucose may exceed this value. A predominance of mononuclear leukocytes is the usual cellular response; however, early in tuberculous meningitis, PMNs may predominate in up to one quarter of patients. A CSF smear for acid-fast bacilli is positive in slightly more than one third of cases, but repeat examination of multiple samples that have been centrifuged increases the sensitivity. Large volumes of CSF should be collected for culture to increase the culture yield. Amplification tests using PCR for tuberculosis are now available. They are highly specific, but their sensitivity does not match culture. A negative CSF PCR therefore does not exclude the diagnosis. A CT or magnetic resonance imaging (MRI) scan with contrast may reveal rounded densities indicative of tuberculomas, basilar arachnoid inflammation, and hydrocephalus. Flow of CSF may be impaired as a consequence of basilar inflammation that blocks travel through the aqueduct of Sylvius.

After appropriate cultures are obtained, treatment should be initiated immediately. Untreated tuberculous meningitis is fatal within 5 to 8 weeks of the onset of symptoms. Prognosis is worse in patients under the age of 5 years or over the age of 50 years. A three-drug regimen consisting of isoniazid, rifampin, and pyrazinamide is recommended. Ethambutol or streptomycin can be added if infection with a resistant organism is suspected. In addition to antituberculous agents, a glucocorticoid (adults: 60 mg prednisone daily; children: 2 to 4 mg/kg daily) or dexamethasone (adults: 10 mg intravenously every 6 hours; children: 0.4 mg/kg daily given intravenously every 6 hours) is recommended in patients with hydrocephalus so as to reduce basilar inflammation.

CRYPTOCOCCAL MENINGOENCEPHALITIS

Cryptococcus neoformans is found predominantly in pigeon droppings. High concentrations of this yeast-like fungus are found in pigeon nesting areas and on ledges where pigeons perch. The organism is inhaled and subsequently gains entry into the bloodstream, where it seeds the brain and meninges, causing a meningoencephalitis.

Cryptococcus has a thick capsule consisting of negatively charged polysaccharides that are immunosup-
pressive, blocking both cell-mediated immune responses and leukocyte migration. These effects explain the minimal inflammatory response elicited by invading cryptococci. Strains that produce melanin demonstrate increased virulence, and this cell wall product is thought to provide protection against oxidants. The high concentrations of dopamine in the CNS serve as a substrate for melanin production. *Cryptococcus* also produces mannitol, a product that may induce cerebral edema and inhibit phagocyte function.

Cryptococci infect immunocompromised hosts most commonly, but infections in normal hosts are also reported. This form of meningitis is the most common in patients with AIDS (see Chapter 17). In the non-HIV-infected patient, cryptococcal CNS infection usually has a slowly progressive, waxing and waning course, characterized by severe intermittent headache, followed by mild confusion and personality changes that can progress to stupor and coma. The subacute onset and nonspecific nature of this illness often delay the diagnosis. On average, the diagnosis is determined 1 month after the onset of symptoms. The progression of this illness tends to be more rapid in HIV-infected patients, and the larger burden of organisms results in marked inhibition of the inflammatory response (see Chapter 17).

Like *Mycobacterium tuberculosis*, *Cryptococcus* produces a basilar meningitis that can cause oculomotor palsies because of dysfunction in the IIIrd, IVth, Vth cranial nerves, hearing loss, and hydrocephalus. Patients may experience decreased visual acuity and diplopia. Neck stiffness is often minimal, and the possibility of meningoencephalitis may not be considered. Papilledema is noted in up to one third of cases. Focal motor deficits and seizures are rare.

The diagnosis is made by lumbar puncture. Pressure of the CSF is often elevated above 200 mm H\(_2\)O, reflecting disturbances in CSF flow and resorption. The CSF formula typically has 20 to 200 WBCs/mm\(^3\), with a predominance of mononuclear cells, mildly elevated protein, and moderately decreased glucose.

- **1.** A lumbar puncture is required for diagnosis; increased cerebrospinal fluid (CSF) pressure often associated.
  - a) White blood cells (WBCs) 20 to 200/mm\(^3\), with a predominance of mononuclear cells
  - b) Mildly elevated protein and moderately depressed glucose
  - c) Positive India ink preparation in 25% to 50% of cases, and positive cryptococcal antigen in approximately 90%
  - d) Culture usually positive in 5 to 7 days

- **2.** Computed tomography or magnetic resonance imaging scan with contrast may show hydrocephalus, cerebral edema, and ring-enhancing lesions (cryptococcomas).

- **3.** Treat with amphotericin B and flucytosine for 2 weeks, fluconazole for 3 to 6 months.

- **4.** Mortality is 25% to 30%; prognosis is worse if CSF produces a positive India ink preparation, an antigen titer higher than 1:32, a WBC count below 20/mm\(^3\), or increased opening pressure; or if extraneural infection is present.

Cryptococcal polysaccharide antigen latex agglutination is highly sensitive and specific. The CSF antigen titer is determined by serially diluting the CSF. In most cases of HIV-associated cryptococcal meningitis, cryptococcal antigen can also be detected in the serum. However, a negative serum antigen test does not exclude cryptococcal meningitis in the normal host. A CSF culture is positive in 90% of patients, and culturing large volumes of CSF (10 to 15 mL) can increase the yield. The organism usually grows within 5 to 7 days on standard media, and use of birdseed agar can enhance growth. In addition to CSF analysis, brain CT or MRI scan with contrast is recommended to assess the degree of hydrocephalus and the extent of cerebral edema, and
Outbreaks of West Nile viral illness in North America, starting in the 1990s, have raised the public’s awareness and concern about viral encephalitis. The causative encephalitides fall into two major groups: those that are arthropod–borne, and those that are caused by viruses that spread person-to-person.

**VIRAL ENCEPHALITIS**

### CASE 6.3

A 74-year-old white man with a history of chronic steroid use (10 mg prednisone daily) and stage I chronic lymphocytic leukemia presented at the emergency room with confusion and fever. Four days before admission, he complained of being increasingly tired. Two days before admission, he became increasingly lethargic, sleeping on floor. His wife had difficulty rousing him, and she noted that he was no longer interested in any activity.

The morning of admission, he displayed bizarre behavior (putting underwear on top of his pajama bottoms, for example). He also became unsteady, requiring help from his wife to walk. His temperature at home was 38.9°C (102°F). On arrival at the ER, he was mildly lethargic, but was talking and answering simple questions.

The man was living in Florida with his wife. His wife reported that he spent considerable time outside and had been bitten by multiple mosquitoes.

Physical examination showed a temperature of 39.8°C (103.6°F). No lesions in the mouth were noted, and the sclera lacked erythema. The neck showed some increased tone, but lacked Kernig’s or Brudzinski’s sign. A few rhonchi were heard in the lungs, but no murmurs or rubs in the heart, and the abdomen was unremarkable. No skin lesions were noted.

A neurologic exam revealed an ataxic gait, all extremities moving, some diffuse hyperreflexia, and generalized increased muscle tone.

By hospital day 2, the patient’s mental status had deteriorated. He only groaned and winced with painful stimuli.

Laboratory workup included CT and MRI scans of the head that were within normal limits. A lumbar puncture showed a WBC count in the CSF of 100/mm³ (40% PMNs, 47% lymphocytes, 13% monocytes), with protein 106 mg/dL and glucose 68 mg/dL. Serum immunoglobulin M (IgM) for West Nile virus was markedly elevated.

Outbreaks of West Nile viral illness in North America, starting in the 1990s, have raised the public's awareness and concern about viral encephalitis. The causative encephalitides fall into two major groups: those that are arthropod–borne, and those that are caused by viruses that spread person-to-person.
Mosquito-borne disease is caused by arboviruses that include the alphaviruses, flaviviruses, and the bunyaviruses (Table 6.5). These infections occur in the summer months when mosquitoes are active. The responsible viruses often infect birds and horses in addition to humans. In the case of West Nile virus, crows are particularly susceptible, and the finding of a dead crow warrants increased surveillance. To document disease activity, public health officials frequently set out sentinel chickens in areas heavily infested with mosquitoes. The various arboviruses tend to be associated with outbreaks in specific areas of the country, and these organisms have somewhat different host preferences (Table 6.5). Prevention is best accomplished by avoiding mosquito bites. Long-sleeved shirts and long pants should be worn outdoors. During times of increased viral encephalitis activity, people should avoid the outdoors in the early evening when mosquitoes prefer to feed. Insect repellants are another important protective measure.

Encephalitis-causing viruses that spread from person-to-person include mumps, measles, Varicella virus, human herpesvirus 6, and the most common form of sporadic encephalitis, HSV-1. These forms of viral encephalitis can occur at any time during the year. Other, rarer causes of viral encephalitis include cytomegalovirus, Epstein–Barr virus, and enteroviruses. A particularly deadly form of encephalitis, rabies, is caused by the rabies virus, which is spread by animal bites, most commonly the bites of bats.

With the exception of rabies, these viruses all present with similar symptoms and signs, and cannot be differentiated clinically. The clinical manifestations of encephalitis differ from those of meningitis. The causative virus directly invades the cerebral cortex and produces abnormalities in upper cortical function. Patients may experience visual or auditory hallucinations. As described in case 6.3, patients may perform peculiar higher motor functions such as unbuttoning and buttoning a shirt or placing underwear over pants. Patients with encephalitis frequently develop seizures that are either grand mal or focal in character. They may also develop motor or sensory deficits such as ataxia. These symptoms and signs are usually accompanied by severe headache. As the disease progresses to cerebral edema, the patient may become comatose. Development of coma is associated with a poor prognosis. In herpes encephalitis, the typical vesicular herpetic lesions on the lip or face are not usually seen, because reactivated virus migrates up the Vth cranial nerve toward the central nervous system rather than toward the periphery.

### Table 6.5. Encephalitis Caused by Arboviruses

<table>
<thead>
<tr>
<th>Disease</th>
<th>Virus</th>
<th>Locations</th>
<th>Hosts</th>
<th>Clinical Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eastern equine encephalitis</td>
<td>Alphavirus</td>
<td>Eastern United States, Canada, Central and South America, Caribbean, Guyana</td>
<td>Birds, horses</td>
<td>Severe disease, high mortality</td>
</tr>
<tr>
<td>Western equine encephalitis</td>
<td>Alphavirus</td>
<td>United States, Canada, Central and South America, Caribbean, Guyana</td>
<td>Birds, small mammals, horses</td>
<td>Mild disease, primarily in children</td>
</tr>
<tr>
<td>Venezuelan equine encephalitis</td>
<td>Alphavirus</td>
<td>Northern South America, Central America, Florida, Texas</td>
<td>Horses, rodents, birds</td>
<td>Febrile illness, encephalitis uncommon</td>
</tr>
<tr>
<td>St. Louis encephalitis</td>
<td>Flavivirus</td>
<td>Western, central, and southern United States, Central and South America, Caribbean</td>
<td>Birds</td>
<td>Attacks people over 50 years of age</td>
</tr>
<tr>
<td>West Nile encephalitis</td>
<td>Flavivirus</td>
<td>Eastern United States (New York, Florida)</td>
<td>Birds</td>
<td>Usually mild disease, severe disease in elderly people</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>Flavivirus</td>
<td>Japan, Siberia, Korea, China, Southeast Asia, India</td>
<td>Birds, pigs, horses</td>
<td>Can cause severe encephalitis</td>
</tr>
<tr>
<td>California group encephalitis</td>
<td>Bunyavirus</td>
<td>United States, Canada</td>
<td>Small mammals</td>
<td>School-age children, permanent behavior changes</td>
</tr>
</tbody>
</table>

These infections occur in the summer months when mosquitoes are active. The responsible viruses often infect birds and horses in addition to humans. In the case of West Nile virus, crows are particularly susceptible, and the finding of a dead crow warrants increased surveillance. To document disease activity, public health officials frequently set out sentinel chickens in areas heavily infested with mosquitoes. The various arboviruses tend to be associated with outbreaks in specific areas of the country, and these organisms have somewhat different host preferences (Table 6.5). Prevention is best accomplished by avoiding mosquito bites. Long-sleeved shirts and long pants should be worn outdoors. During times of increased viral encephalitis activity, people should avoid the outdoors in the early evening when mosquitoes prefer to feed. Insect repellants are another important protective measure.
Patients who contract rabies encephalitis often suffer the acute onset of hydrophobia. On attempting to drink water, they experience spasms of the pharynx. These spasms spread from the pharynx to the respiratory muscles, causing shallow, quick respirations. These abnormalities are thought to be the result of brain stem involvement and damage to the nucleus ambiguus in the upper medulla. Hyperactivity, seizures, and coma usually follow. Pituitary dysfunction is often evident and can result in diabetes insipidus (causing loss of free water) or inappropriate antidiuretic hormone secretion (causing hyponatremia). Cardiac arrhythmias and autonomic dysfunction are also common. Patients usually die within 1 to 2 weeks after the onset of coma. Less commonly, patients present with ascending paralysis resembling the Guillain–Barré syndrome and subsequently develop coma.

Diagnostic studies usually include CT or MRI scan with contrast. The MRI is more sensitive, detecting smaller lesions and early areas of edematous cerebral cortex. In herpes simplex encephalitis, involvement of the temporal lobes is the rule. In other forms of encephalitis, diffuse cerebral edema may be found in severe cases. As seen in case 6.3, however, these imaging studies are often normal. Electroencephalogram is particularly helpful in herpes simplex encephalitis, frequently demonstrating electrical spikes in the region of the infected temporal lobe. Lumbar puncture usually reveals a CSF WBC count below 500/mm³, with a predominance of mononuclear cells. However, in early infection, PMNs may be noted, and this finding warrants a follow-up lumbar puncture to document a shift to lymphocytes. The CSF protein is usually normal or mildly elevated, and the CSF glucose is usually normal, although low glucose may be seen in herpes. In HSV-1 encephalitis increased numbers of red blood cells may also be found in the CSF.

With the exception of rabies, a specific diagnosis is usually difficult to determine. Acute and convalescent serum should be sent for IgM and IgG titers to determine the viral causes of encephalitis. Samples of CSF should be cultured for virus in addition to bacteria and fungi. Throat swabs for viral culture are also recommended. The yield for viral cultures is highest early in the illness.

A CSF PCR for HSV is both sensitive and specific; where available, it is the diagnostic test of choice. In the absence of this test, brain biopsy of the affected temporal lobe remains the diagnostic procedure of choice. Herpes immunofluorescence stain of cortical tissue has an 80% yield. Viral culture of the brain should also be obtained (takes 1 to 5 days to grow). In herpes encephalitis, histopathology classically reveals Cowdry type A intranuclear inclusions. Other stains including smear for acid-fast bacilli and stains for fungi should also be performed.

With the exception of HSV-1, most of the common causes of viral encephalitis have no specific associated treatment. One possible approach is to initiate acyclovir therapy (10 mg/kg intravenously every 8 hours) while awaiting diagnostic tests, recognizing that a delay in therapy of herpes encephalitis worsens the prognosis.

### KEY POINTS

**About Viral Encephalitis**

1. **Three major categories:**
   a) Mosquito-borne (arboviruses)
   b) Animal-to-human (rabies virus)
   c) Human-to-human [herpes simplex 1 (HSV-1), mumps, measles, Varicella, human herpesvirus 6; less commonly, Epstein–Barr virus, cytomegalovirus, and enteroviruses]

2. **Symptoms of cortical dysfunction are evident:**
   a) Hallucinations, repetitive higher motor activity such as dressing and undressing
   b) Seizures
   c) Severe headache
   d) Ataxia

3. **Rabies causes distinct symptoms:**
   a) Hydrophobia
   b) Rapid, short respirations
   c) Hyperactivity and autonomic dysfunction
   d) (Less commonly) ascending paralysis

4. **Diagnosis is often presumptive, requiring acute and convalescent serum analysis.**
   a) Cerebrospinal fluid (CSF) shows a white blood cell count below 500/mm³, mild increase in protein, possibly red blood cells (in cases of HSV-1)
   b) Polymerase chain reaction of CSF diagnoses HSV, culture is seldom positive.
   c) A computed tomography or magnetic resonance imaging scan may show temporal lobe abnormalities in HSV-1 infection.
   d) An electroencephalogram may show localized temporal lobe abnormalities in HSV infection.
   e) Brain biopsy is likely necessary in the presence of temporal lobe abnormalities and no improvement on acyclovir.

5. **Treat with acyclovir for possible HSV-1 infection.**

6. **Prevent disease:** Avoid mosquito bites during epidemics. Wash wounds inflicted by rabies-infected animals; give immune globulin and rabies vaccine.
If temporal lobe abnormalities are found and if the patient fails to improve on acyclovir, a brain biopsy should be strongly considered. In other forms of encephalitis in which no focal cortical abnormalities are noted, the usefulness of brain biopsy remains to be determined. If HSV is confirmed by PCR, culture, or biopsy, intravenous acyclovir should be continued for 14 to 21 days.

The prognosis of viral encephalitis varies depending on the agent. A mortality of 50% to 60% is associated with HSV-1, and the frequency of neurologic sequelae is high. Early treatment reduces mortality. The mortality for rabies is nearly 100%, justifying vaccination of anyone who has potentially been exposed to the rabies virus. The prognoses for arboviruses depend on the patient’s age, the extent of cortical involvement, and the specific agent. Eastern equine encephalitis tends to be the most virulent, having a 70% mortality; Western equine encephalitis is usually mild and often subclinical, infecting primarily young children. West Nile virus infection is also often subclinical or causes just mild disease; however, in elderly individuals, this virus can cause severe, life-threatening disease that can be accompanied by flaccid paralysis. Venezuelan equine encephalitis is also usually mild, and Japanese encephalitis varies in severity.

Management of rabies exposure is complex, and specific guidelines have been published by the Advisory Committee on Immunization Practices [Human rabies prevention—United States, 1999. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 1999;48:1–21]. Bite wounds should be washed with a 20% soap solution and irrigated with a virucidal agent such as povidone iodine solution. Rabies immune globulin (20 IU/kg) should be injected around the wound and given intramuscularly. Several safe and effective anti-rabies vaccines are available. The vaccine should be given on days 0, 3, 7, 14, and 28.

### CNS ABSCESS

### BRAIN ABSCESS

**POTENTIAL SEVERITY**

*Often subacute in onset, but may be life-threatening if improperly managed. Early neurosurgical consultation is of critical importance.*

**CASE 6.4**

A 19-year-old white man noted the gradual onset of severe left frontal headache. The headache was sharp and constant, interfered with sleep, and was not relieved by aspirin. Two weeks after the onset of the headache, the teen was noted to have a grand mal seizure associated with urinary incontinence that lasted 15 minutes. On admission to hospital, he was afebrile and alert, but somewhat confused. He was oriented to person, but not to time or place. Examination of the head, ears, nose, and throat showed teeth in poor repair, with evidence of several cavities and gingivitis. Fundoscopic exam revealed sharp disc margins. Mild left-sided weakness was noted on neurologic exam. A CT scan with contrast demonstrated a 3-cm, ring-enhancing lesion in the right frontal cortex. No evidence of sinusitis.

### KEY POINTS

**About the Clinical Manifestations of Brain Abscess**

1. Symptoms are initially nonspecific, and a delay in diagnosis is common (2 weeks).
   - Severe headache is often localized to the site where the abscess has formed.
   - Neck stiffness noted in occipital brain abscess or after rupture into the ventricle.
   - Alterations in mental status, inattentiveness, lethargy, coma (a bad prognostic sign) may be seen.
   - Vomiting is associated with increased pressure in the cerebrospinal fluid (CSF).
2. Physical findings are often minimal:
   - Fever not present in half of patients.
   - Focal neurologic findings appear late.
   - Papilledema, a late manifestation, seen in 25% of cases.
   - Deficits in the VIth and IIIrd cranial nerves result from increased CSF pressure.
   - Seizures most common in association with frontal brain abscess.
Prevalence and Pathogenesis

Brain abscess is an uncommon disease, found in about 1 in 10,000 general hospital admissions. Infection of the cerebral cortex can result from the direct spread of bacteria from another focus of infection (accounts for 20% to 60% of cases) or from hematogenous seeding.

**Direct Spread**

The direct spread of microorganisms from a contiguous site usually causes a single brain abscess. Primary infections that can spread directly to the cerebral cortex include:

1. Subacute and chronic otitis media and mastoiditis (spread to the inferior temporal lobe and cerebellum).
2. Frontal or ethmoid sinusitis (spread to the frontal lobes).
3. Dental infection (usually spreads to the frontal lobes).

The brain abscess in Case 6.4 likely originated from a dental focus. Brain abscess as a complication of ear infection has decreased in frequency, especially in developed countries. By contrast, brain abscess arising from a sinus infection remains an important consideration in adults and children alike. Bullet wounds to the brain devitalize tissue and may leave fragments of metal that can serve as a focus for infection. Other missiles that have been associated with brain abscesses are pencil-tip injury to the eye and a lawn dart. In such cases, brain abscess may develop many years after the injury. Brain abscess can occasionally result from facial trauma or as a complication of a neurosurgical procedure. The development of brain abscess after neurosurgery may be delayed, with symptomatic infection occurring 3 to 15 months after the surgery.

**Hematogenous Spread**

Abscesses associated with bacteremia are usually multiple and are located in the distribution of the middle cerebral artery. Initially, they tend to be located at the junction of the gray and white matter, where brain capillary blood flow is slow and septic emboli are more likely to lodge. Microinfarction causes damage to the blood–brain barrier, allowing bacteria to invade the cerebral cortex.

Primary infections that lead to hematogenous seeding the brain include:

- Chronic pulmonary infections such as lung abscess and empyema, often in hosts with bronchiectasis or cystic fibrosis.
- Skin infections.
- Pelvic infections.
- Intra-abdominal infections.
- Esophageal dilation and endoscopic sclerosis of esophageal varices.
- Bacterial endocarditis (2% to 4% of cases).
- Cyanotic congenital heart diseases (most common in children).

No primary site or underlying condition can be identified in 20% to 40% of patients with brain abscess.

The location of a brain abscess reflects the site of the primary infection. In order of decreasing frequency, abscesses are most commonly found in the frontal or temporal, frontoparietal, parietal, cerebellar, and occipital lobes.

The histologic changes in the brain depend on the duration of infection. Early lesions (first 1 to 2 weeks) are poorly demarcated and are associated with localized edema. Acute inflammation is evident, but not tissue necrosis. This early stage is commonly called cerebritis. After 2 to 3 weeks, necrosis and liquefaction occur, and a fibrotic capsule surrounds the lesion.

**Microbiology**

The bacterial causes of brain abscess are highly variable. The pathogens involved vary depending on the site of the primary infection, the age of the patient (microorganisms often differ in children and adults), and the immune status of the host. The organism or organisms recovered from a brain abscess frequently provide clues about the primary site of infection and any potentially undiagnosed underlying conditions in the host.

Anaerobic bacteria are common constituents of brain abscesses, generally originating as part of the normal mouth flora. However, intra-abdominal or pelvic
infections can occasionally lead to bacteremia with an anaerobic organism that seeds the cerebral cortex. The anaerobes in such cases usually reflect colonic or female genital tract flora. The anaerobes most frequently cultured from brain abscesses include anaerobic streptococci, Bacteroides species (including B. fragilis), Prevotella melaninogenica, Propionibacterium, Fusobacterium, Eubacterium, Veillonella, and Actinomyces.

Aerobic gram-positive cocci are also frequently encountered, including S. viridans, S. milleri, microaerophilic streptococci, S. pneumoniae (rare), and S. aureus. S. aureus is a more frequent pathogen in brain abscess following trauma or a neurosurgical procedure. S. milleri is particularly common, and this organism possesses proteolytic enzymes that predispose to necrosis of tissue and formation of abscesses.

Aerobic gram-negative rods are not usually recovered in brain abscess except following neurosurgery or head trauma. When gram-negative rods are isolated, E. coli, Pseudomonas, Klebsiella, and Proteus species are most common. Rarer gram-negative rods include H. aphrophilus, Actinobacillus actinomycetemcomitans, Salmonella, and Enterobacter species.

**IMMUNOCOMPROMISED HOST**

In the immunocompromised patient, the range of organisms—particularly opportunistic pathogens—is considerably broader. Toxoplasma gondii can reactivate when the cell-mediated immune system becomes compromised. Nocardia asteroides, a common soil organism, can enter the bloodstream via the lungs and seed the cerebral cortex. Aspergillus, Cryptococcus neoformans, and Coccidioides immitis also can enter through the lungs and subsequently invade the cerebral cortex. Other pathogens causing brain abscess in the immunocompromised host include Candida albicans, mucormycosis (Zygomycetes), Cladosporium trichoides, and Curvularia species.

Individuals infected with HIV frequently develop infections of the cerebral cortex. Toxoplasma gondii is the most common cause of brain abscess in these patients, but more than one CNS infection can occur simultaneously. Tuberculomas, cryptococcomas, early progressive multifocal leukoencephalopathy, and infection with L. monocytogenes, Salmonella, Candida, Histoplasma, and Aspergillus have all been reported to cause CNS lesions in association with HIV infection. In the patient with AIDS, CNS lymphoma also commonly mimics brain abscess (see Chapter 17).

**IMMIGRANTS**

Parasites are the most common cause of brain abscess in individuals who have previously lived outside the United States. Cysticercosis represents 85% of brain infections in Mexico City (see Chapter 12). Other parasites that can cause brain abscess include Entamoeba histolytica, Schistosoma japonicum, and Paragonimus species.

**Clinical Symptoms and Signs**

The symptoms of brain abscess tend come on gradually and are often nonspecific, delaying the diagnosis. The mean interval between the first symptom and diagnosis is 2 weeks.

As observed in case 6.4, headache is the most common symptom. It usually localizes to the side on which the abscess is located, but in some cases, the headache is generalized. As observed with bacterial meningitis, headache is usually severe, and it is not relieved by aspirin or other over-the-counter pain medications. In patients with cyanotic heart disease and unexplained headache, the diagnosis of brain abscess must always be excluded.

About 15% of patients complain of neck stiffness mimicking meningitis. Meningismus is most commonly associated with occipital lobe brain abscess or with an abscess that has leaked into a lateral ventricle.
Changes in mental status are common. In patients with frontal abscess, subtle disturbances in judgment and inattentiveness may be the primary symptom. Lethargy can progress to coma, and these changes are thought to be primarily the consequence of cerebral edema and increased intracranial pressure. The development of coma is associated with a poor prognosis. Vomiting may also develop as a consequence of increased intracranial pressure. The absence of fever does not exclude a diagnosis of brain abscess. A significant percentage of patients (45% to 50%) fail to mount a febrile response. Focal neurologic deficits usually develop days to weeks after the onset of headache and are observed in half of patients at the time of admission. The specific neurologic deficits depend on the location of the abscess (Table 6.6). Palsies as a consequence of increased intracranial pressure on the VIth and IIIrd cranial nerve may be seen. Papilledema is a late manifestation of increased intracranial pressure and is found in 25% of patients. As observed in case 6.4, focal or grand mal seizures develop in 25% of patients and are most commonly associated with frontal lobe brain abscess.

**Diagnosis**

Focal symptoms (for example, unilateral headache) or signs (for example, unilateral cranial nerve deficits, hemiparesis) and papilledema suggest a space-occupying lesion in the cerebral cortex. In this circumstance, a lumbar puncture is contraindicated until this possibility is excluded. The asymmetric cerebral edema associated with brain abscess can cause brain stem herniation in 15% to 30% of patients if CSF pressure is reduced below the tentorium by lumbar puncture. A CT or MRI scan with contrast should be performed before lumbar puncture to exclude a focal cerebral lesion. Blood samples for culture should be drawn (positive in 15% of cases), and empiric parenteral antibiotic therapy initiated before the CT or MRI scan. If the study is negative, the lumbar puncture can then be performed.

**Computed Tomography Scan**

A CT scan is not as sensitive as MRI for diagnosing brain abscess, but it can frequently be obtained more easily on an emergent basis. When brain abscess is a serious consideration, the CT study must be performed with a contrast agent. The lesion has different appearances on scan depending on the duration of the infection, and these differences reflect the histopathology:

1. **Early cerebritis.** The lesion appears as an irregular area of low density that does not enhance following contrast injection.
2. **Later cerebritis.** The lesion enlarges and demonstrates a thick diffuse ring of enhancement following contrast injection. The ring of contrast enhancement represents breakdown of the blood–brain barrier and development of an inflammatory capsule (Figure 6.5).
3. **Late cerebritis.** Necrosis often develops with late cerebritis. Pre-contrast images reveal a ring of higher density than the surrounding edematous brain. Injection of contrast demonstrates a thin ring that is not of uniform thickness.
4. **Healed abscess.** Once the abscess has healed, the resulting collagen capsule becomes isodense (same density as the surrounding tissue), and infusion of contrast no longer results in ring enhancement.

**Magnetic Resonance Imaging**

An MRI scan is the diagnostic study of choice for evaluating brain abscess. The scan should be performed with gadolinium diethylenetriamine pentaacetic acid, which crosses the damaged blood–brain barrier. This agent
and normal CSF protein (Table 6.3). On rare occasions, an abscess may rupture into the lateral ventricle, causing frank meningitis and a resulting CSF formula with a predominance of PMNs (up to 160,000/mm³), low glucose, and high protein.

**Treatment**

The goals of therapy are to sterilize the abscess or abscesses and reduce the mass effect caused by necrosis and cerebral edema. Because surgical drainage of the brain abscess is usually necessary, a neurosurgeon should be contacted as soon as the diagnosis is made.

**Antibiotics**

To cure brain abscess, prolonged intravenous antibiotic therapy (6 to 8 weeks) is required. A number of drugs can be chosen depending upon the probable pathogen or pathogens. Once the causative organisms have been isolated and susceptibility testing performed, the drug regimen can be modified.

High-dose penicillin remains the mainstay of therapy when a dental origin is suspected. Penicillin covers all mouth flora, including aerobic and anaerobic streptococci. Metronidazole is also recommended for most

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**KEY POINTS**

**About the Diagnosis of Brain Abscess**

1. Focal symptoms or neurologic signs plus papilledema suggest the possibility of a space-occupying lesion; lumbar puncture is contraindicated.
2. After blood culture and empiric antibiotics, perform computed tomography (CT) or magnetic resonance imaging (MRI) scan with contrast.
3. An MRI is preferred over CT scan (detects early cerebritis and smaller lesions, and visualizes the brainstem).
4. Four stages detectable on imaging:
   a) Early cerebritis (edema, no ring enhancement).
   b) Later cerebritis (ring enhancement with early capsule, edema).
   c) Late cerebritis (necrosis, ring seen without contrast, thin, non-uniform contrast-enhancing ring).
   d) Healed abscess (no longer ring-enhancing, lesion becomes isodense).
5. Lumbar puncture is contraindicated.
patients, because this antibiotic readily penetrates brain abscesses; intraleional concentrations reach 40 μg/mL. This drug has excellent cidal activity against all anaerobes, but is not active against aerobic organisms. In most patients, a third-generation cephalosporin should also be included in the regimen to cover Enterobacteriaceae that may be present, particularly in patients with a brain abscess associated with a chronic ear infection. High-dose ceftriaxone or cefotaxime are equally effective and should be used unless Pseudomonas aeruginosa is strongly suspected. When P. aeruginosa is cultured, or when a brain abscess develops following a neurosurgical procedure, maximum doses of ceftazidime or cefepime should be used. In patients who develop brain abscess following a penetrating head trauma or craniotomy, and in the patient with S. aureus bacteremia, high-dose oxacillin or nafcillin needs to be included. Aminoglycosides, erythromycin, tetracyclines, and first-generation cephalosporins should not be used to treat brain abscess, because these drugs do not cross the blood–brain barrier.

**Surgery**

Surgical drainage is generally required for both diagnosis and treatment. Needle aspiration is preferred in most cases, because this procedure reduces the extent of neurologic damage. In patients with a traumatic brain abscess, an open procedure is preferred to remove bone chips and foreign material. Surgical removal of the entire capsule greatly increases the likelihood of cure in fungal brain abscesses. In patients with early cerebritis without evidence of cerebral necrosis, and in patients with abscesses located in vital regions of the brain inaccessible to aspiration, surgery can be delayed or avoided. When a decision is made not to drain immediately, careful follow-up with sequential CT or MRI scans is critical. Following the initiation of empiric antibiotics for an established brain abscess, indications for surgical intervention include lack of clinical improvement within a week, depressed sensorium, signs of increased intracranial pressure, multiloculated abscess, abscess size exceeding 2.5 cm, and progressive increase in the ring diameter of the abscess. Contrast enhancement at the site of the abscess may persist for several months, and so that finding is not helpful for deciding on surgical intervention or continued antibiotic therapy.

**Glucocorticoids**

Glucocorticoids should be given only to patients with evidence of mass effect and a depressed mental status. If used, intravenous dexamethasone should be administered at a loading dose of 10 mg, followed by 4 mg every 6 hours. The drug should be discontinued as soon as possible.

The addition of glucocorticoids has several disadvantages. These agents reduce contrast enhancement on CT scan, making changes in abscess size more difficult to monitor. Glucocorticoids also slow capsule formation (increase the risk of ventricular rupture), and reduce antibiotic penetration into the abscess by improving the integrity of the blood–brain barrier.

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**KEY POINTS**

**About the Treatment and Outcome of Brain Abscess**

1. Antibiotic therapy must be prolonged (6 to 8 wks) and must use high doses of intravenous
   a) penicillin (covers mouth flora).
   b) metronidazole (concentrates in abscesses and kills all anaerobes).
   c) ceftriaxone or cefotaxime (covers gram-positive and gram-negative aerobes). If Pseudomonas is a possibility, substitute ceftazidime or cefepime.
   d) Nafcillin or oxacillin (for abscess following head trauma, neurosurgery, or Staphylococcus aureus bacteremia). Use vancomycin if methicillin-resistant S. aureus is suspected.

   a) Needle aspiration is usually preferred (less collateral damage).
   b) Open resection is recommended after head trauma and with fungal abscess.
   c) Use observation in cases of early cerebritis, with frequent follow-up imaging (computed tomography or magnetic resonance).

3. Use dexamethasone in the presence of mass effect and depressed mental status. Avoid when possible, because it
   a) reduces contrast enhancement during imaging.
   b) slows capsule formation and increases the risk of ventricular rupture.
   c) reduces antibiotic penetration into the abscess.

4. Mortality ranges from 0% to 30%. Poor prognosis is associated with
   a) rapid progression in hospital.
   b) coma on admission.
   c) rupture into the ventricle.
Prognosis and Outcome

Mortality from brain abscess currently ranges from 0% to 30%. The use of CT and MRI has improved outcomes by allowing for earlier diagnosis and more accurate monitoring of response to therapy.

Poor prognostic factors for recovery include

- rapid progression of the infection before hospitalization,
- stupor or coma on admission (60% to 100% mortality), and
- rupture of the abscess into the ventricle (80% to 100% mortality).

Surviving patients experience a high incidence of neurologic sequelae (30% to 60%), recurrent seizures being the most common. This persistent problem most frequently follows frontal brain abscess.

INTRACRANIAL EPIDURAL AND SUBDURAL ABSCESS

Intracranial epidural and subdural abscesses are rare. They usually result from spread of infection from a nidus of osteomyelitis after neurosurgery, from an infected sinus (in particular the frontal sinus), or less commonly, from an infected middle ear or mastoid. In infants, subdural effusions may complicate bacterial meningitis; however, unlike the form seen in adults, they rarely require drainage. The bacteria causing these closed-space infections reflect the primary site of infection. *S. aureus* is most common, followed by aerobic streptococci. Other pathogens include *S. pneumoniae, H. influenzae,* and gram-negative organisms. Anaerobes such as anaerobic streptococci and *B. fragilis* can also be associated with this infection. Patients with sinusitis and chronic mastoiditis often have polymicrobial abscesses.

Epidural abscesses form between the skull and the dura (Figure 6.1). Because the dura is normally tightly adherent to the skull, this infection usually remains localized and spreads slowly, mimicking brain abscess in its clinical presentation. On exam, localized erythema, swelling, and tenderness of the subgaleal region may be seen. Subdural empyema in the cranial region progresses much faster than epidural abscess does, usually spreading rapidly throughout the cranium. Patients appear acutely ill and septic. They complain of severe headache that is localized to the site of infection, and nuchal rigidity commonly develops, suggesting the diagnosis of meningitis. Within 24 to 48 hours focal neurologic deficits are noted, and half of these patients develop seizures. Lumbar puncture is contraindicated because of the high risk of brain stem herniation. A CT scan with contrast should be performed, and in most instances, the images demonstrate the abscess and the overlying osteomyelitis, sinus infection, or mastoiditis. In early epidural or subdural abscess, MRI scan is capable of detecting early cortical edema and smaller collections of inflammatory fluid. In patients suspected of having early disease, whose CT scan is negative, an MRI scan should be performed.

Subdural empyema is a neurosurgical emergency. Immediate drainage is required to prevent death from cerebral herniation. Exploratory burr holes and blind drainage have been life-saving in rapidly progressing cases. Antibiotic therapy should be instituted immediately. The same regimens recommended for brain abscess are used. The mortality from subdural empyema remains high at 14% to 18%, the prognosis being especially poor in patients who are comatose. Epidural abscess is less dangerous, but also requires surgical drainage. Mortality is low; however, if left untreated, this infection can spread to the subdural space.

**KEY POINTS**

### About Epidural and Subdural Intracranial Abscess

1. Associated with frontal sinusitis, mastoiditis, and neurosurgery.
2. *Staphylococcus aureus* are a common cause; otherwise, microbiology is similar to that in brain abscess.
3. Epidural abscess progresses slowly, requires surgical drainage.
4. Subdural abscess spreads quickly.
   a) Often mimics meningitis.
   b) Lumbar puncture is contraindicated; use computed tomography scan or magnetic resonance imaging emergently.
   c) Requires immediate drainage.
   d) Mortality ranges from 14% to 18%.
SPINAL EPIDURAL ABSCESS

After the dura passes below the foramen magnum, it no longer adheres tightly to the bone surrounding the spinal cord. Both an anterior and a posterior space that contain fat and blood vessels are present. Infection can spread to the epidural space from vertebral osteomyelitis or disk-space infection. Infection of the epidural space following epidural catheter placement is increasingly common, as is postoperative infection following other surgical procedures in the area of the spinal cord. Skin and soft-tissue infections, urinary tract infections, and intravenous drug abuse can all lead to bacteremia and seeding of the epidural space. In approximately one third of patients, no primary cause is identified.

The inflammatory mass associated with infection can compress the nerve roots as they exit the spinal canal, causing radicular pain, and findings consistent with lower motor neuron dysfunction (decreased reflexes, loss of light touch and pain sensation in specific dermatomes). In addition to radicular pain, patients complain of localized back pain. These symptoms often are accompanied by malaise and fever. As the epidural mass expands, the spinal cord is compressed, resulting in upper motor neuron findings such as a positive Babinski’s reflex, hyperreflexia, loss of motor function, and bladder dysfunction. Usually within 24 hours of the onset of paralysis, the spinal cord’s vascular supply becomes irreversibly compromised, leading to infarction and permanent paraplegia. To prevent this devastating outcome, clinicians need to consider spinal epidural abscess in the differential diagnosis for back pain. In the patient with back pain and fever, spinal epidural abscess must be strongly considered.

A helpful clue can be derived from the physical examination. In posterior epidural abscesses, severe localized tenderness over the infected area is encountered. However, in anterior epidural abscesses (a rarer event) infection is deep-seated, and tenderness cannot be elicited. Epidural abscess formation can be readily visualized on MRI scan (Figure 6.6), which is the preferred test. A CT scan with gadolinium contrast is also an effective method of diagnosis, but is now seldom used.

The bacteriology of epidural abscess reflects the primary site of infection. *S. aureus*, including the methicillin-resistant form (MRSA), is cultured from more than half of cases. Gram-negative aerobes are the second most frequent cause, followed by aerobic streptococci, *S. epidermidis*, and anaerobes. *Mycobacterium tuberculosis* is


**KEY POINTS**

About Spinal Epidural Abscess

1. The spinal canal has both an anterior and a posterior epidural space containing fat and small vessels.
2. The spinal epidural space can become infected by:
   a) spread of infection from osteomyelitis or disk space infection.
   b) spinal surgery or epidural catheter placement.
   c) hematogenous spread from skin or urinary tract infection or intravenous drug abuse.
3. Symptoms and signs include:
   a) low back pain and fever.
   b) radicular pain accompanied by lower motor neuron deficits.
   c) signs of cord compression in later stages (Babinski's reflex, hyperreflexia, loss of motor function, bladder dysfunction). Within 24 hours of onset, irreversible paraplegia may occur.
   d) localized spinous process tenderness in posterior epidural abscesses.
4. In the patient with back pain and fever, always consider spinal epidural abscess.
5. Magnetic resonance imaging (MRI) scan with contrast is the diagnostic study of choice.
6. Treatment involves:
   a) emergency surgical drainage if physical exam suggests neurologic compromise or MRI shows significant cord compression.
   b) Prolonged antibiotic therapy (4 to 6 weeks) with nafcillin or oxacillin, metronidazole, and ceftriaxone. If methicillin-resistant *Staphylococcus aureus* is suspected, vancomycin coverage is also required.

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Another important cause, most commonly associated with tuberculous infection of the thoracic vertebra.

Because of the unpredictability of neurologic complications, surgical decompression is recommended in all cases in which MRI scan suggests any neurologic compromise or evidence of significant cord compression. Drainage is combined with prolonged antibiotic treatment (4 to 6 weeks). High doses of nafcillin or oxacillin (or vancomycin if MRSA is suspected), ceftriaxone, and metronidazole are recommended as empiric therapy pending culture results.

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**FURTHER READING**

**Bacterial Meningitis**


**Aseptic Meningitis**


**Encephalitis**


**Tuberculous Meningitis**


**Cryptococcal Meningitis**


**Brain Abscess**


**Subdural and Epidural Abscess**


Mumps

Time Recommended to complete: 1 day

Yu Hui  Children’s Hospital of Fudan University

Mumps is an acute generalized viral infection that occurs primarily in school-aged children and adolescents. The most prominent manifestation of this disease is nonsuppurative swelling and tenderness of the salivary glands, with one or both parotid glands involved in most cases. The disease is benign and self-limited, with one third of affected persons having subclinical infection. Meningitis and epididymo-orchitis represent the two most important of the less frequent manifestations of this disease. As is characteristic of many viral infections, mumps is usually a more severe illness in persons past the age of puberty than in children and more commonly leads to extrasalivary gland involvement in these older patients.

Pathogen

Mumps virus is a member of the genus Rubulavirus in the Paramyxoviridae family. It is an enveloped negative-stranded RNA virus with an irregular spherical shape ranging in size from 100 to 600 nm. The viral genome is contained in a helical nucleocapsid enclosed in a trilayered envelope studded with glycoproteins possessing hemagglutinin and neuraminidase (HN protein) and cell fusion (F-protein) activities. The virus contains seven structural proteins, including nucleocapsid-associated protein (NP), a phosphoprotein(P), membrane or matrix protein (M), a high-molecularweight protein (L), SH protein, HN protein, and F protein. The NP and HN proteins represent the soluble (S) and viral (V) antigens in the complement fixation (CF) reaction. The gene for the SH protein is the most variable part of the mumps virus genome and amplification of a sequence of the SH gene region by polymerase chain reaction(PCR) is used to classify the virus into different genotypes.

Mumps virus grows well in a number of cell lines, including primary rhesus monkey kidney cells, green monkey kidney cells, Vero cells, HeLa cells, and other mammalian cell cultures. The typical cytopathic effect in tissue culture includes rounding and fusion of cells into giant multinucleated syncytia and the presence of intracytoplasmic inclusions.

Mumps virus is ether-sensitive by virtue of its lipid envelope. It is stable at 4℃ for several days and at −65℃ for months to years; however, repeated freezing and thawing may diminish viral activity.

Epidemiology

Humans are the only known natural host; however, monkeys and other laboratory animals have been experimentally infected. Although persistent infections in cultured cells are commonly established by mumps virus, a carrier state is not known to exist in humans.

The virus is naturally transmitted via direct contact, droplet nuclei, or fomites and enters through the nose or mouth. More
intimate contact is needed to transmit mumps than for measles or varicella. The period of peak contagion is just before or at the onset of parotitis.

Although the disease occurred throughout the year, the peak incidence was between January and May. Epidemics have been reported in military populations and other closed communities such as prisons, boarding schools, ships, and remote islands.

Mumps is uncommon in infants younger than 1 year. Resistance to infection in this age group is on the basis of passive immunity acquired by the placental transfer of maternal antibody. In the prevaccine era, more than 50% of cases occurred in the 5- to 9-year-old age group, and 90% of the cases occurred in children younger than 14 years. Men and women have the same frequency of development of parotitis with mumps infection.

**Pathogenesis**

Mumps infection is acquired after contact with infected respiratory secretions. Viral replication in the nasopharyngeal mucosa and regional lymph nodes is followed by primary viremia, which results in spread of infection to multiple organs, including the central nervous system (CNS) and glandular epithelium. Pathologic changes in the salivary gland include diffuse interstitial edema and serofibrinous exudate with infiltration of lymphocytes and macrophages. The ductal epithelium undergoes degenerative changes with intraluminal accumulation of lymphocytes and debris.

Mumps orchitis results from direct viral infection of the testes; virus has been isolated from testicular biopsy specimens of the affected gland within the first few days of symptoms. Histologic changes within the testes include interstitial edema and lymphocytic infiltration. Focal destruction of the germinal epithelium can occur.

Mumps infection of the CNS is common. The virus probably enters the CNS through the choroid plexus and infects the choroidal epithelium and ependymal cells lining the ventricles. Mumps encephalitis occurs when infection spreads to the brain parenchyma along neuronal pathways.

Specific immunoglobulin (Ig) M, IgA, and IgG antibodies are produced in response to mumps infection. Virus-specific secretory IgA appears concurrently with the cessation of viral shedding in saliva. Intrathecal synthesis of mumps IgG and IgM antibodies has been demonstrated, as well as production of interferon-γ by activated cytotoxic T lymphocytes in the cerebrospinal fluid (CSF).

**Clinical Manifestations**

The incubation period ranges from 12 to 25 days. An estimated 80% to 90% of nonimmune household contacts will become infected. Patients are most infectious 1 to 2 days before the onset of symptoms and for 5 days thereafter; virus has been isolated from saliva 7 days before symptoms and up to 9 days after the appearance of parotid swelling. Both clinical and subclinical infections provide lifelong immunity; reinfection occurs rarely.

One-third of patients with mumps infection have subclinical or mild respiratory disease. The most common manifestation is parotid swelling, which is usually unilateral at the onset of illness, later becoming bilateral in
70% of cases. Prodromal symptoms, including headache, vague abdominal discomfort, and loss of appetite, typically precede the parotid swelling by 12 to 24 hours. Earache on the side of parotid involvement and discomfort with eating or drinking acidic food are common complaints. Parotid pain is most pronounced during the first few days of swelling.

The swollen parotid gland lifts the earlobe upward and outward, and the angle of the mandible is obscured; the opening of the Stensen duct on the buccal mucosa is edematous and erythematous. Trismus (spasm of the masticatory muscles) can occur. Other salivary glands such as the submandibular and sublingual glands may also be involved. Presternal edema can be notable. Morbilliform rash has been reported in association with mumps infection. Systemic symptoms, including fever, usually resolve within 3 to 5 days, and the parotid swelling subsides within 7 to 10 days. Adolescents and adults have more severe disease than young children.

Complications

(1) Central Nervous System Infection

Mumps virus is neurotropic and the degree of neuropathogenicity may depend on the genotype of the virus. CSF pleocytosis occurs in > 50% of individuals with mumps parotitis, but only 1% to 10% of patients have clinical evidence of meningitis or encephalitis. Parotitis does not develop in about 50% of patients with mumps meningitis. Virus can be isolated from CSF in approximately 40% to 50% of individuals with mumps meningitis.

Mumps infection of the CNS is diagnosed three times more often in males than in females, with meningitis more common than encephalitis. Symptomatic CNS disease typically occurs 3 to 10 days after the onset of parotitis, but it can precede or occur without parotitis. Symptoms of meningitis include headache, fever, lethargy, nuchal rigidity, delirium, and vomiting. Seizures occur in 20% of patients.

The CSF white blood cell count is usually less than 1000 cells/mm³, with lymphocytes predominating. CSF protein is normal or mildly elevated, and CSF glucose is decreased in 30% of cases (rarely < 20 mg/dL). CSF pleocytosis can persist for prolonged periods, suggesting persistent infection.

In general, infection of the CNS is self-limited, with no sequelae. However, some children develop ataxia, behavioral problems, aqueductal stenosis with hydrocephalus, sensorineural hearing impairment, paralysis and neuroretinitis. Death occurs in approximately 1.4% of cases of encephalitis.

(2) Orchitis

Orchitis develops in 14% to 35% of males with mumps virus infection. The highest risk is in those 15 to 29 years of age. Orchitis is uncommon in prepubertal males. Symptoms usually begin 4 to 8 days after the onset of parotid swelling, but orchitis can occur before or in the absence of parotitis. Testicular involvement is usually unilateral, and epididymitis is associated with orchitis in most cases. Clinical findings include fever, malaise, vomiting, lower abdominal pain, and testicular pain. The testicle is typically swollen and tender for 3 to 7 days.

(3) Other Sites of Infection

Hematuria and proteinuria can occur in children with mumps, and transient alterations in creatinine clearance are reported. Glomerulonephritis is usually self-limited, but rare reports of death from renal failure have
Arthralgia, polyarticular migratory arthritis with effusion, and monoarticular arthritis are described in temporal association with mumps parotitis. Signs usually appear 1 to 3 weeks after the onset of parotitis, but they can occur before or in the absence of parotitis. Joint complaints are three to four times more common in males; the average age at occurrence is 24 years. Large joints are affected most frequently and include the knee, hip, wrist, ankle, and shoulder. Although the duration of joint symptoms ranges from 2 days to 6 months, recovery with no evidence of persistent or recurrent symptoms is usual.

Electrocardiographic abnormalities consistent with myocarditis have been noted in 4% to 15% of patients with mumps, most commonly in adults. Abnormalities generally resolve within 2 to 4 weeks, although sequelae are reported.

The incidence of pancreatitis with mumps infection is poorly defined; involvement is usually associated with mild epigastric pain, but severe hemorrhagic pancreatitis has been reported. The role of mumps virus in the development of insulin-dependent diabetes mellitus is controversial. Cases have been noted to follow outbreaks of mumps, but no causal relationship has been established.

Oophoritis, mastitis, thyroiditis, thrombocytopenic purpura and hepatitis with acute cholecystitis have been associated with mumps virus infection.

Laboratory Findings

Laboratory findings include increased serum amylase during the first week of illness. The white blood cell count is usually low or normal with a relative lymphocytosis. Mumps infection can be confirmed by the presence of serum mumps IgM, demonstration of a rise in IgG antibody titers to mumps virus antigens in acute and convalescent serum, positive mumps virus culture, or detection of the viral genome by RT-PCR.

The typical CSF findings in mumps meningitis have been described previously. Similar although less marked CSF abnormalities are present in half of patients with mumps parotitis but without apparent CNS involvement. In a patient with aseptic meningitis, an elevated serum amylase level should suggest mumps infection.

Diagnosis And Differential

Diagnosis

The diagnosis of mumps has been made on the basis of a history of exposure and of parotid swelling and tenderness accompanied by mild to moderate constitutional symptoms.

Laboratory confirmation of typical mumps is unnecessary. However, when parotitis is absent or recurrent, when extrasalivary gland manifestations are prominent, or when documentation of the presence of a specific viral disorder is desired, a variety of diagnostic aids can be used.

A variety of entities may simulate mumps but can be easily differentiated from mumps on the basis of chronicity or associated symptoms. Infectious processes involving parotid glands are most likely to be confused with mumps because of their acute onset and associated fever. Parainfluenza 3 virus, coxsackieviruses, and influenza A viruses have been reported to cause acute parotitis. These entities can be differentiated from mumps only by viral culture or serology. Bilateral parotid swelling is often seen in
children with human immunodeficiency virus (HIV) infection. Suppurative parotitis, most often caused by Staphylococcus aureus or gram-negative organisms, usually occurs in the postoperative period, in premature newborns, or in debilitated patients with poor oral intake. The gland is warm, hard, and extremely tender; the overlying skin is erythematous. Massage of the parotid expresses purulent drainage from Stensen’s duct.

Parotid enlargement caused by drugs or metabolic disorders is usually bilateral and asymptomatic. Phenylbutazone, thiouracil, iodides, and phenothiazines have been implicated in this condition. Diabetes mellitus, malnutrition, cirrhosis, and uremia are among the metabolic disorders that can cause parotid swelling.

Tumors, cysts, and obstruction caused by stones or structure are usually unilateral. Rare conditions that may mimic mumps include Mikulicz’s syndrome, Parinaud’s syndrome, uveoparotid fever of sarcoidosis.

**Treatment**

Therapy for mumps is symptomatic and supportive. Treatment with analgesic-antipyretics such as aspirin or acetaminophen relieves pain caused by salivary gland inflammation and reduces fever. Topical application of warm or cold packs to the parotid may also relieve discomfort. Intravenous fluid administration may be necessary for patients with meningitis or pancreatitis who have persistent vomiting. Lumbar puncture may relieve the headache associated with meningitis.

Management of orchitis is purely symptomatic. Bed rest, narcotic analgesics, support of the inflamed testis with a “bridge,” and ice packs make the patient feel more comfortable. An anesthetic block of the spermatic cord with 1% procaine hydrochloride may alleviate severe pain. There is no convincing evidence that the use of steroids or diethylstilbestrol or incision of the tunica albuginea produces more rapid resolution of the orchitis or prevents subsequent atrophy.

**Prevention**

As noted, recommendations for the management of patients with mumps include isolation for 10 days after the onset of parotid swelling to prevent the spread of infection to susceptible persons. This measure may be of little value, particularly in closed populations such as schools or hospitals, because virus is present in saliva days before parotitis develops and because those with clinically inapparent infection can shed virus.

Active immunization with the Jeryl Lynn strain of attenuated mumps virus vaccine has been available in the United States since December 1967. The vaccine is prepared in chick embryo cell culture. A single subcutaneous immunization produces protective levels of mumps-neutralizing antibodies in more than 95% of vaccines.

Although the antibody levels produced are lower than after natural infection, adequate titers are maintained for at least 10.5 years. Adverse reactions to the vaccine are uncommon; transient suppression of tuberculin-delayed hypersensitivity has been reported and parotitis and orchitis have been recognized rarely. Vaccine virus is not present in secretions of immunized children. In Japan, aseptic meningitis associated with mumps vaccine virus occurred in 0.05% to 0.3% of
recipients of the Urabe AM 9 mumps vaccine; manifestations began 2 to 4 weeks after immunization. U.S. studies did not reveal evidence of an increased risk of aseptic meningitis after administration of the Jeryl Lynn strain of mumps vaccine.

All children older than 12 months should be immunized. Vaccination should take place at 12 to 15 months and again at 4 to 6 years of age, as part of immunization with the combined live measles-mumps-rubella (MMR) virus vaccine. A two-dose immunization regimen is recommended for all adolescents and health care personnel without evidence of mumps immunity. Other adults should receive at least one dose of vaccine. Immunization after exposure may not provide protection from natural infection.

vaccine should not be administered to pregnant women, patients receiving immunosuppressive therapy, or those with severe febrile illnesses, advanced malignancies, or congenital or acquire immunodeficiencies. Serious reactions to the mumps component of MMR have not been reported in limited studies in HIV-infected patients. However, a fatal case of measles pneumonitis occurred in a 21-year-old man with advanced HIV disease who was vaccinated with MMR vaccine; therefore, it should not be administered to such patients. Individuals with HIV infection who are not severely immunocompromised may be immunized with MMR vaccine.

As with other live virus vaccines, mumps
InfecTious Diarrhea

Diarrheal illness is one of the leading causes of death worldwide, accounting for nearly 2.5 million deaths annually. It is most commonly encountered in developing countries and is a less serious problem in the United States. Still, the incidence of diarrhea in the United States has been estimated to be 1 episode per person per year.

With appropriate medical care, these infections are rarely fatal. The pathogens that cause diarrhea can be transmitted through food, through water, or through person-to-person spread. Differences in these modes of transmission reflect differences in the ability of each pathogen to survive in the environment. They also reflect the inoculum size required for a given pathogen to cause disease.

Acute Diarrhea

Bacterial Diarrhea

Potential Severity

Can be life-threatening in infants, young children, and elderly people. Most individuals with this illness can be managed as outpatients.

Potential Severity

These disorders are usually self-limiting, but can be fatal in infants, elderly people, and people who develop enteric fever.
The three most common bacterial causes of acute infectious diarrhea are *Salmonella*, *Shigella*, and *Campylobacter*. Other important bacterial pathogens include *Escherichia coli*, *Vibrio parahaemolyticus*, and *Yersinia enterocolitica*. Each of these pathogens has unique life-cycle and virulence characteristics. The various causes of acute bacterial diarrhea are usually not distinguishable clinically, and diagnosis requires isolation of the organism on stool culture.

### CASE 8.1

A 52-year-old black woman with rheumatoid arthritis for 24 years was admitted to the hospital with complaints of fever and diarrhea for the preceding 24 hours.

One month earlier she had been hospitalized for neck surgery and received a 10-day course of a broad-spectrum antibiotic (ceftazidime). Antibiotic treatment was completed the day of discharge (18 days before her second admission). She was doing well in a rehabilitation hospital until 3 days prior to admission, when she developed a fever to 38.9°C associated with shaking chills and persistent severe watery diarrhea (25 to 30 bowel movements daily). One day before admission, she noted abdominal cramps, nausea, vomiting, and anorexia. The rehabilitation nurse found the woman's blood pressure to be 70/50 mm Hg, and referred her to the emergency room. Medications: aspirin and large quantities of antacids.

Epidemiology: Her son had brought her an egg salad sandwich from Famous Deli, which they shared 16 hours before onset of the illness. Her son also has severe diarrhea.

Physical examination: Temperature 39°C, blood pressure 70/50 mm Hg, pulse rate of 120 per minute, and respiratory rate 20 per minute. She was moderately ill-appearing, with dry mucous membranes and a dry, fissured tongue. Abdominal exam revealed hyperactive bowel sounds and mild diffuse tenderness. No skin lesions were seen.

Laboratory findings: White blood cell (WBC) count of 7100/mm³, with 10% polymorphonuclear leukocytes (PMNs), 63% bands, 19% lymphocytes; blood urea nitrogen of 63 mg/dL; and serum creatinine of 2.1 mg/dL. Methylene blue smear of the stool: few PMNs and few mononuclear cells. Gram stain: mixed flora. Stool culture: Salmonella enteritidis.

### Microbiology, Pathogenesis, and Epidemiology

Table 8.1 summarizes the characteristics of the most common bacterial uses of diarrhea.

**Salmonella**

*Salmonella* is an aerobic gram-negative bacillus that can grow readily on simple culture media. It is motile, and most strains do not ferment lactose. As a consequence of DNA sequencing, the speciation of *Salmonella* has recently been revised, and the related nomenclature has become complex.

From a clinical standpoint, the simplest approach is to differentiate typhoidal salmonella (primarily *S. typhi* and *S. paratyphi*) from the many nontyphoidal serotypes that primarily cause gastroenteritis (*S. enteritidis*, *S. typhimurium* most common). One nontyphoidal strain of note is *S. choleraesuis*. This serotype has a higher likelihood of causing bacteremia.

*S. typhi* is adapted to humans and rarely infects other animals; however, the other *Salmonella* species readily infect both wild and domestic animals. These organisms attach to epithelial cells in the small intestine and colon.

### KEY POINTS

**About Salmonella Gastroenteritis**

1. Gram-negative bacillus, does not ferment lactose, motile.
2. Attaches to intestinal and colonic cells, and injects proteins that stimulate internalization.
3. Spreads to mesenteric nodes; *Salmonella choleraesuis* and *S. typhi* often enter the bloodstream.
4. The organism is acid-sensitive, with 10⁻⁴ to 10⁻⁸ organisms required for infection. Risk factors for disease include
   a) antacid use,
   b) prior antibiotics (reduces competition by normal flora), and
   c) depressed immune function (AIDS and transplant patients, sickle cell disease).
5. Contracted from contaminated foods (more commonly in the summer months):
   a) Chicken products (eggs, undercooked meat)
   b) Contaminated processed foods (ice cream, unpasteurized goat cheese, whitefish, contaminated fruits and vegetables)
   c) Infected pet turtles, rodents, iguanas, birds
   d) Contaminated water supply (*S. typhi*)
Once attached they inject into host cells specific proteins that cause the formation large ruffles that surround the bacteria, internalizing them into large vacuoles. There, *Salmonella* are able to replicate and eventually lye the infected cell, escaping into the extracellular environment and in some cases gaining entry to the bloodstream to cause bacteremia. *S. typhi* is particularly adept at surviving within cells. It often causes little intestinal epithelial damage and little diarrhea, primarily entering mesenteric lymph nodes and the bloodstream to cause classic enteric fever. *S. enterica* is also adept at invading the bloodstream. It is the most common cause of nontyphoidal *Salmonella* bacteremia.

Studies in normal volunteers have revealed that large numbers of bacteria (10^-4 to 10^-8 organisms) are required to produce symptomatic disease. However, epidemiologic studies suggest that infection can result from ingestion of 200 organisms. Stomach acidity kills many *Salmonella* before they enter the more hospitable intestinal tract, but in gastrectomy patients or those who use antacids (as in case 8.1), the number of organisms required to cause disease is markedly reduced. The critical inoculum size is also affected by the normal bowel flora. Reduction in the flora as a result of prior antibiotic treatment reduces competition for nutrients (as in case 8.1) and allows *Salmonella* to more readily multiply within the bowel lumen. Depressed immune function increases the risk of salmonellosis, patients with AIDS and lymphoma and other neoplasms being at higher risk. Patients with sickle cell disease have an increased incidence of *Salmonella* bacteremia that is often complicated by osteomyelitis.

Because large numbers of *Salmonella* organisms are required to cause disease, gastroenteritis is almost always associated with ingestion of heavily contaminated food. In case 8.1, the sandwich from the delicatessen likely had become contaminated. Because chickens often excrete *Salmonella* in their stools, eggs, egg products, and undercooked chicken are the foods most commonly associated with disease.

### Table 8.1. Bacterial Diarrhea: Causative Pathogens, Epidemiology, Stool Findings

<table>
<thead>
<tr>
<th>Causative organism</th>
<th>Epidemiology</th>
<th>Stool* PMNs</th>
<th>RBCs</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Salmonella</em></td>
<td>Foodborne, <em>S. typhi</em> waterborne</td>
<td>2+</td>
<td>Rare</td>
<td>May have monocytes in stool; contaminated meat and milk products</td>
</tr>
<tr>
<td><em>Shigella</em></td>
<td>Person-to-person</td>
<td>4+</td>
<td>3+</td>
<td>Mucous, tenesmus; daycare centers in the United States</td>
</tr>
<tr>
<td><em>Campylobacter</em></td>
<td>Foodborne</td>
<td>4+</td>
<td>3+</td>
<td>Gram-stain positive (seagull-like gram-negative bacilli), chicken</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>Enterotoxigenic</td>
<td>Waterborne</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Enteroaggregative</td>
<td>Foodborne and waterborne</td>
<td>0</td>
<td>0</td>
<td>Watery diarrhea; developing countries, travelers’ diarrhea</td>
</tr>
<tr>
<td>Enteropathogenic</td>
<td>Foodborne, waterborne, person to person</td>
<td>0</td>
<td>0</td>
<td>Children under 3 years of age; developing countries</td>
</tr>
<tr>
<td>Enterohemorrhagic</td>
<td>Foodborne</td>
<td>±</td>
<td>4+ visible</td>
<td>O157:H7, contaminated beef, vegetables, mayonnaise, cider</td>
</tr>
<tr>
<td>Enteroinvasive</td>
<td>Foodborne</td>
<td>4+</td>
<td>3+</td>
<td>Rare, developing countries</td>
</tr>
<tr>
<td><em>Vibrio parahaemolyticus</em></td>
<td>Foodborne</td>
<td>0</td>
<td>0</td>
<td>Raw seafood (sushi); common in Japan</td>
</tr>
<tr>
<td><em>Vibrio cholera</em></td>
<td>Waterborne</td>
<td>0</td>
<td>0</td>
<td>Developing countries</td>
</tr>
<tr>
<td><em>Yersinia</em></td>
<td>Foodborne</td>
<td>4+</td>
<td>3+</td>
<td>Common in Europe, rare in the United States; can mimic appendicitis</td>
</tr>
<tr>
<td><em>Clostridium difficile</em></td>
<td>Antibiotic-associated</td>
<td>2–4+</td>
<td>0–3+</td>
<td>Early disease, watery diarrhea; later, extensive colitis</td>
</tr>
</tbody>
</table>

* PMNs = polymorphonuclear leukocytes; RBCs = red blood cells, 4+ = many PMN per hpf, 3+ moderate numbers per hpf, 2+ few PMN per hpf.
foods—examples include ice cream, unpasteurized goat cheese, paprika-powdered potato chips, and whitefish—has resulted in large outbreaks of salmonellosis. *Salmonella*-infected human or animal feces can contaminate fruits and vegetables. Pet turtles, iguanas, rodents, and birds can carry large numbers of organisms, and can infect humans, particularly young children. Contamination of the water supply with sewage also can lead to gastrointestinal infection. *S. typhi* is frequently contracted from contaminated water, and typhoid fever is most commonly found in developing countries where sanitation is poor. Salmonella infections are more common in the summer months, when the warmer temperatures allow the organism to multiply more rapidly on contaminated foods.

**Shigella**

The gram-negative *Shigella* bacillus is nonmotile and does not ferment lactose. It grows readily on standard media. The four major serologic groups, A through D, are common to different areas of the world. Group A *Shigella dysenteriae* and group D *S. boydii* are seldom found in the United States, where the species most commonly encountered are group B *S. flexneri* and group D *S. sonnei*.

*Shigella* contains a series of surface proteins that induce intestinal epithelial cells and M cells to ingest it. Like *Salmonella*, this organism injects proteins into host cells, stimulating ruffling. Unlike *Salmonella*, the phagocytosed *Shigella* uses a surface hemolysin to lyse the phagosome membrane and escape into the cytoplasm. There, the bacterium induces the assembly of actin rocket tails that propel it through the cytoplasm. When the bacterium reaches the cell periphery, it pushes outward to form membrane projections that can be ingested by adjacent cells, efficiently spreading directly from cell to cell. *Shigella* produces a cytotoxic Shiga toxin and induces premature cell death. This combination of efficient cell-to-cell spread and host-cell destruction produces superficial ulcers in the bowel mucosa and induces an extensive acute inflammatory response that usually prevents entry of *Shigella* into the bloodstream.

*Shigella* is relatively resistant to acid, and can survive in the gastric juices of the stomach for several hours. This characteristic explains why ingestion of as few as 200 bacteria can cause disease. The organism first takes up residence in the small intestine. After several days, it is cleared by the small intestine, but then invades the colon, where it causes an intense inflammatory response, forming microabscesses and mucosal ulcerations.

Because such a low inoculum is required to cause disease, the epidemiology of *Shigella* is different from that of *Salmonella*. *Shigella* has no intermediate animal hosts; the bacteria reside only in the intestinal tract of humans. The primary mode of spread is person-to-person by anal–oral transmission. Foodborne and waterborne outbreaks may also occur as a consequence of fecal contamination—incidents that are most commonly reported in developing countries, where public health standards are poor. Toilet seats can become heavily contaminated by *Shigella*, which may account for some cases in the United States. Children in daycare centers have a high incidence of infection, as do institutionalized individuals, particularly mentally challenged children. On U.S. Indian reservations, high numbers of *Shigella* dysentery cases have been reported. In tropical areas, spread of *Shigella* has been attributed to flies, and epidemics of shigellosis have been reported to correlate with heavy fly infestations.

**Campylobacter**

*Campylobacter* are comma-shaped gram-negative rods that, on microscopic examination, are often paired in a distinctive seagull shape. *Campylobacter* are microaerophilic, and with the exception of *Campylobacter fetus*, are unable to grow at 25°C. Ideal growth conditions for *C. jejuni*, the strain that most commonly causes diarrhea, are 42°C, 6% oxygen, and 5% to 10% carbon dioxide. Other bowel flora often overgrow on routine MacConkey’s medium, and so selective Campy–BAP medium (10% sheep blood in Brucella agar containing amphotericin B, cephalothin, vancomycin, polymyxin B, and trimethoprim) is recommended.
The life cycle of Campylobacter is not as well defined as that of Salmonella and Shigella. It can be ingested by monocytes, where it can survive within the cells for 6 to 7 days. Endocytosis by intestinal epithelial cells and M cells is also likely to occur. Once intracellular, Campylobacter induces cell death and tissue necrosis leading to ulceration of the bowel wall and intense acute inflammation. Possibly as a consequence transport by monocytes, Campylobacter can gain entry into the bloodstream. C. fetus, subspecies fetus, is particularly adept at causing bacteremia, often causing little or no diarrhea. This strain’s resistance to the bactericidal activity of serum may explain its ability to produce persistent bacteremia leading to vascular infections, soft-tissue abscesses, and meningitis.

Like Salmonella, Campylobacter is sensitive to acid, and large numbers of organisms (more than 10^8) are therefore required to cause disease. The epidemiology of Campylobacter is similar to that of Salmonella. C. jejuni is the species that primarily causes diarrhea. This species frequently contaminates poultry, and its high carriage rate may be partly explained by the high body temperature in birds, a condition that would be expected to enhance growth of C. jejuni. This organism is 10 times more frequently cultured from commercial chicken carcasses than Salmonella is (approximately 30% vs. 3%). C. jejuni can also be carried in water, raw milk, sheep, cattle, swine, and reptiles. As observed with Salmonella, infections are more common in the summer months.

Escherichia coli

Multiple strains of E. coli can cause diarrheal illness. These strains cannot easily be distinguished from the nonpathogenic strains of E. coli that normally colonize the bowel. Experimental serotyping methods are available that can identify specific lipopolysaccharide antigens (O antigens) and flagellar antigens (H antigens) associated with specific pathogenic characteristics. The diarrhea-causing E. coli strains are generally divided into five major classes based on their mechanisms of virulence:

1. **Enterotoxigenic (ETEC) strains.** Colonize the small bowel and produce a cholera-like or heat-stable toxin that stimulates secretion of chloride, causing watery diarrhea. These organisms are most commonly encountered in developing countries and are contracted from water contaminated with human sewage. These strains are a major cause of travelers’ diarrhea.

2. **Enteroaggregative (EaggEC) strains.** Adhere in large aggregates to human colonic mucosa and produce a low-molecular-weight enterotoxin that causes watery diarrhea. The diarrhea is often prolonged. These strains are contracted by ingesting contaminated water or food. Enteroaggregative Esch. coli are reported in developing countries and are an important cause of travelers’ diarrhea.

3. **Enteropathogenic (EPEC) strains.** Adhere to the small bowel and induce the polymerization of actin filaments to form a pedestal directly beneath the site of bacterial attachment. This process is associated with mild inflammation and usually causes watery diarrhea. These strains are transmitted by contaminated food or water and by person-to-person spread in nurseries. This disease primarily affects children under the age of 3 years, and it is more common in developing countries.

4. **Enterohemorrhagic (EHEC) strains.** Produce verotoxins or Shiga-like cytotoxins that inhibit protein synthesis and cause cell death. In certain strains, the toxin damages vascular endothelium in the bowel and glomeruli, causing hemorrhagic inflammatory colitis and hemolytic uremic syndrome. The strain most commonly associated with this syndrome is O157:H7; however, other toxin-producing serotypes are being identified with increasing frequency. Cattle appear to be the primary reservoir, and the disease is most commonly associated with ingestion of undercooked contaminated ground beef. Less commonly, cases have developed after
**KEY POINTS**

**About *Escherichia coli* Gastroenteritis**

1. Serotyping identifies specific O (lipopolysaccharide) and H antigens (flagellar proteins).
2. Five pathogenic classes have been defined:
   a) Enterotoxigenic (ETEC): Produce a cholera-like toxin. Spread by water contaminated with human sewage in developing countries. Cause of travelers’ diarrhea.
   b) Enteroaggregative (EaggEC): Adhere as large aggregates. Enterotoxin produces watery diarrhea. Cause of traveler’s diarrhea.
   c) Enteropathogenic (EPEC): Induce pedestals that cause mild inflammation. Produce watery diarrhea primarily in children under 3 years of age. Person-to-person spread in developing countries.
   d) Enterohemorrhagic (EHEC): Produce verotoxins or Shiga-like cytotoxin. Damage vessels. The O157:H7 strain causes hemolytic–uremic syndrome. Cattle are the primary reservoir. Spread by undercooked hamburger, unpasteurized milk, contaminated apple cider, and mayonnaise.
   e) Enteroinvasive (EIEC): Similar to *Shigella*. Require large inoculum. Seen in developing countries.

**Vibrio**

The two primary strains of *Vibrio* associated with diarrhea are *V. cholera* and *V. parahaemolyticus*. This small, slightly curved gram-negative rod has a single flagellum at one end that causes the bacterium to move erratically under the microscope. The organism can be isolated from the stool using thiosulfate, citrate, bile salt, sucrose agar, or tellurite taurocholate gelatin agar.

**V. cholera**

The *V. cholera* strain gains entry to the small bowel when the host ingests contaminated water (requires $10^3$ to $10^6$ organisms to cause disease) or food (requires $10^2$ to $10^4$ organisms). Neutralization of stomach acid lowers the inoculum required to cause disease. The organisms attaches to the small intestine, where it produces cholera toxin. This exotoxin binds to a specific receptor in the bowel mucosa that activates adenylate cyclase, causing an increase in cyclic adenosine monophosphate (cAMP). Elevated cAMP in turn promotes secretion of chloride and water, causing voluminous watery diarrhea.

*V. cholera* is able to grow and survive in aquatic environments—particularly in estuaries, where it attaches to algae, plankton, and shellfish. During periods when the environment is unfavorable for growth, the organism can convert to a dormant state that can no longer be cultured. The bacteria can also form a “rugose”—an aggregate of bacteria surrounded by a protective biofilm that blocks killing by chlorine and other disinfectants. These consumption of unpasteurized milk or contaminated apple cider, spinach, lettuce, or commercial mayonnaise. Person-to-person spread can occur in daycare centers and nursing homes. This infection is found primarily in industrialized nations and usually occurs during the summer months.

**5. Enteroinvasive (EIEC) strains.** Invade colonic epithelial cells by the same mechanisms that *Shigella* uses. The EIEC strains do not produce toxins, but rather cause an inflammatory colitis that is indistinguishable from that caused by *Shigella*. These strains require ingestion of a large inoculum ($10^6$ organisms) to cause disease. Outbreaks are rare and are usually associated with contaminated foods in developing countries.

**KEY POINTS**

**About *Vibrio cholera* Diarrhea**

1. *Vibrio* is a slightly curved gram-negative bacillus with a single flagellum. It requires a special culture medium (tellurite taurocholate gelatin).
2. Spread by contaminated water ($10^3$ to $10^6$ organisms) or food ($10^2$ to $10^4$ organisms).
3. Attaches to the small intestine, and produces cholera toxin. Binds to a receptor that increases cyclic adenosine monophosphate, and thereby promotes chloride and water secretion.
4. Survives in algae, plankton, and shellfish. Can convert to dormant state or form aggregates surrounded by biofilm (rugose).
5. Non-cholera toxin strains are seen in the Gulf of Mexico.
6. Cholera toxin strains are spread by contaminated water in India, Bangladesh, Asia, Africa, Europe, South America (Peru), and Central America. Outbreaks occur in the hot seasons of the year.
characteristics allow \textit{V. cholera} to persist in water and shellfish. Oysters harvested during the summer months off the Gulf Coast of the United States are frequently positive for \textit{V. cholera}. Fortunately, these strains do not produce cholera toxin, and they cause only occasional cases of gastroenteritis. Cholera toxin–producing strains are usually found in areas of poor sanitation, where fecal contamination of food and water are common.

This organism is capable of producing large epidemics or pandemics, with major outbreaks frequently taking place in India and Bangladesh. Epidemics have also been reported in Asia, Africa, and Europe. In 1991, a large outbreak occurred in Peru, and cholera has been reported in other regions of South America and in Central America. Epidemics usually begin during the hot seasons of the year.

\textbf{\textit{V. parahaemolyticus}}

The \textit{V. parahaemolyticus} strain is halophilic (“salt loving”) and grows in estuaries and marine environments, attaching to plankton and shellfish. Little is known about its pathogenesis, except for the close correlation between hemolysis and ability to cause disease. Non-hemolytic strains are almost always avirulent. \textit{V. parahaemolyticus} produces an enterotoxin and causes moderate bowel inflammation, resulting in mild to moderately severe diarrhea. Clams and oysters that filter large volumes of water become heavily contaminated with \textit{V. parahaemolyticus}, and the ingestion of raw or undercooked shellfish is the primary cause of human disease. Other forms of inadequately cooked seafood can harbor small numbers of \textit{Vibrio}, and the tradition of eating uncooked seafood (sushi) explains the high incidence of \textit{V. parahaemolyticus} diarrhea in Japan. The increasing popularity of sushi in the United States is likely to be accompanied by an increasing incidence of that illness.

\textbf{\textit{Yersinia}}

\textit{Y. enterocolitica} is a gram-negative bacillus that grows aerobically on standard media. Large numbers of organisms must be ingested to cause disease (10⁹ organisms). The organism primarily invades the mucosa of the terminal ileum, causing painful enlargement of the mesenteric nodes. As a consequence of right-sided abdominal pain, \textit{Yersinia} enterocolitis can be mistaken for appendicitis. \textit{Yersinia} infection is rare in the United States, being more commonly reported in northern Europe, South America, Africa, and Asia. The disease usually occurs in children. \textit{Y. enterocolitica} is generally contracted from contaminated meat products, and because this bacterium can grow at 4°C, refrigerated meats are a particular concern. Contamination of pasteurized milk has been associated with several outbreaks in the United States. In contrast with other forms of bacterial diarrhea that peak during the summer months, most cases of \textit{Y. enterocolitica} occur during the winter months.

\textbf{Clinical Manifestations}

\textbf{Gastroenteritis}

Acute diarrhea is defined as diarrhea lasting less than 14 days, emphasizing the self-limiting nature of the infections. With the exception of certain strains of \textit{E. coli} and \textit{Vibrio}, most cases of bacterial diarrhea present with enterocolitis. As illustrated in case 8.1, the incubation period after ingestion of \textit{Salmonella}-contaminated food is usually 8 to 24 hours (\textit{Shigella}: 36 to 72 hours; EHEC: 4 days).

Enterocolitis is characterized by diarrhea and abdominal pain. Stools may be frequent but small, or (as in Case 8.1) the diarrhea may voluminous. In
some patients, stool may be watery as a consequence of increased secretion of fluids into the bowel. Watery diarrhea is most commonly encountered in ETEC, EPEC, EaggEC, and Vibrio infections. Other patients have purulent, mucousy stools. This latter form of diarrhea is most commonly encountered in Shigella dysentery, reflecting the exuberant acute inflammatory response of the bowel. Stools may be bloody as a result of bowel ulceration and tissue necrosis. Bloody stools are most commonly encountered in Shigella, Campylobacter, EHEC, and EIEC. Visible blood in the stool is particularly prominent with EHEC, often causing the patient to seek medical attention. In patients with significant colonic involvement, tenesmus and marked pain on attempting to defecate are common complaints.

On physical exam, a significant percentage of patients have fever, usually in the 38°C to 39°C range. However patients with EHEC are often afebrile. Abdominal exam reveals hyperactive bowel sounds, reflecting increased peristalsis. Diffuse tenderness is typical, usually not accompanied by guarding or rebound. In some cases, however, severe tenderness with rebound may be present, suggesting the diagnosis of acute appendicitis or cholecystitis. The peripheral leukocyte count is often normal, but some patients develop moderate leukocytosis. Fluid loss can be profound, leading to hypotension and electrolyte abnormalities. Positive blood cultures can accompany Salmonella enterocolitis, but are rare in Shigella or C. jejuni infections.

Enteric fever—Typhoid fever is most commonly associated with S. typhi and S. paratyphi. The incubation is usually 8 to 14 days, being longer with a lower inoculum. Fever is the first manifestation, and the disease usually mimics an influenza-like illness, characterized by continuous frontal headache, generalized aches, malaise, anorexia, and lethargy. A large percentage of patients also have a nonproductive cough. Most patients complain of mild abdominal discomfort and constipation that is often followed by bloody diarrhea during the second week of the illness. Also during the second week, fever increases to 40°C, and the patient often becomes severely ill. Abdominal pain and distension worsen, and mental status dulls. By the third week, in the absence of antibiotic treatment, a significant percentage of patients recover, but 10% die of septic shock or bowel perforation.

Skin shows small rose-colored macules (“rose spots”). Normochromic, normocytic anemia; leukopenia. Positive blood cultures in 90% of patients in the first week.
Blood cultures are positive in 90% of patients during the first week and in 50% during the second week. Stool cultures remain positive for many weeks. C. fetus and Y. enterocolitica can produce a syndrome that is clinically indistinguishable from typhoid fever.

**Diagnosis**

Direct examination of the stool using a methylene blue stain should be performed in all severely ill patients to assess the cellular response. The presence of PMNs on stool smear strongly suggests acute bacterial enterocolitis, but the same result may also be seen in amoebic dysentery and in antibiotic-associated pseudomembranous colitis. An abundant PMN response is seen in Shigella, Campylobacter, and EIEC infections (Table 8.1). Cases of Salmonella enterocolitis tend to have a less vigorous PMN response in the stool, and patients with S. typhi may demonstrate increased numbers of fecal monocytes.

The sensitivity of leukocyte stool smear varies depending on the clinical laboratory. Fecal lactoferrin (a iron-binding protein found in PMNs) is a more sensitive and specific (90% to 100%) test for differentiating acute bacterial enterocolitis from viral gastroenteritis, but it is not widely available. Gram stain should be performed in all severely ill patients to assess the cellular response. The presence of PMNs on stool smear strongly suggests acute bacterial enterocolitis. The bacterial culture is positive in approximately 5% of cases of acute diarrhea. Therefore cultures should be obtained only in patients with severe disease in which hospitalization is being considered, in patients with bloody diarrhea, or in cases in which an outbreak is suspected. The stool sample should be planted immediately on the appropriate media to maximize sensitivity. In the case of Campylobacter, special selective media and microaerophilic conditions must be used (see the earlier discussion of this specific pathogen). Pathogenic strains of E. coli cannot be readily identified by culture; immunologic and molecular biologic methods are required. Slide agglutination using specific antisera against O antigens has been performed in several epidemics. For investigative purposes, primers for polymerase chain reaction (PCR) and probes for DNA hybridization are also available.

**Treatment and Outcome**

Most cases of bacterial enterocolitis are self-limiting, usually lasting 3 to 7 days. They may not require antibiotic therapy (Table 8.2). Fluid and electrolyte replacement is generally the most important supportive measure. Agents that slow peristalsis are contraindicated in patients with bacterial enterocolitis who have fever or bloody stools. These drugs may prolong fever, increase the risk of bacteremia, lead to toxic megacolon, and prolong fecal excretion of the pathogen. Bowel splints can also exacerbate the hemolytic uremic syndrome. Antibiotic therapy for Salmonella enterocolitis prolongs carriage in the stool and has not been shown to shorten the duration of gastroenteritis. Antibiotics are specifically contraindicated in patients with EHEC, because they may exacerbate the hemolytic uremic syndrome.

Patients with typhoid fever should receive immediate antibiotic treatment. Chloramphenicol was the treatment of choice until recently, but relapses occurred with that regimen, and increasing numbers of S. typhi have become resistant to chloramphenicol. A fluoroquinolone (ciprofloxacin, levofloxacin) or a third-generation cephalosporin (ceftiraxone) are the recommended first-line regimens.

To prevent potential complications associated with bacteremia, nontyphoidal salmonella should also be treated with antibiotics when this disease develops in neonates, people over age of 50 years, immunocompromised patients, and patients with prosthetic valves or vascular grafts. Antibiotic therapy should be continued only for 48 to 72 hours, or until the patient no longer has a fever. An oral fluoroquinolone, amoxicillin, or trimethoprim–sulfamethoxazole are generally recommended.

To prevent person-to-person spread and shorten the course of shigellosis, trimethoprim–sulfamethoxazole or ciprofloxacin are usually administered.

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**KEY POINTS**

About the Diagnosis of Bacterial Diarrhea

1. Direct examination of the stool using methylene blue stain assesses polymorphonuclear leukocyte (PMN) response.
   a) Abundant PMNs are seen in Shigella, Campylobacter, and enteroinvasive Escherichia coli infection.
   b) Salmonella infections produces moderate PMNs; with S. typhi, monocytes may be seen,
   c) PMNs are also seen with amoebic dysentery and Clostridium difficile toxin–associated diarrhea.
2. A Gram stain showing seagull-shaped gram-negative forms indicates Campylobacter infection.
3. Culture stools using both standard media and Campylobacter-selective media.
4. E. coli strains can be identified by slide agglutination tests using specific O antisera.
Table 8.2. Antibiotic Treatment of Acute Bacterial Diarrhea

<table>
<thead>
<tr>
<th>Cause</th>
<th>Treatment</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Salmonella</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nontyphoidal</td>
<td>Ciprofloxacin 500 mg PO q12h OR levofloxacin 400 mg PO q24h</td>
<td>5–7 days</td>
<td>Treatment prolongs the carrier state, avoid in most cases; for exceptions see text</td>
</tr>
<tr>
<td>Typhoid fever</td>
<td>Ciprofloxacin 500 mg PO q12h OR ceftriaxone 2 gm IV q24h Children: azithromycin 1 g, then 500 mg PO × 6 days</td>
<td>10–14 days</td>
<td>Delay in therapy increases risk of death; chloramphenicol no longer used in the United States</td>
</tr>
<tr>
<td><strong>Shigella</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin 500 mg PO q12h, OR levofloxacin 400 mg PO q24h OR TMX-sulfa 1 double-strength tablet q12h</td>
<td>3 days</td>
<td>Sterilizes the stool and reduces secondary cases</td>
</tr>
<tr>
<td><strong>Campylobacter jejuni</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Azithromycin 500 g PO q24h OR ciprofloxacin 500 mg PO q12h</td>
<td>3 days</td>
<td>Treatment within 4 days shortens the course; fluoroquinolone resistance increasing</td>
</tr>
<tr>
<td><strong>Escherichia coli</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterotoxigenic</td>
<td>Ciprofloxacin 500 mg PO q12h OR levofloxacin 400 mg PO q24h</td>
<td>3 days</td>
<td>Shortens the course of illness</td>
</tr>
<tr>
<td>Enteropathogenic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enteroinvasive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterohemorrhagic</td>
<td>No treatment</td>
<td></td>
<td>Also avoid anti-motility drugs; both increase toxin release and worsen hemolytic uremic syndrome; supportive care only</td>
</tr>
<tr>
<td><strong>Vibrio parahemolyticus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No treatment</td>
<td></td>
<td>Antibiotics do not shorten the course of illness</td>
</tr>
<tr>
<td><strong>Vibrio cholera</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin 1 g PO Alternative (adults): doxycycline 300 mg PO</td>
<td>1 dose</td>
<td>Reduces diarrhea volume; hydration most important;</td>
</tr>
<tr>
<td><strong>Yersinia enterocolitica</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Doxycycline 100 mg IV q12h PLUS gentamicin 5 mg/kg IV q24h Alternative: ciprofloxacin 500–750 mg PO q12h</td>
<td>3–7 days</td>
<td>Treat only very severe disease; efficacy of antibiotics not proven</td>
</tr>
<tr>
<td><strong>Clostridium difficile</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metronidazole 500 mg PO q8h Alternative: Nitazoxanide 500 mg PO Q12H Preferred for severe colitis: vancomycin 125–500 mg PO q6h</td>
<td>10 days</td>
<td>Discontinue all other antibiotics if possible, nitazoxanide may be helpful in cases refractory to metronidazole</td>
</tr>
</tbody>
</table>
KEY POINTS

About the Treatment of Bacterial Diarrhea

1. These diseases are self-limiting, and seldom require antibiotic treatment.
2. Fluid and electrolyte replacement are most important.
3. Avoid agents that slow peristalsis, which increases the risk of bacteremia, and prolongs fever and the carrier state.
4. Antibiotic treatment of *Salmonella* gastroenteritis prolongs the carrier state. However, to prevent complications associated with bacteremia, use ciprofloxacin, amoxicillin, or trimethoprim–sulfamethoxazole to treat
   a) neonates,
   b) people over the age of 50 years, and
   c) immunocompromised patients or those with prosthetic valves or synthetic vascular grafts.
5. Treat enteric fever emergently with ciprofloxacin or ceftriaxone.
6. Trimethoprim–sulfamethoxazole or ciprofloxacin reduces person-to-person spread of *Shigella*.
7. Erythromycin, azithromycin, or ciprofloxacin shortens the carrier state in *Campylobacter jejuni* infection.
8. *Yersinia* is not usually treated; in severe cases, use trimethoprim–sulfamethoxazole, ciprofloxacin, or ceftriaxone.
10. Ciprofloxacin for 3 to 5 days shortens the course of travelers’ diarrhea.

Although antibiotic treatment of *C. jejuni* diarrhea has not been proven to shorten the course of the illness, it has been shown to shorten the carrier state. Useful antibiotics include erythromycin, azithromycin, or ciprofloxacin. Recently, ciprofloxacin-resistant strains have been reported.

*Y. enterocolitica* is not usually treated; however, in severe cases, trimethoprim–sulfamethoxazole, a fluoroquinolone, or a third-generation cephalosporin may be administered.

*V. parahaemolyticus* usually does not require treatment. The course of travelers’ diarrhea can be shortened to 1.5 days from 3 to 5 days by a brief course of ciprofloxacin.

KEY POINTS

About Prevention of Bacterial Diarrhea

1. Investigation of sources of contamination is a cost-effective preventive measure.
2. Fecal carriage after *Salmonella* infection may continue for an extended period.
   a) The carrier state can often be eradicated by prolonged therapy (4 to 6 weeks) with amoxicillin or ciprofloxacin.
   b) Carrier state often cannot be eliminated in patients with gallstones.

PREVENTION

Public health measures are the most efficient and cost-effective way of reducing these diseases. By understanding the epidemiology of each pathogen, the public health investigator can track down the source of bacterial contamination and prevent additional cases.

After symptomatic disease, *Salmonella* fecal carriage may continue for an extended period, particularly if the patient received antibiotics. This carriage represents a potential health hazard for food handlers. The carrier state can usually be eradicated by prolonged therapy with amoxicillin (standard dose for 4 to 6 weeks) or a fluoroquinolone (ciprofloxacin: standard dose for 4 to 6 weeks). In patients with gallstones, the carrier state often cannot be eliminated.

For individuals visiting areas endemic for travelers’ diarrhea, a nonabsorbable rifamycin derivative, rifaximin, 200 mg orally, once or twice daily is protective.

Antibiotic-Associated Diarrhea

POTENTIAL SEVERITY

*Undiagnosed C. difficile can progress to severe colitis that may require colectomy or result in bowel perforation and death.*

Antibiotic-associated diarrhea develops in up to 30% of hospitalized patients. Systemic antibiotics reduce the normal flora and interfere with bacterial breakdown of carbohydrates. The increased concentrations of undigested carbohydrate increase the intraluminal osmotic
load, preventing water resorption and causing watery diarrhea. Antibiotic-induced reductions in the normal bowel flora also permit overgrowth by resistant bacteria. Staphylococcus aureus and Candida species were suggested as possible causes of this diarrhea, but subsequent studies indicated that the organism can account for some cases of antibiotic-associated diarrhea; however, the most frequent causative agent is C. difficile. This pathogen has been implicated in 20% to 30% of patients with antibiotic-associated diarrhea and 50% to 75% of those who develop antibiotic-associated colitis.

**Microbiology, Pathogenesis, and Epidemiology**

*C. difficile* is an obligate anaerobe, spore-forming, gram-positive rod. The organism’s name reflects the difficulty of isolated the pathogen on routine media. A cycloserine, cefoxitin, fructose agar with an egg-yolk base is capable of selecting this organism from total fecal flora.

When the bowel flora is exposed to broad-spectrum antibiotics, *C. difficile* overgrows and releases two high-molecular-weight exotoxins, toxin A and toxin B, which bind to and kill cells in the bowel wall.

A third toxin, binary toxin, an actin-specific adenosine diphosphate ribosyl transferase, has been detected in up to two thirds of recent *C. difficile* isolates and may be associated with more severe disease. Exposure of tissue-cultured cells to filtrate from *C. difficile*-infected feces resulted in dramatic cytopathic changes, including rounding up and detachment of cells. Death of colonic cells results in the formation of shallow ulcers, an exuberant acute inflammatory response, and the formation of pseudomembranes that are readily seen by colonoscopy. Early lesions are superficial, but as the disease progresses and the toxin levels increase, inflammation can extend through the full thickness of the bowel.

This disease develops in 10% of patients hospitalized for more than 2 days. *C. difficile* diarrhea is rarely encountered in outpatients. The incidence of disease is higher in elderly patients and in those who have severe underlying diseases or have undergone gastrointestinal surgery. An increased incidence is also associated with broad-spectrum antibiotics (clindamycin, ampicillin, amoxicillin, and cephalosporins are associated with the highest incidence), anticancer chemotherapy (methotrexate, 5-fluorouracil, doxorubicin, cyclophosphamide), bowel enemas or stimulants, enteral feedings, and close proximity to another patient with *C. difficile* diarrhea. This infection is spread from patient to patient by hospital personnel. Spores can be readily carried on hands, clothes, and stethoscopes. Numerous hospital outbreaks have been reported, and these outbreaks occur more commonly on wards where clindamycin is frequently administered.

**Clinical Manifestations**

*C. difficile* causes a spectrum of disease manifestations, from an asymptomatic carrier state to fulminant colitis. The severity of symptoms does not appear to relate to amount of toxin released into the stool, but may relate to the number of toxin receptors in the host’s bowel. High titers of immunoglobulin G (IgG) directed against toxin A appear to be protective and are often high in the asymptomatic carrier. The most common form of symptomatic disease is diarrhea without colitis.

Diarrhea usually begins 5 to 10 days after the initiation of antibiotics. However, diarrhea can develop up to 10 weeks after completion of antibiotic therapy. The diarrhea is usually watery, consisting of 5 to 15 bowel movements daily. Crampy, bilateral lower quadrant pain that decreases after a bowel movement, low-grade fever, and mild peripheral blood leukocytosis are common characteristics. Pseudomembranous colitis presents with the same symptoms and findings, except that pseudomembranes are seen on colonoscopy and marked thickened of the colonic bowel wall is seen on computed tomography (CT) scan.
KEY POINTS

About the Clinical Manifestations of Clostridium difficile Diarrhea

1. Symptoms do not correlate with the level of toxin production.
2. Mild-to-moderate disease:
   a) Watery diarrhea and crampy abdominal pain are typical.
   b) Low-grade fever and mild leukocytosis are common.
   c) Patients with colitis have the same symptoms, but pseudomembranes are seen on colonoscopy.
3. Severe disease has a high fatality rate
   a) Diarrhea or constipation both possible.
   b) Diffuse abdominal pain and tenderness; signs of peritonitis indicate impending perforation.
   c) Computed tomography scan may reveal toxic megacolon: bowel dilatation to more than 7 cm, air–fluid levels, bowel-wall thickening, and thumbprinting (can mimic ischemic bowel).
   d) Marked leukocytosis (25,000 to 35,000/mm³); lactic acidosis indicates impending perforation.
   e) High fatality rate.

These forms of C. difficile–induced diarrhea can be difficult to differentiate clinically from the most common form of antibiotic-associated diarrhea, osmotic diarrhea. Lack of fever or leukocytosis, absence of PMNs in the stool, and improvement when oral intake is reduced favor osmotic diarrhea.

Fulminant colitis develops in 2% to 3% of patients infected with C. difficile. This disease is associated with severe morbidity and a high mortality. Diarrhea is usually present; however, some patients develop constipation. Abdominal pain is usually diffuse and severe and can be associated with hypoactive bowel sounds, abdominal distension, and guarding. Findings of peritonitis can develop and usually indicate bowel perforation. Toxic megacolon (bowel loops dilated to more than 7 cm) is a feared complication. Full-thickness involvement of the bowel wall leads to bowel distension and air–fluid levels visible on abdominal CT scan or X-ray. Thumbprinting is often seen, reflecting submucosal edema, which can mimic bowel ischemia (Figure 8.1). Sigmoidoscopy must be performed cautiously under these conditions because of the high risk of perforation. Marked elevation in the peripheral WBC count (25,000 to 35,000 /mm³) is common. The development of lactic acidosis usually indicates impending bowel perforation and irreversible bowel damage that requires immediate surgical intervention.

**DIAGNOSIS**

Stool smear demonstrates PMNs in half of cases and may be heme-positive. Stool culture for C. difficile is not recommended because this organism is difficult and expensive to isolate, and because culture yields many false positive results. Diagnostic laboratories have therefore focused on toxin detection.

The original cytotoxicity assay remains the definitive test. Stool filtrate is overlaid onto fibroblasts. If the toxin is present, the cells round up and eventually detach from the monolayer. Specificity is confirmed if these effects are blocked by incubating the filtrate in advance with toxin-neutralizing antibody. The assay is sensitive (94% to 100%) and specific (99%) when performed by experienced personnel, but it is expensive and requires 2 to 3 days to perform.

Enzyme-linked immunoabsorbent assay (ELISA) kits that detect toxins A and B are now preferred as the initial screening test. They are rapid and less expensive, and they have a comparable specificity, but a lower sensitivity (70% to 90%). Many assays detect only toxin A and fail to detect a small percentage of C. difficile strains that exclusively produce toxin B. In cases in which the
diagnosis is strongly suspected, a negative ELISA assay should be confirmed by the cytotoxic assay.

Sigmoidoscopy is usually not required, because patients with positive findings almost always have a positive toxin test. With caution, endoscopy can be performed in the patient who requires immediate diagnosis, who is unable to produce stool, or in whom other colonic disorders are also being considered. A significant percentage of patients will have negative findings; however, the presence of pseudomembranes is considered diagnostic.

**TREATMENT, OUTCOME, AND PREVENTION**

Whenever possible, the first step should be to discontinue the offending antibiotic or antibiotics. In many cases, patients will fully recover without further intervention. This approach is preferred when symptoms are mild, because it allows the bowel to recolonize with competing normal flora and prevents relapse. In contrast, administration of metronidazole or vancomycin is associated with a 10% to 25% relapse rate.

As in other forms of diarrhea, fluids and electrolytes need to be replaced. Diarrhea serves to protect the mucosa by flushing away *C. difficile* toxins; antiperistaltic agents must therefore be avoided. Use of such agents increases the risk of full-blown colitis and toxic megacolon. If these measures are not effective or practical, specific therapy with oral metronidazole (250 mg four times a day for 10 days) should be initiated. Asymptomatic patients colonized with *C. difficile* should not be treated. Recurrent disease is a consequence of residual spores in the stool that are not killed by the antibiotic. First-time recurrences should be treated with the same regimen used to treat the initial episode. Oral vancomycin should be avoided whenever possible because of the increased risk of selecting for vancomycin-resistant enterococci. Nearly all strains of *C. difficile* are killed by metronidazole, and bactericidal levels are readily achieved in the bowel of symptomatic patients. Cure rates of 95% have been reported with the use of this agent. Recent observational studies suggest a trend toward poorer cure rates and higher relapse rates.

Oral vancomycin (125 mg four times daily for 10 days) should be reserved for patients with severe disease. The bowel does not absorb vancomycin, and stool levels of vancomycin reach concentrations that are 1000 to 3000 times the minimum inhibitory concentration for *C. difficile*. Unlike metronidazole levels, which decrease in stool as the integrity of the bowel mucosa improves, vancomycin levels remain high throughout the course of the disease. Response rates and relapse rates for oral vancomycin are comparable to those for oral metronidazole. In the patient who is unable to take oral medications, intravenous metronidazole (500 mg every 8 hours) should be administered. Intravenous metronidazole is excreted in the biliary tract, and therapeutic levels of the antibiotic are achieved in the stool. Intravenous vancomycin fails to achieve significant intraluminal bowel concentrations and is not recommended.

Two new medications recently became available. Oral nitazoxanide 500 mg twice daily for 7 to 10 days demonstrated response rates comparable to those with metronidazole. Tolevamer, a soluble high-molecular-weight anionic polymer, binds *C. difficile* toxins A and B without altering the other gastrointestinal flora. In mild-to-moderate disease 2 g in an oral dose every

### KEY POINTS

**About the Diagnosis, Treatment, and Prevention of *Clostridium difficile* Diarrhea**

1. **Diagnosis:**
   - a) In 50% of cases, PMNs are found in a stool smear.
   - b) Enzyme-linked immunoabsorbent assay for toxins A and B is the preferred assay. Many assays detect only toxin A and can miss *C. difficile* that produces only toxin B.
   - c) The cytotoxicity assay remains the definitive test, but it is expensive and takes several days.
   - d) Endoscopy is usually not required, and risks perforation.

2. **Treatment:**
   - a) Drugs must be orally administered (except for metronidazole).
   - b) Metronidazole is the treatment of choice; intravenous metronidazole is also effective, being excreted in bile.
   - c) Use vancomycin only for severe illness because of the risk of superinfection with vancomycin-resistant enterococci.
   - d) Nitazoxanide comparable to metronidazole in initial trials.
   - e) Tolevamer binds toxins A and B, but doesn’t change bowel flora.
   - f) Severe disease may require bowel resection; mortality is 30% to 50%.
   - g) Relapse is common because of residual spores. Re-treat with metronidazole.

3. **Prevention:**
   - a) Spread by hospital personnel; hand washing is critical.
   - b) Limiting clindamycin use may reduce the attack rate.
Viral Diarrhea

**POTENTIAL SEVERITY**

A self-limiting disease that can cause dehydration.

Viral diarrhea is the most common form of the disease, usually causing mild self-limiting watery diarrhea. The viruses most common associated with viral diarrhea are noroviruses, rotaviruses, enteric adenoviruses, and astroviruses.

**VIROLOGY, PATHOGENESIS, AND EPIDEMIOLOGY**

**Norovirus**

The single-stranded RNA *Norovirus* belongs to the calicivirus family, a group that derives its name from the distinct cup- or chalice-like indentations of the viral capsid seen on electron microscopy. Because no convenient method is known for propagating the virus, and no animal model of *Norovirus* gastroenteritis exists, little is known about its pathogenesis. Histopathology from infected human volunteers has revealed that the virus causes blunting of villi and PMN infiltration of the lamina propria in the jejunum. Patients present with the acute onset of nausea, vomiting, and watery diarrhea. The virus is shed in the stool for 24 to 48 hours after the onset of illness, and it also is present in high concentrations in vomitus. Ingestion of 100 viral particles can cause disease.

Infection is transmitted by contaminated water and food and by person-to-person spread. In addition to contaminated drinking water, swimming pools and lakes can transmit the disease. Norovirus is relatively resistant to chlorine. Shellfish are a leading food source, and because the virus is relatively heat-resistant, cooking contaminated shellfish does not completely eliminate the risk of infection. Infected food handlers can contaminate food, resulting in large outbreaks. Large outbreaks have also been reported in closed environments such as ships, military installations, hospitals, and nursing homes. Norovirus is more commonly associated with outbreaks in adults, but infants and children may also be infected by this virus or another member of the calicivirus group.

**Rotavirus**

The name *Rotavirus* (from the Latin *rota*, meaning wheel) for this double-stranded RNA virus is derived from the wheel-like appearance of the viral capsid on
The clinical manifestations of viral diarrhea vary. At one end of the clinical spectrum, the patient may experience mild watery diarrhea with minimal symptoms as described in Case 8.2; at the other extreme, the patient may develop severe nausea, vomiting, abdominal cramps, headache, myalgias, and fevers to 39°C. Stool smear reveals no leukocytes, and cultures are negative for bacterial pathogens.

Identification of the specific viral agent is usually not possible. The infecting agents are most readily identified by their appearance on electron microscopy. The PCR technique shows promise for identifying Norovirus in stool and in the environment. Commercial ELISA assays for Rotavirus are available and provide satisfactory results. These diseases are self-limiting and last 2 to 6 days depending on the agent. Maintaining hydration is the primary goal of therapy.

**CHRONIC DIARRHEA**

As compared with acute diarrhea, which lasts less than 14 days, chronic diarrhea is defined as diarrhea lasting more than 30 days. Persistent diarrhea defines a diarrheal illness that lasts for more than 14 days.

**Parasitic Diarrhea**

Amoebiasis can mimic bacterial enterocolitis; other parasites, such as *Giardia lamblia*, *Cryptosporidium*, *Isospora belli*, and *Microsporidium* often present with complaints that mimic viral gastroenteritis. However, in most instances, these parasitic infections are not self-limiting; they persist for prolonged periods.

**AMOEBIASIS**

**Life Cycle and Epidemiology**

Amoebiasis is caused by *Entamoeba histolytica*. Other amoebic species found in the feces of humans, including *Entamoeba coli*, *Entamoeba dispar*, *Entamoeba moshkovskii*, *Entamoeba hartmanni*, *Entamoeba polecki*, *Endolimax nana*, and *Iodamoeba buetschlii* do not cause disease in humans. *Entamoeba histolytica* trophozoites are large (10 to 60 μm in diameter) and contain lucent cytoplasm, a single nucleus, and multiple intracellular granules (Figure 8.2). They crawl by chemotaxis, using an actin-based mechanism that is similar to that used by human macrophages and neutrophils.

Trophozoites attach to specific galactose receptors on host cells, and after contact, rapidly kill the host cells by a calcium-dependent mechanism. The amoeba also releases numerous proteolytic enzymes that break down the cell matrix of the anchoring host. Flask-shaped mucosal ulcers may be found in the colon at sites of trophozoite invasion. Ulcers can extend into the submucosa and result in invasion of the bloodstream.
Amoebae can also travel up the portal vein and form abscesses in the liver. Because *Entamoeba histolytica* can lyse host neutrophils, acute inflammatory cells are rarely seen in regions of active infection. Immunity against amoebae is mediated primarily by generation of immunoglobulin A antibodies and by cell-mediated immune response. Patients with depressed cell-mediated immunity are at greater risk for disseminated disease.

In addition to its trophozoite form, *Entamoeba histolytica* forms dormant cysts under unfavorable environmental conditions. The cyst has a distinctive morphology, consisting of a rounded structure with three or four distinct nuclei (Figure 8.2). These hardy cysts can remain viable for months outside the host in moist, warm environments. Trophozoites are very sensitive to the acid pH of the stomach; however, cysts readily survive the gastric environment, and ingestion of single cyst can cause active infection. Cysts can be spread from person to person by the fecal–oral route and by contaminated food and water. In developing countries, a large proportion of the population becomes infected with *Entamoeba histolytica*, and the infected individuals usually carry the parasite in their stool for 12 months. In the United States, institutionalized patients, particularly the mentally challenged, have a high incidence of stool carriage and disease. An increased incidence has also been observed in sexually promiscuous homosexual males. The risk of amoebiasis is increased by travel to a developing country and is particularly high in individuals who reside in the endemic area for more than 1 month.

### Clinical Manifestations

Symptoms depend on the degree of bowel invasion. Superficial bowel infection is associated with watery diarrhea and nonspecific gastrointestinal complaints. Invasive intestinal disease presents with the gradual onset, over 1 to 3 weeks, of abdominal pain and bloody diarrhea associated with tenesmus and abdominal tenderness. Fever is noted in some patients. Amoebiasis can be mistaken for ulcerative colitis, and administration of corticosteroids can dramatically worsen the disease and lead to toxic megacolon. Amoebic liver abscess can develop in conjunction with colitis. Patients complain of right upper quadrant pain and can also experience pain referred to the right shoulder. Hepatomegaly is noted in half of all cases.

### Diagnosis and Treatment

Stool smears usually demonstrate PMNs. However, because the amoebic trophozoites destroy human PMNs, the numbers are often lower than are seen in patients with shigellosis. In amoebiasis, stools are always heme-positive, reflecting trophozoite invasion and destruction of bowel mucosa. In acute hepatic disease, alkaline phosphatase may not be elevated, but it rises in chronic hepatic infection.

Previously, the diagnosis was made by identifying trophozoites or cysts in the stool. However, two non-
KEY POINTS

About the Clinical Manifestations, Diagnosis, and Treatment of Amoebiasis

1. Clinical presentation depends on the degree of invasion:
   a) Watery diarrhea is associated with superficial infection.
   b) Bloody diarrhea, tenesmus, abdominal pain, and tenderness with more invasive disease.
   c) Can be misdiagnosed as ulcerative colitis; corticosteroids can lead to toxic megacolon.
   d) Right upper quadrant, right shoulder pain, hepatomegaly seen with liver abscess.

2. Diagnosis:
   a) Stool smears show fewer polymorphonuclear leukocytes (PMNs) than are seen with shigellosis (trophozoites destroy PMNs).
   b) Stools are always heme-positive.
   c) Alkaline phosphatase elevated in chronic, but not acute hepatic abscess.
   d) Stool examination is insensitive; fecal antigen or polymerase chain reaction is recommended.
   e) Serum is anti-amoebic antibody positive in most patients after 1 week of symptoms.
   f) Aspirate from liver abscess shows brownish, sterile liquid without PMNs; parasite not usually seen, and antigen may not be detected.

3. Treatment: Metronidazole for active disease; iodoquinol or paromomycin for carrier state.

KEY POINTS

About the Pathogenesis and Epidemiology of Giardiasis

1. *Giardia* exists as trophozoites and dormant cysts.
2. Trophozoites attach to gastrointestinal endothelial cells, causing malabsorption and inflammation.
3. *Giardia* cysts are spread by contaminated water (and sometimes food) and person-to-person contact.
5. A disease of campers (sterilization of water critical for prevention), daycare centers, and sexually active homosexuals.

Pathogenic species *Entamoeba dispar* and *Entamoeba moshkovskii* cannot be morphologically distinguished from *Entamoeba histolytica*. Fecal *Entamoeba histolytica* antigen tests have proven to be more sensitive and specific than stool smears, and they are now the diagnostic test of choice. Identification in stool by the PCR method is also sensitive and specific, but is not widely available. These tests should be ordered in conjunction with a serum anti-amoebic antibody. The latter test is positive in most patients who have had symptomatic disease for more than 1 week. However, antibodies persist for life and therefore are not helpful in detecting reinfection.

Abdominal CT scan should be performed in patients with symptoms consistent with hepatic disease. This test readily identifies abscesses. Serum anti-amoebic antibodies are elevated in 99% of patients with hepatic amoebic abscess. Aspiration of the abscess yields sterile, odorless, brownish liquid without PMNs. Amoebae are not generally seen, and are only rarely cultured because the parasite concentrates in the walls of the abscess. Antigen is detected in hepatic fluid in only 40% of cases.

Invasive enterocolitis and hepatic abscess should be treated with oral metronidazole (750 mg every 8 hours for 10 days) or tinidazole [2 g daily, divided into three doses, for 3 to 5 days (not available in the United States.)]. For asymptomatic cyst excretors, oral iodoquinol (650 mg every 8 hours for 20 days) or paromomycin (25 to 35 mg/kg daily, divided into three doses, for 7 days) is recommended. Diloxanide furoate (500 mg orally every 8 hours for 10 days) can be used as an alternative therapy.

**Giardia lamblia**

**Life Cycle and Epidemiology**

Like amoebae, *Giardia lamblia*, an enteric flagellated protozoan, has two stages: the free-living trophozoite, and the dormant cyst. The trophozoite consists of a dorsal convex surface and a flat disk-shaped ventral surface composed of microtubules and micro-ribbons, two nuclei, and four pairs of flagella. On stained preparations, it has the appearance of a bearded human face (Figure 8.2). Trophozoites adhere to gastrointestinal endothelial cells, disrupt the brush border, cause disaccharidase deficiency, and induce inflammation. All of these mechanisms are thought to account for watery diarrhea and malabsorption. Cell-mediated and
humoral immunity both play a role in host defense. Patients with X-linked agammaglobulinemia have an increased risk of contracting severe prolonged disease, emphasizing the contribution of humoral immunity. Under unfavorable environmental conditions Giardia can form dormant cysts that are excreted in the stool, and account for spread of disease.

Giardiasis is found throughout the world; it is a common infection in the United States. Giardia cysts are most commonly spread by contaminated water, and multiple waterborne outbreaks have occurred in mountainous regions of the Northeast, Northwest, and Rocky Mountain States, and in British Columbia. Campers must aggressively sterilize drinking water from mountain streams to prevent this common infection. Foodborne outbreaks are increasingly being recognized. Giardia can also be transmitted from person to person in daycare centers and other confining institutions. This pathogen also has been spread from person to person by sexually active homosexuals.

**Clinical Manifestations, Diagnosis, and Treatment**

A patient with this parasite usually has only mild symptoms or is asymptomatic. Adults may complain of abdominal cramps, bloating, diarrhea, anorexia, nausea, and malaise. Belching is also a common complaint. Children most often develop watery diarrhea. Symptoms usually resolve spontaneously in 4 to 6 weeks. Chronic disease is less common and results in malabsorption, chronic diarrhea, and weight loss.

A diagnosis of giardiasis should be considered in all patients with prolonged diarrhea. Stool smears reveal no PMNs. Examination for cysts using concentration techniques have a 90% yield after three stool samples. Today, ELISA or immunofluorescence antigen tests with high sensitivity (up to 98%) and specificity (90% to 100%) are available, and they are now the test of choice. Endoscopy and duodenal biopsy, or duodenal aspiration, are no longer necessary in most cases. Oral metronidazole (250 mg every 8 hours for 5 to 7 days) is the treatment of choice.

**CHRONIC DIARRHEAL ILLNESSES PRIMARILY ASSOCIATED WITH IMMUNOCOMPROMISED HOSTS**

The *Cryptosporidium* intestinal protozoan survives and replicates within the intestinal microvilli, eventually generating oocysts that are excreted in the stool and are responsible for the spread of infection (Figure 8.2). Autoinfection can also occur, explaining how ingestion of small numbers of oocysts can cause severe, persistent infection in the immunocompromised host. Loss of cell-mediated immunity increases the risk of infection and explains the higher incidence of *Cryptosporidium* intestinal disease in AIDS patients.

*Cryptosporidium* is classified as an intestinal coccidian; it is related to malarial organisms. The mechanisms by which *Cryptosporidium* causes diarrhea are not completely understood. The pathogen affects intestinal ion transport and causes inflammatory damage to the intestinal microvilli, resulting in malabsorption. This parasite is carried in the intestinal tract of many animals and is also found in water. The oocyst is resistant to chlorination, and large outbreaks resulting from contaminated drinking water supplies have been reported. Infection can also be transmitted in contaminated swimming pools, and an outbreak in a water park has been described. Ingestion of 130 oocysts causes diarrheal disease in 50% of volunteers. Person-to-person spread has also been reported and can occur in households or in institutional settings such as daycare centers and hospitals. Animal-to-person spread can take place after exposure to infected farm animals.

The intestinal coccidian *Isospora belli* is found more frequently in tropical environments, but has been identified as a cause of watery diarrhea in AIDS patients in the United States. A characteristic oocyst is excreted in the stool (Figure 8.2).
The obligate intracellular parasite known as *Microsporidium* is very small in comparison with the other parasites that cause diarrhea (Figure 8.2). It was known to be a common pathogen in insects and fish; however, in 1985, intestinal microsporidiosis was first described in an patient with AIDS. This parasite causes significant diarrhea only in immunocompromised hosts. It infects mucosal epithelial cells, causing villous atrophy, and may ascend into the biliary tract to cause cholangitis. The diagnosis is made by demonstrating the organisms in stool or after intestinal biopsy. Giemsa, Ziehl–Nielsen, or Gram stain may be used to identify the organism.

**Clinical Manifestations, Diagnosis, and Treatment**

*Cryptosporidium*, *Isospora belli*, and *Microsporidium* all present with chronic watery diarrhea, often associated with abdominal cramps. Most cases occur in immunocompromised hosts, most frequently patients with AIDS. Children and immunocompetent adults can develop symptomatic cryptosporidiosis, and acute disease may be followed by chronic intestinal symptoms associated with fatigue, headaches, eye, and joint pains. Minimal findings are noted on physical examination. Patients may appear malnourished and be dehydrated.

Diagnosis can be made by stool smear. Stool samples should be stained not only with iodine, but also with modified Kinyoun's acid-fast stain, and concentrated. *Cryptosporidium* cysts are acid-fast; however, fecal smears have proved less specific and sensitive than fecal antigen tests that are now commercially available. *Isospora belli* sporocysts are transparent and can easily be overlooked. In addition to being acid-fast, they demonstrate blue autofluorescence when observed under a fluorescence microscope with a 330 to 380 nm ultraviolet filter. A modified trichrome stain is recommended for the diagnosis of *Microsporidium*, which stains the cysts reddish-pink. A number of fluorescence stains that are sensitive and specific for *Microsporidium* are commercially available (for example, Calcofluor white stain from Sigma–Aldrich).

Children and immunocompetent adults with persistent *Cryptosporidium* should be treated with oral nitazoxanide for 3 days (adults: 500 mg twice daily; children 1 to 3 years: 100 mg twice daily; children 4 to 11 years: 200 mg twice daily). For treatment of patients with HIV, HAART (highly active antiretroviral therapy) should be combined with 14 days of nitazoxanide treatment. This agent is not effective when the patient’s CD4 count falls below 50 cells/µL.

*Isospora belli* can be effectively treated with trimethoprim–sulfamethoxazole (1 double-strength tablet every 6 hours for 10 day, then twice daily for 3 weeks). In sulfa-allergic patients, pyrimethamine (75 mg/kg daily for 3 to 4 weeks), combined with folic acid (10 to 25 mg daily) has proved to be a successful alternative. Treatment of *Microsporidium* with oral albendazole (400 mg twice daily for 3 weeks) leads to clinical improvement; however, most patients relapse when the medication is discontinued. Fumagillin (20 mg every 8 hours for 2 weeks), an antibiotic derived from *Aspergillus fumigatus*, results in clearance of spores, but relapse occurs in a few patients. Fumagillin is toxic to bone marrow and may result in reversible neutropenia or thrombocytopenia, or both.

**INTRA-ABDOMINAL INFECTIONS**

The overall incidence of intra-abdominal infections is difficult to ascertain, but certainly this group of diseases
accounts for a significant number of admissions through the emergency room. Intra-abdominal infections often fall at the interface of internal medicine and surgery. In many cases, the infectious disease specialist, gastroenterologist, radiologist, and general surgeon need to coordinate their care to assure the most favorable outcome.

**PRIMARY OR SPONTANEOUS PERITONITIS**

**POTENTIAL SEVERITY**

A frequently fatal infection that requires immediate paracentesis and empiric antibiotic therapy.

**Microbiology and Pathogenesis**

In adults, spontaneous (primary) peritonitis develops in patients with severe cirrhosis and ascites. Ascites caused by congestive heart failure, malignancy, and lymphedema can also be complicated by this infection. Bacteria may enter the peritoneal space by hematogenous spread, lymphatic spread, or migration through the bowel wall. In patients with severe cirrhosis, the reticuloendothelial system of the liver is often bypassed secondary to shunting, increasing the risk of prolonged bacteremia. Bowel motility is also slowed in these patients, resulting in bacterial overgrowth. The most common pathogens are enteric bowel flora, *E. coli* being most common, followed by *K. pneumoniae*. *Streptococcus pneumoniae* and other streptococci, including enterococci, may also be cultured. *S. aureus* and anaerobes are infrequently encountered.

**Clinical Manifestations**

The initial symptoms and signs may be subtle, and physicians need to maintain a low threshold for diagnostic and therapeutic intervention. Fever is the most common manifestation, and initially, it is often low grade (38°C range). Abdominal pain is usually diffuse and constant, and differs from the usual sensation of tightness experienced with tense ascites. A third common manifestation is a deterioration of mental status. Infection is well known to exacerbate hepatic encephalopathy. Diarrhea may precede other symptoms and signs, and is usually precipitated by overgrowth of the bowel flora. Abdominal tenderness is diffuse and not associated with guarding, because the ascites separates the visceral and parietal peritoneum, preventing severe inflammatory irritation of the abdominal wall muscles. In the late stages of infection, rebound tenderness may be elicited. If hypotension and hypothermia develop before antibiotics are initiated, the prognosis is grave.

**Diagnosis**

The diagnosis of spontaneous peritonitis is made by sampling the ascitic fluid. Needle aspiration of peritoneal fluid is a simple and safe procedure. Significant bleeding requiring transfusion occurs in less than 1% of patients, despite abnormally elevated prothrombin times in a high percentage of cases. Paracentesis is a minimally traumatic procedure and does not require prophylactic plasma transfusions.

Proper handling of the samples is critical for making an accurate diagnosis. A minimum of 10 mL of ascitic fluid should be inoculated into a blood culture flask. Care must be taken to exchange the needle used to penetrate the skin for a new sterile needle that is used to puncture the blood culture flask. A second sample should be inoculated into a tube containing anticoagulant for cell counts. If this precaution is not taken, the ascites fluid may clot, preventing accurate cytologic analysis. A third tube should be sent to

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**KEY POINTS**

**About the Microbiology, Pathogenesis, and Clinical Presentation of Primary Peritonitis**

1. Most commonly associated with end-stage liver disease and portal hypertension.
2. Organisms infect the ascitic fluid by hematogenous spread, lymphatic spread, and bowel leakage.
3. Infecting organisms:
   - a) Enteric gram-negative pathogens are most common (*Escherichia coli* and *Klebsiella pneumoniae*).
   - b) *Streptococcus pneumoniae* and enterococci are also possibilities.
   - c) Anaerobes and *Staphylococcus aureus* are uncommon.
4. Clinical presentation may be subtle:
   - a) Low-grade fever (38°C)
   - b)Constant, diffuse abdominal pain without guarding
   - c) Worsening mental status
measure total protein, albumin, lactic dehydrogenase (LDH), glucose, and amylase levels. A separate syringe or tube should also be sent for Gram stain.

The leukocyte count in the ascitic fluid of patients with spontaneous peritonitis almost always exceeds 300 cells/mm³ with predominance of PMNs. The diagnosis is strongly suggested by an absolute PMN count exceeding 250/mm³. Urinalysis leukocyte esterase strips can be used to rapidly assess acute inflammation, a reading of 2+ or higher indicating probable infection. Gram stain is positive in 20% to 40% of cases. Other ascites fluid values help to differentiate primary from secondary peritonitis. High total protein, LDH, and amylase, accompanied by low glucose in the ascitic fluid are more commonly found in secondary peritonitis and should raise the possibility of bowel perforation.

**Treatment and Outcome**

Empiric therapy should be initiated emergently. Delays in therapy can result in sepsis, hypotension, lactic acidosis, and death. In the patient with cirrhosis and ascites who has fever, abdominal pain, or tenderness, changes in mental status, or more than 250 PMNs/mm³ in their ascitic fluid, antibiotics should be initiated as soon as blood, urine, and ascites fluid cultures have been obtained. A third-generation cephalosporin (cefotaxime or ceftriaxone) covers most of the potential pathogens. If secondary peritonitis is suspected, anaerobic coverage with metronidazole should be added. Treatment should be continued for 5 to 10 days, depending on the response to therapy.

Mortality remains high in this disease (60% to 70%), reflecting the severe underlying liver disease in these patients and the serious nature of the infection. Early diagnosis may reduce mortality to the 40% range. Death is often the result of end-stage cirrhosis, spontaneous peritonitis being a manifestation of this terminal disease. Patients who have had a first bout of spontaneous peritonitis should strongly be considered for liver transplant.

Intermittent prophylaxis may be considered in patients at risk for recurrent spontaneous peritonitis. Prophylactic regimens have included trimethoprim–sulfamethoxazole (1 double-strength tablet orally for 5 of 7 days) or oral ciprofloxacin (750 mg once weekly).
KEY POINTS

About the Microbiology and Pathogenesis of Secondary Peritonitis

1. Bacteriology depends on the site of perforation.
   a) Gastric perforation: Mouth flora, including *Candida* and anaerobes are common.
   b) Lower bowel contains $10^{11}$ bacteria/mL, and perforation causes massive soilage: Anaerobes are a major component, *Bacteroides fragilis* being common; among aerobic gram-negative bacteria, *Escherichia coli* predominates; *Klebsiella*, *Proteus*, and *Enterobacter* species are also common; gram-positive *Streptococcus viridans*, enterococci, and *Clostridia perfringens* are also seen.

2. Peritoneum exudes 300 mL to 500 mL of proteinaceous material hourly, with masses of polymorphonuclear lymphocytes; cleared by the lymphatics, but then reach the bloodstream. Fibrinous material can wall off abscesses.

3. Metabolic acidosis, hypoxia, multi-organ failure, and death may follow.

KEY POINTS

About the Clinical Presentation of Secondary Peritonitis

1. Abdominal pain is usually sharp and begins at the site of spillage.
2. Any movement or deep breathing worsens the pain.
3. Peritoneal inflammation causes abdominal spasm (guarding) and rebound.
4. Rectal tenderness may be found.
5. Elderly patients often lack the typical findings of peritonitis.

Species. Aerobic gram-negative bacteria are abundant, *E. coli* predominating. *Klebsiella*, *Proteus*, and *Enterobacter* species are also common. Gram-positive bacteria also are found in the bowel flora, with *S. viridans*, enterococci, and *C. perfringens* predominating.

The peritoneal response to infection is usually rapid and exuberant. Large quantities of proteinaceous exudate are released into the peritoneum, and a massive influx of PMNs and macrophages occurs. The influx of fluid can result in intravascular fluid losses of 300 mL to 500 mL hourly. Mechanically, the diaphragmatic lymphatic system can clear large numbers of bacteria quickly, but once in the lymphatic system, the bacteria usually invade the bloodstream. Phagocytic cells ingest large numbers of bacteria and kill them. Deposition of fibrinous exudate can wall off the infection to form discrete abscesses. When the peritoneal host defense is overwhelmed, the patient develops metabolic acidosis, tissue hypoxia, irreversible shock, and multi-organ failure. Death follows.

Clinical Manifestations

The anterior peritoneum is richly enervated, and the first manifestation of inflammation is abdominal pain that is usually sharp, localized to the initial site of spillage, and aggravated by motion. Pain is almost always accompanied by loss of appetite and nausea. Fever, chills, constipation, and abdominal distension are common. Patients usually lie still in bed, breathing with shallow respirations. Fever, tachycardia, and hypotension develop in the later stages.

On abdominal exam, the bowel sounds are decreased or absent, and the abdomen is tender to palpation. Guarding and involuntary spasm of the abdominal muscles can result in a board-like abdomen. If slow compression of the abdomen followed by rapid release of pressure causes severe pain, the patient has rebound tenderness, indicating peritoneal irritation. On rectal exam, tenderness may be elicited. Elderly patients often fail to present with the classic findings of peritonitis. They often have only mild to moderate tenderness, and do not exhibit guarding or rebound. A high index of suspicion must be maintained when an elderly patient presents with abdominal pain. These patients are at increased risk for diverticulitis, perforated colonic carcinoma, and bowel ischemia.

Diagnosis and Treatment

Serial abdominal examinations, careful monitoring of vital signs, and peripheral WBC count are helpful in deciding whether an exploratory laparotomy is necessary. A high peripheral WBC count in the range 17,000 to 25,000 WBCs per cubic millimeter with an increased percentage of PMNs and band forms is usually noted. A normal peripheral leukocyte count without a predominance of PMNs should call into question the diagnosis of secondary peritonitis. Supine and upright abdominal X-rays should be performed to exclude free air under the diaphragm (indicative of bowel or gastric perforation), to assess the bowel gas pattern, and to search for areas of
thickened edematous bowel wall. A chest X-ray must always be performed to exclude lower lobe pneumonia, which can cause ileus and upper quadrant tenderness mimicking peritonitis. A CT scan of the abdomen and pelvis following oral and intravenous contrast is now considered the initial diagnostic test of choice for patients with suspected intra-abdominal infection. This diagnostic procedure often obviates the need for exploratory laparotomy and can assist in the accurate diagnosis of appendicitis, localization and needle aspiration of abscesses, and identification of areas of bowel obstruction.

Antibiotic treatment should be initiated emergently in patients suspected of secondary peritonitis. Broad-spectrum antibiotic coverage is necessary to cover the multiple organisms infecting the peritoneum. A number of regimens have been recommended. Single agents are available that are effective for community-acquired infections of mild to moderate severity; these include high doses of cefoxitin, cefotetan, and ticarcillin–clavulanate. Imipenem–cilastatin or meropenem can be used as a single agent in severe peritonitis or in hospital-acquired or resistant infections. Combination therapy is often used in severe cases:

1. Cefoxitin or cefotetan plus gentamicin
2. Metronidazole and a third-generation cephalosporin (ceftriaxone, cefotaxime, cefixime)
3. Metronidazole plus a fluoroquinolone (ciprofloxacin, levofloxacin, gatifloxacin)
4. Clindamycin plus aztreonam

When secondary peritonitis is being considered, a general surgeon should be consulted emergently. Repeated abdominal exam allows the surgeon to follow the progression of findings and if tenderness becomes more diffuse and guarding and rebound increase, exploratory laparotomy is often required for diagnosis, drainage, and bowel repair. Peritoneal irrigation is performed intraoperatively, and drains are placed at sites where purulent collections are noted. Multiple operations are often required for the surgical treatment of patients with diffuse purulent peritonitis. Antibiotic coverage should be adjusted based on the cultures and sensitivities of the intraoperative cultures.

SECONDARY PERITONITIS ASSOCIATED WITH PERITONEAL DIALYSIS

Bacterial peritonitis is a frequent complication of chronic ambulatory peritoneal dialysis and is the most frequent reason for discontinuation of that therapy. *S. aureus*, including methicillin-resistant strains (MRSA), or a single gram-negative bacteria are most commonly associated with this infection. The incidence of *S. epidermidis* infection has decreased over the past decade. *Pseudomonas aeruginosa* grows readily in water and is the causative agent in up to 5% of cases. Fungal peritonitis has become increasingly common. Atypical mycobacteria and, less commonly, *Mycobacterium tuberculosis* have also caused peritonitis in this setting.

As observed in spontaneous peritonitis, fever and diffuse abdominal pain are the most common complaints. The peritoneal dialysis fluid usually becomes cloudy as a consequence of inflammatory cells. Peritoneal fluid WBC counts usually exceed 100 /mm³, with a predominance of PMNs. A predominance of lymphocytes should raise the possibility of fungal or tuberculous infection. Cultures of the peritoneal fluid (two cultures,
**KEY POINTS**

**About Secondary Peritonitis Associated with Peritoneal Dialysis**

1. Clinical presentation is similar to primary peritonitis, accompanied by cloudy dialysate.
2. *Staphylococcus epidermidis* and *S. aureus* most common; *Pseudomonas aeruginosa*, fungi, and atypical mycobacteria are also found. *Mycobacterium tuberculosis* is less common.
3. Diagnosis:
   a. White blood cell count in peritoneal fluid exceeds 100/mm³, with a predominance of polymorphonuclear leukocytes,
   b. Inoculate two blood culture flasks with 10 mL peritoneal fluid each
   c. Blood cultures are seldom positive.
4. Treat with intraperitoneal antibiotics: Empiric therapy is a first-generation cephalexin or vancomycin plus a once-daily aminoglycoside.

10 mL in each blood culture flask) and Gram stain should be obtained. Yield from a Gram stain is low, but properly obtained peritoneal cultures are positive in more than 90% of cases. Blood cultures should be obtained if systemic symptoms are present, but such cultures are rarely positive.

After samples for culture have been obtained, antibiotic should be added to the dialysate. Initial empiric therapy should include a first-generation cephalexin (cefoxitin 500 mg/L loading dose, followed by 125 mg/L in each dialysate bag), or vancomycin if MRSA is suspected (1000 mg loading dose, followed by 25 mg in each bag), and an aminoglycoside (gentamicin or tobramycin 0.6 mg/kg or amikacin 2 mg/kg per exchange, once daily). Once-daily aminoglycoside therapy rather than constant treatment is recommended to reduce the risk of ototoxicity. If the patient fails to improve within 48 hours, removal of the dialysis catheter should be considered.

**HEPATIC ABSCESS**

**POTENTIAL SEVERITY**

*Usually presents subacutely. With appropriate drainage and antibiotics, prognosis is excellent.*

**Pathogenesis and Microbiology**

Spread of pyogenic infection to the liver can occur in multiple ways. Biliary tract infection is most common, followed by portal vein bacteremia associated with intra-abdominal infection, primarily appendicitis, diverticulitis, or inflammatory bowel disease. Direct extension into the liver from a contiguous infection can occur after perforation of the gallbladder or duodenal ulcer, or in association with a perinephric, pancreatic, or subphrenic abscess. Penetrating wounds and postoperative complications may result in liver abscess. Bacteremia from any source can seed the liver via the hepatic artery and result in the formation of multiple abscesses. In approximately one quarter of cases, a cause cannot be determined.

The bacteriology of this infection reflects the primary site of infection. As in secondary peritonitis, this infection is usually polymicrobial. Anaerobes are commonly cultured, including *Bacteroides* species. *Fusobacterium*, *Peptostreptococcus*, and *Actinomyces* species, and microaerophilic streptococci (*S. milleri* being most common) are frequently found. Enteric gram-negative rods are also important pathogens, *K. pneumoniae* (particularly the K1 serotype) being most common. *Candida* can also invade the liver, candidal abscesses usually occurring in leukemia patients following chemotherapy-induced neutropenia. Amoebic liver abscess is rare, but complicates 3% to 9% of patients with amoebic colitis.

**KEY POINTS**

**About the Pathogenesis and Microbiology of Liver Abscess**

1. Bacteria seed the liver by multiple routes:
   a) Biliary tract (most common)
   b) Portal system in association with intra-abdominal infection
   c) Direct extension from intra-abdominal infection
   d) Penetrating wounds and postoperative complications
   e) Hematogenous spread
2. Bacteriology is usually similar to secondary peritonitis:
   a) *Klebsiella* (increasing in frequency), microaerophilic streptococci (mainly *S. milleri*)
   b) *Candida* in leukemia patients following neutropenia
Clinical Manifestations

Fever with or without chills is the most common presenting complaint. It may also be the only complaint, hepatic abscess being one of the more common infectious causes of fever of undetermined origin (See Case 3.1). Abdominal pain develops in about half of these patients, often confined to the right upper quadrant. Pain is usually dull and constant. Weight loss (more than 10 pounds in less than 3 months) is another frequent complaint. Physical exam often reveals tenderness over the liver. Jaundice is rare. In patients with abscess in the upper regions of the right hepatic lobe, pulmonary exam may reveal decreased breath sounds on that side because of atelectasis or pleural effusion.

Diagnosis, Treatment, and Outcome

With the exception of amoebic liver abscess, the peripheral WBC count is usually elevated (above 20,000/mm³), with increased numbers of immature neutrophils. Serum alkaline phosphatase is also elevated in most cases. Blood cultures are positive in up to half of patients. Abdominal CT scan is the most sensitive test for identifying liver abscesses; it demonstrates a discrete area of attenuation at the abscess site. Ultrasound is somewhat less sensitive, but also useful. Abscesses are found most commonly in the right lobe of the liver. If a single large abscess is noted, amoeba serology should be ordered. That test is positive in more than 90% of patients with amoebic hepatic abscess. Ultrasound and CT can both be used to guide needle aspiration for culture and drainage. A finding of brownish fluid without a foul odor suggests the possibility of amoebic abscess.

Initial empiric antibiotic therapy should be identical to that for secondary peritonitis. The antibiotic regimen can subsequently be tailored to the abscess culture results. Percutaneous drainage in combination with antibiotics is now the treatment of choice. Open surgical drainage should be considered in patients who continue to have fever after 2 weeks of antibiotic treatment and percutaneous drainage. Open surgery may also be required in patients with biliary obstruction, multiloculated abscesses (other than Echinococcus—see Chapter 12), and highly viscous abscesses. Mortality was high in early series (approaching 100%) when abscesses were not drained; however, with modern antibiotics and drainage techniques, nearly 100% of patients are now cured.

PANCREATIC ABSCESS

1. Necrotic tissue can become infected by contaminated bile or hematogenous spread.
2. Abscesses are polymicrobial
3. Use computed tomography scan and ultrasound to guide drainage.
4. Open surgical drainage and debridement of necrotic tissue is usually required.
5. The same broad-spectrum coverage used for secondary peritonitis is recommended.
6. Fatal outcome is more likely in elderly patients.
infected by reflux of contaminated bile or by hematogenous spread. Like other intra-abdominal abscesses, pancreatic abscesses are usually polymicrobial. Ultrasound and CT scan are employed for culture and drainage. Because of the significant quantity of necrotic tissue, open drainage and debridement are usually required in combination with broad-spectrum antibiotics. The same antibiotic regimens recommended for secondary peritonitis offer excellent empiric coverage pending cultures and sensitivities. Survival is improved by early surgical drainage. A fatal outcome is more likely in elderly patients, who more often have accompanying biliary tract disease.

CHOLECYSTITIS AND CHOLANGITIS

**POTENTIAL SEVERITY**

An acute, potentially life-threatening infection that can be complicated by sepsis. Rapid treatment reduces morbidity and mortality.

**Pathogenesis and Microbiology**

Biliary obstruction is most frequently caused by gallstones and results in increased pressure in and distension of the gallbladder. These changes compromise blood flow and interfere with lymphatic drainage, leading to tissue necrosis and inflammation, which lead to cholecystitis. Although infection is not the primary cause of acute cholecystitis, obstruction prevents flushing of bacteria from the gallbladder and is associated with infection in more than half of all cases. If treatment is delayed, infection can spread from the gallbladder to the hepatic biliary ducts and common bile duct, causing cholangitis.

The organisms associated with cholecystitis and cholangitis reflect the bowel flora and are similar to the organisms encountered in secondary peritonitis. *E. coli*, *Klebsiella* species, enterococci, and anaerobes are most frequently cultured from biliary drainage.

**Clinical Manifestations**

The acute onset of right upper quadrant pain, high fever, and chills are most common. Jaundice may also be noted, fulfilling Charcot’s triad (fever, right upper quadrant pain, and jaundice). On physical exam, marked tenderness over the liver is commonly elicited. Hypotension may be present, indicating early gram-negative sepsis. Elderly patients may not complain of pain, presenting solely with hypotension. Marked peripheral leukocytosis with increased numbers of PMNs and band forms is the rule.

**Liver function tests** are usually consistent with obstruction, demonstrating an elevated serum alkaline phosphatase, gamma-glutamyl transpeptidase, and bilirubin. On rare occasions, serum aminotransferase enzymes, reflecting hepatocellular damage, may also be elevated (up to 1000 IU) as a result of microabscess formation in the liver. Blood cultures are frequently positive.

**Diagnosis and Treatment**

Ultrasoundography is the preferred diagnostic study, and it can usually detect gallstones, dilatation of the gallbladder, and dilatation of the biliary ducts, including the common bile duct. Other adjunctive tests may include CT scan or magnetic resonance imaging; however, these tests are
generally not recommended for initial screening. Endoscopic retrograde cholangiopancreatography (ERCP) is helpful for confirming the diagnosis, dilating the sphincter of Oddi, removing stones, and placing stents to maintain biliary flow in constricted, fibrotic biliary channels. This procedure should be performed under antibiotic coverage and should be avoided in cases of cholangitis because of the risk of precipitating high-level bacteremia.

Broad-spectrum antibiotics should be initiated immediately. Regimens similar to those for secondary peritonitis may be used. Many experts prefer ampicillin and gentamicin because this regimen covers enterococci in addition to the enteric gram-negative pathogens. Imipenem also covers enterococci, plus the enteric gram-negative rods and anaerobes. Despite its poor activity against enterococci, levofloxacin has also proved effective. Metronidazole may be added to the levofloxacin to improve anaerobic coverage.

Prompt surgical intervention is required for patients with a gangrenous gallbladder and gallbladder perforation. In cases of acute cholecystitis, decompression of the gallbladder and stone removal is now most commonly accomplished by ERCP. Percutaneous drainage is another option for decompression. Urgent decompression should be performed in patients with persistent abdominal pain, hypotension, fever above 39°C, and mental confusion. Outcome is usually favorable for mild-to-moderate disease, but mortality approaches 50% in those with severe cholangitis.

**Clinical Manifestations, Diagnosis, and Treatment**

Patients with *H. pylori* peptic ulcer disease usually have the classic symptom of dyspepsia: burning pain several hours after meals that is relieved by food and antacids. Belching, indigestion, and heartburn are also frequent.

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**KEY POINTS**

About *Helicobacter pylori*–Associated Peptic Ulcer Disease

1. This small, curved, microaerophilic gram-negative rod
   a) survives on the mucosal surface of the stomach, and
   b) synthesizes high concentrations of urease, which produces ammonium ions to neutralize acid.
2. Dyspepsia, belching, and heartburn are the most common symptoms.
3. Diagnosis:
   a) Test only symptomatic patients.
   b) Endoscopic biopsy with CLOtest for urease is preferred.
   c) Culture only for refractory cases.
   d) Urease breath test is expensive, but accurate.
   e) Enzyme-linked immunoabsorbent antibody test produces false positives in patients over 50 years of age; titer decreases with treatment.
4. Treatment:
   a) Proton pump inhibitor, plus amoxicillin, plus clarithromycin (for the penicillin-allergic, replace amoxicillin with metronidazole)
   b) Proton pump inhibitor, plus bismuth, plus amoxicillin, plus clarithromycin (or metronidazole or tetracycline)
   c) For relapse, use a proton pump inhibitor, plus levofloxacin, plus amoxicillin
complaints. Other than mild mid-epigastric tenderness, the physical examination is usually normal.

Testing for *H. pylori* is recommended only in symptomatic patients. Noninvasive tests include the urease breath test, in which the patient ingests \(^{13}\text{C}\)- or \(^{14}\text{C}\)-labeled urea, and their breath is analyzed for \(^{13}\text{C}\) or \(^{14}\text{C}\) over the next hour. This test requires expensive equipment, but it is specific and sensitive. Measurement of IgG antibody levels by ELISA assay is now commercially available, and this test is inexpensive and sensitive. False negatives may occur in elderly individuals. A stool antigen test is also available, and in the absence of proton pump inhibitor (PPI) administration or gastrointestinal bleeding, it is also sensitive and specific. All three tests may become negative with treatment and can be used to monitor response to therapy. The urea breath test remains the most cost-effective diagnostic method.

Diagnosis is most commonly made by endoscopic biopsy. A biopsy specimen should be first tested for urease (CLO test) which has high sensitivity and specificity in patients not taking bismuth, H2 blockers, or PPIs. Biopsy is the most cost-effective diagnostic method. Specimens can also be cultured using selective media and microaerophilic conditions. Culture to obtain antibiotic sensitivities should be performed in patients who have proved refractory to therapy. *H. pylori* can also be visualized using silver, Gram, or Giemsa stain, and by immunofluorescence.

Multiple regimens have been used to treat *H. pylori*, and the ideal regimen has not been determined. Triple therapy with a PPI (lansoprazole 30 mg or omeprazole 20 mg twice daily), oral amoxicillin (1 g twice daily), and oral clarithromycin (500 mg twice daily) for 2 weeks is associated with a 90% cure rate. In the patient who is penicillin-allergic, oral metronidazole (500 mg twice daily) can be substituted for amoxicillin. A PPI can also be combined with bismuth (525 mg every 6 hours) and two other oral antibiotics (amoxicillin, clarithromycin, metronidazole, tetracycline). For patients who relapse, triple therapy with oral levofloxacin (500 mg) combined with amoxicillin and a PPI has been found to be superior to quadruple therapy with bismuth, tetracycline (500 mg every 6 hours), metronidazole, and a PPI.

**Acute viral hepatitis** is a common disease that affects approximately 700,000 people in the United States annually. Three viral agents, hepatitis A, hepatitis B, and hepatitis C virus are primarily responsible for acute hepatitis. Less common causes include hepatitis D (“delta agent”) and hepatitis E. A number of other viral agents affect multiple organs in addition to the liver. Epstein–Barr virus and cytomegalovirus are the most common viruses in this category. Less commonly, herpes simplex viruses, Varicella virus, coxsackievirus B, measles, rubella, rubeola, and adenovirus can infect the liver. Fulminant hepatitis is rare, but serious, occurring in approximately 1% of cases with icteric hepatitis. Fulminant disease is most commonly reported with hepatitis B or D, but it is also reported in pregnant woman with hepatitis E.

**Clinical Manifestations of Acute Hepatitis**

No clinical feature definitively differentiates one form of viral hepatitis from another.

Acute viral hepatitis has four stages of illness:

1. **Incubation period.** This period varies from a few weeks to 6 months, depending on the viral agent (Table 8.3). During this period, the patient has no symptoms.

2. **Preicteric stage.** The symptoms during this stage are nonspecific. The most common initial complaint is malaise, with patients reporting a general sense of not feeling well. Fatigue may also be a prominent complaint, accompanied by generalized weakness. Anorexia, nausea, and vomiting are other common symptoms. Loss of taste for cigarettes is reported among smokers. Dull right upper quadrant pain is also a frequent complaint. Some patients experience a flu-like illness consisting of myalgias, headache, chills, and fever. A few develop a serum-sickness syndrome consisting of fever, rash, and arthritis or arthralgias. These symptoms are the result of immune-complex (virus plus antibody) deposition. Most of the symptoms associated with viral hepatitis dramatically resolve with the onset of jaundice.

3. **Icteric stage.** This stage begins 4 to 10 days after the onset of the preicteric stage. Jaundice and dark urine are the classic symptoms. Scleral icterus may go unnoticed; it is best visualized in natural rather than artificial light. Pale-colored stools can develop as a consequence of reduced excretion of bile pigments. Immune-complex formation at this stage can result in vasculitis (primarily with hepatitis B), and glomerulonephritis can develop in association with hepatitis B or C infection.

4. **Convalescent stage.** The duration of this phase depends on the severity of the attack and the viral etiology.
The most prominent physical finding is icterus that can be detected in the sclera or under the tongue when bilirubin levels reach 2.5 to 3.0 mg/dL. Slight hepatic enlargement with mild-to-moderate tenderness is common. Tenderness can be elicited by placing one hand over the liver and pounding this site gently with the fist of the other hand (termed “punch tenderness”). The skin may exhibit scratch marks as result of severe pruritus. Fulminant hepatitis may be accompanied by hepatic encephalopathy, causing depression in mental status and asterixis (irregular flapping of the out-stretched hands after forcible dorsiflexion).

Laboratory findings are distinctive in viral hepatitis. Aminotransferase levels—aspartate aminotransferase (AST) and alanine aminotransferase (ALT)—often increase to between 1000 and 2000 IU, and the ratio of AST/ALT is usually less than 1. In alcoholic hepatitis, the latter ratio is usually more than 1.5. Alkaline phosphatase, a reflection of biliary obstruction or cholestasis, is only mildly elevated. Similarly, LDH is only mildly elevated. Transaminase values usually peak in the early icteric stage. Direct and indirect bilirubin fractions are usually equally elevated. High levels of direct or conjugated bilirubin suggest cholestasis, and high levels of indirect or unconjugated bilirubin usually indicate red blood cell hemolysis that can develop in patients with viral hepatitis who also have glucose-6-dehydrogenase deficiency or sickle cell anemia. Significant elevation of the prothrombin time is a bad prognostic sign. A prothrombin time above 100 s indicates irreversible hepatic damage, and these patients should be promptly considered for liver transplant.

In fulminant hepatitis, disseminated intravascular coagulation can develop, leading to thrombocytopenia. Liver biopsy is generally not required to diagnose acute viral hepatitis. This test should be performed when several causes of hepatitis are possible or when therapy is being considered. Histopathologic examination classically reveals ballooning and hepatocyte necrosis, disarray of liver lobules, mononuclear cell infiltration, and cholestasis.

Chronic hepatitis can follow acute hepatitis B and C infections. Particularly in patients with hepatitis C, chronic infection can follow asymptomatic acute infection. Most patients experience no symptoms until they progress to liver failure. In most instances of hepatitis C, hepatic failure takes more than 20 years; in hepatitis B virus infection, hepatic failure usually occurs more rapidly. Elevations of transaminase values are often

<table>
<thead>
<tr>
<th>Virus type</th>
<th>Incubation period</th>
<th>Epidemiology</th>
<th>Sequeleae</th>
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</thead>
<tbody>
<tr>
<td>Hepatitis A</td>
<td>4 Weeks</td>
<td>Fecal-oral</td>
<td>Self-limiting disease; can relapse up 6 months post primary attack; fulminant hepatitis rare</td>
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<td></td>
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<td>Foodborne</td>
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<td>Waterborne</td>
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<td></td>
<td>Sexually transmitted</td>
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<tr>
<td>Hepatitis B</td>
<td>12 Weeks</td>
<td>Person to person</td>
<td>Chronic infection common (90% neonates, 20% to 50% children, 5% to 10% adults); hepatocellular carcinoma</td>
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<td></td>
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<td>Blood and blood products</td>
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<td>Other body fluids</td>
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<td>IV drug abuse</td>
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<tr>
<td></td>
<td></td>
<td>Sexually transmitted</td>
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<tr>
<td>Hepatitis C</td>
<td>6–10 Weeks</td>
<td>Person to person</td>
<td>Usually a chronic infection; cirrhosis in 25%; requires liver transplant; hepatocellular carcinoma</td>
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<td></td>
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<td>Blood and blood products</td>
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<td></td>
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<td>IV drug abuse</td>
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<td></td>
<td>Sexually transmitted (rare)</td>
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<td></td>
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<td>Higher risk with HIV infection</td>
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<tr>
<td>Hepatitis D + B</td>
<td>12 Weeks</td>
<td>Person to person</td>
<td>Same as hepatitis B; Hepatic failure more common among IV drug abusers</td>
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<td>Blood and blood products</td>
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<td>Sexually transmitted</td>
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<td></td>
<td></td>
<td>Household contacts</td>
<td></td>
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<tr>
<td>Hepatitis E</td>
<td>4 Weeks</td>
<td>Fecal-oral route</td>
<td>Self-limiting disease; fulminant hepatitis in pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Only in developing countries</td>
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</tbody>
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detected during routine screening. Levels are usually mildly to moderately elevated and do not exceed 7 to 10 times normal values. Mild fatigue may develop, causing the patient to seek medical attention. Other patients may present with symptoms and signs of cirrhosis. Chronic generation of high antibody levels directed against the virus can result in the production of immune complexes that deposit in the glomeruli and the small- to medium-sized blood vessels, causing membranous glomerulonephritis and vasculitis in some patients with chronic disease. Polyarteritis nodosa is frequently associated with persistent hepatitis B infection.

**Hepatitis A**

**Virology, Pathogenesis, and Epidemiology**

Hepatitis A is a small, non-enveloped single-stranded RNA virus. This picornavirus is highly resistant to heating and drying. It is inactivated by chlorine and does not survive well in buffered saline, but in protein solutions such as milk, the virus is able to withstand high temperatures for brief periods. In tissue culture, the virus is not cytopathic, and replication has to be detected by immunofluorescence staining of antibodies. Isolation of the wild-type virus is often unsuccessful, making tissue culture an ineffective diagnostic tool.

The virus enters the host via the gastrointestinal tract, traversing the intestine and infecting the hepatocyte, where it survives and multiplies within the cell cytoplasm. The virus infects primarily hepatocytes, and it is then released into the bloodstream and excreted into the bile, resulting in high levels of virus in the stool. Hepatocyte damage is caused by the host's cell-mediated immune response. Peak titers of virus in the blood and stool occur just before or when liver function tests become abnormal. Virus continues to be excreted in the feces for several weeks.

Hepatitis A causes an estimated 1.4 million cases of acute hepatitis worldwide. This virus is spread by the fecal–oral route and is highly infectious. Spread occurs readily in households. Preschool daycare centers are an important source of infection, because children under the age of 2 years develop asymptomatic disease and excrete high concentrations of the virus in their stool. The virus can then readily spread detected during routine screening. Levels are usually mildly to moderately elevated and do not exceed 7 to 10 times normal values. Mild fatigue may develop, causing the patient to seek medical attention. Other patients may present with symptoms and signs of cirrhosis. Chronic generation of high antibody levels directed against the virus can result in the production of immune complexes that deposit in the glomeruli and the small- to medium-sized blood vessels, causing membranous glomerulonephritis and vasculitis in some patients with chronic disease. Polyarteritis nodosa is frequently associated with persistent hepatitis B infection.

**Hepatitis A**

**Virology, Pathogenesis, and Epidemiology**

Hepatitis A is a small, non-enveloped single-stranded RNA virus. This picornavirus is highly resistant to heating and drying. It is inactivated by chlorine and does not survive well in buffered saline, but in protein solutions such as milk, the virus is able to withstand high temperatures for brief periods. In tissue culture, the virus is not cytopathic, and replication has to be detected by immunofluorescence staining of antibodies. Isolation of the wild-type virus is often unsuccessful, making tissue culture an ineffective diagnostic tool.

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Hepatitis A causes an estimated 1.4 million cases of acute hepatitis worldwide. This virus is spread by the fecal–oral route and is highly infectious. Spread occurs readily in households. Preschool daycare centers are an important source of infection, because children under the age of 2 years develop asymptomatic disease and excrete high concentrations of the virus in their stool. The virus can then readily spread through water, milk, bivalve shellfish, fruits, as well as vegetables.
to nonimmune parents and caretakers. Sexual transmission of the virus occurs in male homosexuals, and intravenous drug abusers readily spread the virus to each other. Spread by blood transfusions is rare, however. Common-source outbreaks occur as consequence of contaminated water, milk, and food. Raw and or undercooked clams, oysters, and mussels are major sources of foodborne disease. These bivalve shellfish filter large volumes of contaminated water, concentrating the virus. Two large foodborne outbreaks were recently described in the United States, one caused by contaminated frozen strawberries and the second by contaminated green onions from Mexico. Infected food handlers have caused several outbreaks, and hand-washing is an important measure for preventing spread of this disease. Breakdowns in sanitary conditions that occur during natural disasters and war increase the risk of hepatitis A. Inactivation of the virus can readily be accomplished by treating potentially contaminated surfaces with a 1:100 dilution of household bleach.

**KEY POINTS**

**About the Clinical Manifestations**

1. Incubation period is 4 weeks.
2. Self-limiting illness has a duration of 2 to 3 months.
3. Relapse can occur up to 6 months after the primary attack.
4. Chronic hepatitis does not develop.
5. Diagnosis:
   a) Antibody titer for immunoglobulin M is detected when symptoms begin; persists for 6 months.
   b) Antibody titer for immunoglobulin G increases later and peaks at 4 months; persists for decades.

**CLINICAL COURSE AND DIAGNOSIS**

After a 4-week incubation period, patients infected with hepatitis A usually experience the acute onset of a flu-like illness. The disease is usually self-limiting, resolving within 2 to 3 months (Figure 8.3). However, 10% of hospitalized patients follow a relapsing course characterized by improvement followed by a second episode of jaundice that usually develops 6 to 12 weeks later, but that can occur up to 6 months after the first symptomatic attack. Prolonged, but benign, cholestasis has also been reported. Patients with hepatitis A do not develop chronic hepatitis. Young children who have a less robust immune response to the virus often have few symptoms and do not develop jaundice. Fulminant hepatitis is a rare complication and occurs more frequently in patients who are coinfection with hepatitis C or hepatitis B.

![Figure 8–3. Clinical course of hepatitis A virus (HAV). IgM, A, G = immunoglobulins M, A, G; ALT = alanine aminotransferase. Vertical axis = relative concentration (Schematic adapted from Hoeprich Infectious Diseases, 1994)](image-url)
The diagnosis is made by measuring serum anti-hepatitis A immunoglobulin M (IgM) antibody titers. Levels are observed at the time of symptomatic disease and usually persist for 6 months. Anti-hepatitis A IgG antibodies progressively increase. Low titers are observed during early symptomatic disease, but they continue to rise, peaking at about 4 months. The heightened IgG titers persist for decades (Figure 8.3).

**TREATMENT AND PREVENTION**

Most people can be managed as outpatients. No therapy is available to alter the course of infection. Strict bed rest is not warranted, and moderate activity as tolerated is now recommended. In patients with fulminant hepatitis, exchange transfusions and glucocorticoids fail to alter the clinical course, and liver transplantation may be required for survival.

Administration of pooled human immunoglobulin has been shown to prevent or reduce the symptoms of hepatitis A. Prophylaxis should be given within 2 weeks of exposure. The duration of protection is dose-dependent, with intramuscular administration of 0.02 mL/kg affording 2 months of protection, and 0.06 mL/kg usually providing protection for 5 months. Administration of immunoglobulin should be considered in U.S. residents who plan to travel in endemic areas outside of the usual tourist routes. Postexposure prophylaxis is recommended after recognition of the index case for household and sexual contacts; daycare center staff and attendees; classroom contacts in school-centered outbreaks; people residing or working in institutions with crowded living conditions such as prisons, military barracks, and facilities housing disabled people; and for hospital personnel who have come in direct contact with feces or body fluids from an infected patient. Prophylaxis is not recommended for casual contacts and is not effective for common-source outbreaks, because the outbreak will not become apparent until after the 2-week window of immunoglobulin efficacy.

A safe and effective formalin-killed vaccine is available and is now being given to children over the age of 2 years in many areas of the country. As a consequence, the incidence of Hepatitis A in these regions has decreased by two thirds. The vaccine should also be considered for individuals at high risk of hepatitis A: homosexual men, intravenous drug abusers, heterosexuals with multiple sexual partners, individuals requiring repeated administration of concentrated coagulation factors, and people with an occupational risk of exposure. The vaccine is also recommended for patients with pre-existing chronic liver disease. The duration of protection has been estimated to be 20 to 30 years.

**Hepatitis E**

This small, single-stranded RNA virus is related to the caliciviruses. Its pathogenesis, epidemiology, and clinical manifestations are similar to those of hepatitis A (Table 8.3). The virus is secreted in the stool and spread by the fecal–oral route. Outbreaks have been associated with contaminated water in India, Nepal, Southeast Asia, Africa, China, and Mexico. Infection occurs in areas where sanitation is poor and fecal contamination of water is likely. Indigenous cases have not been reported in the United States, Canada, or the developed countries of Europe and Asia. In those countries, infection is reported in tourists who have traveled to endemic areas. As observed with hepatitis A, the disease is self-limiting and does not result in chronic hepatitis. The hepatitis E virus can cause fulminant hepatitis in pregnant women in their third trimester, with resulting mortality.

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**KEY POINTS**

**About the Treatment and Prevention of Hepatitis A**

1. No therapy is available.
2. Pooled immunoglobulin is protective if given within 2 weeks of exposure.
3. Immunoglobulin prophylaxis is recommended for
   a) household and sexual contacts,
   b) daycare center staff and attendees,
   c) classroom contacts in school-centered outbreaks,
   d) persons residing or working in institutions with crowded living conditions,
   e) hospital personnel with direct contact with feces or body fluids from an infected patient, and
   f) travelers to endemic areas.
4. Prophylaxis is not recommended for casual contacts or in common-source outbreaks.
5. Vaccine indications are evolving. Vaccine should be given to
   a) children over the age of 2 years,
   b) homosexual men,
   c) intravenous drug abusers,
   d) heterosexuals with multiple sexual partners,
   e) people requiring repeated administration of concentrated coagulation factors,
   f) people with occupational risk of exposure, and
   g) Patients with preexisting chronic liver disease.
rates of 15% to 25%. The diagnosis can be made by PCR of serum and by a rise in IgM antibody against hepatitis E. Injections of immunoglobulin have not been proven to protect against hepatitis E, and no vaccine is currently available.

**Hepatitis B**

**Virology and Pathogenesis**

Hepatitis B is a small, enveloped, spherical, partially double-stranded DNA virus classified as a hepadnavirus. The outer core contains lipid and the hepatitis B surface antigen (HBsAg—Figure 8.4). The host directs viral-neutralizing antibody (anti-HBV) against the HBsAg. The bloodstream of infected patients contains not only fully competent viral particles, but an even higher abundance of defective viral particles that form small spheres and filaments. These latter forms are noninfectious and are composed of HbsAg and host membrane lipid.

The virus has a unique tropism for hepatocytes and a narrow host range that includes humans, chimpanzees, and a few other higher primates. Hepatitis B virus cannot be reliably maintained in tissue-culture cells. It survives in serum for months at 4°C and for years frozen at –20°C, but it is killed within 2 minutes when heated to 98°C and when treated with many detergents. Hepatitis B viral DNA can integrate into host cell DNA, and that integration may account for the increased incidence of hepatocellular carcinoma in patients who are chronic carriers of hepatitis B virus. These inserts may alter the expression of critical regulatory genes and upregulate host oncogenes.

**Epidemiology**

Hepatitis B virus is spread from person to person primarily by blood and blood products. Blood transfusion remains a major mode of transmission in the United States; however, screening of donors has reduced the risk to 1 in 63,000 transfusions. Screening tests fail to exclude a small percentage of donors who have infectious viral particles in their blood despite being negative for HBsAg. Hepatitis B virus is also found in other body fluids, including urine, bile, saliva, semen, breast milk, and vaginal secretions. It is not found in feces, however. Membrane contact with any of these body fluids can result in transmission. The virus can be spread to sexual partners, and it is prevalent in homosexual men and heterosexuals with multiple partners. It can be readily spread from mother to neonate at the time of vaginal delivery—a common mode of transmission in developing countries. Intravenous drug abusers have a high incidence of hepatitis B. Reuse of needles has also led to transmission of the virus during placement of tattoos and ear-piercing. Crowded environments, such as institutions for the mentally handicapped, favor spread. The virus has also been spread to transplant organ recipients when the donated organ originates from

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**KEY POINTS**

**About Hepatitis E**

1. This single-stranded RNA virus is related to the caliciviruses.
2. Incubation period is 1 month.
3. Transmitted by the fecal–oral route.
4. Reported in developing countries with poor sanitation, but not in the United States, except in travelers.
5. The disease is self-limiting.
6. Causes fulminant hepatitis in women in their third trimester of pregnancy.
7. No blood test is available.
8. Pooled immunoglobulins are not helpful for prevention.
a hepatitis B–infected donor. Hepatitis B virus infection is very common; 280,000 primary infections occur annually in the United States, and the virus is estimated to have infected approximately 5% of the world’s population.

CLINICAL COURSE AND DIAGNOSIS

The clinical picture of hepatitis B is similar to that of hepatitis A, with two major differences: the average incubation period (12 weeks) is longer than with hepatitis A, and hepatitis B is not always self-limiting. Symptoms usually resolve over 1 to 3 months, and transaminase values usually return to normal within 1 to 4 months. Afterward, the full virus remains in the liver for a decade, and in a significant percentage of patients, elevations in transaminase values persist for more than 6 months. This latter finding indicates progression to chronic active hepatitis. The percentage that progress to chronic disease is age dependent, being 90% in neonates, 20% to 50% in children 1 to 5 years of age, and 5% to 10% in adults.

A number of serum tests are available to assist in the diagnosis of hepatitis B. These tests are based on the general understanding of the structure and life cycle of the virus (Figures 8.4 and 8.5):

1. Viral capsid surface antigen and the antibody directed against the surface antigen (anti-HBs). The HBsAg test was the first available for detecting hepatitis B. HBsAg appears in serum within 1 to 10 weeks after exposure; its disappearance within 4 to 6 months indicates recovery (Figure 8.5). The persistence of HBsAg beyond 6 months indicates chronic disease. The disappearance of HBsAg may be preceded by the appearance of anti-HBs, and during this period, patients may develop a serum-sickness-like illness. In a large percentage of patients, anti-HBs does not rise to detectable levels for several weeks to months after the disappearance of HBsAg. During this window HBsAg and anti-HBs are both negative (Figure 8.5), and if these two tests alone are used for screening blood donors, a small percentage of infected donors may be missed. To prevent this occurrence, blood banks also test for IgM antibody directed against HBcAg (see point 2). Anti-HBs rises slowly over 6 to 12 months and usually persists for life, providing protection against reinfecion.

2. Antibody directed against the core antigen (anti-HBc). HBcAg is detected in infected hepatocytes, but is not released into serum; however, IgM antibody directed against HBcAg (anti-HBc) is usually the earliest anti-hepatitis B antibody detected in the infected patient (Figure 8.5). The IgM anti-HBc is usually interpreted as a marker for early acute disease; however, in some patients, anti-HBc IgM levels can persist for up to 2 years after acute infection, and in patients...
with chronic active hepatitis, IgM antibody levels can rise during periods of exacerbation. An anti-HBc IgM titer is particularly helpful for screening blood donors, because this antibody is usually present during the window between HBsAg disappearance and anti-HBs appearance. The IgG antibodies directed against the core antigen develop in the later phases of acute disease and usually persist for life.

3. Secreted core antigen (HBeAg) and its antibody (anti-HBe). Naked DNA strands and associated proteins make up HBeAg (Figure 8.4). The presence of HBeAg in serum indicates active viral replication, and it persists in patients with chronic disease, its presence correlating with infectivity. As the patient with acute hepatitis B recovers, HBeAg disappears, and anti-HBe appears. Seroconversion from HBeAg to anti-HBe usually corresponds with the disappearance of hepatitis B virus DNA from the serum.

4. Hepatitis B viral DNA (HBV-DNA). Quantitation of viral DNA in serum is most commonly used in the assessment of patients with chronic active hepatitis. In the patient with acute hepatitis, this test provides no significant advantages over that for HBeAg. Both tests indicate active viral replication. In patients with fulminant hepatitis, assays for HBV-DNA has been positive in the absence of other positive markers for hepatitis B.

TREATMENT AND PREVENTION

The approach to the treatment of acute hepatitis B is identical to that of hepatitis A, being that no therapeutic intervention can alter the course of acute disease. Prevention requires education of those who engage in high-risk behaviors, screening of the blood supply, and universal precautions by hospital personnel. High-titer hepatitis B immunoglobulin reduces the incidence of clinical hepatitis B. Immunoglobulin is prepared from the serum of patients with high titers of anti-HBs, and ameliorates the severity of infection if given within 7 days of exposure (0.05 to 0.07 mL/kg intramuscularly).

A safe and effective recombinant hepatitis B vaccine is available, and vaccination should be initiated in most individuals at the time of exposure. This vaccine is now recommended for all neonates. In the United States, vaccination is also recommended for all children who did not receive the vaccine as a neonate. Among adults, vaccination is recommended for health care workers, laboratory workers who handle blood and blood products, patients who require repeated blood transfusions or clotting factors, hemodialysis patients, morticians, people with multiple sexual partners, intravenous drug users, residents and staff of closed institutions such as prisons and institutions for the mentally handicapped, and household and sexual contacts of carriers. The vaccine should be given intramuscularly in three doses at months 0, 1 to 2, and 6 to 12. In neonates born to mothers with
unknown or positive HBsAg, status, the first dose of vaccine should be given within 12 hours of delivery, with the booster doses given at 1 and 6 months. The vaccine is highly effective, and has markedly reduced the incidence of hepatitis B in health care workers.

TREATMENT AND PROGNOSIS OF CHRONIC HEPATITIS B

Patients with a positive HBsAg for more than 20 weeks are defined as chronic HBsAg carriers. The carrier state develops in 5% to 10% of adults. The course of chronic disease depends on the balance between viral replication and the host's immune response. This chronic illness has several stages:

1. **Replicative phase, immune tolerance.** During this phase, the host's immune system demonstrates tolerance to the virus, allowing active replication. Hepatic inflammation is minimal. This stage can persist for 20 to 30 years in neonates.

2. **Replicative phase, immune clearance.** The immune system recognizes the virus as a foreign antigen, and active inflammation ensues. Symptoms of hepatitis may develop, although most patients remain asymptomatic. Liver function tests become abnormal, indicating active hepatitis. During this phase, the virus may clear from the serum. In some patients, however, viral replication may continue, and those patients are said to have had an episode of abortive immune clearance.

3. **Nonreplicative phase.** In this phase, HBeAg is negative, and anti-HBe appears. In some of these patients, HBsAg may persist and may be associated with progression of liver disease.

   Patients with persistent HbsAg and ongoing hepatic inflammation can progress to cirrhosis and liver failure. Chronic carriage of hepatitis B is also associated with an increased risk of hepatocellular carcinoma, and HBsAg-positive individuals who develop cirrhosis have an annual 1.6% incidence of hepatocellular carcinoma. To prevent these complications, treatment is recommended in chronic carriers of hepatitis B virus with positive HBeAg. The goal of therapy is to achieve HBeAg seroconversion.
About Chronic Hepatitis B

1. Chronic disease is defined as positive HBsAg for more than 20 weeks.
2. Three stages:
   a) Replicative stage with immune tolerance, laboratory findings within normal limits, viral load high.
   b) Replicative stage with immune clearance, laboratory findings are abnormal.
   c) Non-replicative stage, HBsAg disappears, HBeAg may persist.
3. Chronic carriers can progress to cirrhosis and hepatic failure. Risk of hepatocellular carcinoma is increased.
4. Treatment:
   a) Multiple antiviral agents are being tested.
   b) Interferon α reserved for patients with persistent HBeAg and elevated transaminase values.

Hepatitis D

The hepatitis D virion is a small, single-stranded RNA virus that is surrounded by a single hepatitis D antigen and a lipoprotein envelope provided by hepatitis B. The hepatitis D virus, also called delta agent, can replicate only in a human host who is co-infected with hepatitis B. When the D virus is present, hepatitis B replication is suppressed. Hepatitis D virus replicates at very high levels in the nuclei of hepatocytes. During acute disease, it is thought to be directly responsible for cytotoxic damage in those cells. Clinically, hepatitis D+B is indistinguishable from hepatitis B. A higher incidence of hepatic failure has been noted with combined infection in intravenous drug abusers. The rate of progression to chronic active hepatitis is the same.

Hepatitis D virus is endemic in the Mediterranean basin, having been first discovered in Italy. A high prevalence is also seen in the eastern Asia (Pacific Islands, Taiwan, Japan). Person-to-person spread may be the result of mucosal contact with infected body fluids or injection of blood or blood products. Spread among household contacts is common and is associated with poor hygiene and low socioeconomic status. The virus can be spread by sexual contact and is common among intravenous drug abusers. In the Western hemisphere, infection with hepatitis D virus is uncommon, being found primarily in individuals requiring multiple blood transfusions or coagulation products, and in abusers of intravenous drugs. The diagnosis is made by measuring anti-hepatitis D IgM and IgG serum titers. No specific treatment is available for hepatitis D. Measures designed to prevent hepatitis B also eliminate the risk of this virus.
**Hepatitis C**

**Virology, Pathogenesis, and Epidemiology**

Hepatitis C is a single-stranded RNA virus that is thought to be enveloped. As the virus replicates, it demonstrates ineffective proofreading, generating multiple mutations and virions (called “quasi-species”) in the blood. These constant mutations allow the virus to evade the host’s immune system and cause chronic disease. The virus cannot be propagated by routine methods, explaining the great difficulty encountered in originally identifying the cause of non-A, non-B transfusion-associated hepatitis.

Hepatitis C has a very narrow host range, infecting only humans and chimpanzees. Within the liver, the virus infects only hepatocytes, leaving biliary epithelium and stromal cells uninfected. The mechanism of hepatocyte damage has not been clarified, but probably involves both cytopathic and immune-mediated mechanisms. In addition to acute hepatitis, the virus can cause chronic persistent hepatitis and chronic active hepatitis. The latter disease is characterized by periportal infiltration with lymphocytes and piecemeal necrosis. It is often followed by fibrosis, leading to cirrhosis.

This virus has a worldwide distribution, and in the United States, seroprevalence ranges from 0.25% in low-risk blood donors to 2% among those who exhibit high-risk behaviors such as intravenous drug abuse. A similar range of seroprevalence is encountered internationally. Approximately 150,000 new cases develop annually in the United States, and 2 to 4 million people are estimated to have chronic disease. The infection is spread primarily by the parenteral administration of blood or blood products and by needle sharing among intravenous drug abusers. Spread from an infected mother to her neonate is reported, but this form of transmission is less common than is observed with hepatitis B. The risk is higher in mothers who are co-infected with HIV. Sexual transmission may occur, but it is less efficient than in the case of hepatitis B virus or HIV. Co-infection with hepatitis C and HIV is common in the United States and has created new therapeutic challenges (see Chapter 17).

**Clinical Manifestations and Diagnosis**

The incubation period for hepatitis C is 6 to 10 weeks. A high proportion of acute attacks remain asymptomatic, with only one quarter of infected patients experiencing the typical symptoms of acute hepatitis. Hepatitis C alone does not cause fulminant hepatitis, but 50% to 70% of acutely infected patients are estimated to progress to chronic hepatitis C infection. Serum transaminase values fluctuate during chronic illness. During some periods, they may be normal; at other times, they increase to 7 to 10 times normal values.

Disease is detected by an ELISA assay designed to measure antibodies directed against specific hepatitis C antigens. The most recent generation of this test (E12)
has a greater than 95% sensitivity and a high positive predictive value. In low-risk populations, the ELISA assay should be confirmed by recombinant immunoblot assay. This latter test has a higher specificity and, when positive, indicates true infection. Detection of serum viral RNA by the PCR method allows for quantitation of the serum viral load, and some assays claim to detect levels as low as 100 copies per milliliter.

**TREATMENT AND PROGNOSIS**

Unlike hepatitis B (which may spontaneously clear over time), hepatitis C seldom clears spontaneously. Approximately 20% to 25% of patients progress to cirrhosis over a period of 20 to 30 years. Hepatitis C is one of the leading causes of hepatic failure requiring liver transplantation. Like chronic hepatitis B, chronic hepatitis C is associated with an increased incidence of primary hepatocellular carcinoma.

Treatment with pegylated interferon α-2a once weekly, combined with oral ribavirin (1 to 1.2 g daily) results in the best response rates, and is now recommended as initial therapy for hepatitis C. After 12 weeks of therapy, a quantitative test for hepatitis C RNA should be performed. If a greater than 2 log decline is observed, treatment should be continued for 48 weeks. Duration of therapy and rates of response vary with the virus genotype.

**FURTHER READING**

**Infectious Diarrhea**


**Antibiotic-Associated Diarrhea**


**Primary and Secondary Peritonitis**


Liver Abscess

Helicobacter Pylori

Hepatitis A


Hepatitis B

Hepatitis C
Scarlet fever (known as scarlatina in older literature references) is characterized by sore throat, fever, bright red tongue with a "strawberry" appearance and characteristic rash. It is caused by group A streptococci (GAS) that elaborates streptococcal pyrogenic exotoxins (erythrogenic toxins). Although this disease is usually associated with pharyngeal infections, it may follow streptococcal infections at other sites such as wound infections or puerperal sepsis. Scarlet fever is predominantly a childhood disease.

**Etiology**

Group A streptococcus (GAS) is synonymous with *Streptococcus pyogenes*. GAS are gram-positive coccoid-shaped bacteria that tend to grow in chains. They are broadly classified by their reactions on mammalian red blood cells. GAS produce clear β-hemolysis on blood agar, a bacteriologic feature important in their recognition and in their differentiation γ-hemolytic streptococci that cause no hemolysis and from α-hemolytic (viridons) streptococci that, which cause partial or green hemolysis. Rare strains of GAS are not hemolytic. The β-hemolytic streptococci can be divided into groups by a group-specific polysaccharide (Lancefield carbohydrate C) located in the cell wall. Serologic grouping by the Lancefield method is precise, but group A organisms can be identified more readily by any one of a number of latex agglutination, coagglutination, or enzyme immunoassay procedures. Group A strains can also be distinguished from other groups by differences in susceptibility to bacitracin. A disc containing 0.04 units of bacitracin inhibits growth of most group A strains, whereas other groups generally are resistant.

GAS can be subdivided into > 100 serotypes by the M-protein antigen that is located on the cell surface and by fimbriae (hairlike fuzz) that project from the outer edge of the cell. Typing of the surface M protein has relied on available polyclonal antisera for testing. However, it is frequently difficult to detect M proteins in this way. Recently, a molecular approach to M typing of GAS was developed using the polymerase chain reaction technique and based on sequencing the *emm* gene that encodes the M protein. More than 200 distinct M genotypes have been identified using *emm* typing, and there has been a good correlation between known serotypes and *emm* types.

M serotyping has been valuable for epidemiologic studies; particular GAS diseases tend to be associated with certain M types. The M types commonly associated with pharyngitis rarely cause skin infections, and the M types commonly associated with skin
infections rarely cause pharyngitis. A few of the ‘‘pharyngeal’’ strains (e.g., M type 12) have been associated with glomerulonephritis, but far more of the ‘‘skin’’ strains (e.g., M types 49, 55, 57, and 60) have been considered nephritogenic. A few of the ‘‘pharyngeal’’ serotypes, but none of the ‘‘skin’’ strains, have been associated with ARF. However, recent evidence suggests that rheumatogenic potential is not solely dependent on the serotype, but rather is a characteristic of specific strains within several serotypes.

The GAS cell is a complex structure. In rapidly dividing strains (e.g., young cultures, epidemic strains), the cell is covered with a hyaluronic acid capsule that gives the colonies a mucoid or waterdrop appearance. Protruding from the cell surface and into the hyaluronic capsular layer are microscopic hairlike fimbriae, which are responsible for adherence of GAS to epithelial cells. A basic chemical component of these fimbriae is lipoteichoic acid. The M protein is also associated with these fimbriae. Other surface proteins of interest are the T and R proteins, the serum opacity factor (SOF) proteins, and proteins that bind nonspecifically to the Fc fragment of gamma globulins. Strains of a particular M type are generally associated with a particular T-agglutination pattern. In strains of GAS that produce SOF, the serologically specific SOF protein correlates closely with the M type of the strain. At present, there are more than 30 recognized SOF types. All of these characteristics are useful in epidemiologic studies of streptococcal infections, either in an individual patient or in a community.

The carbohydrate moiety of GAS responsible for group specificity (e.g., group A carbohydrate) is also found in the cell wall in a position sufficiently superficial to permit reaction with specifically directed antibody. The group A carbohydrate is a polymer of rhamnose units with side chains of N-acetyl-glucosamine and is responsible for its group (e.g., A) specificity. The structure providing rigidity for the cell wall is another large polymer, a peptidoglycan, consisting of glycan strands crosslinked by peptide bridges. Its role in the pathogenesis of infection is incompletely defined.

Within the cell wall of the GAS there is a cell membrane composed mainly of lipoproteins and proteins, including the five penicillin-binding proteins responsible for cell wall synthesis, and endostreptosin, which may be important in the pathogenesis of PSAGN. Intracellular constituents of the GAS include, in addition to DNA and RNA, a number of enzymes and hemolysins. Plasmids have been identified that control resistance to certain antibiotics, for example, erythromycin. Bacteriophages play an important role in the genetics of GAS, including the transfer of the determinants of antibiotic resistance and the control of pyrogenic exotoxin production.

GAS produce and release into the surrounding medium a large number of biologically active extracellular products. Some of these are toxic for human and other mammalian cells. Both streptolysin O (the oxygen-labile hemolysin) and streptolysin S (the oxygen-stable hemolysin) injure cell membranes, not only lysing red blood cells, but also damaging other eukaryotic cells (including myocardial cells) and membranous subcellular organelles. Streptolysin O is antigenic; streptolysin S is not. The latter hemolysin is loosely bound to the streptococcal cell and is released in a complexed, stable form with a variety of carrier molecules. Streptococcal pyrogenic exotoxins (SPEs) are important virulence factors and resemble endotoxin in exhibiting both a primary or intrinsic toxicity and a secondary toxicity resulting from the
acquisition of host hypersensitivity. GAS also produces bacteriocins, low-molecular-weight proteins that can kill a variety of other gram-positive bacteria, and thus may play a role in promoting infection or even persistence of colonization.

**Epidemiology**

As many as 10% of the population contracts group A streptococcal pharyngitis. Of this group, as many as 10% then develop scarlet fever. GAS can be found in secretions and discharge from the nose, ears, throat, and skin. Person-to-person spread by means of respiratory droplets is the most common mode of transmission. Transmission can be spread from infected patients and asymptomatic carriers. It can rarely be spread through contaminated food. The organism is able to survive extremes of temperature and humidity, which allows spread by fomites.

The incubation period for scarlet fever ranges from 12 hours to 7 days. Patients are contagious during the acute illness and during the subclinical phase.

Scarlet fever predominantly occurs in children aged 5-15 years, though it can also occur in older children and adults. By the time children are 10 years old, 80% have developed lifelong protective antibodies against streptococcal pyrogenic exotoxins. Scarlet fever is rare in children younger than 2 years because of the presence of maternal antieoxotoxin antibodies and lack of prior sensitization. In adulthood, incidence decreases markedly as immunity develops to the most prevalent serotypes.

Immunity, which is type specific, may be induced by a carrier state or overt infection.

Although infections may occur year-round, the incidence of pharyngeal disease is highest in school-aged children (5-15 y) during winter and spring and in a setting of crowding and close contact. Geographic distribution of skin infections tends to favor warmer or tropical climates and occurs mainly in summer or early fall in temperate climates.

**Clinical manifestation**

Scarlet fever is characterized by sore throat, fever, bright red tongue with a "strawberry" appearance and characteristic rash. The rash is the most striking sign of scarlet fever, which usually appears on the second day of clinical illness as a diffuse red blush with many points of deeper red that blanch on pressure. It is often first noted over the upper part of the chest and then spreads to the remainder of the trunk, neck, and extremities. The palms, soles, and usually the face are spared. Skin folds in the neck, axillae, groin, elbows, and knees appear as lines of deeper red (Pastia’s lines). There are scattered petechiae, and the Rumpel-Leeds test of capillary fragility is positive. Occlusion of sweat glands imparts a sandpaper texture to the skin, a particularly helpful finding in dark-skinned patients.

The face appears flushed except for marked circumoral pallor. In addition to findings of exudative pharyngitis and tonsillitis, patients display an enanthem characterized by small, red, hemorrhagic spots on the hard and soft palate. The tongue is initially covered with a yellowish white coat through which may be seen the red papillae ("white strawberry tongue"). Later the coating disappears, and the tongue is beefy red in appearance ("red strawberry tongue"). The skin rash fades over the course of 1 week and is followed by
extensive desquamation lasting for several weeks. A modest eosinophilia may be present early in the course of the illness. Severe forms of scarlet fever, either associated with local and hematogenous spread of the organism (septic scarlet fever) or with profound toxemia (toxic scarlet fever), are characterized by high fever and marked systemic toxicity. The course may be complicated by arthritis, jaundice, and, very rarely, hydrops of the gallbladder. Such severe forms of the disease are quite infrequent in the antibiotic era. Intracutaneous administration of erythrogenic toxin in humans elicits local erythema (positive Dick test). No reaction occurs in persons with acquired immunity to the toxin. This test is not used clinically at the present time.

**Complications**

Scarlet fever can be associated with suppurative and nonsuppurative complications. Suppurative complications result from the spread of GAS to adjacent structures and include peritonsillar abscess, retropharyngeal abscess, cervical lymphadenitis, sinusitis, otitis media, and mastoiditis. Before antimicrobial agents were available, suppurative complications of GAS pharyngitis were common; however, antimicrobial therapy has greatly reduced the frequency of such complications.

Acute rheumatic fever, acute poststreptococcal glomerulonephritis, and poststreptococcal reactive arthritis are recognized nonsuppurative sequelae of GAS pharyngitis (see Chapter 118, *Streptococcus pyogenes*). Acute rheumatic fever occurs after an episode of GAS pharyngitis (usually after a 2- to 4-week latent period) and not after GAS infections of the skin. Appropriate antimicrobial therapy begun within 9 days of the onset of pharyngitis can prevent this complication. In contrast to acute rheumatic fever, acute poststreptococcal glomerulonephritis can occur after a GAS infection of either the pharynx or skin and does not appear to be prevented by antimicrobial therapy of the antecedent GAS infection. The latent period for glomerulonephritis is about 3 weeks following skin infection and 10 days following upper respiratory tract infection. Poststreptococcal reactive arthritis is similar to other postinfectious arthritides. The relationship of this entity to acute rheumatic fever is still unclear.

**Differential diagnosis**

The clinical syndrome is similar in most respects to that associated with nontoxigenic strains, save for the scarlatinal rash. The latter must be differentiated from those of viral exanthems, drug eruptions, staphylococcal toxic shock syndrome, and Kawasaki disease.

**Pathophysiology**

As the name “scarlet fever” implies, an erythematous eruption is associated with a febrile illness. The circulating toxin, produced by GAS and often referred to as erythemogenic or erythrogenic toxin A, B, and C, are responsible for the rash of scarlet fever and stimulate the formation of specific antitoxin antibodies that provide immunity against the scarlatiniform rash but not against other GAS infections. However, because GAS can produce different rash-producing pyrogenic exotoxins (A, B, and C), repeated attacks of scarlet fever can occur. Usually, the sites of GAS replication in scarlet fever are the tonsils and pharynx. The rash
develops in less than 10% of cases of “strep throat.” Clinically indistinguishable, scarlet fever may follow streptococcal infection of the skin and soft tissue, surgical wounds (ie, surgical scarlet fever), or the uterus (ie, puerperal scarlet fever). Exotoxin-mediated streptococcal infections range from localized skin disorders (eg, bullous impetigo) to the systemic rash of scarlet fever to the uncommon but highly lethal streptococcal toxic shock syndrome.

**Diagnosis**

Diagnosis of scarlet fever is clinical. The majority of cases of scarlet fever are associated with strep throat. GAS can usually be demonstrated in throat culture or rapid antigen detection test. Blood culture is rarely positive. In the uncommon scenario that the streptococcal infection is arising from an alternative site, appropriate evaluation and testing of these areas to confirm a streptococcal infection needs to be undertaken.

The blood test shows marked leukocytosis with neutrophilia, high erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) (both indications of inflammation). Elevation of antistreptolysin O titer can provide evidence of a previous streptococcal infection, but not useful in the acute phase of the illness.

**Prognosis**

Today, as a result not only of antibiotic therapy but also of enhanced immune status of the population and improved socioeconomic conditions, scarlet fever usually follows a benign course. Most patients recover fully after 4-5 days, with resolution of skin symptoms over several weeks. Attacks may recur.

In the preantibiotic era, infections due to GAS were major causes of mortality and morbidity. Historically, scarlet fever resulted in death in 15-20% of those affected. However, scarlet fever is no longer associated with the deadly epidemics that made it so feared in the 1800s. Since the advent of antibiotic therapy, the mortality rate for scarlet fever has been less than 1%.

**Treatment**

Antimicrobial therapy is indicated for individuals with scarlet fever after the presence of GAS in the throat has been confirmed by either throat culture or rapid antigen detection test. In situations in which the clinical and epidemiologic findings are highly suggestive of GAS-associated scarlet fever, antimicrobial therapy can be initiated while awaiting microbiologic confirmation. Antimicrobial therapy for scarlet fever shortens the clinical course of the illness. In addition, the initiation of antimicrobial therapy can be delayed for up to 9 days after the onset of scarlet fever and still prevent the occurrence of acute rheumatic fever.

Penicillin and its congeners (such as ampicillin and amoxicillin), as well as numerous cephalosporins, macrolides, and clindamycin, are effective treatment for scarlet fever. Group A streptococcus has remained exquisitely susceptible to beta-lactam agents over five decades. Amoxicillin is often used because of acceptable taste of suspension; efficacy appears to equal penicillin. Orally administered erythromycin is indicated for patients allergic to penicillin. Other macrolides, such as clarithromycin or
azithromycin, are also effective. First-generation cephalosporins are acceptable in penicillin-allergic patients who do not manifest immediate-type hypersensitivity to beta-lactam antibiotics. Sulfa drugs, including trimethoprim-sulfamethoxazole, and tetracyclines are not effective and should not be used for GAS pharyngitis.

Oral penicillin must be administered multiple times a day for 10 days in order to achieve maximal rates of eradication of GAS. Reduced frequency of dosing and shorter treatment courses (< 10 days) may result in better patient adherence to therapy than is seen with 10 days of oral penicillin. It has been reported that several antimicrobial agents, including clarithromycin, cefuroxime, cefixime, cefibuten, cefdinir, and cefpodoxime, are effective in eradication of GAS from the pharynx when administered for \( \leq 5 \) days. However, many of the studies of short-course therapy have serious methodologic flaws that cloud validity of conclusions. In addition, the spectra of these antibiotics are much broader than that of penicillin, and, even if administered for short courses, they are more expensive. Therefore, additional studies are needed before these short-course regimens can be recommended.

Attempts to treat GAS pharyngitis with a single daily dose of penicillin have been unsuccessful. In recent years, investigators have demonstrated that several antimicrobial agents, including azithromycin, cefadroxil, cefixime, cefibuten, cefpodoxime, cefprozil, and cefdinir, are effective in eradicating pharyngeal streptococci when given as a single daily dose. However, these agents are expensive and have broad spectra of activity compared with penicillin. Preliminary investigations have demonstrated that once-daily amoxicillin therapy is effective in the treatment of GAS pharyngitis. If confirmed by additional investigations, once-daily amoxicillin therapy, because of its low cost and relatively narrow spectrum, could become an alternative regimen for the treatment of GAS pharyngitis. Intramuscular benzathine penicillin G is preferred in those patients unlikely to complete a full 10-day course of oral therapy. In case of penicillin allergy, clindamycin or erythromycin can be used with success.

Although penicillin resistance has not occurred in GAS anywhere in the world, there have been geographic areas with relatively high levels of resistance to macrolides and clindamycin, which are high in mainland China, about 70~90%. Clinicians should be aware of local resistance rates.

Patients should no longer be infectious after taking antibiotics for 24 hours.

**Prevention**

Children with scarlet fever should not return to school or day care until they have completed 24 hours of antibiotic therapy.

The only specific indication for long-term use of antibiotics to prevent GAS infection is for patients with a history of ARF or rheumatic heart disease (RHD). Mass prophylaxis is generally not feasible except to control epidemics of pharyngitis in military populations and in schools.

Measures to prevent spread of GAS infections have variable effectiveness. Spread of throat or skin infection within a family unit often occurs before the index case is identified and isolated or treated. In epidemic situations, especially when there are cases of rheumatic fever or acute nephritis, a culture survey with treatment of all individuals with positive cultures (mass prophylaxis) may be indicated.
Reduction of crowding, especially in sleeping quarters, seems to be an effective long-term method of minimizing spread of GAS pharyngitis among some population groups. In families in which persistence or recurrence of streptococcal infection is a problem, simultaneous throat culture and/or culture of skin lesions of all members and treatment of all positives has been successful in eradicating the organism.

Because the strategy of antimicrobial agents to prevent GAS infections has limited benefit, streptococcal vaccines have been pursued. Several common protective antigens considered for use in a GAS vaccine include: C5a-peptidase, SPE A, SPE B (cysteine protease), fibronectin-binding proteins, group A carbohydrate, and streptococcal protective antigen (Spa). In addition the C-terminal region of M protein contains the so-called “C-repeat” and is highly conserved among GAS. The 26-valent vaccine includes 80% to 90% of serotypes that caused invasive infections or pharyngitis, as demonstrated by recent surveillance in North America, and could have significant impact on the overall burden of GAS disease. However, vaccine type-specific coverage may be less complete for Asia and other developing areas of the world. In addition, emergence of new emm types and the possibility that nonvaccine serotypes or genotypes of clinical importance may replace those contained in the vaccine are concerns.
Streptococcus pyogenes

(Group A Streptococcus)

Time Recommended to complete: 1 day

Zeng Mei  Children’s Hospital of Fudan University

DESCRIPTION OF PATHOGEN

Microbiology

GAS are gram-positive coccoid-shaped bacteria that tend to grow in chains. They are broadly classified by their reactions on mammalian red blood cells. GAS produce clear β-hemolysis on blood agar, a bacteriologic feature important in their recognition and in their differentiation γ-hemolytic streptococci that cause no hemolysis and from α-hemolytic (viridons) streptococci that, which cause partial or green hemolysis. Rare strains of GAS are not hemolytic. The β-hemolytic streptococci can be divided into groups by a group-specific polysaccharide (Lancefield carbohydrate C) located in the cell wall. Serologic grouping by the Lancefield method is precise, but group A organisms can be identified more readily by any one of a number of latex agglutination, coagglutination, or enzyme immunoassay procedures. Group A strains can also be distinguished from other groups by differences in susceptibility to bacitracin. A disc containing 0.04 units of bacitracin inhibits growth of most group A strains, whereas other groups generally are resistant.

GAS can be subdivided into > 100 serotypes by the M-protein antigen that is located on the cell surface and by fimbriae (hairlike fuzz) that project from the outer edge of the cell. Typing of the surface M protein has relied on available polyclonal antisera for testing. However, it is frequently difficult to detect M proteins in this way. Recently, a molecular approach to M typing of GAS was developed using the polymerase chain reaction technique and based on sequencing the emm gene that encodes the M protein. More than 130 distinct M genotypes have been identified using emm typing, and there has been a good correlation between known serotypes and emm types.

M serotyping has been valuable for epidemiologic studies; particular GAS diseases tend to be associated with certain M types. The M types commonly associated with pharyngitis rarely cause skin infections, and the M types commonly associated with skin infections rarely cause pharyngitis. A few of the “pharyngeal” strains (e.g., M type 12) have been associated with glomerulonephritis, but far more of the “skin” strains (e.g., M types 49, 55, 57, and 60) have been considered nephritogenic. A few of the “pharyngeal” serotypes, but none of the “skin” strains, have been associated with ARF. However, recent evidence suggests that rheumatogenic potential is not solely dependent on the serotype, but rather is a characteristic of specific strains within several serotypes.
The GAS cell is a complex structure. In rapidly dividing strains (e.g., young cultures, epidemic strains), the cell is covered with a hyaluronic acid capsule that gives the colonies a mucoid or waterdrop appearance. Protruding from the cell surface and into the hyaluronic capsular layer are microscopic hairlike fimbriae, which are responsible for adherence of GAS to epithelial cells. A basic chemical component of these fimbriae is lipoteichoic acid. The M protein is also associated with these fimbriae. Other surface proteins of interest are the T and R proteins, the serum opacity factor (SOF) proteins, and proteins that bind nonspecifically to the Fc fragment of gamma globulins. Strains of a particular M type are generally associated with a particular T-agglutination pattern. In strains of GAS that produce SOF, the serologically specific SOF protein correlates closely with the M type of the strain. At present, there are more than 30 recognized SOF types. All of these characteristics are useful in epidemiologic studies of streptococcal infections, either in an individual patient or in a community.

The carbohydrate moiety of GAS responsible for group specificity (e.g., group A carbohydrate) is also found in the cell wall in a position sufficiently superficial to permit reaction with specifically directed antibody. The group A carbohydrate is a polymer of rhamnose units with side chains of N-acetyl-glucosamine and is responsible for its group (e.g., A) specificity. The structure providing rigidity for the cell wall is another large polymer, a peptidoglycan, consisting of glycan strands crosslinked by peptide bridges. Its role in the pathogenesis of infection is incompletely defined.

Within the cell wall of the GAS there is a cell membrane composed mainly of lipoproteins and proteins, including the five penicillin-binding proteins responsible for cell wall synthesis, and endoestreptosin, which may be important in the pathogenesis of PSAGN. Intracellular constituents of the GAS include, in addition to DNA and RNA, a number of enzymes and hemolysins. Plasmids have been identified that control resistance to certain antibiotics, for example, erythromycin. Bacteriophages play an important role in the genetics of GAS, including the transfer of the determinants of antibiotic resistance and the control of pyrogenic exotoxin production.

GAS produce and release into the surrounding medium a large number of biologically active extracellular products. Some of these are toxic for human and other mammalian cells. Both streptolysin O (the oxygen-labile hemolysin) and streptolysin S (the oxygen-stable hemolysin) injure cell membranes, not only lysing red blood cells, but also damaging other eukaryotic cells (including myocardial cells) and membranous subcellular organelles. Streptolysin O is antigenic; streptolysin S is not. The latter hemolysin is loosely bound to the streptococcal cell and is released in a complexed, stable form with a variety of carrier molecules. Streptococcal pyrogenic exotoxins (SPEs) are important virulence factors and resemble endotoxin in exhibiting both a primary or intrinsic toxicity and a secondary toxicity resulting from the acquisition of host hypersensitivity. GAS also produces bacteriocins, low-molecular-weight proteins that can kill a variety of other gram-positive bacteria, and thus may play a role in promoting infection or even persistence of colonization.

PATHOGENESIS AND VIRULENCE

GAS induces serious human disease by at least three mechanisms: suppuration, as in pharyngitis and pyoderma; toxin elaboration, as in STSS; and immune-mediated
inflammation, as in ARF and PSAGN. No complete explanation is available for the predilection of certain body sites for infection by GAS or for the ability of strains of certain M types to produce pharyngitis and of other M types to produce pyoderma.

Virulence of GAS depends primarily on the M protein, and strains rich in M protein resist phagocytosis in fresh human blood, whereas M-negative strains do not. GAS isolated from chronic pharyngeal carriers contain little or no M protein and are relatively avirulent. In the nonimmune host, M protein exerts its antiphagocytic effect by interfering with opsonization in the alternate complement pathway. The hyaluronic acid capsule of GAS also asets the organism in resisting phagocytosis. However, the capsular hyaluronate is chemically quite similar to that found in human connective tissue, and, therefore, it is a poor immunogen, not likely to elicit a specific antibody response. GAS strains rich in M protein and capsular hyaluronate are mucoid and extremely virulent, and mucoid strains have long been known to be associated with severe, invasive infections. In addition, the appearance of mucoid strains has been a harbinger of outbreaks of ARF.

A large number of potential adherence factors for GAS have been described, but the most extensively studied have been lipoteichoic acid, M protein, and fibronectin-binding proteins. Lipoteichoic acid facilitates adherence of GAS by binding to fibronectin on human buccal epithelial cells, whereas M protein mediates adherence to skin keratinocytes. GAS fibronectin-binding proteins appear to be important in adherence to both throat and skin.

Animal studies suggest that M protein may be important in the process of colonization of the upper respiratory tract. Both M protein and fibronectin-binding proteins have also been demonstrated to be important in the process through which GAS penetrates into respiratory epithelial cells.

GAS produces several extracellular products that may serve as virulence factors by facilitating the liquification of pus and the spreading of GAS through tissue planes. These products include: four antigenically distinct enzymes that participate in the degradation of DNA (DNAses A, B, C, and D); hyaluronidase, which enzymatically degrades hyaluronic acid in the connective tissue; streptokinase, which promotes the dissolution of clots; streptococcal exotoxin B (SPE B), which is a potent protease; and C5a peptidase, which cleaves the chemotaxin C5 at the polymorphonuclear-binding site.

The SPEs are a family of over 15 bacterial superantigens, including the bacteriophage-encoded SPE A and SPE C. These superantigens induce antigen-nonspecific T-lymphocyte activation, suppress antibody synthesis, potentiate endotoxic shock, induce fever, promote release of proinflammatory cytokines, produce reticuloendothelial blockade, and may contribute to multiorgan failure characteristic of STSS. In the United States, STSS is commonly associated with infections with SPE A-producing strains. SPE B is genomic and present in virtually all GAS strains. Although initially believed to be a superantigen, SPE B is now thought to contribute to virulence solely through its protease activity. Only a small fraction of individuals colonized or infected with strains capable of initiating STSS actually develop the syndrome. Susceptibility to STSS appears to be related to the absence of antibodies to both M protein and superantigens as well as
the presence of specific human leukocyte antigen (HLA) haplotypes.\textsuperscript{18} The SPEs share homology with staphylococcal enterotoxins but not with staphylococcal toxic shock syndrome toxin-1. SPE A, B, and C are responsible for the rash of scarlet fever and stimulate the formation of specific antitoxin antibodies that provide immunity against the scarlatiniform rash but not against other GAS infections. However, because GAS can produce different rash-producing pyrogenic exotoxins (A, B, and C), repeated attacks of scarlet fever can occur.

**Immunologic Response**

Although many GAS constituents and extracellular products are antigenic, protective immunity is type-specific, mediated by opsonic anti-M-protein antibodies. These antibodies protect against infection with a homologous M type but confer no immunity against other M types.\textsuperscript{20,21} Therefore, multiple GAS infections attributable to different M types are common during childhood and adolescence. By adult life, individuals are probably immune to many of the common M types in the environment, but, because of the large number of serotypes, it is doubtful that total immunity is ever achieved. However, some reports indicate that type-specific immunity may be specific only to certain strains within a given serotype.\textsuperscript{22,23} The significance of this potentially important observation in the epidemiology of streptococcal infections has not been fully defined. Anti-M antibodies persist for years, perhaps for life, protecting against invasive infection but not against pharyngeal carriage.\textsuperscript{24} Type-specific antibody may be transferred across the placenta from mother to fetus.\textsuperscript{25} Type-specific antibody against M protein is not usually detectable until 6 to 8 weeks after infection.\textsuperscript{26} Therefore, its primary role may not be in the limitation or termination of active infection, but rather in the prevention of reinfection by the same serologic type. Opsonic type-specific antibodies do not appear after early and effective antimicrobial therapy.\textsuperscript{27}

Humoral antibodies to specific streptococcal extracellular products such as antistreptolysin O (ASO) and anti-DNAse B (ADB) can be demonstrated readily by neutralization assays.\textsuperscript{28} However, ASO and ADB antibodies provide no protection. They have been particularly useful in allowing a more precise method of defining GAS infection in clinical and epidemiologic studies and in documenting the occurrence of a preceding GAS infection in patients with a suspected nonsuppurative complication.

The ASO assay is the most commonly used streptococcal antibody test. Because streptolysin O is also produced by group C and G streptococci, the test is not specific for GAS infections. The ASO response can be feeble in patients with streptococcal impetigo or pyoderma.\textsuperscript{29} In contrast, the ADB response is demonstrable after both skin and throat infections. Neutralizing antibody titers to streptolysin O peak at 3 to 6 weeks and to ADB at 6 to 8 weeks. Another antibody test, the Streptozyme agglutination test, is based on antibody agglutination of erythrocytes coated with a mixture of streptococcal extracellular antigens. It has the theoretical appeal of simplicity, speed, and reaction with a number of streptococcal antigens. However, because of documented problems of standardization of this reagent (e.g., variable results may be obtained with different lots) and because of problems with group specificity, this test
should be interpreted with caution\textsuperscript{[30]}, the World Health Organization has recommended that it not be used.\textsuperscript{[31]}

Antibody titers against GAS extracellular antigens reported by clinical immunology laboratories may vary. Upper limits of normal are higher for children than for adults and these values, even for the same age group, are higher in some populations than in others. Interpretation of antibody titers for clinical purposes must take these factors into consideration. Values given by laboratories for upper limits of normal are often determined using adult sera; these values are often much too low to be used in a pediatric population.

**Prevention**

The only specific indication for long-term use of antibiotics to prevent GAS infection is for patients with a history of ARF or rheumatic heart disease (RHD). Mass prophylaxis is generally not feasible except to reduce the number of infections during epidemics of impetigo and to control epidemics of pharyngitis in military populations and in schools.

Measures to prevent spread of GAS infections have variable effectiveness. Spread of throat or skin infection within a family unit often occurs before the index case is identified and isolated or treated. In epidemic situations, especially when there are cases of rheumatic fever or acute nephritis, a culture survey with treatment of all individuals with positive cultures (mass prophylaxis) may be indicated. Reduction of crowding, especially in sleeping quarters, seems to be an effective long-term method of minimizing spread of GAS pharyngitis among some population groups. In families in which persistence or recurrence of streptococcal infection is a problem, simultaneous throat culture and/or culture of skin lesions of all members and treatment of all positives has been successful in eradicating the organism. Some have advocated a role for family pets (dogs) in transmission of streptococcal infections. However, available data do not support such transmission.\textsuperscript{[46][47]}

Although the risk of subsequent invasive GAS disease among household contacts is higher than the risk among the general population, subsequent invasive GAS infections among household contacts are rare. Given the infrequency of these infections and the lack of a clearly effective chemoprophylactic regimen, the available data do not support a recommendation for routine testing for GAS colonization or for routine administration of chemoprophylaxis to all household contacts of persons with invasive GAS disease. The Centers for Disease Control and Prevention recommend that healthcare providers inform household contacts of persons with invasive GAS about the clinical manifestation of pharyngeal and invasive GAS infections and emphasize the importance of seeking immediate medical attention if contacts develop such symptoms.\textsuperscript{[48]} In addition, healthcare providers may choose to offer chemoprophylaxis to household contacts aged 65 years and older or those at increased risk for sporadic invasive GAS infections (e.g., human immunodeficiency virus infection, diabetes mellitus, chickenpox, cancer, heart disease).\textsuperscript{[48]}

Because the strategy of antimicrobial agents to prevent GAS infections has limited benefit, streptococcal vaccines have been pursued. Several common protective antigens considered for use in a GAS vaccine include: C5a-peptidase, SPE A, SPE B (cysteine protease), fibronectin-binding proteins, group A carbohydrate, and streptococcal protective
antigen (Spa). In addition the C-terminal region of M protein contains the so-called “C-repeat” and is highly conserved among GAS.\textsuperscript{[49]}

Two approaches have been taken to utilize the protective immunity of M protein without incurring the risks of molecular mimicry and autoimmune disease. One has used a conserved, noncrossreactive, C-repeat region of the M protein, found in the carboxy-terminal of the M protein proximal to the cell wall. Although this approach has the advantage of eliciting immunity to multiple serotypes, and although mucosal immunity has been demonstrated in animal models, these vaccines have not yet advanced to the stage of clinical trials. The second approach uses the type-specific regions of the M protein, found in the amino-terminal of the M protein distal to the cell wall. Investigators have systematically defined the epitopes within each M protein that elicit opsonic and protective antibodies and systematically excluded epitopes that have been found to evoke tissue crossreactive antibodies. Such a vaccine has been engineered using recombinant fusion proteins containing amino-terminal peptides linked in a tandem array to include multiple serotypes in a single vaccine construct. A prototype hexavalent vaccine\textsuperscript{[50]} as well as a 26-valent plus Spa M-protein-based recombinant vaccine\textsuperscript{[51]} have been evaluated in adults in phase I trials. Both vaccines were well tolerated, did not induce crossreactive antibodies, and stimulated vigorous immune responses with bactericidal activity. \textsuperscript{8} The 26-valent vaccine includes 80\% to 90\% of serotypes that caused invasive infections or pharyngitis, as demonstrated by recent surveillance in North America, and could have significant impact on the overall burden of GAS disease. However, vaccine type-specific coverage may be less complete for Asia and other developing areas of the world. In addition, emergence of new \textit{emm} types and the possibility that nonvaccine serotypes or genotypes of clinical importance may replace those contained in the vaccine are concerns.
Diphtheria is an acute toxic infection caused by Corynebacterium species, typically Corynebacterium diphtheriae and rarely toxigenic strains of Corynebacterium ulcerans. Although diphtheria was reduced from a major cause of childhood death to a medical rarity in the Western hemisphere in the early 20th century, current reminders of the fragility of this success emphasize the necessity to continue vigorous promotion of those same principles across the global community.

ETIOLOGY
Corynebacteria are aerobic, nonencapsulated, non–spore-forming, mostly nonmotile, pleomorphic, gram-positive bacilli. C. diphtheriae is by far the most commonly isolated agent of diphtheria. C. ulcerans is more commonly isolated from cattle and can cause similar disease. As corynebacteria are not fastidious in growth requirements, their isolation is enhanced by use of a selective medium (i.e., cystine-tellurite blood agar or Tinsdale agar) that inhibits growth of competing organisms and, when reduced by C. diphtheriae, renders colonies gray-black. Differentiation of C. diphtheriae from C. ulcerans is based on urease activity, because C. ulcerans is urease-positive.

Four C. diphtheriae biotypes (mitis, intermedius, belfanti, gravis) are capable of causing diphtheria and are differentiated by colonial morphology, hemolysis, and fermentation reactions. The ability to produce diphtheritic toxin results from acquisition of a lysogenic Corynebacteriophage by either C. diphtheriae or C. ulcerans, which encodes the diphtheritic toxin gene and confers diphtheria-producing potential on these strains. Thus, indigenous nontoxigenic C. diphtheriae can be rendered toxigenic and disease-producing after importation of a toxigenic C. diphtheriae and transmission of the bacteriophage. Demonstration of diphtheritic toxin production or potential for toxin production by an isolate is necessary to confirm disease. The former is done in vitro using the agar immunoprecipitin technique (Elek test) or in vivo with the toxin neutralization test in guinea pigs, the latter by polymerase chain reaction testing for carriage of the toxin gene. Toxigenic and nontoxigenic strains are indistinguishable by colony type, microscopic features, or biochemical test results.
**EPIDEMIOLOGY**

Unlike other diphtheroids (coryneform bacteria), which are ubiquitous in nature, *C. diphtheriae* is an exclusive inhabitant of human mucous membranes and skin. Spread is primarily by airborne respiratory droplets, direct contact with respiratory secretions of symptomatic individuals, or exudate from infected skin lesions. Asymptomatic respiratory tract carriage is important in transmission. Where diphtheria is endemic, 3-5% of healthy individuals can carry toxigenic organisms, but carriage is exceedingly rare if diphtheria is rare. Skin infection and skin carriage are silent reservoirs of *C. diphtheriae*, and organisms can remain viable in dust or on fomites for up to 6 mo. Transmission through contaminated milk and an infected food handler has been proven or suspected.

In the 1920s, >125,000 diphtheria cases, with 10,000 deaths, were reported annually in the USA, with the highest fatality rates among the very young and the elderly. The incidence then began to decrease and, with widespread use of diphtheria toxoid in the USA after World War II, declined steadily through the late 1970s. Since then, ≤5 cases have occurred annually in the USA, with no epidemics of respiratory tract diphtheria. Similar decreases occurred in Europe. Despite the worldwide decrease in disease incidence, diphtheria remains endemic in many developing countries with poor immunization rates against diphtheria.

When diphtheria was endemic, it primarily affected children <15 yr of age. Since the introduction of toxoid immunization, the disease has shifted to adults who lack natural exposure to toxigenic *C. diphtheriae* in the vaccine era and have low rates of booster immunization. In the 27 sporadic cases of respiratory tract diphtheria reported in the USA in the 1980s, 70% occurred among persons >25 yr of age. The largest outbreak of diphtheria in the developed world since the 1960s occurred from 1990 to 1996 in the newly independent countries of the former Soviet Union, involving >150,000 cases in 14 of 15 countries. Of these, >60% of cases occurred in individuals >14 yr of age. Case fatality rates ranged from 3% to 23% by country. Factors contributing to the epidemic included a large population of underimmunized adults, decreased childhood immunization rates, population migration, crowding, and failure to respond aggressively during early phases of the epidemic. Cases of diphtheria among travelers from these endemic areas were transported to many countries in Europe.

Most proven cases of respiratory tract diphtheria in the USA in the 1990s were associated with importation of toxigenic *C. diphtheriae*, although clonally related toxigenic *C. diphtheriae* has persisted in this country and Canada for at least 25 yr.

Cutaneous diphtheria, a curiosity when diphtheria was common, accounted for >50% of reported *C. diphtheriae* isolates in the USA by 1975. This indolent local infection, compared with mucosal infection, is associated with more prolonged bacterial shedding, greater contamination of the environment, and increased transmission to the pharynx and skin of close contacts. Outbreaks are associated with homelessness, crowding, poverty, alcoholism, poor hygiene, contaminated fomites, underlying dermatosis, and introduction of new strains from exogenous sources. It is no longer a tropical or subtropical disease; 1,100 *C. diphtheriae* infections were documented in a neighborhood in Seattle (site of the last major
The U.S. outbreak, from 1971 to 1982; 86% were cutaneous, and 40% involved toxigenic strains. Cutaneous diphtheria is an important source for toxigenic *C. diphtheriae* in the USA, and its importation is frequently the source for subsequent sporadic cases of respiratory tract diphtheria. To focus attention on respiratory tract diphtheria, the condition more likely to cause acute respiratory complications and toxic manifestations, *C. diphtheria* isolates from cutaneous disease were removed from annual diphtheria statistics reported by the Centers for Disease Control and Prevention (CDC) after 1979.

**PATHOGENESIS**

Both toxigenic and nontoxigenic *C. diphtheriae* cause skin and mucosal infection and can rarely cause focal infection after bacteremia. The organism usually remains in the superficial layers of skin lesions or respiratory tract mucosa, inducing local inflammatory reaction. The major virulence of the organism lies in its ability to produce the potent 62-kd polypeptide exotoxin, which inhibits protein synthesis and causes local tissue necrosis. Within the first few days of respiratory tract infection (usually in the pharynx), a dense necrotic coagulum of organisms, epithelial cells, fibrin, leukocytes, and erythrocytes forms, advances, and becomes a gray-brown, leather-like adherent pseudomembrane (*Diphthera* is Greek for leather). Removal is difficult and reveals a bleeding edematous submucosa. Paralysis of the palate and hypopharynx is an early local effect of diphtheritic toxin. Toxin absorption can lead to systemic manifestations: kidney tubule necrosis, thrombocytopenia, cardiomyopathy, and/or demyelination of nerves. Because the latter 2 complications can occur 2-10 wk after mucocutaneous infection, the pathophysiology in some cases is suspected to be immunologically mediated.

**CLINICAL MANIFESTATIONS**

The manifestations of *C. diphtheriae* infection are influenced by the anatomic site of infection, the immune status of the host, and the production and systemic distribution of toxin.

**Respiratory Tract Diphtheria**

In a classic description of 1,400 cases of diphtheria in California (1954), the primary focus of infection was the tonsils or pharynx (94%), with the nose and larynx the next 2 most common sites. After an average incubation period of 2-4 days, local signs and symptoms of inflammation develop. Infection of the anterior nares is more common among infants and causes serosanguineous, purulent, erosive rhinitis with membrane formation. Shallow ulceration of the external nares and upper lip is characteristic. In tonsillar and pharyngeal diphtheria, sore throat is the universal early symptom: Only half of patients have fever, and fewer have dysphagia, hoarseness, malaise, or headache. Mild pharyngeal infection is followed by unilateral or bilateral tonsillar membrane formation, which can extend to involve the uvula (which may cause toxin-mediated paralysis), soft palate, posterior oropharynx, hypopharynx, or glottic areas. Underlying soft tissue edema and enlarged lymph nodes can cause a bull-neck appearance. The degree of local extension correlates directly with profound prostration, bull-neck appearance, and fatality due to airway compromise or toxin-mediated complications.

The characteristic adherent membrane, extension beyond the faucial area, dysphagia,
and relative lack of fever help differentiate diphtheria from exudative pharyngitis caused by *Streptococcus pyogenes* or Epstein-Barr virus. Vincent angina, infective phlebitis with thrombosis of the jugular veins (Lemierre disease), and mucositis in patients undergoing cancer chemotherapy are usually differentiated by the clinical setting. Infection of the larynx, trachea, and bronchi can be primary or a secondary extension from the pharyngeal infection. Hoarseness, stridor, dyspnea, and croupy cough are clues. Differentiation from bacterial epiglottitis, severe viral laryngotracheobronchitis, and staphylococcal or streptococcal tracheitis hinges partially on the relative paucity of other signs and symptoms in patients with diphtheria and primarily on visualization of the adherent pseudomembrane at the time of laryngoscopy and intubation.

Patients with laryngeal diphtheria are at significant risk for suffocation because of local soft tissue edema and airway obstruction by the diphtheritic membrane, a dense cast of respiratory epithelium, and necrotic coagulum. Establishment of an artificial airway and resection of the pseudomembrane can be lifesaving, but further obstructive complications are common, and systemic toxic complications are inevitable.

**Cutaneous Diphtheria**

Classic cutaneous diphtheria is an indolent, nonprogressive infection characterized by a superficial, ecthymic, nonhealing ulcer with a gray-brown membrane. Diphtheritic skin infections cannot always be differentiated from streptococcal or staphylococcal impetigo, and these conditions frequently coexist. In most cases, a primary process such as dermatosis, laceration, burns, bite, or impetigo becomes secondarily infected with *C. diphtheriae*. Extremities are more often affected than the trunk or head. Pain, tenderness, erythema, and exudate are typical. Local hyperesthesia or hypesthesia is unusual. Respiratory tract colonization or symptomatic infection with toxic complications occurs in the minority of patients with cutaneous diphtheria. Among infected adults in the Seattle outbreak, 3% with cutaneous infections and 21% with symptomatic nasopharyngeal infection, with or without skin involvement, demonstrated toxic myocarditis, neuropathy, or obstructive respiratory tract complications. All had received at least 20,000 U of equine antitoxin at the time of hospitalization.

**Infection at Other Sites**

*C. diphtheriae* occasionally causes mucocutaneous infections at other sites, such as the ear (otitis externa), the eye (purulent and ulcerative conjunctivitis), and the genital tract (purulent and ulcerative vulvovaginitis). The clinical setting, ulceration, membrane formation, and submucosal bleeding help differentiate diphtheria from other bacterial and viral causes. Rare cases of septicemia are described and are universally fatal. Sporadic cases of endocarditis occur, and clusters among intravenous drug users have been reported in several countries; skin was the probable portal of entry, and almost all strains were nontoxigenic. Sporadic cases of pyogenic arthritis, mainly due to nontoxigenic strains, have been reported in adults and children. Diphtheroids isolated from sterile body sites should not be routinely dismissed as contaminants without careful consideration of the clinical setting.

**COMPLICATIONS**
Respiratory tract obstruction by pseudomembranes may require bronchoscopy or intubation and mechanical ventilation. Two other tissues usually remote from sites of C. diphtheriae infection can be significantly affected by diphtheritic toxin: the heart and the nervous system.

**Toxic Cardiomyopathy**

Toxic cardiomyopathy occurs in 10-25% of patients with respiratory diptheria and is responsible for 50-60% of deaths. Subtle signs of myocarditis can be detected in most patients, especially the elderly, but the risk for significant complications correlates directly with the extent and severity of exudative local oropharyngeal disease as well as delay in administration of antitoxin. The 1st evidence of cardiac toxicity characteristically occurs during the 2nd and 3rd weeks of illness as the pharyngeal disease improves but can appear acutely as early as the 1st wk of illness, a poor prognostic sign, or insidiously as late as the 6th wk. Tachycardia out of proportion to fever is common and may be evidence of cardiac toxicity or autonomic nervous system dysfunction. A prolonged PR interval and changes in the ST-T wave on an electrocardiographic tracing are relatively frequent findings; dilated and hypertrophic cardiomyopathy detected by echocardiogram has been described. Single or progressive cardiac dysrhythmias can occur, including 1st-, 2nd-, and 3rd-degree heart block. Temporary transvenous pacing may improve outcomes. Atrioventricular dissociation and ventricular tachycardia are also described, the latter having a high associated mortality. Heart failure may appear insidiously or acutely. Elevation of the serum aspartate aminotransferase concentration closely parallels the severity of myonecrosis. Severe dysrhythmia portends death. Histologic postmortem findings are variable: little or diffuse myonecrosis with acute inflammatory response. Recovery from toxic myocardopathy is usually complete, although survivors of more severe dysrhythmias can have permanent conduction defects.

**Toxic Neuropathy**

Neurologic complications parallel the severity of primary infection and are multiphasic in onset. Acutely or 2-3 wk after onset of oropharyngeal inflammation, it is common for hypesthesia and local paralysis of the soft palate to occur. Weakness of the posterior pharyngeal, laryngeal, and facial nerves may follow, causing a nasal quality in the voice, difficulty in swallowing, and risk for aspiration. Cranial neuropathies characteristically occur in the 5th wk, leading to oculomotor and ciliary paralysis, which can cause strabismus, blurred vision, or difficulty with accommodation. Symmetric polyneuropathy has its onset 10 days to 3 months after oropharyngeal infection and causes principally motor deficits with diminished deep tendon reflexes. Distal muscle weakness in the extremities with proximal progression is more commonly described than proximal muscle weakness with distal progression. Clinical and cerebrospinal fluid findings in the former are indistinguishable from those of Guillain-Barré syndrome. Paralysis of the diaphragm may ensue. Complete neurologic recovery is likely, but rarely, 2-3 wk after onset of illness, vasomotor center dysfunction can cause hypotension or cardiac failure.

Recovery from the myocarditis and neuritis is often slow but usually complete. Corticosteroids do not diminish these complications and are not recommended.
**DIAGNOSIS**

Specimens for culture should be obtained from the nose and throat and any other mucocutaneous lesion. A portion of membrane should be removed and submitted for culture along with underlying exudate. The laboratory must be notified to use selective medium. *C. diphtheriae* survives drying. If obtained in a remote area, a swab specimen can be placed in a silica gel pack and sent to the laboratory. Evaluation of a direct smear using Gram stain or specific fluorescent antibody is unreliable. Culture isolates of coryneform organisms should be identified to the species level, and toxigenicity and antimicrobial susceptibility tests should be performed for *C. diphtheriae* isolates.

**PROGNOSIS**

The prognosis for patients with diphtheria depends on the virulence of the organism (subspecies gravis has the highest fatality rate), patient age, immunization status, site of infection, and speed of administration of the antitoxin. Mechanical obstruction from laryngeal diphtheria or bull-neck diphtheria and the complications of myocarditis account for most diphtheria-related deaths. The case fatality rate of almost 10% for respiratory tract diphtheria has not changed in 50 yr; the rate was 8% in a Vietnamese series described in 2004. At recovery, administration of diphtheria toxoid is indicated to complete the primary series or booster doses of immunization, because not all patients develop antibodies to diphtheritic toxin after infection.

**TREATMENT**

Specific antitoxin neutralizes free toxin only; therefore, if the clinical findings and epidemiology support the diagnosis, antitoxin should be administered before cultural confirmation. Mortality is less than 1% if antitoxin is administered on the first day of disease and increases 20-fold if treatment is delayed until the fourth day. Antitoxin of human origin is available in some countries. Antitoxin is administered once at an empiric dosage based on the degree of toxicity, site and size of the membrane, and duration of illness (Table 1). The intravenous route is preferred with infusion over 30 to 60 minutes. Antitoxin is probably of no value for local manifestations of cutaneous diphtheria, but is recommended because toxic sequelae can occur. Approximately 8% of patients given equine antitoxins develop serum sickness. Up to 10% of individuals have pre-existing hypersensitivity to horse protein. Even very sick patients must be tested before infusion, with desensitization by protocol performed in those showing immediate reactions. For those with negative tests, a preliminary intravenous dose of 0.5 mL of antitoxin diluted in 10 mL possible with 30 minutes of observation; the remainder is then diluted 1:20 and given at a rate not to exceed 1 mL/min.24 Commercially available immune globulin preparations for intravenous use contain antibodies to diphtheria toxin, but the amounts likely vary from lot to lot. Their use for therapy of diphtheria is not proved or recommended. Antitoxin is not recommended for asymptomatic carriers.
### Table 1 Administration of Antitoxin for Treatment of Diphtheria

<table>
<thead>
<tr>
<th>Condition</th>
<th>Range of Antitoxin Dosage (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous lesions only</td>
<td>20,000–40,000</td>
</tr>
<tr>
<td>Pharyngeal/laryngeal disease of ≤ 48 hours duration</td>
<td>20,000–40,000</td>
</tr>
<tr>
<td>Nasopharyngeal lesions</td>
<td>40,000–60,000</td>
</tr>
<tr>
<td>Extensive disease of ≥ 72 hours duration</td>
<td>80,000–100,000</td>
</tr>
<tr>
<td>Diffuse swelling of the neck</td>
<td>80,000–100,000</td>
</tr>
</tbody>
</table>

The role of antimicrobial therapy is to halt toxin production, treat localized infection, and prevent transmission of the organism to contacts. C. diphtheriae is usually susceptible to various agents in vitro, including penicillins, erythromycin, clindamycin, rifampin, and tetracycline. Resistance to erythromycin is common in populations if the drug has been used broadly. Only erythromycin or penicillin is recommended; erythromycin is marginally superior to penicillin for eradication of nasopharyngeal carriage. Appropriate therapy is erythromycin (40–50 mg/kg/day divided every 6 hr by mouth [PO] or intravenously [IV]; maximum 2 g/day), aqueous crystalline penicillin G (100,000-150,000 U/kg/day divided every 6 hr IV or intramuscularly [IM]), or procaine penicillin (25,000-50,000 U/kg/day divided every 12 hr IM) for 14 days. Antibiotic therapy is not a substitute for antitoxin therapy. Some patients with cutaneous diphtheria have been treated for 7-10 days. Elimination of the organism should be documented by negative results of at least 2 successive cultures of specimens from the nose and throat (or skin) obtained 24 hr apart after completion of therapy. Treatment with erythromycin is repeated if either culture yields C. diphtheriae.

### Other Measures

Strict isolation is recommended for patients with pharyngeal diphtheria; contact isolation is sufficient for patients with cutaneous diphtheria. Isolation is continued until at least two cultures from the nose and throat (and skin lesions, if present) taken after cessation of therapy, are negative. Cutaneous wounds should be thoroughly cleansed with soap and water. Bedrest is recommended during the acute phase of disease. Return to physical activity should be guided by degree of toxicity and cardiac involvement. Complications of airway obstruction and aspiration should be anticipated with careful observation of oropharyngeal and laryngeal diphtheria, and an artificial airway should be established pre-emptively. Congestive heart failure and malnutrition should be anticipated and prevented when possible.

Corticosteroid therapy is not recommended. In a study of 66 children with respiratory tract diphtheria alternately treated with prednisone or no steroid therapy for 14 days from the time of diagnosis, toxic myocarditis occurred in 26%, neuritis in 17%, and bullneck diphtheria in 10%, with no difference in occurrence or death in those who received steroids.22 Use of digitalis for treatment of myocarditis is
associated with excess occurrence of arrhythmia.

**Exposed Persons**

Public health officials should be notified promptly when a diagnosis of diphtheria is suspected or proved. Investigation is aimed at preventing secondary cases in exposed individuals and at determining the source case and carriers to halt spread to unexposed individuals. Reported rates of carriage in household contacts of case-patients have ranged from 0% to 25%. The risk of developing diphtheria after household exposure to a case is approximately 2%; it is 0.3% after similar exposure to a carrier.

**Asymptomatic Case Contacts**

Prompt identification and investigation of close contacts (defined as all household contacts and those who have had intimate respiratory or habitual physical contact with the patient) are the highest priorities. The following steps should be taken in these individuals:

1. Monitor closely for illness through the 7-day incubation period.
2. Perform cultures of the nose, throat, and any cutaneous lesion.
3. Give antimicrobial prophylaxis, regardless of immunization status, with oral erythromycin (40 to 50 mg/kg per day for 7 to 10 days, maximum 2 g/day). If the individual is intolerant to erythromycin or if complete compliance is not assured, intramuscular benzathine penicillin should be administered (600,000 U for those < 30 kg or 1,200,000 U for those 30 kg). The efficacy of antimicrobial prophylaxis is presumed but not proved and the efficacy of newer macrolides, such as clarithromycin and azithromycin, has not been evaluated for their ability to eliminate carriage of *C. diphtheriae*.
4. Give diphtheria toxoid vaccine doses or other suitable combination vaccine (e.g., adult diphtheria and tetanus (DT); childhood diphtheria, tetanus toxoids, and whole cell pertussis (DTP); adult or childhood diphtheria and tetanus toxoids, and acellular pertussis (Tdap) vaccines; or adult tetanus and diphtheria toxoid (Td)), appropriate for age, to immunized individuals who have not received a booster dose within 5 years. Some experts suggest that the duration of protective antibody is variable and recommend a booster be given to close contacts if 1 year has elapsed since immunization. Tdap adolescent and adult vaccines have not been evaluated in control of outbreaks, but should be reliable based on the immune responses to these vaccines which produce high antibody levels when given to subjects who have received a primary series of DTaP. Children who have not received their fourth or fifth dose of DTaP should be vaccinated. Those who have received fewer than three doses of diphtheria toxoid or for whom knowledge of immunization status is lacking are immunized with an age-appropriate preparation on a primary schedule.

**Asymptomatic Carriers**

When an asymptomatic carrier is identified, the following steps should be taken:

1. Give antimicrobial prophylaxis for 7 to 10 days.
2. Give age-appropriate preparation of diphtheria toxoid immediately if the individual has not received a booster within 1 year.
3. Place individuals in strict isolation (respiratory tract colonization) or contact isolation (cutaneous colonization only) until at least two subsequent cultures taken at least 24 hours apart after cessation of therapy are negative for *C. diphtheriae*. 
4. Perform repeat cultures at a minimum of 2 weeks after completion of therapy in cases and carriers, and, if cultures are positive, an additional 10-day course of oral erythromycin should be given and follow-up cultures performed.

Neither antimicrobial agent eradicates carriage in 100% of individuals. In one report, 28 eradication failed in 21% of carriers after a single course of therapy. Antitoxin is not recommended for close contacts or asymptomatic carriers even if they are inadequately immunized because of the adverse effects of horse serum and no demonstrable evidence of benefit above antimicrobial prophylaxis. Booster immunization elicits rapid rise in antitoxin levels. Transmission of diphtheria in modern hospitals is rare. Meticulous handwashing and handling of secretions are mandatory. Only those who have had unusual contact with respiratory or oral secretions should be managed as contacts. Investigation of casual contacts of patients and carriers, or persons in the community without known exposure, has generally yielded extremely low carriage rates and is not routinely recommended.

PREVENTION

Universal immunization with vaccines containing diphtheria toxoid to provide constant protective antitoxin levels and to reduce indigenous C. diphtheriae is the only effective control measure. This requires multiple injections in childhood and adulthood. Serum antitoxin levels, measured by toxin neutralization tests in Vero cell culture or rabbit skin or measured by hemagglutination, are roughly equivalent. Concentration of 0.01 to 0.1 IU/mL is conventionally accepted as the minimum protective level although the protective limit of antibody has not been precisely defined. In outbreaks, 90% of individuals with clinical disease have had antitoxin levels < 0.01 IU/mL and 92% of asymptomatic carriers have had titers > 0.1 IU/mL.

Vaccine Preparations

Diphtheria toxoid is prepared by formaldehyde treatment of toxin and is standardized for potency according to the United States Food and Drug Administration. Toxoid is adsorbed to aluminum salts, which enhances immunogenicity. Two preparations of diphtheria toxoids are formulated according to limit of flocculation (Lf) content, a measure of quantity of toxoid. Pediatric preparations (DTP, DT, DTaP) contain ≥ 6.7 Lf units of diphtheria toxoid/0.5-mL dose whereas adult preparations of combination vaccines of diphtheria–tetanus (dT) or tetanus–diphtheria–acellular pertussis (Tdap) contains no more than 2 Lf units of toxoid/0.5-mL dose. The higher potency (D) formulation of toxoid is used for the primary series and booster doses for children through 6 years of age because of superior immunogenicity and minimal reactogenicity. For individuals 7 years of age and older, Td or Tdap is recommended for primary series and booster doses because the lower concentration of diphtheria toxoid is adequately immunogenic and because increasing content of diphtheria toxoid heightens reactogenicity with increasing age.

Schedules

Children from 6 Weeks to 7th Birthday

Five 0.5-mL doses of diphtheria-containing (D) vaccine should be given. The adult preparations (d) should not be used in children younger than 7 years because of reduced immunogenicity. The primary series includes
doses at approximately 2, 4, and 6 months of age. The fourth dose is an integral part of the primary series and is given approximately 6 to 12 months after the third dose to maintain adequate immunity during preschool years. A booster dose is given at 4 to 6 years (unless the fourth primary dose was administered after the fourth birthday).

**Persons 7 Years of Age or Older**

Three 0.5-mL doses of diphtheria containing (dT or Tdap) vaccine are recommended as a primary series; this primary series includes 2 doses 4 to 8 weeks apart and a third dose 6 to 12 months after the second dose. The only contraindication to diphtheria toxoid is a history of neurologic or severe hypersensitivity reaction after a previous dose.

Children in Whom Pertussis Immunization is Contraindicated D or d toxoids (DT or Td) are used as follows: those who began with either diphtheria–tetanus–pertussis or DT at age < 1 year should have a total of 5 0.5-mL doses of D-containing vaccine by 6 years. For those beginning at or after 1 year of age, the primary series is 2 0.5-mL doses of D vaccine, with a third dose 6 to 12 months later, and a booster given at 4 to 6 years unless the third dose was given after the fourth birthday. Further

life. Booster doses of 0.5 mL Td should be given every 10 years (most conveniently given to most persons at 15 years, 25 years, 35 years of age, and so forth). It is likely, that Tdap will reduce in the number of cases of diphtheria in industrialized countries will require universal booster immunization throughout replace Td for routine administration at 10-year intervals. Vaccination with diphtheria toxoid should be used whenever tetanus toxoid is indicated to ensure continuing diphtheria immunity. There is no known association of DT or Td with increased risk of convulsions. Local side effects alone do not preclude continued use. Persons who experience Arthus-type hypersensitivity reactions or a temperature > 39.4°C (103°F) after a dose of Td usually have high serum tetanus antitoxin levels and should not be given Td more frequently than every 10 years, even if significant tetanus-prone injury is sustained. DT preparations or Td can be given concurrently with other vaccines. Haemophilus influenzae conjugate vaccines containing diphtheria toxoid (PRP-D) or the variant of diphtheria toxin, CRM197 protein (HbOC), are not substitutes for diphtheria toxoid immunization.
What does the infectious disease specialist mean by parasitic infection?

Most infectious agents fulfill the definition of a parasite: an organism that grows, feeds, and shelters on or in a different organism and contributes nothing to the host. However, medical science has created the classification “parasite” to include a complex group of nonfungal eukaryotic human pathogens. Unlike fungi, parasites have no cell wall and are often motile. In addition, many parasites require two or more host species to complete their life cycle, and they reproduce both sexually and asexually. The host in which sexual reproduction takes place is called the “definitive host,” and the one in which asexual reproduction occurs is called the “intermediate host.”

Previously, parasitic infections were almost exclusively a health problem in developing countries with poor sanitation. However, with the current marked rise in international travel and increased military deployments to endemic areas, these infections are now increasingly being diagnosed in the United States, Europe, and other developed countries. The incidence of symptomatic parasitic infections has also increased because of the ever-increasing population of immunocompromised hosts. Organ transplant, cancer chemotherapy, and infection with HIV all lead to depressed cell-mediated and humoral immunity, allowing dormant parasites to reactivate and cause disease. More than ever before, thorough travel and exposure histories are critical steps in accurately diagnosing parasitic infections. An awareness of geography and environmental conditions and a familiarity with the life cycles of various parasites are all required for proper diagnosis and treatment.

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**GUIDING QUESTIONS**

1. **What is meant by a parasitic infection?**
2. **Why are parasitic infections increasing in incidence in the United States and Europe?**
3. **What patient population is particularly at risk for severe and life-threatening parasitic infections?**

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**BLOODPROTOZOA**

**POTENTIAL SEVERITY**

*Hours can make the difference between life and death. Rapid diagnosis and treatment are critical.*

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**MALARIA**

**GUIDING QUESTIONS**

1. **Which form of malaria is the most dangerous, and why?**
2. **Which disease does malaria most commonly mimic?**
3. **How is malaria diagnosed? Is there a particular time in the course of illness when diagnostic studies should be performed?**
4. **Why are many African Americans more resistant to some forms of malaria?**
5. **What are the current recommendations for malaria treatment, and what are the factors that dictate the regimen of choice?**
6. **When should chemoprophylaxis be begun, and how long after completion of a trip to an endemic area should preventive therapy be continued?**
Prevalence

The combination of deteriorating political and economic conditions in the countries of sub-Saharan Africa and the development of chloroquine drug resistance in many parts of the world have resulted in a resurgence of malaria. Climate change and the increased resistance of mosquitoes to insecticides have also contributed to this trend. The worldwide annual incidence of malaria is between 300 and 500 million cases, causing between 1 and 2 million deaths. Areas with significant numbers of malaria cases include Africa, the Middle East, India, Southeast Asia, South America, Central America, and parts of the Caribbean.

Chloroquine resistance is now the rule in most countries. Plasmodium falciparum in Southeast Asia is frequently resistant not only to chloroquine, but also to pyrimethamine–sulfadoxine, mefloquine, and halofantrine. Areas in which P. falciparum remains sensitive to chloroquine include Central America and the Caribbean, in particular Haiti. In the United States, secondary cases have been reported around airports, and an outbreak of P. vivax was recently described in Palm Beach, Florida. Because the sensitivity patterns of malaria continue to change annually, the Centers for Disease Control and Prevention (CDC) should be consulted for the most up-to-date information (Web address: www.cdc.gov/travel).

Epidemiology and Life Cycle

Humans contract malaria after being bitten by the anopheline female mosquito. Only the female mosquito takes a blood meal, because blood is required for the development of the mosquito egg. Certain strains appear to be more efficient transmitters of disease. In particular Anopheles gambiae and A. funestus are thought to account for the high transmission rates in sub-Saharan Africa. These strains are not present in South America and Southeast Asia where transmission rates are lower. Clearly the larger the number of mosquito bites a person receives, the greater the risk of contracting malaria. Therefore, in addition to chemoprophylaxis (discussed later in this subsection), mosquito netting, long-sleeved shirts, long pants, insect repellent, and staying in a protected environment during the times of the day when mosquitoes are at their most active are all recommended as preventive measures.

The sporozoites introduced into the human bloodstream by the female anopheline mosquito quickly travel to the liver and invade hepatocytes (Figure 12.1). Sporozoites contain a specific protein thought to be critical for binding and entry into hepatocytes. This circumsporozoite protein binds to specific host-cell membrane receptors (heparin sulfate proteoglycans and low-density lipoprotein receptor–related protein). Within the hepatocytes, most sporozoites mature to tissue schizonts. Some sporozoites become dormant. This dormant form, called a hypnozoite takes 6 to 11 months to activate into a tissue schizont. Each schizont-infected hepatocyte then produces 10,000 to 30,000 merozoites that are released into the bloodstream following cell lysis. Each merozoite can invade a single red blood cell and asexually replicate five times over 48 to 72 hours to produce 32 merozoites. The red blood cell then undergoes lysis, releasing the newly formed merozoites, which can infect additional red blood cells.

Under ideal conditions, a single sporozoite could theoretically account for the infection of nearly 1 million red blood cells (many of the free merozoites are intercepted by host macrophages, thus reducing the efficiency of red cell infection). As observed with sporozoite entry into hepatocytes, a specific protein on the merozoite surface (erythrocyte-binding antigen 175 in P. falciparum and Pv135 in P. vivax) binds to a specific red blood cell membrane receptor (glycophorin A in P. falciparum and Duffy factor in P. vivax) allowing attachment and entry. Once the merozoite enters the red blood cell, it matures to a trophozoite. This form looks like a signet ring and can readily be seen in parasitized red blood cells following Giemsa or
**KEY POINTS**

**About the Lifecycle of Plasmodium falciparum**

*P. falciparum* is the most dangerous form of malaria because it

1. infects red blood cells (RBCs) of all ages and causes high levels of parasitemia.
2. induces the formation of knobs on the RBC surface that adhere to vessel walls and to uninfected RBCs, causing obstruction and local hypoxia.
3. can cause severe hemolysis, renal failure, central nervous system damage, and pulmonary edema.

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Wright staining (Figure 12.2). As the trophozoite matures, it loses its signet ring morphology, becoming larger and subsequently developing into a red blood cell schizont, which then splits into multiple merozoites.

Upon entry into the red blood cell, some merozoites mature into sexual forms called gametocytes rather than into asexual forms. The male form is smaller and is called a microgametocyte; the larger female form is called a macrogametocyte. Because sexual mating does not occur in the human host, but only in the mosquito, the mosquito is considered the definitive host, and humans are considered the intermediate host.

Once fertilization occurs, a zygote is formed that subsequently develops into an oocyst. The oocyst then forms thousands of infectious sporozoites that gain entry into the mosquito salivary gland, where they are transmitted to the human host.

**Life cycle Differences Between the Various Plasmodium Species**

*P. falciparum* is the most common, and most dangerous, form of malaria. Unlike the sporozoites of other strains, all falciparum sporozoites that enter the liver remain active and develop into tissue schizonts that proceed to form thousands of merozoites. And unlike the merozoites of other strains, *P. falciparum* merozoites can infect red blood cells of all ages, explaining the high level of parasitized red blood cells observed in falciparum malaria. Moreover, in the non-falciparum forms of malaria only a single merozoite gains entry into a given red cell; in falciparum malaria, multiple merozoites can infect and mature within a single red blood cell.

Once a merozoite has invaded a red blood cell, it rapidly matures, asexually divides, and within 48 hours, lyges the host cell. This rapid asexual reproduction produces a rapid rise in the percentage of infected host red blood cells, and as the percentage of parasitized red blood cells increases, the risk of death or serious complications also increases.

*P. falciparum* is more harmful to the host because invasion by this strain is uniquely associated with the formation of red blood cell membrane knobs that tightly adhere to the vascular endothelium. These knobs express erythrocyte membrane protein 1 on their surface, and this protein binds complement receptor 1 (CR-1) on uninfected red cells, causing red cell clumping ("rosetting"). These adherent red blood cells block blood flow in small blood vessels, causing severe hypoxic damage, particularly to the brain and kidneys. Because red blood cell adherence develops as the merozoite matures beyond the early trophozoite stage, other maturation stages of the parasite (with the exception of the banana-shaped gametocytes) are rarely seen in the peripheral blood (see Table 12.1 and Figure 12.2).

*P. vivax* is the next most common form of malaria. *P. malariae* is less common, and *P. ovale* is a rare human infection. When a female anopheline mosquito bites an infected human, gametocytes are taken in with the blood. *P. vivax* and *P. ovale* can form hypnozoites that can remain dormant within the liver for months before becoming active tissue schizonts. This behavior explains the ability of these strains to relapse 6 to 11 months after initial treatment. *P. malariae* has no dormant liver phase, but can persist as a low-level infection for up to 30 years. *P. vivax* and *P. ovale* merozoites bind only young red blood cells, having the highest affinity for reticulocytes. *P. malariae* tends to

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**Figure 12–2.** Typical blood smear findings for various forms of malaria. (Adapted from Schaechter M, Engleberg NC, Eisenstein BI, Medoff G, editors. *Mechanisms of Microbial Disease.* 3rd edition. Baltimore, Md.: Lippincott Williams and Wilkins; 1999)
infect older red blood cells. The inability of these strains to infect a broad age range of red blood cells explains their low level of parasitemia. Furthermore, these three strains do not form knobs and do not obstruct the microcirculation, explaining their milder clinical manifestations.

In Malaysia, *P. knowlesi*, a form of malaria formerly thought to infect only monkeys, has been identified in humans. Its trophozoite stage is similar in morphology to that of *P. falciparum*, and its schizont stage is similar to that of *P. malariae*. The level of parasitism can be high, resulting in serious infections. *P. knowlesi* should be considered in individuals traveling to forested tropical regions where monkeys are known to be infected.

### Genetic and Other Determinants of Susceptibility to Malaria

In areas in which malaria is endemic, the high prevalence of genetic traits that reduce susceptibility to malaria serves as remarkable examples of Darwinian evolution. Specific mutations that affect the surface proteins, cytoskeleton, and hemoglobin of red blood cells all interfere with *Plasmodium* invasion, survival, and spread, and thereby provide a survival advantage to the infected host. Absence of the Duffy blood group antigen blocks invasion by *P. vivax*. This strain of malaria must bind to this particular blood group antigen to gain entry into red blood cells. A significant number of black Africans are Duffy-negative and are resistant to *P. vivax*. Individuals with mutations in CR-1 demonstrate reduced rosetting in association with *P. falciparum* and have a decreased propensity to produce cerebral malaria. Individuals with hereditary ovalocytosis, elliptocytosis, and spheroctytosis all have defects in specific red blood cell cytoskeleton proteins, and these defects interfere with entry and release of the malaria parasite.

A broad range of hemoglobinopathies are protective against malaria. The high prevalence of sickle cell disease and sickle cell trait in Africa illustrates the frighteningly efficient selective powers of the deadly *P. falciparum* parasite. Parasite growth is slowed in cells with sickle cell hemoglobin (Hb S). In addition, when parasitized red blood cells that contain Hb S form membrane knobs and become trapped in small vessels, oxygen tension decreases, and the Hb S polymerizes, resulting in sickling of red blood cells. The polymerization of Hb S kills the *P. falciparum* parasite, preventing the infection from progressing. As a consequence, people with sickle cell trait and sickle cell disease are resistant to severe *P. falciparum* infection. Because the other strains of malaria do not form knobs and do not become trapped in blood vessels, Hb S does not protect against *P. vivax*, *P. ovale*, or *P. malariae*. A number of other hemoglobinopathies including Hb C, Hb E, β-thalassemia, and to a lesser extent, α-thalassemia reduce the severity of *P. falciparum*, accounting for their increased prevalence in endemic areas. Neonates are protected from severe malaria as a consequence of fetal hemoglobin, which interferes with the intracellular growth of *P. falciparum*.

In areas that have a high incidence of malaria, the indigenous population is continually exposed the parasite, resulting in a high level of immunity. In these regions, severe disease is rare. However, because the immune response to malaria is short-lived, immunity wanes in regions in which malaria has been controlled and the attack rate is low. Paradoxically, the percentage of patients developing severe disease increases in these regions.
KEY POINTS
About Genetics and Other Factors that Affect Susceptibility to Malaria

1. Surface proteins on red blood cells:
   a) Individuals negative for the Duffy blood group antigen are resistant to *Plasmodium vivax*.
   b) Complement receptor 1 mutations reduce the severity of *P. falciparum* infection.

2. Cytoskeleton defects in red blood cells are protective:
   a) Hereditary ovalocytosis
   b) Hereditary elliptocytosis
   c) Hereditary spherocytosis

3. Hemoglobinopathies confer resistance:
   a) Sickle cell disease and sickle cell trait are resistant to *P. falciparum*.
   b) Other hemoglobin mutations and fetal hemoglobin are also resistant to *P. falciparum*.

4. Low-level immunity increases the risk for severe disease:
   a) Population immunity wanes in areas with low attack rates.
   b) Tourists lack immunity.
   c) In pregnant women, the placenta is affected, resulting in low birth weight infants.

Tourists with no previous exposure to malaria are at highest risk for life-threatening disease (see case 10.1). Pregnant women and their fetuses are also at risk. *P. falciparum* binds to chondroitin sulfate A in the intervillous space of the placenta, causing hemolytic anemia, which leads to low birth weight infants.

As described in case 12.1, the clinical manifestations of malaria are nonspecific. If the exposure history is not appreciated, the infection can be mistaken for other febrile illnesses. The incubation period is generally 9 to 40 days, but it may be prolonged in cases of non-*falciparum* malaria (6 to 12 months in *P. vivax*, and years for *P. malariae* and *P. ovale*).

The hallmark of all forms of malaria is fever. Fever can occur at regular 2 to 3-day intervals in *P. vivax* and *P. malariae*, or in a more irregular pattern with *P. falciparum*. Fever generally occurs soon after lysis of the red blood cells and release of the merozoites. Three classic stages of the febrile paroxysms have been described:

1. The initial “cold stage” occurs 15 to 60 minutes before the onset of fever. During this period, the patient feels cold and has shaking chills.

2. These symptoms are followed by the “hot stage,” during which body temperature rises to between 39°C and 41°C. Fever is associated with lassitude, loss of appetite, and vague pains in the bones and joints. In nonendemic areas, these symptoms are most commonly mistaken for influenza. The clinician must always consider malaria in individuals who develop flu-like symptoms after returning from a developing country. Other symptoms associated with the fever include tachycardia, hypotension, cough, headache, back pain, nausea, abdominal pain, vomiting, diarrhea, and altered consciousness.

3. Usually within 2 to 6 hours, symptoms progress to the third “sweating” stage, at which time the patient develops marked diaphoresis, followed by resolution of the fever, profound fatigue, and a desire to sleep.
Other symptoms depend on the strain of malaria. In cases of *P. vivax*, *P. ovale*, and *P. malariae*, there are a few additional symptoms. However, depending on the prior immune status of the host, individuals with *P. falciparum* can develop a severe fatal illness similar to that described in case 12.1. Because *P. falciparum* infects red blood cells of all ages and induces the formation of knobs on the red blood cell surface that adhere to endothelial cells and obstruct small vessels, this parasite can cause severe damage, particularly to the kidneys, brain, and lungs. Tourists who have no immunity to *P. falciparum* and people who have undergone splenectomy can develop very high levels of parasitemia that result in profound hemolysis. The marked release of hemoglobin can exceed the metabolic capacity of the liver. The resulting rise in unconjugated bilirubin in the bloodstream produces jaundice. Hemoglobin also may be excreted into the urine, causing the urine to become dark. The combination of jaundice and hemoglobinuria has been called blackwater fever.

Severe malaria is commonly complicated by renal failure. Heavy infection with *P. falciparum* also results in obstruction of the small arteries in the central nervous system (CNS), leading to hypoxia. Hypoglycemia may also contribute to CNS dysfunction. Confusion and obtundation can rapidly progress to coma. Grand mal seizures may also develop. Pulmonary edema is a less common complication of *P. falciparum* infection, being the result of fluid leakage from pulmonary capillaries into the alveoli.

### Diagnosis

Microscopic examination of a Giemsa-stained blood smear remains the primary way to identify malaria. In *P. falciparum*, blood smears are best taken just after the fever peak, when early ring forms are most abundant in peripheral red blood cells. At other times, *P. falciparum* becomes trapped in the capillaries and may not be found in the peripheral blood. In *P. vivax*, *P. malariae*, and *P. ovale*, various stages of the parasite are present at all times, and therefore diagnostic smears can be taken at any time. Because parasites can be absent between attacks, the blood must be examined on 3 to 4 successive days before malaria can be ruled out. Presence of pigment in peripheral monocytes or neutrophils should encourage a continued search for parasites. Thin smears need to be examined for at least 15 minutes using a high-power oil objective microscope (1000× magnification). Thick smears are the most reliable method for detecting malaria. A 5-minute search will generally yield the diagnosis.

<table>
<thead>
<tr>
<th>KEY POINTS</th>
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<tbody>
<tr>
<td><strong>About Laboratory Diagnosis of Malaria</strong></td>
</tr>
<tr>
<td>1. The focus must be on differentiating falciparum malaria from other forms of the disease.</td>
</tr>
<tr>
<td>2. Blood smear remains the preferred method, but enzyme-linked immunoabsorbent assay and polymerase chain reaction methods are now available.</td>
</tr>
<tr>
<td>3. In falciparum malaria, signet-ring forms are most abundant on peripheral smear immediately after a fever spike.</td>
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</tbody>
</table>

The clinician’s primary goal is to differentiate potentially fatal *P. falciparum* from other, more benign forms of malaria (see Table 12.1). For this purpose, three new assays have been developed: an enzyme-linked immunoabsorbent assay (ELISA) for histidine-rich *P. falciparum* antigen, an immunoassay for species-specific parasite lactic dehydrogenase isoenzymes, and polymerase chain reaction (PCR) amplification of parasite DNA or mRNA.

Anemia, elevated levels of lactic dehydrogenase, and increased reticulocytes are associated with red blood cell hemolysis. An elevated unconjugated bilirubin level without a significant increase in hepatic enzymes is also observed when hemolysis is severe. A reduced white blood cell (WBC) count is noted in a high percentage of patients, and thrombocytopenia is common. Elevated serum creatinine, proteinuria, and hemoglobinuria are found in severe cases of *P. falciparum*. Hypoglycemia may also complicate severe cases of *P. falciparum*, requiring close monitoring of blood sugars during the acute illness.

### Prophylaxis and Treatment

Drug treatment exploits unique targets in the parasite not found in host cells. The aminoquinolones,
chloroquine, quinine, mefloquine, primaquine, and halofantrine inhibit proteolysis of hemoglobin in the food vacuole and inhibit the heme polymerase that Plasmodium requires for production of malaria pigment. Inhibition of these functions kills the organism. Pyrimethamine, sulfonamides, and dapsone are folate antagonists (see Chapter 1). Atovaquone inhibits parasite mitochondrial transport. Artemisinin derivatives bind iron in the malarial pigment to produce free radicals that damage parasite proteins. These derivatives are faster-acting than quinine, and they have activity against all stages of the intraerythrocytic life cycle.

In recent years, many areas of Africa, northern South America, India, and Southeast Asia have become populated with chloroquine-resistant *P. falciparum*. These strains contain an energy-dependent chloroquine efflux mechanism that prevents the drug from concentrating in the parasite. Resistance to mefloquine and halofantrine has also developed, being seen primarily in Southeast Asia.

Chemoprophylaxis should start 2 weeks before departure to an endemic area and continue until 4 weeks after return. Because of the continual changes in resistance patterns, up-to-date prophylactic and treatment regimens should be reviewed at the CDC’s Web site (www.cdc.gov/travel). For areas with chloroquine-susceptible *P. falciparum*, chloroquine is the drug of choice. The adult dosage is 300 mg base (500 mg of chloroquine phosphate) orally per week. In areas of chloroquine-resistance, mefloquine 250 mg (228 mg base) orally per week, or doxycycline 100 mg orally per day, or primaquine 0.5 mg/kg base per day, or atovaquone 250 mg combined with proguanil 100 mg orally per day (in a combination tablet called Malarone), or chloroquine at the formerly mentioned dose combined with proguanil 200 mg per day.

A vaccine is not available, and the immune response required to protect the host against malaria is poorly understood, making development of an effective vaccine a formidable task.

All individuals without previous immunity who contract falciparum malaria should be hospitalized, because their clinical course can be unpredictable. Patients with the *P. vivax*, *P. ovale*, and *P. malariae* strains can usually be treated as outpatients if follow-up will be reliable. The treatment for these three strains and for chloroquine-susceptible *P. falciparum* is the same: an initial dose of oral chloroquine 600 mg base (1000 mg chloroquine phosphate), followed 6 hours later by 300 mg base (500 mg phosphate), repeated on days 2 and 3. To prevent relapse of *P. vivax* or *P. ovale*, these infections also require treatment with oral primaquine 15.3 mg phosphate base (26.5 mg phosphate salt) daily for 14 days, or 45 mg base (79 mg salt) weekly for 8 weeks. This agent kills dormant hepatic hypnozoites, preventing their subsequent development into infective schizonts. Before the primaquine is administered, the patient should be tested for glucose-6-phosphate dehydrogenase deficiency, because patients with this deficiency are at risk of severe hemolysis during primaquine treatment.

Given the worldwide prevalence of chloroquine resistance, unless absolute assurance can be obtained that travel was only in regions with chloroquine-sensitive *P. falciparum*, patients should be presumed to have a resistant strain. Treatment of chloroquine-resistant *P. falciparum* is evolving and has become complex. Although artemisinin derivatives are not currently available in the United States, they have shown superior efficacy for severe chloroquine-resistant *P. falciparum* infection. They also reduce gametocyte carriage. Their use therefore decreases infectivity after treatment, and they can eliminate malaria transmission in endemic areas. These agents are short-acting, and they should be combined with one or more other classes of antimalarial agents. Dihydroartemisinin (6.3 mg/kg daily) combined with piperaquine (50 mg/kg daily) has produced superior response rates; however, trials of various combinations are ongoing. Monotherapy is discouraged because of the rapid development of resistance. Artemisinin manufacturing quality is not currently reliable, and these agents are therefore not recommended as standard therapy.

In the United States, quinine 650 mg every 8 hours for 3–7 days, plus doxycycline 100 mg twice daily for 7 days remains the recommended regimen. Atovaquone–proguanil (250 mg/100 mg tablets) four times daily for 3 days is equally efficacious. A single high dose of mefloquine (1250 mg) alone has been recommended as alternative therapy; however, this treatment frequently causes intolerable side effects, including vertigo (10% to 20%), gastrointestinal disturbances, seizures, and (less commonly) psychosis. In addition, mefloquine-resistant *P. falciparum* is increasing in frequency.

If a patient is too ill to take oral medicines, intravenous quinidine is the treatment of choice. This drug is three to four times more active than is intravenous quinine, and serum levels can be measured. Furthermore,
**KEY POINTS**

**About Choosing Chemotherapy for Plasmodium Infection**

1. Determine whether the traveler came from a chloroquine-resistant area:
   a) For chloroquine-sensitive strains, use chloroquine.
   b) For resistant strains, use quinine or an equivalent regimen.
   c) Artemisinin derivatives have improved efficacy for severe disease, but manufacturing quality is unreliable. Monotherapy is discouraged. Not available in the United Kingdom or the United States.
2. Determine whether the patient is too ill to take oral medicines (requires intravenous quinidine).
3. Determine whether the patient has *Plasmodium vivax* or *ovale* (requires primaquine, if not deficient in glucose-6-phosphate dehydrogenase).
4. Refer to Web sites run by health authorities for the most current antimalarial regimens (Table 12.2).

**Table 12.2.** Online Sources of Current Guidelines for Antimalarial Therapy

<table>
<thead>
<tr>
<th><strong>U.K. Health Protection Agency, Committee on Malaria Prevention in U.K. Travellers</strong></th>
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<tbody>
<tr>
<td>Infectious Diseases</td>
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<tr>
<td><a href="http://www.hpa.org.uk/infections/topics_az/malaria/Treat_guidelines.htm">www.hpa.org.uk/infections/topics_az/malaria/Treat_guidelines.htm</a></td>
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<table>
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<tr>
<th><strong>U.S. Centers for Disease Control and Prevention</strong></th>
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<tbody>
<tr>
<td>Malaria</td>
</tr>
<tr>
<td><a href="http://www.cdc.gov/malaria/diagnosis_treatment/tx_clinicians.htm">www.cdc.gov/malaria/diagnosis_treatment/tx_clinicians.htm</a></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>World Health Organization, Global Malaria Programme</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Global Malaria Programme</td>
</tr>
<tr>
<td><a href="http://www.who.int/malaria/treatmentguidelines.html">www.who.int/malaria/treatmentguidelines.html</a></td>
</tr>
<tr>
<td>(a detailed review of all aspects of malaria treatment)</td>
</tr>
</tbody>
</table>

**KEY POINTS**

**About Managing Patients with Plasmodium falciparum**

1. Levels of parasitemia above 5% constitute a medical emergency and require immediate institution of antimalarial treatment.
2. Hematocrit, blood sugar, volume status, cardiac rhythm, renal function, central nervous system function, and arterial oxygenation must all be closely monitored.
3. In the nonimmune host, the course of *P. falciparum* infection is not predictable.
4. The severity of organ damage and risk of death correlate with the level of parasitemia.

The risk of end-organ damage and death increases with the patient’s level of parasitemia. Levels above 5% constitute a medical emergency, and patients with these levels require intensive treatment. Patients with no immunity and levels of *P. falciparum* parasitemia above 10% to 15% should be considered for exchange transfusion, a measure that can be life-saving. However, patients with levels of parasitemia of greater than 50% have survived without blood exchange. Volume status, renal function, and serum glucose must be carefully monitored. Respirator support may be required in cases of severe pulmonary edema. Intravenous steroids have been shown to be harmful in cases of cerebral malaria, and those agents should therefore be avoided. Because of the risk of arrhythmias associated with quinine, quinidine, mefloquine, and halofantrine, cardiac function should be monitored in patients treated with those agents.
BABESIOSIS

POTENTIAL SEVERITY

Usually causes mild disease, but in splenectomized patients can be fatal.

GUIDING QUESTIONS

1. How is babesiosis contracted?
2. Why has the incidence of this infection increased in the United States?
3. How does life cycle of Babesia differ from that of Plasmodium, and how might these differences relate to the differences in clinical manifestations?
4. Which other infection do patients with babesiosis often contract at the same time, and why?
5. Is this blood protozoan treated in the same way as Plasmodium is?

Prevalence, Epidemiology, and Life Cycle

Babesiosis was once thought to be a disease only of cattle and wild animals. However, in the last 30 years this organism has been found to occasionally infect humans. More than 100 cases of human babesiosis have been described, many occurring in Massachusetts on the islands of Nantucket and Martha’s Vineyard. Other cases have been described throughout New England, New York, Maryland, Virginia, Georgia, Wisconsin, Minnesota, Washington State, and California.

Like malaria, Babesia is a blood protozoan. It has a lifecycle similar to that of Plasmodium, however, Babesia is transmitted by the deer tick, Ixodes scapularis. Curiously, Babesia do not infect deer. However, the intermediate host, the white-footed deer mouse, is readily infected by Babesia microti, the primary strain causing human disease in the United States. In endemic areas, the percentage of these rodents infected by Babesia can reach 60%. During its larval and nymph phases, the tick lives on the deer mouse, where it obtains blood meals. The nymph can leave the deer mouse and attach to humans. After attachment, this tiny tick (2 mm in diameter) eats a blood meal and introduces the Babesia sporozoite. The sporozoites enter human red blood cells. The mature signet-ring-shaped trophozoite multiplies asexually by binary fission, forming characteristic tetrads. Subsequently, it lysets the host red blood cell. Because multiplication is asynchronous, massive hemolysis is not seen. Also, unlike Plasmodium, Babesia lacks a hepatic phase.

The rise in the incidence of babesiosis has been attributed to the decreased popularity of deer hunting and the associated increase in deer and deer tick populations. Also, migration to the suburbs in the United States has brought humans in closer proximity to the mouse reservoirs harboring the infectious Ixodes scapularis nympha. The infection is contracted by humans during the months of May through September when the nymphs are feeding.

Clinical Presentation

CASE 12.2

A 65-year-old white female presented with intermittent fever for the preceding 2 months, associated with intermittent myalgias and fatigue. She had just returned from a 2-month summer vacation in Martha’s Vineyard, Massachusetts. She denied any history of tick bites. One month
earlier, she had been diagnosed with Lyme disease. However, despite appropriate treatment, her fevers did not resolve. Aside from a mild anemia, her routine blood tests were normal; however, Giemsa stain of her peripheral blood revealed occasional red blood cells containing ring forms, some in tetrads. Treatment with clindamycin and quinine caused a rapid resolution of her fever.

The symptoms of babesiosis are nonspecific, making the disease difficult to diagnose clinically. Generally, patients present 1 to 3 weeks after exposure with a flu-like illness. Fever, chills, myalgias, arthralgias, fatigue, and anorexia are most common. The illness presents during the summer months as a “summer flu.” In endemic areas, the clinician should inquire about recent hiking in tick-infested locations, particularly those with tall grasses and brush. Patients often do not give a history of tick bites, having failed to detect the attached nymph because of its small size (the diameter of a small freckle). In the normal host, the disease may cause minimal symptoms and resolve spontaneously. However, in older patients or in those who have undergone splenectomy, infection can be more severe and persistent. Cases of adult respiratory distress syndrome and hypotension have been reported, and on rare occasions, patients have died. In Europe, cases have strictly involved splenectomized patients, and the clinical presentation has been more fulminant, being associated with severe hemolysis and death.

Patients with babesiosis may also have symptoms suggestive of Lyme disease, particularly the skin rash of erythema migrans. *Ixodes scapularis* is also the vector for *Borrelia burgdorferi*, and in one series of cases, 54% of patients with babesiosis also had antibodies against the Lyme spirochete, suggesting that these patients had dual infections.

### Diagnosis and Treatment

Giemsa stain of thick and thin smears from the peripheral blood should be examined under an oil-immersion objective. Small ring forms, often grouped in tetrads (Figure 12.3) are the only form seen. Babesiosis is frequently mistaken for *P. falciparum*. The classic tetrad is not observed in *Plasmodium* infection, and the banana-shaped gametocytes observed in *P. falciparum* are never observed in *Babesia*. An indirect immunofluorescence antibody titer that measures antibody against *B. microti*, the primary form that causes

**KEY POINTS**

**About the Clinical Presentation of Babesiosis**

1. Presents as the “summer flu” 1 to 3 weeks after exposure.
2. History of hiking in tick-infested areas.
3. Often no history of tick bite, because the *Ixodes scapularis* nymph is mistaken for a small freckle.
4. More serious disease occurs in splenectomized patients and elderly individuals.
5. Patients with babesiosis may also have Lyme disease, because *Ixodes scapularis* transmits both infections.

![Life Cycle of Babesia](image)
babesiosis in the United States, is available through the CDC. Significant increases in antibody titer develop 3 to 4 weeks after the infection is contracted.

Treatment should be initiated in splenectomized patients and in other patients with serious disease. Clindamycin combined with oral quinine is the preferred regimen (see Table 12.3). Another equally effective regimen is azithromycin and atovaquone. This combination is associated with fewer adverse reactions than is clindamycin and quinine.

Chloroquine, often initiated when Babesia is mistaken for P. falciparum, is not effective. Similarly, doxycycline, pentamidine, primaquine, and pyrimethamine–sulfadoxine (Fansidar) are not efficacious.

Table 12.3. Antiparastic Therapy Dosing

<table>
<thead>
<tr>
<th>Parasite</th>
<th>Preferred therapya</th>
<th>Alternative therapya</th>
</tr>
</thead>
<tbody>
<tr>
<td>Babesia</td>
<td>Intravenous clindamycin 1.2 g q12h, OR Clindamycin 600 mg q8h for 7–10 days, AND quinine 650 mg q8h for 7–10 days</td>
<td>Atovaquone 750 mg q12h for 7–10 days, AND azithromycin 600 mg daily for 7–10 days</td>
</tr>
<tr>
<td>Leishmania</td>
<td>Liposomal amphotericin B 3 mg/kg daily on days 1–5, 14, 21</td>
<td>Intravenous or intramuscular sodium stibogluconate 20 µg/kg daily for 28 days</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>Intravenous or intramuscular sodium stibogluconate 20 mg/kg daily for 21 days</td>
<td>Liposomal amphotericin B for unresponsive lesions</td>
</tr>
<tr>
<td>Trypanosoma cruzi (Chagas' disease)</td>
<td>Nifurtimox 8–10 mg/kg daily divided q6h for 90–120 days</td>
<td>Benznidazole 5 mg/kg daily for 60 days</td>
</tr>
<tr>
<td>Trichuris (whip worm)</td>
<td>Mebendazole 100 mg q12h for 3 days, OR Albendazole 400 mg q24h for 3 days</td>
<td>Ivermectin 200µg/kg daily for 3 days, OR Nitazoxanide 500 mg q12h for 3 days</td>
</tr>
<tr>
<td>Ascaris</td>
<td>Mebendazole 100 mg q12h for 3 days</td>
<td>Pyrantel pamoate 11 mg/kg (maximum 1 g) q12h for 3 days, OR Albendazole 400 mg once, OR Nitazoxanide 500 mg q12h for 3 days</td>
</tr>
<tr>
<td>Enterobius (pin worm)</td>
<td>Mebendazole 100 mg once, OR Albendazole 400 mg once, OR Pyrantel pamoate 11 mg/kg (maximum 1 g) once</td>
<td>Repeat selected treatment after 2 weeks</td>
</tr>
<tr>
<td>Strongyloides</td>
<td>Ivermectin 200 µg/kg daily for 2 days For disseminated disease, continue for 7 days (longer if immunocompromised)</td>
<td>Albendazole 400 mg q24h for 3 days</td>
</tr>
</tbody>
</table>

KEY POINTS

About Diagnosis and Treatment of Babesiosis

1. Giemsa stain of the peripheral blood remains the best way to make the diagnosis.
2. Only ring forms are seen.
3. Frequently mistaken for Plasmodium falciparum.
4. Tetrad ring forms strongly support the diagnosis of babesiosis.
5. Many malaria regimens, including chloroquine and primaquine, are not effective in babesiosis.
<table>
<thead>
<tr>
<th>Parasite</th>
<th>Preferred therapy*</th>
<th>Alternative therapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hook worm</strong></td>
<td>Albendazole 400 mg once, OR Mebendazole 100 mg q12h for 3 days, OR Pyrantel pamoate 11 mg/kg (maximum 1 g) for 3 days</td>
<td></td>
</tr>
<tr>
<td><strong>Trichinella</strong></td>
<td>Steroids for severe symptoms, PLUS mebendazole 200–400 mg q8h for 3 days, THEN 400–500 mg q8h for 10 days</td>
<td>Albendazole 400 mg q12h for 8–14 days</td>
</tr>
<tr>
<td><strong>Echinococcus granulosus (hydatid cyst)</strong></td>
<td>Aspiration or surgical excision, PLUS perioperative albendazole</td>
<td>Albendazole 400 mg q12h for 1–6 months</td>
</tr>
<tr>
<td><strong>Echinococcus multilocularis</strong></td>
<td>Surgical excision or aspiration</td>
<td></td>
</tr>
<tr>
<td><strong>Taenia solium (cysticercosis)</strong></td>
<td>Albendazole 400 mg q12h for 8–30 days, repeated as necessary Concurrent steroids for central nervous system disease</td>
<td>Praziquantel 50–100 mg/kg daily divided q8h for 30 days Surgery</td>
</tr>
<tr>
<td><strong>Schistosomes (Schistosoma)</strong></td>
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<tr>
<td><em>S. mansoni</em></td>
<td>Praziquantel 40 mg/kg divided q12h over 1 day</td>
<td>Oxamniquine 15 mg/kg once (30 mg/kg once for East Africa; 30 mg/kg q24h for 2 days for Egypt and South Africa)</td>
</tr>
<tr>
<td><em>S. haematobium</em></td>
<td>Praziquantel as for <em>S. mansoni</em></td>
<td></td>
</tr>
<tr>
<td><em>S. japonicum</em> and <em>S. mekongi</em></td>
<td>Praziquantel 60 mg/kg divided q8h over 1 day</td>
<td></td>
</tr>
<tr>
<td><strong>Clonorchis sinensis</strong></td>
<td>Praziquantel 75 mg/kg divided q8h over 1 day</td>
<td></td>
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<tr>
<td><strong>Fasciola hepatica</strong></td>
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<tr>
<td><strong>Paragonimus westermani</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>Wuchereria bancrofti and Brugia malayi</strong></td>
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<tr>
<td><strong>Onchocerca volvulus</strong></td>
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<td><strong>Loa loa</strong></td>
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* All therapies are oral unless otherwise indicated.
**LEISHMANIASIS**

**Prevalence, Epidemiology, and Life Cycle**

*Leishmania* has caused major epidemics in eastern India, Bangladesh, and East Africa. Urban outbreaks have been reported in the cities of northeastern Brazil. A small number of American military personnel contracted leishmaniasis during the Persian Gulf War in 1991 and in Afghanistan more recently. Indigenous cases have been reported occasionally in the United States, but most U.S. cases result from travel to a tropical country. Leishmaniasis has emerged as an opportunistic infection in patients with HIV or an organ transplant.

The *Leishmania* parasite is transmitted by the female phlebotomine sandfly. Sandflies breed in cracks in the walls of dwellings, in rubbish, and in rodent burrows. Because they are weak fliers, sandflies remain close to the ground near their breeding sites, resulting in localized pockets of infectious insects. Humans and other animals infected with *Leishmania* serve as reservoirs. The sandfly bites the infected host and ingests blood containing the nonflagellated form called an amastigote. In the digestive tract of the insect, the amastigote develops into a flagellated spindle-shaped promastigote. When the infected sandfly takes its blood meal from an uninfected human, the promastigote enters the host's bloodstream. The promastigote then binds to complement receptors on macrophages and is ingested. Within the phagolysosome the promastigote differentiates into an amastigote. The amastigote is resistant to lysozyme damage and depends on the low pH of the phagolysosome for uptake of nutrients. The parasite multiplies by simple division and eventually is released to infect other cells.

Cell-mediated immunity plays an important role in controlling leishmaniasis. Interferon γ activates macrophages to kill the amastigote by inducing the production of nitric oxide. Resolution of leishmanial infection is associated with the expression of CD4+ T cells of the Th1 type, which secrete interferon γ and interleukin 2. Progression of infection is associated with *Leishmania*-induced expansion of CD4+ cells of the Th2 type that produce interleukin 4, a cytokine that inhibits the production of Th1 cells and the activation of interferon γ production.

**Clinical Presentation**

There are three forms of leishmaniasis: visceral, cutaneous, and mucosal. A single species can produce more
than one syndrome, and each syndrome is produced by multiple different species.

**Visceral Leishmaniasis (Kala-azar)**

In different areas of the world, certain *Leishmania* species tend to be most commonly associated with the visceral form of the disease: *L. donovani* (in India), *L. infantum* (Middle East), *L. chagasi* (Latin America), and *L. amazonensis* (Brazil). After inoculation of promastigotes into the skin, a small papule may be noticed. *Leishmania* amastigotes subsequently silently invade macrophages throughout the reticuloendothelial system. Usually 3 to 8 months pass before the burden of organisms increases to a level that causes symptoms.

The onset of symptoms can be gradual or sudden. In subacute cases, the patient will experience slow but progressive enlargement of the abdomen as a result of hepatosplenomegaly. Increased abdominal girth is accompanied by intermittent fever, weakness, loss of appetite, and weight loss. This presentation can be mistaken for lymphoma, infectious mononucleosis, brucellosis, chronic malaria, and hepatosplenic schistosomiasis. In acute cases, an abrupt onset of high fever and chills mimics malaria or an acute bacterial infection. On physical examination, the spleen may be massively enlarged, hard, and nontender. Hepatomegaly is also present. The skin tends to be dry and thin, and in light-skinned individuals, it takes on a grayish tint. This characteristic accounts for the Indian name Kala-azar, which means “black fever.” On laboratory examination anemia, leukopenia, and hypergammaglobulinemia are common.

The diagnosis is made when a biopsy of lymphatic tissue or bone marrow demonstrates amastigotes on Wright or Giemsa stain. Enzyme-linked immunosorbent assays usually demonstrate high anti-leishmanial antibody titers. However, this test frequently cross-reacts with antibodies to other pathogens. Patients with HIV infection frequently fail to develop antibody titers. Splenomegaly may not be present in these patients, and infection may disseminate to the lungs, pleura, gastrointestinal tract, or bone marrow (causing aplastic anemia). In patients with HIV, amastigotes may be identified in macrophages from bronchoalveolar lavage, pleural effusion, bone marrow aspiration, or even buffy coat samples of the peripheral blood.

**Cutaneous Leishmaniasis**

The cutaneous form of leishmaniasis is widespread, and it is a problem chiefly for farmers, settlers, troops, and tourists in the Middle East and Central and South America. The species most commonly associated with cutaneous disease are *L. major* and *L. tropica* (found in the Middle East, India, Pakistan, and Asia), *L. mexicana, L. braziliensis, L. amazonensis,* and *L. panamensis* (in Central and South America). *L. mexicana* has been reported in Texas.

After a sandfly bite, significant skin lesions generally take 2 weeks to several months to develop. Lesions usually develop on exposed areas. They are the result of amastigotes multiplying in mononuclear cells within the skin and causing a granulomatous inflammatory reaction. Single or multiple lesions may be found, with varying morphology. Lesions may be crusted and dry, or moist and exudative. Shallow and circular ulcers with sharp, raised borders may develop and progressively increase in size, becoming “pizza-like” in appearance as a result of the beefy red of the ulcer base being combined with a yellow exudate. Lesions may become secondarily infected with staphylococci or streptococci.

The diagnosis is made from a biopsy of the raised border of the skin lesion where *Leishmania*-infected macrophages are most abundant. Amastigotes are seen on Giemsa stain.

**Mucosal Leishmaniasis**

Mucosal leishmaniasis is a less common manifestation that is caused primarily by *L. braziliensis*. Only 2% to 3% of patients with skin lesions develop this complication. Organisms invade mononuclear cells in the mucosa. The nose is most commonly involved, resulting in nasal stuffiness, discharge, pain, or epistaxis. Later, the nasal septum is destroyed, and the nose collapses. Involvement of the genital mucosa and trachea have also been reported. Diagnosis is made by biopsy.
KEY POINTS

About Cutaneous and Mucosal Leishmaniasis

1. A problem for farmers, settlers, troops, and tourists; incubation period is 2 weeks to 2 months.
2. Found throughout the world; cases have been reported in Texas.
3. Lesions occur primarily on exposed areas.
4. Dry or moist in appearance, ulcers have sharp, raised boarders; “pizza-like” lesions are common.
5. Mucosal disease is rarer, usually involves the nose.
6. Diagnosis is made by biopsy, always from the border of skin lesions.

Treatment

The only drug approved in the United States for treatment of leishmaniasis is liposomal amphotericin B. For visceral leishmaniasis in immunocompetent patients, administer 3 mg/kg daily on days 1 to 5, 14, and 21. The course can be repeated if the parasite persists. For the immunocompromised host, the recommended regimen is amphotericin B 4 mg/kg daily administered on days 1 to 5, 10, 17, 24, 31, and 38. Relapses are common in HIV-infected hosts.

Outside the United States, pentavalent antimony continues be used; however, this treatment is associated with many side effects, including abdominal pain, anorexia, nausea and vomiting, and myalgias. Amylase and lipase levels often rise. Miltefosine, a phosphocholine analog has anti-leishmanial activity in vitro and in vivo, and acts by interfering with the parasite's cell-signaling pathways and membrane synthesis. This agent has successfully treated Indian visceral disease.

Treatment of cutaneous leishmaniasis depends on the location of the infection. The lesions can heal spontaneously, and so, if there is no mucosal involvement and if the lesions are located in areas of no cosmetic concern, they can be followed without therapy or treated topically with 15% puromycin and 12% methylbenzethonium chloride. Thermotherapy (warming the affected region with radiofrequency waves to 50°C for one treatment of 30 seconds) has proven effective in a high percentage of cases, and that approach compares favorably with 21 days of intralesional administration of pentavalent antimony. Patients with mucosal involvement, progressive lesions, or lesions in cosmetically sensitive areas require treatment with intravenous or intramuscular pentavalent antimony (20 mg/kg daily for 20 days, available through the CDC). Fluconazole (500 mg twice daily for 6 weeks) has been associated with modest response rates. Miltefosine has proved successful against some forms of cutaneous leishmaniasis, but other species are refractory.

KEY POINTS

About the Treatment of Leishmaniasis

1. Visceral disease:
   a) Liposomal amphotericin B is the only approved therapy.
   b) Miltefosine appears promising, but had not been approved in the United States at the time of writing.
2. Cutaneous:
   a) May heal spontaneously.
   b) Thermotherapy is safe and effective.
   c) In cases of mucosal involvement, infection in a cosmetically sensitive site, or failure to heal, fluconazole or pentavalent antimony are recommended.
   d) Miltefosine effective for some Leishmania species, but not others.
3. Which insect is responsible for transmitting this disease, and is the disease commonly transmitted to tourists? Why, or why not?
4. How does this insect’s toilet habits affect transmission to the human host?
5. Which organs are most commonly affected by chronic Chagas’ disease?

POTENTIAL SEVERITY

A chronic disorder that can lead to fatal cardiomyopathy.
Prevalence, Epidemiology, and Life Cycle

Chagas’ disease caused by *Trypanosoma cruzi* is found throughout Central and South America. Between 16 and 18 million people worldwide are infected with *T. cruzi*, and nearly 0.5 million die from Chagas’ disease annually. With improvement of substandard housing, the incidence of this disease among young people is decreasing.

The parasite is transmitted by reduviid bugs that suck blood from their host. This insect contains trypomastigotes in its gut. At the same time that it bites the host, it also defecates, depositing trypomastigotes on the skin. The human host then scratches the itchy bite, introducing the parasite into the wound and subsequently into the bloodstream. Mucous membranes, the conjunctiva, and breaks in the skin are common sites of entry. Once in the bloodstream, the trypomastigotes enter host cells and differentiate into amastigotes that multiply, filling the cell cytoplasm. They then differentiate again into trypomastigotes, and the cell ruptures, spreading the parasite to adjacent cells and into the bloodstream. Asymptomatic parasitemia is common. In endemic areas, the parasite can be transmitted by blood transfusions. Because the reduviid bug takes up residence in the cracks of primitive homes, this infection occurs almost exclusively among poor rural people. The disease is most commonly transmitted in young children. If one member of a family presents with acute disease, all pediatric family members should be screened for asymptomatic disease.

Chagas’ disease has not been reported in tourists, because they are unlikely to be exposed to primitive living quarters. Vector control measures and educational programs have helped to reduce the incidence of disease. Insecticide impregnation of bed nets has proven to be an inexpensive and effective control measure.

Clinical Presentation

Acute Chagas’ disease often causes minimal symptoms. About 1 week after the parasite enters the skin, an area of localized swelling called a chagoma develops, often in association with local lymph node swelling. Entry of the parasite via the conjunctiva causes periorbital edema (Romana’s sign). Onset of local edema is quickly followed by fever, malaise, anorexia, and edema of the face and legs. Occasionally, myocarditis or encephalitis may develop.

Years to decades after the primary infection 10% to 30% of individuals go on to develop chronic Chagas’ disease. The heart is the organ that is primarily damaged. Severe cardiomyopathy results in thromboembolism, congestive heart failure, and life-threatening arrhythmias. Esophageal involvement can lead to megasphagus associated with dysphagia, regurgitation, and aspiration pneumonia. Chagasic megacolon is another manifestation of chronic disease causing constipation and bowel obstruction that can lead to perforation and bacterial sepsis. In immunocompromised hosts such as organ transplant patients and patients with AIDS, *T. cruzi* can reactivate, presenting with manifestations of chronic Chagas’ disease. Unlike normal hosts, immunocompromised patients are also at risk for developing *T. cruzi* brain abscesses.

Diagnosis

Acute disease can be diagnosed by examining Giemsa-stained blood or buffy coat smears. The trypomastigotes (whose length is approximately twice the diameter of a red blood cell) can readily be seen by microscopy.

### KEY POINTS

**About the Clinical Presentation of Chagas’ Disease**

1. Acute disease is associated with localized areas of swelling called chagomas.
2. Chronic disease develops in 10% to 30% of cases decades after initial infection.
3. Chronic disease affects:
   a) the heart, causing a cardiomyopathy associated with congestive heart failure, emboli, and arrhythmias; and
   b) The gastrointestinal tract, causing megasphagus and megacolon.

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### KEY POINTS

**About the Life Cycle of *Trypanosoma Cruzi***

1. Transmitted by the reduviid bug, which carries the trypomastigote in its feces.
2. The host allows the parasite to enter the bloodstream by scratching and rubbing infected insect feces into the skin.
3. The reduviid bug lives in the cracks of substandard housing.
4. The disease affects mainly poor rural people, not tourists.
In chronic disease, the diagnosis is made by detecting immunoglobulin G (IgG) antibodies. A number of sensitive serologic tests are available, but they frequently yield false positive results. In the United States, two ELISA tests have been approved by the U.S. Food and Drug Administration for detecting clinical disease. A recently developed ELISA has been shown to have high sensitivity and specificity, and may prove useful for screening the blood supply. The polymerase chain reaction (PCR) method has demonstrated promise, but it is not yet commercially available.

Treatment

*T. cruzi* is not sensitive to most antiparasitic drugs (see Table 12.3). Nifurtimox cures about 70% of acute cases. This drug causes gastrointestinal and neurologic side effects in many patients. Benznidazole has a similar cure rate. Peripheral neuropathy, granulocytopenia, and rash are the most common side effects with that agent. Treatment with these two agents is now recommended for chronic Chagas’ disease. Recent studies have shown that treatment slows the progression of heart disease.

**TRYPANOSOMA BRUCEI COMPLEX**

**POTENTIAL SEVERITY**

Over weeks to months, this disease can progress to coma, followed by death.

*T. brucei* complex refers to several *Trypanosoma* subspecies that are spread by the blood-sucking tsetse fly. Unlike *T. cruzi*, which takes up residence within cells, *T. brucei* trypomastigotes multiply within the bloodstream, evading the humoral immune system indefinitely by changing their surface antigens every 5 days. This disease is confined to Africa. No more than a single case per year is imported to the United States. After the initial bite, the infection progresses slowly, with systemic symptoms of fever and lymph node swelling being noted weeks to months later. In the West African form, neurologic manifestations do not develop until months or years after the initial symptoms. In East African trypanosomiasis, systemic complaints may develop days after the insect bite, and CNS complaints may develop within weeks. Symptoms include somnolence, which explains the name “sleeping sickness” and choreiform movements, tremors, and ataxia mimicking Parkinson’s disease. Coma and death frequently ensue.

The diagnosis is made by observation of trypomastigotes in Giemsa-stained thick and thin smears of peripheral blood. Trypomastigotes can also be found in the cerebrospinal fluid. The treatment for *T. brucei* is complex and depends on the species of the infecting parasite, whether the CNS is involved, and tolerance to the side effects of the treatment regimen. Potential medications include eflornithine; suramin alone or in combination with the arsenical tryparsamide; pentamidine; and the arsenical melarsoprol.
2. How does the life cycle of Ascaris differ from that of Trichurus, and how does the difference manifest itself clinically?

3. How is Strongyloides able to persist in the human host for three to four decades?

4. What are the conditions that precipitate Strongyloides hyperinfection syndrome, and why?

5. Which helminth most commonly causes iron deficiency anemia, and why?

Helminths include the roundworms (nematodes), flukes (trematodes), and tapeworms (cestodes). These parasites are large, ranging in size from 1 cm to 10 m, and they often live in the human gastrointestinal tract without causing symptoms. Only when the infection is very heavy or the worm migrates to an extraintestinal site do patients seek medical attention. Transmission to humans results in most cases from contact with human waste. The diagnosis is generally made by examining the stool for eggs, larvae, or adult worms (Figure 12.4).

**INTESTINAL NEMATODES (ROUNDWORMS)**

Nematodes can be classified into two groups. Those that gain entry to the host by egg ingestion (Trichuris, Ascaris, and Enterobius), and those that are capable of producing larvae that penetrate the skin of their host (Strongyloides and hookworm). Roundworm life cycles can also be classified into two groups. One group, Trichuris and Enterobius, attach and grow in the intestine soon after being ingested. The second group, Ascaris, Strongyloides, and hookworm, first penetrate the venous system, enter the lungs, and migrate up the bronchi to the trachea, where they are swallowed. They then take up residence in the gastrointestinal tract (Figure 12.5). These differences in life cycle account for some of the unique clinical characteristics of the various species of nematodes.

**Figure 12–4.** Stool helminths. All eggs drawn to scale. In Strongyloides, only the rhabditiform larvae are usually seen.

**Nematodes Acquired by Ingestion**

**Trichuris trichiura (Whip Worm)**

*Trichuris trichiura* is one of the most prevalent helminths. More than 2 million people are estimated to be infected in the United States. This parasite is most commonly found in the rural Southeast, particularly Puerto Rico, where the moisture and temperature favor egg maturation. Worldwide, this worm causes infection mainly in poor rural communities with poor sanitation. Humans are the principal host, and infection results from ingestion of embryonated eggs.

Under optimal conditions of shade and moisture, eggs excreted in the stool undergo embryonic development within 2 to 4 weeks. Then, when ingested by humans, the larvae break out of the eggshell and penetrate the intestinal villi of the small intestine. Over 3 to
10 days, they migrate down to the cecum, and over 1 to 3 months, they develop into egg-producing adults. Most *Trichuris trichiura* infections are asymptomatic. Heavy infections can result in iron deficiency and abdominal pain and tenderness. Bloody diarrhea, growth retardation, and rectal prolapse are potential complications of a heavy infection.

Diagnosis is made by fecal smear. The ova has a classic lemon shape with plug-like ends (Figure 12-4). Mebendazole is a highly effective treatment and is seldom associated with side effects. Albendazole is also recommended as first-line therapy; ivermectin or nitazoxanide are efficacious alternatives (see Table 12.3).

**ASCARIS**

*Ascaris* is the most common helminthic infection of humans, being estimated to infect more than 1 billion humans worldwide. In the United States, infections are found predominantly in the southeast, where weather conditions favor egg embryonation.

Like *Trichuris*, *Ascaris* is a parasite of humans, the infection being contracted by ingesting material contaminated with human feces. Under proper temperature and moisture conditions, eggs develop into infective embryos within 5 to 10 days. When ingested, the parasites hatch in the small intestine. Embryos then penetrate the intestinal wall and enter the venous bloodstream. On reaching the capillaries of the lung, they break into the alveoli, crawl up through the bronchi and trachea, and then are swallowed, re-entering the gastrointestinal tract, where they mature over a period of 2 months. Each mature gravid female can produce 200,000 eggs per day.

As in other roundworm infections, most patients with *Ascaris* are asymptomatic. However, patients with high worm burdens can experience obstruction of the small intestine, accompanied by vomiting and abdominal pain. Patients may vomit worms during such attacks or may pass them in their stool. Heavy infections may also be associated with malabsorption, steatorrhea, and weight loss. A single *Ascaris* worm can migrate up the biliary tree and obstruct the common bile duct, precipitating symptoms of cholecystitis, including epigastric abdominal pain, nausea, and vomiting. As the worms migrate into the lungs, some patients experience respiratory symptoms and develop pneumonia visible on chest radiographs, accompanied by peripheral eosinophilia (sometimes called Loeffler's syndrome). On occasion, worms can migrate to other sites in the body, causing local symptoms.

Because of the large number of eggs excreted daily, this infection is easily diagnosed by stool smear (Figure 12.4). *Ascaris* infection is effectively cured with mebendazole. Alternative treatments include pyrantel pamoate, albendazole, and nitazoxanide (Table 12.3). Improved sanitation is critical for controlling this infection. Hand-washing and boiling of water have been shown to prevent reinfection. Alternatively, all school-age children in endemic areas can be treated twice or three times per year to reduce the worm burden.

**ENTEROBIA (PINWORM)**

Pinworm is the most common worm infection in countries within the temperate zone. This infection is very common in children of all socioeconomic groups in the United States. Between 20 and 40 million people are estimated to be infected. The eggs of this parasite resist drying and can therefore contaminate bed linens and dust. As a result, infection in one young child can lead to infestation of the entire family. After ingestion, the eggs hatch in the duodenum and jejunum, and the larvae mature in the cecum and large intestine. At night, gravid females migrate to perianal area, where they lay eggs and cause localized itching. When this area is scratched, eggs are trapped under fingernails and are subsequently ingested by the host, resulting in repeated autoinfection.

The major clinical manifestation is nocturnal itching of the perianal area that often interferes with sleep. This parasite rarely causes other symptoms. Because *Enterobius* rarely migrates through tissue, this infection is not associated with peripheral eosinophilia. Diagnosis is made by pressing adhesive cellophane tape onto the perianal area in the early morning. Small, white, thread-like
**KEY POINTS**

About Nematodes Acquired by Ingestion

1. Tend to cause minimal symptoms and are not life-threatening.
2. Contracted by contact with fecal material.
3. *Trichuris trichiura* can cause iron-deficiency anemia; excretes lemon-shaped ova.
4. *Ascaris* passes through the lung and can initially cause respiratory symptoms; can also cause biliary obstruction; excretes round, thick-walled ova.
5. *Enterobius* is common in children and readily spreads by dust and contaminated linens. Diagnosed when the adhesive cellophane tape test demonstrates worms in the anal area.
6. Mebendazole or albendazole is effective treatment.

**KEY POINTS**

About the Epidemiology and Life Cycle of *Strongyloides*

1. Endemic in warm areas, including the southeast United States.
2. Larvae in soil contaminated with fecal material penetrate the skin of bare feet.
3. Larvae enter the bloodstream, invade the lung, crawl up the bronchi to the trachea, are swallowed, and mature in the small intestine.
4. Adult worms deposit eggs in the bowel wall where the eggs hatch.
5. Larvae in the bowel can enter the bloodstream, causing autoinfection.
6. Infection can persist for 35 to 40 years.

Worms and eggs become attached to the tape and can be easily identified using a low-power (100X) microscope. Two doses of mebendazole or albendazole taken 2 weeks apart is curative. All symptomatic family members should be treated simultaneously.

**NEMATODES ACQUIRED BY SKIN PENETRATION**

*Strongyloides*

**Prevalence, Epidemiology, and Life Cycle**

*Strongyloides* infection occurs less commonly than do infections involving the other roundworms; however, strongyloidiasis is widely distributed throughout the tropics and commonly infects people in the southern United States. Because *Strongyloides* can cause a fatal hyperinfection syndrome in the immunocompromised host, clinicians need to be familiar with this parasite.

The filariform larvae excreted in the feces are capable of penetrating the skin. Humans become infected as a result of skin exposure to feces or soil contaminated by feces. Walking barefoot on contaminated soil is the most common way of contracting this infection. After skin penetration, the larvae enter the bloodstream and lymphatics. Subsequently, they become trapped in the lungs, where they enter the alveoli and are coughed up and then swallowed, entering the gastrointestinal tract. The larvae mature in the upper gastrointestinal tract, where females are able to penetrate the bowel mucosa and deposit their eggs. Eggs hatch in the mucosa, releasing rhabditiform larvae that either mature within the intestine, forming filariform larvae capable of penetrating the bowel wall and causing autoinfection, or are passed in the feces. In warm moist soil, the excreted larvae can mature into the infectious form. Because *Strongyloides* can re-infect the human host, an initial infection can persist for 35 to 40 years. The intensity of the infection depends not only on the initial inoculum, but also on the degree of autoinfection. In the immunocompromised host, autoinfection can be intense and can cause severe disseminated illness.

**Clinical Presentation**

**CASE 12.3**

A 60-year-old white man was admitted to the hospital for elective cardiac and renal transplantation. He had long-standing diabetes mellitus and had experienced multiple myocardial infarcts leading to severe ischemic cardiomyopathy. He had also developed end-stage diabetic nephropathy. Following transplantation, he received mycophenolate mofetil, tacrolimus, and high doses of methylprednisolone. One month after transplant, he suddenly developed fever and increasing shortness of breath, associated with a cough productive of clear watery sputum. Two days later, he began coughing up bloody sputum.

A social history found that this patient had never smoked. He had never traveled outside of northern Florida, having lived in the area his entire life.

Physical examination showed a blood pressure of 133/72 mm Hg, a pulse of 81 per minute, a respiratory
As observed with other roundworm infections, most patients with *Strongyloides* have no symptoms when they harbor only a small number of worms. Heavier infestations can cause symptoms associated with the parasite's life cycle. When the filariform larvae first penetrate the skin, rate of 20 per minute, and a temperature of 37.6°C. This patient appeared acutely ill, being short of breath on a Ventimask.

An examination of ears, nose, and throat was unre-markable. The patient’s neck was supple, without lymphadenopathy.

Coarse breath sounds were heard bilaterally in the lungs, and the midline sternal wound was clean and without drainage. The heart showed normal S1 and S2, with no murmurs, rubs, or gallops. The abdomen was soft and nontender. No organomegaly was noted, and bowel sounds were normal.

Some leg edema was noted (3+ in the left lower leg, and 1+ in the right lower leg), but pedal pulses were intact. A neurologic exam uncovered no focal deficits. The patient was able to follow simple commands.

A laboratory workup showed a WBC count of 3700/mm³, with 85%, neutrophils, 5.4% lymphocytes, 2% eosinophils, 0.6% basophils, and 4.4% monocytes. Hematocrit was 29%, and platelet count was 301,000/mm³. Serum sodium was 137 mEq/L, and liver function tests were within normal limits. Arterial blood pH was 7.02, with a PaCO₂ of 59 mm Hg, a PaO₂ of 51 mm Hg, an HCO₃ of 15 mEq/L, and oxygen saturation of 66% (FiO₂ 95%).

A chest radiograph revealed diffuse bilateral parenchymal opacities consistent with pulmonary edema (Fig. 12-6A). A computed tomography (CT) scan of the chest showed diffuse reticular interstitial infiltrates consistent with pulmonary edema (Fig 12-6B) and two subsequent bronchoscopy exams revealed no pathogens. Diffuse alveolar hemorrhage was observed.

Despite treatment with voriconazole, ganciclovir, and broad-spectrum antibiotics, the patient became hypotensive and remained hypoxic, dying 7 days after the onset of his acute respiratory illness. All blood cultures and sputum culture were negative for pathogens.

At autopsy numerous *Strongyloides* stercoralis filariform larvae were found to be present within the alveolar spaces, alveolar septa, and connective tissue (Figure 12.6C). Occasional filariform larvae were also seen within the sinuses of the hilar lymph nodes and were identified within the myocardial interstitium. Filariform larvae were seen within the walls of the esophagus, stomach, small bowel, and colon, with the heaviest infestation being observed in the colon.

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**Figure 12–6.** Strongyloidiasis hyperinfection syndrome. A. A chest radiograph demonstrates diffuse opacification of both lung fields. B. A computed tomography scan of the chest shows diffuse interstitial infiltrates consistent with pulmonary edema. C. Lung biopsy with hematoxylin and eosin staining shows inflammatory cells within the alveoli and a rhabditiform larva (middle of the field).
**KEY POINTS**

**About the Clinical Presentation of Strongyloides**

1. Many patients are asymptomatic.
2. Skin penetration can cause an itchy, erythematous rash.
3. Lung invasion can produce Loeffler’s syndrome (cough, wheezing, pneumonia, and eosinophilia).
4. Heavy infection can cause abdominal pain and eosinophilia.
5. Treatment with high-dose steroids can cause a fatal hyperinfection syndrome (accelerated autoinfection).
6. Hyperinfection causes diffuse pneumonia, meningitis, abdominal pain, and gram-negative sepsis, hemoptysis, and skin rashes. Eosinophilia is absent.

**About the Diagnosis and Treatment of Strongyloidiasis**

1. Diagnosis is difficult. (Stools do not contain ova.)
2. Larvae are found in the stool; duodenal endoscopy may be required.
3. Peripheral eosinophilia may be the only finding.
4. Treat asymptomatic infections.
5. Ivermectin is the drug of choice.

they can cause itching and a papular erythematous rash. Migration into the lungs can cause respiratory symptoms, pneumonia, and peripheral eosinophilia (Loeffler’s syndrome). Once Strongyloides takes up residence in the gastrointestinal tract, the parasite can cause burning abdominal pain that mimics peptic ulcer disease or a colicky abdominal pain that mimics gallbladder disease. Abdominal pain may be associated with diarrhea and the passage of mucus. Malabsorption, nausea, vomiting, and weight loss may also be present. Because the female worm penetrates the bowel mucosa and the filariform larvae can migrate through the bowel wall, the host responds by producing eosinophils, and peripheral eosinophilia is a prominent finding in strongyloidiasis. When larvae penetrate the perianal area, a localized snakelike urticarial rash may be seen. A generalized urticarial rash may also be seen.

As illustrated by case 12.3, when asymptomatic individuals who harbor small numbers of organisms receive immunosuppressants such as high-dose corticosteroids, or develop depressed cell-mediated immunity because of severe malnutrition or AIDS, the level of autoinfection can increase markedly, resulting in a hyperinfection syndrome. Symptoms may include diffuse pulmonary infiltrates, severe abdominal pain, meningitis, and gram-negative sepsis, the latter manifestation being the result of filariform larvae compromising the integrity of the bowel wall. Other clinical manifestations can include hemoptysis and a skin rash. Periumbilical purpura, diffuse nonpalpable purpura, angioedema, or erythoderma mimicking a drug-related allergic eruption have all been described. As in case 12.3, eosinophilia is usually absent in the hyperinfection syndrome. When an immunocompromised patient presents with this clinical constellation and was raised in the rural south or previously lived in a tropical region, hyperinfection with Strongyloides needs to be considered.

**DIAGNOSIS AND TREATMENT**

Because the eggs usually hatch in the gastrointestinal tract, Strongyloides ova are rarely seen on stool smear. Diagnosis depends on identifying rhabditiform larvae in the feces or duodenal fluid. Diagnosis requires expertise, because hookworm larvae can easily be misdiagnosed as Strongyloides. At least three stools need to be examined under a low-power (100X) microscope; if results are negative, endoscopy should be considered. The ELISA serum test is sensitive and specific, but it cannot differentiate recent from past infection. In the Strongyloides-infected immunocompromised host, the ELISA test may be negative. An important clue is the presence of peripheral eosinophilia, which may increase to between 10% and 20% of peripheral WBCs. However, lack of eosinophilia, particularly in the hyperinfection syndrome, does not exclude the diagnosis of strongyloidiasis.

Ivermectin for 2 days is curative in most cases. Albendazole can be given as alternative therapy. Because of the potential danger of severe autoinfection, all patients with Strongyloides, even asymptomatic patients, should be treated. Patients who develop the hyperinfection syndrome should be treated for a minimum of 7 days. However, despite treatment, the mortality associated with this syndrome remains high. Patients with a past history of Strongyloides or unexplained eosinophilia should therefore be thoroughly examined, tested, and treated before receiving immunosuppressive therapy.

**Hookworm**

**PREVALENCE, EPIDEMIOLOGY, AND LIFE CYCLE**

Hookworm (Ancylostoma duodenale and Necator americana) has been estimated to infect nearly one quarter of
the world’s population, being found throughout the tropical and subtropical zones. Infection is prevalent in areas where untreated human feces are allowed to contaminate the soil, and people walk barefoot. *Necator americanus* (“New World hookworm”) is found primarily in the Western hemisphere, but also in southern Asia, Indonesia, Australia, and Oceania. *Ancylostoma duodenale* (“Old World hookworm”) is found predominantly in the Mediterranean region, northern Asia, and the west coast of South America. As a result of sanitary waste disposal policies in the United States, hookworm infection has a low prevalence, being found primarily in the southeast.

The life cycle of hookworm is very similar to that of *Strongyloides*. Like *Strongyloides*, the hookworm filariform larvae penetrate the skin, enter the bloodstream and lymphatics, pass into the lung, migrate up the bronchi to the trachea, are swallowed, and finally take up residence in the upper small intestine (Figure 12-5). They attach by means of a buccal capsule that is used to suck blood from the host. A single *Necator americanus* worm can remove 0.03 mL of blood daily, and a single *Ancylostoma duodenale* worm, 0.2 mL. Worldwide, hookworm is a major cause of iron deficiency anemia. It is responsible for an estimated blood loss of 7 million liters daily—the total blood volume of more than 1 million people!

The life cycle of the hookworm also differs from that of *Strongyloides* in several important ways, and the differences account for hookworm’s milder clinical manifestations. The *Strongyloides* ova mature quickly, hatching in the bowel wall of the host; hookworm ova mature more slowly, requiring several days of incubation in warm, moist, shady soil. As a result, human hookworm infestation is confined to geographic areas with a warm climate. The longer maturation time for hookworm eggs also means that autoinfection does not occur and that infection by fresh feces is not possible.

**Clinical Presentation**

When hookworm larvae penetrate the skin they can cause intense pruritus, sometimes called “ground itch.” Itching is associated with local erythema and a papular rash at the site of penetration. As is observed with both *Ascaris* and *Strongyloides*, respiratory symptoms and patchy pneumonia associated with peripheral eosinophilia (Loffler’s syndrome) can develop as the worm penetrates the lung. The abnormalities most commonly associated with hookworm are iron deficiency and protein malnutrition. These abnormalities depend both on the worm burden on the nutritional status of the patient. Other complaints may include abdominal pain, diarrhea, and weight loss.

**Diagnosis and Treatment**

Adult female worms release between 10,000 and 20,000 worms daily, making diagnosis by stool smear simple. The eggs are readily seen using a low-power (100×) microscope (Figure 12.4). Quantitation of the egg count allows for an estimate of the worm burden. Mebendazole for 3 days is usually curative (see Table 12.3).

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### Tissue and Blood Helminths

#### Guiding Questions

1. Which tissues do *Trichinella*, *Echinococcus*, and *Taenia solium* prefer to infect?
2. Why is *Trichinella* uncommon in the United States?
3. What is a hydatid cyst, and how is it treated?
4. Why does treatment with praziquantel often exacerbate the manifestations of neurocysticercosis?

#### Trichinella

**Potential Severity**

Usually asymptomatic, but heavy infections can lead to severe myocarditis, pneumonia, and encephalitis that can be fatal.
Prevalence, Epidemiology, and Life Cycle

Trichinosis is found worldwide, wherever contaminated meat is undercooked. *Trichinella* is a roundworm whose larvae are released from cyst walls in contaminated meat by acid–pepsin digestion in the stomach. Upon entering the small intestine, larvae invade the intestinal microvilli and develop into adult worms. Females then release larvae that enter the bloodstream and seed skeletal and cardiac muscle. The larvae grow in individual muscle fibers and eventually become surrounded by a cyst wall. Once encysted, the larvae can remain viable for many years. If the cyst-containing muscle tissue is ingested, *Trichinella* is able to take up residence in the new host.

The domestic animal that primarily becomes infected with *Trichinella* is the pig. In many countries, including the United States, pigs are fed with grain, which explains the low incidence of trichinosis. In the United States, laws were enacted to prevent the feeding of uncooked garbage to pigs, and as a result, fewer than 100 trichinosis cases are reported annually. Most cases of trichinosis result from improperly processed pork, but undercooked bear, walrus, cougar, wild boar, and horse meat have also been sources of *Trichinella* infection.

Clinical Presentation

Symptoms correlate with the numbers of worms in tissues. Because the number of cysts ingested is often low, most infections are asymptomatic. Heavier infestations can result in diarrhea, abdominal pain, and vomiting during the intestinal phase, followed in 1 to 2 weeks by fever, periorbital edema, subconjunctival hemorrhages, and chemosis. Muscle pain, swelling, and weakness are common. The extraocular muscles are frequently involved first, followed by the neck and back, arms and legs. Occasionally, a macular or petechial diffuse body rash may be seen. These symptoms usually peak within 2 to 3 weeks, but they may be followed by a prolonged period of muscle weakness. Death is uncommon, but can result from severe myocarditis leading to congestive heart failure. Fatal encephalitis and pneumonia have also been reported.

Diagnosis and Treatment

An elevated peripheral eosinophil count associated with periorbital edema, myositis, and fever strongly suggest the diagnosis. Eosinophil counts are often very high. Serum creatine phosphokinase is also elevated, reflecting muscle damage. A specific diagnosis requires biopsy of a symptomatic muscle to demonstrate *Trichinella* larvae. Because exposure history and the clinical manifestations are usually distinct, a biopsy is rarely required. Antibody to *Trichinella* increases within 3 weeks and can be detected by ELISA.

Mebendazole is recommended for treatment. Myositis may be reduced by using a dosing regimen that starts with a lower dose for 3 days, and then follows with higher doses for 10 days (see Table 12.3). Albendazole can be given as alternative therapy. In critically ill patients, corticosteroids (prednisone 50 mg daily for 10 to 15 days) may be helpful, but no controlled trials have been conducted proving efficacy. Cooking meat above 55°C until all pink flesh is browned kills encysted larvae and prevents trichinosis.

Echinococcosis

*Echinococcus* is member of the cestode (tapeworm) family. Infections with *Echinococcus granulosus* are found worldwide, including in Africa, the Middle East, southern Europe, Latin America, and the southwestern United States. A second species, *Echinococcus multilocularis* is...
CASE 12.4

A 33-year-old woman, an immigrant from Jordan, presented with a chief complaint of bloody cough and shortness of breath for a period of 2 weeks. At age 22, she had undergone a CT scan of the abdomen as part of a workup for polycystic ovaries. She was noted at that time to have a large liver cyst consistent with Echinococcus. Although she was asymptomatic, resection of the left lobe of the liver was performed that year. Despite surgical resection, she experienced recurrent cysts and on three occasions underwent percutaneous aspiration followed by injection of hypertonic saline. One month before admission and 6 years after her last aspiration and injection procedure, she began coughing up blood. At the same time, she noted shortness of breath. She received several courses of oral antibiotics, but failed to improve. Her coughing then became productive of gelatinous, foul-smelling serosanguinous fluid.

Pulmonary exam revealed decreased breath sounds and dullness to percussion at the right base. Bronchial breath sounds and E-to-A changes were noted in the right posterior mid-lung field. The liver was not palpable. A CT scan of the chest and abdomen revealed a fluid collection over the dome of the liver and an 8x5-cm abscess in the right lower lobe that contained an air-fluid level.

Clinical Presentation

Most patients with echinococcosis are asymptomatic, the infection being detected incidentally on an imaging study. Symptoms generally develop when the hydatid cyst reaches a size of 8 to 10 cm and begins compressing vital structures or eroding into the biliary tract or a pulmonary bronchus (as occurred in case 12.4). The cysts can also become superinfected, resulting in a bacterial abscess. Cyst leakage or rupture can result in an anaphylactic reaction, causing fever and hypotension. Cysts can also develop in the brain, heart, kidneys, eyes, and bones. Asymptomatic disease caused by Echinococcus granulosus rarely progresses; however, 90% of cases of asymptomatic Echinococcus multilocularis infection eventually progress to symptomatic disease.

Diagnosis and Treatment

Ultrasonography, CT scan, or magnetic resonance imaging reveal a characteristic hydatid cyst with a distinct septated structure representing daughter cysts (Figure 12.7). Often, tapeworm heads can also be visualized. The stage of infection can be classified based on ultrasound findings, but CT scan has been found to be the most effective diagnostic method for delineating the extent of disease. The diagnosis can be confirmed by ELISA, which is highly sensitive for liver cysts, but less sensitive for cysts in other organs.
Complete surgical resection of the hydatid cyst is often recommended in symptomatic disease. The cyst should be removed intact, taking great care to avoid a rupture, which will spread the infection by daughter cysts. To reduce the risk of spread, aspiration of the cyst is recommended—a procedure that involves removing a fraction of the contents and instilling a hypertonic saline solution (30% NaCl), iodophore, or 95% ethanol to kill the germinal layer and daughter cysts. Surgical resection should be performed 30 minutes after instillation of the solution. In cases with biliary communication, the foregoing cidal agents are not recommended because of the risk of inducing sclerosing cholangitis.

As compared with medical treatment alone, debulking of cysts does not improve outcome, but it may relieve symptoms in specific cases. Treatment in the perioperative period with three to four cycles of albendazole 400 mg twice daily for 4 weeks, followed by a 2-week rest period is generally recommended to limit the risk of intraoperative dissemination. The same medical therapy is recommended for patients with inoperable hydatid cyst (see Table 12.3). In selected cases, CT or ultrasound has been used to guide percutaneous needle aspiration drainage and instillation of cidal agents (hypertonic saline or ethanol) to sterilize the cyst, followed by re-aspiration after 15 minutes to remove the cidal agent (“PAIR”). The PAIR treatment is often curative, and it is becoming the treatment of choice. The efficacy of PAIR has not be confirmed by randomized trials, however.

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**KEY POINTS**

*About Echinococcus*

1. Spread primarily by domestic dogs, who excrete eggs in their feces. Eggs survive in dust and contaminate food.
2. Eggs hatch in the intestine and oncospheres enter the bloodstream, where they migrate to the liver or lung, or (less commonly) to the brain, where they form hydatid cysts.
3. Hydatid cysts survive and grow over decades, causing symptoms when they reach 8 to 10 cm in diameter.
4. Diagnosis is made by computed tomography scan or ultrasonography.
5. Treatment involves administration of albendazole, combined with surgical resection preceded by instillation of an agent cidal to the germinal layer. Alternatively, percutaneous needle drainage and cidal agent instillation (“PAIR”) may be curative.

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**Prevalence, Epidemiology, and Life Cycle**

*Taenia solium* is another cestode (tapeworm) common in Central and South America, Mexico, the Philippines, Southeast Asia, India, Africa, and southern Europe. Like *Echinococcus*, *Taenia* can be contracted by ingesting viable eggs or by eating raw or undercooked pork containing encysted larvae. Once ingested, the eggs hatch or the encysted larvae are released into the stomach, where they migrate into the intestine and develop into adult worms that can reach 8 m in length. Autoinfection can occur as a result of regurgitation of eggs into the stomach or accidental ingestion of eggs from the host’s own feces.

**Clinical Presentation**

Adult intestinal worms rarely cause symptoms. However, larvae can penetrate the intestine, enter the bloodstream and eventually encyst in the brain, causing neurocysticercosis. Cysts may lodge in the cerebral ventricles (causing hydrocephalus), the spinal cord (resulting in cord compression and paraplegia), the subarachnoid space (causing chronic meningitis), or the cerebral cortex (causing seizures). Cysts may remain asymptomatic for many years, becoming clinically apparent only when the larvae die, an event associated with cyst swelling and increased inflammation. Larvae also encyst in other tissues (skin and muscle), but rarely cause symptoms. Eye involvement is also reported.

**Diagnosis and Treatment**

Computed tomography or nuclear magnetic resonance scan are the preferred diagnostic studies, demonstrating discrete cysts that may enhance following the administration of contrast media depending on the degree of surrounding inflammation. In CNS infection, multiple lesions are generally detected. Older lesions are often calcified (Figure 12.8). In the absence of cerebral edema, lumbar puncture can be performed. Analysis of the cerebrospinal fluid usually...
KEY POINTS

About Cysticercosis (Taenia solium infection)

1. Contracted by ingesting eggs in fecally contaminated food or encysted larvae in undercooked pork.
2. Larvae enter the bloodstream, encysting primarily in the brain.
3. Symptoms develop after many years when the larvae die, causing increased inflammation.
4. Can cause seizures, hydrocephalus, paraplegia, and meningitis.
5. Diagnosis is made by computed tomography scan, magnetic resonance imaging, or serology.
6. Treatment involves administration of albendazole plus corticosteroids for symptomatic disease; surgical resection can be performed in selected patients.

SCHISTOSOMIASIS

GUIDING QUESTIONS

1. Why doesn’t primary schistosomiasis occur in the United States?
2. How is schistosomiasis contracted?
3. Which Schistosoma strain causes swimmer’s itch?
4. What is Katayama fever?
5. In late disease, how does egg deposition cause clinical symptoms?

POTENTIAL SEVERITY

Usually a chronic disorder resulting in debilitating complications. Occasionally fatal during the early stage of infection as a result of a severe serum-sickness syndrome.

Prevalence, Epidemiology, and Life Cycle

Schistosoma mansoni, S. haematobium, and S. japonicum are members of the fluke (trematode) family. Schistosomes are estimated to infect between 200 and 300 million people worldwide. Primary infection does not occur in the United States because the critical intermediate host—a specific type of freshwater snail—is absent. However, approximately 400,000 imported cases occur in immigrants from Puerto Rico, South America (particularly Brazil), the Middle East, and the Philippines. S. mansoni is found primarily in South America, the Caribbean, Africa, and countries of the Arab Middle East. S. haematobium is found in Africa and the Middle East, and S. japonicum is found primarily in China and the...
Philippines. Two other strains that have more recently been found to cause disease are *S. intercalatum* (Western and Central Africa) and *S. mekongi* (Indochina).

The parasite is contracted by exposure to fresh water containing infectious cercariae. The fork-tailed cercariae are able to swim to and penetrate the skin of people wading in stagnant infested freshwater pools or rice paddies. Once inside the host, cercariae lose their tails and mature into schistosomulae that enter the bloodstream. From the bloodstream, they penetrate the lung and liver, where over a period of 6 weeks, they mature to adult worms. The adult worms then migrate through the venous plexus to various sites, depending on the *Schistosoma* strain. *S. mansoni* worms take up residence in the inferior mesenteric veins responsible for venous drainage of the large intestine; *S. japonicum*, in the superior mesenteric veins that drain the small intestine, and *S. haematobium*, in the vesicular plexus that drains the urinary bladder.

Once resident in the host, the worms can live for decades, releasing eggs into the bowel or bladder. Improper handling of contaminated stool and urine leads to egg contamination of water. Eggs hatch in fresh water, forming miracidia whose cilia enable them to swim and infect freshwater snails. Each species of schistosome requires a specific freshwater snail intermediate, which explains the geographic distribution of each strain. The miracidia multiply within the snail, and within 4 to 6 weeks, they release large numbers of cercariae capable of infecting humans.

### KEY POINTS

**About the Life Cycle of Schistosoma**

1. Cercariae swimming in fresh water can penetrate human skin.
2. Cercariae mature into schistosomulae that enter the bloodstream and migrate to the liver and lung, where they mature.
3. Mature worms migrate to the venous system of the small (*S. japonicum*) or large bowel (*S. mansoni*) or to the bladder venous plexus (*S. haematobium*).
4. The worms release eggs into stool or urine for many years, resulting in contamination of fresh water.
5. Freshwater snails are infected by miracidia, a necessary step in the production of cercariae and infection of humans.

### CASE 12.5

A 32-year-old man was evaluated for a lesion of the urinary bladder. He had been well until 16 months earlier. Soon after returning from a 1-week vacation in Malawi, he had an episode of perineal pain associated with painful ejaculation and brown-colored ejaculate. His condition improved after treatment with ciprofloxacin.

Four months before the evaluation, this patient had begun experiencing urinary frequency, with intermittent passage of small blood clots in the urine. His symptoms failed to improve on ciprofloxacin treatment. An epidemiologic history noted frequent travel outside the United States. Most recently, the man had traveled to Malawi with his wife. While there, he had repeatedly swum in a lake that he was assured was “safe.”

A laboratory workup showed a normal peripheral WBC count and differential. Urinalysis confirmed hematuria. Cytology found no malignant cells. A urogram and ultrasound demonstrated a round structure, 8 × 10 mm in diameter, adherent to the bladder wall. Cystoscopic examination disclosed multiple, slightly raised, polypoid lesions that were less than 5 mm in diameter. The lesions were erythematous, with focal yellow areas.

Low-power microscopic examination of material from a bladder biopsy revealed a polypoid inflammatory lesion of the bladder mucosa with dense inflammatory infiltrate surrounding clusters of eggs in the submucosa. At higher magnification, the granulomas were found to contain clusters of helminthic eggs surrounded by epithelioid histiocytes, chronic inflammatory cells, and eosinophils. The eggs were oval and had a terminal spine characteristic of *S. haematobium* (Figure 12.9). The man’s wife was subsequently examined, and Schistosoma eggs were found in her urine. Both were treated with praziquantel, and the eggs disappeared from both patients’ urine.

### Clinical Presentation

The three stages of the disease correspond to the life cycle of the parasite in the human host.

The first stage occurs at the time of penetration and is commonly termed “swimmer’s itch.” A very itchy macular papular rash develops within 24 hours of the
cercariae penetrating the skin. The lesions spontaneously resolve as the organisms spread to the bloodstream. An avian schistosome is also able to penetrate the skin, but it is not capable of entering the bloodstream. This benign form of swimmer's itch is common in the Great Lakes of the north-central United States and in freshwater lakes in Europe.

The second stage of clinical disease occurs 4 to 8 weeks later, when the worms mature and begin releasing eggs. Patients develop a serum-sickness-like syndrome as they react with elevated levels of immunoglobulin E and peripheral eosinophilia to egg antigens. Fever, headache, cough, chills, and sweating are accompanied by lymphadenopathy and hepatosplenomegaly. This clinical constellation has been called "Katayama fever" and is most commonly associated with *S. japonicum*. The symptoms usually resolve spontaneously, but in heavy infections, this acute reaction can be fatal.

The third, chronic, stage results from granulomatous reactions to egg deposition in the intestine, liver, bladder, and (less commonly) the lung and CNS. Granulomatous reactions in the bowel can lead to chronic diarrhea, abdominal pain, and blood loss. Eggs may enter the portal venous system and gain entry to the liver, where chronic inflammation is followed by fibrosis leading to portal hypertension, splenomegaly, and bleeding esophageal varices. Because the hepatic parenchyma is seldom compromised, liver function tests are usually normal. Peripheral eosinophilia is commonly encountered. Hepatosplenomegaly with normal liver function tests, peripheral eosinophilia, and a history of residence in an endemic area should raise the possibility of chronic hepatic schistosomiasis. The development of collateral venous channels in association with portal hypertension can result in egg deposition in the pulmonary arteries, causing pulmonary hypertension and right-sided congestive heart failure. Deposition of eggs in the CNS is less common and can cause seizures or, if eggs are deposited in the region of the spinal cord, transverse myelitis. In *S. haematobium*, eggs are deposited in the bladder wall, leading to hematuria, bladder obstruction, hydronephrosis, and recurrent urinary tract infections. Bladder cancer may also complicate chronic *S. haematobium* infection.

**Diagnosis and Treatment**

Demonstration of eggs in the stool or urine allows a specific diagnosis to be made. Quantitative egg counts are helpful in assessing the intensity of the infection. Urine is best collected between noon and 2 PM. Passing the urine through a 10-mm filter concentrates the eggs. Eggs may also be identified on tissue biopsies. Rectal biopsy is particularly helpful in diagnosing *S. mansoni*. The eggs of *S. mansoni*, *S. japonicum*, and *S. haematobium* have distinct morphologies, allowing them to be readily identified using a low-power (100X) microscope (Figure 12.4). In chronic disease, the egg burden may be low, making the diagnosis difficult. Anti-schistosome antibody tests are now available for detecting chronically infected patients; however, the specificity and sensitivity of these tests limit their value. Furthermore, the tests cannot be used in lifelong residents of endemic areas, because serology in these

**Figure 12–9.** Bladder biopsy showing an egg of *Schistosoma haematobium*. (Picture from the N. Engl. J. Med 343:1105-1111, 2000)

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**KEY POINTS**

**About the Clinical Presentation of Schistosomiasis**

1. Skin penetration causes “swimmer’s itch.”
2. A serum-sickness syndrome with eosinophilia and high immunoglobulin E levels may follow. This constellation of symptoms is called Katayama fever.
3. Granulomatous reaction to egg deposition leads to chronic diarrhea, portal hypertension and hepatosplenomegaly, and pulmonary hypertension in *Schistosoma mansoni* and *S. japonicum*.
4. Eggs deposited in the bladder can lead to hematuria, bladder obstruction, hydronephrosis, recurrent urinary tract infections, and sometimes bladder cancer in cases of *S. haematobium*. 

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individuals is frequently positive in the absence of active infection.

Praziquantel is effective treatment for all forms of schistosomiasis (see Table 12.3). Side effects of treatment are mild and include fever, abdominal discomfort, and headache.

OTHER, LESS COMMON TISSUE FLUKES

Other flukes that can infect humans undergo a life cycle similar to that of Schistosoma, requiring snails as the intermediate host. However, rather than gaining entry by penetrating the human skin, the cercariae take up residence in other food sources and become encysted. Infection is contracted when the human host eats cercariae contaminated food.

Clonorchis sinensis (Chinese liver fluke) infections result from the ingestion of raw or undercooked freshwater fish. Infections occur in China, Hong Kong, and Vietnam. Worms gain entry into biliary tract via the ampulla of Vater. Infection can be complicated by cholangitis and, later, by cholangiocarcinoma. Infections are effectively treated with praziquantel.

Fasciola hepatica, another liver fluke, is found in sheep-raising areas of the world, including South America, Australia, China, Africa, and Europe. Ingestion of vegetables contaminated with encysted cercariae is the most common route of infection. This fluke is treated with praziquantel or bithionol.

Paragonimus westermani (lung fluke) is contracted by eating raw or pickled crawfish or freshwater crabs. This parasite is found in Central and South America, West Africa, India, and East Asia. This parasite first enters the gastrointestinal tract and subsequently penetrates through the diaphragm, entering the pleural cavity and lungs, causing respiratory symptoms. Praziquantel is the treatment of choice.

KEY POINTS

About the Diagnosis and Treatment of Schistosomiasis

1. Characteristic eggs in the stool or urine (check between noon and 2 pm) or on tissue biopsy are diagnostic; consider rectal biopsy in Schistosoma mansoni.
2. Eggs may not be seen in chronic disease, anti-schistosome antibody may be helpful,
3. Praziquantel is the treatment of choice.

FILARIOSIAS (WUCHERERIA BANCROFTI AND BRUGIA MALAYI)

GUIDING QUESTIONS

1. How is filariasis transmitted?
2. What is the key characteristic that helps to differentiate inflammatory filariasis from bacterial cellulitis?
3. Is elephantiasis an early or late manifestation of filariasis?
4. When during the day are blood smears most likely to be positive?

POTENTIAL SEVERITY

A chronic debilitating infection that can cause severe disfiguring complications by blocking lymphatic drainage.

Prevalence, Epidemiology, and Life Cycle

Microfilaria is less common than many parasites, being estimated to infect approximately 120 million people. Several strains of worm can cause this disease. Wuchereria bancrofti is found throughout the tropics, and Brugia malayi is restricted to the southern regions of Asia. A third strain, Brugia timori is found only in Indonesia.

Infectious larvae are transmitted by the bite of a mosquito. Larvae pass from the skin into the lymphatic system, where, over several months, they mature near the lymph nodes. Adult worms (40 to 100 mm in length) can survive in the lymphatic system for 5 to 15 years. During this period, males and females mate, daily producing an average of 10,000 microfilaria (dimensions: 200 to 300 mm in length, and 10 µm in width). The microfilaria are released into the bloodstream. The time from initial insect bite to appearance of microfilaria in the infected human is usually 12 months. In W. bancrofti, the highest concentration of microfilaria in the blood is generally found in the middle of the night, explaining why midnight blood smears are recommended for diagnosis.

If a mosquito bites an infected human, the microfilaria are ingested and, over 10 to 14 days, they develop into infective larvae that can be transmitted to a new human host. The percentage of mosquitoes containing infective larvae has been estimated to be just 1% in
endemic areas. Repeated mosquito bites are therefore generally required to contract this infection, which may explain why adults—particularly men—more commonly contract this infection.

Clinical Presentation

Asymptomatic Filariasis

Many individuals have asymptomatic infection. Peripheral eosinophilia and palpable lymphadenopathy may be the only clinical manifestations. Children usually experience no symptoms, despite high numbers of microfilaria in their blood.

Inflammatory Filariasis

Adults more commonly react with strong allergic reactions to the invasion by worms that begins approximately 1 year after exposure. Fever, chills, vomiting, headache, and malaise may be associated with lymphangitis of an extremity, orchitis, epididymitis, or scrotal swelling. The affected extremity becomes hot, swollen, erythematous, and painful, mimicking cellulitis. These symptoms are associated with peripheral leukocytosis and an increased percentage of eosinophils (6% to 25%). Unlike cellulitis, which usually begins peripherally and moves up the limb, inflammatory filariasis begins centrally near the lymph nodes and extends peripherally. Attacks may occur monthly and do not respond to antibiotics. The granulomatous response in the lymphatic tissue is thought to be a host inflammatory reaction to dying worms. Death of the worms is associated with release of the rickettsial-like bacteria Wolbachia that live in a symbiotic relationship within the adult worms.

Obstructive Filariasis

Over time, chronic inflammation leads to fibrosis and permanent obstruction of lymphatic flow. This syndrome is the result of continuous microfilaria infection. Persistent lymphatic obstruction and edema lead to marked skin thickening and deposition of collagenous material, eventually causing elephantiasis. Patients suffer with debilitating enlargement of the legs or massive enlargement of the scrotal tissue, making walking difficult. Cellulitis caused by streptococci or Staphylococcus aureus may periodically recur, requiring antibiotic treatment. Rupture of the lymphatics into the kidney or bladder can result in chyluria, and rupture into the peritoneum can cause chylous ascites.

Diagnosis and Treatment

Giemsa- or Wright-stained peripheral smears should be obtained at midnight in all cases except for those from the South Pacific. Identification of adult worms in the blood is definitive; however, in early and late disease, worms often are not seen. Antibody and antigen assays are highly sensitive and specific. An IgG4 antibody titer correlates with active disease. An ELISA for W. bancrofti circulating antigen is now the diagnostic test of choice, and titers correlate with adult worm burden. A PCR test for W. bancrofti has been developed, but it is not widely available. Biopsy of infected lymph nodes is generally not recommended, but when performed, may reveal adult worms in addition to granuloma. Ultrasonography of dilated lymphatics in the spermatic cord have revealed motile worms. In early infection and during the inflammatory stage, peripheral eosinophilia is commonly seen.

KEY POINTS

About the Clinical Presentation of Filariasis

1. Many people, particularly children, are asymptomatic.
2. Inflammatory filariasis is associated with periodic erythema, warmth, pain, and swelling that mimic cellulitis (associated with peripheral eosinophilia).
3. Obstructive disease results in chronic limb swelling (elephantiasis) because of lymphatic fibrosis.
4. Obstructive disease can lead to recurrent bacterial cellulitis.
5. Rupture of lymphatics can cause chyluria or chylous ascites.
6. Release of the rickettsial-like bacteria Wolbachia from the adult worms may be the major stimulus for inflammation.

KEY POINTS

About the Life Cycle of Wuchereria bancrofti and Brugia malayi

1. Transmitted by the bite of an infected mosquito.
2. Repeated mosquito bites are required.
3. Microfilaria live in the lymphatic system, and worms enter the bloodstream at midnight (except in the South Pacific).
4. Mosquitoes are infected by biting humans.
During the chronic stages of disease, eosinophilia is generally not present. If worms cannot be identified, the diagnosis has to be made on clinical grounds.

Diethylcarbamazine in a single dose is the recommended therapy, but fails to kill adult worms (see Table 12.3). A reduction in the level of microfilaria in the blood is usually observed. Treatment may increase inflammation and may not halt progression to fibrosis and lymphatic obstruction. Ivermectin 200 to 400 mg/kg, combined with albendazole 400 mg, is another effective regimen that may more effectively kill the adult worms. For more severely infected patients, a 3-week course of doxycycline kills the symbiote Wolbachia, resulting in sterility of the adult worms. This treatment can be followed by diethylcarbamazine or ivermectin plus albendazole. Normally, these agents exacerbate the host’s inflammatory reaction as the microfilaria die, but doxycycline eradication of the Wolbachia eliminates this complication. Anti-inflammatory agents may be used to reduce the extent of inflammation, and elastic support stockings can be helpful in reducing moderate lymphedema.

**DIROFILARIASIS (DOG HEARTWORM)**

Humans are an accidental host in dirofilariasis. The disease is most commonly found in the southeastern United States and is transmitted by mosquitoes. After developing in the subcutaneous tissue, the young adult filaria migrate. In dogs, they migrate to the right side of the heart and right pulmonary vessels, where they survive. In humans, they migrate to the lung, but fail to develop. Their deaths produce local granulomatous inflammation. Most human cases present as an asymptomatic pulmonary coin lesion mimicking an early neoplasm. Microscopic examination of the lung biopsy reveals a dead worm. Treatment of human cases is not necessary.

**ONCHOCERCIASIS**

The *Onchocerca volvulus* parasite is found primarily in Africa, where it infects approximately 20 million people. Cases are occasionally seen in Central and South America. The infection is transmitted by a black fly that swarms around the face, often biting around the eyes and depositing *Onchocerca* larvae onto the skin. These larvae penetrate and crawl through the skin and connective tissue. The worms initially cause an itchy erythematous rash. Later, fibrous skin nodules develop. Worms often migrate into the anterior chamber of the eye, causing inflammation and blindness. Because the offending black fly is commonly found near streams, this disease has been called “river blindness.”

The diagnosis is made by skin snips or by visualizing worms in a slit lamp examination of the eyes. The treatment of choice is a single dose of ivermectin repeated at 3-month intervals until symptoms resolve (see Table 12.3). Fever, itching, and an urticarial rash may develop as result of dying microfilaria.

**LOIASIS**

The loa loa microfilaria is also transmitted by a fly, and the disease is found in Western and Central Africa. The microfilaria migrate through the skin, causing localized edema called Calabar swellings. Several hours before swelling occurs, local itching and pain are noted. Occasionally the microfilaria can be seen migrating through the subconjunctiva, causing intense conjunctivitis. Active microfilaria migration is associated with marked peripheral eosinophilia.

The diagnosis is made by daytime blood smear. Diethylcarbamazine or ivermectin are recommended as treatment (see Table 12.3). Diethylcarbamazine can precipitate encephalitis in heavily infected patients.

**FURTHER READING**

**General**


**Malaria**


Leishmaniasis


Trypanosomiasis


Intestinal helminths


Cysticercosis


Schistosomiasis


Filariasis


Onchocerciasis


As a consequence of increased outdoor activities, increasing populations of deer in close proximity to urban areas, and the spread of housing to more rural settings, humans are increasingly coming in contact with animals and with disease-spreading insect vectors. As a consequence, the natural spread of infection from lower mammals to humans, termed “zoonotic infection,” has greatly increased since the middle 1970s.

Zoonotic infections represent one of the most important classes of emerging infectious diseases. By combining new understandings of the genomic structures of pathogens with highly sensitive and specific polymerase chain reaction (PCR) detection methods, a number of newly discovered zoonotic diseases have been identified—for example, Bartonella and Ehrlichia.

**GUIDING QUESTIONS**

1. Why have zoonotic infections increased in frequency?
2. How is Lyme Disease contracted and what animal is responsible for spreading this infection?
3. What is the significance of erythema migrans and does this skin lesion require treatment?
4. Should patients with a positive Lyme Disease antibody titer and chronic fatigue be treated with antibiotics?
5. What activities are associated with the highest risk for Leptospirosis and why?
6. How is Rocky Mountain Spotted fever treated and how quickly should therapy be instituted?
7. What are morulae and in what disease are they most frequently seen?
8. What organism causes Cat Scratch Fever and how should this infection be treated?
9. Skinning of what animal carries a high risk of developing Brucellosis?

**SPIROCHETES**

**LYME DISEASE**

**POTENTIAL SEVERITY**

*Can present acutely or result in a chronic disease that is occasionally life-threatening.*

**Epidemiology**

Lyme disease is the most common insect-borne infection in the United States. More than 10,000 cases are
reported annually in United States between the months of May and September. Cases are concentrated in three areas of the country: the Northeast (Massachusetts to Maryland), the Midwest (primarily Wisconsin), and the far West (primarily California and Oregon). Lyme disease is also found in the temperate regions of Europe, Scandinavia, parts of the former Soviet Union, China, Korea, and Japan. Children and middle-aged adults are at greatest risk of acquiring this infection. A variant disease called “southern tick-associated rash illness” (STARI) that can cause an erythema migrans–like rash is found in Missouri and regions of the southeastern United States. This disease is caused by Borrelia lonestari.

Pathogenesis

Lyme disease is caused by the spirochete Borrelia burgdorferi, the longest and narrowest member of the Borrelia species at 20 to 30 μm in length and 0.2 to 0.3 μm in width. Like other spirochetes, it is microaerophilic and fastidious, but it can be grown in vitro using Barbour–Stoenner–Kelly medium. B. burgdorferi expresses a number of lipoproteins on its outer surface (called Osps—“outer surface proteins”) that are thought to help the organism survive both within the tick and within mammals and birds. A fibronectin-binding protein, flagellar antigen, and two heat-shock proteins have also been described. The heat-shock proteins cross-react with human proteins and may play a role in the development of the rheumatologic complaints commonly associated with late Lyme disease.

Like Babesia, B. burgdorferi is transmitted the deer tick Ixodes scapularis. Other Ixodes species are responsible for transmission in the far western United States, Europe, and Asia. The increased incidence of Lyme disease since the end of the 1980s is thought to be the result of the rise in the deer population in suburban areas. Deer and other large mammals are the primary host for the adult tick, but do not play direct role in transmission of the spirochete. The adult Ixodes tick does not transmit Lyme disease to humans. As observed with Babesia (see Chapter 12), infection is spread to humans by the young Ixodes nymph.

These small ticks survive primarily on the white-footed mouse, but they can also be found on other rodents. They attach to humans who walk through brush or tall grass. Because the nymph is the size of a small freckle, it is often not detected and is allowed to remain attached for 36 to 48 hours, the period required to efficiently transmit infection. As the tick feeds, spirochetes escape from the salivary gland of the insect into the skin of a human host. As observed with primarily syphilis, B. burgdorferi multiplies locally in the skin and after an incubation period of 3 to 32 days, begins forming a distinct, slowly expanding, circular erythematous lesion called erythema migrans. The organism then disseminates throughout the body.

During the dissemination stage, the organism can be cultured from blood and cerebrospinal fluid (CSF). Initially, the immune response is suppressed; however, over days to weeks, cell-mediated immunity is activated, and macrophages are stimulated to produce the proinflammatory cytokines, tumor necrosis factor, and interleukin 1. During this period, immunoglobulin M (IgM) and G (IgG) antibodies are slowly generated. Levels of IgM usually peak between 3 and 6 weeks after the initial infection; levels of IgG rise gradually over months. Sites of infection are infiltrated by lymphocytes and plasma cells, and evidence of small-vessel vasculitis is often apparent. However, despite these immune responses, B. burgdorferi can survive for years in the synovial fluid, nervous system, and skin of the untreated patient.

### KEY POINTS

**About the Epidemiology, Cause, and Pathogenesis of Lyme Disease**

1. The most common insect-borne disease in the United States. Found in
   a) the Northeast United States, Wisconsin, California, and Oregon.
   b) temperate regions of Europe, Scandinavia, the former Soviet Union, China, Korea, and Japan.
2. Caused by Borrelia burgdorferi, a microaerophilic spirochete, that can be grown on Barbour–Stoenner–Kelly medium.
   a) Expresses lipoproteins on its surface help the organism survive in hosts.
   b) Produces fibronectin-binding protein, flagellar antigen, and two heat-shock proteins that cross-react with human proteins.
3. Transmitted by the nymph of the Ixodes tick. Moves from deer to white-footed mouse to humans.
   a) Size of a freckle, commonly missed.
   b) Must attach for 36 to 48 hours to transmit the spirochete.
4. Begins in the skin, and then disseminates.
5. Induces cell-mediated and humoral immunity. Can survive for years in joint fluid, the central nervous system, and skin of untreated humans.
Clinical Manifestations

CASE 13.1

A young man sought medical attention because of neck stiffness, shoulder pain, and a rash on his leg. On examination, he was noted to have a macular erythematous circular lesion on one leg. Further examination revealed a wood tick attached to his other leg, indicating recent tick exposure. The tick was subsequently identified as Ixodes pacificus. Western Blot assay demonstrated specific IgG and IgM antibodies to B. burgdorferi. He was treated with doxycycline and his symptoms resolved. (Adapted from Murakami EK, Shojaania N, Christie S, Internet case report.)

Just as is observed in syphilis (see Chapter 9), Lyme disease has three stages:

1. Early localized infection (“primary Lyme disease”).

Case 13.1 presented with erythema migrans, the hallmark of Lyme disease, noted in 90% of patients (Figure 13.1). The lesion begins within a month of exposure as a red macule or papule at the site of the tick bite. It then expands over days, forming a bright red flat border at the advancing edge. As the lesion expands, central clearing may develop, and in some cases, the site takes on the appearance of a target. However, in many patients, the lesion remains diffusely erythematous. Erythema migrans are usually large, reaching an average size of 15 cm (range: 3 to 70 cm). They are commonly located in moist, warm areas of the body where ticks prefer to feed (axilla, behind the knees, and at the belt line). Despite their size, warmth, and bright color, the lesions are usually painless, but they can cause burning or itching.

2. Early disseminated disease (“secondary Lyme disease”).

Several days after the onset of erythema migrans, small annular satellite lesions may be observed, reflecting early dissemination. Also at this time, patients often experience a viral-like syndrome consisting of malaise, fatigue, myalgias, arthralgias, and headache. They may also develop generalized lymphadenopathy. Migratory joint, tendon, muscle, and bone pain are common complaints. In a significant percentage of patients, symptoms attributable to the nervous system and heart commonly develop at this stage.

Nervous system involvement. The spirochete often initially disseminates to the nervous system, causing a severe generalized headache that waxes and wanes. If the disease is not treated, about 10% of cases develop more serious neurologic manifestations. Frank meningitis can result in neck stiffness, and CSF lymphocytic pleocytosis (usually about 100 cells/mm³), in elevated CSF protein with normal CSF glucose. Cranial nerve deficits can accompany meningitis, bilateral Bell’s palsy being the most common cranial nerve dysfunction. Lymphocytic infiltration of small vessels supplying axons can lead to axonal degeneration and peripheral neuritis. The triad of meningitis,

KEY POINTS

About Primary and Secondary Lyme Disease

1. Hallmark of primary disease is erythema migrans:
   a) Macular expanding erythematous lesion, central clearing.
   b) Begins one month after the tick bite.
   c) Mean diameter 15 cm.
   d) Painless, can cause itching.

2. Dissemination is associated with small annular lesions and a flu-like illness.
   a) Central nervous system involvement can cause waxing and waning headache. Lymphocytosis of the cerebrospinal fluid (100 cells/mm³), cranial nerve deficits (Bell’s palsy), and peripheral neuritis is called Bannworth’s syndrome.
   b) In cardiovascular involvement, spirochetes infiltrate the myocardium, causing conduction defects.
cranial nerve deficits, and radiculoneuritis has been termed Bannworth’s syndrome. This syndrome is more commonly reported in Europe than in the United States. **Cardiovascular involvement.** Among untreated patients, 5% to 8% develop cardiac manifestations within several weeks of the onset of illness. Spirochetes can directly infiltrate the myocardium, causing lymphocytic inflammation. Conduction defects are most common, and an electrocardiogram should be ordered in all patients with symptomatic Lyme disease. First-degree heart block is most common, but second-degree and complete heart block may also develop. However, complete heart block rarely persists for longer than 7 days and does not usually require placement of a pacemaker. More severe myocarditis accompanied by congestive heart failure is rare.

**3. Late disease ("tertiary lyme disease").**

Late disease develops months to years after primary infection. Some patients never experience symptoms from the earlier stages. Musculoskeletal complaints are most common at this stage, but neurologic complaints, skin disease, and generalized symptoms may also occur. **Musculoskeletal manifestations.** Approximately 60% to 80% of untreated patients experience musculoskeletal symptoms. Migrating arthralgias or frank arthritis causing joint swelling most commonly involve the knees and other large joints. Less commonly, small joints may be affected. Joint aspiration may reveal white blood cell (WBC) counts of 500 to 110,000 /mm³, with a predominance of polymorphonuclear leukocytes (PMNs). The presence of spirochetes in the joint fluid can be detected by PCR in most patients, and arthritis usually resolves after antibiotic therapy.

**Neurologic manifestations.** Just as is observed in syphilis, *B. burgdorferi* may invade the cerebral cortex and cause a chronic encephalopathy associated with mood, cognitive, and sleep disorders. Subtle language disturbances have also been observed. The CSF may reveal elevated protein levels and increased titers of antibodies to *B. burgdorferi*. Patients may also develop peripheral neuropathies leading to paresthesias and radicular pain. Evaluation of these neurologic complaints can be complicated, and the neurocognitive complaints associated with fibromyalgia are often misdiagnosed as central nervous system Lyme disease. The response to antibiotic therapy is variable.

**Other manifestations.** Acrodermatitis chronica atrophicans can develop years after erythema migrans. It begins as a bright red skin lesion that later becomes atrophic, mimicking localized scleroderma. *B. burgdorferi* can be cultured from these lesions up to 10 years after their onset. A very difficult management problem arises from the small percentage of patients who experience persistent diffuse aches and pains. Some patients with Lyme disease develop a fibromyalgia-like syndrome; others may experience a chronic fatigue–like syndrome. The contribution of *B. burgdorferi* infection to these complaints remains controversial, and many patients with these complaints fail to improve after antibiotic therapy.

**Diagnosis**

Although *B. burgdorferi* can be grown in vitro, cultures are rarely positive because the number of organisms in skin lesions, blood, and CSF is very low. The diagnosis is based on clinical manifestations and a history of possible tick exposure in an endemic area, combined with serologic testing. In considering the diagnosis, it is important keep in mind that many patients with confirmed Lyme disease deny being bitten by a tick.

The Lyme disease enzyme-linked immunosorbent assay (ELISA) uses a sonicate of *B. burgdorferi* as the antigen and detects IgG and IgM antibodies directed against the spirochete. Acute and convalescent titers spaced 2 to 4 weeks apart should be collected. In early disease, a significant rise in antibody titer is detected in only 60% to 70% of patients. Negative titers at this stage therefore do not exclude Lyme disease. Also, antibiotic therapy can abort a full antibody response, further complicating serologic diagnosis. For these reasons, ELISA testing is not recommended for patients with classic erythema migrans, because the lesion is

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**KEY POINTS**

**About Late or Tertiary Lyme Disease**

1. Symptomatic disease develops months to years after primary disease.
2. Musculoskeletal complaints are most common:
   a) Migrating arthritis and arthralgias
   b) Joint fluid contains 500 to 110,000 cells/mm³, primarily polymorphonuclear leukocytes
   c) Patient usually improve with antibiotics
3. Central nervous system encephalopathy can cause mood, cognitive, and sleep disorders:
   a) Elevated protein and antibody against *Borrelia burgdorferi* in cerebrospinal fluid
   b) Response to antibiotics variable
4. Acrodermatitis chronica atrophicans, a chronic skin infection, contains spirochetes
5. Fibromyalgia-like or chronic fatigue–like syndrome may occur; controversial, antibiotics not helpful.
A number of other diagnostic tests have been described, but their usefulness has not been substantiated. Serologic tests are best utilized for the patient with suspected early disease who does not have erythema migrans or for the patient with symptoms of late disease. Negative serology in early disease may require follow-up testing because of the delay in the rise of antibody titers in some patients. In patients with suspected late disease, a negative IgG titer virtually excludes the diagnosis.

**Treatment**

For the treatment of early disease, amoxicillin or doxycycline for 21 to 28 days are equally effective (see Table 13.1). The ideal duration of therapy has not been determined, and many physicians opt for the longer course. Cefuroxime axetil is an effective alternative. Oral erythromycin (250 mg every 6 hours) and oral azithromycin (500 mg daily) have proved to be less effective.

For early disseminated disease with isolated palsy of the VIIth cranial nerve, multiple erythema migrans lesions, or carditis with first-degree heart block, both doxycycline and ceftriaxone are effective. A Jarisch-Herxheimer-like reaction may be observed in up to 15% of patients during the first 24 hours of therapy for disseminated disease. In patients with meningitis or other neurologic abnormalities, and in patients experiencing carditis with high-degree heart block, intravenous

### KEY POINTS

**About the Diagnosis of Lyme Disease**

1. Cultures are rarely positive and are not recommended
2. Diagnosis is made by a combination of epidemiology, clinical manifestations, and serology.
3. Many patients with Lyme disease deny a tick bite.
4. Enzyme-linked immunosorbent assay (ELISA) detects immunoglobulin G (IgG) and M (IgM) antibodies:
   a) Not recommended in the presence of classic erythema migrans, which is pathognomonic.
   b) Titer rise is aborted by early antibiotic treatment.
   c) IgM begins to rise at 2 weeks, declines by 2 to 3 months.
   d) IgG rises at 6 to 8 weeks, persists for life; negative IgG titer excludes late disease.
   e) False positive rate is 3% to 65.
5. Western Blot recommended to confirm all positive ELISA tests.
   a) The 23-kDa OspC protein and the 41-kDa flagellar antigen most commonly cross-react.
   b) Strict criteria for a positive Western Blot have been established by the U.S. Centers for Disease Control and Prevention.

### KEY POINTS

**About the Treatment and Prevention of Lyme Disease**

1. Treat early disease with amoxicillin or doxycycline for 21 to 28 days.
2. Treat disseminated disease characterized by mild carditis (first-degree heart block) or VIIth nerve palsy with doxycycline for 21 days or intramuscular ceftriaxone for 14 days.
3. Meningitis or carditis with high-degree heart block should be treated with intravenous ceftriaxone or penicillin for 14 to 30 days.
4. Treat chronic arthritis cases with doxycycline or amoxicillin for 30 to 60 days, or use a meningitis regimen.
5. Failure to improve on antibiotics suggests another diagnosis.
6. Prophylactic antibiotics are recommended if a small tick has been attached for more than 24 hours or if an engorged tick is found.
Table 13.1. Antibiotic Treatment of Zoonotic Infections

<table>
<thead>
<tr>
<th>Infection</th>
<th>Drug</th>
<th>Dose</th>
<th>Relative Efficacy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lyme disease</strong></td>
<td>Amoxicillin, or doxycycline</td>
<td>500 mg PO q8h for 14–21 days</td>
<td>First line</td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>Cefuroxime</td>
<td>100 mg PO q12h for 14–21 days</td>
<td>First line</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>500 mg PO q12h for 14–21 days</td>
<td>Alternative</td>
<td></td>
</tr>
<tr>
<td><strong>Early disseminated</strong></td>
<td>Doxycycline, or ceftriaxone</td>
<td>100 mg PO q12h for 14–21 days</td>
<td>Jarisch–Herxheimer reaction common</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 g IM q24h for 14–21 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heart block or meningitis</strong></td>
<td>Ceftriaxone, or penicillin G</td>
<td>2 g IV q24h for 14–28 days</td>
<td></td>
<td></td>
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<tr>
<td><strong>Chronic arthritis</strong></td>
<td>Doxycycline, or amoxicillin, or</td>
<td>100 mg PO q12h for 28 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(duration 30–60 days)</td>
<td>amoxicillin</td>
<td>500 mg PO q8h for 28 days</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>(duration 30–60 days)</td>
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<tr>
<td><strong>Leptospirosis</strong></td>
<td>Penicillin G, or ampicillin</td>
<td>1.5×10^6 U IV q6h for 5–7 days</td>
<td>Jarisch–Herxheimer reaction common</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>Ceftriaxone</td>
<td>0.5–1 g IV q6h for 5–7 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(duration 5–7 days)</td>
<td>Doxycycline</td>
<td>1 g IV q24h for 5–7 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>amoxicillin</td>
<td>100 mg PO q12h for 5–7 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(duration 5–7 days)</td>
<td>500 mg PO q8h for 5–7 days</td>
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<tr>
<td><strong>Rocky Mountain Spotted Fever</strong></td>
<td>Doxycycline</td>
<td>100 mg PO or IV q12h</td>
<td>First line</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>for 3 days after afebrile</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Chloramphenicol</td>
<td>Children &lt;45 kg: 2.2 mg/kg per dose q12h</td>
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<tr>
<td></td>
<td></td>
<td>for 3 days after afebrile</td>
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<tr>
<td></td>
<td></td>
<td>500 mg PO or IV q6h for 3 days after afebrile</td>
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<tr>
<td><strong>Typhus</strong></td>
<td>Doxycycline</td>
<td>100 mg PO or IV q12h</td>
<td>First line</td>
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<tr>
<td></td>
<td></td>
<td>for 3–5 days after afebrile</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chloramphenicol</td>
<td>Children: Same as Rocky Mountain Spotted</td>
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<tr>
<td></td>
<td></td>
<td>Fever</td>
<td></td>
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<tr>
<td></td>
<td>Add rifampin in areas</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>with resistant strains</td>
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<tr>
<td></td>
<td></td>
<td>600–900 mg PO q24h for 3–5 days after afebrile</td>
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<tr>
<td><strong>Ehrlichiosis and anaplasma</strong></td>
<td>Doxycycline</td>
<td>100 mg PO or IV q12h</td>
<td>Also preferred for children</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>for 3–5 days after afebrile</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children: Same as Rocky Mountain Spotted</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fever</td>
<td></td>
<td></td>
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<tr>
<td><strong>Q fever</strong></td>
<td>Doxycycline, plus hydroxychloroquine</td>
<td>100 mg PO or IV q12h</td>
<td>Add hydroxychloroquine for endocarditis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>200 mg PO q8h</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bartonella Lymphatic disease</strong></td>
<td>Azithromycin, or clarithromycin, or</td>
<td>500 mg PO once, then 250 mg</td>
<td>All equally effective</td>
<td></td>
</tr>
<tr>
<td><strong>Severe disease</strong></td>
<td>doxycycline, or ciprofloxacin</td>
<td>500 mg PO q12h</td>
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<td></td>
<td></td>
<td>100 mg PO q12h</td>
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<td></td>
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<td>500 mg PO q12h</td>
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<tr>
<td></td>
<td>Azithromycin, plus rifampin</td>
<td>500 mg PO q24h</td>
<td>Efficacy not proven</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>600 mg PO or IV q24h</td>
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</tbody>
</table>

(Continued)
ceftriaxone for 30 days or high-dose penicillin is recommended. Patients with intermittent or chronic arthritis may be treated with a very prolonged course of doxycycline or amoxicillin for 30 to 60 days.

A rare but difficult management problem arises in the patient who complains of persistent symptoms despite appropriate therapy. Patients must be warned that symptoms can linger for up to 6 months after treatment. In the patient whose symptoms persist for more prolonged periods, objective evidence for relapse is rarely found. Repeat antibiotic therapy rarely relieves symptoms. The wisest course of action is re-evaluation rather than re-treatment, because the most likely explanation for a lack of response to therapy is misdiagnosis.

Prevention

Because of the extensive publicity surrounding Lyme disease, people often panic when they sustain a tick bite. In endemic areas, frantic calls to the physician’s office are a frequent occurrence during the summer months. A logical approach to the management of tick bites will reduce unnecessary administration of antibiotics. Assessment of the risk of contracting Lyme disease requires a careful history of the nature of the tick bite. The questioner needs inquire about:

- The size of the tick. Lyme disease is primarily spread by the *Ixodes scapularis* nymph. This tick is very small, about the size of a small freckle. Larger ticks are unlikely to transmit Lyme disease.
- Attachment. If the tick fails to attach to the skin it cannot transmit disease. The likelihood of being bitten by a tick can be reduced by wearing long pants and shirts when walking in areas with brush and high grasses. In endemic areas, public health officials recommend that, upon returning from the outdoors, people perform a complete body check for ticks. Removing ticks before they attach is an excellent preventive measure. If an attached tick is discovered, the duration of attachment needs to be estimated. If attachment is less than 24 hours, the risk of disease transmission is low.
- Engorgement. If the tick is engorged with blood, prolonged attachment and an increased risk of disease transmission is suggested.

Prophylactic antibiotics consisting of a single dose of oral doxycycline (200 mg) within 72 hours of the tick bites can prevent the development of Lyme disease. The incidence of Lyme disease is approximately 1 in 100 in areas in which a high percentage of ticks harbor *B. burgdorferi*. In these locations, prophylaxis should be strongly considered. A more targeted approach of administering prophylactic antibiotics to the person who reports attachment of a small tick for more than 24 hours or who finds an engorged tick may prove more efficacious. In patients who do not fulfill these criteria, a careful explanation of the risk and natural progression of Lyme disease will usually calm the concerned caller.

LEPTOSPIROSIS

**POTENTIAL SEVERITY**

*Can cause a life-threatening systemic illness. Early diagnosis and treatment reduce the severity of the disease.*

Epidemiology

Leptospirosis is seldom diagnosed in the United States, except in Hawaii, where annual rates of 128 per 100,000 population have been reported. Leptospirosis is found throughout the world in temperate and tropical climates. Infection often follows hurricanes and flooding in Central and South America and Caribbean islands. In endemic areas, the incidence of leptospirosis is 5% to 20% annually.

The acute illness often causes nonspecific symptoms that never require medical attention, explaining the low incidence detected by passive surveillance studies. Dogs, livestock, rodents, amphibians, and reptiles can become infected. They often harbor *Leptospira* in their renal tubules, excrete the pathogen in the urine, and contaminate both soil and water, where the organism can persist for weeks to months. Humans at risk of becoming
1. Found in temperate and tropical climates:
   a) Rare in the United States, except for Hawaii
   b) Follows flooding, particularly in Central and South America, Caribbean islands
2. Dogs, livestock, rodents, amphibians excrete in *Leptospira* urine, contaminating soil and water.
3. Trappers, hunters, dairy farmers, livestock workers, veterinarians, military, and sewer workers at risk.
4. Outdoor freshwater activities predispose to disease.

Infected include trappers and hunters, dairy farmers, livestock workers, veterinarians, military personnel, and sewer workers. Infection has also been associated with outdoor activities in fresh water, including wading, swimming, whitewater rafting, kayaking, and canoeing. In cities, humans may be inadvertently exposed to infected rat and dog urine.

**Pathogenesis**

Leptospirosis is caused by *Leptospira interrogans*, a tightly spiraled spirochete with 18 or more coils per cell. Like other spirochetes, it is narrow, 0.1 μm in width, and long, 6 to 12 μm in length, and is best visualized by darkfield microscopy. *Leptospira* are obligate aerobes and grow slowly. There are more than 200 serovars of *L. interrogans*, and different serovars have predilections for different animals.

These organisms gain entry to the human host through cuts, abrasions, and skin softened by prolonged water exposure. Mucous membranes and conjunctivae are other portals of entry. Inhalation of aerosolized droplets can lead to pulmonary invasion. Once in the host, the spirochetes spread to the lymphatic system and then enter the bloodstream, disseminating throughout the body. The organisms’ outer wall is coated with lipopolysaccharide (LPS) that serves as a major antigenic stimulus. The spirochete releases a glycolipoprotein toxin that displaces long-chain fatty acids from host vascular endothelial cells, causing breakdown of the vessel walls and fluid leakage, allowing the organisms to escape from the bloodstream to the tissues. The host generates IgM and IgG antibodies directed against the *Leptospira* LPS. These antibodies are opsonins that enhance phagocytosis by macrophages in the reticuloendothelial system and enhance clearing of the organisms from the bloodstream.

**Clinical Manifestations**

A 25-year-old man presented to the hospital with complaints of fever and headache of 3 days’ duration. His symptoms began 3 days after he completed a 12-day survival race with three teammates, in Sabah State on Borneo Island, Malaysia. The day before his admission, one of his teammates was admitted to the hospital with similar complaints.

Physical examination revealed a body temperature of 37.9°C and a pulse rate of 90 per minute (regular). Conjunctiva were hyperemic, but nonicteric. Lymph nodes were not palpable, and no skin eruption was seen. A neurologic exam was normal.

A laboratory workup showed a WBC count of 13,100/mm³, with 91% neutrophils; a hemoglobin of 14.8 g/dL; a platelet count of 190,000/mm³; and total bilirubin 0.5 mg/dL. Liver enzymes were 63 IU/L (aspartate aminotransferase (AST)) and 66 IU/L (alanine aminotransferase (ALT)). Lactate dehydrogenase (LDH) was 420 IU/L; blood urea nitrogen (BUN), 12.5 mg/dL; and creatine, 0.9 mg/dL.

Minocycline was administered intravenously on the third hospital day, and fever subsided over 48 hours. The intravenous minocycline was continued...
The incubation period for leptospirosis is usually 5 to 14 days, but can be up to 30 days. The severity of illness varies greatly, and probably depends on the degree of exposure and the infecting serovar. Certain serovars from cows cause mild disease; others (contracted from rats) are more likely to cause severe disease. Classically, symptomatic disease occurs in two phases, the bacteremic phase and the immunologic phase; however, fewer than half of patients actually experience a biphasic illness. More than 90% of cases are self-limiting, but a small percentage experience a severe—sometimes fatal—illness called Weil’s disease.

As illustrated in case 13.2, the onset of illness is usually sudden. Symptoms may include fever, rigors, sweating, headache, photophobia, and severe myalgias accompanied by marked tenderness of the calves, thighs, and mid back. Other manifestations can include epistaxis, cough, and sore throat. Severe abdominal pain can mimic an acute abdomen. Nausea, vomiting, and diarrhea may also develop. On examination, the vessels in the conjunctiva are often very prominent because of vascular dilatation. Transient skin rashes may be noted. Capillary fragility can result in macular, maculopapular, purpuric, urticarial lesions, or diffuse skin redness. During the acute phase, Leptospira can be cultured from the blood and CSF.

Resolution of fever may herald the onset of the second, immune, phase of the illness. This phase can last 4 to 30 days. Blood cultures turn negative at this time. Prominent conjunctivitis with or without hemorrhage is seen, accompanied by photophobia, retrobulbar pain, neck stiffness, diffuse lymphadenopathy, and hepatosplenomegaly. Aseptic meningitis with or without symptoms is characteristic of this stage and is immune-mediated. Lymphocytes (<500 mm³) are seen in the CSF, together with moderate protein elevation (50 to 100 mg/mL and a normal glucose level.

Weil’s disease can develop after the acute phase and consists of hemorrhage, jaundice, and renal failure.

Severe hemorrhagic pneumonitis may also develop. Jaundice is caused by vascular injury to the hepatic capillaries without significant hepatocellular necrosis. Transaminase levels seldom exceed 200 U/L, and an elevated prothrombin time is uncommon. Creatine phosphokinase (CPK, MM fraction) reflecting myositis is often disproportionately high in comparison with the serum transaminase values. Marked elevations in conjugated bilirubin are the hallmark of liver involvement and can reach levels of 80 mg/dL, associated with mild-to-moderate elevations of alkaline phosphatase. The constellation of a high direct bilirubin, mild elevation in alkaline phosphatase, mild elevation in transaminase values, combined with a high creatine phosphokinase.

b) Renal failure accompanied by thrombocytopenia

c) Hemorrhagic pneumonia

Further investigation revealed that 51 of 78 participants had developed symptoms consistent with leptospirosis. Activities had included jungle trekking, canoeing, kayaking, rafting, scuba diving, mountain biking, and cave exploring. Local rivers were flooded at the time of the race. (Adapted from Sakamoto M, Sagara H, Koizumi N, Watanabe H. Infect Agent Survell Rep. 2001;22:5–6)

KEY POINTS

About the Clinical Manifestations of Leptospirosis

1. Incubation period is 5 to 14 days, and severity depends on inoculum and serovar (rat serovars being more severe).
2. Two phases in fewer than half of patients:
   a) Bacteremic phase—Sudden onset; fever, rigors, headache, photophobia, and severe myalgias; dilated conjunctival vessels, marked tenderness calves, thighs, and mid back; macular rash
   b) Immunologic phase (after 4 to 30 days)—Conjunctivitis, photophobia, retrobulbar pain, neck stiffness, diffuse lymphadenopathy, hepatosplenomegaly, and aseptic meningitis with lymphocytosis in the cerebrospinal fluid.
3. Weil’s disease is rare, severe; mortality 5% to 40%:
   a) High direct bilirubin, mild elevation in alkaline phosphatase, mild elevation in transaminase values, combined with a high creatine phosphokinase.
   b) Renal failure accompanied by thrombocytopenia
   c) Hemorrhagic pneumonia

for a week, followed by 2 weeks of oral doxycycline. Acute sera were negative for Leptospira antibody, but convalescent serum 2 weeks later revealed a 1:160 titer of antibody directed against L. interrogans serovar hebdomadis.

Further investigation revealed that 51 of 78 participants had developed symptoms consistent with leptospirosis. Activities had included jungle trekking, canoeing, kayaking, rafting, scuba diving, mountain biking, and cave exploring. Local rivers were flooded at the time of the race. (Adapted from Sakamoto M, Sagara H, Koizumi N, Watanabe H. Infect Agent Survell Rep. 2001;22:5–6)
of disseminated intravascular coagulopathy. Renal biopsy demonstrates acute interstitial nephritis, and immune-complex glomerulonephritis may also be seen. Pulmonary disease can develop in the absence of hepatic or renal involvement. This hemorrhagic pneumonia is generally associated with a bloody cough, and chest X-ray reveals nodular densities in the lower lobes. Histopathology reveals damage to the capillary endothelium and intra-alveolar hemorrhage. Cardiovascular collapse can develop suddenly. The mortality rate for severe leptospirosis ranges from 5% to 40%.

**Diagnosis and Treatment**

Even in endemic areas, the early clinical diagnosis of leptospirosis is difficult to make because the clinical manifestations are often nonspecific. *Leptospira* can be cultured in vitro on special media (Fletcher's, Ellinghausen's, or polysorbate 80). Significant growth may be detected after 1 to 2 weeks, but can take up to 3 months. Blood, CSF, and urine are positive during the first 7 to 10 days of illness, and urine remains positive during the second and third weeks of the illness.

The sensitivity of culture is low, and therefore the diagnosis must usually be made by measuring acute and convalescent antibody titers. The microscopic agglutination test is the most specific test and allows identification of serum antibodies to specific serovars. Live leptospires are placed on a slide, and the highest serum dilution at which more than 50% of the spirochetes agglutinate on darkfield microscopy is defined as the positive titer. Antibody titers can be detected as early as 3 days into the illness, but usually take 2 weeks, and continue to rise for 3 to 4 weeks. A rise in titer by a factor of 4 or more is defined as serologic confirmation of leptospirosis. A single titer above 1:800 in combination with appropriate symptoms is considered indicative of active disease, and a single titer of 1:200 or a persistent titer of 1:100 is suggestive evidence. This test is technically demanding and potentially hazardous; it is performed only by CDC reference laboratories. An ELISA test for IgM antibodies is commercially available and has a sensitivity that varies from 100% to 77% and a specificity of 93% to 98%. Methods using PCR are under development, but are currently only experimental.

Penicillin G, ampicillin, or ceftriaxone are recommended for severe disease. In severe disease, penicillin treatment has been shown to reduce the duration of illness. As observed in the treatment of other spirochetes, therapy may be associated with a Jarisch–Herxheimer reaction. For mild leptospirosis, oral doxycycline or amoxicillin may be administered. When exposure in endemic areas is anticipated, prophylaxis with oral doxycycline (200 mg daily) has been shown to be efficacious (see Table 13.1).

**KEY POINTS**

About the Diagnosis and Treatment of Leptospirosis

1. Can be cultured from blood, cerebrospinal fluid, and urine. Low yield.
2. Serology is most helpful.
   a) Microscopic agglutination test (only in CDC reference labs): positive at 2 weeks, rises at 3 to 4 weeks (a rise by a factor of 4 or more is diagnostic), titer above 1:800 plus symptoms indicates active disease, 1:200 is suggestive.
   b) Enzyme-linked immunoabsorbent assay for immunoglobulin M antibodies is commercially available and has good sensitivity and specificity.
3. Treat with intravenous penicillin, ampicillin, or ceftriaxone for severe disease, oral doxycycline or amoxicillin for milder disease.
4. For prophylaxis in endemic areas use doxycycline.

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**RICKETTSIA AND RELATED INFECTIONS**

The Rickettsiae family encompasses two genera: *Rickettsia* and *Ehrlichia*. These organisms are small gram-negative coccobacilli (coccal forms 0.3 μm in diameter, bacillary forms 0.3×1 to 2 μm) whose cell wall consists of a peptidoglycan layer sandwiched between two lipid membranes. They are all obligatory intracellular pathogens.

*Rickettsia* gains entry by inducing host cells to phagocytose them. Some strains—for example, *Rickettsia rickettsii*—produce a phospholipase that dissolves the confining phagolysosome membrane, allowing them to escape into the cytoplasm. Other strains multiply and survive within the phagolysosome by blocking the release of toxic enzymes into the phagolysosome (*Ehrlichia* species, for instance). All rickettsial diseases are spread to humans by arthropods: ticks, mites, lice, and fleas.

Clinically, the rickettsial family of diseases have been classified into four groups:

1. **The spotted fever group**. Includes *R. rickettsii* (Rocky Mountain spotted fever), *R. conorii*...
(Boutonneuse fever), R. australis (Queensland tick typhus), R. sibirica (North Asian tick typhus), and R. akari (rickettsial pox).

2. The typhus group. Includes R. prowazekii (louse-borne or epidemic typhus and Brill–Zinsser disease), R. typhi (murine typhus), and Orienta tsutsugamushi (scrub typhus).


4. A final disease, Q fever. That does not fall into any of the above categories. It is caused by Coxiella burnetii.

ROCKY MOUNTAIN SPOTTED FEVER

POTENTIAL SEVERITY

Untreated Rocky Mountain spotted fever can be fulminant and fatal.

Epidemiology

Rocky Mountain spotted fever (RMSF) is the most severe disease in the spotted fever group of rickettsial diseases. It occurs throughout the United States, Mexico, and Central and South America. Although first recognized in the Rocky Mountains, the disease is most commonly reported in the southeastern and south-central United States. Small endemic areas are also found in Long Island and Cape Cod. Cases have also been reported in urban parks.

The disease occurs in the late spring and summer, the seasons in which ticks feed. In the south, the dog tick (Dermacentor variabilis) is the primary vector, and in states west of the Mississippi the wood tick (Dermacentor andersoni) is primarily responsible for transmitting disease. A recent outbreak in Arizona was associated with the common brown dog tick (Rhipicephalus sanguineus).

Pathogenesis

After the tick has attached to the host for between several hours and a day, it injects the rickettsiae into the dermis. Once exposed to the warmer temperature and mammalian blood, R. rickettsii activates and proliferates in the skin. The organism resides in the cytoplasm of host cells, where it divides by binary fission and spreads from cell to cell by a mechanism similar to that used by Listeria monocytogenes. Both organisms induce host-cell actin filament assembly to propel them to the periphery of the cell, where they are ingested by adjacent cells, forming plaques of necrotic cells.

R. rickettsii contains outer membrane proteins ("Omps") and lipoproteins that stimulate cell-mediated immunity, resulting in infiltration of lymphocytes and macrophages. After multiplying in the skin, the organism disseminates via the bloodstream, where it prefers to invade vascular endothelial cells. Damage to endothelial and vascular smooth muscle cells results in a vasculitis that can involve the lungs, heart, and central nervous system. Discrete areas of hemorrhage can be found in these organs and also in the skin, intestine, pancreas, liver, skeletal muscle, and kidneys. Hemorrhage often leads to platelet consumption and thrombocytopenia, but disseminated intravascular coagulopathy is rare. Increased vascular permeability and fluid leakage result in edema, low serum protein levels, hypovolemia, and shock. Decreased intravascular volume can induce antidiuretic hormone secretion and hyponatremia. In severe cases, shock can also precipitate acute tubular necrosis and renal failure.
A 7-year-old girl arrived in the emergency room in Oklahoma with a 2-day history of fever (39.3°C), malaise, abdominal pain, nausea, and vomiting. She was discharged with a diagnosis of viral gastroenteritis. Four days later, she was seen at a second emergency room with complaints of persistent fever, anorexia, irritability, photophobia, cough, diffuse myalgias, nausea, and vomiting.

On physical exam she was noted to have hepatosplenomegaly and an erythematous papular rash with scattered petechiae on the trunk, arms, legs, palms, and soles. Laboratory findings included an elevated WBC count of 11,400/mm³, a low platelet count of 19,000/mm³, and elevated liver enzymes (AST: 279 IU/L; ALT: 77 IU/L). Intravenous doxycycline was initiated to treat suspected RMSF, and she was placed in intensive care. Her mental status declined, and she developed metabolic acidosis and respiratory failure, dying 6 days after her first visit to the emergency room.

A serum sample drawn 2 days before her death revealed a 1:128 IgG anti–R. rickettsiae antibody titer. Spotted-fever group rickettsiae were detected by immunohistochemical staining of autopsy specimens from brain, skin, heart, lung, spleen, and kidney. On questioning, the parents reported that their child played frequently in grassy areas near their home. They did not note any recent tick bite, but ticks had been frequently observed on the family's pet dogs and often were manually removed by members of the household. (Adapted from CDC Fatal cases of Rocky Mountain spotted fever in family clusters—three states, 2003. MMWR Morb Mortal Wkly Rep. 2004;53:407–410)

As case 13.3 illustrates, the course of unrecognized and untreated RMSF can be fulminant. The incubation period is 2 to 14 days after a tick bite. The early symptoms and signs of this disease are nonspecific. Patients complain of fever, headache, malaise, myalgias, and nausea. Some patients experience severe abdominal pain, particularly children, suggesting the diagnosis of cholecystitis, appendicitis, or bowel obstruction—or as in case 13.3 with milder abdominal complaints mimicking viral gastroenteritis.

A rash usually develops within 5 days of the onset of illness, and in case 13.3, a rash alerted the physicians to the possibility of RMSF. However, in up to 10% of patients, a rash may never appear. “Spotless” fever occurs more commonly in elderly and in dark skin individuals. Patients often seek medical attention before the rash develops, and therefore, as in the above case, the physician may fail to consider the diagnosis. Lesions are nonpruritic. They are usually first noted on the ankles and wrists, subsequently spreading centrally and to the palms and soles. Initially they are macular or maculopapular, subsequently becoming petechial. The presence of urticarial lesions or a pruritic skin rash makes RMSF unlikely.

As the disease progresses, headache may become an increasingly prominent complaint. Severe headache can be accompanied by neck stiffness and photophobia suggesting meningitis, and the CSF may contain lymphocytes or PMNs, together with elevated protein; however, low CSF glucose is unusual. Conjunctivitis may be noted, and fundoscopic examination may reveal manifestations of small-vessel vasculitis (flame hemorrhages and arterial occlusion), venous engorgement, and papilledema. Respiratory complaints may become prominent, and chest X-ray may reveal alveolar infiltrates or pulmonary edema, indicating the development of adult respiratory distress syndrome.

### KEY POINTS

#### About the Clinical Manifestations of Rocky Mountain Spotted Fever

1. Incubation period is 2 to 14 days.
2. Acute onset of nonspecific symptoms: fever, headache, malaise, myalgias, and nausea. Abdominal pain may mimic cholecystitis or appendicitis.
3. Macular, petechial rash begins on ankles and wrists and spreads to trunk 5 days after symptoms begin,
   a) “Spotless” infection occurs in 10%—usually elderly and dark skinned individuals.
   b) Urticaria or pruritic rash makes the diagnosis unlikely.
4. Other symptoms include aseptic meningitis, conjunctivitis, fundoscopic hemorrhages, and acute respiratory distress syndrome in severe disease.
5. Death within 8 to 15 days if treatment is not initiated within 5 days.
syndrome. In severe cases, gangrene of the digits can also develop as a consequence of occlusion of small arterioles.

Laboratory findings tend to be nonspecific. The peripheral WBC count can be normal, elevated, or depressed. Thrombocytopenia is common in more severe cases. Elevations in BUN and serum creatinine may be noted. Hyponatremia develops in patients with hypotension. Transaminase values and bilirubin levels may be elevated as well. As illustrated by case 13.3, if appropriate therapy is not given within the first 5 days of symptomatic disease, RMSF can progress and cause death within 8 to 15 days.

**Diagnosis**

Because of the rapid course of this disease and the inability of most laboratories to culture the organism, the diagnosis of RMSF is usually made based on epidemiology and clinical manifestations. A significant percentage of patients deny a tick bite, making the diagnosis particularly difficult. In the first few days, RMSF is most commonly mistaken for a viral syndrome. If penicillin or a cephalosporin is mistakenly prescribed during this period, the subsequent rash of RMSF may be mistaken for a drug allergy. Severe headache and abnormalities in the CSF may suggest viral meningoencephalitis. The development of petechial skin lesions may raise the possibility of meningococcemia or leptospirosis.

During the spring and summer months, patients in endemic areas must always be treated for Rocky Mountain spotted fever pending culture results. Skin biopsy is helpful in confirming the diagnosis. Immunofluorescence staining using antibodies specifically directed against *R. rickettsii* can be helpful (70% sensitivity and 100% specificity). If antibiotics for RMSF have been initiated, skin biopsy is not recommended, because the organisms are difficult to identify after treatment has been initiated. Acute and convalescent serum antibody titers can be measured by indirect immunofluorescence, latex agglutination, or complement fixation, and a significant rise in titer allows for a retrospective diagnosis. However, these tests are of no help in managing the acutely ill patient. The Weil–Felix test that detects cross-reactive antibodies to *Proteus vulgaris* are not only nonspecific, but also insensitive, and are no longer recommended.

**Treatment**

Because of the unpredictable course of RMSF, physicians in endemic areas should have a low threshold for initiating doxycycline or tetracycline therapy in patients who have a nonspecific febrile illness of more than 2 days’ duration during the spring and summer. The disease responds rapidly to antibiotic therapy, and patients usually defervesce within 48 to 72 hours.

Therapy with doxycycline is the treatment of choice for adults and children alike (see Table 13.1). Short courses of doxycycline are reported to cause minimal damage to developing teeth, but the potential benefits of doxycycline far outweigh this potential toxicity. Chloramphenicol is recommended in pregnancy. Antibiotic therapy should be continued for at least 3 days after the patient has defervesced. The mortality in untreated patients varies depending on the strain and inoculum, but in one retrospective series, was 22% in untreated patients and 6% in patients who received treatment within 5 days of the onset of illness.

**Other Spotted Fevers**

A number of other rickettsial species cause skin rashes and fever in humans. *R. conorii* shares 90% DNA homology with *R. rickettsii* and many of the same proteins; it causes Mediterranean spotted fever (“Bou- toneuse fever”). This tick-borne illness is found in southern Europe, Africa, and the Middle East, and is clinically very similar to RMSF. A black eschar called a *tache noire* may be noted at the site of the tick bite. This lesion is caused by vascular endothelial damage that leads to dermal and epidermal necrosis. A diffuse macular-papular rash develops within 3 to 5 days of the onset

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**KEY POINTS**

**About the Diagnosis and Treatment of Rocky Mountain Spotted Fever**

1. Presumptive diagnosis must be made based on epidemiology and clinical manifestations.
2. Culture not recommended.
3. Skin biopsy with immunofluorescence staining has high specificity. Not recommended if antibiotics have been given.
4. Serology provides a retrospective diagnosis: indirect immunofluorescence, latex agglutination, or complement fixation.
5. Can be mistaken for viral syndrome, drug allergy, and meningococcemia.
6. Physicians in endemic areas should have a low threshold for treatment:
   a) Doxycycline for adults and children
   b) Chloramphenicol for pregnant women
7. Mortality has been reported as 22% untreated, 6% with treatment.
of the febrile illness; however, as observed with RMSF, some patients fail to develop a black eschar or rash.

*R. africae* also results in an eschar at the site of the tick bite, and for 60 years, this infection was mistaken for that caused by *R. conorii*. This disease, called African tick-bite fever, is found mainly in rural regions of Zimbabwe, South Africa, and the eastern Caribbean.

The disease is usually mild, but can be associated with persistent neuropathy.

Rickettsialpox, caused by *R. akari*, is transmitted by a blood-sucking mouse mite.

a) Causes papulovesicular rash, often mistaken for chickenpox.

b) In the United States the disease is found in Boston, Pittsburgh, and Cleveland, and in Arizona and Utah.

c) Also found in Mexico, South Africa, Ukraine, Croatia, and Korea.

d) Self-limiting disease, responds quickly to tetracycline or doxycycline.

### TYPHUS

1. Mediterranean spotted fever is caused by *Rickettsia conorii*, which is clinically similar to Rocky Mountain spotted fever:
   a) Forms a black eschar called a *tache noire* at the site of the tick bite.
   b) Found in Europe, Africa, and the Middle East.
2. African tick bite fever is caused by *R. africae* (previously misidentified as *R. conorii*).
3. Rickettsialpox, caused by *R. akari*, is transmitted by a blood-sucking mouse mite.
   a) Causes papulovesicular rash, often mistaken for chickenpox.
   b) In the United States the disease is found in Boston, Pittsburgh, and Cleveland, and in Arizona and Utah.
   c) Also found in Mexico, South Africa, Ukraine, Croatia, and Korea.
   d) Self-limiting disease, responds quickly to tetracycline or doxycycline.

This group of diseases received the name “typhus” because the illness caused by species of *Rickettsia* that clinically mimics typhoid fever (see Chapter 8).

### Epidemiology, Pathogenesis, and Clinical Manifestations

*R. prowazekii* causes the most serious form of typhus. This disease has been called “louse-borne typhus” and “epidemic typhus.” It is spread from person to person by body lice.

The louse harbors high concentrations of *Rickettsia* in its alimentary canal. When an infected louse bites a human and ingests a blood meal, it also defecates, releasing rickettsial organisms onto the skin. The unwitting host scratches the site and inoculates the infected feces into the wound or onto mucous membranes. This disease is most commonly encountered during periods of war and famine. During World War II, louse-borne typhus was common in Eastern European and North African concentration camps. Since the end of the 1980s, infections have been reported most commonly in Africa and less commonly in South and Central America. Rare cases have been reported in the eastern and central United States. Those cases are thought to have been transmitted by lice or fleas from flying squirrels.

The incubation period is approximately 1 week, after which the disease starts with the abrupt onset of...
high fever, severe headache, and myalgias. The headache is retro-orbital and bifrontal, comes on suddenly, and is unremitting. As observed with severe RMSF, tissue necrosis develops as a result of small-vessel vasculitis, a process that involves multiple organs, including the lungs, liver, gastrointestinal tract, central nervous system, and skin. Skin rash is observed in 60% of patients and begins on the trunk, spreading outward over 24 to 48 hours. Lesions are initially macular, but quickly progress to a maculopapular form and then to petechiae. Peripheral gangrene can develop as a consequence of small-vessel occlusion. Central nervous system involvement can lead to drowsiness and confusion, and in severe cases, grand mal seizures and focal neurologic deficits can result. Louse-borne typhus has been associated with 30% to 70% mortality.

After primary infection, *R. prowazekii* can remain latent for decades, reactivating after physical or psychological stress, particularly in elderly people. This reactivated form of typhus is called Brill–Zinsser disease, and it is similar in clinical presentation to primary disease, except that the disease is milder. *R. typhi*, responsible for flea-borne (also called murine or endemic typhus) also causes a milder form of the disease and is found throughout the world. The prognosis for Brill–Zinsser disease and flea-borne typhus is much better than for primary louse-borne typhus, mortality being less than 5% for both diseases.

A third form of typhus called scrub typhus is caused by *R. tsutsugamushi*. This infection is transmitted by mite larvae (commonly called chiggers). These insects crawl on vegetation and then attach themselves to small mammals and humans as they pass through the brush. This disease is most often contracted by agricultural workers and military personnel in endemic areas. Scrub typhus is found in Japan, eastern Asia, Australia, and in the western and southwestern Pacific islands. The incubation period is similar to that of the other rickettsial diseases (6 to 21 days); however, the onset is usually gradual rather than sudden. Headache, high fever, chills, and anorexia are the most common symptoms. Diffuse lymphadenopathy, splenomegaly, conjunctivitis, and pharyngitis are common physical findings. Within 1 week of the onset of symptoms, a high percentage of patients develop a maculopapular skin rash. A black eschar may be noted at the site of the chigger bite in approximately half of patients.

### Diagnosis and Treatment

The diagnosis of these febrile illnesses is presumptive and based on clinical and epidemiologic findings. Acute and convalescent antibody titers to the specific forms of *Rickettsia* can be performed, and the specific diagnosis made retrospectively. Immunofluorescence staining of the primary eschar (where available) can yield a more rapid diagnosis. The once-popular Weil–Felix Proteus agglutination test is no longer recommended because of its poor sensitivity and lack of specificity.

The treatment for all forms of typhus is identical to that for the spotted fever group: doxycycline or chloramphenicol (see Table 13.1). Therapy should usually be continued for 3 to 5 days after defervescence. In some regions in which antibiotic resistance has developed, oral rifampin (600 to 900 mg daily) may be more efficacious. Early treatment aborts the antibody response, and as a consequence, relapse may occur after treatment is completed. Patients respond well to re-treatment.
EHRLICHIA

There are two forms of ehrlichiosis: human monocytic ehrlichia, HME, caused by Ehrlichia chaffeensis, and human granulocyte anaplasma, HGA, caused by Anaplasma phagocytophilum.

Epidemiology

Both species of Ehrlichia are transmitted to humans by ticks, and the seasonal nature of these diseases is identical to those of other tick-borne illnesses. Most cases of human monocytotropic ehrlichiosis are associated with bites from the Lone Star tick (Amblyomma americanum). This tick also infests the whitetail deer, the natural reservoir for E. chaffeensis. This disease is very common in the southeast, and attack rates have been estimated to be 5 per 100,000 population; however, in certain endemic areas, incidences as high as 660 per 100,000 have been reported. In addition to hikers and outdoor workers, golfers are at risk for contracting this disease.

Human granulocytotropic anaplasma was first reported in 1994, and therefore the understanding of its epidemiology is evolving. To date, cases have been associated with tick bites from Ixodes scapularis, the same tick that transmits the pathogens that cause Lyme disease and babesiosis. Cases have been reported in California, Minnesota, Wisconsin, Massachusetts, Connecticut, New York, and Florida.

Pathogenesis

Once the organism is inoculated into the skin by the tick, it enters the lymphatic system and bloodstream. E. chaffeensis prefers to invade macrophages and monocytes; less commonly, it enters lymphocytes, and occasionally, polymorphonuclear leukocytes. Once phagocytosed by these cells, E. chaffeensis remains in the phagosomes, where it survives by inhibiting fusion of the lysosomes that release the toxic products that normally kill invading pathogens. In addition, this organism blocks the signal transduction pathways that enhance production of interferon γ and simultaneously upregulates cytokine genes important for generation of the inflammatory response. Finally, it induces clustering of transferrin receptors in the phagosome membrane, allowing it to compete effectively for iron, a vital nutrient for bacterial growth. As the bacteria divide by binary fusion, they cluster together, forming intracellular inclusions called morulae. Anaplasma phagocytophilum invades primarily PMNs (also called neutrophils or granulocytes) and uses strategies similar to those of E. chaffeensis to survive within those cells. Both pathogens not only invade peripheral leukocytes, but also infect the bone marrow, causing disruption of the normal maturation processes and blocking production of leukocytes, red blood cells, and platelets.

KEY POINTS

About the Diagnosis and Treatment of Typhus

1. Presumptive diagnosis must be made by clinical and epidemiologic findings.
2. Antibody titers are available; immunofluorescence staining of primary lesion is helpful.
3. Weil–Felix Proteus agglutination is no longer recommended.
4. Treat with doxycycline or chloramphenicol; patient may relapse, requiring re-treatment.

KEY POINTS

About the Epidemiology and Pathogenesis of Ehrlichiosis

1. Human monocytotropic ehrlichiosis is caused Ehrlichia chaffeensis.
   a) Transmitted by the Lone Star tick found on the whitetail deer.
   b) Common in the southeast United States; hikers, outdoor workers, and golfers are at risk.
2. Human granulocytotropic anaplasma is caused by Anaplasma phagocytophilum.
   a) Transmitted by Ixodes, the same tick that transmits Lyme disease and babesiosis.
   b) Found in California, Minnesota, Wisconsin, Massachusetts, Connecticut, New York, and Florida.
Clinical Manifestations

CASE 13.4

A 49-year-old white man presented to the hospital with a 2-week history of fever and malaise. Fever came on gradually and was associated with generalized headaches. He was given trimethoprim–sulfamethoxazole by his primary physician for presumed sinusitis, but he failed to improve. Fever increased to between 39.4°C and 40°C, the generalized headache persisted, and a nonproductive cough developed.

An epidemiologic history indicated that the patient was an avid hunter and had been hunting with his father on several occasions during the last 2 months. He reported extensive tick exposure. His father had died in the hospital from “influenza pneumonia” that had developed at the same time as his current illness.

In the emergency room, the patient was noted to have a fever of 39.4°C, a pulse of 96 beats per minute, a respiratory rate of 22 breaths per minute, and a blood pressure of 144/60 mm Hg. He appeared septic and somewhat lethargic and inattentive. Conjunctiva were injected with bilateral hemorrhages. Tender cervical lymphadenopathy was noted, but the neck was supple. A few hyperpigmented macular lesions over the anterior shins were observed, but there was no evidence of tick bites.

A laboratory workup showed a hematocrit of 34%, a platelet count of 61,000/mm³, and a peripheral WBC count of 3600/mm³, with 66% PMNs, 17% lymphocytes, and 16% monocytes. No morulae were noted in a blood smear. Serum sodium was 125 mEq/L; AST, 185 IU/L; ALT, 151 IU/L. Two blood cultures showed no growth. The CSF formula was 205 WBCs (2% PMNs, 78% lymphocytes, 20% monocytes), 0 red blood cells, total protein 139 mg/dL, and glucose 153 mg/dL. A chest X-ray was within normal limits.

The patient was treated with doxycycline and defervesced within 48 hours. One week after hospital discharge, his serum IgG and IgM titers came back positive for E. chaffeensis.

Case 13.4 represents a classic presentation of human monocytotropic ehrlichiosis. Both forms of ehrlichiosis have incubation periods of approximately 7 days. *Ehrlichia* varies in its severity, and fatality rates of approximately 5% have been reported in both diseases. Manifestations tend to be more severe in elderly and immunocompromised patients.

Like rickettsiosis, ehrlichiosis is a multisystem disease. Both forms of *Ehrlichia* present with the gradual onset of fever, chills, headache, myalgias, anorexia, and malaise. The monocytotropic form can result in respiratory insufficiency, renal insufficiency, and meningoencephalitis. It is very much possible that the patient’s father in case 13.4 may have died of respiratory complications from ehrlichiosis. Neck stiffness, depressed mental status, coma, and seizures are accompanied by CSF lymphocytosis and elevated CSF protein. Case 13.4 had a depressed mental status and typical CSF findings. The granulocytotropic form can also be associated with respiratory insufficiency. Rhabdomyolysis has also been described. Meningoencephalitis has not been described in granulocytotropic anaplasma. Some patients with the HGA form have developed fatal opportunistic infections. Hypotension can develop with either infection and mimic other forms of gram-negative sepsis. A macular, maculopapular, or petechial rash is observed in 30% to 40% patients with HME, but in only 2% to 11% of patients with HGA.

Thrombocytopenia is a prominent finding in both diseases, and this finding combined with the epidemiology strongly suggested the diagnosis of ehrlichiosis in case 13.4. The platelet count is depressed (50,000 to 140,000/mm³) in most patients. Platelet counts can drop below 20,000/mm³ in severe disease and can be associated with gastrointestinal bleeding. Leukopenia (1300 to 4000/mm³) is also a frequent finding, peripheral neutrophil or lymphocyte counts (or both) being depressed in HME. In the granulocytotropic form, neutropenia predominates and is commonly associated with a left shift and relative lymphocytosis. As observed in case 13.4, elevated transaminase values (AST and ALT) are found in nearly all patients.

Diagnosis and Treatment

If the diagnosis of *Ehrlichia* is being considered, a Wright stain of the peripheral blood and a buffy coat smear should be carefully examined for the presence of morulae. These intracellular inclusions are seen in the peripheral monocytes of only a small percentage of patients with HME, but in HGA, granulocyte morulae can be identified in 25% to 80% of patients (Figure 13.2). The percentage of granulocytes containing morulae varies from 1% to 44%, with higher levels of intracellular invasion being seen in elderly patients.

In these diseases, culture techniques are impractical and insensitive, and PCR methods remain
KEY POINTS

About the Clinical Manifestations, Diagnosis, and Treatment of Ehrlichiosis

1. Incubation period is 7 days, and mortality is 5% (mainly elderly and immunocompromised).
   a) Gradual onset of fever, chills, headache, myalgias, anorexia, and malaise.
   b) Severe monocytic form: respiratory insufficiency, renal insufficiency, and meningoencephalitis (with lymphocytosis noted in the cerebrospinal fluid).
   c) Severe granulocytic form: respiratory insufficiency, rhabdomyolysis, and neutropenia resulting in gram-negative sepsis.
   d) Macular, petechial rash in 30% to 40% of cases of the monocytic form, but in 2% to 11% of cases of the granulocytic form.

2. Diagnosis presumptive in most cases.
   a) Thrombocytopenia and leukopenia are common (neutropenia in granulocytic form).
   b) Moderate transaminase elevations are seen.
   c) Morulae are rare in peripheral blood smears in the monocytic form, common in the granulocytic form.
   d) Retrospective serology makes the diagnosis.

3. Treat with doxycycline. Chloramphenicol has no activity in vitro, and therefore doxycycline is also recommended for children.

COXIELLA BURNETII

Epidemiology

The main reservoirs for C. burnetii, the cause of Q fever, are farm animals: sheep, goats, and cows. Pet cats and dogs may also carry the organism. Mammals shed the pathogen in their urine, feces, and birth products. Transmission occurs most commonly in association with birthing, organisms being aerosolized from the placenta, and inhaled by humans. C. burnetii is resistant to drying and can survive for long periods in the environment, and wind-borne particles can be inhaled weeks after parturition. Q fever is rare in the United States, 20 to 60 cases being reported annually. Outbreaks occur worldwide, but may be missed because of the nonspecific symptoms and signs in this disease. Significant numbers of cases have been reported in Spain, France, England, Australia, and Canada. In some areas, the incidence of Q fever has been estimated to be 50 per 100,000 population.

Pathogenesis

C. burnetii is a small pleomorphic rod (0.3 to 1 μm), whose cell wall has many similarities to gram-negative
rods. Although this pathogen was originally classified in the rickettsial family, DNA sequencing has indicated that the organism is more closely related to *Legionella* and *Francisella*, and is a proteobacteria. This organism is capable of varying its LPS antigens in response to environmental conditions. In the external environment, the organism usually has phase II LPS antigens; however, on invading the host, a shift to phase I antigens occurs.

*C. burnetii* infects the host primarily through the respiratory tract. Infectious particles are inhaled and are then phagocytosed by pulmonary macrophages, where they survive and grow within the acidic environment of the phagolysosome. The ability of the organism to hide within these acidic compartments may be the reason that curing chronic Q fever with antibiotics is so difficult. Pulmonary infection induces infiltration by mononuclear cells and can cause areas of focal necrosis and hemorrhage. Infection can spread to the liver, causing granuloma formation. In patients with damaged heart valves, *C. burnetii* can survive for prolonged periods and cause chronic infection.

**Clinical Manifestations**

The incubation period is approximately 3 weeks in most cases. Symptoms are often very mild or even absent. When symptoms are reported, most patients develop a self-limiting flu-like illness. Onset of fever is usually abrupt and is associated with headache and myalgias. Some patients complain of a nonproductive cough, and a few rales may be detected on pulmonary exam. Chest X-ray is suggestive of a viral pneumonia with mild bilateral lower lobe infiltrates. Occasionally, patients can develop acute respiratory distress syndrome or pleural effusions. Hepatitis may be asymptomatic or be associated with anorexia and malaise. Transaminase values are elevated, but jaundice is uncommon. Liver biopsy typically reveals doughnut-like granulomas consisting of a lipid vacuole surrounded by a fibrinoid ring. Other, less common manifestations include a maculopapular rash (10% of patients), myocarditis, and pericarditis (1%), and meningitis or encephalitis (1%).

A chronic infection persisting for longer than 6 months develops in about 5% of patients and primarily involves the heart, causing symptoms of subacute bacterial endocarditis. Conventional blood cultures are negative, however. Most cases of endocarditis develop in patients with valvular damage or a prosthetic valve. Vegetations are seldom seen on cardiac echo, and this negative result often delays the diagnosis. Embolic phenomena and digital clubbing may be observed in late stages of the infection. Valve replacement is commonly required as a consequence of severe valve dysfunction, and mortality in Q fever endocarditis is high (65% to 45%). Less commonly, chronic infection can develop in an aneurysm, vascular graft, liver, lungs, joints, or bone. If the infection is contracted during pregnancy, the mother may be asymptomatic. However, if untreated, infection is associated with a high rate of spontaneous abortion.

**Diagnosis and Treatment**

The organism can be readily grown using cell culture techniques; however, cultures are not performed in most facilities because of the danger to lab personnel and the need for a P3 containment facility. The PCR test for this illness has improved in specificity and sensitivity, and it is available in some locations. Immuno-fluorescence antibody testing remains the primary method of diagnosis. Anti-phase I and phase II IgG, IgM, and immunoglobulin A (IgA) antibody titers should be tested. Elevated IgG (above 1:200) and IgM (above 1:50) antibody titers against phase II antigens indicate acute disease. Elevated IgG (above 1:800) and IgA (above 1:100) antibody titers against phase I antigens are diagnostic of chronic Q fever.

Antibiotics are less effective in Q fever than in rickettsial diseases, and acute disease is usually
KEY POINTS

About Clinical Manifestations, Diagnosis, and Treatment of Q Fever

1. Incubation period is 3 weeks, usually causing an abrupt flu-like illness with cough.
2. Less commonly (10% of cases), a maculopapular rash appears. Other, rarer complications include
   a) severe respiratory comprise with acute respiratory distress syndrome;
   b) hepatitis with elevated transaminases, but minimal elevations in bilirubin;
   c) myocarditis and pericarditis;
   d) meningitis; and
   e) chronic endocarditis (negative echo early in the disease, high mortality).
3. Diagnosis is made by determining immunoglobulin G (IgG) and M (IgM) antibodies against phase I and II antigens (blood cultures negative):
   a) IgG (titer above 1:200) and IgM (titer above 1:50) anti-phase II antigens indicate acute disease.
   b) IgG (titer above 1:800) and IgA (titer above 1:100) anti-phase I antigens indicate chronic disease.
   c) Polymerase chain reaction is sensitive and specific (available in some locations).
4. Treatment not as effective as for rickettsial infections.
   a) Treat with doxycycline for 2 weeks for acute disease; fluoroquinolones may also be helpful.
   b) Treat with doxycycline and hydroxychloroquine for 18 months to 4 years or life for chronic endocarditis.

self-limiting, lasting 2 weeks. Tetracyclines have been shown to shorten the duration of fever in acute disease by 1 to 2 days. Oral or intravenous doxycycline is the treatment of choice (see Table 13.1), and fluoroquinolones are considered a reasonable alternative. In patients with Q fever endocarditis, cure rates have been improved by combining doxycycline with hydroxychloroquine. Therapy for endocarditis must be considerably prolonged—between 18 months and 4 years—to sterilize the valves. In some patients, antibiotics have been continued for life.

KEY POINTS

About the Epidemiology of Bartonella Infections

1. Cat scratch disease is caused by Bartonella henselae:
   a) Transmitted primarily by young cats and, less commonly, by cat fleas.
   b) Common throughout North America; higher incidence in warm, humid areas.
2. Bacillary angiomatosis is caused by B. henselae and B. quintana:
   a) B. quintana is transmitted by human body lice.
   b) Spreads in areas with poor sanitation, among people with poor personal hygiene.
3. B. bacilliformis is transmitted by the sandfly in the Andes mountains of South America.

EPIDEMIOLOGY

Cat scratch disease is most commonly contracted by young people under the age of 21 years. This disease is distributed broadly throughout North America and is found worldwide. The incidence in the United States has been estimated to be between 9 and 10 per 100,000 population. Cat scratch disease is more common in warm humid climates.

As the name implies, all epidemiologic data point to the cat as the primary vector for disease. Young cats are most commonly implicated. Kittens have a very high incidence of asymptomatic bacteremia with Bartonella...
henselae, and they are more likely to scratch humans. In addition to cat scratches, this disease may be transmitted to humans by fleas, and the flea is also responsible for spread from cat to cat.

*B. henselae* not only causes cat scratch disease, it is one cause of bacillary angiomatosis. The other species that causes the latter disease, *B. quintana*, is also globally distributed. It is transmitted by human body lice (*Pediculus humanus*) and causes disease in areas where sanitation and personal hygiene are poor. A third pathogenic strain, *B. bacilliformis*, causes Oroya fever and Verruga peruana, diseases found only in the Andes mountains of South America, where the disease is transmitted by the sandfly. Other potentially pathogenic species of *Bartonella* have been identified; however, their relationship to disease is currently under active investigation.

**PATHOGENESIS**

*Bartonella* are pleomorphic gram-negative bacilli that take up Gram stain poorly. However, the organism binds silver and can be identified by Warthin–Starry stain. *Bartonella* enter the host through a break in the skin caused by a cat scratch or insect bite. The bacteria multiply at this site and subsequently spread to the local lymphatic system and adjacent lymph nodes. The bacteria contain flagella that allow them to move within the host. Flagellar and other surface proteins mediate attachment to red blood cells and endothelial cells. The attached bacteria can enter red cells, where they can multiply in vacuoles or in the cytoplasm. *Bartonella* are ingested by endothelial cells and multiply within a vacuole, forming intracellular clusters similar to the morulae of *Ehrlichia*. Certain species of *Bartonella*, including *B. bacilliformis*, *B. henselae*, and *B. quintana*, induce the formation of new vessels, and a *Bartonella* angiogenesis factor has been identified.

Because *Bartonella* grows in both the intracellular and extracellular environments of the host, it induces both a granulomatous reaction consisting of macrophages and histiocytes, and an acute inflammatory response consisting primarily of PMNs. This vigorous mixed immune response usually limits the spread of infection, which explains why most *Bartonella* infections remain localized. In individuals with depressed immunity, such as AIDS patients, this bacteria can cause bacteremia and disseminate throughout the body.

**CLINICAL MANIFESTATIONS**

**CASE 13.5**

A 21-year-old white man presented to the emergency room with a 2-hour history of severe right lower abdominal pain, nausea, vomiting, and loose stools. His temperature was 39.7°C; pulse, 133 per minute; and blood pressure, 101/40 mm Hg. His abdomen was soft and nontender; normal bowel sounds were heard. A warm, very tender mass, 1.5 x 1.5 x 6 cm, was palpated in the right inguinal area. Genitalia were normal, without ulcers. A computed tomography scan demonstrated a soft-tissue mass.

The patient’s peripheral WBC count was 12,000/mm³ (54% PMNs, 34% bands), and his hematocrit was 43%. Urethral swabs were negative for Chlamydia and gonococcus. Emergency surgical exploration revealed enlarged, matted right inguinal lymph nodes. Histopathology demonstrated an acute inflammatory response, and silver stain identified multiple rods.

Three days following oral administration of ciprofloxacin, the patient defervesced. On further questioning, this college student reported that he had been playing with wild cats near his apartment over the 2 weeks before his admission, but said that he did not recall being scratched.

**KEY POINTS**

About the Pathogenesis of *Bartonella* Infections

1. Pleomorphic gram-negative rods. Takes up Gram stain only weakly; silver stain preferred.
2. Enters via breaks in the skin and spreads to the local lymphatics; rarely disseminates except in patients with AIDS.
3. Survives within host-cell intracellular vacuoles and extracellularly.
4. Produces an angiogenesis factor that stimulates the growth of new blood vessels.
5. Induces both a granulomatous and an acute inflammatory reaction that attracts polymorphonuclear leukocytes and prevents dissemination.

**Cat Scratch Disease**

Cat scratch disease usually presents as a single enlarged, warm, and painful lymph node near the site of skin inoculation. Lymph node swelling usually occurs within 2 weeks of inoculation. Case 13.5 developed unusually
acute lymph node swelling that caused the sudden onset of severe pain, raising the possibility of a strangulated hernia and precipitating surgical exploration. The node can enlarge to between 8 and 10 cm in diameter; however, in most cases, the involved node expands to a diameter of 1 to 5 cm. Enlargement of a single node is the rule (85% of cases); however, as observed in case 13.5, some patients develop enlargement of a cluster of nodes or, less commonly, experience lymph node enlargement in two distinct anatomic sites. Generalized lymphadenopathy is rare.

The site of lymph node enlargement depends on the site of inoculation. Axillary node involvement is most common. Epitrochlear, supraclavicular, submandibular, and inguinal are other likely sites. In addition to being painful, warm, and erythematous, about 10% to 15% of the lymph nodes drain pus. The lymphadenopathy usually resolves over a period of 1 to 4 months, but can persist for several years if not treated with antibiotics.

On careful questioning, the patient may report a skin lesion in the region where the lymph node drains. Within 3 to 10 days after inoculation, a vesicular lesion develops that becomes erythematous and then papular. The skin lesions usually persist for 1 to 3 weeks, and by the time the patient seeks medical attention, the site of the scratch may be overlooked. However, if actively searched for, the primary lesion is detected in two thirds of patients. A primary lesion was not identified in case 13.5. When questioned, a significant percentage of patients do not recall a cat scratch, but nearly all patients provide a history of contact with a cat or (less commonly) a dog.

Low-grade fever and malaise accompany lymphadenopathy in about half of cases. Conjunctivitis occasionally develops when the eye is the portal of entry, and the combination of conjunctivitis and preauricular

**Bacillary Angiomatosis**

Bacillary angiomatosis develops predominantly in indigent patients with AIDS who also have body lice, the primary vector for spread of *B. quintana*. The disease is also seen in other immunocompromised patients and develops when the CD4 count drops below 100/mm$^3$.

The skin lesions usually begin as cluster of small reddish papules that can enlarge to form nodules. Lesions appear vascular and bleed profusely when traumatized. They can be mistaken for Kaposi's sarcoma, pyogenic granuloma, cherry angiomas or hemangiomas. Skin biopsy reveals multiple small blood vessels, enlarged endothelial cells, and polymorphonuclear leukocyte infiltration. *B. henselae* has also been identified as a cause of bacillary angiomatosis. *B. quintana* can infect the liver and, less commonly, the spleen, resulting the formation of discrete blood-filled cystic structures. This disease has been called bacillary peliosis.

**Bacteremic Illness**

*B. quintana* can seed the bloodstream and cause trench fever. This disease was common during World Wars I and II, but is rare today, being seen primarily in

**KEY POINTS**

**About the Clinical Manifestations of Cat Scratch Disease**

1. Presents with a warm, tender, swollen lymph node 2 weeks after the scratch.
   a) Axillary node is most common, but the involved node depends on the site of inoculation.
   b) The primary scratch can often be identified.
   c) Low-grade fever is common.
2. Rarer manifestations include conjunctivitis, encephalopathy, and lesions in the liver and spleen.

**KEY POINTS**

**About the Clinical Manifestations of Bartonella quintana**

1. Organism is the major cause of bacillary angiomatosis (*B. henselae*, less commonly).
   a) Seen in indigent patients with AIDS who also have body lice (CD4 count is usually below 100/mm$^3$).
   b) Small reddish papules coalesce into nodules, bleed profusely.
   c) Histopathology shows multiple small vessels, enlarged endothelial cells, and infiltration by polymorphonuclear leukocytes.
2. Bacteremic illness is rare (seen in some homeless individuals); characterized by recurrent 5-day fever, shin pain, malaise.
homeless individuals with poor hygiene. Cases have been reported in the homeless in Seattle, Washington, and Marseilles, France.

Symptoms of fever, malaise, and bone pain involving the anterior shins usually begin 5 to 20 days after exposure. Splenomegaly is common, and in some patients, a maculopapular rash may be seen. Recurrent fever every 5 days (quintan fever) is the most common presentation, and it is the basis for the name of the organism. After the primary episode patients continue to have asymptomatic bacteremia lasting weeks to months. Both \textit{B. quintana} and \textit{B. henselae} can cause bacterial endocarditis, and these pathogens should be considered in cases of culture-negative bacterial endocarditis.

\textbf{DIAGNOSIS}

\textit{Bartonella} grows slowly on fresh blood agar, rabbit-heart infusion agar, and chocolate agar. If \textit{Bartonella} is suspected, the physician should contact the clinical microbiology laboratory to assure that all cultures are incubated for prolonged periods (at least 21 days) in 5\% to 10\% CO\textsubscript{2} and high moisture. Because the organism adheres to the sides of glass blood culture flasks, the liquid medium will not appear turbid. The slow rate of growth of this bacterium also impairs recognition by standard CO\textsubscript{2} detection methods. Staining of broth with Warthin–Starry stain or acridine orange has been used to overcome these limitations.

Biopsies of lymph nodes and skin lesions are generally not required for diagnosis, and the histopathology of mixed granulomatous and acute inflammatory reaction is not specific. Pallisading epithelioid cells are commonly seen, and a positive Warthin–Starry silver stain demonstrating black bacilli provides strong evidence for the diagnosis. However, organisms may be difficult to detect in chronically infected lymph nodes. Bacillary angiomatosis lesions demonstrate characteristic plump endothelial cells, neovascularity, and clusters of bacteria on silver staining.

An indirect immunofluorescence assay and enzyme immunosorbent assay are available to detect antibodies directed against \textit{Bartonella}, and these tests have now replaced the cat scratch skin test. The skin test was previously considered to be a useful diagnostic tool, but it is no longer recommended. Unlike antibody titers (which have been ineffective at differentiating between species), PCR probes have proven to be more specific and are now commercially available.

\textbf{TREATMENT}

Azithromycin (standard 5 day course) is effective, and it is the treatment of choice in patients with lymph node disease (See Table 13.1). Oral clarithromycin, oral doxycycline, or oral ciprofloxacin for 10 to 14 days may also be effective. In severe cases, intravenous azithromycin or gentamicin plus rifampin (efficacy not proven).

\textbf{BRUCELLOSIS}

\textbf{POTENTIAL SEVERITY}

\textit{This febrile illness is often difficult to diagnose, but seldom fatal.}
Epidemiology

The bacteria that produce brucellosis are transmitted to humans primarily by infected wild and domestic animals. Direct animal contact, contact with animal products, or ingestion of unpasteurized dairy products are the most common ways in which humans can contract brucellosis. Cattle, buffalo, camels, yaks, goats, and sheep are the domestic animals most commonly responsible for disease transmission. In the wild, swine, fox, caribou, antelope, and elk have been implicated. Bacteria enter the host through abrasions or cuts, the conjunctiva, or the gastrointestinal tract. People at risk are farmers, hunters, and eaters of unpasteurized cheeses or other unpasteurized dairy products. The disease is found worldwide, being most common in the Mediterranean region, Arab Gulf basin, Indian subcontinent, Mexico, and Central and South America. In the United States, brucellosis is most frequently reported in the south and southwest. As a consequence of a rigorous farm animal screening and vaccination program, and pasteurization of all dairy products, the overall incidence of brucellosis in the United States is low, 0.05 per 100,000 population, with most cases being contracted by travelers who visit endemic areas.

Pathogenesis

Brucella are small aerobic gram-negative coccobacilli. The three strains that most commonly cause human disease are B. abortis, B. suis, and B. melitensis. The organism expresses LPS on its surface, and expression of the smooth form enhances intracellular survival, making an important contribution to virulence.

Brucella is a facultative intracellular pathogen. After entering the skin, the bacteria quickly attract PMNs. These cells ingest the pathogen, where it easily survives within the phagolysosome by producing a superoxide dismutase to neutralize toxic oxygen byproducts. The bacteria subsequently invade the lymphatic system and bloodstream, disseminating primarily to organs with rich reticuloendothelial systems (liver, spleen, and bone marrow). Here, the bacteria are ingested by resident macrophages and survive in these cells by blocking phagosome–lysosome fusion, as is observed with Ehrlichia.

Clinical Manifestations

CASE 13.6

A 40-year-old white man was seen in the emergency room complaining of right-sided chest pain for 4 days. Pain was sharp and very severe, and was made worse by taking a deep breath. Pain was localized to the right chest, right upper quadrant, but occasionally radiated to the shoulder. The chest pain had been preceded by 2 weeks of a low-grade intermittent fever accompanied by sweating. He noted a mild cough with minimal yellow sputum production.

An epidemiologic history indicated that the patient periodically hunted wild pigs and had been hunting 5 weeks before his hospitalization. Past medical history included renal transplant surgery 4 years earlier; patient was on prednisone and azathioprine.

On physical examination a temperature of 36.7°C, a pulse rate of 102 per minute, a respiratory rate of 24 per minute, and a blood pressure of 126/94 mm Hg were recorded. He was ill appearing, breathing shallowly. No lymph nodes were palpable. Bilateral inspiratory rales were heard at the lung bases, with a small area of dullness in the right lower lung field. No abdominal organomegaly or tenderness was noted. Extremities showed 2+/H11545 edema. Chest X-ray showed a small right pleural effusion.

Laboratory results showed a hematocrit of 37.5% and a WBC count of 13,700/mm³, with 69% PMNs, 17% bands. Transaminases were 84 IU/L (AST) and 32 IU/L (ALT); alkaline phosphatase, 482 IU/L; total bilirubin, 2.4 mg/dL (1.5 mg/dL direct). Analysis of pleural fluid revealed a WBC count of 250/mm³, with 92% PMNs; LDH 741 IU/L; total protein 3.8 mg/dL;
Fever, chills, malaise, anorexia, headache, and back pain usually develop 2 to 4 weeks after inoculation or ingestion of *Brucella*. In case 13.6, the history of intermittent low-grade fever and sweats was typical. These nonspecific symptoms can persist for weeks, making the diagnosis difficult to ascertain. As a result, brucellosis is among the listed infectious causes of fever of undetermined origin (see Chapter 3).

The physical exam is usually unimpressive; often, the only positive findings are lymphadenopathy and splenomegaly. As observed in case 13.6, approximately one third of patients develop a focal infection. Localized disease is more likely in patients who have had untreated infection for 30 or more days. Immunosuppression probably predisposed case 13.6 to develop a localized pleural infection as well as moderate hepatic involvement.

Septic arthritis is associated with mononuclear cells in the joint fluid, and *Brucella* can be cultured in half of the cases. Sacroiliitis is particularly common. Osteomyelitis is rare and usually involves the vertebral bodies, mimicking tuberculous osteomyelitis. Granulomas are detected in bone marrow in up to 75% of cases. Infection of the marrow can lead to anemia, leukopenia, and thrombocytopenia.

The liver is probably always infected. Mild elevations of liver function tests are noted, and granulomas may be found on liver biopsy, particularly with *B. abortus*. Pusulent abscesses are rare, but may be seen with *B. suis* and less commonly with *B. melitensis*. *Brucella* can often be recovered from the urine, but invasion of the kidney is rare. Orchitis is reported in up to 20% of men with brucellosis, the testes being infiltrated with lymphocytes and plasma cells.

Meningitis is the most frequent complication of the central nervous system and is associated with a CSF lymphocytic pleocytosis, elevated protein, and normal or depressed glucose. Encephalitis and brain abscesses are rare. Endocarditis is rare, but can be fatal. Generally, valve replacement must be combined with prolonged antibiotic therapy. Pulmonary involvement is rare, but discrete granulomas can form, and bronchopneumonia occasionally occurs.

**Diagnosis**

Blood samples for culture should be drawn in all patients who are suspected of having brucellosis. Cultures are positive in up to 70% of patients. However, the organism is slow–growing, taking up to 35 days. However, blood cultures usually take 7 to 21 days to turn positive.

The clinical microbiology laboratory should be alerted so that cultures are held for beyond 7 days. Bone marrow culture is also a high-yield diagnostic test and should be considered in patients with negative blood cultures. Serology is the most common method for making the diagnosis. Serum agglutination titers measure IgG and IgM antibodies against the three major pathogenic *Brucella* strains, but do not detect *B. canis* (a rare cause of disease). A titer above 1:160 in the presence of appropriate symptoms is supportive of the diagnosis, as is a rise in the titer by a factor of four between acute and convalescent sera. ELISA methods for IgG and IgM are also available and demonstrate sensitivity and specificity similar to those of the serum agglutination tests.

**Treatment**

Because *Brucella* survives within phagocytes, antibiotics with good intracellular penetration are recommended (see Table 13.1). The treatment of choice is doxycycline and rifampin for 6 weeks. Single-drug
therapy is not recommended because of the high likelihood of relapse. Doxycycline combined with intramuscular streptomycin or gentamicin (5 mg/kg) are useful alternatives. For children, trimethoprim-sulfamethoxazole (10 to 12 mg/kg of the trimethoprim component daily, divided into two doses) and rifampin (20 mg/kg daily) are recommended. In cases of meningitis or endocarditis, a three-drug regimen consisting of doxycycline, rifampin, and trimethoprim-sulfamethoxazole has been used. Therapy for these diseases must be prolonged (several months to more than 1 year). In patients with endocarditis, replacement of the infected valve is usually required for cure.

FURTHER READING

Lyme Disease


Leptospirosis


Rickettsial Diseases


Ehrlichiosis


Q Fever


Bartonella Infections


Brucellosis


Biologic weapons are intended to kill and terrorize their victims. Treatment must be immediate, and public health measures must be instituted quickly and efficiently to prevent additional casualties.

Bioterrorism was once called biologic warfare, a term that should now be avoided because it suggests that biologic agents are legitimate weapons for defeating a true or perceived enemy. In 1975, biologic weapons were rightfully condemned as inhumane and cowardly, and the civilized world agreed to ban them. Such agents cause great pain and suffering, and have the potential to kill large numbers of innocent bystanders. They subvert science conducted to save lives, to kill and maim instead.

The term “biologic weapons” is defined as the use of “microbial . . . agents . . . for hostile purposes or in armed conflict.” “Ideal” biologic agents would be expected to

- reliably cause permanently debilitating or fatal disease in a high percentage of victims.
- be capable of being targeted precisely to the enemy, and not cause a worldwide epidemic that could harm friendly soldiers or civilians.
- be capable of being produced in large quantities at reasonable cost.
- be capable of being stored for prolonged periods without losing potency.
- be capable of being readily aerosolized to allow rapid delivery over a broad geographic area.

Only a limited number of biologic pathogens fulfill most of these criteria. Four agents are of particular concern today. However, new “advances” that create super pathogens genetically designed to fit the needs of the bioterrorist are likely to add new organisms to the “most wanted” list. Currently, experts usually list anthrax, plague, tularemia, and smallpox as the top four potential biologic weapons. Other organisms that could be used include Clostridium botulinum (botulinum toxins),

GUIDING QUESTIONS

1. What are the key characteristics of the ideal bioterrorist agent?
2. What can physicians do to help in the early phases of a bioterrorist attack?
3. What are the clinical clues that should raise the possibility of an anthrax attack?
4. How is bubonic plague normally transmitted, and what are the usual clinical manifestations of plague?
5. Which groups are normally at risk for developing tularemia?
6. How does the clinical presentation of smallpox differ from that of chickenpox?
Brucella, Coxiella burnetii (Q fever), alpha viruses (Venezuelan equine encephalitis, Eastern and Western encephalitis), and viral hemorrhagic fevers (Ebola virus and Marburg agent).

Medical personnel must be aware of the clinical manifestations, modes of transmission, appropriate diagnostic tests, and available treatment and prophylactic options for managing a biologic attack. The U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) recommends a 10-step approach:

1. **Maintain a high index of suspicion.** Whenever possible, these diseases should be treated in the early phase of illness, when symptoms tend to be nonspecific. Without a high index of suspicion, treatment may be delayed, and mortality greatly increased.

2. **Protect thyself.** Use of high-efficiency particulate air (HEPA) filters or even surgical masks is warranted when a contagious respiratory illness is suspected or an aerosolized pathogen has been released. All health care workers should be up-to-date with appropriate immunizations.

3. **Assess the patient.** History of recent symptoms; epidemiologic clues (see point 9); vital signs; pulmonary, cardiovascular, and skin examination; and assessment of motor function should all be quickly obtained.

4. **Decontaminate when necessary.** Patients usually present several days after exposure to biologic agents, making decontamination unnecessary. Decontamination is more commonly required after exposure to chemical agents. Bleach (0.1%) is an effective decontaminant that kills even the hardiest biologic agent, anthrax spores.

5. **Establish a diagnosis.** The approaches to diagnosis depend on the agent and are reviewed in this chapter. Where appropriate, nasal and throat swabs (use rayon rather than cotton swabs), blood, urine, and sputum cultures should be obtained, and environmental samples should be analyzed. Improved rapid diagnostic tests are currently under development, and samples should be provided to the Centers for Disease Control and Prevention (CDC: emergency contact number 1-770-488-7100), the USAMRIID (1-888 USARIID), or the Emergency Operations Centers Special Pathogens Branch (1-301-619-4728).

6. **Render prompt treatment.** Therapy is most effective in the prodrome period, when clinical signs may not allow for a specific diagnosis. Delay of treatment until the clinical manifestations are more developed often results in serious complications or death. In the proper setting, empiric therapy should be strongly considered in patients with an undifferentiated febrile illness or pneumonia. Doxycycline is particularly useful when a bioterrorist agent is being considered, because this antibiotic treats anthrax, plague, tularemia, Q fever, and brucellosis. Fluoroquinolones also may have a potential role in empiric therapy.

7. **Practice good infection control.** For most agents, standard precautions provide adequate protection. The three exceptions are smallpox (requires strict airborne precautions), pneumonic plague (requires droplet precautions), and viral hemorrhagic fevers (require contact precautions).

8. **Alert the proper authorities.** Public health officials and the clinical lab should be immediately notified of a potential biologic attack. Rapid action on the part of public health officials to deliver stockpiles of appropriate medications, establish appropriate triage and management teams, and assess the extent of the attack will reduce casualties and save lives.

9. **Assist in epidemiologic investigation.** It is critical that all health care personnel have a fundamental knowledge of epidemiologic principles. Whenever possible, an occupational and travel history, immunizations, exposure to contaminated food or water, and history of friends or coworkers becoming ill should be obtained and provided to public health personnel.

10. **Maintain proficiency.** During a time of increased threat, health care personnel are inundated with facts concerning various biologic agents, but knowledge and proficiency can wane over time. It is critical that each person maintain “proficiency in dealing with this low probability, but high consequence problem.”

(Adapted from the USAMRIID’s handbook called *Medical Management of Biological Casualties.* Visit www.usamriid.army.mil/education for additional training.)

### ANTHRAX

Anthrax is a natural infection of animals, primarily herbivores. Humans can contract the disease from infected animals or animal products. With the advent of domestic animal vaccinations, this disease is now seldom encountered in developed countries. As a consequence, most health professionals are unfamiliar with the clinical manifestations of this potentially deadly organism.

The United States, the former Soviet Union, and Iraq have all manufactured anthrax spores capable of being disseminated as aerosols. For the first time in history, anthrax spores were used in 2001 as a biologic weapon against U.S. citizens. That attack underscored the importance of early recognition and treatment of pulmonary and cutaneous anthrax.
MICROBIOLOGY AND PATHOGENESIS

*Bacillus anthracis* is a gram-positive rod that can be easily grown on conventional nutrient media. On blood agar plates, the nonhemolytic colonies are gray-white in color with ragged edges. Colonies adhere tightly to the media and cannot easily be displaced by a culture loop. When this bacterium encounters unfavorable environmental conditions, it readily forms endospores. The spores are highly resistant to adverse conditions and are able to survive extreme temperatures, high pH and salinity levels, and disinfectants.

When spores are inhaled, their small size allows them to reach small bronchioles and alveoli, where macrophages phagocytose and carry them to the hilar and perihilar lymph nodes. Under the favorable environmental conditions in a host, the spores then germinate, and bacteria begin to quickly multiply.

The bacteria produce three exotoxins: protective antigen, lethal factor, and edema factor. Protective antigen binds to specific receptors on the cell surface and forms a channel that facilitates the entry of edema and lethal factor. These two agents result in cell swelling and death. Lethal factor is a protease that cleaves specific MAP (mitogen-activated protein) kinase kinases, blocking cell signals important for neutrophil chemotaxis, macrophage cell survival, and immune cell cytokine production. As a result, the host’s immune system is paralyzed, and the bacteria continue to grow rapidly and quickly entering the bloodstream to cause overwhelming bacteremia, shock, and meningitis.

Epidemiology

Most cases of anthrax in the United States occur as a result of contact with animal products imported from Asia, the Middle East, and Africa. Wool, goat hair, and animal hides are the most common sources of infection. A case of inhalation anthrax contracted from contaminated hides was recently reported in Pennsylvania. Cases have also been traced to shaving-brush bristles, wool coats, yarn, goat-skin bongo drums, and heroin preparations.

The largest outbreak of anthrax in recent years occurred in Sverdlovsk (now Yekaterinburg), Russia, in 1979. The approximately 96 inhalation cases resulted in 64 deaths. The accidental release of anthrax spores from a germ-warfare facility was suspected, and recent polymerase chain reaction (PCR) analysis of tissue samples from 11 victims confirmed that suspicion.

The deliberate introduction of anthrax spores into letters sent through the United States Postal Service in 2001 caused 11 cases of inhalation and 11 cases of cutaneous anthrax. Postal workers were at particular risk, because of spores released from sealed envelopes during mail processing. Cross contamination of mail also occurred. As a consequence of those events, all mail recipients have been instructed to avoid opening suspicious mail. If powder is found in an envelope, the letter should be gently set down, the room quickly vacated, and appropriate authorities immediately notified. These events of 2001 emphasize the importance of training public health and law enforcement personnel on the proper handling of potentially contaminated samples and on decontamination and prophylaxis.

CLINICAL MANIFESTATIONS

**CASE 14.1**

A 63-year-old man was taken by his wife to the emergency room with four-day history of fever, myalgias, and malaise. His wife reported he had no complaints of sore throat, rhinorrhea, and other upper respiratory tract symptoms. He awoke confused and disoriented...
It is critical that health care personnel be familiar with the clinical manifestations of anthrax. In patients with a febrile illness or cutaneous lesions of unclear cause, an exposure and occupational history may be particularly helpful in focusing on the possibility of anthrax. During the 2001 bioterror attack in the United States, early recognition of the index case (case 14.1) in South Florida by an infectious disease specialist led to rapid institution of antibiotic prophylaxis and saved many lives. Unfortunately, several other physicians failed to recognize the early manifestations of inhalation anthrax.

The patient’s laboratory workup showed a hematocrit of 46% and a peripheral white blood cell (WBC) count of 9400/mm³, with 77% polymorphonuclear leukocytes (PMNs), 15% lymphocytes, and 8% monocytes. A chest x-ray revealed basilar infiltrates and a widened mediastinum (Figure 14.1(A)). Cloudy fluid from a lumbar puncture contained red blood cells (1375/mm³), WBCs (4750/mm³, with 81% PMNs and 19% monocytes), 666 mg/dL protein, and 57 mg/dL glucose. A Gram stain of the cerebrospinal fluid (CSF) revealed many PMNs and many large gram-positive bacilli, both single and in chains (Figure 14.1(B)). Cultures of blood and CSF grew B. anthracis.

Despite administration of high-dose penicillin, the patient suffered grand mal seizures, hypotension, acidosis, and renal failure. On the third hospital day, he died of an asystolic cardiopulmonary arrest. Autopsy revealed no pulmonary parenchymal consolidation. Other findings included 50 mL gross blood in the mediastinum and several enlarged lymph nodes (1 cm to 2 cm). On cross-sectional examination, the lymph nodes were hemorrhagic. (Adapted from Bush LM, Abrams BH, Beall A, Johnson CC. Index case of fatal inhalational anthrax due to bioterrorism in the United States. N Engl J Med. 2001;345:1607–1610)
anthrax in postal workers, and those patients were discharged from the emergency room only to return later with full-blown fatal disease. The earlier recognition of several cutaneous anthrax cases could have alerted the authorities in New York in a more timely manner that a bioterror attack had also been launched in that state.

### Inhalation Anthrax (Woolsorters’ Disease)

It is important that clinicians be aware of the biphasic presentation of inhalation anthrax. Recognition and treatment during the first phase can be life saving.

Case 14.1 in all likelihood inhaled spores from a contaminated letter sent to his newspaper, and a flu-like illness was present for 4 days before the onset of fulminating mediastinal involvement, with bacteremia and meningitis. Because the patient failed to seek medical attention during the early phase of his illness, his fatal outcome could not have been prevented.

**FIRST PHASE**

From 1 to 5 days after inhalation of spores, the patient has symptoms suggestive of a viral syndrome: nonproductive cough, malaise, fatigue, myalgia, and mild fever. Occasionally, the sensation of chest heaviness is reported. Rhonchi may be heard on examination, but aside from fever, no other abnormal physical findings are observed. As noted in case 14.1, pharyngitis and rhinitis do not usually accompany inhalation anthrax.

Unless a careful exposure and occupational history is obtained, and inhalation anthrax is included in the differential diagnosis, patients are often sent home with antipyretics for a presumed viral syndrome. It is during this period that spores are being transported by pulmonary macrophages from the lung parenchyma to the mediastinal lymph nodes. At this stage, antibiotic treatment should prevent progression to the second phase.

**SECOND PHASE**

Within 2 to 4 days, symptoms temporarily resolve, but are rapidly followed by the second, more severe, stage of the disease. At this time, the spores have germinated in the mediastinal lymph nodes, and protective antigen, lethal factor, and edema factor are being produced by rapidly multiplying anthrax bacilli. Necrosis and hemorrhagic inflammation quickly develop, causing the sudden onset of severe respiratory distress with dyspnea, cyanosis, and diffuse diaphoresis accompanied by fever, tachycardia, and tachypnea. On pulmonary auscultation, moist, crepitating rales are evident, and findings consistent with pleural effusions may be apparent. Chest x-ray demonstrates a widened mediastinum without a definite parenchymal infiltrate. Pleural effusions are often also revealed [Figure 14.1(A)].

The combination of a widened mediastinum accompanied by pleural effusions should immediately raise the possibility of inhalation anthrax. Thoracentesis reveals hemorrhagic fluid, and Gram stain and culture are both usually positive. As described in case 14.1, confusion followed by lethargy and coma may develop in about half of all cases as a consequence of meningitis. On lumbar puncture, the CSF contains PMNs and large boxcar-like gram-positive rods [Figure 14.1(B)]. In the terminal stages of the illness, blood cultures are usually positive for *B. anthracis*. Death usually occurs within 24 hours and may be accompanied by septic shock. Death can be very sudden, and patients have been reported to die “in mid-sentence.”

**Cutaneous Anthrax**

Skin disease is the most common manifestation of anthrax. Between 1 and 7 days after spores are inoculated into the skin, a small papule develops. Over the next 3 to 4 days, the lesion progresses to a vesicle, 1 cm to 3 cm in diameter. Erythema and non-pitting edema often surround the vesicle. Initially, the vesicular fluid is serous and contains large numbers of...
organisms. The vesicle subsequently ruptures, and a black eschar becomes evident at the base of the ulcer (Figure 14.2). The name “anthrax” (Greek for coal) refers to this characteristic black eschar.

Despite the erythema and swelling, lesions are not painful, but they may be mildly pruritic. Lymphangitis, lymphadenopathy, fever, and malaise may accompany infection of the skin. After several weeks, the skin lesion dries, and a permanent scar is formed. Lesions occur primarily on exposed regions of the body. The arms are the most frequent site of infection; the face and neck are also commonly involved. A single lesion is usually found, although multiple sites may become infected as a result of simultaneous inoculations.

**Gastrointestinal Anthrax**

Gastrointestinal infection has not been reported in the United States, and it is not an expected clinical consequence of a bioterrorist attack. This disease occurs primarily in developing countries, usually after ingestion of contaminated meat. The incubation period is usually 3 to 5 days. Patients initially have nausea, vomiting, anorexia, and fever. These symptoms are rapidly followed by acute abdominal pain, hematemesis, and bloody diarrhea. Findings on examination suggest an acute surgical abdomen, and moderate leukocytosis with immature band forms is seen. Rapid progression to toxemia and shock leads to death within 2 to 5 days after the initial onset of symptoms.

An oropharyngeal form of anthrax has also been described. Inflammatory lesions that resemble the cutaneous lesions develop on the posterior pharynx, hard palate, or tonsils. Tissue necrosis and edema are accompanied by sore throat, dysphagia, fever, regional lymphadenopathy, and toxemia.

**DIAGNOSIS**

A careful epidemiologic history is the single most important means of reaching the diagnosis. In cases of natural infection, a history of contact with herbivores or products from these animals, particularly if the products come from outside the United States, should raise the possibility of anthrax. In the setting of a possible bioterrorist attack, employment history and a history of being present in a contaminated area are important clues. By the time Gram stains and cultures of blood and CSF are positive, the illness has progressed to the second fatal phase. Diagnosis must therefore be presumptive, and the threshold for treatment low to prevent progression from mildly symptomatic to life-threatening disease.

For epidemiologic purposes, samples from the nose and face can be obtained using rayon-tipped swabs. Cultures from these sites are specific, but insensitive, and, in the individual patient, cannot be used to decide whether to begin treatment. Nasal samples can be used to determine the physical perimeters of exposure, and the resulting data can be used to determine who should receive prophylactic antibiotics. The physical appearance of the skin lesions is characteristic, and Gram stains and cultures of the ulcer base are frequently positive. Enzyme-linked immunosorbent assays (ELISAs) are available that measure antibody titers against lethal and edema toxin. A rise in multiple titers by a factor of four over 4 weeks or in a single titer to 1:32 is considered positive.
**KEY POINTS**

**About the Diagnosis of Anthrax**

1. Epidemiologic history is important, and the diagnosis is often presumptive.
2. Nasal swabs are helpful for determining the physical parameters of exposure, but not for deciding individual treatment or prophylaxis.
3. Gram stain and culture of skin lesions are often positive.
4. Positive cultures of blood and cerebrospinal fluid usually accompany a fatal outcome.
5. Enzyme-linked immunosorbent assays for antibodies against lethal toxin and edema toxin are available.

**TREATMENT**

Although penicillin has been recommended as the treatment of choice for naturally occurring anthrax, penicillin-resistant natural strains have been reported. Penicillin-resistant strains of anthrax have also been genetically engineered as bioterrorist weapons, and the military protocol recommends intravenous ciprofloxacin (400 mg twice daily) or doxycycline (200 mg loading dose, followed by 100 mg twice daily) as first-line therapy (see Table 14.1). Penicillin is recommended as an alternative once sensitivities have been obtained. Because penicillin treatment induces β-lactamase activity, penicillin should be combined with an additional antibiotic. Other antibiotics that demonstrate activity against anthrax—and that may be combined with any of the above agents in the seriously ill patient—include rifampin, vancomycin, imipenem, clindamycin, and clarithromycin. Treatment should be continued for 60 days, with a switch to oral antibiotics as the patient’s clinical condition improves. Excision of skin lesions is contraindicated because of the increased risk of precipitating bacteremia. However, after appropriate antibiotic therapy, excision and skin grafting may be necessary.

Before antibiotics became available, cutaneous disease resulted in a mortality of 10% to 20%. With appropriate antibiotic treatment, fewer than 1% of patients die. Despite appropriate antibiotics and respiratory support, inhalation anthrax is frequently fatal. In the 2001 U.S. bioterrorist attack, half of the patients who contracted inhalation anthrax survived, proving that rapid institution of antibiotics can be life-saving in early second-phase pulmonary anthrax. Gastrointestinal disease is also associated with high mortality (25% to 100%).

**PROPHYLAXIS**

A killed vaccine derived from a component of the anthrax exotoxin is available and is recommended for all industrial workers at risk for exposure to contaminated animal products. As a result of increased concerns about biologic warfare and bioterrorism, military personnel are now vaccinated. To date, surveillance studies have not detected any serious or unexpected adverse reactions. The vaccination (BioThrax), which is available through the CDC (telephone: 770-488-7100; Web: http://cdc.gov), is administered in six doses at two-week intervals.

In cases of suspected exposure to *B. anthracis*, antibiotic prophylaxis and vaccination are recommended. The regimen of choice is an oral fluoroquinolone or, if fluoroquinolones are contraindicated, doxycycline (see Table 14.1). Prophylaxis should be continued until exposure is excluded. If exposure is confirmed, prophylaxis should be continued for 4 weeks in individuals who have received three or more doses of the vaccine, and for 60 days in the unvaccinated patient.

**KEY POINTS**

**About the Treatment and Prevention of Anthrax**

1. The treatment threshold must be very low in the setting of a bioterrorist attack.
   a) Give intravenous ciprofloxacin, levofloxacin, or doxycycline.
   b) Combination therapy is recommended for the seriously ill patient: add rifampin, vancomycin, imipenem, clindamycin, or clarithromycin to the basic regimen.
   c) Avoid excision of skin lesions, which carries a danger of precipitating bacteremia.
   d) Continue therapy for 60 days; newly germinating spores can cause relapse.
2. All individuals suspected of exposure should receive prophylaxis:
   a) Give a fluoroquinolone (ciprofloxacin, levofloxacin, or ofloxacin) or alternatively doxycycline for 60 days.
   b) Vaccine based on inactivated exotoxin is given to military personnel and workers at risk of exposure; 6 doses required for immunity, followed by annual booster.
   c) Decontaminate exposed areas and personal items with 0.5% hypochlorite.
### Table 14.1. Antibiotic Treatment of Bioterror Bacterial Agents

<table>
<thead>
<tr>
<th>Disease</th>
<th>Drug</th>
<th>Dose</th>
<th>Relative efficacy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthrax, prophylaxis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin</td>
<td>500 mg PO q12h</td>
<td></td>
<td>Duration: 60 days</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin</td>
<td>500 mg PO q24h</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Doxycycline</td>
<td>100 mg PO q12h</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anthrax, treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin, or doxycycline</td>
<td>400 mg IV q12h, 200 mg, then 100 mg IV q12h</td>
<td>First line</td>
<td>Duration: 60 days</td>
</tr>
<tr>
<td></td>
<td>In serious disease can be combined with:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Penicillin G, or</td>
<td>$4 \times 10^6$ U IV q4h</td>
<td></td>
<td>Only if anthrax is confirmed penicillin-sensitive</td>
</tr>
<tr>
<td></td>
<td>rifampin, or</td>
<td>600 mg PO or IV q24h</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>vancomycin, or</td>
<td>1 g IV q12h</td>
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<tr>
<td></td>
<td>imipenem, or</td>
<td>500 mg IV q6h</td>
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<tr>
<td></td>
<td>clindamycin, or</td>
<td>600–900 mg IV q8h</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>clarithromycin</td>
<td>500 mg PO q12h</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Plague, prophylaxis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Doxycycline</td>
<td>100 mg q12h</td>
<td></td>
<td>Duration: 7 days</td>
</tr>
<tr>
<td><strong>Plague, treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Streptomycin, or gentamicin, or doxycycline</td>
<td>15 mg/kg IM q12h, 5 mg/kg IV q24h, 200 mg, then 100 mg IV q12h</td>
<td>First line</td>
<td>Equally effective</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin</td>
<td>400 mg IV q12h</td>
<td>Alternative</td>
<td>Likely to be effective, but little clinical experience</td>
</tr>
<tr>
<td></td>
<td>Chloramphenicol</td>
<td>500 mg IV q6h</td>
<td></td>
<td>Treatment for meningitis</td>
</tr>
<tr>
<td><strong>Tularemia, prophylaxis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Ciprofloxacin</td>
<td>500 mg PO q12h</td>
<td></td>
<td>Duration: 2 weeks</td>
</tr>
<tr>
<td></td>
<td>Doxycycline</td>
<td>100 mg PO q12h</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tularemia, treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gentamicin</td>
<td>5 mg/kg IV q24h</td>
<td>First line</td>
<td>Duration: 10–14 days</td>
</tr>
<tr>
<td></td>
<td>Streptomycin</td>
<td>10–15 mg/kg IM q12h</td>
<td>Alternative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Doxycycline</td>
<td>200 mg, then 100 mg IV q12h</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notably, in the 2001 bioterrorist attack in the United States, only 44% of exposed individuals adhered to the recommended 60-day regimen. Failure to complete the regimen was not accompanied by any adverse outcomes. However, because spores may remain in the body for prolonged periods before germinating, prophylaxis needs to be prolonged, and patients should be closely observed after completion of antibiotics. Within the first several days, exposed skin should be washed extensively with soap and water, and personal items should be decontaminated with 0.5% hypochlorite (one part household bleach to 10 parts water).
PLAGUE

Like anthrax, plague is primarily a disease of animals. The causative organism, *Yersinia pestis*, primarily infects rodents. In the United States, the most common reservoirs are squirrels and prairie dogs. An outbreak associated with cats was also reported in the southwestern United States. The disease is transmitted to humans by infected rodent fleas. Approximately 10 human cases are reported annually in the southwestern United States during the late spring, summer, and early fall. Disease outbreaks frequently occur in developing countries throughout the world.

*Y. pestis* was used as a biologic weapon during World War II when the Japanese released plague-infected fleas in China. However the spread of the disease proved to be unpredictable and ineffective. Subsequently both the United States and the former Soviet Union developed reliable and effective methods of aerosolizing this agent.

MICROBIOLOGY AND PATHOGENESIS

*Y. pestis* is a gram-negative bacillus that grows aerobically on standard nutrient plates including blood and MacConkey agar. The organism grows slowly, often requiring 48 hours to become apparent, and the colonies are small and grayish.

When an infected flea bites a human, it regurgitates thousands of organisms into the skin, where they are phagocytosed by PMNs and monocytes. *Y. pestis* is usually killed by PMNs, but is able to survive and replicate within monocytes, evading the host’s immune system. Infected monocytes carry the organism to lymph nodes, where the pathogen actively replicates, causing marked acute inflammation and tissue necrosis. Regional lymph nodes become enlarged, forming buboes. *Y. pestis* can also quickly enter the bloodstream. Like other gram-negative bacteria, it produces endotoxin and also possesses other virulence factors including a coagulase and a fibrinolysin.

CLINICAL MANIFESTATIONS

Natural infection resulting from flea bites causes bubonic plague. The incubation period is usually 2 to 8 days, ending with the abrupt onset of fever, chills, weakness, and headache. Within hours, the patient notes an enlarged extremely painful cluster of regional lymph nodes termed a “bubo.” Marked swelling is noted, and pain is so severe that the patient avoids moving the infected area. Buboes are usually egg-shaped swellings 1 cm to 10 cm in length. Within 2 to 4 days, the patient dies of septic shock. Thrombosis of small vessels can develop, causing peripheral tissue necrosis and gangrene that may require amputation. In some patients, no bubo appears, and the patient presents in a moribund state caused by high-grade bacteremia. Meningitis may develop in a small percentage of patients.

If bioterrorists were to aerosolize *Y. pestis*, the primary clinical presentation would be pneumonic plague. After an incubation period of 2 to 4 days, fever, chills, and myalgias suddenly begin. Within 24 hours, patients begin coughing up blood as bacterial production of
coagulase and fibrinolysin leads to tissue necrosis. Sputum can also be mucopurulent or watery. Chest pain, abdominal pain, nausea, vomiting, and diarrhea are other common symptoms. If antibiotics are not begun within 18 hours, the outcome is fatal. Patients experience increasing dyspnea, stridor, and cyanosis, followed by respiratory arrest and circulatory collapse.

**DIAGNOSIS**

The possibility of a biologic attack with *Y. pestis* should be considered if large numbers of patients begin presenting to the emergency room with hemoptysis and severe, rapidly progressive pneumonia. Sputum Gram stain frequently reveals gram-negative rods. A presumptive diagnosis can also be made by finding bacilli on peripheral blood smear. Chest x-ray demonstrates bilateral bronchopneumonia. Definitive diagnosis is made by sputum and blood cultures that often take more than 48 hours because of the organism's slow growth rate. A rapid ELISA antigen test (takes 15 minutes) has been developed that is highly sensitive and specific. Detection by PCR is under development and, in fleas, is specific and highly sensitive (can detect as few as 11 organisms).

**TREATMENT**

If pneumonic plague is not considered and if conventional antibiotic treatment for community-acquired pneumonia is mistakenly begun, the infection will quickly progress, resulting in death. Streptomycin, gentamicin, and doxycycline (see Table 14.1 for doses) are the treatments of choice and should be continued for 10 to 14 days. Ciprofloxacin is another potentially effective regimen, but clinical experience with that agent is limited. Chloramphenicol is recommended for the treatment of meningitis.

Surgical debridement of buboes should not be performed, because of the risk of spreading the infection to others. Needle aspiration of lymph nodes may provide some relief and also provide material for culture and Gram stain. The lymph nodes usually slowly shrink on antibiotic therapy. The overall mortality for pneumonic plague is 60%; however, if appropriate therapy is delayed for more than 24 hours, then mortality is nearly 100%. The fatality rate for bubonic plague is 14%, but with early therapy, all patients should survive.

**PROPHYLAXIS**

Person-to-person spread of *Y. pestis* does occur. Patients with pneumonic plague can cough and aerosolize the organism, leading to secondary cases of pneumonia. Patients with pulmonary disease therefore require strict isolation with droplet precautions for at least 48 hours after the start of antibiotic therapy. People who have had face-to-face contact with patients with plague pneumonia should receive oral doxycycline prophylaxis (100 mg twice daily) for 7 days or for the duration of potential exposure plus 7 days. In patients with bubonic plague, only standard precautions are required, and prophylaxis is unnecessary. Contacts should be observed for 7 days.

A vaccine is not currently available. Production of a licensed killed vaccine was discontinued in 1998. The vaccine was effective for prevention of the bubonic, but not the inhalation disease. A new recombinant protein vaccine that has been shown to be effective for inhalation disease in animals, has been developed and could be approved by the U.S. Food and Drug Administration in the near future.

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**TULAREMIA**

*Francisella tularensis* is another zoonotic pathogen that, under natural conditions, incidentally infects humans. Infection is usually contracted following contact with rabbits, muskrats, beaver, squirrels, and birds. A case was also reported following a pet hamster bite. Hunters develop the disease after skinning, dressing,
and eating infected animals. Less commonly, the infection can be spread to humans by ticks, biting flies, and mosquitoes. Aerosol droplets of contaminated water or mud can be produced by lawn-mowing and other gardening activities.

Tularemia is most commonly encountered in temperate climates during the summer months (insect transmission) and during hunting season. The United States (and possibly other countries) has weaponized this agent. Dry and wet forms have both been created. Like *B. anthracis* and *Y. pestis*, *F. tularensis* is most efficiently delivered in lethal doses by aerosol.

**MICROBIOLOGY AND PATHOGENESIS**

*Francisella* is a small aerobic gram-negative coccobacilli that does not routinely grow on standard media; it requires either cysteine or cystine for growth. Glucose–cystine blood agar supports growth; however, a selective medium is often required to isolate this pathogen from normal skin and mouth flora. The cell wall of this bacterium has a capsule with high fatty acid content that resists serum bactericidal activity. *Francisella* produces no known exotoxins, but it expresses a lipopolysaccharide (LPS) endotoxin that is one one-thousandth as potent as LPS from *E. coli*.

Like most natural infections, tularemia begins when *F. tularensis* bacteria gain entry to the body through a small break in the skin. The organism is phagocytosed by monocytes, where it is able to survive intracellularly. *F. tularensis* can also grow in hepatocytes and endothelial cells.

As the organisms grow and lyse cells, they induce an acute inflammatory reaction, and tissue necrosis is followed by granuloma formation. Cell-mediated immunity plays a critical role in controlling this intracellular pathogen. Only 10 to 50 bacteria are required to cause skin and pulmonary infection, making this organism extremely dangerous to laboratory workers.

**CLINICAL MANIFESTATIONS**

The clinical picture of tularemia is very similar to that of plague. The incubation period is usually 3 to 5 days, ending with the abrupt onset of high fever, chills, malaise, myalgias, chest discomfort, vomiting, abdominal pain, and diarrhea. A severe generalized headache is often a prominent complaint.

Natural disease most commonly takes the ulceroglandular form. At the site of bacterial entry, a painful ulcer with raised borders develops, associated with painful regional adenopathy. The pneumonic form is rare under natural circumstances, but can occur in sheep shearers, farmers, and laboratory workers. The pneumonic form would be the expected presentation after an aerosol bioterrorist attack. The clinical presentation is identical to that of pneumonic plague, with the exception that the cough is usually dry and hacking rather than productive. Hemoptysis can occur, but is rare. In some patients, respiratory...
complaints may not be prominent, and primary complaints may mimic typhoid fever.

**DIAGNOSIS**

Presentation of a large number of patients with severe bronchopneumonia associated with a nonproductive cough should raise the possibility of a bioterror attack involving *F. tularensis*. Chest x-ray demonstrates changes consistent with a bronchopneumonia in 50% of cases after inhalation. Pleural effusions may be noted in 15% of those with pneumonia. Aspiration of the pleural fluid usually reveals lymphocytes, suggesting tuberculosis. Gram stain of sputum and wounds are usually negative. The organism can be identified in lymph nodes by silver stain. Gram stain of sputum and wounds are usually negative. The organism can be identified in lymph nodes by silver stain. Blood cultures and tissue sample cultures may be positive, but the organism must be grown using medium containing a sulfhydryl compound. The organism should be handled in a biosafety level 3 containment facility because of the risk to laboratory personnel.

The diagnosis is usually made by testing for antibodies to the organism. Two weeks are required before significant antibody titers (above 1:160) develop.

**TREATMENT**

Effective treatment regimens include streptomycin and gentamicin (see Table 14.1). In a presumed bioterror attack, gentamicin would be preferred over streptomycin, because a streptomycin-resistant strain was developed in the 1950s and may have been obtained by other countries. (That strain was sensitive to gentamicin.) Doxycycline is another alternative for treatment.

The mortality from tularemia pneumonia is 30%, making weaponized *Francisella* a less deadly agent than either anthrax or plague.

**PREVENTION**

Person-to-person transmission is not reported with tularemia. Standard precautions are therefore sufficient. Prophylaxis should be administered within 24 hours of exposure. Ciprofloxacin or doxycycline for 2 weeks is recommended (see Table 14.1). An investigational live-attenuated vaccine given by scarification is available. The vaccine provides significant protection against the inhalation and typhoidal forms of the disease.

### SMALLPOX

Endemic smallpox was eradicated in 1977. As a result, smallpox vaccinations were discontinued for civilians in 1980 and for military recruits in 1989, leaving a high percentage of the world's population without immunity to this deadly virus. Although only two repositories of the *Variola* virus are known (the CDC in Atlanta and the Research Institute of Viral Preparations in Moscow), stockpiles of the virus may be in the hands of others.

**EPIDEMIOLOGY**

Smallpox is spread person-to-person and has no other animal reservoirs. The incubation period before symptomatic illness is 7 to 17 days (average: 12 days). The period of communicability begins with the onset of rash and continues until all scabs separate from the skin, 3 to 4 weeks after the onset of illness. The virus is shed from lesions in the oropharynx and on the skin, producing airborne droplets and skin fragments that can be inhaled. Patients are most infectious if they are coughing or have the hemorrhagic form of disease. The communicability of smallpox is low as compared with chickenpox and measles; secondary cases occur most commonly in household contacts and hospital personnel. The virions are relatively resistant to drying and to many disinfectants; they can remain infectious for months at room temperature. Autoclaving, chlorine preparations, iodophores, and ammonia inactivate them.
A number of factors make Variola a potentially dangerous biologic weapon:

- Infection can be aerosol-spread, and the virions can survive in the environment.
- Person-to-person transmission facilitates continued spread after an initial attack.
- Routine vaccination was discontinued, creating large susceptible civilian and military populations.
- The potency of stored vaccine may be declining.
- The disease causes severe morbidity and mortality.
- Health care personnel have no clinical experience with the disease, and delays in diagnosis, treatment, and prevention would therefore be expected.

VIROLOGY AND PATHOGENESIS

Variola is a large, double-stranded DNA virus. It replicates in the cytoplasm of host cells that release new viral particles by bud formation on the cell surface. Virus-containing airborne droplets and dust particles are inhaled. The virus then spreads from the upper respiratory tract to the regional lymph nodes, where it enters the bloodstream, causing transient viremia before it invades virtually all body tissues. Epithelial cells are particularly susceptible, accounting for the prominent skin lesions.

Initially, edema develops at infected sites in the skin, accompanied by perivascular infiltration with mononuclear and plasma cells, causing the formation of macular skin lesions. Subsequently, the epithelial cells undergo ballooning degeneration, and spherical inclusion bodies containing clusters of virions (Guarnieri bodies) form in the cell cytoplasm. These changes are accompanied by the formation of papular skin lesions. Cell necrosis follows, accompanied by the formation of skin vesicles. Viral replication then ceases, and the skin lesions become crusted and dry, eventually healing and forming prominent scars.

CLINICAL MANIFESTATIONS

The first clinical manifestations of the disease are nonspecific and consist of the acute onset of fever, rigors, malaise, headache, backache, and vomiting. Delirium develops in approximately 15% of cases, and a transient erythematous rash may appear. This clinical prodrome lasts 2 to 4 days and is caused by high-level viremia. During this period, virus can be readily cultured from the blood.

Next, the exanthem becomes apparent. Lesions begin on the face, hands, and forearms, subsequently spreading to the lower extremities and, over the following week, to the trunk [see Figure 14.3(A)]. The distribution of skin lesions is centrifugal—that is, lesions are first seen on the distal extremities and face and then progress to the trunk. Initially, macules are seen that subsequently form papules, and then progress to pustular vesicles [see Figure 14.3(B)]. After about 2 weeks, the lesions form dry scabs that fall off, leaving scars. The skin lesions progress in a synchronous fashion—that is, at any one time, all skin lesions are at a similar stage.

The clinician must be able to differentiate smallpox from chickenpox (varicella virus), a common, naturally
occurring infection. Three clinical characteristics are most helpful in differentiating the two diseases:

- First, chickenpox is usually not associated with a significant prodrome. Patients often feel well before the onset of skin lesions.
- Second, the lesions of chickenpox and of smallpox begin in different locations. In chickenpox, lesions are first seen on the trunk, and they often spare the face. Subsequently, lesions spread to the arms and legs. That is, the distribution of chickenpox lesions is centripetal—that is, first seen on the central trunk and later on the distal extremities and face—rather than centrifugal (like smallpox).
- Third, the morphology of the skin lesions differs. Skin lesion development is asynchronous in chickenpox: macules, papules, vesicles, and scabs can all be seen at the same time on an individual patient. Chickenpox lesions are also irregular in shape and size, and are usually superficial. Smallpox lesions have smooth borders, are of similar size, and often extend to the dermis. The vesicles of smallpox feel shot-like; chickenpox vesicles are soft and collapse easily.


**DIAGNOSIS**

Full-blown disease can be readily diagnosed clinically. The diagnosis can be confirmed by viral culture on chorioallantoic membrane. Diagnostic techniques using PCR are under development and will allow for more rapid diagnosis.

A particular problem from an epidemiologic standpoint is the potential for failure to recognize relatively mild cases of smallpox in people with partial immunity. These patients may shed virus from the oropharynx in the absence of skin lesions.

**TREATMENT AND PROGNOSIS**

Currently, no treatment for smallpox other than supportive care is available. Cidofovir is active against poxviruses and may be considered for treatment. In animal studies, the tyrosine kinase inhibitor imatinib has been shown to reduce the spread of the closely related Vaccinia virus. Imatinib blocks the Abl family of tyro-
sine kinases, whose activity is required for extracellular release of the virus. Two additional antiviral drugs are under development. One interferes with a specific host signal transduction pathway required for viral spread, and the other blocks synthesis of a vital poxvirus protein. The overall mortality for smallpox is 30% in unvaccinated and 3% in vaccinated patients. Mortality is highest in very young and very old patients.

PREVENTION

The identification of a smallpox case represents a public health emergency, and public health officials should be notified immediately. Vaccination of all exposed individuals as quickly as possible is recommended, and vaccination within 7 days is protective.

The vaccine contains *Vaccinia* virus (cowpox virus) and is administered by intradermal inoculation using a bifurcated needle. Successful vaccination should result in vesicle formation at the site of inoculation, followed by scarification. Immunity has recently been shown to be lifelong. Side effects include low-grade fever and axillary adenopathy. Disseminated *Vaccinia* occurs in approximately 3 in 10,000 vaccinations. The vaccine is contraindicated in people with HIV infection, immunosuppression, or a history or presence of eczema, or in people who are in close contact with individuals having one of the foregoing conditions.

Other complications reported during the recent vaccination of 38,000 first responders included myocarditis or pericarditis, cardiac ischemic events and postvaccinal encephalitis. *Vaccinia* immune globulin (VIG) may be protective, but the large volume required for intramuscular administration (0.6 mL/kg—for example, 42 mL in a 70-kg person) make it an impractical tool for mass prophylaxis.

Infected patients must be strictly isolated. Placement in a negative air-pressure room, with the door closed, is recommended. Masks, gowns, and gloves must be worn when entering the room. Transport of the patient should be limited. All surfaces and supplies must be treated as contaminated. Large numbers of patients would quickly overwhelm isolation facilities and would necessitate separate temporary isolation facilities.

FURTHER READING

**General**


**Anthrax**


**Plague**


**Tularemia**


**Smallpox**


VARICELLA IN THE ADULT

Varicella virus [also called varicella-zoster virus (VZV)] is a double-stranded DNA herpesvirus that causes two diseases: varicella (chickenpox) and zoster (shingles). Chickenpox is a manifestation of primary infection; zoster is caused by reactivation of latent infection.

EPIDEMIOLOGY

Approximately 3 to 4 million cases of chickenpox and 500,000 cases of zoster occurred each year in the United States before the introduction of the VZV vaccine in 1995. Since then, dramatic reductions in chickenpox incidence have been reported.

Chickenpox is primarily a disease of childhood. Nevertheless, 10% of the adult population is estimated to be at risk for infection, and 10% of cases occur in patients over the age of 13 years. For unclear reasons, chickenpox occurs more frequently in adults who reside in tropical regions. The virus circulates exclusively in humans, and no other reservoirs of infection are known. The disease becomes epidemic in the susceptible population in winter and early spring, affecting both sexes and all races equally. Transmission occurs via the respiratory route and requires close contact even though the virus is highly infectious, with attack rates of 70% to 90% in susceptible family members.

In contrast, zoster affects primarily elderly people. Zoster is caused by reactivation of latent VZV in people who previously had chickenpox. Zoster occurs in up to 1% of people over 60 years of age, and 75% of cases occur in those over the age of 45 years. The development of zoster is not associated with exposure to other people with chickenpox or zoster, although patients with zoster may themselves be capable of transmitting the virus to susceptible individuals. Zoster occasionally occurs in younger individuals, particularly those who are immunosuppressed.
PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

Chickenpox is popularly felt to be a benign childhood rite of passage. Nevertheless, from 1990 to 1994, approximately 100 deaths each year in the United States were attributed to chickenpox and its complications. Deaths continue to occur in healthy adults and children despite the availability of a vaccine. The overall risk of death is about 15 times higher in adults than in children, being estimated at more than 3 per 10,000 cases. Most deaths in adults are a result of the development of visceral complications as discussed later in this subsection.

The disease begins with infection by the respiratory route. The virus then replicates at local sites (which have not been clearly identified) and infects the reticuloendothelial system. Viremia ensues, followed by diffuse seeding of the skin, internal organs, and nervous system. Replication of the virus occurs in the corium and dermis, leading to degenerative changes and the formation of multinucleated giant cells, producing the characteristic diffuse vesicular rash. A mild prodrome of fever and malaise of 3 to 5 days usually precedes the rash.

The rash initially appears on the face and trunk and spreads outward. It may also be present on the oral mucosa. It begins as small erythematous papules less than a centimeter in diameter that rapidly evolve into vesicles. As viral replication proceeds and infiltration by polymorphonuclear leukocytes occurs, the lesions appear purulent. A hallmark of chickenpox is that lesions at all stages of development—maculopapules, vesicles, and scabs—are all found together. As they evolve, the lesions appear umbilicated in the center. Successive crops of lesions occur over several days, with complete healing by 10 to 14 days in uncomplicated cases. The virus establishes lifelong latent infection in the dorsal root ganglia.

Reactivation of VZV can result in zoster, also known as herpes zoster and shingles. Zoster presents as a localized eruption along the course of one or more dermatomes, most commonly the thoracic or lumbar. The rash, which is often preceded by localized pain, begins as erythematous papules that evolve into vesicles. The vesicles may coalesce into large, confluent blisters with a hemorrhagic component. Healing occurs over the course of 2 weeks, although permanent skin changes such as discoloration and scarring may occur.

When zoster affects the first branch of the trigeminal nerve, herpes zoster ophthalmicus may occur, with involvement of the cornea and potentially sight-threatening complications. Involvement of other branches of the trigeminal or facial nerves may result in unusual presentations with intra-oral vesicles. The constellation of lesions in the external auditory canal, loss of taste, and facial palsy is termed Ramsay Hunt syndrome.

DIAGNOSIS

The diagnosis of chickenpox can usually be made on clinical grounds, based on the characteristics described earlier. Since the eradication of all known natural human reservoirs of smallpox and the discontinuation of universal vaccination, the clinical diagnosis of chickenpox has been relatively straightforward. Nevertheless, the possibility of smallpox as a biologic weapon and resumption of vaccination of larger segments of the population may necessitate considering smallpox or disseminated Vaccinia in the differential diagnosis of a diffuse vesicular rash in an adult.

A diffuse vesicular eruption, Kaposi's varicelliform eruption, occasionally occurs in patients with eczema. This syndrome may be caused either by vaccination with Vaccinia virus or by herpes simplex virus. The diagnosis can be made on the basis of the history and identification of the virus in vesicle fluid. Occasionally, enteroviral infection may cause diffuse cutaneous
vesicular lesions that mimic early chickenpox. These lesions are often found on the palms, soles, and oral mucosa and do not progress like those of chickenpox.

The diagnosis of zoster may sometimes be more difficult, with the primary alternative diagnosis being herpes simplex virus. Culture of the virus from unroofed vesicles remains the most reliable method of differentiating viral agents in this situation, although polymerase chain reaction (PCR)-based tests are also highly specific and sensitive. Antibody-based assays performed on lesion scrapings or vesicle fluid may also be useful if available.

**COMPLICATIONS**

**CASE 15.1**

A 36-year-old mother of two presented to the emergency room with complaints of shortness of breath. She had noted the onset of the skin lesions and low-grade fever 2 days before admission. Her son was recovering from a recent bout of chickenpox. Aside from the rash, she had been feeling well until the day of admission, when she began experiencing a dry cough and increasing shortness of breath.

On exam, this woman had a temperature of 38.5°C and a respiratory rate of 30 breaths per minute. She appeared in moderate respiratory distress. Her extensive skin rash involved the trunk and face. Lesions varied in character, some being vesiculopustular, and others nodular. A few crusted lesions were noted. Pulmonary exam revealed a few rales. A chest X-ray revealed bilateral lower lobe infiltrates with a fine reticulonodular pattern. Arterial blood gas registered a pH of 7.45, a PaCO₂ of 35 mm Hg, and a PaO₂ of 70 mm Hg on room air.

Intravenous acyclovir was begun. New crops of skin lesions were noted over the first 24 hours; however, the patient then defervesced, and her respiratory status slowly improved. She did not require intubation, and she was discharged on oral acyclovir.

The major complications of varicella result from involvement of the pulmonary and nervous systems. Varicella pneumonitis is more common in adults and immunocompromised patients than in children. It has been estimated that as many as 1 in 400 adults with chickenpox have some pulmonary involvement, although most cases appear to be subclinical. When clinical varicella pneumonitis occurs in adults, it is often associated with high morbidity and mortality. Fortunately case 15.1 responded quickly to acyclovir and did not suffer severe respiratory compromise. The disease can be particularly severe in pregnant women during the later stages of pregnancy, possibly because of both the respiratory impairment resulting from a gravid uterus and the immunologic changes associated with pregnancy. Smoking and the presence of a large number of skin lesions have been identified as risk factors for the development of varicella pneumonia. Tachypnea, dyspnea, and fever with nodular or interstitial markings on chest X-ray are typically observed. Development of encephalitis in association with chickenpox in adults is relatively uncommon, occurring in up to 0.1% to 0.2% of patients, with mortality being as high as 20%. Seizures are common and are accompanied by headache, fever, and progressive obtundation.

The major complications of zoster are also neurologic. Involvement of the central nervous system (CNS) can almost always be demonstrated in relatively asymptomatic patients with zoster when the cerebrospinal fluid (CSF) is examined. The most common

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**KEY POINTS**

**About the Complications Associated with Varicella Infection**

1. Pneumonia in adults can be fatal.
   a) Severity is increased in pregnant women and smokers.
   b) Severity often correlates with extent of the skin lesions.
2. Encephalitis is a rare complication associated with seizures, headache, obtundation, and 20% mortality.
3. Zoster is associated with multiple complications:
   a) Postherpetic neuralgia occurs in up to 50% of cases. More common in patients more than 50 years of age.
   b) Guillain–Barré syndrome, transverse myelitis, and encephalitis are occasionally seen.
   c) Ophthalmic-branch keratitis, iridocyclitis, blindness, and granulomatous cerebral angiitis are also possible.
4. Dissemination in immunosuppressed patients is often fatal.
complication is postherpetic neuralgia, especially in people over 50 years of age. As many as half of these patients will have persistent severe pain in the area where the lesions appeared. Encephalitis, transverse myelitis, and Guillain–Barré syndrome can also occur in association with an episode of zoster. A specific complication, particularly of ophthalmic zoster, is the subsequent development of granulomatous cerebral angiitis, which may result in stroke. Ophthalmic zoster may also result in keratitis, iridocyclitis, and (in severe cases) loss of vision.

Chickenpox and zoster are often more severe in the immunosuppressed patient. Bone marrow transplant recipients and children with hematologic malignancies are especially prone to visceral dissemination, with associated high mortality, and they require early and aggressive antiviral therapy.

TREATMENT

The mainstay of treatment for VZV is acyclovir and related nucleoside analogs that inhibit the viral DNA polymerase. Oral acyclovir therapy is recommended for adults and adolescents with chickenpox. Treatment reduces the total number of lesions and shortens the duration of lesion formation by about 1 day. Whether treatment reduces the likelihood of the serious complications described earlier in adults is unknown. The recommended adult dosage is 800 mg five times daily.

The minimum inhibitory concentration of acyclovir for VZV is 2 to 6 mmol/L, which is difficult to achieve by oral administration. Intravenous treatment is indicated in cases of varicella pneumonia and should be considered in other cases of visceral or CNS involvement. The usual dosage is 5 to 10 mg/kg every 8 hours. Prompt infectious disease consultation should be obtained in all cases of complicated varicella or varicella in the immunocompromised patient.

Antiviral treatment of zoster reduces acute neuritis and accelerates healing. Treatment in the immunosuppressed patient prevents dissemination. Ophthalmic zoster is usually treated with oral acyclovir or with the more bioavailable agents valacyclovir and famciclovir. Treatment of cutaneous zoster may also reduce the incidence or duration of postherpetic neuralgia, but the data supporting these effects has been questioned. Nevertheless, oral famciclovir and valacyclovir are approved for this indication and are more convenient than acyclovir because they are administered less frequently. Concurrent administration of corticosteroids to treat postherpetic neuralgia is also controversial, but some studies claim improvement in quality of life when steroids are added to antiviral therapy.

PREVENTION

A live attenuated varicella vaccine has been available since 1995. It is close to 100% effective in preventing serious disease, and it has a low incidence of side effects. Immunity has been persistent over the period since initial licensure. Varicella vaccination is recommended for all susceptible individuals over the age of 12 months. Although rates of zoster are lower in vaccinees, the vaccine strain may actually reactivate more frequently, but subclinically. Further, a decrease in circulating wild-type virus may result in less frequent natural boosting of immunity and therefore lead to an increased incidence of zoster in previously infected individuals. Vaccination also becomes more important as its acceptance rate increases, because the likelihood of infection during childhood decreases, increasing the risk of adult disease. The most recent recommendations are that all children

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**KEY POINTS**

About the Treatment and Prevention of Varicella and Zoster Infections

1. **Acyclovir** is recommended for adolescents and adults with chickenpox. Those with serious infection should receive high-dose intravenous therapy.

2. **Antiviral treatment (acyclovir, famciclovir, or valacyclovir)** is recommended for all cases of zoster.
   a) Reduces acute neuritis and accelerates healing.
   b) Prevents dissemination in the immunocompromised host.
   c) May reduce postherpetic neuralgia.
   d) Efficacy of concurrent treatment with corticosteroids to reduce postherpetic neuralgia is controversial.

3. **Live attenuated vaccine** is highly efficacious for chickenpox.
   a) Recommended for all susceptible individuals over the age of 12 months.
   b) Impact on zoster has not been clarified.

4. **Zoster vaccine was released in 2006.**
   a) It reduces the attack rate by 50%, and
   b) it reduces postherpetic neuralgia.

5. **Varicella-zoster immune globulin** is effective at preventing active disease.
   a) Give within 96 hours of exposure.
   b) Recommended for all exposed pregnant women and immunocompromised patients.
receive two doses of varicella vaccine before the age of 4 to 6 years, with the first dose at 12 to 15 months of age. Adults without evidence of prior infection should also be vaccinated, and children and adults who have received only 1 dose in the past should receive a second catch-up dose. The vaccine should not be administered to pregnant women.

In 2006, a zoster vaccine was approved for use in patients over 60 years of age who have not previously had zoster. The vaccine achieved an approximately 50% reduction in the incidence of zoster and a 67% reduction in postherpetic neuralgia, suggesting that the vaccine may lessen the likelihood of complications even if zoster occurs. Varicella-zoster immune globulin is effective in preventing disease in susceptible individuals when administered within 96 hours of exposure. Its use should be considered in all immunocompromised patients and in susceptible pregnant women who have been exposed.

**EPSTEIN–BARR VIRUS**

**EPIDEMIOLOGY**

Infection with Epstein–Barr (EBV) is ubiquitous, with 90% to 95% of all adults displaying serologic evidence of a past infection. In the United States, approximately 50% of children are seropositive by 5 years of age, with a second period of seroconversion occurring in early adulthood. Infection occurs earlier in developing countries and in certain areas of the United States. Most cases of EBV infection are transmitted by the presence of virus in oropharyngeal secretions of asymptomatic sheds. Blood transfusions and transplantation of solid organs or bone marrow may also be associated with EBV transmission.

**PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS**

**CASE 15.2**

An 18–year-old college freshman presented to the student health office with fever and sore throat for 1 week. His temperature was 38.9°C, his tonsils were enlarged, and he had diffuse nontender lymphadenopathy. The possibility of mononucleosis was raised, and titers for viral capsid antigen (VCA) immunoglobulins G (IgG) and M (IgM) were 1:20 and 1:80 respectively at that time. Over the next week, he became increasingly ill, developing scleral icterus and fever to 40.6°C.

On physical examination, the student was noted to have a tender, enlarged liver and palpable spleen. Multiple petechiae were noted on both lower legs. Laboratory workup showed elevated liver transaminases: 550 IU/L aspartate aminotransferase, 1000 IU/L alanine transaminase, 4000 IU/L lactate dehydrogenase (LDH), and bilirubin 6.0 mg/dL (total) and 4.8 mg/dL (direct). His hematocrit was 25%, and his white blood cell (WBC) count was 860/mm³, with 3% polymorphonuclear leukocytes (PMNs), 19% bands, 70% lymphocytes, and 10% monocytes. Numerous atypical lymphocytes were seen on smear. Platelets measured 23,000/mm³, and his erythrocyte sedimentation rate was 12 mm/h. Repeat serology revealed a VCA IgM of 1:160 and a VCA IgG of 1:640. Glucocorticoid therapy was considered; however, over the next 2 weeks, the fever spontaneously resolved, liver function tests returned to normal, hematocrit increased to 35%, WBC count improved to 3000/mm³ (with 70% PMNs), and platelets rose to 100,000/mm³. The young man’s spleen remained enlarged, and he was warned to avoid contact sports for the next few months.

Epstein–Barr virus is associated with a variety of clinical disorders arising from various pathogenic mechanisms. Infection during childhood is often asymptomatic or associated with nonspecific symptoms. Infection during adolescence or adulthood more commonly results in the syndrome of acute infectious mononucleosis, characterized by a vigorous humoral and cellular immune response to rapidly proliferating EBV-infected B cells. The most common signs and symptoms of mononucleosis include fever, sore throat, malaise, and lymphadenopathy. The pharyngitis may be exudative and severe. As noted in case 15.2, the enlarged lymph nodes are usually not tender. Other findings, in order of decreasing likelihood, include splenomegaly, hepatitis, palatal petechiae, jaundice, and rash. The rash, when seen, is nonspecific and may be transient. Administration of ampicillin during early EBV-associated mononucleosis very commonly results in a maculopapular rash.

Many aspects of the clinical syndrome of acute infectious mononucleosis—for example, fever, lymphadenopathy, splenomegaly, atypical lymphocytosis—are the result of vigorous T cell and natural killer (NK) cell proliferation and a cytokine response by the immune system rather than a result of direct viral infection, replication, and cytolysis. A few individuals develop a chronic active infection characterized by ongoing lytic EBV replication and multiple organ system disease such as pneumonitis, hepatitis, pancytopenia, and iritis.
KEY POINTS

About the Epidemiology, Pathogenesis, and Clinical Manifestation of Epstein–Barr Virus

1. Spread by oral secretions, with 95% of adults carrying the virus.
2. Infects B cells, and illness manifestations are the result of vigorous T cell and natural killer (NK) cell inflammatory response.
3. Fever, sore throat, and lymphadenopathy are the classic triad of mononucleosis.
4. Acute complications of the infection include splenic rupture, neurologic syndromes, and airway obstruction. Less commonly, hepatitis, hemolytic anemia, thrombocytopenia, and neutropenia sometimes occur.
5. Complications of chronic infection include hairy leukoplakia, B cell lymphoma, NK cell lymphoma, gastric adenocarcinoma, and leiomyosarcoma.

Individuals with a rare, inherited immunodeficiency linked to the X chromosome and known as X-linked lymphoproliferative syndrome or Duncan syndrome are prone to overwhelming lethal primary infection with EBV. Survivors are at risk for the subsequent development of lymphoma and agammaglobulinemia. The genetic defect in these patients has been mapped to a small cytoplasmic protein (Sap) that is implicated in regulation of T and NK cell signaling.

After resolution of primary infection, EBV persists for life as a latent infection in B cells and as a lytic infection in the oropharynx. Persistent EBV infection is controlled by a virus-specific immune response and most humans remain asymptomatic. However, immunosuppression associated with HIV infection, transplantation, or congenital immunodeficiency can result in uncontrolled oligoclonal or monoclonal B cell proliferation of latently infected cells. Uncontrolled lytic infection in the oropharynx is manifested as oral hairy leukoplakia in immunosuppressed hosts.

Persistent, latent EBV infection is also associated with development of Burkitt’s lymphoma, nasopharyngeal carcinoma, certain types of Hodgkin’s disease, gastric adenocarcinoma, and leiomyosarcomas in immunosuppressed hosts. Infection of NK cells by EBV has recently been associated with hypersensitivity to mosquito bites and the development of NK cell leukemia.

COMPLICATIONS

Serious and life-threatening complications of EBV infection occasionally occur. These include autoimmune hemolytic anemia, erythrophagocytic syndrome, thrombocytopenia, splenic rupture, and neurologic syndromes. The neurologic syndromes, although rare, include encephalitis and Guillain–Barré syndrome. The most common causes of death from EBV-associated mononucleosis in healthy adults are neurologic complications, splenic rupture, and airway obstruction. It should be emphasized that mononucleosis-associated encephalitis is rare and usually benign. Nevertheless, any of these complications may be the presenting sign of mononucleosis and “atypical” cases are not unusual.

DIAGNOSIS

Diagnosis of mononucleosis is usually based on clinical suspicion confirmed by laboratory testing. The clinical diagnosis in the typical adolescent or young adult is usually not too difficult. However, many cases occur in which few or none of the classic signs are evident at initial presentation.

Other causes of the infectious mononucleosis syndrome that should be considered in the young adult are cytomegalovirus, acute HIV infection, human herpesvirus 6, toxoplasmosis, cat scratch disease, and lymphoma. Laboratory confirmation of EBV infection is achieved primarily by serologic testing. Heterophil antibodies directed against sheep erythrocyte agglutinins are positive in about 90% of cases during the primary infection. Commercially available monospot testing for heterophil antibodies is less sensitive in children, and sequential monospot testing or determination of EBV-specific antibodies is indicated when clinical findings are suggestive of EBV infection, and the initial monospot is negative. The presence of IgM antibodies to VCA is the most sensitive and specific indicator of acute infection. The antibodies are usually detectable at initial presentation, along with IgG VCA antibody (see Table 15.1). By 4 to 8 weeks, the IgM VCA antibodies decline and disappear, but IgG VCA antibodies persist for life. Antibodies to Epstein–Barr viral nuclear antigens (EBNAs) do not develop until approximately 4 weeks after onset of symptoms, but they persist for life. Seroconversion to anti-EBNA positivity is therefore indicative of recent EBV infection. Although antibodies to EBV early antigens are often elevated during acute infection, they may persist for variable periods. These antibodies are occasionally detectable in healthy convalescent patients many years after infection, and they are therefore of limited utility in diagnosing acute infection.

At the time of presentation, VCA IgM antibody is positive, and VCA IgG and early lytic antigen (EA) antibody are also usually positive. As convalescence proceeds, EBNA antibodies become detectable, and VCA IgM antibody disappears. The EBNA and VCA IgG
antibodies remain detectable for life, and EA antibodies are also usually detectable, although at low titers.

Quantifying the EBV DNA load in peripheral blood by PCR identifies immunosuppressed patients who have or who are at high risk for developing EBV-associated B cell lymphomas. Although an elevated EBV DNA load in blood is clearly associated with the development of post-transplant lymphoproliferative disease (PTLD), the predictive value of such a finding is not uniformly high, given that only approximately 50% of bone marrow transplant patients with elevated EBV DNA develop PTLD. An increasing EBV DNA load may be predictive of the development of PTLD, underscoring the need for serial monitoring in high-risk patients.

**THERAPY**

Treatment of EBV-associated diseases is closely linked with the underlying pathogenesis of the disease. The usual treatment for EBV-associated malignancies involves cancer chemotherapy and radiation therapy as opposed to antiviral strategies, and those options are not discussed here.

**Infectious Mononucleosis**

More than 95% of infectious mononucleosis cases resolve uneventfully without specific therapy, and so supportive treatment is generally indicated. Acetaminophen can be used to reduce fever. Use of concomitant antibiotics for possible bacterial pharyngitis should be judicious, with support from positive bacterial culture results, because a high incidence of allergic reactions to antibiotics such as ampicillin is observed during acute infectious mononucleosis.

The use of corticosteroids for uncomplicated infectious mononucleosis remains controversial. Corticosteroids have been shown to reduce fever and shorten the duration of constitutional symptoms. However, adverse drug complications can arise from even short courses of corticosteroids, and corticosteroid use is probably best avoided in routine infectious mononucleosis, given its self-limiting nature. Corticosteroids are generally reserved for infectious mononucleosis cases complicated by potential airway obstruction from enlarged tonsils, severe thrombocytopenia, or severe hemolytic anemia. These complications result from the excessive immune response rather than from uncontrolled viral infection, and a short course of corticosteroids (1 mg/kg prednisone daily) with tapering over 1 to 2 weeks can be effective for treating the excessive tonsillar proliferation or autoimmune symptoms. Corticosteroids might also be used for other autoimmune complications occasionally associated with infectious mononucleosis—for example, CNS involvement, myocarditis, or pericarditis. Unless

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**Table 15.1.** Typical result patterns in serologic testing for Epstein–Barr virus during various stages of infection.

<table>
<thead>
<tr>
<th>Clinical status</th>
<th>VCA IgM Ab</th>
<th>EA Ab</th>
<th>VCA IgG Ab</th>
<th>EBNA Ab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Acute infection</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Early convalescence</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Late convalescence</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Previous infection</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>(low)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VCA = viral capsid antigen; IgM = immunoglobulin M; Ab = antibody; IgG = immunoglobulin G; EA = early lytic antigen; EBNA = Epstein–Barr virus nuclear antigen.
contraindicated, administration of corticosteroids concurrently with acyclovir is the author's general practice.

In general the combination of acyclovir and corticosteroids for uncomplicated infectious mononucleosis inhibits oral viral replication, but provides no clinical benefit. In rare, complicated cases of primary EBV infection and infectious mononucleosis in which the patient is immunosuppressed or severely ill, acyclovir or ganciclovir treatment may be rational, given the safety profile of these drugs, their ability to inhibit EBV replication in vitro and in vivo, and anecdotal reports of clinical response in unusual cases in which excessive EBV replication may have been pathogenic.

Splenic rupture is a rare, but potentially fatal, complication of infectious mononucleosis, occurring in approximately 0.1% of cases. Splenic rupture is more common in men, and approximately half of cases are spontaneous (not associated with trauma or other contributory factors). In one review of 55 cases of splenic rupture associated with infectious mononucleosis, all cases occurred within 3 weeks after the start of the illness. Another case–control study that combined physical, ultrasound, and laboratory examinations of patients with infectious mononucleosis found that physical examination was an insensitive method of detecting splenomegaly (17%), but that all patients were found to have splenomegaly for the first 20 days, and the severity of laboratory abnormalities did not correlate with splenic enlargement.

Although various strategies to minimize the risk of splenic rupture have been advanced, incorporating the results of physical exam and ultrasound imaging, no studies have validated the utility of any approach. It therefore seems prudent to recommend that the patient avoid, for a minimum of 4 weeks after the onset of illness, contact sports or activities (such as weightlifting) that raise intra-abdominal pressure.

Patients recovering from infectious mononucleosis may shed virus in their saliva for a period of several months after recovery despite being clinically well (see “Epidemiology” earlier in this subsection). Furthermore, it is clear that all latently infected humans may intermittently shed EBV in saliva. It is therefore difficult for seronegative subjects to avoid the risk of acquiring EBV infection. It appears that intimate sexual contact is more likely to transmit EBV infection.

**Chronic Active EBV Infection**

Occasionally, patients have an unusual clinical course following infectious mononucleosis with severe illness and evidence of chronic active EBV infection, as described earlier. These patients typically have extremely high antibody responses to EBV early antigens, lack antibodies to EBNA-1, and exhibit severe disease with end-organ involvement or evidence of increased viral load in affected tissues. Clinical responses and failures with acyclovir or corticosteroids have both been noted in anecdotal reports of these unusual patients with chronic active EBV infection.

**CHRONIC FATIGUE SYNDROME**

Infection with EBV has also been implicated as a cause of fatigue syndrome. However, seroepidemiologic studies have argued against a pathogenic role for EBV in chronic fatigue syndrome. In addition, a placebo-controlled study with acyclovir has shown no efficacy for patients with chronic fatigue syndrome.

**ORAL HAIRY LEUKOPLAKIA**

Oral hairy leukoplakia is an unusual lesion of the tongue found in HIV-infected patients. Vigorous EBV lytic replication is present in the excessively proliferating epithelium. This is the only instance in which disease appears to be a direct consequence of lytic EBV replication, and oral acyclovir therapy (3.2 g daily) can temporarily reverse the lesions. However, because nucleoside analogs have no effect on persistent, latent EBV infection, lytic EBV replication and oral hairy leukoplakia frequently recur upon withdrawal of therapy.

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**KEY POINTS**

About Therapy of Epstein–Barr Virus

1. Patients with acute mononucleosis are generally given supportive care.
   a) Avoid antibiotics when possible.
   b) Ampicillin almost always causes a rash.
   c) Use prednisone for airway obstruction, thrombocytopenia, or hemolytic anemia.
   d) Acyclovir or ganciclovir may be helpful in very severe cases.

2. Chronic active infection with Epstein–Barr virus (EBV)
   a) Involves very high antibodies to early antigens and no EBNA antibody production;
   b) Produces severe end-organ involvement; and
   c) May benefit from antiviral therapy.

3. In chronic fatigue syndrome, antiviral therapy is of no benefit.

4. Oral hairy leukoplakia can result from lytic EBV infection in HIV-infected patients.
   a) Acyclovir can control the infection.
   b) Relapse often occurs when treatment is discontinued.
KEY POINTS

About Hantavirus

1. Spread by rodents that shed the virus in their saliva and urine; virus is inhaled as an aerosol.
2. Found in the Four Corners area (New Mexico, Arizona, Colorado, Utah), New England, and the Midwest.
3. Starts as a mild febrile illness with abdominal pain, and proceeds to fulminant respiratory failure.
   a) Virus causes a pulmonary capillary leak syndrome with acute respiratory distress syndrome (ARDS).
   b) Severe hypoxia, hemoconcentration, and increased partial thromboplastin time and LDH are typical.
4. Serologies, polymerase chain reaction, and immunohistochemical staining are all available for diagnosis.
5. If supportive care and cautious fluid administration assist the patient to survive the ARDS, full recovery is possible.
immunohistochemical staining. If HPS is suspected, infectious disease consultation should be obtained immediately, and the Centers for Disease Control and Prevention (CDC) should be notified.

**THERAPY AND PREVENTION**

If the patient can be supported through the period of hypoxia and shock, recovery can be complete. It is important to realize that in HPS the vascular permeability of the lung is abnormal; fluid administration should be performed with this fact in mind. Intravenous ribavirin has been used in experimental treatment protocols; however, efficacy has not been demonstrated to date.

Prevention of HPS consists of personal precautions to avoid inhalation of aerosolized material contaminated by rodents, and general measures to reduce rodent infestation.

### SEVERE ACUTE RESPIRATORY SYNDROME

**EPIDEMIOLOGY**

In March 2003, the World Health Organization (WHO) orchestrated a worldwide effort to control a sudden outbreak a progressive respiratory illness termed Severe Acute Respiratory Syndrome (SARS). This epidemic first arose in Guangdong Province, China, and quickly spread. In February 2003, an infected business man traveling from China stayed in a hotel in Hong Kong and infected 10 other individuals staying on the same floor. These individuals in turn spread the illness to five different countries, including Hong Kong, Singapore, Vietnam, Thailand, and Canada. The illness was spread primarily through air droplets in closed spaces including airplanes. Family members and hospital personnel who failed to maintain respiratory precautions were primarily affected. The virus is also shed in the stool, and in one regional outbreak, infection spread through an apartment complex as consequence of a defective sewage system.

**CAUSE AND PATHOGENESIS**

The causative agent of SARS was quickly identified as a single-stranded RNA coronavirus. This virus has characteristics similar to those of the influenza and measles viruses. However, before the SARS outbreak, coronaviruses were known to be among the most common causes of adult viral upper respiratory infection (URI), producing clinical symptoms and signs identical to those caused by rhinoviruses. The SARS strain has a unique genomic sequence, being most closely related to bovine and avian coronaviruses and distantly related to other human coronaviruses. This enveloped virus does not withstand drying, but may remain infectious in a warmer, moist environment. On average, the virus survives on surfaces and hands for approximately 3 hours.

The virus attaches to cells in the respiratory tract and enters the cytoplasm, where it multiplies. It is then released from dead cells or extruded from living cells. The severe tissue damage associated with SARS infection is thought to be largely a result of the host’s overly vigorous immune response to the virus. Coronavirus is spread primarily by respiratory droplets produced by coughing. Epidemiologic studies suggested that a small subset of SARS patients were particularly efficient at spreading the virus to others; they have been called “super spreaders.” These individuals had severe infection and were suspected to be producing small droplets that more efficiently aerosolized and remained in the air for prolonged periods.

**CLINICAL MANIFESTATIONS**

The infection attacks primarily adults aged 25 to 70 years who are healthy. Children are generally spared, although a few cases have been suspected in children under the age of 15 years. The incubation period typically lasts 2 to 7 days, but can take as long as 10 days. The illness usually begins with a severe febrile prodrome (fever being defined as temperature above 38.0°C for epidemiologic purposes). This fever is often high and can be associated with chills and rigors. Fever is accompanied by headache, malaise, and myalgias. During this phase of the illness, respiratory symptoms are mild. Rash and neurologic symptoms and signs are usually absent. Gastrointestinal symptoms are also usually absent at this stage, although diarrhea has been reported in some cases. The lower respiratory phase of the illness begins 3 to 7 days after the onset of symptoms. Patients begin to experience a severe, dry, nonproductive cough, accompanied by dyspnea and hypoxemia. Respiratory distress is often severe, with 10% to 20% of patients requiring intubation and mechanical ventilation.

Laboratory findings may include a decreased absolute lymphocyte count. The total peripheral WBC count is usually normal or decreased. At the peak of the respiratory illness, 50% of patients develop leukopenia and thrombocytopenia (50,000 to 150,000/µL). Muscle and hepatic enzymes are often elevated early in the respiratory phase, reflecting the onset of rhabdomyolysis and hepatitis. Levels of creatine phosphokinase can be as high as 3000 IU/L, and hepatic transaminases usually are 2 to 6 times normal. Serum LDH is elevated in 70% to 80% of patients. Renal function usually remains normal.

Chest x-ray is usually normal during the febrile prodrome, but changes dramatically during the respiratory phase. The initial abnormalities seen are focal
interstitial infiltrates that quickly progress to more generalized, patchy, interstitial infiltrates. In the late stages, these interstitial infiltrates develop into areas of dense consolidation. At autopsy, lung pathology may reveal pulmonary edema, hyaline membranes, and desquamation of type 2 pneumocytes. In later stages, fibroblast proliferation is observed in the interstitium and alveoli.

**DIAGNOSIS**

For epidemiologic purposes, the diagnosis must be made quickly based on clinical criteria. For this purpose, the WHO created a series of case definitions (See Table 15.2).

Real-time reverse transcriptase PCR tests have been developed to rapidly and sensitively identify the SARS coronavirus in clinical samples. However, in the absence of ongoing worldwide SARS transmission, the probability that a positive test will be a false positive is high. In addition, sample collection technique is extremely important to maximize sensitivity and specificity. Therefore testing should be ordered only after informed consent is obtained from the patient and preferably after consultation with state public health authorities and the CDC. A reliable enzyme-linked immunoabsorbent assay has been developed to measure SARS antibody titers in patient serum. However, detectable antibody titers are generally not observed until the second week of the illness.

**TREATMENT AND OUTCOME**

No specific treatment for SARS is available. At the present time, meticulous supportive care is all that medical science has to offer. A number of specific therapies have been attempted without clear benefit. Antibiotics may prevent bacterial superinfection and should be considered later in the disease course based on Gram stain findings (see Chapters 1 and 4). Oseltamivir, intravenous ribavirin, and combined ribavirin and corticosteroids have not been shown to be of benefit. Some patients have worsened as corticosteroids have been tapered.

In the 2003 outbreak, the overall fatality rate was 11% worldwide. A poorer prognosis was associated with older age: patients above the age of 60 years had a 43% mortality. A high serum LDH or high peripheral neutrophil count is also associated with a worse outcome.

**PREVENTION**

Given the unavailability of curative therapies, infection control practices are critical for preventing the spread of this deadly infection. All suspected cases must be placed in strict respiratory isolation. Hospitalized patients should be placed in negative pressure rooms. Respirator masks (N-95) should be worn in combination with gowns, gloves, and protective eyewear. Health care workers are at particularly high risk if present during intubation of an infected patient. In the Toronto outbreak, one

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**Table 15.2. World Health Organization Case Definitions for Severe Acute Respiratory Syndrome (SARS)**

<table>
<thead>
<tr>
<th>Case type</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected</td>
<td>Fever above 38°C, PLUS cough or difficulty breathing, PLUS residence in an area with recent local transmission of SARS within 10 days of the onset of symptoms.</td>
</tr>
<tr>
<td>Probable</td>
<td>A suspected case with radiographic findings of pneumonia or with acute respiratory distress syndrome (ARDS), OR a suspected case with a positive test for SARS, OR a suspected case with an unexplained respiratory illness leading to death with autopsy demonstrating ARDS pathology without a defined cause.</td>
</tr>
</tbody>
</table>

**KEY POINTS**

About Severe Acute Respiratory Syndrome

1. Caused by a unique strain of coronavirus that is spread by aerosolized droplets and is excreted in stool. Beware of “super spreaders.”
2. Attacks mainly people over the age of 15 years. Most cases occur in people 25 to 70 years of age.
3. Incubation period is 2 to 7 days. Illness occurs in two stages:
   a) Febrile prodrome
   b) Respiratory phase with infiltrates and hypoxia
4. Diagnosis based on clinical criteria.
5. Only current treatment is meticulous supportive care.
6. Mortality is 11% overall, and 43% in people over 60 years of age.
7. Strict respiratory isolation and standard contact isolation are used to prevent transmission.
case of SARS was mistakenly diagnosed as congestive heart failure, and respiratory precautions were not instituted.

Possibly infected patients who do not require hospitalization should be instructed not leave home until they have been asymptomatic for 10 days. They should use separate utensils, towels, and sheets. Contacts may leave home as long as they are asymptomatic. Travel to areas where the WHO has determined the presence of multiple active cases of SARS should be avoided.

1. **Influenza**

   **Virology and Epidemiology**

   Influenza virus is a major cause of morbidity and mortality worldwide. Influenza A and B both cause epidemic illnesses, and influenza A can cause pandemics such as the 1918–1919 pandemic in which at least 20 million people died. (Some estimates suggest that the number may have even reached 100 million.) Influenza routinely causes epidemics every 1 to 3 years. The number of cases always increases in the winter months.

   The influenza virus, an enveloped RNA virus, has eight gene segments that encode proteins. Two of these genes, the hemagglutinin (HA) and neuraminidase (NA) genes, are important mediators of pathogenicity and immunogenicity. Virus binding and infection requires HA, and virion release requires NA. The antibody responses to HA and NA are critical for protection against infection.

   Influenza strain nomenclature consists of the type (A or B), the geographic source of the initial isolate, the isolate number, the year of isolation, and the HA and NA gene subtypes. Thus a strain of influenza A virus that was isolated in Hong Kong in 1968 is designated A/Hong Kong/03/68[H3N2].

   The influenza virus changes the structure of its HA and NA proteins by genetic mutation—a process known as antigenic drift. Antigenic drift produces variant strains against which human populations have less protective antibody. Occasionally, influenza A virus acquires a completely different set of antigens by a process known as antigenic shift. The unique strains produced by antigenic shift can infect large segments of the population, because cross-reactive or protective antibodies are lacking, thus leading to a pandemic. The virus is thought to undergo antigenic shift by reassortment (exchange of segments of genome with avian influenza species). The process of reassortment and production of virulent human influenza species may occur in pigs, which can be infected with human and avian species of influenza alike.

   Influenza attack rates are highest in the very young, but the greatest morbidity and mortality are seen among elderly patients. Influenza is also particularly dangerous to people with underlying pulmonary disease or those who are immunocompromised. In the United States, influenza annually causes about 15 million excess cases of respiratory illnesses in young people and about 4 million cases in older adults. The virus is efficiently transmitted by aerosols of respiratory secretions generated by coughing, sneezing, and talking.

   In 1997, direct transmission of avian influenza from birds to humans was documented in Hong Kong. Sporadic cases of bird-to-human transmission have been occurring since 2003, primarily in Southeast Asia. Although occasional human-to-human transmission has been reported, efficient spread of avian strains among humans has not yet occurred. Recent data derived from

<table>
<thead>
<tr>
<th><strong>KEY POINTS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>About the Virology and Epidemiology of Influenza</strong></td>
</tr>
<tr>
<td>1. Influenza is caused by an enveloped RNA virus that is classified by specific surface proteins:</td>
</tr>
<tr>
<td>a) Hemagglutinins (HA)</td>
</tr>
<tr>
<td>b) Neuraminidases (NA)</td>
</tr>
<tr>
<td>2. Influenza A and B both cause epidemics; influenza A also causes pandemics.</td>
</tr>
<tr>
<td>3. Epidemics occur every 1 to 3 years, mainly in the winter.</td>
</tr>
<tr>
<td>4. “Antigenic drift” refers to changes in hemagglutinin and neuraminidase proteins resulting from genetic mutation.</td>
</tr>
<tr>
<td>5. “Antigenic shift” refers to reassortment (exchange of genomic segments with other virus strains).</td>
</tr>
<tr>
<td>a) Occurs in influenza A.</td>
</tr>
<tr>
<td>b) Produces pandemic-causing viral strains.</td>
</tr>
<tr>
<td>c) Reassortment may occur in pigs.</td>
</tr>
<tr>
<td>6. Virus is spread by aerosolized respiratory secretions.</td>
</tr>
<tr>
<td>7. In the United States, 15 million infections occur annually in young people and 4 million in older adults.</td>
</tr>
<tr>
<td>8. Avian influenza (“bird flu”) is a concern:</td>
</tr>
<tr>
<td>a) The 1918 pandemic strain may have evolved from an avian strain.</td>
</tr>
<tr>
<td>b) The H5N1 strain has recently caused human disease in Southeast Asia (direct spread from birds; human-to-human spread is minimal).</td>
</tr>
</tbody>
</table>
sequencing of isolates obtained from formalin-fixed, paraffin-embedded lung tissue from 1918 influenza cases and a frozen sample from a victim buried in permafrost since 1918 have shed light on the nature of the 1918 pandemic strain. The sequences suggest that the 1918 strain was derived from an avian strain by adaptation to a human host rather than by reassortment. Experiments in mice also suggest that the 1918 strain possesses strong and unique virulence determinants. These findings have raised the possibility that the H5N1 avian influenza strains sporadically infecting humans today could mutate to become more infectious and transmissible among humans while retaining a high level of lethality.

**PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS**

The onset of influenza is abrupt. The patient can often say exactly when they fell ill with fever, headache, shaking chills, and myalgias. The fever may be quite high. It remains elevated for at least 3 days and usually resolves within 1 week. Fever and systemic symptoms predominate in the clinical picture, but a dry cough is invariably present and usually persists after the fever is gone. Rhinorrhea, cervical adenopathy, and non-exudative pharyngitis are common. Recovery can be prolonged, taking up to 3 weeks or even longer; during this period, the patient experiences cough and persistent fatigue.

Once influenza virus infects the respiratory epithelium, it kills the host cell as it replicates. The virus multiplies rapidly, producing large numbers of infectious viruses in the respiratory secretions and causing diffuse inflammation and damage. In severe cases, extensive necrosis occurs. Pulmonary function is abnormal even in normal hosts and may remain abnormal for a period of weeks after recovery.

Human cases of avian influenza differ from typical human influenza in several ways. Although experience with H5N1 avian influenza remains limited, the disease typically presents with fever, cough, and respiratory failure, often accompanied by diarrhea. Almost all cases report close contact with poultry, and the virus has predominantly infected children. Lymphopenia and abnormalities on chest x-ray are common. Mortality has been high among hospitalized cases, although the full clinical spectrum of infection is not well established. Unlike most previous influenza strains, H5N1 is particularly virulent in children over the age of 12 years with no underlying disease (those that would be predicted to have a strong immune system). Within 6 to 29 days of the onset of fever, many of these patients develop a respiratory distress syndrome and die of respiratory failure. Of the 23 cases reported from Southeast Asia in 2004, 18 (78%) died. The initial cases were reported in China, Thailand, and Vietnam. Subsequently, cases were reported in Azerbaijan, Djibouti, Egypt, Indonesia, Iraq, Laos, Nigeria, and Turkey. The WHO is tracking new cases, and up-to-date information can be obtained by visiting http://www.who.int/csr/disease/avian_influenza/en/.

**COMPLICATIONS**

The major complications of influenza are viral pneumonia and secondary bacterial pneumonia.

In influenza pneumonia, rapid progression to dyspnea and hypoxia occurs. The clinical and radiographic picture is that of ARDS, and antibiotics are ineffective. Mortality in this situation is very high. The lungs are hemorrhagic, and there is diffuse involvement, but little inflammation. This complication was a major cause of death among young adults during the 1918 pandemic, but is rarely seen today. However, recent experience with avian influenza virus suggests that, if the H5N1 strain adapts to humans, the incidence of this complication could greatly increase.

<table>
<thead>
<tr>
<th>KEY POINTS</th>
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</thead>
<tbody>
<tr>
<td>About the Pathogenesis and Clinical Manifestations of Influenza</td>
</tr>
<tr>
<td>1. Infects the respiratory epithelium, causing cell necrosis and acute inflammation.</td>
</tr>
<tr>
<td>2. Is characterized by abrupt onset of high fever, shaking chills, headache, myalgias, pharyngitis, and rhinorrhea.</td>
</tr>
<tr>
<td>3. Several complications are possible:</td>
</tr>
<tr>
<td>a) Viral pneumonia [can progress to fatal acute respiratory distress syndrome (ARDS) and pulmonary hemorrhage]</td>
</tr>
<tr>
<td>b) Superinfection with Staphylococcus aureus, Haemophilus influenzae, or Staphylococcus pneumoniae</td>
</tr>
<tr>
<td>c) Reye's syndrome (associated with use of aspirin)</td>
</tr>
<tr>
<td>a) Severe disease occurs in children more than 12 years of age.</td>
</tr>
<tr>
<td>b) Symptoms include diarrhea and severe cough, in addition to fever.</td>
</tr>
<tr>
<td>c) Lymphopenia occurs, with prominent infiltrates on chest x-ray.</td>
</tr>
<tr>
<td>d) Acute onset of ARDS that develops 6 to 29 days after onset of fever leads to 78% mortality.</td>
</tr>
<tr>
<td>e) Cases have been seen in Southeast Asia, the Middle East, Turkey, and Nigeria.</td>
</tr>
</tbody>
</table>
In some cases of influenza pneumonia, patients initially appear to be recovering from the virus, but then suddenly relapse with fever and typical signs of bacterial pneumonia (see Chapter 4, case 4.1). As a consequence of damage to the tracheobronchial epithelial lining, secondary bacterial pneumonia develops, with *Staphylococcus aureus*, *Haemophilus influenzae*, and *Streptococcus pneumoniae* being the most common offenders (see Chapter 4).

As noted with varicella virus, use of aspirin during influenza has been associated with the development of Reye’s syndrome. Reye’s syndrome is characterized by fatty infiltration of the liver and changes in mental status, such as lethargy or even delirium and coma. No specific treatment for Reye’s syndrome is available other than correction of metabolic abnormalities and reduction of elevated intracranial pressure.

**DIAGNOSIS**

The most useful characteristic distinguishing influenza from other respiratory illnesses is the predominance of the systemic symptoms. In addition, the epidemic nature of the disease in the community is helpful in making a diagnosis. When influenza is circulating in a community, an adult displaying the symptoms described earlier is highly likely to have influenza. Rapid antigen tests are now available, and some can detect both the A and B types of influenza in throat and nasal swabs. However, the sensitivity of these tests is somewhat variable, depending on the source and quality of the specimen and on other factors, possibly being as low as 60%.

**TREATMENT**

Amantadine and rimantadine inhibit influenza A virus infection by binding to a virus membrane protein. These drugs were long used for prevention and treatment of influenza A. However, influenza A is now widely resistant to both amantadine and rimantadine, and the U.S. Advisory Committee on Immunization Practices therefore recommends that amantadine and rimantadine not be used for the treatment or chemoprophylaxis of influenza A in the United States.

Two NA inhibitors, zanamivir and oseltamivir are highly effective in inhibiting type A and B influenza alike. Zanamivir has to be administered by inhalation; oseltamivir is given orally. Both agents can be used for prophylaxis and treatment, and they are most effective when administered soon after the onset of infection. Recently, rare but serious psychiatric and neurologic side effects have been associated with oseltamivir, particularly in pediatric patients. These side effects include panic attacks, delusions, delirium, convulsions, depression, loss of consciousness, and suicide.

Both oseltamivir and zanamivir are active against H5N1 avian influenza in animal and in vitro models. Resistance to oseltamivir has already been documented. Whether widespread resistance to oseltamivir will present a significant obstacle in the management of an avian influenza outbreak is unknown.

**PREVENTION**

Influenza vaccine is a trivalent inactivated vaccine directed against types A and B influenza. The strains selected for each year’s vaccine are based on the strain that was circulating worldwide the previous year. The effectiveness of the vaccine depends to some degree on the success of the match between the vaccine and the circulating strains. Vaccination decreases both disease severity and the infection rate. The groups that should be targeted for influenza vaccination include:

A. Groups at increased risk for influenza complications;

1. People 65 years of age or older
2. Residents of nursing homes or other chronic care facilities
3. All people with chronic pulmonary or cardiovascular disease (including asthma)
4. All children under 18 years of age on chronic aspirin therapy
5. Women who will be in the second or third trimester of pregnancy during the influenza season
B. Those at increased risk of transmitting influenza to high-risk individuals:

1. Health care personnel
2. Employees of nursing homes or other chronic care facilities who have patient contact
3. Home care providers and household contacts of people at high risk

A live attenuated influenza vaccine (LAIV) that is administered as a nasal spray is also available. This vaccine is approved for use in patients 5 to 49 years of age. The LAIV is considered as equally efficacious as inactivated vaccine. Side effects are generally minor and consist mainly of cough and rhinorrhea, which may be more common in adults than children. An increased risk of respiratory side effects has been noted in younger children. Because of the potential risks of a live vaccine, LAIV should not be administered to immunocompromised patients. Because of the potential risk of shedding and transmission of LAIV, health care workers should avoid contact with severely immunocompromised patients for 7 days after vaccination. The "Populations That Should Not Be Vaccinated with Live Attenuated Influenza Vaccine" below shows a complete list of patients in whom LAIV is contraindicated.

The U.S. Advisory Committee on Immunization Practices has recommended a broader policy for the administration of the vaccine (see the box Populations That Should Be Vaccinated).

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**HERPES SIMPLEX VIRUS**

**EPIDEMIOLOGY**

Herpes simplex virus (HSV) is a ubiquitous human pathogen with two distinct types, HSV-1 and HSV-2. The HSV-1 type causes primarily orolabial lesions; HSV-2 causes genital lesions. More than 90% of adults worldwide exhibit serologic evidence of infection with HSV-1. The prevalence of HSV-2 infection is considerably lower, but ranges from at least 10% to as high as 80% depending on the population studied. As sexual activity (number of sexual partners and other STDs) increases the likelihood of HSV-2 infection also increases. Transmission of HSV usually occurs person-to-person, by direct contact with infected secretions or mucosal surfaces.

**PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS**

Once HSV enters a mucosal or skin surface, it replicates in the epithelium and infects a nerve ending. It is then transported to the nerve ganglion where it establishes a latent infection that persists for the lifetime of the host. The trigeminal and sacral ganglia are the most common sites of HSV-1 and HSV-2 latency. Viral replication occurs in the ganglion during the initial infection.

Initial infection with HSV-1 is often subclinical and many people never experience clinical reactivation, although they are clearly seropositive. Others experience gingivostomatitis (especially small children). The lesions are usually ulcerative and exudative, and may involve extensive areas of the lips, oral cavity, pharynx, and perioral skin. Healing occurs over a period of several days to 2 weeks, usually without scarring. Secondary
episodes result in fever blisters—the typical vesicular and ulcerative lesions. These occur most commonly at the vermilion border of the lips, but may also occur at other sites on the face or in the mouth. Many environmental factors may trigger a recurrence, such as sunlight exposure, stress, and viral infections. Secondary episodes are usually much less severe.

In both women and men, HSV-2 causes genital herpes. Lesions may be vesicular, pustular, or ulcerative, involving the penis in men and vagina and cervix in women. Typical symptoms are pain, itching, dysuria, and vaginal or urethral discharge. Upon primary infection, symptoms tend to be more severe in women. Primary infection can be associated with an aseptic meningitis and mild systemic symptoms such as fever. Occasionally, inflammation is severe enough to lead to temporary bladder or bowel dysfunction.

Both HSV-1 and HSV-2 can also affect many other sites in the body where they have been inoculated. “Whitlow” is an HSV infection of the fingers, resulting from the inoculation of virus into abraded skin. This condition may be seen in health care workers and others who have been exposed to the virus either from autoinoculation or person-to-person transmission. The lesions are vesicular and pustular, with local erythema, pain, and drainage. They are often mistaken for bacterial infections, resulting in unnecessary drainage and antibiotics. “Herpes gladiatorum” is the name given to HSV infection acquired by wrestlers, in whom the virus is inoculated into breaks in the skin during wrestling competition.

**COMPLICATIONS**

A potentially dangerous consequence of HSV infection of the cornea is HSV keratitis. This infection may be caused by either HSV-1 or HSV-2, but more commonly by HSV-1. Once HSV keratitis has occurred, the patient remains at risk for recurrences. This infection is one of the most common causes of blindness in the United States. Symptoms consist of tearing, pain, erythema, and conjunctival swelling. Dendritic corneal lesions are easily visualized by fluorescein staining (See Chapter 5, Figure 5-2). Involvement of deeper structures or corneal scarring can lead to blindness.

Annually, HSV encephalitis occurs in approximately 1 of 250,000 to 500,000 population. A preponderance of these cases are attributable to HSV-1; concurrent skin lesions are usually not present. Although HSV encephalitis may be the result of primary infection, most patients can be shown to have been previously infected. The disease is characterized by fever, altered mentation, and focal neurologic signs. Personality changes and bizarre behavior are common, and many patients experience seizures. The disease process typically affects the temporal lobe and is usually unilateral. It may progress in a fulminant manner with frank hemorrhagic necrosis of the affected areas of the brain. With antiviral treatment, mortality has been reduced, but remains above 15%, and most survivors exhibit long-term cognitive impairment.

Widespread cutaneous dissemination (eczema herpeticum) can be seen in people with eczema. Visceral dissemination of HSV is rare in the normal host, but herpetic tracheobronchitis is often seen in debilitated, intubated hospitalized patients, in whom it may occasionally progress to pneumonitis.

**DIAGNOSIS**

The clinical diagnosis of labial or genital herpes is usually not difficult; however, the typical vesicle on an erythematous base, the “dewdrop on a rose petal,” is not always present. Culture of vesicle fluid is highly...
**KEY POINTS**

**About the Diagnosis and Treatment of Herpes Simplex Virus**

1. The diagnosis is made clinically, or with immunofluorescence and viral culture. For encephalitis, a polymerase chain reaction test of the cerebrospinal fluid is useful.
2. Primary skin infections can be treated with acyclovir, famciclovir, or valacyclovir.
3. Treatment of recurrent episodes is more controversial. Treat during the prodrome; suppressive therapy can be used for recurrent genital herpes.
4. Use high-dose, intravenous acyclovir for encephalitis or disseminated disease.

**CYTOMEGALOVIRUS**

**Epidemiology**

Human cytomegalovirus (CMV) is a common infection worldwide. Prevalence of the infection varies greatly based on socioeconomic factors, but no clear link to hygienic practices exists. In the United States, from 40% to 80% of children are infected by puberty. Young children may be a major source of infection for adults; caretakers of young children may have a risk of infection that is 20 times normal. Person-to-person spread can occur by contact with almost any human body fluid or substance: blood, urine, saliva, cervical secretions, feces, breast milk, and semen. The virus is therefore also spread by sexual contact and by blood transfusion and organ donation.

**Pathophysiology and Clinical Manifestations**

Most human CMV infections are thought to be subclinical, but primary infection in the normal host occasionally results in a mononucleosis syndrome. Approximately 10% of mononucleosis cases are thought to be caused by CMV, which is the major cause of heterophil (monospot)–negative mononucleosis. Mononucleosis caused by CMV is more common in slightly older adults, but it can be difficult to distinguish clinically from EBV-associated mononucleosis. Pharyngitis and cervical adenopathy have been suggested to be less common with CMV, but both may be observed with CMV mononucleosis. Fever in CMV mononucleosis lasts on average for more than 3 weeks. Rash is present in about 30% of patients, and ampicillin provocation of rash has been noted. Other complications of CMV infection in the normal host include hepatitis, pneumonitis, and Guillain–Barré syndrome. Many of the laboratory findings of EBV mononucleosis are also seen in CMV infection.

In the immunocompromised host, infection with CMV produces most of the morbidity and mortality associated with the virus. Infection produces severe disease in multiple organs, causing retinitis, hepatitis, pneumonitis, gastrointestinal disease (gastric and esophageal ulcers and colitis), and polyradiculopathy. Further details of preventive strategies in these patients are discussed in Chapter 16.

**Diagnosis**

Viral culture is not useful for diagnosing CMV infection in the normal host. Virus may be shed for long periods in the urine and intermittently by persons infected in the past. The most reliable test is a rise in CMV IgG titer to about four times baseline value.

sensitive and specific. Direct staining for HSV antigens can also be used to diagnose infection. Staining of lesion scrapings and examination for giant cells (the Tzanck test) is quick, but nonspecific and insensitive. The diagnosis of HSV encephalitis can be difficult, especially early in the course of the illness. A mild lymphocytic CSF pleocytosis is common, as are red blood cells and an elevated protein level. However, none of these findings are diagnostic. A PCR test of the CSF for HSV is highly sensitive and specific—the optimal laboratory test to confirm the diagnosis. Magnetic resonance imaging of the brain and electroencephalography often show abnormalities localizing to the temporal areas even early in the disease.

**Treatment**

First episodes of all types of HSV infection benefit from treatment. For both orolabial and genital herpes, oral acyclovir, famciclovir, and valacyclovir are all effective. Treatment of recurrent episodes of HSV-1 or HSV-2 is somewhat unsatisfactory. Although treatment may somewhat reduce duration of symptoms, especially in HSV-2, the results are not dramatic. Some patients find that early institution of therapy (as soon as prodromal symptoms such as tingling or itching appear) can be helpful. For patients with frequent and severe recurrent genital herpes, suppressive therapy can be helpful. Any of the three antivirals mentioned earlier can be used. For HSV encephalitis, treat every 8 hours with intravenous acyclovir 10 mg/kg, for a minimum of 14 days. Disseminated HSV infection, particularly in the immunosuppressed host, a usually requires high-dose intravenous acyclovir therapy.
Detection of IgM is also strong evidence for acute infection, although IgM can occasionally be seen in normal hosts during virus reactivation. Quantitative PCR of viral DNA is also widely available. Diagnosis of the various manifestations of CMV disease in the immunocompromised host is discussed in Chapter 16.

**TREATMENT**

Antiviral treatment of CMV infection is almost never required in the normal host. Spontaneous resolution, even after a lengthy illness, is almost invariant. However, corticosteroids may be used for the same autoimmune or hemato logic complications as are seen in EBV infection. Treatment with ganciclovir or foscarnet may be considered in those rare cases in which CMV appears to be causing specific organ-system disease (such as esophagitis) in the normal host. These agents should be used in the immunocompromised patient (See Chapter 16).

**FURTHER READING**

**Varicella Virus**


**Epstein–Barr Virus**


**Hanta Virus**


**Severe Acute Respiratory Syndrome**


Huang J, Ma R, Wu CY. Immunization with SARS-CoV S DNA vaccine generates memory CD4+ and CD8+ T cell immune responses. *Vaccine.* 2006;24:49054913.


**Influenza**


**Cytomegalovirus**


Pertussis is an acute respiratory tract infection that was well described initially in the 1500s. Sydenham first used the term pertussis, meaning intense cough, in 1670; it is preferable to whooping cough because most infected individuals do not “whoop.”

**ETIOLOGY**

*Bordetella pertussis* is the sole cause of epidemic pertussis and the usual cause of sporadic pertussis. *Bordetella parapertussis* is an occasional cause of sporadic pertussis that contributes significantly to total cases of pertussis in Eastern and Western Europe but accounts for <5% of *Bordetella* isolates in the USA. *B. pertussis* and *B. parapertussis* are exclusive pathogens of humans and some primates.

*B. bronchiseptica* is a common animal pathogen. Occasional case reports in humans may involve any body site and typically occur in immunocompromised persons or young children with intense exposure to animals. Protracted coughing (which in some cases is paroxysmal) can be caused by *Mycoplasma*, parainfluenza viruses, influenza viruses, enteroviruses, respiratory syncytial viruses, or adenoviruses.

**EPIDEMIOLOGY**

There are 60 million cases of pertussis each year worldwide, resulting in >500,000 deaths. Before vaccination was available, pertussis was the leading cause of death due to communicable disease among children <14 yr of age in the USA, with 10,000 deaths annually. Widespread use of pertussis vaccine led to a >99% decline in cases. The pivotal role of vaccination in disease control is reflected in the continued high incidence of pertussis in developing countries and the resurgence in other countries where vaccine coverage is low or where less potent vaccine may have been used.

After the low number of 1,010 cases in the USA reported in 1976, there was an increase in annual pertussis incidence to 1.2 cases/100,000 population from 1980 through 1989, with epidemic pertussis in many states in 1989-1990, 1993, and 1996. Since then pertussis has become increasingly endemic, with less cycling or seasonality and with
shifting burden of disease to young infants, adolescents, and adults. By 2004, the incidence of reported pertussis in the USA was 8.9 cases/100,000 populations, and the number of cases (25,827) was the highest reported since 1959. Of these cases, 10% occurred among infants <6 mo of age (incidence of 136.5/100,000 population). A total of 40 pertussis-related deaths were reported in 2005, and 16 in 2006; >90% occurred among young infants. Approximately 60% of cases currently are in adolescents and adults. Pertussis is the only vaccine-preventable disease for which universal immunization in the USA is recommended that continues to be endemic. Prospective and serologic studies suggest that pertussis is underrecognized, especially among adolescents and adults, in whom the actual number of cases is estimated to be 600,000 annually. A number of studies have documented pertussis in 13-32% of adolescents and adults with cough illness for >7 days.

Pertussis is extremely contagious, with attack rates as high as 100% in susceptible individuals exposed to aerosol droplets at close range. B. pertussis does not survive for prolonged periods in the environment. Chronic carriage by humans is not documented. After intense exposure as in households, the rate of subclinical infection is as high as 80% in fully immunized or previously infected individuals. When carefully sought, a symptomatic source case can be found for most patients.

Neither natural disease nor vaccination provides complete or lifelong immunity against pertussis re-infection or disease. Protection against typical disease begins to wane 3-5 yr after vaccination and is unmeasurable after 12 yr. Subclinical re-infection undoubtedly has contributed significantly to immunity against disease ascribed previously to both vaccine and prior infection. Despite history of disease or complete immunization, outbreaks of pertussis have occurred in the elderly, in nursing homes, in residential facilities with limited exposures, in highly immunized suburbia, and in preadolescents, adolescents, and adults with significant time since immunization. Possible explanations for change in epidemiology include waning immunity post immunization, an aging cohort who received less effective vaccine, and increased awareness and diagnosis. Without natural re-infection with B. pertussis or repeated booster vaccinations, adolescents and adults are susceptible to clinical disease if exposed, and mothers provide little if any passive protection to young infants. Coughing adolescents and adults (usually not recognized as having pertussis) are the major reservoir for B. pertussis and are the usual sources of infection for infants and children.

PATHOGENESIS

Bordetella organisms are tiny, fastidious, gram-negative coccobacilli that colonize only ciliated epithelium. The exact mechanism of disease symptomatology remains unknown. Bordetella species share a high degree of DNA homology among virulence genes. Only B. pertussis expresses pertussis toxin (PT), the major virulence protein. PT has numerous proven biologic activities (e.g., histamine sensitivity, insulin secretion, leukocyte dysfunction), some of which may account for systemic manifestations of disease. PT causes lymphocytosis immediately in experimental animals by rerouting lymphocytes to remain in the circulating blood pool. PT appears to have a central but not a singular role in pathogenesis. B. pertussis produces an array of other biologically active substances, many
of which are postulated to have a role in disease and immunity. After aerosol acquisition, filamentous hemagglutinin (FHA), some agglutinogens (especially fimbriae [Fim] types 2 and 3), and a 69-kd nonfimbrial surface protein called pertactin (Pn) are important for attachment to ciliated respiratory epithelial cells. Tracheal cytoxin, adenylate cyclase, and PT appear to inhibit clearance of organisms. Tracheal cytoxin, dermonecrotic factor, and adenylate cyclase are postulated to be predominantly responsible for the local epithelial damage that produces respiratory symptoms and facilitates absorption of PT.

**CLINICAL MANIFESTATIONS**

Classically, pertussis is a prolonged disease, divided into catarrhal, paroxysmal, and convalescent stages. The catarrhal stage (1-2 wk) begins insidiously after an incubation period ranging from 3-12 days with nondistinctive symptoms of congestion and rhinorrhea variably accompanied by low-grade fever, sneezing, lacrimation, and conjunctival suffusion. As initial symptoms wane, coughing marks the onset of the paroxysmal stage (2-6 wk). The cough begins as a dry, intermittent, irritative hack and evolves into the inexorable paroxysms that are the hallmark of pertussis. A well-appearing, playful toddler with insignificant provocation suddenly expresses an anxious aura and may clutch a parent or comforting adult before beginning a machine-gun burst of uninterrupted cough on a single exhalation, chin and chest held forward, tongue protruding maximally, eyes bulging and watering, face purple, until coughing ceases and a loud whoop follows as inspired air traverses the still partially closed airway. Post-tussive emesis is common, and exhaustion is universal. The number and severity of paroxysms escalate over days to a week and remain at that plateau for days to weeks. At the peak of the paroxysmal stage, patients may have more than 1 episode hourly. As the paroxysmal stage fades into the convalescent stage (≥2 wk), the number, severity, and duration of episodes diminish.

Infants <3 mo of age do not display the classic stages. The catarrhal phase lasts only a few days or is unnoticed, and then, after the most insignificant startle from a draft, light, sound, sucking, or stretching, a well-appearing young infant begins to choke, gasp, gag, and flail the extremities, with face reddened. Cough may not be prominent, especially in the early phase. Whoop infrequently occurs in infants <3 mo of age who at the end of a paroxysm lack stature or muscular strength to create sudden negative intrathoracic pressure. Apnea and cyanosis can follow a coughing paroxysm, or apnea can occur without a cough. Apnea may be the only symptom. Apnea and cyanosis both are more common with pertussis than with neonatal viral infections, including respiratory syncytial virus (RSV). The paroxysmal and convalescent stages in young infants are lengthy. Paradoxically, in infants, cough and whooping may become louder and more classic in convalescence. Convalescence includes intermittent paroxysmal coughing throughout the 1st yr of life, including “exacerbations” with subsequent respiratory illnesses; these are not due to recurrent infection or reactivation of *B. pertussis*.

Adolescents and previously immunized children have foreshortening of all stages of pertussis. Adults have no distinct stages. Classically, adolescents and adults describe a sudden feeling of strangulation followed by uninterrupted coughs, feeling of suffocation, bursting headache, diminished awareness, and then a gasping breath, usually without a whoop. Post-tussive emesis and intermittency of paroxysms separated by hours of
well-being are specific clues to the diagnosis in adolescents and adults. At least 30% of older individuals with pertussis have nonspecific cough illness, distinguished only by duration, which is usually >21 days.

Findings on physical examination generally are uninformative. Signs of lower respiratory tract disease are not expected unless complicating secondary bacterial pneumonia is present. Conjunctival hemorrhages and petechiae on the upper body are common.

**COMPLICATIONS**

Infants <6 mo of age have excessive mortality and morbidity; infants <2 mo of age have the highest reported rates of pertussis-associated hospitalization (82%), pneumonia (25%), seizures (4%), encephalopathy (1%), and death (1%). Infants <4 mo of age account for 90% of cases of fatal pertussis. Preterm birth and young maternal age are significantly associated with fatal pertussis. Neonates with pertussis have substantially longer hospitalizations, greater need for oxygen, and greater need for mechanical ventilation than neonates with viral respiratory infection.

The principal complications of pertussis are apnea, secondary infections (such as otitis media and pneumonia), and physical sequelae of forceful coughing. Fever, tachypnea or respiratory distress between paroxysms, and absolute neutrophilia are clues to pneumonia. Expected pathogens include Staphylococcus aureus, Streptococcus pneumoniae, and bacteria of oropharyngeal flora. Increased intrathoracic and intra-abdominal pressure during coughing can result in conjunctival and scleral hemorrhages, petechiae on the upper body, epistaxis, hemorrhage in the central nervous system (CNS) and retina, pneumothorax and subcutaneous emphysema, and umbilical and inguinal hernias. Laceration of the lingual frenulum occurs occasionally.

The need for intensive care and mechanical ventilation is usually limited to infants <3 mo of age and infants with underlying conditions. Respiratory failure due to apnea may precipitate need for intubation and ventilation through the days when disease peaks; prognosis is good. Progressive pulmonary hypertension in very young infants and secondary bacterial pneumonia are severe complications of pertussis and are the usual causes of death. Pulmonary hypertension and cardiogenic shock with fatal outcome are associated with extreme elevations of lymphocyte and platelet counts. Autopsies in fatal cases show luminal aggregates of leukocytes in the pulmonary vasculature. Extracorporeal membrane oxygenation of infants with pertussis in whom mechanical ventilation failed has been associated with >80% fatality (questioning the advisability of this procedure). Exchange transfusion or leukopheresis, however, has been associated with drop in lymphocyte and platelet counts, with recovery in several reported cases.

CNS abnormalities occur at a relatively high frequency in pertussis and are almost always a result of hypoxemia or hemorrhage associated with coughing or apnea in young infants. Apnea or bradycardia or both may result from apparent laryngospasm or vagal stimulation just before a coughing episode, from obstruction during an episode, or from hypoxemia following an episode. Lack of associated respiratory signs in some young infants with apnea raises the possibility of a primary effect of PT on the CNS. Seizures are usually a result of hypoxemia, but hyponatremia from excessive secretion of antidiuretic hormone during pneumonia can occur. The only neuropathology documented in humans is parenchymal hemorrhage and ischemic
necrosis.

Bronchiectasis has been reported rarely after pertussis. Children who have pertussis before the age of 2 yr may have abnormal pulmonary function into adulthood.

**LABORATORY TESTS**

Leukocytosis (15,000-100,000 cells/mm$^3$) due to absolute lymphocytosis is characteristic in the catarrhal stage. Lymphocytes are of T- and B-cell origin and are normal small cells, rather than the large atypical lymphocytes seen with viral infections. Adults, partially immune children, and, occasionally, young infants have less impressive lymphocytosis. Absolute increase in neutrophils suggests a different diagnosis or secondary bacterial infection. Eosinophilia is not a manifestation of pertussis. A severe course and death are correlated with extreme leukocytosis (median peak white blood cell count in fatal vs nonfatal cases, $94 \text{ vs } 18 \times 10^9$ cells/L, respectively) and thrombocytosis (median peak platelet count in fatal vs nonfatal cases, $782 \text{ vs } 556 \times 10^9$/L, respectively). Mild hyperinsulinemia and reduced glycemic response to epinephrine have been demonstrated, although hypoglycemia is reported only occasionally. Chest radiographic findings are only mildly abnormal in the majority of hospitalized infants, showing perihilar infiltrate or edema (sometimes with a butterfly appearance) and variable atelectasis. Parenchymal consolidation suggests secondary bacterial infection. Pneumothorax, pneumomediastinum, and subcutaneous emphysema can be seen occasionally.

All current methods for confirmation of infection due to *B. pertussis* have limitations in sensitivity, specificity, or practicality. Isolation of *B. pertussis* in culture remains the gold standard for diagnosis. Careful attention must be directed to specimen collection, transport, and isolation technique. The specimen is obtained with deep nasopharyngeal aspiration or with the use of a flexible swab, preferably a Dacron or calcium alginate–tipped swab, held in the posterior nasopharynx for 15-30 sec (or until cough occurs). A 1.0% casamino acid liquid is acceptable for holding a specimen up to 2 hr; Stainer-Scholte broth or Regan-Lowe semisolid transport medium is used for longer transport periods, up to 4 days. The preferred isolation media are Regan-Lowe charcoal agar with 10% horse blood and 5-40 μg/mL cephalaxin and Stainer-Scholte media with cyclodextrin resins. Cultures are incubated at 35-37°F in a humid environment and examined daily for 7 days for slow-growing, tiny, glistening colonies. Direct fluorescent antibody (DFA) testing of potential isolates using specific antibody for *B. pertussis* and *B. parapertussis* maximizes recovery rates. Direct testing of nasopharyngeal secretions by DFA is a rapid test but is reliable only in laboratories with continuous experience. Polymerase chain reaction (PCR) analysis to test nasopharyngeal wash specimens has a sensitivity similar to that of culture and averts difficulties of isolation, but a standardized validated test is not yet available universally. Results of DFA, culture, and PCR are all expected to be positive in unimmunized, untreated children during the catarrhal and early paroxysmal stages of disease. Less than 10% of any of these test results are positive in partially or remotely immunized individuals tested in the paroxysmal stage. Serologic tests for detection of antibodies to *B. pertussis* antigens in acute and convalescent samples are the most sensitive tests in immunized individuals and are useful epidemiologically. A single serum sample showing
immunoglobulin G (IgG) antibody to pertussis toxin elevated >2 standard deviations above the mean of the immunized population (≈100 EU/mL) indicates recent infection. Standardization of tests and cut point for a positive result are currently being investigated. Tests for IgA and IgM pertussis antibody, or antibody to antigens other than PT, are not reliable methods for diagnosis of pertussis.

**DIAGNOSIS**

Pertussis should be suspected in any individual who has pure or predominant complaint of cough, especially if the following features are absent: fever, malaise or myalgia, exanthem or enanthem, sore throat, hoarseness, tachypnea, wheezes, and rales. For sporadic cases, a clinical case definition of cough of ≥14 days’ duration with at least 1 associated symptom of paroxysms, whoop, or post-tussive vomiting has a sensitivity of 81% and a specificity of 58% for culture confirmation. Pertussis should be suspected in older children whose cough illness is escalating at 7-10 days and whose coughing episodes are not continuous. Pertussis should be suspected in infants <3 mo of age with gagging, gasping, apnea, cyanosis, or an apparent life-threatening event (ALTE). Sudden infant death is occasionally caused by *B. pertussis*.

Adenoviral infections are usually distinguishable by associated features, such as fever, sore throat, and conjunctivitis. *Mycoplasma* causes protracted episodic coughing, but patients usually have a history of fever, headache, and systemic symptoms at the onset of disease as well as more continuous cough and frequent finding of rales on auscultation of the chest. Epidemics of *Mycoplasma* and *B. pertussis* in young adults can be difficult to distinguish on clinical grounds. Although pertussis is often included in the laboratory evaluation of young infants with afebrile pneumonia, *B. pertussis* is not associated with staccato cough (breath with every cough), purulent conjunctivitis, tachypnea, rales or wheezes that typify infection due to *Chlamydia trachomatis*, or predominant lower respiratory tract signs that typify infection due to RSV. Unless an infant with pertussis has secondary pneumonia (and then appears ill), the findings on examination between paroxysms are entirely normal, including respiratory rate.

**TREATMENT**

Goals of therapy are to limit the number of paroxysms, to observe the severity of the cough, to provide assistance when necessary, and to maximize nutrition, rest, and recovery without sequelae. Infants <3 mo of age with suspected pertussis are always admitted to hospital, as are those between 3 and 6 mo of age unless witnessed paroxysms are not severe, and patients of any age if significant complications occur. Prematurely born young infants and children with underlying cardiac, pulmonary, muscular, or neurologic disorders have a high risk for severe, potentially fatal disease.

The specific, limited goals of hospitalization are to: (1) assess progression of disease and likelihood of life-threatening events at peak of disease; (2) prevent or treat complications; and (3) educate parents in the natural history of the disease and in care that will be given at home. Heart rate, respiratory rate, and pulse oximetry are monitored continuously with alarm settings so that paroxysms can be witnessed and recorded by health care personnel. Detailed cough records and documentation of feeding, vomiting, and weight change provide data to assess severity. Typical paroxysms that are not life threatening have the following features: duration <45 sec;
red but not blue color change; tachycardia, bradycardia (not <60 beats/min in infants), or oxygen desaturation that spontaneously resolves at the end of the paroxysm; whooping or strength for self-rescue at the end of the paroxysm; self-expectorated mucus plug; and post-tussive exhaustion but not unresponsiveness. Assessing the need to provide oxygen, stimulation, or suctioning requires skilled personnel who can document an infant’s ability for self-rescue but who will intervene rapidly and expertly when necessary. The benefit of a quiet, dimly lighted, undisturbed, comforting environment cannot be overestimated or forfeited in a desire to monitor and intervene. Feeding children with pertussis is challenging. The risk of precipitating cough by nipple feeding does not warrant nasogastric, nasojejunal, or parenteral alimentation in most infants. The composition or thickness of formula does not affect the quality of secretions, cough, or retention. Large-volume feedings are avoided.

Within 48-72 hr, the direction and severity of disease are obvious, usually from analysis of recorded information. Many infants have marked improvement upon hospitalization and antibiotic therapy, especially if they are hospitalized early in the course of disease or have been removed from aggravating environmental smoke, excessive stimulation, or a dry or polluting heat source. Hospital discharge is appropriate if over a 48-hr period disease severity is unchanged or diminished, no intervention is required during paroxysms, nutrition is adequate, no complication has occurred, and parents are adequately prepared for care at home. Apnea and seizures occur in the incremental phase of illness and in patients with complicated disease. Portable oxygen, monitoring, or suction apparatus should not be needed at home.

Infants who have apnea, paroxysms that repeatedly lead to life-threatening events despite passive delivery of oxygen, or respiratory failure require intubation, pharmaceutically induced paralysis, and ventilation.

**Antibiotics**

An antimicrobial agent is always given when pertussis is suspected or confirmed, primarily to limit the spread of infection and secondarily for possible clinical benefit. Macrolides are preferred agents and are similar to one another in terms of in vitro activity (Table 1). Resistance has been reported rarely. A 7- to 10-fold relative risk for infantile hypertrophic pyloric stenosis (IHPS) has been reported in neonates treated with orally administered erythromycin. Azithromycin is the preferred agent for most patients and particularly in neonates, although cases of IHPS have followed its use. All infants <1 mo of age treated with any macrolide should be monitored for symptoms of pyloric stenosis. Benefits of post-exposure prophylaxis for infants far outweigh risk of IHPS.

**Adjunct Therapies**

No rigorous clinical trial has demonstrated a beneficial effect of $\beta_2$-adrenergic stimulants such as salbutamol and albuterol. Fussing associated with aerosol treatment triggers paroxysms. No randomized, blinded clinical trial of sufficient size has been performed to evaluate the usefulness of corticosteroids in the management of pertussis; their clinical use is not warranted.

**Isolation**

Patients with suspected pertussis are placed in respiratory isolation with use of masks by all health care personnel entering the room. Screening for cough should be performed upon entrance of patients to emergency
departments, offices, and clinics to begin isolation immediately and until 5 days after initiation of macrolide therapy. Children and staff with pertussis in child-care facilities or schools should be excluded until macrolide prophylaxis has been taken for 5 days.

**Care of Household and Other Close Contacts**

A macrolide agent should be given promptly to all household contacts and other close contacts, such as those in daycare, regardless of age, history of immunization, and symptoms. The same age-related drugs and doses used for prophylaxis are used for treatment. Visitation and movement of coughing family members in the hospital must be assiduously controlled until erythromycin has been taken for 5 days. In close contacts <7 yr of age who have received fewer than 4 doses of pertussis-containing vaccines, vaccination should be initiated or continued to complete the recommended series. Children <7 yr of age who received a 3rd dose >6 mo before exposure or a 4th dose ≥3 yr before exposure should receive a booster dose. Individuals ≥9 yr of age should be given a Tdap (adolescent/adult formulation of tetanus and diphtheria toxoids and acellular pertussis) booster if they have not previously received Tdap. Unmasked health care personnel (HCP) exposed to untreated cases should be evaluated for post-exposure prophylaxis and follow-up. Coughing HCP with or without known exposure to pertussis should be promptly evaluated for pertussis.

**PREVENTION**

Universal immunization of children with pertussis vaccine, beginning in infancy with periodic reinforcing doses through adolescence and adulthood, is central to the control of pertussis. There is no serologic correlate of protection from *B. pertussis*.

**DTaP Vaccines**

Several diphtheria and tetanus toxoids combined with acellular pertussis (DTaP) vaccines or combination products currently are licensed in the USA for children <7 yr of age. DTaP vaccines have fewer adverse effects than the vaccines containing whole-cell pertussis (DTP), which continue to be given to infants and children in many other countries. Acellular pertussis vaccines all contain inactivated PT and 2 or more other bacterial components (FHA, Pn, and Fim 2 and 3). Clinical efficacy against severe pertussis, defined as paroxysmal cough ≥21 days, is 80-85%. Mild local and systemic adverse events as well as more serious events (including high fever, persistent crying of ≥3 hr in duration, hypotonic hyporesponsive episodes, and seizures) occur significantly less frequently among infants who receive DTaP than in those who receive DTP vaccine. DTaP-containing vaccines can be administered simultaneously with any other vaccines used in standard schedules for children.

Four doses of DTaP should be administered during the 1st 2 years of life, generally at ages 2, 4, 6, and 15-18 mo of age. The 4th dose may be administered as early as 12 mo of age, provided that 6 mo have elapsed since the 3rd dose. The 5th dose of DTaP is recommended for children at 4-6 yr of age; a 5th dose is not necessary if the 4th dose in the series is administered on or after the 4th birthday. A birth dose of DTaP is not effective, but commencement of vaccination at 6 wk of age, with monthly doses through the 3rd dose, can be considered in high-risk settings.

Exempting children from pertussis immunization should be considered only in the narrow limits as recommended. Exemptors have been shown to have significantly increased risk for pertussis and to play a role
in outbreaks of pertussis among immunized populations. Although well-documented pertussis confers short-term protection, the duration of protection is unknown; immunization should be completed on schedule in children diagnosed with pertussis. Improper vaccine storage reduces immunity.

**Tdap Vaccines**

Two tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine, adsorbed (Tdap) products were licensed in 2005 and were recommended universally in 2006 for use in individuals 11-18 years of age and in older individuals as a single-dose booster vaccine to provide protection against tetanus, diphtheria, and pertussis. Because of heightened risk in adolescents for pertussis and the evidence of association of pertussis with young infants of adolescent mothers, the American Academy of Pediatrics (AAP) includes pregnant adolescents who are in their second or third trimester in Tdap recommendations. The preferred age for Tdap vaccination is 11-12 yr. All adolescents 11-18 yr of age who received Td, but not Tdap, should receive a single dose of Tdap to provide protection against pertussis. There is no minimum interval required between vaccines containing tetanus or diphtheria toxoid and Tdap. There is no contraindication to concurrent administration of any other indicated vaccine. In 2010, Tdap was recommended for children 7-10 yr old with incomplete pertussis vaccination prior to age 7 yr as well as for those ≥65 yr who have contact with infants. An important objective of administering Tdap is to protect adolescents and adults against pertussis in order to control endemic and epidemic spread to young infants who have not completed primary immunization and are at high risk for pertussis and its complications. In provinces and territories in Canada where Tdap was administered to 14 to 16 yr old adolescents, marked reduction in pertussis has been documented in adolescents and younger age groups, possibly as a result of herd protection. In 2008 and pending further data, the CDC recommendations for pregnant adult women showed preference for the cocoon strategy (immediate postpartum Tdap immunization of mother and all household and other contacts of the infant) over maternal immunization during pregnancy.

### Table 1 RECOMMENDED TREATMENT AND POSTEXPOSURE PROPHYLAXIS FOR PERTUSSIS, BY AGE GROUP

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>PRIMARY AGENTS</th>
<th>ALTERNATE AGENT *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Azithromycin</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>&lt; 1mo</td>
<td>Recommended</td>
<td>Not preferred.</td>
</tr>
<tr>
<td></td>
<td>10mg/kg/day in a single dose for 5 days (only limited safety data available)</td>
<td>Erythromycin is substantially associated with infantile icterus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypertrophic pyloric stenosis. Use if azithromycin is unavailable; 40-50 mg/kg/day in 4 divided</td>
</tr>
<tr>
<td>Age Group</td>
<td>Dosing Details</td>
<td>Contraindications</td>
</tr>
<tr>
<td>-----------</td>
<td>----------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>1-5 mo</td>
<td>10mg/kg/day in a single dose for 5 days</td>
<td>Contraindicated at age &lt; 2 mo. For</td>
</tr>
<tr>
<td></td>
<td>40-50mg/kg/day in 4 divided doses for 14 days</td>
<td>infants aged ≥2 mo. For</td>
</tr>
<tr>
<td></td>
<td>15mg/kg/day in 2 divided doses for 7 days</td>
<td>TMP 8mg/kg/day plus SMZ</td>
</tr>
<tr>
<td></td>
<td>40mg/kg/day in 2 divided doses for 14 days</td>
<td>Infants aged ≥6 mo and children</td>
</tr>
<tr>
<td>Infants aged ≥6 mo and children</td>
<td>10mg/kg in a single dose on day 1 (maximum 2g/day) in 4 divided doses for 14 days</td>
<td>15mg/kg/day in 2 divided doses (maximum 1g/day) for 7 days</td>
</tr>
<tr>
<td></td>
<td>2g/day in 4 divided doses for 14 days</td>
<td>40mg/kg/day in 2 divided doses for 14 days</td>
</tr>
<tr>
<td>Adults</td>
<td>500 mg in a single dose on day 1, then 250mg/day on days 2-5</td>
<td>TMP 320mg/day, SMZ 1,600mg/day in 2 divided doses for 14 days</td>
</tr>
</tbody>
</table>

* Trimethoprim-sulfamethoxazole (TMP-SMZ) can be used as an alternative agent to macrolides in patients aged ≥2 mo who are allergic to macrolides, who cannot tolerate macrolides, or who are infected with a rare macrolide-resistant strain of Bordetella pertussis.

HIV Infection

Time Recommended to Complete: 3 days

Bernard Herschel, M.D.

GUIDING QUESTIONS

1. How is HIV primarily transmitted, and how do genital ulcers increase the risk of HIV transmission?
2. Which cells does the HIV virus primarily infect?
3. What are the symptoms and signs of primary HIV infection?
4. What is the preferred test for diagnosis of HIV, and how is AIDS defined?
5. What is meant by the term “the window period”?
6. How is HIV activity monitored?
7. What is the CD4 count below which the host begins to experience opportunistic infections?
8. What are the indications for initiating antiretroviral therapy?
9. What are the goals for therapy, and what are the factors that increase the risk of developing resistance?

POTENTIAL SEVERITY

Management of HIV is challenging and complex. The associated opportunistic infections are often difficult to diagnose and frequently life-threatening.

EPIDEMIOLOGY

Having originated in Eastern Africa between 1910 and 1950, by transmission of a precursor virus from a chimpanzee, HIV infection has now spread across the world. Sub-Saharan Africa remains the epicenter of the epidemic: 3 to 4 million new infections occur annually, 30 million Africans are living with HIV, and more than 10 million have already died. Uganda alone has lost 2.5 million people to AIDS: 300 to 400 deaths daily, every day from 1985 to 2006, in a country with a population of 20 million. In the sub-Saharan countries, transmission occurs predominantly by heterosexual intercourse, with as many women as men being infected. On average, infected women are younger than infected men, but overall, the most productive age strata is where the infection predominates, contributing to the disastrous socioeconomic impact of the AIDS epidemic.

The problems of North America and Western Europe pale in comparison with those of Africa. Nonetheless, the number of HIV-infected people living in the United States has reached almost 1 million. Incidence figures are difficult to determine, because most newly acquired infections are not diagnosed. Judging from the number of first positive tests (which may be the result of an infection acquired years earlier), infection rates declined during the 1990s, reaching a plateau around 1998. Some reports claim that infections have increased slightly since 1998, perhaps because of an increase in sexual-risk taking linked to a false sense of security created by the existence of highly active antiretroviral therapy (HAART). However, by decreasing viremia, HAART may also be having a positive effect on transmission of HIV.

The probability of acquiring an HIV infection varies depending on the type of exposure. Transfusion with a unit of HIV-infected blood is almost certain to infect the recipient. In the absence of treatment, the child of an HIV-positive mother has about a 30% chance of
infection. The chance of acquiring an infection after a needle-stick injury involving infected bodily fluids is about 1 in 300. Most infections occur with sexual exposure, the primary determinant of infectivity being the level of viremia, which is particularly elevated during primary HIV infection. Local genital factors modulate that risk. Inflammation such as may be caused by sexually transmitted diseases attracts lymphocytes. In an infected person, these may harbor HIV, and in the recipient, they may provide a reservoir of cells vulnerable to HIV infection. Recently, circumcision was found to reduce a man’s risk of contracting HIV by approximately 50%.

Depending on the level of viremia, the risk of HIV infection varies from roughly 1% to 0.01% for each act of vaginal or anal intercourse. Compared with infection rates for other sexually transmitted diseases, this risk is quite low, although in the presence of genital ulcers, infection rates as high as 10% have been reported. These rates compare with rates of infection of 20% to 40% after exposure to syphilis or gonorrhea. Nonetheless, repeated sexual exposure—as occurs in a serodiscordant couple—entails substantial risk, typically reaching 1% per month. The risk is likely higher during the first months of a sexual partnership than later. Indeed, some studies show an HIV-specific, potentially protective cellular immune response in seronegative sexual partners of seropositive individuals. However, absence of infection in the past is no guarantee for the future: increasing immune deficiency and viremia are part of the natural history of untreated HIV infection, and they carry with them an increased risk of transmission.

Anal and vaginal intercourse are approximately equally effective in transmitting HIV. Some (but not all) studies have found that the risk of transmission from an HIV-infected man to a woman is higher than the reverse. Compared with vaginal or anal intercourse, oral sex is certainly much less risky—specifically, it is too low to be quantified. However, any sizable HIV center encounters examples of transmission by oral sex. Condoms are effective in preventing transmission. Transmission has never been observed in a large series of couples who declared “always” to have used condoms. However, perfect compliance with condom use, and avoidance of slippage and breakage is difficult to achieve in practice. Preventive efforts have had varying success:

- Transmission of HIV infection through infected blood products has almost been eliminated. Rare cases may still occur (less than 1 transmission in 500,000 blood transfusions) if blood is donated during the “window period.”
- Use of antiretroviral therapy in the mother has the potential to decrease mother-to-child transmission from more than 30% to less than 1%. Such transmission has now become very rare in Western Europe and the United States, and is almost always the result of some procedural failure.
- Needle exchange programs and methadone or even heroin substitutions have reduced the incidence of HIV infection in intravenous drug users by more than 90%.
- As noted earlier, condoms are effective in decreasing HIV transmission, particularly in stable couples. Incidence rates of HIV have declined in homosexual communities that practice safer sex. The decrease in the prevalence of HIV may also have contributed to a reduced rate of infection among younger homosexual men, even without necessarily perfect adherence to safer-sex guidelines. Among both homosexual and heterosexual communities, some subgroups continue high-risk practices, with a concomitant high incidence of sexually transmitted diseases and HIV. From 1999 to 2004, several instances of small epidemics of syphilis were reported in Dublin, Bristol, Baltimore,
Paris, and California. Interestingly, these epidemics were nowhere accompanied by a rise in HIV infections. As noted earlier, the explanation for this seeming paradox may lie in the protective effect of HAART.

When contemplating the use of scarce resources to fight HIV infection, it is important to realize that prevention is much more cost-effective than cure. Even with unrealistically favorable assumptions regarding the efficacy and costs of HAART, costs per life–year saved are 20 to 100 times lower for condoms than for antiretroviral treatment. But it is the sick who are crying for help, not the healthy who are crying for condoms...

PATHOGENESIS

The primary targets of the human immunodeficiency virus are probably the dendritic cells in the mucosa of the genital tract. The virus uses a specific receptor called DC-SIGN to attach to those cells. The dendritic cells then transport HIV into lymph nodes, where the virus infects lymphocytes.

The receptors for HIV are mainly the CD4 molecules on the surface of a sub-population of T lymphocytes. A co-receptor is also necessary for infection. Viruses that preferentially interact with the co-receptor CCR5 are called “R5 viruses” (or “monocytotropic,” or “nonsyncytiotium–inducing”), and they predominate in early infection. Later on, HIV often acquires the capacity to interact with the CXCR4 receptor; such viruses are called “X4” (“syncytiotium-inducing,” or “lymphocytoprotic”). The CD4 lymphocytes whose T-cell receptor is specific for HIV proteins proliferate and are preferentially infected. This preferential infection (followed by destruction) may explain the specific deficiency of immunity to HIV as described next.

More than 98% of lymphocytes are localized in the lymph nodes and spleen. Nonetheless, the viruses produced by the newly HIV-infected lymphocytes flood the blood and are transported into all tissues within a matter of days. Viremia reaches high levels—up to millions of HIV genomes per cubic millimeter. During this time, many patients become symptomatic with fever, skin lesions, pharyngitis, and swollen lymph nodes. This self-limiting disease (Figure 17.1), lasting usually a few days to a few weeks, is called “primary HIV infection,” “acute retroviral syndrome,” or “seroconversion syndrome.” Then, the immune response kicks in; antibodies directed against HIV appear in the blood, and cytotoxic T cells specific for HIV-infected cells proliferate. This HIV immune response rapidly achieves partial control of the HIV infection. Viremia levels decrease by several orders of magnitude, stabilizing at a lower level, called “plateau level.” This level can vary from fewer than 50 to several hundred thousand copies of HIV RNA per cubic millimeter, and it correlates closely with further evolution toward immune deficiency: the higher the level, the faster the development of AIDS.

A progressive reduction in the level of CD4 T cells is the hallmark of HIV-induced immune deficiency. A fall from the normal level of approximately 1000 CD4 cells per cubic millimeter occurs during acute HIV infection. After seroconversion, the level of CD4 lymphocytes again rises, but rarely returns to normal. Later, during the chronic phase of HIV infection, a progressive annual loss of about 70 cells per cubic millimeter occurs. However, the speed at which immune deficiency progresses is extremely variable. In rare individuals, AIDS may appear as early as 1 or 2 years after infection. An incubation period of 10 years is more typical, but occasionally other
KEY POINTS

About the Pathogenesis of HIV Infection

1. Dendritic cells in the mucosa transport the virus to CD4 T cells in the lymph nodes.
2. Early infection is caused by monocytotropic (R5) virus; later infection, by lymphocytotropic (X4) virus.
3. Viral particles enter the bloodstream during primary infection reaching levels of millions per cubic millimeter.
4. Anti-HIV antibodies develop and cytotoxic T cells proliferate, controlling the infection. Viral load usually drops to a plateau level of 30,000 copies per cubic millimeter.
5. The CD4 count drops below 1000/µm³, and then returns to normal. Subsequently, the CD4 count drops annually by 70/µm³.
6. Age and genetic factors affect progression. At a CD4 count below 200/µm³, opportunistic infections begin.
7. Chronic asymptomatic infection is associated with the production of $10^9$ to $10^{11}$ viral particles daily, and destruction of $10^{11}$ CD4 cells daily. High risk of virus mutation requires multidrug therapy.

patients, called “long-term nonprogressors” or “elite controllers,” show no evidence of damage to the immune system at all. These nonprogressors survive many years with low viremia and a normal number of CD4 cells.

An enormous amount of research has been conducted to find factors that influence the rate of progression. A number of genetic traits are thought to correlate with faster or slower development of immune deficiency. Age at the time of infection also plays a role; the older the individual, the more likely it is that progression will be rapid. (The late fetal and perinatal period is an exception; HIV acquired neonatally may progress very rapidly.) Unfortunately, neither age nor genetic inheritance is easily changed, and no easily influenced factors for progression (“Drink carrot juice, and you’ll never get AIDS”) has been found so far.

The CD4 cells are the conductors of the immunologic orchestra; they are critical for some of its most important functions, including development of specific CD8 T cell cytotoxic responses, and production of neutralizing antibodies. When the number of CD4 cells declines below a critical level of about 200/µm³, the “AIDS defining diseases” start to appear. The list of these diseases (see Table 17.1) is relatively short: *Pneumocystis jiroveci* pneumonia (PCP) rather than aspergillosis, Kaposi’s sarcoma and lymphoma rather than tumors of other types. Some of these infections—for example, PCP—are highly suggestive of HIV infection; others—pneumococcal pneumonia, *Candida* stomatitis, and tuberculosis—also occur in patients with normal immune systems or with immune deficiencies caused by conditions other than AIDS. Most of the opportunistic diseases are caused by reactivation of latent herpes viruses [for example, cerebral lymphoma resulting from Epstein–Barr virus, or retinitis from cytomegalovirus (CMV)], by fungi (PCP), or by bacteria (tuberculosis). Other infections—such as salmonellosis or cryptococcosis—may be newly acquired.

As described earlier, the nascent HIV immune response controls the runaway viral proliferation observed during acute HIV infection. How can the eventual failure of this immune response be explained?

Despite thousands of papers written on the subject, a clear answer is not currently available. The long-term nonprogressors tend to have a vigorous HIV-specific cytotoxic immune response, but overlap with populations showing progression is considerable. The role of antibodies to HIV is also unclear; individual cases show no clear correlation between the existence of neutralizing antibodies and progression. Attention has recently shifted to the nonspecific components of the immune system such as natural killer cells and toll-like receptors. The extreme mutability of HIV leads to the emergence of HIV quasispecies that are no longer recognized by the immune response (the “immune escape phenomenon”). In addition, HIV preferentially infects proliferating lymphocytes, but the lymphocytes that proliferate in response to HIV infection are precisely those whose receptors recognize HIV-derived peptides. Infection of these lymphocytes eventually leads to their destruction.

Effective therapy reverses most of the immune deficiency. Given enough time, recovery of the CD4 cell count occurs even in patients who have practically no cells left when treatment starts. Cell counts continue to increase for several years, finally reaching a plateau of 500 to 1000/µm³. The immune response to the most important pathogens recovers, as can be seen by the disappearance of opportunistic diseases. But one exception remains: the immune response to HIV itself stays deficient even after successful treatment.

In North America and Western Europe, most patients come to medical attention during the latent or plateau period of chronic HIV infection, when clinical signs and symptoms are rare or absent. Nonetheless, the infection remains active, with the production of $10^9$ to $10^{11}$ viral particles daily. At the
### Table 17.1. Indicator Conditions in the Case Definition of AIDS in Adults $^a$

<table>
<thead>
<tr>
<th>Condition</th>
<th>$n$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidiasis of esophagus, trachea, bronchi, or lungs</td>
<td>3846 (16)</td>
</tr>
<tr>
<td>Cervical cancer, invasive</td>
<td>144 (0.6)</td>
</tr>
<tr>
<td>Coccidioidomycosis, extrapulmonary</td>
<td>74 (0.3)</td>
</tr>
<tr>
<td>Cryptococcosis, extrapulmonary</td>
<td>1168 (5)</td>
</tr>
<tr>
<td>Cryptosporidiosis with diarrhea for more than 1 month</td>
<td>314 (1.3)</td>
</tr>
<tr>
<td>Cytomegalovirus of any organ other than liver, spleen, or lymph nodes; or of eye</td>
<td>1638 (7)</td>
</tr>
<tr>
<td>Herpes simplex with mucocutaneous ulcer for more than 1 month, or bronchitis, pneumonitis, or esophagitis</td>
<td>1250 (5)</td>
</tr>
<tr>
<td>Histoplasmosis, extrapulmonary</td>
<td>208 (0.9)</td>
</tr>
<tr>
<td>HIV-associated dementia (disabling cognitive or other dysfunction interfering with occupation or activities of daily living)</td>
<td>1196 (5)</td>
</tr>
<tr>
<td>HIV-associated wasting (involuntary loss of more than 10% of baseline weight, plus chronic diarrhea (2 or more loose stools daily for 30 days or more), or chronic weakness and documented enigmatic fever for 30 days or more)</td>
<td>4212 (18)</td>
</tr>
<tr>
<td><em>Isospora belli</em> infection with diarrhea for more than 1 month</td>
<td>22 (0.1)</td>
</tr>
<tr>
<td>Kaposi's sarcoma</td>
<td>1500 (7)</td>
</tr>
<tr>
<td>Lymphoma:</td>
<td></td>
</tr>
<tr>
<td>Burkitt's</td>
<td>162 (0.7)</td>
</tr>
<tr>
<td>Immunoblastic</td>
<td>518 (2.3)</td>
</tr>
<tr>
<td>Primary central nervous system</td>
<td>170 (0.7)</td>
</tr>
<tr>
<td><em>Mycobacterium avium</em>, disseminated</td>
<td>1124 (5)</td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1621 (7)</td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td>491 (2)</td>
</tr>
<tr>
<td>Nocardiosis</td>
<td>– (&lt;1)</td>
</tr>
<tr>
<td><em>Pneumocystis jiroveci</em> pneumonia</td>
<td>9145 (38)</td>
</tr>
<tr>
<td>Pneumonia, recurrent bacterial (2 or more episodes in 12 months)</td>
<td>1347 (5)</td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy</td>
<td>213 (1)</td>
</tr>
<tr>
<td><em>Salmonella</em> septicemia (non-typhoid), recurrent</td>
<td>68 (0.3)</td>
</tr>
<tr>
<td>Strongyloidesis, extraintestinal</td>
<td>None</td>
</tr>
<tr>
<td>Toxoplasmosis of internal organ</td>
<td>1073 (4)</td>
</tr>
<tr>
<td>Wasting syndrome because of HIV</td>
<td>1980 (18)</td>
</tr>
</tbody>
</table>

$^a$ The listed numbers and percentages indicate the frequencies of occurrence in the database of the Swiss HIV cohort study, an ongoing registry of more than 11,000 patients.

At the same time, several billion CD4 cells are destroyed and replaced each day. Production of $10^{11}$ viral particles daily provides the potential for a mutation at every single nucleotide position. Unsurprisingly, under the selective pressure of a partially effective immune response or partially effective therapy, resistant mutations rapidly emerge. To obtain a durable antiviral effect, several drugs must be combined to completely abolish viral production. Once this goal is achieved, emergence of resistance becomes much less likely, and in those circumstances, patients may be treated for many years without viral breakthrough. Nonetheless, the virus persists in reservoirs that are not accessible to current treatment. These reservoirs may include non-productive infection in pools of long-lived lymphocytes. Sensitive molecular techniques suggest that the
half-life of this type of reservoir may reach several years, making eradication by continuous treatment unrealistic.

**CLINICAL MANIFESTATIONS OF PRIMARY HIV INFECTION**

The incubation period for symptomatic infection is 2 to 4 weeks, but can be as prolonged as 10 weeks. Onset of fever can be abrupt and is associated with diffuse lymphadenopathy and pharyngitis. The throat is usually erythematous, without exudates or enlarged tonsils. Painful ulcers can develop in the oral and genital mucosa (Figure 17.1). Gastrointestinal complaints are common, with many patients experiencing nausea, anorexia, and diarrhea. A skin rash often begins 2 to 3 days after the onset of fever and usually involves the face, neck, and upper torso. The lesions are small pink-to-red macules or maculopapules (Figure 17.1). Headache is another prominent symptom, and aseptic meningitis is noted in about one quarter of patients. Headache is often retro-orbital and worsened by eye movement. Findings in the cerebrospinal fluid (CSF) are consistent with viral meningitis: lymphocytes, normal glucose, and mildly elevated protein. Guillain–Barré syndrome and palsy of the VIIth cranial nerve have been reported. Peripheral leukocyte count may be normal or slightly below normal, with a decrease in CD4 lymphocytes and an increase in CD8 lymphocytes (the CD4:CD8 ratio is commonly below 1.0). Liver transaminase values may be moderately elevated. The illness is self-limiting, with severe symptoms usually resolving over 2 weeks. Lethargy and fatigue may persist for several months.

**LABORATORY EVALUATION OF HIV INFECTION**

**DIAGNOSIS**

Infection with HIV is diagnosed by the detection of HIV-specific antibodies in plasma or serum. These antibodies appear a few weeks after infection, shortly before or after the symptoms of the acute retroviral syndrome. From studies in which the date of infection is precisely known (for instance, in individuals infected by a blood transfusion), the delay to the appearance of antibodies can be determined: about 5% of patients seroconvert within 7 days, 50% within 20 days, and more than 95% within 90 days. Therefore, a period exists (called the “window period”) during which, although the patient is infected, antibodies cannot be detected in the plasma. For a few days, the HIV-specific p24 antigen is detectable alone, without antibodies [Figure 17.1(A)]. Therefore, screening tests now combine the detection of antigen and antibody. Gene amplification tests [polymerase chain reaction (PCR), as well as other hybridization techniques] for the detection of viral genomes should not be used for early diagnosis. They are much more expensive than the antibody tests. Antibody tests remain positive for the lifetime of HIV-infected people, except possibly in very rare cases when treatment was started before seroconversion.

Antibody tests for HIV are among the most reliable of all medical tests, with specificity and sensitivity largely exceeding 99%. Nonetheless, in view of the importance of the diagnosis and the possibility of clerical errors (mislabeled tubes and such), confirmation of the diagnosis by a second blood sample is recommended. Confirmation is especially important when the pre-test probability is low, raising the proportion of false positive results.

True false-positives are much rarer than “Indeterminate” test results. An indeterminate result arises when substances in the patient’s plasma interact with impurities in the HIV antigen preparations. Usually, the color reaction of the enzyme-linked immunoabsorbent assay is above the threshold for positivity, but much below the results of a routine positive test. To diminish these indeterminate reactions, manufacturers are using recombinant technology to purify the HIV protein. In the presence of an indeterminate test, and particularly in the absence of risk factors for HIV infection, the patient should be reassured that the result is negative, with the negativity confirmed by a second test using a different method. Such a method might involve use of the Western blot. In a Western blot test, the HIV proteins are first separated by electrophoresis and then
**KEY POINTS**

**About Diagnosing HIV Infection**

1. Diagnosis of HIV infection is made by measuring anti-HIV antibodies.
2. Following exposure, 5% of people seroconvert within 7 days, 50% within 20 days, and more than 95% within 90 days.
3. The “window” period of viremia with negative serology lasts from a few days to several weeks.
4. Tests based on gene amplification (polymerase chain reaction, for example) are not recommended for diagnosis.
5. Tests for HIV antibody are highly specific and sensitive.
6. An “indeterminate” test is usually a false positive; confirm by Western blot analysis.

**CLASSIFICATION**

The stages of HIV infection are defined by clinical events and by CD4 lymphocyte count (Table 17.2). This classification, established in 1992, indicates clearly the immunosuppression and symptomatic status of the patient.

The meaning of the word “AIDS” is not the same on both sides of the Atlantic. In the United States, every person with a CD4 count below 200/\(\mu\text{m}^3\) is considered to have AIDS (shaded area in Table 17.2); alternatively, patients may be considered to have AIDS if they have an AIDS defining opportunistic infection (Table 17.1). In Europe, the CD4 count does not enter into the definition of AIDS, which remains synonymous with the occurrence of an opportunistic disease as those defined in Table 17.1. The stage of HIV infection is defined by the CD4 lymphocyte count (biologic stage 1, 2, or 3) and clinical events (A, B, or C). Occurrence of a type C disease defines AIDS. In addition, in the United States, AIDS is also defined by a CD4 count below 200/\(\mu\text{m}^3\) (categories C1, C2, C3, A3, or B3).

<table>
<thead>
<tr>
<th>CD4 cell category</th>
<th>Patients (%)</th>
<th>A&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Clinical category</th>
<th>B&lt;sup&gt;b&lt;/sup&gt;</th>
<th>C&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Asymptomatic, or PGL, or acute HIV infection</td>
<td>Symptomatic (not A or C)</td>
<td>AIDS indicator conditions (1987)</td>
<td></td>
</tr>
<tr>
<td>1) &gt;500/(\mu\text{m}^3)</td>
<td>((\geq 29))</td>
<td>A1</td>
<td>B1</td>
<td>C1</td>
<td></td>
</tr>
<tr>
<td>2) 200–499/(\mu\text{m}^3)</td>
<td>(14–28)</td>
<td>A2</td>
<td>B2</td>
<td>C2</td>
<td></td>
</tr>
<tr>
<td>3) &lt;200/(\mu\text{m}^3)</td>
<td>(&lt;14)</td>
<td>A3</td>
<td>B3</td>
<td>C3</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Clinical signs associated with stage A are primary HIV infection, persistent generalized lymphadenopathy (PGL), or lack of symptoms (asymptomatic patients).

<sup>b</sup> Clinical signs and symptoms associated with stage B are oral candidiasis, relapsing vaginal candidiasis, herpes zoster, localized neoplasia of the cervix, any other clinical manifestations not defined by categories A and C.

<sup>c</sup> Corresponds to the occurrence of an “AIDS-defining opportunistic disease” as listed in Table 17.1.

<sup>d</sup> Dark shaded areas designate the stages of illness that are defined as AIDS in the United States.
TREATMENT AND PROGNOSIS

Monitoring Tests

Infection with HIV has been likened to a train speeding towards a wreck: the speed corresponds to the level of viremia, and the distance to the site of the wreck corresponds to the CD4 count.

To determine viral load, genomic tests are now almost universally used. These tests measure HIV genomes per cubic millimeter of plasma. Because the genomes consist of RNA, the RNA first has to be transcribed into DNA, which is then amplified, most often by PCR. Patients with untreated HIV infection typically have 500 to 1 million copies of HIV RNA per cubic millimeter; with treatment, this number declines to undetectability. Depending on the test being used, “undetectability” means fewer than 5 to 50 copies of HIV RNA. Ideally, after 2 to 6 months of treatment, all patients on modern antiretroviral therapy should have fewer than 50 copies of HIV RNA per cubic millimeter.

Many studies have shown that the long-term prognosis for untreated HIV infection depends on the viremia. However, within this broad correlation, large inter-individual variations occur, with patients remaining in good health for many years despite viremia exceeding 100,000 copies per cubic millimeter.

For short-term prognosis, the CD4 count is more useful. The occurrence of opportunistic infections and tumors is unusual with CD4 counts above 200/μm³. Below this value, the incidence of such infections rises exponentially. It is very unusual for patients to die of AIDS with CD4 counts above 50/μm³.

Antiretroviral Resistance Tests

Although antiretroviral combination therapy is effective in most patients, resistance may occur, and treatment may need to be adjusted. To guide the choice of therapy, tests measuring antiretroviral resistance have been developed.

Two types of tests are currently in use:

1. **Genotypic tests.** Determine the sequence of the relevant viral genes: the reverse transcriptase, protease, gp-41, and integrase genes. The sequence shows the presence or absence of mutations that are associated with antiretroviral resistance. However, with rare exceptions, the occurrence of a specific mutation does not predict a specific resistance phenotype. Rather, the combination of many mutations must be considered. A prediction of resistance from such a combination of mutations has been marketed as a “virtual phenotype.”

2. **Phenotypic tests.** Excise the relevant gene from amplified patient virus and insert the excised portion into a standard virus of known growth properties. This recombinant virus is then exposed to various drugs and its resistance is ascertained. Phenotypic tests are more expensive than genotypic tests, and they take 1 to 3 weeks to complete.

The value and use of resistance tests are subjects of continuing controversy. It has been difficult to show that they improve the outcome of treatment, but they may allow ineffective drugs to be discontinued, thus sparing side effects and costs. The use of resistance testing is further discussed in the subsection on HIV therapy later in this chapter.

Caveats Regarding Laboratory Tests

Modern antiretroviral treatment would be impossible without the use of laboratory tests. However, physicians...
HIV INFECTION

and patients need to be aware of the limits of the tests and, in particular, of the need to avoid over-interpretation of small changes. The precision of measurements of viral load is only about 0.3 log (a factor of 2). This means that values of 200 and 400 copies per cubic millimeter may actually be the same. Another problem with the interpretation of HIV viremia is the expression “undetectable” viremia. Detectability depends on the assay used. Experimental assays with sensitivities as low as 1 or 3 copies per cubic millimeter actually show viremia in almost all patients who have started their treatment during chronic HIV infection. Whether viremia that is very low (for example, fewer than 10 copies per cubic millimeter) is better for the patient than viremia that is detectable but between 10 and 50 copies per cubic millimeter is unknown.

In patients with viremia that is low on treatment, some values may nonetheless exceed 50 or 100 copies from time to time. These “blips” of viremia are of no great prognostic significance, and they should not prompt a change in treatment. On the other hand, values that rise above 500 copies per cubic millimeter are clearly predictive of subsequent resistance and escape.

Similarly, the CD4 count is not a precise measure. It results from the multiplication of two percentages (the percentage of lymphocytes among leukocytes and the percentage of CD4-positive lymphocytes among all lymphocytes). The number of lymphocytes varies during the day, depending on food intake, physical activity, and steroid levels, among other factors. In addition, laboratories and lab technicians vary in their interpretation of the morphology of leukocytes. Therefore, CD4 counts may vary as much as 10% to 30% when counts are repeated at frequent intervals within the same individual.

But besides these successes, HAART also produced problems. Present-day drugs do not eradicate HIV, and often, patients cannot comply with long-term combination treatment. Moreover, HAART causes unexpected and ill-understood side effects. The dogma of earliest possible treatment has therefore come under attack.

Table 17.3 summarizes the Ten Principles governing antiretroviral treatment. Starting and maintaining HAART is complex. Within the last few years, the numbers of antiretroviral agents, of their known and potential interactions with each other and with non-HIV drugs, and of their side effects have all increased exponentially. Usually, a physician specializing in HIV care should be consulted whenever HAART is started or changed. It is this specialist’s job to guarantee that the treatment chosen is optimal for the particular patient. Mismanagement of antiretroviral therapy can lead to untoward toxicities and the development of resistant viruses that can no longer be treated.

### MODERN ANTI-HIV THERAPY

#### INTRODUCTION

**The Ten Principles of Antiretroviral Treatment**

Since 1996, treatment with HAART, consisting usually of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus an HIV protease inhibitor (PI), has been widely used. These regimens produced durable suppression of viral replication, with undetectable plasma levels of HIV RNA, in more than half of treated patients. Immunity recovered, and morbidity and mortality fell by more than 80%. Treatment was thought to be particularly effective when started early; HAART was therefore recommended for essentially all HIV-infected people willing to commit themselves to lifelong therapy.
Table 17.3. Ten Principles for Highly Active Antiretroviral Therapy

<table>
<thead>
<tr>
<th>1. Indication</th>
<th>The presence of HIV infection establishes theoretically the indication for treatment, but treatment does not usually start until subclinical immune deficiency is apparent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Combination</td>
<td>Antiretroviral treatment consists of at least three drugs.</td>
</tr>
<tr>
<td>3. First chance = best chance</td>
<td>The choice of drugs during a first treatment course determines which possibilities remain when a second and different treatment becomes necessary later on. Chances for success are best first. Later on, alternatives are limited by selection of resistant mutants.</td>
</tr>
<tr>
<td>4. Complexity</td>
<td>Antiretroviral treatment is complex, in particular because of drug interactions and side effects.</td>
</tr>
<tr>
<td>5. Resistance</td>
<td>Selection of resistant quasispecies occurs frequently. Within substance classes, cross-resistance is complete among available non-nucleoside reverse transcriptase inhibitors, and partial among protease inhibitors, and nucleoside reverse transcriptase inhibitors.</td>
</tr>
<tr>
<td>6. Information</td>
<td>Starting and maintaining effective antiretroviral treatment is time-consuming, because the information needs of physician and patients are considerable.</td>
</tr>
<tr>
<td>7. Motivation and compliance</td>
<td>The patient’s willingness to take the drugs regularly at prescribed times and dosages will largely determine the success of treatment. Patients must understand the relationship between insufficient compliance and drug resistance.</td>
</tr>
<tr>
<td>8. Monitoring</td>
<td>Efficacy of antiretroviral treatment is established by regular measures of viral RNA and of CD4 counts.</td>
</tr>
<tr>
<td>9. Goals of treatment</td>
<td>The goal of treatment is durable suppression of viral RNA below 50 copies per cubic millimeter of plasma. Such suppression minimizes selection of resistant mutants and assists in immune reconstitution and avoidance of morbidity and mortality.</td>
</tr>
<tr>
<td>10. Studies</td>
<td>Antiretroviral treatment continues to evolve toward greater simplicity and efficacy. Patients should be encouraged to participate in clinical studies that aim to optimize therapy.</td>
</tr>
</tbody>
</table>

Table 17.4. Indications for Starting Antiretroviral Treatment

<table>
<thead>
<tr>
<th>Clinical stage</th>
<th>Laboratory values</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute HIV infection</td>
<td>Irrelevant</td>
<td>Consider HAART, obtain specialized consultation</td>
</tr>
<tr>
<td>Chronic asymptomatic HIV infection (stage A)</td>
<td>CD4 count</td>
<td>Viral load</td>
</tr>
<tr>
<td>&gt;500</td>
<td>&lt;50,000</td>
<td>Wait</td>
</tr>
<tr>
<td>350–500</td>
<td>Wait</td>
<td>Consider HAART</td>
</tr>
<tr>
<td>&lt;350</td>
<td>Treat</td>
<td></td>
</tr>
<tr>
<td>Symptomatic chronic HIV infection (stage B or C)</td>
<td>Irrelevant</td>
<td>Treat</td>
</tr>
</tbody>
</table>

HAART = highly active antiretroviral therapy.
Table 17.5. Potential Advantages and Disadvantages of Early Antiretroviral Treatment

<table>
<thead>
<tr>
<th>Possible advantages</th>
<th>Possible disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal suppression of viral replication; as a consequence, lesser risk of selection of resistant mutants</td>
<td>Risk of resistance as a consequence of suboptimal compliance</td>
</tr>
<tr>
<td>Prevention of immune deficiency and more complete immune reconstitution</td>
<td>Duration of efficacy of treatment may be limited</td>
</tr>
<tr>
<td>Less risk of side effects in patients whose general state of health is excellent</td>
<td>Loss of quality of life through short-term side effects, and possible long-term toxicity</td>
</tr>
<tr>
<td>Healthy carriers are less contagious when treated (Lesser number of new infections?)</td>
<td>Transmission of new infections with drug-resistant viruses</td>
</tr>
</tbody>
</table>

are therefore only approximations, because individual factors, although often decisive, do not lend themselves to abstractions in a table. Table 17.5 outlines the advantages and disadvantages of an early start to treatment.

The course of HIV infection has been compared to a train speeding toward a wreck. The patient's CD4 count represents the distance to the site of the wreck, and the viral load represents the train's speed. In the absence of symptoms, those two factors are used to determine the timing of antiretroviral therapy so as to prevent AIDS.

Four different classes of drugs are currently available:

1. The Nucleoside reverse transcriptase inhibitors (NRTIs), such as abacavir (ABC), didanosine (ddI), emtricitabine (FTC), lamivudine (3TC), stavudine (d4T), tenofovir (TDF), and zidovudine (AZT)
2. The non-nucleoside reverse-transcriptase inhibitors (NNRTIs), such as efavirenz (EFV) and nevirapine (NVP)
3. The PIs, such as amprenavir (APV), darunavir (DRV), indinavir (IDV), lopinavir/ritonavir (LPV/r), nelfinavir (NFV), ritonavir (RTV), and saquinavir (SQV) and tipranavir (TPV)
4. The fusion inhibitor enfuvitide.

The following treatment options are not recommended:

- Therapy with only one or two drugs
- Combinations of zidovudine plus d4T (antagonism), or TDF plus ddI (dosage adjustment necessary because of an increase in the area-under-the-curve for ddI), d4T plus ddI (overlapping toxicity), ABC plus TDF (rapid emergence of mutants with the resistance mutation K65R)
- Use of protease inhibitors without concomitant ritonavir (insufficient drug levels). Atazanavir is an exception to this rule, and can be used without ritonavir at a dose of 400 mg/day.

Monitoring Treatment

TOLERANCE AND SIDE EFFECTS

Nucleoside reverse-transcriptase inhibitors can be toxic to mitochondria, producing liver damage, lactic acidosis,
### Table 17.6. Anti-HIV drugs available in 2007

<table>
<thead>
<tr>
<th>Generic name (Abbreviation)</th>
<th>Trade name</th>
<th>Usual Dosage in the absence of renal failure</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir (ABC)</td>
<td>Ziagen</td>
<td>300 mg bid, or 600 mg qd</td>
<td>NRTI</td>
</tr>
<tr>
<td>Didanosine (ddl)</td>
<td>Videx</td>
<td>300-400 mg qd*</td>
<td>NRTI</td>
</tr>
<tr>
<td>Emtricitabine (FTC)</td>
<td>Emtriva</td>
<td>200 mg qd</td>
<td>NRTI</td>
</tr>
<tr>
<td>Lamivudine (3-TC)</td>
<td>3-TC</td>
<td>150 mg qd or 300 mg qd**</td>
<td>NRTI</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>Zerit</td>
<td>30 mg bid**</td>
<td>NRTI</td>
</tr>
<tr>
<td>Tenofovir (TFV)</td>
<td>Viread</td>
<td>245 mg qd</td>
<td>NRTI</td>
</tr>
<tr>
<td>Zidovudine (AZT)</td>
<td>Retrovir</td>
<td>250 mg qd</td>
<td>NRTI</td>
</tr>
<tr>
<td>AZT + 3-TC</td>
<td>Combivir</td>
<td>1 tab bid</td>
<td>NRTI</td>
</tr>
<tr>
<td>AZT + 3-TC + ABC</td>
<td>Trizivir</td>
<td>1 tab bid</td>
<td>NRTI</td>
</tr>
<tr>
<td>ABC + 3-TC</td>
<td>Epzicom (US), Kivexa (Europe)</td>
<td>1 tab qd</td>
<td>NRTI</td>
</tr>
<tr>
<td>TDF + FTC</td>
<td>Truvada</td>
<td>1 tab qd</td>
<td>NRTI</td>
</tr>
<tr>
<td>TDF + FTC + EFV</td>
<td>Atripla</td>
<td>1 tab qd</td>
<td>NRTI</td>
</tr>
<tr>
<td>Efavirenz (EFV)</td>
<td>Sustiva or Stocrin</td>
<td>600 mg qd</td>
<td>NNRTI</td>
</tr>
<tr>
<td>Nevirapine (NVP)</td>
<td>Viramune</td>
<td>200 mg bid</td>
<td>NNRTI</td>
</tr>
<tr>
<td>Etravirine (ETV)</td>
<td>Undetermined as of 8/07</td>
<td>400 mg bid</td>
<td>NNRTI</td>
</tr>
<tr>
<td>Atazanavir (ATZ)</td>
<td>Reyataz</td>
<td>300 mg qd*** or 400 mg qd</td>
<td>PI</td>
</tr>
<tr>
<td>Darunavir (DRV)</td>
<td>Prezista</td>
<td>600 mg bid*** or 800 mg qd***</td>
<td>PI</td>
</tr>
<tr>
<td>Fosamprenavir (FPV)</td>
<td>Lexiva (US), Telzir (Europe)</td>
<td>700 mg bid*** or 1400 mg qd***</td>
<td>PI</td>
</tr>
<tr>
<td>Indinavir (IDV)</td>
<td>Crixivan</td>
<td>800 mg bid***</td>
<td>PI</td>
</tr>
<tr>
<td>Lopinavir/ritonavir (LPV/r)</td>
<td>Kaletra</td>
<td>400/100 mg bid***</td>
<td>PI</td>
</tr>
<tr>
<td>Nelfinavir (NFV)</td>
<td>Viracept</td>
<td>1250 mg bid</td>
<td>PI</td>
</tr>
<tr>
<td>Ritonavir (RTV)</td>
<td>Norvir</td>
<td>100 mg ****</td>
<td>PI</td>
</tr>
<tr>
<td>Saquinavir hard gel (SQVh)</td>
<td>Invirase</td>
<td>1000 mg bid***</td>
<td>PI</td>
</tr>
<tr>
<td>Maraviroc (MVC)</td>
<td>Selzentry</td>
<td>300 mg bid</td>
<td>CCR5 inhibitor</td>
</tr>
<tr>
<td>Raltegravir (RTG)</td>
<td>Isentress</td>
<td>400 mg bid</td>
<td>Integrase inhibitor</td>
</tr>
<tr>
<td>Enfuvirtide (T-20)</td>
<td>Fuzeon</td>
<td>90 mg bid</td>
<td>Fusion inhibitor</td>
</tr>
</tbody>
</table>

NRTI = nucleoside reverse-transcriptase inhibitors; NNRTI = non-nucleoside reverse-transcriptase inhibitors; PI = protease inhibitors

* 250-300 mg qd if weight < 60 kg; adjust dose in case of renal failure
** 30 mg bid if weight < 60 kg; adjust dose in case of renal failure
*** when co-administered with 100 mg of RTV
**** 100 mg when used to boost serum concentration of other protease inhibitors

Lipoatrophy, and polyneuropathy. Protease inhibitors cause nausea, vomiting, and diarrhea; elevate plasma cholesterol and triglycerides; induce insulin resistance and glucose intolerance; and contribute, together with NRTIs, to the redistribution of fatty tissue (atrophy in the face and extremities, contrasting with fat accumulation in breasts and abdomen). Treatment of dyslipidemia with statins is problematic because of the potential for drug interactions. All drugs produce various specific side effects; Table 17.8 presents an overview. In the table, gray shading means that the corresponding side effect has been reported in 5% or more of patients; black shading designates a
### Table 17.7. PIs compared to NNRTIs in initial treatment, when combined with NRTIs

<table>
<thead>
<tr>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protease inhibitors</td>
<td>well documented clinical efficacy</td>
</tr>
<tr>
<td></td>
<td>relatively slow selection for resistance when treatment is suboptimal</td>
</tr>
<tr>
<td></td>
<td>partial cross-resistance only; possible efficacy of a second PI in case of failure</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-nucleosides</td>
<td>only a few pills to swallow</td>
</tr>
<tr>
<td></td>
<td>better compliance</td>
</tr>
<tr>
<td></td>
<td>possibly less lipodystrophy</td>
</tr>
</tbody>
</table>

### Table 17.8. Frequent Side Effects of Anti-HIV Drugs

<table>
<thead>
<tr>
<th>Reverse-Transcriptase Inhibitors</th>
<th>NRTIs</th>
<th>NNRTIs</th>
<th>Protease Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td><img src="image" alt="Abdominal pain" /></td>
<td><img src="image" alt="Abdominal pain" /></td>
<td><img src="image" alt="Abdominal pain" /></td>
</tr>
<tr>
<td>Alterations of taste</td>
<td><img src="image" alt="Alterations of taste" /></td>
<td><img src="image" alt="Alterations of taste" /></td>
<td><img src="image" alt="Alterations of taste" /></td>
</tr>
<tr>
<td>Bleeding</td>
<td><img src="image" alt="Bleeding" /></td>
<td><img src="image" alt="Bleeding" /></td>
<td><img src="image" alt="Bleeding" /></td>
</tr>
<tr>
<td>CNS symptoms</td>
<td><img src="image" alt="CNS symptoms" /></td>
<td><img src="image" alt="CNS symptoms" /></td>
<td><img src="image" alt="CNS symptoms" /></td>
</tr>
<tr>
<td>Diarrhea</td>
<td><img src="image" alt="Diarrhea" /></td>
<td><img src="image" alt="Diarrhea" /></td>
<td><img src="image" alt="Diarrhea" /></td>
</tr>
<tr>
<td>Drug rash</td>
<td><img src="image" alt="Drug rash" /></td>
<td><img src="image" alt="Drug rash" /></td>
<td><img src="image" alt="Drug rash" /></td>
</tr>
<tr>
<td>Fat accumulation</td>
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<td><img src="image" alt="Fat accumulation" /></td>
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<tr>
<td>Fat loss</td>
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<td><img src="image" alt="Fat loss" /></td>
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<tr>
<td>Fatigue</td>
<td><img src="image" alt="Fatigue" /></td>
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<tr>
<td>Fever</td>
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<td><img src="image" alt="Fever" /></td>
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<tr>
<td>Headaches</td>
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<td><img src="image" alt="Headaches" /></td>
<td><img src="image" alt="Headaches" /></td>
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<tr>
<td>Hypersensitivity syndrome</td>
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<tr>
<td>Kidney stones</td>
<td><img src="image" alt="Kidney stones" /></td>
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<td><img src="image" alt="Kidney stones" /></td>
</tr>
<tr>
<td>Myalgia</td>
<td><img src="image" alt="Myalgia" /></td>
<td><img src="image" alt="Myalgia" /></td>
<td><img src="image" alt="Myalgia" /></td>
</tr>
<tr>
<td>Nausea</td>
<td><img src="image" alt="Nausea" /></td>
<td><img src="image" alt="Nausea" /></td>
<td><img src="image" alt="Nausea" /></td>
</tr>
<tr>
<td>Pancreatitis</td>
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<td><img src="image" alt="Pancreatitis" /></td>
<td><img src="image" alt="Pancreatitis" /></td>
</tr>
<tr>
<td>Paresthesias</td>
<td><img src="image" alt="Paresthesias" /></td>
<td><img src="image" alt="Paresthesias" /></td>
<td><img src="image" alt="Paresthesias" /></td>
</tr>
<tr>
<td>Polyneuropathy</td>
<td><img src="image" alt="Polyneuropathy" /></td>
<td><img src="image" alt="Polyneuropathy" /></td>
<td><img src="image" alt="Polyneuropathy" /></td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td><img src="image" alt="Sleep disturbances" /></td>
<td><img src="image" alt="Sleep disturbances" /></td>
<td><img src="image" alt="Sleep disturbances" /></td>
</tr>
<tr>
<td>Stomatitis</td>
<td><img src="image" alt="Stomatitis" /></td>
<td><img src="image" alt="Stomatitis" /></td>
<td><img src="image" alt="Stomatitis" /></td>
</tr>
<tr>
<td>Vertigo</td>
<td><img src="image" alt="Vertigo" /></td>
<td><img src="image" alt="Vertigo" /></td>
<td><img src="image" alt="Vertigo" /></td>
</tr>
<tr>
<td>Vomiting</td>
<td><img src="image" alt="Vomiting" /></td>
<td><img src="image" alt="Vomiting" /></td>
<td><img src="image" alt="Vomiting" /></td>
</tr>
</tbody>
</table>

(Continued)
principal side effect of the associated drug. Because drugs have usually been tested in combination, assignment of a particular side effect to a particular drug is often uncertain; this situation is particularly true of the various aspects of the lipodystrophy syndrome. Lipoatrophy and lactic acidosis are more strongly associated with d4T than with other NRTIs, and fat accumulation may be particularly frequent with the combination of saquinavir and ritonavir.

These potential side effects necessitate regular patient visits. One usual schedule requires a telephone consultation after three days and visits after 1, 2, and 4 weeks of treatment; if all goes well, interval between visits may then lengthen to every 2 to 6 months. For surveillance of toxicity, a complete blood count, liver enzymes, lactates, and serum cholesterol and triglycerides are useful.

**Drug Interactions**

Protease inhibitors and NNRTIs are preferentially metabolized by cytochrome P3A. The potential for drug interactions is therefore large. Drugs such as rifamycin or Hypericum (St. John’s Wort) may lower PI and NNRTI concentrations by inducing cytochrome P3A. Other drugs may accumulate because they compete with NNRTIs and PIs for cytochrome P3A. Examples include ergot alkaloids (dramatic cases of ergotism with amputation have been published) and many benzodiazepines. Hardly a week goes by without new interactions being reported; consultation of Web resources for up-to-date information is recommended. Among the best of the available sites are those produced by the Liverpool HIV Pharmacology Group of the University of Liverpool (www.hiv-druginteractions.org) and the electronic journal Medscape (http://medscape.com/hiv).

Ritonavir deserves special mention. It is the most powerful inhibitor of cytochrome P3A known in medical practice.

Table 17.8. Frequent Side Effects of Anti-HIV Drugs (Contd…)

<table>
<thead>
<tr>
<th>Clinical symptom</th>
<th>NRTIs</th>
<th>NNRTIs</th>
<th>Protease Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amylase↑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin↑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol↑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine↑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytopenias</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose↑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOT/GPT↑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate↑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrocytosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: Black = principle side effect, gray = side effect in > 5% of patients

* Tipranavir dramatically lowers the plasma concentration of many other drugs, including other protease inhibitors

** At the time of writing, darunavir has been on the market for less than 6 months. Other, rare side effects may yet appear.
Resistant to antiretroviral therapy. Its capacity to inhibit metabolism of other PIs can be put to good use: increasingly, other PIs such as indinavir, lopinavir, saquinavir, ritonavir, darunavir and amprenavir, are being combined with small doses of ritonavir (100 mg twice daily) to boost plasma drug levels and to lengthen intervals between dosages.

**Utility of Ritonavir**

Ritonavir is the most powerful inhibitor of cytochrome P3A known in medical therapeutics. It can be used to boost plasma levels of other protease inhibitors.

**Compliance**

Patients must acquire an adequate understanding of HIV pathogenesis, of the goals of HIV treatment, and of pharmacokinetics. They should be able to recognize the most frequent side effects and know how to manage them.

Aids to improve compliance abound, although few have been tested rigorously. Pill boxes are popular; these contain all the drugs taken during one week in separate compartments. The establishment of a detailed written schedule, showing how and when to take prescribed drugs in relation to meals and drinks, is recommended. More elaborate and expensive procedures involve use of electronic pill boxes, involving a device that records each time a bottle cap is unscrewed; the information can be downloaded into a computer and discussed with the patient. Directly observed therapy is becoming a possibility with once-daily regimens; this approach may be particularly appropriate in combination with methadone maintenance.

**Efficacy**

Viral suppression as measured by decline in the viral load, a rise in the CD4 count, and clinical efficacy are all closely related. Above approximately 50 copies per cubic millimeter, the nadir of viral load reached through treatment predicts duration of viral suppression. Time to optimal viral suppression depends on the initial viral load and on the sensitivity of the viral load test. Combination treatment must produce a rapid fall in viral load, which should drop to fewer than 400 copies per cubic millimeter after 12 weeks and to fewer than 50 copies after 24 weeks. Measurements of viral load and CD4 count are recommended every 3 months.

**Resistance Tests**

Suboptimal treatment, lack of compliance, insufficient bioavailability, or drug interactions can result in prolonged periods of low blood and tissue drug concentrations with continued viral replication and selection of resistant mutants. The presence of resistance genotypes and phenotypes can be detected using commercially available methods. Studies show that these tests are useful mainly for excluding drugs to which the virus is resistant; they are less helpful for finding drugs to which the virus is sensitive. Resistance tests are recommended in patients who are yet untreated, but who have likely been infected since 1997, because they may harbor a primarily resistant HIV variant. Resistance tests are also recommended after early treatment failure.

**Measurement of Plasma Drug Concentrations**

In prospective studies, trough concentrations of PIs correlated well with degree and duration of viral suppression. However, the utility of these measures in clinical practice is not established. They are recommended in cases of unexpected toxicity, of suspected problems with compliance that cannot be otherwise investigated, or when multiple medications may produce unforeseeable pharmacokinetic interactions.

**Key Points**

About Resistance Testing

1. Resistance tests are useful mainly for excluding ineffective drugs.
2. Resistance tests should be ordered before treatment commences in patients who are likely to have been infected in 1997 or later.
Treatment Modification and Simplification

Once a complicated drug regimen has suppressed viremia, patients and physicians would like to simplify treatment. When the PI is replaced by an NNRTI, viral suppression persists for at least 2 years. It is also possible to replace a PI+2NRTI combination with the three NRTIs ABC/AZT/3TC, provided that patients had received no antiretroviral drugs before starting triple therapy. Scheduled treatment interruptions have been evaluated in clinical trials, the largest of which (the SMART trial) showed a 1.6% per year increase in AIDS and death among those who interrupted treatment, compared to those who continued therapy. These AIDS/death events were more frequent in those with lower CD4 counts. When treatment is interrupted, it would seem prudent to limit the length of interruption to less than four months, and to start treatment again before the CD4 count falls below 350 per cubic millimeter.

Procedures in Case of Failure

Treatment must often be changed because of intolerance, drug interactions, or side effects. If viremia is below 50 copies per cubic millimeter, a single offending drug can be replaced. In cases of lipodystrophy replacement of stavudine, ddi or AZT with tenofovir or abacavir may be helpful: however, patience is necessary, as an increase in limb fat usually takes over 6 months. In cases of virologic failure—that is, viremia that does not decline to fewer than 50 copies per cubic millimeter after 6 months (9 months if the initial viremia exceeded 1 million copies per cubic millimeter) or that rises to more than 200 copies requires a different approach. In this situation, a new combination should be chosen, containing (if possible) a drug from a class that has not already been used. At least one additional drug should also be replaced by another to which the patient is unlikely to be resistant, given personal medication history and resistance tests.

However, changes to new therapy are not automatic, especially in patients who have experienced long-standing failure, with exposure to many drugs. Such patients often maintain CD4 counts at relatively high levels and are thus protected against clinical complications. On the other hand, salvage regimens may be ineffective or toxic, and drug holidays may produce falling CD4 counts. Maintenance of a virologically failing regimen is therefore often the best option.

Start and End of Prophylaxis for Opportunistic Infections

Efficacious antiretroviral treatment—provided that it is started in time—prevents immune deficiency and obviates the need for prophylaxis of opportunistic infections. Even if started late, effective HAART is followed by immune reconstitution. Prophylaxis of opportunistic infections can be discontinued after the patient's CD4 count has risen above a given level for at least 3 months. This level is 100/μm³ for stopping prophylaxis of CMV and non-tuberculous mycobacteria, and 200/μm³ for stopping prophylaxis of PJP and Toxoplasm encephalitis.

CONCLUSIONS AND OUTLOOK

Antiretroviral treatment has profoundly changed the prognosis of HIV infection, but such treatment is complex. Chances for success are best in the previously untreated; therefore, every effort must be made to optimize the first treatment given. A specialist should be consulted when starting or changing antiretroviral treatment. Compliance remains essential for treatment success; all drugs must be taken as prescribed. In asymptomatic patients with CD4 counts above 350/μm³, it is better to abstain than to risk failure through insufficient treatment. Talking reluctant patients into accepting drugs makes no sense; refusal of HAART must be respected.

Treatments continue to evolve. In 2006, a once-a-day combination pill combining efavirenz, FTC and tenofovir (Atripla) has become available. Drugs for new targets will follow. Within 5 years, judicious use of strategic treatment interruption and of immune stimulation may permit survival in good health, without drugs, at least for some patients.

KEY POINTS

About Failing Regimens

1. A new combination should be chosen, containing (if possible) a drug from a class that has not already been used.
2. At least one additional drug should also be replaced by another to which the patient is unlikely to be resistant.
3. In the absence of alternatives, a virologically failing regimen should be maintained. Such a regimen often preserves the CD4 count.

RESPECTING PATIENT CHOICE

It makes no sense to talk reluctant patients into accepting drugs; refusal of HAART must be respected.
A 28-year-old black man was admitted to the hospital with a 3-week history of progressive shortness of breath accompanied by a nonproductive cough. Two weeks earlier, he had been seen by his local doctor for the same complaints and had been given an oral antibiotic at that time. He noted no improvement in his symptoms.

An epidemiologic history noted that the patient reported multiple episodes of unprotected homosexual intercourse 3 years earlier, but several months’ abstinence recently. The patient denied intravenous drug use and said that he had never smoked cigarettes. This was an anxious-appearing man who was short of breath.

On physical examination a temperature of 38.2°C, a pulse of 120 per minute, a blood pressure of 110/60 mm Hg, and a respiratory rate of 34 per minute were recorded. No lymphadenopathy was evident, but white plaques consistent with thrush were seen on the posterior pharynx. Breath sounds were clear, with no rales or rhonchi. A II/VI systolic ejection murmur was not, but no rubs or gallops. No organomegaly was evident on abdominal exam, and the genitalia was within normal limits. Skin was clear, and no edema of the extremities was noted.

On laboratory workup, arterial blood gases measured pH 7.44, PaCO₂ 32 mm Hg, PaO₂ 62 mm Hg, HCO₃ 20 mEq/L on room air. Chest x-ray revealed bilateral, interstitial, diffuse, fluffy infiltrates forming a butterfly pattern. Bronchial lavage with Giemsa stain revealed P. jiroveci (Figure 17.2).

The patient was started on intravenous methylprednisolone and trimethoprim–sulfamethoxazole. His shortness of breath gradually improved over the next 3 days, and he was discharged on oral trimethoprim–sulfamethoxazole. An antibody test for HIV was positive, subsequently confirmed by Western blot. The patient’s CD4 count was 150/μm³.
tests on initial evaluation are necessary for a timely start to prophylaxis.

Opportunistic infections have a tendency to relapse. Therefore, as long as the underlying immune deficiency is not corrected, secondary prevention is necessary. Of course, preventive therapy has risks and side effects such as allergies, drug interactions, and development of resistance, but the risk–benefit ratio has been proven favorable, especially for prevention of PCP and cerebral toxoplasmosis by trimethoprim–sulfamethoxazole. On the other hand, once antiretroviral therapy is efficacious and the patient’s CD4 count has risen durably above 200/μm³, these preventive measures can be discontinued. Table 17.9 summarizes the common preventive regimens.

**PULMONARY INFECTIONS**

The differential diagnosis of pulmonary disease in HIV-infected patients depends on the patient’s epidemiologic history (presence of intravenous drug abuse, previous episodes of bacterial pneumonia, exposure to tuberculosis), CD4 lymphocyte count, and use of preventive therapy. (see Table 17.9)
During the early years of the AIDS epidemic, PCP was the initial opportunistic infection in one third of cases. The infection remains frequent, but its incidence has greatly decreased because of the use of trimethoprim–sulfamethoxazole and HAART. Bacterial pneumonia, in particular that caused by *Streptococcus pneumoniae*, is 10 to 100 times more frequent in HIV-positive than in HIV-negative patients. Tuberculosis can occur at any degree of immune deficiency, but it is particularly frequent in patients who grew up in developing countries.

With a lobar infiltrate in a patient with a CD4 count above 200/µm³, the presumptive diagnosis is bacterial pneumonia. Empiric treatment should start with amoxicillin–clavulanate, a cephalosporin, or one of the quinolones with activity against gram-positive bacteria. If immune deficiency is more profound (CD4 count is below 200/µm³), PCP is most likely, except if the patient has faithfully taken trimethoprim–sulfamethoxazole prophylaxis. The chest x-ray pattern is usually normal. Chest radiographs, which can be normal, typically show a reticulonodular bilateral infiltrate that can be asymmetrical (see Table 17.11 and Figure 17-2). Classically, the infiltrates form a butterfly pattern, mimicking pulmonary edema associated with left-sided congestive heart failure. Occasionally, a standard chest x-ray shows cystic lesions or a pneumothorax. When PCP prophylaxis is delivered by pentamidine inhalation, the chest x-ray is often atypical, with asymmetrical infiltrates limited to the lung apex.

### Table 17.10. Lung Diseases Linked to HIV

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Signs and symptoms</th>
<th>Laboratory results</th>
<th>Radiology</th>
<th>Initial treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial pneumonia</td>
<td>Rapid onset of fever, dyspnea, cough, and sputum production</td>
<td>Leukocytosis with neutrophilia; blood cultures often positive</td>
<td>Lobar or diffuse infiltrate</td>
<td>Amoxicillin–clavulanate or cephalosporin</td>
</tr>
<tr>
<td>(<em>Streptococcus pneumoniae</em>)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumocystis jiroveci pneumonia</td>
<td>Fever, dyspnea, cough for several weeks; auscultation is usually normal</td>
<td>Hypoxemia, elevated lactate dehydrogenase; diagnosis through bronchoalveolar lavage</td>
<td>Diffuse reticulonodular interstitial infiltrate</td>
<td>Trimethoprim–sulfamethoxazole</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Weight loss, fever, cough, night sweats, lymphadenopathy</td>
<td>Positive sputum smear by Ziehl stain; positive sputum and blood cultures; typical histopathology of lymph nodes</td>
<td>Mediastinal adenopathy; variable pulmonary infiltrate; cavitary upper lobe lesions are rare</td>
<td>Isoniazid, plus rifampin, plus pyrazinamide, plus ethambutol</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>Usually associated with skin or mucosal lesions</td>
<td>Typical lesions seen on bronchoscopy</td>
<td>Nodular infiltrates with perihilar location</td>
<td>Treatment for HIV; rarely requires radiotherapy or chemotherapy</td>
</tr>
<tr>
<td>Interstitial lymphoid pneumonia</td>
<td>Transitory fever and dyspnea</td>
<td>No specific findings</td>
<td>Reticulonodular infiltrates</td>
<td>Possibly steroids; diagnosis by exclusion!</td>
</tr>
</tbody>
</table>
Tests of the peripheral blood are usually nonspecific, but lactate dehydrogenase (LDH) is found to be elevated in more than 90% of patients with *Pneumocystis* infection. Higher values and a persistent elevation despite appropriate therapy are associated with a poorer prognosis. The $^{67}$Ga citrate scan is very sensitive and demonstrates increased uptake in infected areas of the lung. However,
HIV INFECTION

Gallium scan is most useful in patients with suspected PCP who have a normal chest x-ray.

The diagnosis of PCP is established by special stains of bronchoalveolar lavage fluid or of sputum induced by a 30-minute inhalation of 3% NaCl. If clinical suspicion of PCP is high, starting treatment before confirmation of the diagnosis is recommended, because PCP can still be found in lavage fluid 1 to 3 days later. In rare cases, the diagnosis may necessitate a transbronchial biopsy—particularly if pentamidine inhalations have been used.

Treatment modality will depend on the gravity of PCP. Patients who are very short of breath, with a PaO₂ of less than 70 mm Hg, particularly if accompanied by nausea or vomiting, will usually be admitted to hospital and treated intravenously. If signs of grave disease are absent, and if the patient is not nauseated, outpatient treatment is possible. The drug of choice is high-dose trimethoprim–sulfamethoxazole, 2 double-strength tablets (sulfamethoxazole 1600 mg and trimethoprim 320 mg every 8 hours for 21 days), followed by secondary prophylaxis with sulfamethoxazole 400 mg and trimethoprim 80 mg daily until the patient’s CD4 count durably exceeds 200/µm³.

Trimethoprim–sulfamethoxazole has numerous side effects, of which drug rash is the most frequent. If the skin lesions are extensive (and, in particular, if mucosal involvement is evident), if leukopenia and thrombocytopenia are severe, or if renal or hepatic toxicity or serious vomiting occurs, alternative treatment is necessary. In an attempt to reduce the incidence of bone marrow suppression, folinic acid has been added to the treatment regimen; however, it diminishes the efficacy of treatment and is not recommended. Many alternatives to trimethoprim–sulfamethoxazole are available, but their efficacy is in general inferior, and many have other serious side effects. Table 17.12 summarizes the alternatives.

At the start of the AIDS era, patients with Pneumocystis, even if correctly treated, often experienced increased respiratory distress and worsening lung infiltrates during the first few days. In many cases, this initial deterioration necessitated intubation or caused death. Severe respiratory compromise that necessitates intubation can be prevented by giving steroids (prednisone 1 mg/kg daily for 5 days, then 40 mg daily for 5 days, followed by 20 mg daily for 11 days) in cases of severe pneumocystosis with a PaO₂ below 70 mmHg. Prednisone should be given before or simultaneously with initiation of anti-Pneumocystis therapy.

### Prevention

In HIV patients with CD4 counts below 200/µm³, the annual risk of PCP is roughly 20%. The risk of relapse after a first episode is even higher: 40% after 6 months.

<table>
<thead>
<tr>
<th>Table 17.12. Treatment of <em>Pneumocystis jiroveci</em> pneumonia: trimethoprim–sulfamethoxazole and alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
</tr>
<tr>
<td>Trimethoprim–sulfamethoxazole</td>
</tr>
<tr>
<td>Dapsone, plus</td>
</tr>
<tr>
<td>trimethoprim</td>
</tr>
<tr>
<td>Clindamycin, plus</td>
</tr>
<tr>
<td>primaquine</td>
</tr>
<tr>
<td>Atovaquone</td>
</tr>
</tbody>
</table>

### KEY POINTS

**About Prophylaxis of Pneumocystis jiroveci Pneumonia**

1. In HIV patients with a CD4 count below 200/µm³ not on prophylaxis, the annual incidence of *Pneumocystis jirovecii* pneumonia (PCP) is 20%.
2. Trimethoprim–sulfamethoxazole is the drug of choice: efficacious, inexpensive, and equally active in preventing toxoplasmosis.
3. Alternatives are not as effective:
   a. Dapsone does not cover toxoplasmosis; pyrimethamine must be added.
   b. Pentamidine is associated with cough and asthma.
   c. Atovaquone is expensive.
Primary prophylaxis diminishes the risk of pneumocystis, but if severe immunosuppression persists without HAART, the risk is still 19% after 3 years of prophylaxis with trimethoprim–sulfamethoxazole, and 33% after 3 years of pentamidine aerosols. Primary and secondary prophylaxis strategies use the same treatment options:

- Trimethoprim–sulfamethoxazole 1 double-strength tablet three times weekly, or 1 single–strength tablet daily. Trimethoprim–sulfamethoxazole has the advantages of great efficacy, protection against cerebral toxoplasmosis, and low price. However, almost 50% of patients will develop signs of cutaneous intolerance. Desensitization permits re-administration in most cases, but desensitization has been used mostly in cases of treatment, when alternatives to agents are clearly less satisfactory. The mechanisms of trimethoprim–sulfamethoxazole intolerance are not well understood. Dose dependency is one of the features that argues against “allergy.” Another is the observation that up to 60% of patients who have shown cutaneous intolerance do not relapse when re-exposed.

- Dapsone, 100 mg daily, does not protect against cerebral toxoplasmosis. If anti-Toxoplasma IgG antibodies are present, add pyrimethamine to dapsone. Daily (dapsone 50 mg, plus pyrimethamine 50 mg) and weekly schedules (dapsone 200 mg, plus pyrimethamine 75 mg) are equivalent.

- Pentamidine by inhalation (Respirgard nebulizer), 300 mg every 4 weeks. Some patients, particularly smokers, cannot tolerate inhaled pentamidine because of cough and asthma. Preventive use of a bronchodilator may be helpful.

- Atovaquone 750 mg divided into two daily doses. Well tolerated, but expensive.

### Bacterial Pneumonia

As a complication of HIV infection, bacterial pneumonia produces the same symptoms and signs as pneumonias in HIV-negative patients: sudden onset of fever, chills, cough, and dyspnea. By far the most frequent cause is S. pneumoniae, but Haemophilus influenzae (particularly in smokers), Staphylococcus aureus, Pseudomonas aeruginosa, and Rhodococcus equi may also be implicated. Bacteremia and relapses are frequent. Empiric treatment consists of amoxicillin–clavulanate, or a second-or third-generation cephalosporin; treatment duration is 10 to 14 days (see Chapter 4).

### Tuberculosis

Tuberculosis usually presents as a subacute disease with weight loss, cough, fever, night sweats, and lung lesions. However, if immune suppression is very advanced, the chest x-ray may be atypical for the disease. Interstitial infiltrates may predominate, without cavitary lesions; CNS tuberculosis becomes more frequent; mediastinal adenopathy is evident on the chest x-ray, and blood cultures are often positive. Diagnosis relies on acid-fast stain of the sputum; however, this test is frequently negative in disseminated (miliary) tuberculosis. For culture, liquid media are recommended because results are more rapid: growth is usually evident by 10 to 14 days, and presumptive identification of Mycobacterium can be made by nucleic acid probes.

Susceptibility testing should always be done, because multiresistant tuberculosis (MDR-TB) is a serious threat to an HIV-positive individual, with mortality exceeding 50%, and extensively resistant tuberculosis (XDR-TB) is associated with a near 100% mortality in HIV patients. Initial treatment should include four drugs: oral isoniazid 300 mg daily (plus vitamin B _6_), rifampicin 600 mg daily, pyrazinamide 20 to 30 mg/kg daily, and ethambutol 15 mg/kg daily. This quadruple therapy should be continued during the first 2 months, followed by isoniazid and rifampicin for a further 7 months. Patients respond well to classic antituberculous treatment, but without HAART and reversal of the underlying immune deficiency, a high risk remains of persistent disease and death as a consequence of other complications of AIDS. In cases of isoniazid or rifampicin resistance (or both), consultation with a specialist is advised.

The co-administration of HAART and treatment for TB is a particular problem: on the one hand, PIs and rifampicin mutually modify one another’s plasma levels;
on the other hand, concomitant administration of seven or more drugs may be toxic to the liver and gut. In addition, immune reconstitution disease caused by HAART is difficult to distinguish from paradoxical inflammatory reactions that are sometimes observed at the start of anti-TB treatment. If immune suppression is not very advanced, it is often more reasonable to postpone HAART for a few months while anti-TB drugs take effect.

**Mycobacterium Kansasii**

In HIV-positive patients, *M. kansasii* causes a disease resembling classical TB with fever, cough, weight loss, and pulmonary infiltrates predominating at the apex. Very occasionally, apical cavities are observed. Classical antituberculous drugs such as isoniazid, rifampicin, and ethambutol are efficacious.

**Mycobacteria Other Than Tuberculosis**

*Mycobacterium avium intracellulare* (and similar mycobacteria) do not usually cause pulmonary disease, but rather a systemic illness with fever, weight loss, night sweats, and liver involvement. However, mycobacteria other than tuberculosis (MOTT) are frequently found in sputum, where their pathogenic significance remains uncertain.

**Pulmonary Kaposi’s Sarcoma**

In patients with obvious cutaneous Kaposi’s sarcoma, involvement of the mucosal surfaces is frequent (30% to 50% of cases) and, in general, asymptomatic. When lung is involved, the chest x-ray shows reticulonodular infiltrates with a perihilar distribution, hilar lymphadenopathy, and occasionally, pleural effusions [Figure 17.3(D)]. Treatment with radiotherapy or chemotherapy is indicated for relief of cough or dyspnea. In general, lung lesions, like other manifestations of Kaposi’s sarcoma, improve on antiretroviral combination therapy.

**Other Rare Pulmonary Diseases**

**Interstitial Lymphoid Pneumonia**

Interstitial lymphoid pneumonia is usually diagnosed by exclusion. It is particularly frequent in children and presents with fever and dyspnea. The chest x-ray shows reticulonodular infiltrates that may vary and disappear spontaneously. Pathogenesis is not clear; HIV itself may perhaps be implicated. Treatment relies on corticosteroids.

**Histoplasmosis**

In contrast to the localized pulmonary disease observed in immunocompetent populations (see Chapter 4), histoplasmosis in AIDS is often disseminated and accompanied by anemia, enlargement of liver and spleen, and positive blood cultures. Gastrointestinal involvement with ulcers, skin lesions, and lymphadenopathies are also frequent. The diagnosis is established by blood or bone marrow culture. Treatment relies on amphotericin B or fluconazole.
Coccidiomycosis

Coccidiomycosis is restricted to the southwestern United States and to Central America. Symptoms are fever, cough, and reticulonodular infiltrates. Diagnosis relies on culture of sputum or bronchoalveolar lavage fluid. Treatment is by amphotericin B (0.5 to 1 mg/kg daily) or fluconazole (400 to 800 mg daily).

Disseminated Toxoplasmosis

Rarely, and only in the presence of extreme immunosuppression (CD4 count below 20), *Toxoplasma gondii* can cause a devastating disseminated disease, with prominent lung involvement. Typically, the lactate dehydrogenase (LDH) is extremely elevated. Toxoplasma organisms can be seen in the bronchoalveolar lavage. This form of toxoplasmosis is treated like cerebral toxoplasmosis.

Nocardia asteroides

*N. asteroides* is a cause of chronic pneumonia and nodular pulmonary lesions. Other organs than the lung, such as the kidney and the brain, can be involved. The disease is diagnosed by direct stain of the sputum, where delicate, gram-labile, branched filaments are detected. Treatment relies on prolonged administration of high doses of trimethoprim-sulfamethoxazole; alternatives are imipenem and the newer fluoroquinolones.

Invasive Aspergillosis

Aspergillosis is often a terminal complication with a disastrous prognosis in hospitalized patients who have received steroids and are experiencing neutropenia. Cardiac and CNS lesions may be associated with pneumonia.

Rhodococcus Equi

*Rhodococcus* causes cavitary acute pneumonias that carry a very somber prognosis. Contact with horses is found in about half of patients. Treatment relies on vancomycin, which can be combined with ciprofloxacin. Other regimens include imipenem, amikacin, or rifampin.

Gastrointestinal System

Also see Chapter 8 for a discussion of infections that can affect both immunocompetent and immunocompromised individuals.

Oral Cavity and Esophagus

Candidiasis

Candidiasis is the most frequent of the opportunistic infections, occurring in virtually all HIV-positive patients with severe immunosuppression. Usually, oral candidiasis presents with yellowish-white plaques on the oral mucosa (“oral thrush”; see Figure 17.4). These

Table 17.13. Gastrointestinal Diseases Associated with HIV Infection

<table>
<thead>
<tr>
<th>Location</th>
<th>Disease</th>
<th>Cause</th>
<th>Signs and symptoms</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>Thrush</td>
<td>Candida stomatitis <em>(Candida albicans)</em></td>
<td>Whitish plaques</td>
<td>Inspection</td>
</tr>
<tr>
<td></td>
<td>Leukoplakia</td>
<td>Epstein–Barr virus</td>
<td>Whitish spots with irregular surface on margin of tongue</td>
<td>Inspection and biopsy</td>
</tr>
<tr>
<td></td>
<td>Aphthous ulcers</td>
<td>Herpes simplex, Cytomegalovirus <em>(CMV), idiopathic or unknown</em></td>
<td>Painful erosions of about 5 mm</td>
<td>Culture or biopsy</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Candida esophagitis</td>
<td><em>Candida albicans</em></td>
<td>Dysphagia, retrosternal pain with coexisting Candida stomatitis</td>
<td>Clinical signs and symptoms, endoscopy</td>
</tr>
<tr>
<td></td>
<td>Ulcers and erosions</td>
<td>Cytomegalovirus, or herpes simplex</td>
<td>Dysphagia and retrosternal pain</td>
<td>Endoscopy (longitudinal ulcers) and histology</td>
</tr>
<tr>
<td>Stomach</td>
<td>Gastritis</td>
<td><em>Candida, CMV, herpes, Helicobacter pylori?</em></td>
<td>Various signs and symptoms, frequently pH is elevated; malabsorption</td>
<td>Endoscopy and biopsy</td>
</tr>
<tr>
<td>Small intestine</td>
<td>Diarrhea</td>
<td><em>Cryptosporidium, Isospora belli, Enterocytozoon bieneusi, Salmonella, Shigella, Campylobacter</em></td>
<td>Chronic watery diarrhea; loss of weight; malabsorption</td>
<td>Examination of feces</td>
</tr>
<tr>
<td></td>
<td>Malignant lymphoma</td>
<td>CMV?</td>
<td>Loss of weight; intestinal obstruction; perforation</td>
<td>Computed tomography scan and biopsy</td>
</tr>
<tr>
<td>Biliary system</td>
<td>Cholangitis</td>
<td>CMV? <em>Cryptosporidium? HIV? Microsporidium?</em></td>
<td>Epigastric pain, nausea, anorexia, weight loss</td>
<td>Endoscopy or x-ray examination showing segmental stenosis without gallstones</td>
</tr>
<tr>
<td>Liver</td>
<td>Hepatitis</td>
<td><em>Mycobacterium avium intracellulare</em></td>
<td>Fever; weight loss; abdominal pain</td>
<td>Biopsy or blood culture</td>
</tr>
<tr>
<td>Colon</td>
<td>Colitis</td>
<td>CMV or herpes simplex</td>
<td>Diarrhea; abdominal; pain tenesmus</td>
<td>Biopsy</td>
</tr>
</tbody>
</table>

plaques detach easily, revealing reddish mucosa beneath. The erythematous form of candidiasis consists of brilliant red spots on the tongue or palate. Candidiasis can also present as angular cheilitis or perlèche. The clinical diagnosis is usually evident; cultures are difficult to interpret, because *Candida* is found in the mouth of many people without stomatitis.

Often, *Candida* stomatitis is associated with esophagitis, which may cause dysphagia and retrosternal pain. *Candida esophagitis* is one of the designated AIDS-defining opportunistic infection; patients with this complication are stratified into class C. Patients with stomatitis only are stratified into class B.

Oral imidazoles, especially fluconazole, have become the treatment of choice. In previously untreated patients, single doses of 150 to 400 mg are effective. Options for subsequent management vary. Relapses can be prevented by HAART’s reversal of immune suppression. If achieving...
reversal is not possible, some physicians prefer to wait for a relapse, which they then re-treat; others favor preventive therapy—for instance, fluconazole 50 mg daily or 150 mg weekly.

After years of intermittent treatment or prevention, relapses become more frequent and resistance of *Candida* is common. Such cases may present difficult problems of management. Other imidazoles—such as itraconazole solution, voriconazole, or ketoconazole—may remain effective. In other cases, intravenous therapy with amphotericin B at doses of 20 to 30 mg daily, are necessary. Newer agents such as the echinocandins (See Chapter 1) are easier to administer.

**MOUTH ULCERS AND APHTHOUS STOMATITIS**

Superficial lesions of the oral and esophageal mucosa can cause pain and dysphagia. Differential diagnoses includes herpes simplex, CMV, medication side effects (f), and idiopathic ulcers. If the lesion persists, a biopsy with viral culture or immunofluorescence is often necessary for diagnosis.

**ORAL HAIRY LEUKOPLAKIA**

Oral hairy leukoplakia, a whitish lesion with an irregular border located along the lateral part of the tongue, is caused by Epstein–Barr virus. Often, the lesion is bilateral. Histology shows epithelial hyperplasia. Usually, treatment is not necessary, but in resistant cases, topical application of podophyllotoxin can be effective. Acyclovir can also be administered, but usually it causes only temporary regression of the lesions (see Chapter 15).

**TUMORS**

Kaposi’s sarcoma frequently involves the oral cavity. It produces painless macules or nodules with characteristic purple coloration on the palate, gingivae, or tongue.

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**KEY POINTS**

**About Oral Candidiasis**

1. Develops in all HIV-infected patients with serious immunocompromise.
2. Typically seen as white plaques that detach when scraped, or as red spots on the tongue and palate.
3. Often accompanied by esophagitis, an AIDS-defining illness.
4. Fluconazole is the treatment of choice.
5. Recurrent pharyngitis is common; suppression often results in resistance.

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**KEY POINTS**

**About Esophagitis in HIV**

1. *Candida albicans* is the most common cause.
2. Cytomegalovirus is less common, causing longitudinal ulcers and viral inclusions on biopsy.
3. Herpes simplex virus type 1 is moderately frequent; type 2 and herpes zoster are less common. Diagnosis is made by culture or immunofluorescence.
4. Thalidomide may help idiopathic esophageal ulcers.

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**SALIVARY GLANDS**

Benign lymphoepithelial lesions and cystic hyperplasia involve mostly the parotid gland. They can be associated with xerostomia. The clinical picture is similar to that in Sjögren’s syndrome. The parotid lesions are particularly frequent in children; they are attributed to HIV itself.

**DIFFERENTIAL DIAGNOSIS OF ESOPHAGITIS**

As noted earlier, the most frequent cause of esophagitis is infection by *Candida albicans*. However, when esophageal symptoms occur in a patient who does not have clear evidence of *Candida stomatitis*, other causes must be sought.

- Cytomegalovirus causes longitudinal ulcers. The lesion can be diagnosed only by biopsy: characteristic viral inclusions are seen in endothelial, epithelial, or smooth-muscle cells.
- Involvement of the esophagus by herpes is most often caused by herpes simplex type 1 and less commonly by herpes type 2 or by herpes zoster. Lesions are typically small. Diagnosis is made by biopsy plus immunofluorescence, or culture, or both.
- Idiopathic ulcer is a diagnosis by exclusion. Treatment with thalidomide may bring relief.

**Small and Large Intestine**

**DIARRHEA**

Diarrhea associated with weight loss is one of the hallmarks of AIDS, particularly in Africa, where AIDS, diarrhea, and weight loss are practically synonymous (“slim disease”). Infection with HIV itself, plus many opportunistic pathogens and tumors, can involve the small and large intestine and cause diarrhea. The differential diagnosis is vast. This subsection briefly comments on the most frequent causes (also see Chapter 8).
Drugs. Many of the antiretroviral drugs can cause diarrhea—in particular all protease inhibitors, and didanosine. Because patients with HIV often receive antibiotics, the possibility of colitis associated with *Clostridium difficile* must often be considered, and the *C. difficile* toxin must be sought in feces.

*SALMONELLA, CAMPYLOBACTER, SHIGELLA.* These organisms are frequent causes of acute gastroenteritis both in non-HIV and HIV-infected populations. In HIV infection, bacteremia is extremely frequent, particularly as a result of infection with *S. typhimurium* or *S. enteritidis.*

**ABDOMINAL TUBERCULOSIS.** Abdominal tuberculosis presents with fever, pain, weight loss, or obstruction. These symptoms are difficult to distinguish from those of abdominal lymphoma. Often, the diagnosis is made only at laparoscopy.

**MOTT.** Infections with “mycobacteria other than tuberculosis” are often caused by *M. avium,* but other mycobacterial species cause similar clinical signs and symptoms, and may be more difficult to diagnose, because they grow poorly in culture (for instance, *M. genavense*). The MOTT organisms cause a systemic illness with fever, weight loss, and positive blood cultures. In biopsies of the gastrointestinal tract, the submucosa may be filled with characteristic acid-fast microorganisms. Diarrhea and abdominal pain dominate the clinical picture.

**CYTOMEGALOVIRUS COLITIS.** Diseases caused by CMV are typically the result of reactivation of latent CMV infection—that is, IgG antibodies against CMV were present before symptoms started—in immunosuppressed patients, usually those with a CD4 count below 50/μm³. Symptoms may be severe, with diarrhea, abdominal pain, tenesmus, and fever. Colonoscopy shows multiple erosions, and biopsies reveal the characteristic intranuclear inclusions. Cytomegalovirus is also implicated in some cases of cholangitis and pancreatitis.

**CRYPTOSPORIDIUM.** In immunocompetent individuals, *C. parvum* causes asymptomatic infections and acute diarrhea. In immunosuppressed patients, diarrhea becomes chronic, causing malabsorption. Oocysts can be found in the feces. No treatment has so far proven effective, although oral paromomycin (500 to 750 mg every 8 hours), macrolides such oral azithromycin (1250 mg daily), oral clarithromycin (500 mg twice daily), and oral albendazole (400 mg daily) can be tried, in addition to symptomatic treatment of diarrhea (loperamide, narcotics).

**MICROSPORIDIA.** Three types of *Microsporidia* are found in cases of diarrhea:

- *Enterocytozoon bieneusi* (most frequent)
- *Encephalitozoon intestinalis* (which can also involve the biliary tract)
- *Encephalitozoon cuniculi*

Some patients do not exhibit symptoms; however, more often, patients experience profuse diarrhea, abdominal pain, and weight loss. Up to 30% of cases of chronic diarrhea in immunosuppressed HIV-positive patients may be a result of *Enterocytozoon bieneusi.* A special stain (modified trichrome stain) reveals the parasite in feces. Past treatments were not very effective, and eradication of the organism was usually impossible. Fumagillin (20 mg three times daily for 2 weeks) clears the spores and prevents relapse in most patients (see Chapter 8). Albendazole (400 mg twice daily) is useful in cases of *Encephalitozoon intestinalis* infection.

**ISOSPORA BELLI.** Diarrheas caused by *I. belli* are frequent in developing countries (in African countries and Haiti, for instance). The treatment of choice is trimethoprim–sulfamethoxazole, which is also effective in primary and secondary prophylaxis.

**RECTUM AND ANUS**

Many HIV-infected patients are at risk for other sexually transmitted infections such as gonococcal proctitis, syphilis, and venereal warts. Herpes simplex can cause rectitis with tenesmus and bleeding; in addition, in severely immunosuppressed patients, herpes simplex may cause persistent and debilitating ulcerations (see Figure 17.5). Such lesions may necessitate admission to hospital and parenteral therapy with high-dose acyclovir. Resistance to acyclovir may develop; the alternative treatment is foscarnet. Less commonly, such ulcerations can be caused by CMV.
Anal and rectal carcinoma are particularly frequent among homosexual patients. The development of this tumor is related to the human papilloma virus. Screening programs in homosexual patients for this virus have been considered, analogous to those that screen for cervical cancer, as well as vaccination of adolescents. However, these are not yet part of routine clinical practice.

**Tumors of the Digestive System**

**Kaposi’s Sarcoma**

When patients with cutaneous Kaposi’s sarcoma undergo endoscopy, gastric or intestinal involvement is found in about half of cases. However, such involvement is usually asymptomatic, and involvement of the gastrointestinal tract without involvement of skin is rare. Occasional complications include bleeding, obstruction, invagination, and perforations.

**Lymphoma**

The AIDS-associated lymphomas preferentially involve the gastrointestinal tract (and the brain), causing diarrhea, abdominal pain, fever, and weight loss. Symptoms of lymphoma are therefore difficult to distinguish from those of opportunistic infections. Chemotherapy is theoretically effective, but often very difficult to administer to these severely immunosuppressed patients.

**Liver**

**Viral Hepatitis**

Transmission of both HCV and HIV occurs parenterally, which is why HIV–HCV co-infection is particularly common in intravenous drug users and patients with hemophilia. Transmission of HBV occurs sexually, and its incidence is increased in men who have sex with men.

In HIV–HCV co-infection, the two viruses influence one another. Co-infected patients tend to have unfavorable prognostic indices for hepatitis C: higher incidence of HCV type 1 cirrhosis, and higher levels of HCV viremia. Conversely, HCV influences HIV infection: notably, the CD4 response to HAART is less vigorous in co-infected patients than in those infected with HIV alone. Experience with interferon treatment of co-infection is frequent in intravenous drug abusers and patients with hemophilia.

Transmission of HBV occurs sexually, and its incidence is increased in men who have sex with men.

**Figure 17.5.** Herpesvirus group infections (from www.aids-mages.ch) A. Herpes simplex virus 1. These chronic perioral lesions have become resistant to acyclovir. B. Ulcer on the buttocks resulting from infection with herpes simplex virus 2 (diameter: 5 cm). C. Cytomegalovirus retinitis. Left: Initial lesions, showing perivascular sheathing. Right: Later lesions, showing necrosis and hemorrhage. (picture courtesy of E. Baolivo).

See color image on color plate 4
HIV–HCV co-infection was previously disappointing. However, as a consequence of HAART for HIV and combination therapy with pegylated interferon and ribavirin for HCV response to therapy has improved.

Nevertheless, treatment of HCV in co-infected patients remains a challenge. Interactions between liver disease and HAART are frequent and unfavorable, and contraindications to the use of interferon (for instance, a history of depression) and of ribavirin (anemia) are frequent.

Lamivudine (3TC) Lamivudine (3-TC), emtricitabine (FTC), and tenofovir (TDF) are active against both HIV and HBV. In HBV–HIV co-infected patients, HAART that includes lamivudine diminishes HBV viremia. After years of therapy, however, the risk of development of lamivudine resistance is high. Lamivudine-resistant HBV is also resistant to emtricitabine. However, tenofovir remains effective.

Liver Damage Induced by Antiretroviral Drugs
Almost all antiretroviral agents may cause liver damage. However, the nature of that damage varies with the drug:

- The NRTIs occasionally cause severe steatosis associated with elevated plasma lactate levels. This side effect is more frequent with stavudine than with other NRTIs.
- The PIs indinavir and atazanavir cause asymptomatic hyperbilirubinemia (pseudo–Gilbert’s syndrome). Ritonavir and nelfinavir can occasionally cause cholestasis and hepatitis.
- The NNRTIs are also associated with toxic hepatitis. Severe cases, with death and liver transplantation, have been reported after use of nevirapine. Risk factors include female sex, pregnancy, obesity, and CD4 counts above 400. Such severe cases have not been reported with efavirenz.

Central Nervous System
Table 17.14 summarizes the CNS diseases most often seen in HIV infection. See also Chapter 6 for a discussion of infections that can affect both immunocompetent and immunocompromised individuals.

Primary HIV Infection
About half of patients with the acute retroviral syndrome complain of headaches, and in 5% to 20%, clinical signs of meningitis such as neck stiffness or photophobia are evident. Encephalitis, with symptoms ranging from confusion to coma, is rare. In the CSF, lymphocytes predominate, with a cell count of 5 to 200/μm³. Cranial nerve involvement may occur. Symptoms usually disappear spontaneously.

HIV Encephalopathy
The disease called HIV encephalopathy is synonymous with HIV dementia or AIDS-related dementia. This syndrome includes cognitive, behavioral, and motor symptoms and signs. The diagnosis is often one of exclusion, after neuroradiologic and CSF examinations have failed to show an opportunistic disease.

The first signs are usually memory problems, mental slowness, and lack of precision. Apathy and withdrawal may be interpreted as a depression. Clinical examination shows difficulties in comprehension and coordination, abnormal gait, nystagmus, and arcaic reflexes. Without treatment, dementia progresses within a few months. Convulsions may appear. Neuroradiologic investigation usually shows cerebral atrophy. O magnetic resonance imaging (MRI) scan, the T2 signal is increased in the subcortical white matter, preferentially in the parasagittal regions. The CSF shows a variable increase in protein and mononuclear cells.

Since the introduction of HAART, the incidence of HIV dementia has greatly decreased. In established dementia, the effect of HAART is variable, but spectacular improvements are noted in some patients. Despite HAART, many patients continue to complain of subtle symptoms, such as forgetfulness and difficulties with concentration. This may represent a milder form of HIV-related dementia, perhaps related to the lack of penetration of HARRT into the CNS.

Focal CNS Lesions
Cerebral toxoplasmosis, primary cerebral lymphoma, and progressive multifocal leukoencephalopathy (Figure 17-6) cause 90% of focal lesions of the CNS in HIV infection. Differential diagnosis relies upon computed tomography (CT) scan, MRI, and PCR amplification of the DNA from the putative infectious agents in the CSF. Cerebral biopsy remains an option in exceptional cases.

Key Points

About HIV Encephalopathy

1. The diagnosis is made by exclusion.
2. Dementia symptoms are accompanied by apathy and withdrawal that can be mistaken for depression.
3. Magnetic resonance imaging shows an increased T2 signal in the subcortical white matter preferentially in parasagittal regions.
4. Highly active antiretroviral therapy has dramatically decreased the incidence of HIV dementia.
Table 17.14. Central Nervous System Involvement in HIV Infection

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Symptoms and signs</th>
<th>Laboratory and CSF findings</th>
<th>CT/MRI/PET–SPECT findings</th>
<th>Treatment of choice</th>
<th>Evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral toxoplasmosis</td>
<td>Focal deficit, headache, fever, seizures</td>
<td>CD4 count &lt;200/µL; presence of IgG antitoxoplasmosis antibodies; PCR positive if untreated</td>
<td>Multiple corticomedullary lesions with contrast enhancement; edema; PET scan shows hypodense lesions</td>
<td>Sulfadiazine, plus pyrimethamine, plus folinic acid</td>
<td>Better than 80% response to treatment Prophylaxis until immune reconstitution</td>
</tr>
<tr>
<td>Primary cerebral lymphoma</td>
<td>Slow onset of reduced consciousness, headache, or focal deficits</td>
<td>CD4 count &lt;100/µL; CSF PCR always positive for EBV; cytology is seldom positive</td>
<td>Variable number of lesions; periventricular contrast enhancement; lesions are positive in PET scan</td>
<td>Radiotherapy with or without chemotherapy</td>
<td>Very serious prognosis</td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy</td>
<td>Progressive decline in superior cerebral functions, focal lesions</td>
<td>CD4 count &lt;100/µL; CSF usually positive for papovavirus JC</td>
<td>Reduced density of white substance on CT, no contrast enhancement or edema; increased T2 signal in MRI without gadolinium enhancement</td>
<td>No specific treatment; cidofovir (?); intensify anti-HIV treatment</td>
<td>Has improved since HAART</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>Fever, headache; meningeal signs can be present or absent</td>
<td>CD4 count &lt;100/µL; blood and LCR positive for cryptococcal antigen; direct stain of CSF</td>
<td>No useful information</td>
<td>Amphotericin B with or without flucytosine, or fluconazole</td>
<td>Better than 80% response; prophylaxis with fluconazole until immune reconstitution</td>
</tr>
<tr>
<td>HIV encephalopathy and dementia</td>
<td>Cognitive and motor impairment</td>
<td>CD4 &lt;200/µL; rise in HIV in the CSF; moderate rise in CSF cells and proteins</td>
<td>Cortical or subcortical atrophy; MRI shows enhanced T2 signal</td>
<td>Intensify antiretroviral treatment</td>
<td>Progressive dementia within a few months</td>
</tr>
<tr>
<td>Aseptic meningitis</td>
<td>Headache, neck stiffness, photophobia, nausea during primary HIV infection</td>
<td>Moderate or no immunosuppression; moderate rise in CSF cell count</td>
<td>Normal</td>
<td>No specific treatment</td>
<td>Spontaneous resolution</td>
</tr>
<tr>
<td>CMV encephalitis</td>
<td>Confusion, lethargy, cranial nerve palsies, nystagmus</td>
<td>CD4 &lt;50/µL; PCR in the LCR is positive</td>
<td>Periventricular contrast enhancement</td>
<td>Foscarnet and ganciclovir</td>
<td>Bad prognosis</td>
</tr>
</tbody>
</table>

CSF = cerebrospinal fluid; CT = computed tomography; MRI = magnetic resonance imaging; PET–SPECT = positron emission tomography–single-photon emission computed tomography; IgG = immunoglobulin G; PCR = polymerase chain reaction; EBV = Epstein–Barr virus; LCR.
HIV INFECTION

TOXOPLASMA ENCEPHALITIS

Toxoplasma encephalitis (Figure 17.6) follows from reactivation of latent Toxoplasma infection. Such latent infection is present in 10% (in the United States) to more than 90% (in developing countries) of HIV-infected people.

Toxoplasma encephalitis usually starts with a focal deficit (hemiplegia, for instance), convulsions, headaches, fever, or confusion. In a preponderance of cases, the CD4 count is below 200/μm³, and if performed, testing for Toxoplasma IgG antibody will be positive. If antibody is absent, or if the patient has taken trimethoprim–sulfamethoxazole prophylaxis, another diagnosis should be considered first. The CT or MRI scan shows abscesses that are usually multiple and preferentially located at the corticomedullary junction and in the basal ganglia. Annular contrast or gadolinium enhancement is typical, as is marked edema.

If the IgG antibody are positive and the images are typical, empiric treatment is warranted. If the diagnosis is


KEY POINTS

About Central Nervous System Toxoplasmosis

1. Usually presents with focal findings, in the presence of a CD4 count below 200/μm³ and a positive test for Toxoplasma immunoglobulin G antibody.
2. Computed tomography (CT) or magnetic resonance imaging (MRI) scan demonstrates multiple contrast-enhancing ring-like lesions.
3. Empiric treatment is indicated if symptoms and MRI findings are typical. Polymerase chain reaction testing of the cerebrospinal fluid is confirmatory.
4. Treat using a combination of sulfadiazine and pyrimethamine, with added folinic acid.
5. Follow-up CT or MRI scan at 2 weeks should demonstrate improvement.
6. After treatment, secondary prophylaxis is required.
in doubt, *Toxoplasma gondii* DNA can be amplified from the CSF. The rate of DNA positivity decreases when PCR is attempted after treatment has already started. The treatment of choice is a combination of oral sulfadiazine (1 to 1.5 g every 6 hours) and oral pyrimethamine (200 mg the first day, then 50 mg every 6 hours) combined with folic acid (10 mg daily) to prevent bone marrow toxicity. Steroids (intravenous dexamethasone 4 mg every 6 hours) may be administered to diminish the cerebral edema. This treatment should be continued for 4 to 6 weeks; after that, secondary prevention using oral sulfadiazine 2 g daily and oral pyrimethamine 25 mg daily is indicated. The foregoing regimen will also prevent PCP. After 2 weeks, improvement on repeat brain CT or MRI scan is expected.

Often, treatment of toxoplasmosis is not well tolerated because of cutaneous, renal, or hepatic toxicity from sulfadiazine and bone marrow toxicity from both sulfadiazine and pyrimethamine. As an alternative, clindamycin (600 mg every 6 hours, and then 600 mg every 12 hours) can be combined with pyrimethamine; tolerance of that regimen is usually better, but efficacy is reduced. Another alternative is atovaquone suspension (750 mg every 12 or 8 hours) combined with pyrimethamine.

**PRIMARY BRAIN LYMPHOMA**

HIV infected patients can develop highly malignant B cell brain lymphoma consisting of large immunoblastic lymphocytes. The tumor always contains the genome of Epstein–Barr virus. Clinical signs usually progress rapidly over a few weeks, with confusion, focal signs, and headache. A CT or MRI scan shows one or several lesions with irregular contrast enhancement and preferential periventricular localization (Figure 17.6). Occasionally, lymphomatous cells can be seen in the CSF, where PCR for Epstein–Barr virus is almost always positive. Newer techniques such as single-photon emission computed tomography and positron emission tomography show hyperactivity in the lesions and are useful to differentiate lymphoma from cerebral toxoplasmosis and from progressive multifocal leukoencephalopathy. Although these tumors are sensitive to radiation and to chemotherapy, the prognosis is poor. Long-term survivors are predominantly those with CD4 counts above 200/μm³ at diagnosis.

**PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY**

Progressive multifocal leukoencephalopathy follows reactivation of papovavirus JC, to which 75% of the population is seropositive. The virus infects oligodendrocytes, which are localized in the white matter. Their destruction causes demyelinization.

The disease starts insidiously with loss of memory or dysphasia, visual disturbances, aphasia, or motor signs—or, more rarely, with convulsions. A CT or MRI scan shows one or several subcortical lesions without contrast enhancement or edema (Figure 17.6). Usually, a PCR test of the CSF is positive for papovavirus JC. No specific treatment is available (cidofovir and cytosine arabinoside have been tried, with inconsistent results). HAART is a double-edged sword; after starting HAART symptoms may worsen; however over time stabilization and even clinical improvement may ensue.
Meningitis

Cryptococcal Meningitis

_Cryptococcus neoformans_, a yeast, is the most frequent cause of meningitis in HIV infected patients. Cryptococcosis occurs in profoundly immunosuppressed patients and is particularly frequent in Africa and in the United States.

The disease usually starts with headaches and fever; curiously, meningeal signs can be absent. The diagnosis can be made by direct examination of CSF stained with India ink, by finding of cryptococcal antigen in the CSF or in the blood, or by culture of CSF or blood. The CSF shows moderate pleocytosis and an increase in protein; however, in some cases, the CSF formula is only minimally abnormal. A CT or MRI scan is noncontributory (see Chapter 6 for a complete discussion).

Treatment in severe cases consists of intravenous amphotericin B (0.7 mg/kg) for at least 2 weeks. Some authorities recommend the addition of flucytosine (25 mg/kg every 6 hours), but that drug has substantial gastrointestinal and bone marrow toxicity. After 2 weeks, the amphotericin B is replaced with fluconazole 400 mg daily for 6 to 10 weeks, and then 200 mg daily until immune function recovers. In less severe cases (without intracranial hypertension, with normal mental status, and with cryptococcal antigen in the CSF at less than 1:1000 dilution), fluconazole can be used from the start. Itraconazole is not a good choice because it does not penetrate well into the CSF.

CNS Infection by Cytomegalovirus

Cytomegalovirus can cause various nervous system diseases in HIV infection: polyradicular myelitis, peripheral neuropathy, and encephalitis. Patients with encephalitis are usually profoundly immunosuppressed with a CD4 cell count below 50/µm³.

Diagnosis is difficult and is usually made after exclusion of other more frequent causes in patients who are confused and lethargic, and who are showing cranial nerve palsies and nystagmus. The typical finding in an MRI or CT scan is periventricular contrast enhancement. A PCR test of the CSF is more than 80% sensitive, and specific. Although foscarnet and ganciclovir should theoretically be effective, the prognosis is unfavorable.

Cerebrovascular Diseases

Cerebrovascular accidents are much more frequent in the HIV-infected populations than in comparable populations of the same age. The pathogenesis is uncertain, but direct involvement of HIV in vasculitis is suspected. Transient ischemic attacks have also been described.

Other Rare Cerebral Disorders

Rare focal diseases in the HIV-infected population include cryptococcoma (in these cases, the cryptococcal antigen test in CSF and blood can be negative), tuberculosis, varicella virus encephalitis, and secondary or tertiary syphilis. In intravenous drug abusers, septic emboli may be associated with cerebral abscesses and mycotic aneurisms.

Peripheral Neuropathy

Distal Symmetric Polyneuropathy

Distal symmetric polyneuropathy may cause painful paresthesia and dysesthesia in hands and feet, associated with diminished reflexes and motor weakness in the legs, and autonomic dysfunction.

These polyneuropathies can be very difficult to manage. Amitriptyline or carbamazepine may be useful. Aggravating circumstances include concomitant vitamin deficiencies, diabetes, alcohol abuse, and use of medications such as dapsone, vincristine, and isoniazid. Among antiretroviral drugs, stavudine cause neuropathy, as do didanosine and lamivudine on occasion. The foregoing drugs can usually be replaced by other nucleosides if necessary.

Inflammatory Demyelinating Polyneuropathy

Inflammatory demyelinating polyneuropathy usually occurs during the early stages of HIV infection. Presentation is similar to that of Guillain–Barré syndrome. With steroids, plasmapheresis, or intravenous immunoglobulins, evolution is usually favorable. In some cases, CMV infection is involved.

### KEY POINTS

**About Cryptococcal Meningitis in HIV**

1. _Cryptococcus neoformans_ is the most common cause of meningitis in HIV-infected patients.
2. Headache and fever are the most common complaints; neck stiffness is absent.
3. Lymphocytosis of the cerebrospinal fluid (CSF) is usual, but the CSF formula may be only minimally abnormal.
   a) India ink test positive.
   b) Antigen testing of the CSF or blood is positive.
   b) Culture of CSF or blood is frequently positive.
4. Treat with amphotericin B with or without flucytosine for 2 weeks; followed with fluconazole.
CHAPTER 17

**MONONEURITIS MULTIPLEX**

Sudden palsies of one or several nerves, including cranial and laryngeal nerves, can occur at any stage of HIV infection. Varicella virus can be the cause in cases of advanced immunodeficiency.

**MYELOPATHY**

Myelopathy presents with gait disturbance, ataxia, spastic paraparesis, and urinary or fecal incontinence. An MRI scan is usually normal, but edema or even enhancing lesions may be seen. Autopsy findings show vacuolization of myelin and an accumulation of macrophages. No specific treatment is available, but potentially reversible causes of myelopathy such as epidural abscess, toxoplasmosis, infection with human T lymphotropic virus type 1, herpes simplex or zoster, CMV, or a vitamin B₁₂ deficit should be excluded.

**OPHTHALMOLOGY**

Also see Chapter 5 for a discussion of infections that can affect both immunocompetent and immunocompromised individuals.

**HIV Retinopathy**

HIV retinopathy is frequent and benign; it does not require treatment. “Cotton wool” exudates are characteristically observed; these correspond to focal lesions of ischemia. Besides exudates, intraretinal hemorrhages, telangiectasias, and microaneurysms may occur; these conditions must be distinguished from retinal lesions caused by diabetes or hypertension. HIV retinopathy does not interfere with vision.

**Cytomegalovirus Retinitis**

Chorioretinitis from CMV occurs in patients with profound immunosuppression (CD4 count below 50/μm³); CMV IgG antibodies are invariably present. Before HAART became available, 25% to 30% of patients with AIDS developed retinitis before death. All patients with HIV should be repeatedly questioned about changes in vision—blurring of vision, loss of central vision or other blind spots, floaters, or flashing lights.

Cytomegalovirus retinitis is a subacute disease in which visual deficits progress within a few weeks. The diagnosis is easily made by examining the retina, which shows a characteristic mix of exudates, hemorrhages, and atrophy. Exudates often sheath the vessels. Without treatment, lesions invariably progress to retinal detachment with progressive loss of vision. Often, both eyes are involved, as are other organs such as the colon, esophagus, or brain.

Treatment starts with high doses of medication, followed by secondary prophylaxis using the same drugs at lower doses. Three drugs are available: ganciclovir, foscarnet, and cidofovir.

**KEY POINTS**

**About Peripheral Neuropathies in HIV**

1. In distal symmetrical polyneuropathy associated with paresthesias and weakness, drugs that cause neuropathy should be discontinued. Treat with amitriptyline or carbamazepine.
2. Treat inflammatory demyelinating polyneuropathy with plasmapheresis or a cytomegalovirus regimen.
3. Mononeuritis multiplex can be caused by varicella virus.
4. Myelopathy can lead to spastic paraparesis; look for reversible causes.

**About Cytomegalovirus Retinitis**

1. Before the advent of highly active antiretroviral therapy, 35% to 30% of AIDS patients developed this infection.
2. Visual symptoms—blurred vision, scotomas, floaters, or flashing lights—are subacute in onset.
3. Retinal findings are characteristic: mix of exudates, hemorrhages, and atrophy; vascular sheathing.
4. Treatment is required to prevent progression to retinal detachment and blindness.
   a) Ganciclovir is the drug of choice; causes bone marrow toxicity, and dosing must be corrected for renal dysfunction.
   b) Foscarnet is associated with renal failure; intravenous NaCl is protective.
   c) Cidofovir, a once-weekly therapy, is associated with renal failure 25% of patients; probenecid and intravenous NaCl are helpful protective measures.
5. Maintenance therapy is required in patients with a CD4 count below 100/μm³; primary prophylaxis reduces the incidence, but is expensive and associated with side effects.
Ganciclovir 5 mg/kg is administered intravenously every 12 hours. Its main side effects are leukopenia and thrombocytopenia. Ganciclovir accumulates in patients with renal failure, and doses have to be adapted. Oral valganciclovir (450 mg BID) has good bioavailability and is as efficacious as iv ganciclovir for treatment as well as for maintenance therapy.

Foscarnet 60 mg/kg is administered every 8 hours. It is nephrotoxic (hydration with 1 L 0.9% NaCl is necessary) and causes numerous electrolyte disturbances (hypocalcemia, hypokalemia, hypophosphatemia, and hypomagnesemia), convulsions, and genital ulcers.

Cidofovir has the advantage of infrequent administration (5 mg/kg once weekly for 2 weeks, then 5 mg/kg every 2 weeks), but it is also nephrotoxic in 25% of patients and may cause neutropenia. Nephrotoxicity can be diminished, but not eliminated, by administering oral probenecid 2 g before the cidofovir and 1 g at 1 and 8 hours after, in conjunction with intravenous NaCl. Particular care is needed when cidofovir is co-administered with tenofovir.

After an initial treatment course lasting at least 2 weeks, doses can be lowered: valganciclovir 450 mg daily, foscarnet 100 mg/kg daily 5 days per week, cidofovir 5 mg/kg every 2 weeks. Treatment with intravenous ganciclovir or foscarnet (or both) necessitates use of a permanent catheter.

Secondary prophylaxis of CMV retinitis is onerous. In patients with a good response to HAART and a durable rise in CD4 count above 100/μm³, treatment can be discontinued without risk of relapse.

Patients with persistently low CD4 counts should be regularly examined so as to detect CMV retinitis and institute early treatment to prevent loss of vision. Preventive administration of oral ganciclovir diminishes the incidence of CMV retinitis by at least 50%. However, because of expense, inconvenience, and side effects, such prevention has not commonly been used. Of course, the best prevention of all is correction of the underlying immunodeficiency by effective HAART.

Retinal Necroses

Retinal necrosis is a medical emergency necessitating treatment within hours. This disease is caused by varicella virus. Two clinical presentations can be distinguished:

1. **Acute Retinal Necrosis.** Acute retinal necrosis (ARN) causes orbital pain and inflammation visible in the anterior ocular segment with hypopyon. At the same time, peripheral retinal necrosis with vasculitis occurs. Without treatment, progression to retinal detachment and blindness is rapid.

Other Infectious Eye Diseases

*P. jiroveci* may occasionally involve the retina. Cryptococcal meningitis may be complicated by papillary edema. Particularly in intravenous drug abusers, *Candida albicans* and other bacteremia may cause retinitis. Uveitis can complicate the administration of rifabutin, particularly when rifabutin levels are boosted by co-administration of macrolides or PIs.

SKIN DISEASES

It is important to recognize skin diseases during HIV infection. The development of a new skin rash often warrants immediate action (see Table 17.15). For instance, new acneiform lesions accompanied by fever suggest primary HIV infection. New onset of a maculopapular total body rash is indicative of a drug reaction. New crops of macular, papular, pustular, or vesicular lesions may represent the first manifestation of an opportunistic infection. Even benign skin diseases may have a major psychological impact when they reveal the patient’s HIV status to the outside world.
### Table 17.15. Skin Diseases in HIV

<table>
<thead>
<tr>
<th>Disease</th>
<th>Signs and symptoms</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute HIV infection</td>
<td>Reddish macules on trunk, face, palms of hands, and soles of feet</td>
<td>Rise in viremia and P24 antigenemia</td>
<td>HAART</td>
<td>Standard screening test for HIV can still be negative</td>
</tr>
<tr>
<td>Oral leukoplakia</td>
<td>Whitish plaques on the lateral aspect of the tongue</td>
<td>Clinical aspect</td>
<td>No treatment</td>
<td>Associated with advancing immunodeficiency</td>
</tr>
<tr>
<td>Kaposi’s sarcoma (result of HHV8)</td>
<td>Macules, papules, or nodules of purple to dark blue color; edema and ulcers are possible</td>
<td>Inspection and histology</td>
<td>HAART; local treatment; cryotherapy, radiotherapy, and systemic chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Bacillary angiomatosis (Bartonella henselae)</td>
<td>Red-to-violet papule or nodule</td>
<td>Histology (culture is difficult)</td>
<td>Antibiotics (macrolides, quinolones, and tetracyclines)</td>
<td>Rare; associated with advanced immunodeficiency</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>Vesicles on a red surface, necrosis, dermatal distribution</td>
<td>Thorough inspection, possibly confirmed by culture and immunofluorescence</td>
<td>Oral valacyclovir, or famciclovir, or acyclovir; in serious cases, IV acyclovir</td>
<td>Chronic and disseminated forms are possible in advanced immunodeficiency</td>
</tr>
<tr>
<td>Seborrheic dermatitis (mold, Malassezia?)</td>
<td>Red and squamous plaques on face and trunk</td>
<td>Inspection</td>
<td>Topical ketoconazole</td>
<td>Prevalence &gt; 30%</td>
</tr>
<tr>
<td>Acute condylomata</td>
<td>Wart-like papules resembling a rooster’s comb</td>
<td>Inspection, or histology and typing of HPV</td>
<td>Curettage, podophyllin, electrocoagulation, or laser</td>
<td>Treat sexual partner at the same time</td>
</tr>
<tr>
<td>Molluscum contagiosum (virus pox)</td>
<td>Umbilicated papules</td>
<td>Inspection and histology</td>
<td>Curettage or electrocoagulation</td>
<td></td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>Painful vesicles or ulcers that can become very large</td>
<td>Inspection, culture, and immunofluorescence</td>
<td>Valacyclovir, or famciclovir; possibly IV acyclovir</td>
<td>Lesions are primarily perianal, vulvar, or peribuccal</td>
</tr>
<tr>
<td>Prurigo nodularis</td>
<td>Isolated, very itchy squamous papules</td>
<td>Histology</td>
<td>Symptomatic treatment</td>
<td>Possibly with UV irradiation</td>
</tr>
</tbody>
</table>

HHV8 = human herpesvirus 8; HPV = human papilloma virus; UV = ultraviolet.

### Primary HIV Infection

Primary HIV infection causes erythematous macules or papules with ill-defined borders and symmetrical distribution on the front and back of the trunk, the face, and sometimes on the palms and soles. The skin lesions neither itch nor hurt. They resemble Gilbert’s pityriasis or the lesions of secondary syphilis, which are the principal differential diagnoses. Other differentials include viral exanthema as a result of Epstein–Barr virus, CMV, rubella, or a toxic or allergic reaction to medication. The lesions persist for a median of 2 weeks, and then fade spontaneously. Less commonly, painful mucosal ulcers occur (Figure 17-1).
Opportunistic Infections with Skin or Mucosal Involvement

**Chronic Herpes Simplex**

In severely immunosuppressed patients, herpes simplex type I or II may cause persistent genital, perianal or perioral ulcerations. Although herpes simplex is by far the most likely causative agent, the differential diagnosis is large, including infections by fungi, mycobacteria, CMV, and varicella virus, and malignant skin tumors. Confirmation is obtained by biopsy and immunofluorescence or by culture of a virus. The preferred treatment is valacyclovir 500 mg or famciclovir 125 mg twice daily. Herpes simplex virus may become resistant to acyclovir and its derivatives, necessitating alternative treatment with foscarnet.

**Herpes Zoster**

Herpes zoster caused by reactivation of varicella virus occurs almost 20 times more frequently in HIV-positive individuals than in HIV-negative individuals of the same age, and the condition can present at any stage of immunosuppression. In the severely immunosuppressed patient, herpes zoster may extend beyond one or two dermatomes, causing atypical, ulcerated, and painful lesions that are difficult to treat. In cases in which the skin lesions are atypical, biopsy with direct immunofluorescence establishes the diagnosis. Particularly in cases in which immune suppression is severe, treatment is indicated: use valacyclovir 1 g every 8 hours or famciclovir 500 mg twice daily. In patients with severe immune suppression, intravenous acyclovir may be preferred.

**Kaposi’s Sarcoma**

Kaposi’s sarcoma is a very unusual “tumor.” Infection by a virus—human herpesvirus 8 (HHV8)—is a necessary but not sufficient condition. Kaposi’s sarcoma appears in patients who are HHV8 seropositive and who have a variable degree of immunosuppression. Very often, Kaposi’s sarcoma is multifocal from the start. Karyotypic anomalies have not been described. Lesions resemble reactive hypoplasia rather than typical malignancies. In the United States and in Europe, Kaposi’s sarcoma is essentially a disease of patients who acquired their HIV infection by homosexual contact. Although cases can occur in patients with a nearly normal CD4 count, immune suppression greatly increases the risk.

The lesions of Kaposi’s sarcoma are macules, papules, or nodules of characteristic purple color. Preferred locations are the extremities, the tip of the nose, and the palate. Often, the lesions are only slowly progressive and do not cause pain. In rare cases, Kaposi’s sarcoma may run an aggressive course with nodular, ulcerated lesions; limb edema; and gastrointestinal and pulmonary involvement. Kaposi’s sarcoma is easy to recognize; when in doubt, a skin biopsy showing vascular proliferation and fusiform cells will yield the diagnosis.

The incidence and severity of Kaposi’s sarcoma is favorably influenced by HAART, which has become the mainstay of treatment. If the lesions persist or enlarge, local treatment by cryotherapy or radiotherapy is recommended. Systemic treatment is necessary in cases with edema of extremities, genitalia, or the face, or in cases of massive visceral involvement. Many chemotherapeutic agents produce remissions, but these are rarely of long duration. For reasons of relative lack of side effects and good efficacy, liposomal preparations of doxorubicin, used at a dose of 40 mg/m² every 2 to 3 weeks are currently popular. The combination of bleomycin 10 mg/m² and vincristine 2 mg is also effective, as is high-dose intravenous α-interferon (up to 50 × 10⁶ U 5 days per week) in patients with a CD4 count above 200/μl.

**Bacillary Angiomatosis**

Bacillary angiomatosis is caused by Bartonella henselae, the agent that is responsible for cat scratch disease (see Chapter 13). In HIV infection, B. henselae causes papules and nodules of a red-to-violet color. These are present in variable numbers, are not painful, and may be ulcerated. Patients are usually febrile and extremely immunosuppressed. Liver (“peliosis hepatitis”) and bone may be involved.
A biopsy with silver impregnation stain can show the *Bartonella* and differentiate the disease from Kaposi’s sarcoma. A serologic test is also available. Prolonged treatment with clarithromycin 500 mg twice daily, azithromycin 250 mg daily, or ciprofloxacin 500 mg twice daily is necessary.

**SEBORRHEIC DERMATITIS**

Seborrheic dermatitis is frequent in the general population. However, in HIV-infected patients, the disease may be particularly severe. Reddish plaques covered by small scales appear on the face (nose, between the eyebrows), the scalp, and the sternum. Ketoconazole creams and shampoos are efficacious.

**MOLLUSCUM CONTAGIOSUM**

The lesions of molluscum contagiosum are caused by poxvirus. The multiple, umbilicated, painless flesh-colored papules or nodules appear particularly on the face and the genitalia. In immunosuppressed patients, they can persist for months and become extremely numerous. The lesions can be destroyed by curettage, electrocoagulation, or cryotherapy. Cidofovir may be effective in extreme cases.

**Drug Reactions**

Drug rashes are frequent during HIV infection and can constitute an emergency. Conjunctivitis or lesions of the buccal mucosa, generalized erythroderma, and detachment of the skin are alarming; these signs necessitate hospitalization and specialized consultation. However, drug rashes are more often mild and will disappear even if the drug is continued—particularly in the case of early reactions to efavirenz and nevirapine. Because alternative treatments often have disadvantages of their own, an effort should be made to “treat through” drug eruptions that are not severe.

**Skin Diseases Aggravated by HIV**

Many common skin diseases—for instance, dryness of the skin, psoriasis, reactions to insect stings, and dermatomycosis—seem to be more severe in patients who also have HIV infection.

**SEXUALLY TRANSMITTED DISEASES**

The occurrence of sexually transmitted diseases (also see Chapter 9) in an HIV-positive patient is a reminder of unsafe sexual practices and an occasion to reinforce educational messages about the need to prevent transmission of HIV.

**Syphilis**

Treatment of syphilis in the HIV-infected individual has elicited a great deal of controversy. Contrary to widespread belief, serologic tests for syphilis are as valid in HIV-infected people as in an uninfected population. The recommended treatment regimens are benzathine penicillin $2.4 \times 10^6$ U intramuscularly at weeks 0, 1, and 2 in cases of secondary or latent tertiary syphilis, and a prolonged course of high-dose intravenous penicillin or ceftriaxone in cases of suspected neurosyphilis.

**FURTHER READING**

Some of the best (and certainly the most up-to-date) resources can be accessed via the Internet.

**General**


**Drug Interactions**


**Epidemiology**


**Up-to-Date Treatment Guidelines**

Varicella-zoster virus (VZV) causes two distinct clinical diseases. Varicella, more commonly called chickenpox, is the primary infection and results from exposure of a person susceptible to the virus. Chickenpox is ubiquitous and extremely contagious, but for the most part, it is a benign illness characterized by a generalized exanthematous rash. It occurs seasonally and in epidemics. Recurrence of infection results in the more localized phenomenon known as herpes zoster, often referred to as shingles, a common infection among the elderly.

Pathogen

VZV is a member of the Herpesviridae family and shares structural characteristics with other members of the family. The virus has icosapentahedral symmetry and contains centrally located double-stranded DNA with a surrounding envelope. The size of the virus is approximately 150 to 200 nm, and it has a lipid-containing envelope with glycoprotein spikes. The naked capsid has a diameter of approximately 90 to 95 nm. The DNA contains 125,000 base pairs, or approximately 80 megadaltons, and encodes about 75 proteins. The organization of the viral genome is similar to that of other herpesviruses. There are unique long (105-kb) and unique short (5.2-kb) regions of the viral genome. Each unique sequence contains terminal repeat sequences. With replication, the unique short (Us) region can invert upon itself and result in two isomeric forms.

Five families of VZV glycoproteins (gp) have been identified: gpI, gpII, gpIII, gpIV, and gpV. The herpes simplex virus (HSV) homologues are gE, gB, gH, Us7, and gC, respectively. Viral infectivity can be neutralized by monoclonal antibodies directed against gpI, gpII, and gpIII. These glycoproteins have been the subject of intense investigative interest because they represent the primary markers for both humoral and cell-mediated immune responses.

Epidemiology

Humans are the only known reservoir for VZV. Chickenpox follows exposure of the susceptible or seronegative person to VZV and represents the primary form of infection. Chickenpox was a common infection of childhood and affects both genders equally and people of all races. To a certain extent, the virus is endemic in the population at large; however, it becomes epidemic among susceptible persons during seasonal periods of late winter and early spring. Intimate contact appears to be the key determinant for transmission. Overall, chickenpox is a disease of childhood, because 90% of cases occur in children younger than 13 years. Typically, the virus is introduced into the susceptible school-aged or preschool child.

Although chickenpox exists worldwide among children, it occurs more frequently in
adults who reside in tropical regions than in those who reside in other geographic areas. Stokes noted a higher incidence of chickenpox among soldiers serving abroad during World War II, in whom the incidence was 1.41 to 2.27 per 1000 persons annually.

Pathogenesis

The pathogenesis of primary VZV infection begins with mucosal inoculation by virus transferred via the respiratory route or by direct contact with skin lesions of patients with varicella or herpes zoster. Based upon an analogy with mousepox, VZV was then presumed to spread to mononuclear cells in regional lymph nodes, leading to a primary viremia, infection of cells of the reticuloendothelial system in the liver, and a secondary viremia late in the incubation period that caused skin infection. The 10-to-21-day incubation period appears to be the interval required for VZV to overcome this vigorous innate epidermal cell response. VZV viremia may then be enhanced as uninfected T lymphocytes traffic through infected skin; replication in reticuloendothelial tissues may also contribute to this amplification. VZV is carried back to respiratory mucosal sites during the late incubation period, as is evident from transmission to susceptible contacts exposed 24 to 48 hours before the appearance of cutaneous lesions in the index case. The release of infectious virus into respiratory droplets is a pathogenic characteristic that differentiates VZV from other human herpesviruses.

Primary VZV infection elicits memory in T lymphocytes that exhibit helper and cytotoxic activity as well as continued production of antibodies to the virus. Immune subjects also have delayed-type hypersensitivity responses to VZV skin test antigens. Persistent VZV immunity may be maintained by periodic re-exposure to the virus during annual epidemics or by repeated antigenic stimulation from subclinical reactivation. Diminished T-lymphocyte recognition of VZV antigens probably accounts for the increased risk of herpes zoster in immunocompromised children. The short interval between primary and recurrent VZV infections in children with human immunodeficiency virus (HIV) infection and herpes zoster in young children after intrauterine or early postnatal varicella probably reflects poor induction of cell-mediated immunity.

Clinical Manifestations

The incubation period of primary VZV
infection is 10 to 21 days; symptoms most commonly begin between 14 and 16 days.

Varicella is often mild enough to escape diagnosis, but subclinical varicella is rare when exposed, susceptible children are examined prospectively during the period of risk. About half of children have prodromal symptoms, including fever, malaise, anorexia, headache, and, occasionally, mild abdominal pain, for 24 to 48 hours before the appearance of rash. Constitutional symptoms are prominent during the 24 to 72 hours after the first cutaneous lesions develop, but significant respiratory or gastrointestinal symptoms are unusual. Temperature elevation is usually moderate, ranging from 37.8°C to 38.8°C, but may be as high as 41.1°C.

Varicella lesions appear first on the scalp, face, or trunk. The initial exanthem consists of erythematous macules that evolve to form clear, fluid-filled vesicles; vesicles with surrounding irregular margin of erythema are often described as resembling “dewdrops on a rose petal”. Varicella lesions in their early stages usually are pruritic. After 24 to 48 hours, fluid becomes cloudy, and some lesions exhibit characteristic umbilication as crusting begins. As initial lesions begin to resolve, new crops form on the trunk and then the extremities. Late lesions may disappear without progressing to vesicle formation. Crusts are sloughed during the final phase as new epithelium is generated beneath the lesion site. Vesicles or small ulcers on mucous membranes of the oropharynx, conjunctivae, and vagina are common.

Complications

1. In Healthy Children
   
   (1) Bacterial Infections

Secondary bacterial infections constitute the most common cause of morbidity in otherwise healthy children. S. aureus and Streptococcus pyogenes are usual pathogens. “Impetigo”is often diagnosed but is difficult to differentiate from larger lesions caused by the virus alone. Bullous varicella can represent an unusual presentation of cutaneous lesions caused directly by VZV or can be due to bacterial superinfection. Cellulitis is the most common diagnosis, but lymphadenitis and subcutaneous abscesses also occur. Cellulitis of the soft tissues of the neck can result in severe edema that compromises the airway. Varicella lesions provide a portal of entry occasionally resulting in transient bacteremia or septicemia associated with high fever, cardiovascular collapse, and disseminated intravascular coagulopathy. Varicella can be complicated by methicillin-resistant S. aureus. Hematogenous spread of the bacteria can result in focal infection, including pneumonia, arthritis, and osteomyelitis.

(2) Neurologic Complications

Neurologic complications are the second most common indication for hospitalization of immunocompetent children with varicella. The incidence of central nervous system morbidity is highest among patients younger than 5 and older than 20 years. Neurologic manifestations include cerebellar disease as well as encephalitis, with some overlap of signs occurring in individual patients. Meningoencephalitis manifests as sudden onset of seizures, diminished level of consciousness, nuchal rigidity, and extensor plantar reflexes. Some patients have meningitis only, without seizures or altered consciousness. Cerebellar ataxia is characterized by a more gradual evolution of gait disturbance, nystagmus, and slurred speech. Signs of varicella encephalitis and of cerebellar ataxia have been described during
the incubation period, but the neurologic symptoms occur between 2 and 6 days after the onset of the rash in most cases. These neurologic syndromes may have a vasculitic or immune-mediated pathogenesis and occasionally occur after the resolution of cutaneous disease. Symptoms of cerebellar ataxia last for several days and sometimes weeks, but resolution is almost always complete. Some neurologic signs accompanying varicella may be due to Reye syndrome, but this complication is rare now that salicylates are known to be contraindicated in children with varicella. Transverse myelitis has been described as a complication of varicella; Guillain-Barré syndrome is reported rarely.

(3) Other Complications

Varicella hepatitis usually is subclinical, although some children with the highest elevations of AST (range, 200 to 800 IU/L) have severe vomiting.

Acute thrombocytopenia, associated with petechiae and purpuric skin lesions, hemorrhage into the varicella vesicles, epistaxis, hematuria, and gastrointestinal bleeding, is a reported complication of varicella. Clinical manifestations are usually brief, but platelet counts can remain low for days to weeks. Some patients have postinfectious thrombocytopenia beginning more than 1 or 2 weeks after varicella; bleeding complications persist for an average of 5 weeks. Purpura fulminans, due to arterial thrombosis, is a rare but life-threatening complication of varicella.

Renal complications of primary VZV infection are rare. Nephritis with hematuria, diffuse edema, and hypertension is described within 3 weeks after varicella exanthem; many of these cases represent poststreptococcal glomerulonephritis. Nephrotic syndrome and hemolytic uremic syndrome have been reported in a few children with varicella. Viral arthritis is an infrequent complication of varicella, but VZV has been isolated from joint fluid; arthritis resolves spontaneously within 3 to 5 days and has not been associated with residual joint disease.

Other rare complications of varicella are myocarditis, pericarditis, pancreatitis, and orchitis. Many children have vesicular lesions on the eyelids and conjunctivae, but serious ocular complications of varicella are unusual.

2. In High-Risk Populations

(1) Adolescents and Adults

Clinically significant varicella pneumonia is rare in children, but otherwise healthy adults are more susceptible to this complication, a factor that accounts for most of the increased morbidity and mortality caused by primary VZV infection in this age group. VZV pneumonia is associated with cough and dyspnea usually beginning within 1 to 6 days (average 3 days) after the onset of the rash. Patients have cough, with or without cyanosis, pleuritic chest pain, and hemoptyis. Hypoxemia often is more severe than is suggested by the physical findings. The chest radiograph may be normal or may show diffuse bilateral infiltrates with small nodular densities, especially in the perihilar area. Varicella pneumonia often is transient, resolving completely within 24 to 72 hours, but in severe cases, interstitial pneumonitis can progress rapidly to respiratory failure.

(2) Pregnancy

Varicella acquired during pregnancy can have severe consequences for both the mother and the fetus. Spontaneous abortion, fetal demise, and premature delivery can occur,
although the frequency of these complications is low. In rare instances, maternal varicella results in congenital varicella syndrome. The highest risk of severe embryopathy accompanies varicella acquired during the first 20 weeks of gestation and is estimated to occur in fewer than 2.0% of cases of maternal varicella. Infants affected after maternal varicella contracted later in pregnancy are described, but defects are limited to cutaneous scarring, diminished limb growth, or unilateral ocular defects. The most striking anomalies of the congenital varicella syndrome are unusual cutaneous defects with cicatricial skin scars, atrophy of an extremity, and evidence of damage to the autonomic nervous system. Many affected infants have microcephaly and cortical atrophy secondary to probable intrauterine VZV encephalitis; seizures and mental retardation are common sequelae. Chorioretinitis, microphthalmia, and cataracts also occur. Dysfunction of the autonomic nervous system produces neurogenic bladder, hydrourter, hydronephrosis, and severe astrosophageal reflux with recurrent aspiration pneumonia. Limb anomalies and other sequelae of intrauterine varicella can be detectable with fetal ultrasonography. Some infants who are asymptomatic at birth have been infected in utero, as shown by VZV-specific immunity or the occurrence of herpes zoster in infancy, without any intervening episode of varicella. Although a few cases of fetal abnormalities have been reported after maternal herpes zoster, clinical evidence indicates that recurrent VZV infection does not cause the congenital varicella syndrome or neonatal varicella. When maternal varicella occurs during the last few days of gestation, the infant is at risk for neonatal varicella, with an attack rate of approximately 20%. Infants who are born at least 5 days after the onset of varicella in the mother are not at high risk; these infants have lesions at birth or within the first 5 days of life but are protected from severe disease because the interval between maternal infection and delivery permits transplacental transfer of maternal IgG antibodies to VZV. Those who are born within 4 days after or 2 days before the onset of maternal varicella can exhibit progressive varicella, with an untreated mortality rate of 30%. Exposure of an infant to nonmaternal contacts with varicella rarely causes varicella in the infant because most infants are born to seropositive mothers. Rare cases of postnatally acquired varicella that have occurred in infants younger than 2 months who were born to seronegative mothers do not suggest a severe course, but careful observation of such infants is necessary.

(3) Malignancy

Without effective antiviral drugs, 32% to 50% of children with lymphoproliferative malignancies or solid tumors experience visceral dissemination; varicella pneumonia occurs in 20% of cases of varicella, and the mortality rates range from 7% to 17%. Progressive disease is characterized by a prolonged period of new lesion formation, pneumonia, hepatitis, encephalitis, and disseminated intravascular coagulopathy. The risk of progressive varicella is highest if chemotherapy is given during the incubation period, especially within 5 days before the appearance of the rash, and when the absolute lymphocyte count is < 500 cells/mm3 at the onset of the rash. Pneumonia is the most common life-threatening complication; in one large series, all varicella-related deaths occurred within 3 days after the diagnosis of varicella pneumonia.47 Hemorrhage into cutaneous lesions also is a clinical sign of severe varicella in the immunocompromised child. Severe abdominal or back pain is another marker of potentially lifethreatening
varicella, although its pathogenesis is uncertain. Some patients experience progressive encephalitis with coma, but varicella encephalitis is rarely the immediate cause of death among immunocompromised patients. The syndrome of inappropriate secretion of antidiuretic hormone can accompany disseminated varicella with or without clinical encephalitis. Disseminated VZV infection in children with cancer also is associated with pancreatitis, necrotizing splenitis, esophagitis, and enterocolitis in some patients.

(4) Other Immunodeficiency States

Children who acquire varicella after organ transplantation are at risk of progressive VZV infection unless they receive antiviral therapy. Thrombocytopenia and hepatitis are the major clinical complications in renal transplant recipients. Children receiving long-term, low-dose corticosteroid therapy for asthma are not usually at risk of serious varicella. However, fatal varicella is described in patients who receive higher doses of prednisone, especially during the incubation period.

Untreated varicella is severe or fatal in children with defects of T-lymphocyte function, including severe combined immunodeficiency, cartilage hair hypoplasia-short-limbed dwarfism, Wiskott-Aldrich syndrome, and ataxia telangiectasia. Unusual clinical findings in varicella, including lesions that develop a unique hyperkeratotic appearance and formation of new lesions for weeks or months, have been described in children with HIV infection, but varicella does not appear to accelerate the progression of HIV-related disease.

Laboratory evaluation is not necessary for management of healthy children with varicella. Abnormal laboratory values are common. The total white blood cell count often is decreased during the first 72 hours of rash, followed by lymphocytosis; lymphoblasts and prolymphocytes can be noted in peripheral blood. Slight to moderate abnormalities of serum hepatic enzyme values are common. The cerebrospinal fluid (CSF) in patients with neurologic complications of varicella usually shows a mild lymphocytic pleocytosis with fewer than 100 cells/mm3 and a slight to moderate elevation of protein (< 200 mg/dL); glucose concentration is usually normal. CSF pleocytosis and protein concentrations are higher in patients with encephalitis than in those with cerebellar disease. Patients with uncomplicated herpes zoster may have CSF pleocytosis consisting predominantly of mononuclear cells as well as elevated protein concentration.

In contrast to the disease in healthy children, specific diagnosis of VZV often is important to guide decisions about antiviral therapy when varicella is suspected in immunocompromised children. The definitive diagnosis of VZV infection requires the recovery of infectious virus with the use of tissue culture methods. However, VZV is difficult to isolate in tissue culture, and the time to viral identification is 3 to 7 days; therefore, viral cultures primarily serve to confirm diagnoses made with rapid antigen detection methods. Rapid diagnosis of cutaneous VZV infection is accomplished by obtaining epithelial cells from the base of a newly formed vesicle and staining the specimen with immunohistochemical reagents that detect viral proteins in infected cells. Cytologic methods can be used to detect multinucleated giant cells in lesion specimens or tissue sections, but false-negative results
are common, and these methods do not differentiate VZV from HSV. Enzyme immunoassay methods can be used to detect VZV antigens in solubilized preparations of cells and vesicle fluid from cutaneous VZV lesions.

VZV can be detected in clinical specimens through in situ hybridization or polymerase chain reaction testing, but must be done by a laboratory with experience using these methods.

Antibodies are not present in serum during most of the incubation period, but can be measured in low concentrations at the time of onset of the varicella exanthem. VZV IgG antibodies become detectable in almost all patients within 3 days and exhibit a marked increase during convalescence. VZV IgG antibodies persist for life after primary infection. Many laboratory methods can be used to detect VZV IgG antibodies, but serologic diagnosis is rarely useful because it is retrospective and available methods have limitations in sensitivity. Testing for VZV IgM antibodies should not be used for clinical diagnosis because false-positive and false-negative results are unavoidable with all commercially available methods.

**Diagnosis And Differential Diagnosis**

The localization and distribution of a vesicular rash make the diagnosis of herpes zoster highly likely; however, other viral exanthemas can occasionally be confused with this disease.

Impetigo and varicella can also be confused clinically. Impetigo is usually caused by group A β-hemolytic streptococci, often follows an abrasion of the skin or inoculation of bacteria at the site of the skin break, and can be associated with the formation of small vesicles in the surrounding area. Systemic signs of disease may be present if progressive cellulitis or secondary bacteremia develops. Unroofing lesions and careful Gram staining of the scraping of the base of the lesion should reveal gram-positive cocci in chains, suggestive of streptococci, or gram-positive cocci in clusters, suggestive of staphylococci, another cause of vesicular skin lesions, or both organisms. Treatment for these latter infections is distinctly different from that for chickenpox and requires administration of an appropriate antibiotic.

In a smaller number of cases, disseminated vesicular lesions can be caused by HSV. In these cases, disseminated HSV infection is usually a consequence of an underlying skin disease such as atopic dermatitis or eczema. An unequivocal diagnosis can be made only by isolation of the virus in tissue culture.

Disseminated enteroviral infections, particularly those caused by group A coxsackieviruses, have been reported to cause widespread distal vesicular lesions. These rashes are more commonly morbilliform in nature, with a hemorrhagic component rather than a vesicular or vesiculopustular appearance. Generally, these infections occur during the enterovirus season in late summer.
and early fall and are associated with lesions of the oropharynx, palms, and soles. This latter finding is helpful in distinguishing enteroviral disease from chickenpox.

**Treatment**

The medical management of chickenpox in the normal host is directed toward reduction of complications. For chickenpox, hygiene is important, including bathing, astringent soaks, and closely cropped fingernails to avoid a source for secondary bacterial infection associated with scratching of the pruritic skin lesions. Pruritus can be decreased with topical dressing or the administration of antipruritic drugs. Acetaminophen should be used to reduce fever in patients with chickenpox because of the association between aspirin and Reye’s syndrome.

Acyclovir is approved for the treatment of chickenpox in the normal host. Oral acyclovir therapy in normal children, adolescents, and adults shortens the duration of lesion formation by about 1 day, reduces the total number of new lesions by approximately 25%, and diminishes constitutional symptoms in one third of patients. In children 2 to 16 years old, the oral dosage is 20 mg/kg 4 times daily for 5 days (maximum of 800 mg daily). Adolescents and adults can receive up to 800 mg 5 times a day.

Acyclovir therapy diminishes the clinical severity of varicella in immunocompromised children by terminating cell-associated viremia in spite of impaired host response. Early antiviral therapy prevents progressive varicella and visceral dissemination; mortality is decreased particularly because the risk of varicella pneumonia is reduced. When acyclovir was given intravenously to children with malignancy in a placebo-controlled trial, the incidence of varicella pneumonia was decreased from 45% to 0. The dosage of acyclovir for varicella in high-risk patients is 1.5 g/m2/day, administered intravenously in three divided doses for 7 days.

Management of varicella pneumonia and other complications requires excellent supportive nursing care in addition to evaluation, on an individual basis, of the potential need for antiviral therapy.

**Prevention**

A vaccine is licensed for the prevention of chickenpox in immunocompetent persons. Studies performed to date indicate excellent protection after vaccination. The Oka strain of VZV was developed by Takahashi and colleagues in Japan and studied as a vaccine extensively in both healthy and leukemic children. In immunocompromised children, serologic evidence of host response after vaccination has been achieved in between 89% and 100% of vaccinated individuals. Vaccine-induced rash, however, is not uncommon and occurs in variable percentages of patients from approximately 6% to as high as 47%.
Definition

Typhoid fever is a bacterial disease caused by Salmonella typhi. It is characterized by prolonged fever, abdominal pain, diarrhea, delirium, rose spots, and splenomegaly and complicated sometimes by intestinal bleeding and perforation.

Etiology

The typhoid bacillus is a motile gram-negative rod in the family Enterobacteriaceae. It possesses a flagellar (H) antigen, a cell wall (O) lipopolysaccharide antigen, and a polysaccharide virulence (Vi) antigen located in the cell capsule. The polysaccharide side chain of the O antigen confers serologic specificity to the organism and is essential in virulence because salmonellae other than S.typhi and S.enteritidis bioserotype paratyphi A or B do not produce enteric fever in humans.

Pathogenesis and pathology

After S.typhi is ingested, the part of the inoculum that survives stomach acid enters the small intestine, where bacteria penetrate that mucosa and enter mononuclear phagocytes of ileal Peyer’s patches and mesenteric lymph nodes. The incubation period ranges from 8 to 28 days, depending on inoculums size and immune status of the host. Bacteria proliferate in mononuclear phagocytes and spread by way of the blood to the spleen, liver, and bone marrow, where further proliferation in
macrophages occurs. Inflammatory reactions occur in the spleen, liver, bone marrow. Peyer’s patches mainly in the terminal ileum, and skin, consisting of mononuclear cell infiltration, hyperplasia, and focal necrosis. Focal collections of mononuclear leukocytes are called “typhoid nodules”.

**Signs and symptoms**

Classically, the course of untreated typhoid fever is divided into four individual stages, each lasting approximately one week.

<table>
<thead>
<tr>
<th>Disease period</th>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Week</td>
<td>Fever, chills gradually increasing and persisting; headache</td>
<td>Abdominal tenderness</td>
</tr>
<tr>
<td>Second Week</td>
<td>Rash, abdominal pain, diarrhea or constipation, delirium, prostration</td>
<td>Rose spots, splenomegaly, hepatomegaly</td>
</tr>
<tr>
<td>Third Week</td>
<td>Complications of intestinal bleeding and perforation, shock</td>
<td>Melena, ileus, rigid abdomen, coma</td>
</tr>
<tr>
<td>Fourth Week and later</td>
<td>Resolution of symptoms, relapse, weight loss</td>
<td>Reappearance of acute disease, cachexia</td>
</tr>
</tbody>
</table>

**Diagnosis**

The preferred method of diagnosis is isolation of S.typhi from a blood culture, which is positive in most patients during the first 2 weeks of illness. Urine and stool cultures are less frequently positive. The bone marrow culture is the most sensitive test, positive in nearly 90% of cases, and can be used when a bacteriologic diagnosis is crucially needed or in patients who have been pretreated with antibiotics.

The Widal test for agglutinating antibodies against the somatic (O) and flagellar (H) antigens of S.typhi is widely used for serodiagnosis. An O agglutinin titer of ≥1:80 or a fourfold rise supports a diagnosis of typhoid fever, whereas the H agglutinins are more often nonspecifically elevated by immunization or previous infections with other bacteria. Serodiagnosis is of limited value because false-positive results are often obtained in endemic areas and false-negative results occur in some cases of bacteriologically proven typhoid fever.

**Treatment**

**Medical Treatment**

Patients who are dehydrated, anorectic, or suffering from diarrhea should receive intravenous saline with attention to electrolyte and acid-base disturbances. Patients with brisk intestinal bleeding require blood transfusion.

The first choice is a fluoroquinolone such as ciprofloxacin and third-generation cephalosporins such as ceftriaxone or cefotaxime. Chloramphenicol has remained the drug of choice since its introduction in
1948. Other drugs that are effective include ampicillin, amoxicillin, trimethoprim-sulfamethoxazole.

Resistance to the traditional antimicrobial agents ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole defines multidrug resistance (MDR). Patients with MDR can be treated with fluoroquinolone or third-generation cephalosporin.

However, the widespread use of fluoroquinolones has also been associated with decreased susceptibility and documented resistance to this class of drugs. A single chromosomal mutation in the quinolone resistance determining region of the gyrA gene may be sufficient to result in decreased ciprofloxacin susceptibility. In this circumstance, third-generation cephalosporins, such as ceftriaxone, may be used. However, the cost and route of administration make ceftriaxone less suitable for patient treatment in some low- and middle-income countries, and the oral third-generation cephalosporin cefixime appears to be inferior to other oral agents both in terms of fever clearance time and treatment failure. In these circumstances, recent clinical trials suggest that azithromycin treatment (500 mg once daily for 7 days for adults or 20 mg/kg/day up to a maximum of 1000 mg/day for 7 days for children) is useful for the management of uncomplicated typhoid fever. Because of its pharmacokinetic profile, gatifloxacin has potential as a new agent for treating patients infected with isolates with decreased ciprofloxacin susceptibility but carries risk for dysglycemia, which may limit its widespread use.

**Surgical Treatment**

Surgery is usually indicated in cases of intestinal perforation. Most surgeons prefer simple closure of the perforation with drainage of the peritoneum. Small-bowel resection is indicated for patients with multiple perforations.

If antibiotic treatment (6 weeks) fails to eradicate the hepatobiliary carriage, the gallbladder should be resected. Cholecystectomy is not always successful in eradicating the carrier state because of persisting hepatic infection.

**Prognosis**

Case fatality rates >10% continue to be reported in developing countries despite availability of antibiotics, whereas developed countries show case fatality rates <1%. About 1 to 3% of patients become chronic fecal carriers after recovery.

**Prevention**

Sanitation and hygiene are the critical measures that can be taken to prevent typhoid. Typhoid does not affect animals and therefore transmission is only from human to human. Careful food preparation and washing of hands are crucial to preventing typhoid.

There are two vaccines licensed for use for the prevention of typhoid: the live, oral Ty21a vaccine (sold as Vivotif Berna) and the injectable Typhoid polysaccharide vaccine (sold as Typhim Vi by Sanofi Pasteur and Typherix by GlaxoSmithKline). Both are between 50% to 80% protective and are recommended for travellers to areas where typhoid is endemic. Boosters are recommended every five years for the oral vaccine and every two years for the injectable form.
Table 2 Dosage and schedule for typhoid fever vaccination

<table>
<thead>
<tr>
<th>Vaccination</th>
<th>Age (yrs)</th>
<th>Dose (mode of administration)</th>
<th>No. of doses</th>
<th>Dosing interval</th>
<th>Boosting interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral live attenuated Ty21a vaccine (Vivotif)</td>
<td>≥6</td>
<td>1 capsule (oral)</td>
<td>4</td>
<td>48 hrs</td>
<td>NA</td>
</tr>
<tr>
<td>Booster</td>
<td>≥6</td>
<td>1 capsule (oral)</td>
<td>4</td>
<td>48 hrs</td>
<td>Every 5 yrs</td>
</tr>
<tr>
<td>Vi capsular polysaccharide vaccine (Typhim Vi)</td>
<td>≥2</td>
<td>0.50 mL (intramuscular)</td>
<td>1</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Booster</td>
<td>≥2</td>
<td>0.50 mL (intramuscular)</td>
<td>1</td>
<td>NA</td>
<td>Every 2 yrs</td>
</tr>
</tbody>
</table>

NA = Not applicable