ANTIBIOTICS SIMPLIFIED

SECOND EDITION

Jason C. Gallagher

Conan MacDougall

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Contents

Introduction

Antibiotics—the word sends terror coursing through the veins of students and makes many healthcare professionals uncomfortable. The category of antibiotics actually contains many different classes of drugs that differ in spectrum of activity, adverse effect profiles, pharmacokinetics and pharmacodynamics, and clinical utility. These classes can seem bewildering and beyond comprehension. We believe that taking a logical, stepwise approach to learning the pharmacotherapy of infectious diseases can help burn away the mental fog preventing optimal use of these drugs.

Learning the characteristics of antibiotics simplifies learning infectious disease pharmacotherapy. Students and clinicians who attempt to learn the antibiotics of choice for different types of infections before knowing the characteristics of those drugs never truly understand the context of what they are attempting to learn. Once the characteristics of the antibiotics are known, making a logical choice to treat an infection is much easier. This approach takes some time up front, but it will be well worth the effort when the clinician realizes that the pharmacotherapy of all infections is fundamentally similar and logical.

How to Use This Book

We wrote this book in an effort to condense the many facts that are taught about antibiotics in pharmacology and pharmacotherapy courses into one quick reference guide. It is meant to supplement material learned in pharmacology, not to supplant it. Use this book as a reference when you encounter a class of antibiotics that you know you have heard about; it will remind you of key points you may have forgotten.

This book contains six parts. Part 1 reviews basic microbiology and how to approach the pharmacotherapy of a patient with a presumed infection. The chapters in Parts 2–6 provide concise reviews of various classes of antibacterial, antimycobacterial, antifungal, antiviral, and antiparasitic drugs. Again, this book is intended to supplement your other pharmacology textbooks. These chapters give key points about each class of antibiotics—they are not thorough reviews. The appendices contain references that may help in daily use.

Format of the Drug Class Reviews

Each drug class chapter follows the same basic format. The agents belonging to each class are listed first. The drugs used most commonly in practice are **bolded**.

Spectrum

The spectra listed are not exhaustive. This section summarizes key organisms against which each class has or does not have activity.

Adverse Effects

This section lists key adverse effects. This list is not exhaustive, but it gives the most common and/or concerning adverse effects of each class.

Dosing Issues

This section discusses common problems or potential errors in drug dosing for select drug classes.

Important Facts

This section provides a summary of significant facts for each drug class.

What They're Good For

This section lists some of the most common and/or useful indications for the agents in the class. Often the agents discussed have not been approved for these indications by the Food and Drug Administration (FDA), but they are commonly used for them anyway. Conversely, many FDA indications that the antibiotics do have are not listed here, because they are often out-of-date.

Don't Forget!

In this section, we list points that are often overlooked or especially important when dealing with the drug class.

As you read this book, try to think of situations in which the antibiotics would be useful to your patients. Think of *why* an antibiotic is useful for an indication; don't just learn *that* it is. It is our sincere hope that you too have that magic moment where the world of antibiotics and the study of infectious diseases click together. Let us know when it happens.

New to the *Second Edition*

The *Second Edition* of *Antibiotics Simplified* expands on the drug classes covered in the first while retaining the "key point" focus of the text that has made it successful. In addition to antibacterial and antifungal agents, the *Second Edition* includes antiviral agents (including antiretrovirals for HIV), antimycobacterial agents, and antiparasitic agents. A new appendix includes empiric regimens for common infections for quick reference.

Acknowledgments

Our thanks go to those who helped to edit this text, and to our wives, who put up with us while we wrote it.

We dedicate this text to the pharmacy students of Temple University and University of California–San Francisco. We hope you find it useful.

Considerations with Antibiotic Therapy

PART 1

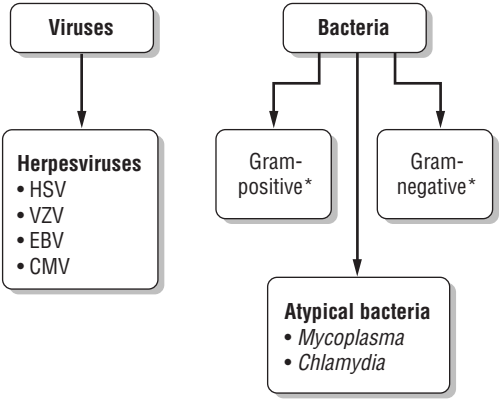
The Wonderful World of Microbiology

1

Despite the promises of the household-products industry, almost *every surface* is covered in microorganisms almost *all the time*. Swab a countertop, your skin, or your dinner and you will find a little world—and that covers only the estimated 10% of bacteria that can be cultured! Obviously, trying to sterilize our patients (and our countertops) is futile; we have to try to target the bad organisms and let the rest happily crawl all over us. See Appendix 1 for an illustration of how "not clean" we are.

In the microbial world, bacteria lie toward the "less like us" end of the spectrum (**Figure 1–1**). They are prokaryotes, not eukaryotes like fungi, protozoa, and humans. Viruses are even more different from us—they are basically just a package of genetic instructions in a protein coat (**Figure 1–2**). Differences between cells of microorganisms and humans in anatomy, biochemistry, and affinity of antibiotics for their targets are what allow for the safe and efficacious use of antibiotics. In this section we will concentrate on the microbiology of bacteria. Discussion of the unique characteristics of fungi, viruses, mycobacteria, and parasites will be covered in the sections where agents active against those organisms are introduced.

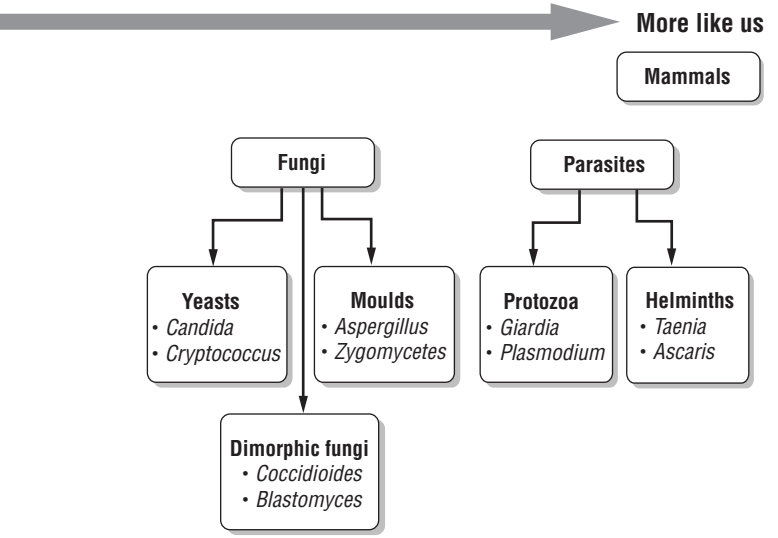
Less like us



*See Figure 1–3.

Figure 1–1
The Microbial World

Differentiating bacteria that are responsible for infection from those just along for the ride can be difficult. Many bacteria that can cause human disease are also normal commensal flora, including *Escherichia coli, Streptococcus pneumoniae,* and *Staphylococcus aureus*. Thus, growth of one of these organisms from a culture is not necessarily synonymous with infection. Suspicion of infection is increased greatly if the organism grows from a normally sterile site, such as the bloodstream or cerebrospinal fluid (CSF). Indicators of infection in nonsterile sites (such as sputum and wound cultures) are a high number of organisms, presence of inflammatory cells, and symptoms referable to the



culture site (e.g., cough or dyspnea in a patient with a sputum culture growing *S. pneumoniae,* redness and pain in a patient with a skin culture growing *S. aureus*).

Definitive identification and susceptibility testing may take anywhere from hours to months, depending on the organism and the methods used. Microscopic examination and staining may allow for rapid preliminary identification. For bacteria, the most important of these techniques is the Gram's stain. Being able to interpret preliminary results of microbiology testing will allow you to provide the most appropriate therapy to your patients as early as possible.

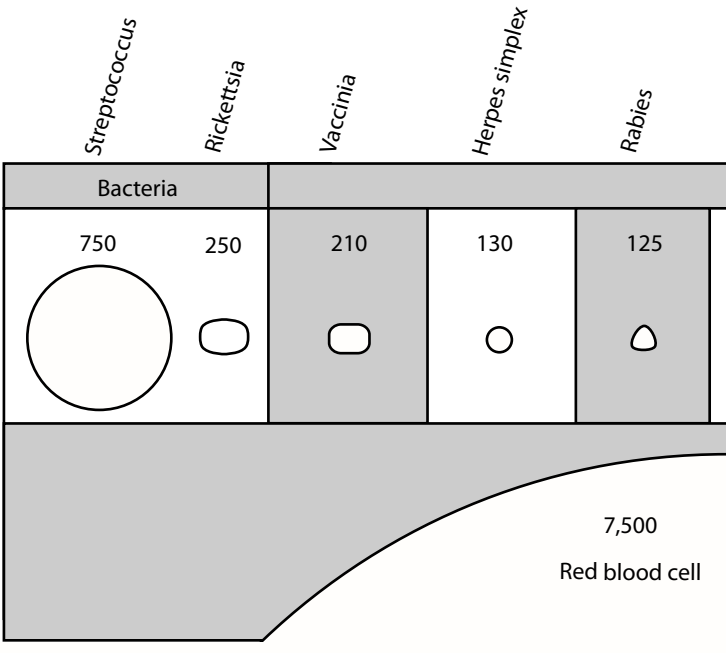
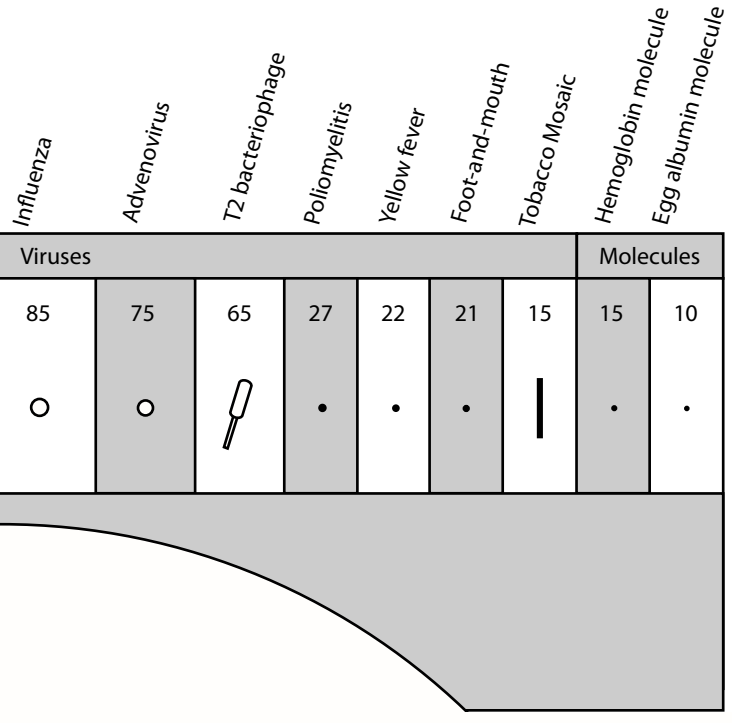


Figure 1–2
Relative Sizes of Microorganisms

One of the most fundamental differences among types of bacteria is how they react to a Gram's stain. Gram's stain (crystal violet) is a substance that selectively stains the cell walls of Gram-positive bacteria but is easily washed away from Gram-negative bacteria. Why? In Gram-positive bacteria, the outermost layer is a thick layer of peptidoglycan, a cellular substance that gives bacterial cells rigidity. In contrast, Gram-



negative bacteria have an outer membrane of lipopolysaccharides that blocks the stain from adhering to the peptidoglycan within the cell (**Figure 1–3**). Gram-negatives also contain peptidoglycan, but in smaller amounts, and it is not the outermost layer of the cell. Both Gram-positive and Gram-negative organisms contain an inner cell membrane that separates the cell wall from the cytoplasm of the organism.

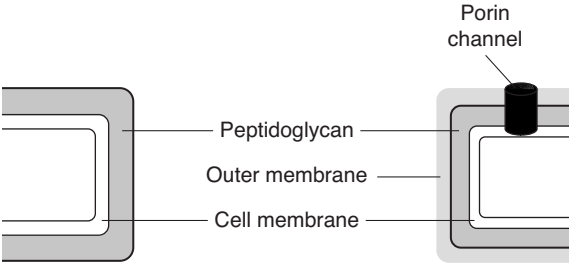


Figure 1–3
Cell Walls of Gram-Positive and Gram-Negative Organisms

Figures 1–4 and 1–5 show how you can identify different bacteria by differences in morphology, oxygen tolerance, and biochemical identification.

Figure 1–4
Gram-Positive Bacteria

Rapid identification of Gram-positive bacteria based on morphology and preliminary biochemical tests can help to direct therapy.

1. **Morphology:** Most medically important Gram-positive pathogens are cocci (spheres) rather than bacilli (rods). The finding of Gram-

positive bacilli should be interpreted within the clinical context: in blood cultures, Gram-positive bacilli often represent common skin contaminants (such as *Propionibacterium*, *Corynebacterium*, and *Bacillus* species). Detection of Gram-positive bacilli from necrotizing wound infections suggests clostridial infection, whereas the finding of Gram-positive bacilli in CSF cultures raises the concern for *Listeria*.

2. **Colony clustering:** Within the Gram-positive cocci, the staphylococci tend to form clusters, whereas the streptococci (including enterococci) typically appear in pairs or chains. Again, the clinical context aids in interpretation: The finding of streptococci in a respiratory culture suggests *S. pneumoniae*, while a report of "streptococci" from an intra-abdominal culture suggests *Enterococcus* (which may be identified preliminarily as a *Streptococcus*).

3. **Biochemistry and appearance on agar:** The rapid catalase test helps to differentiate staphylococci from streptococci. The coagulase test is useful for differentiating the more virulent (coagulase-positive) *S. aureus* from its cousin the coagulase-negative *S. epidermidis*. *S. epidermidis* is a frequent contaminant of blood cultures; if only one of a pair of blood samples is positive for coagulase-negative staphylococci, treatment may not be required. The pattern of hemolysis (clearing around colonies on agar plates) helps to differentiate among the streptococci: the oral flora (α-hemolytic *S. pneumoniae* and the viridans strep); pathogens of the skin, pharynx, and genitourinary tract (β-hemolytic Group A and B strep); and the bugs of gastrointestinal origin (non-hemolytic enterococci: the more common *E. faecalis* and the more resistant *E. faecium*).

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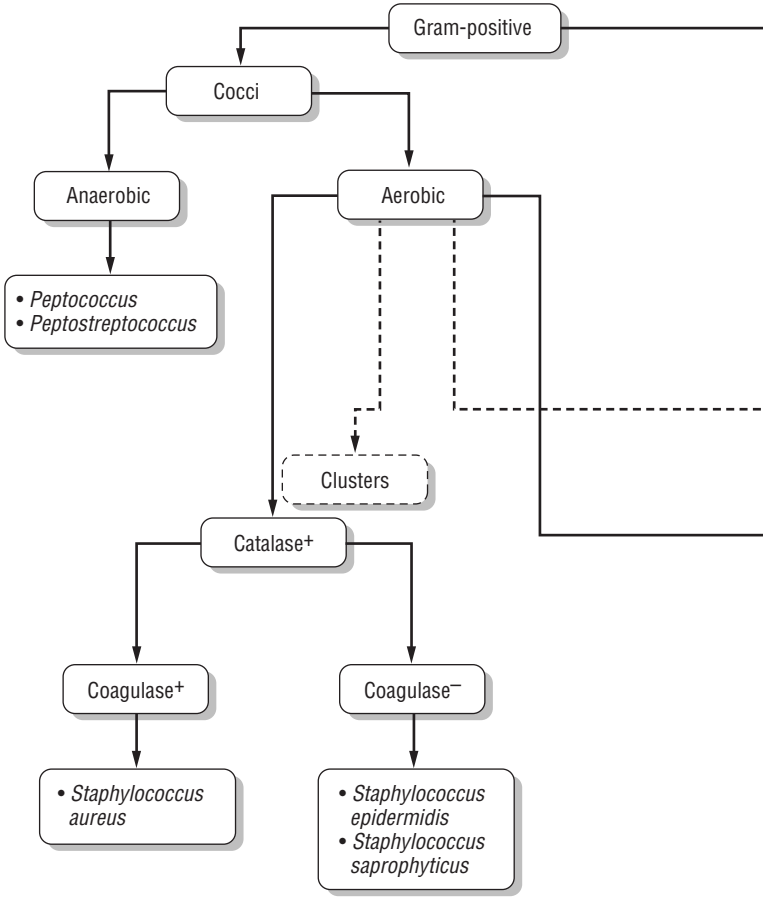
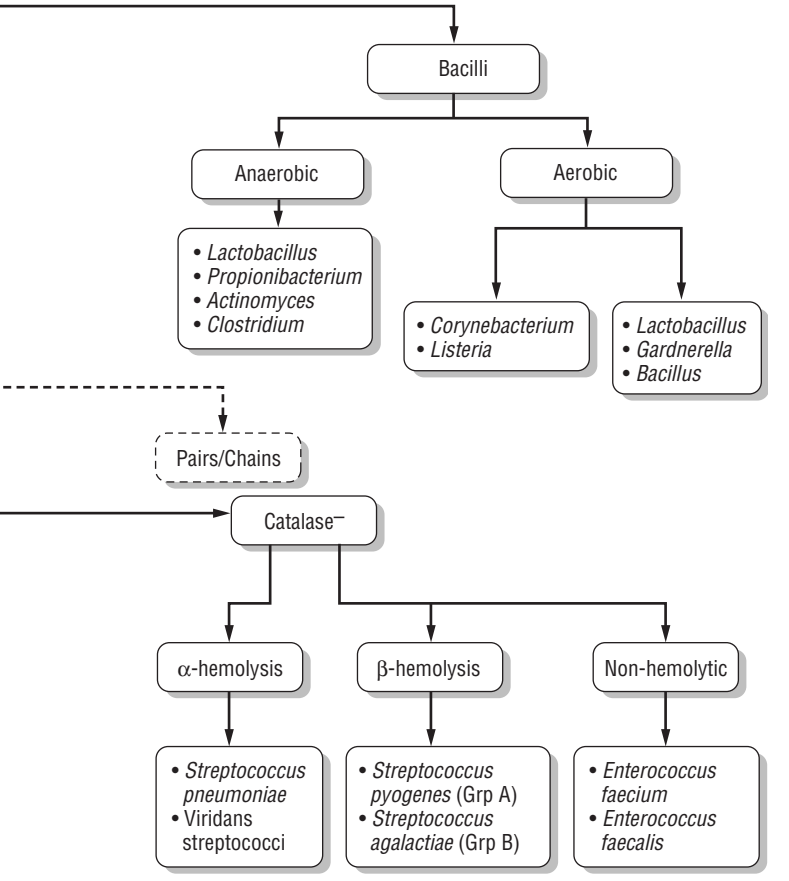


Figure 1–4
Gram-Positive Bacteria *(continued)*


Bacilli
Anaerobic
Aerobic
• Lactobacillus
• Propionibacterium
• Actinomyces
• Clostridium
• Corynebacterium
• Listeria
• Lactobacillus
• Gardnerella
• Bacillus
Pairs/Chains
Catalase⁻
α-hemolysis
β-hemolysis
Non-hemolytic
• Streptococcus pneumoniae
• Viridans streptococci
• Streptococcus pyogenes (Grp A)
• Streptococcus agalactiae (Grp B)
• Enterococcus faecium
• Enterococcus faecalis

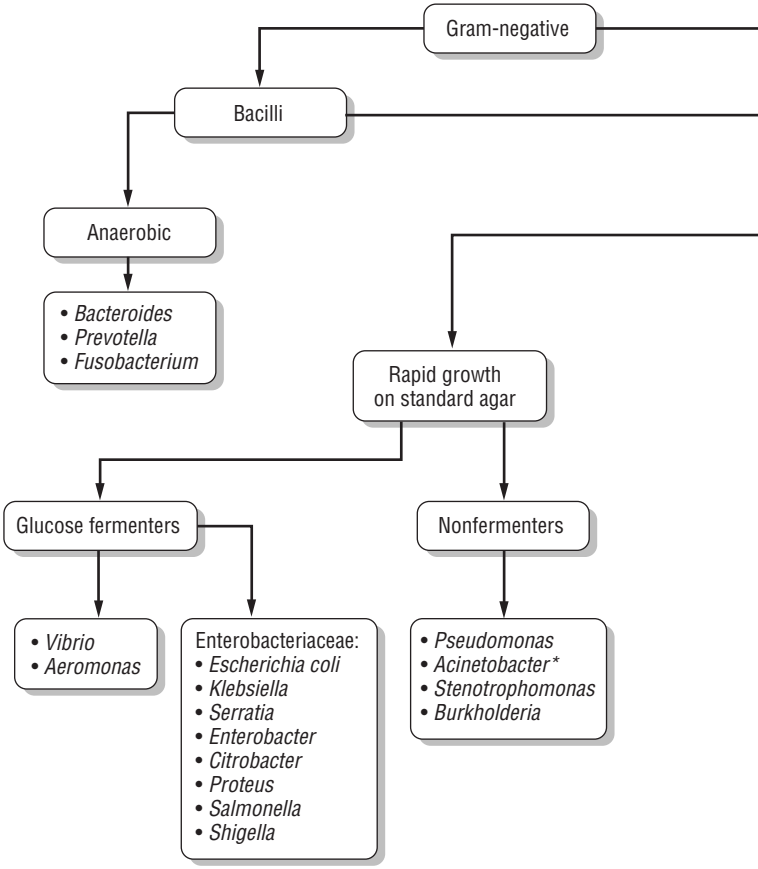
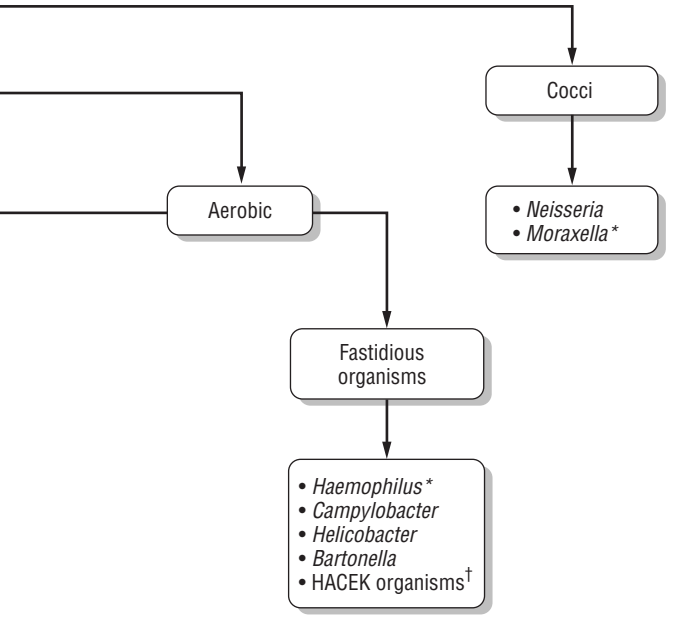


Figure 1–5
Gram-Negative Bacteria

Preliminary identification is somewhat less useful with the Gram-negative bacteria because more extensive biochemical tests are usually needed to differentiate among them.

1. **Morphology:** Among Gram-negative pathogens, the bacilli predominate. The situation in which identification of Gram-negative cocci



* = these organisms may appear as coccobacilli
† = *Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, *Kingella*

would be most useful is in the setting of meningitis, where this finding would strongly suggest *Neisseria meningitidis*. Note also that some organisms have an intermediate or "coccobacillary" appearance, which may suggest *H. influenzae*, *Moraxella*, or *Acinetobacter*.

2. **Glucose/lactose fermentation:** The pathogens within the family Enterobacteriaceae (including *E. coli*, *Klebsiella*, *Serratia*, *Proteus*, and *Enterobacter*) generally ferment glucose/lactose; at this point

the lab may identify them as "enteric Gram-negative rods." In contrast, *Pseudomonas*, *Acinetobacter*, *Stenotrophomonas*, and *Burkholderia* are "nonfermenters"; a report of "nonfermenting Gram-negative rods" should lead you to reassess and if necessary broaden your antibiotic coverage, because these organisms have in common a high level of antibiotic resistance.

3. **Fastidious organisms:** These organisms are picky eaters—they grow slowly and often require specially supplemented media. Thus, it may take a few days to a few weeks for them to grow from culture.

General Approach to Infectious Diseases

2

The pharmacotherapy of infectious diseases confuses many clinicians, but the approach to the patient with an infection is relatively simple and consistent. Understanding this approach is the first step in developing a useful expertise in infectious diseases and antibiotic use.

A note: technically the term *antibiotic* refers only to a subset of antibacterial drugs that are natural products. The terms *anti-infective* and *antimicrobial* encompass antibacterial, antifungal, antiviral, and antiparasitic drugs. However, because *antibiotic* is the more commonly used term, we will use it to refer to antimicrobials in general or antibacterials specifically.

Prophylactic Therapy

The use of antimicrobial chemotherapy—that is, the treatment of microorganisms with chemical agents—falls into one of three general categories: prophylaxis, empiric use, and definitive therapy. *Prophylaxis* is treatment given to prevent an infection that has not yet developed. Use of prophylactic therapy should be limited to patients at high risk of developing an infection, such as those on immunosuppressive therapy, those with cancer, or patients who are having surgery. These patients have weak-

ened natural defenses that render them susceptible to infection. Because the likelihood of infection by some types of organisms in these patients is high and the consequences of infection are dire, we administer antimicrobial drugs to prevent infections from occurring. However, the world is not sterile and breakthrough infections do occur. The key to understanding antimicrobial prophylaxis is to remember that patients who receive it do not have an infection, but they are at risk for one.

Empiric Therapy

Unlike prophylactic therapy, *empiric therapy* is given to patients who have a proven or suspected infection, but the responsible organism(s) has or have not yet been identified. It is the type of therapy most often initiated in both outpatient and inpatient settings. After the clinician assesses the likelihood of an infection based on physical exam, laboratory findings, and other signs and symptoms, he or she will usually collect samples for culture and Gram staining. For most types of cultures, the Gram stain is performed relatively quickly. In the Gram stain, details about the site of presumed infection are revealed, such as the presence of organisms and white blood cells (WBCs), morphology of the organisms present (e.g., Gram-positive cocci in clusters), and the nature of the sample itself, which in some cases indicates if the sample is adequate. The process of culturing the sample begins around the time that the clinician performs the Gram stain. After a day or so, biochemical testing will reveal the identification of the organism, and eventually the organism will be tested for its susceptibility to various antibiotics.

However, this process takes several days, so empiric therapy is generally initiated *before* the clinician knows the exact identification and susceptibilities of the causative organism. Empiric therapy is our best guess of which antimicrobial agent or agents will be most active against the likely cause of infection. Sometimes we are right, and sometimes we are wrong. Keep in mind that empiric therapy should not be directed against every known organism in nature—just those most likely to cause the infection in question. In other words, broad-spectrum antibiotics are not a substitute for rational thought!

Definitive Therapy

After culture and sensitivity results are known, the *definitive therapy* phase of treatment can begin. Unlike empiric therapy, with definitive therapy we know on what organisms to base our treatment and which drugs should work against them. At this phase it is prudent to choose antimicrobial agents that are safe, effective, narrow in spectrum, and cost effective. This helps us avoid unneeded toxicity, treatment failures, and the possible emergence of antimicrobial resistance, and it also helps manage costs. In general, moving from empiric to definitive therapy involves decreasing coverage, because we do not need to target organisms that are not causing infection in our patient. In fact, giving overly broad-spectrum antibiotics can lead to the development of superinfections, infections caused by organisms resistant to the antibiotics in use that occur during therapy.

The clinician who is treating an infected patient should always strive to make the transition to

definitive therapy. Although it seems obvious, this does not always occur. If the patient improves on the first antibiotic, clinicians may be reluctant to transition to more narrow-spectrum therapy. Also, some infections may resolve with empiric therapy before culture results would even be available, as happens with uncomplicated urinary tract infections (UTIs). In other cases, cultures may not be obtained or may be negative in spite of strong signs that the patient has an infection (e.g., clinical symptoms, fever, increased WBC count). In most situations it is important that clinicians continuously consider the need to transition to definitive therapy. Overly broad-spectrum therapy has consequences, and the next infection is likely to be harder to treat. Keep in mind the general pathway for the treatment of infectious diseases shown in **Figure 2–1**.

Examples of Therapy

Here are a few examples of each type of therapy:

Prophylaxis

- Trimethoprim/sulfamethoxazole (TMP/SMX) to prevent *Pneumocystis jirovecii* (formerly *carinii*) pneumonia in a patient on cyclosporine and prednisone after a liver transplant
- Azithromycin to prevent *Mycobacterium avium intracellularae* (MAI or MAC) in an advanced HIV patient
- Cefazolin given before surgery to prevent a staphylococcal skin infection of the surgical site

Empiric Therapy

- Levofloxacin initiated for a patient with presumed community-acquired pneumonia

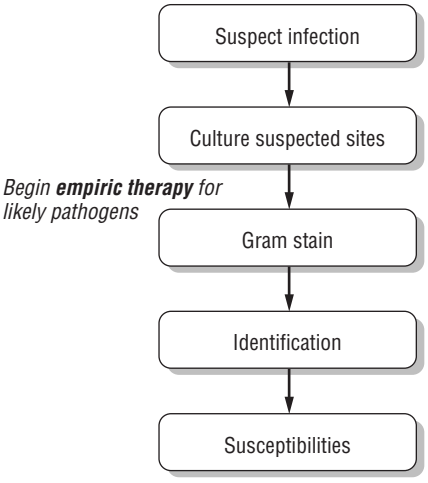


Figure 2–1
General Approach to Infectious Diseases

- Ceftriaxone given for the treatment of suspected pyelonephritis
- Voriconazole initiated for a neutropenic bone marrow transplant patient with shortness of breath and a radiograph suggestive of pulmonary aspergillosis
- Vancomycin, tobramycin, and meropenem for a patient with probable hospital-acquired pneumonia in the intensive care unit

Definitive Therapy

- Transitioning from piperacillin/tazobactam to ampicillin in a patient with a wound infection caused by *Enterococcus faecalis*, which is susceptible to both drugs

- Discontinuing ceftriaxone and initiating ciprofloxacin for a patient with a UTI caused by *Klebsiella pneumoniae* that is resistant to ceftriaxone but susceptible to ciprofloxacin
- Stopping caspofungin and initiating fluconazole for a patient with *Candida* in a blood isolate when the species is identified as *Candida albicans* (which is reliably susceptible to fluconazole)
- Narrowing therapy from vancomycin, ciprofloxacin, and imipenem/cilastatin to vancomycin alone for a patient with hospital-acquired pneumonia whose deep respiratory culture grew only methicillin-resistant *Staphylococcus aureus* (MRSA) that is susceptible to vancomycin

Case Study

Here is an example of treating a patient with an infection by the above pathway:

> TR is a 63-year-old man with a history of diabetes, hypertension, and coronary artery disease who comes to the hospital complaining of pain, redness, and swelling around a wound on his foot. Close inspection reveals that he has an infected diabetic foot ulcer. He is admitted to the hospital (Day 1). The clinician performs surgical debridement that evening and sends cultures from the wound during surgery as well as blood cultures. The clinician initiates *empiric therapy* with vancomycin and piperacillin/tazobactam.
>
> On Day 2, Gram stain results from the wound are available. There are many WBCs with many Gram-positive cocci but no Gram-negative rods (GNRs), so the clinician discontinues piperacillin/tazobactam. Blood cultures do not grow any organisms.

The following day (Day 3), culture results from the wound reveal many *Staphylococcus aureus*. Because vancomycin is usually effective against this organism, its use is continued.

On Day 4, susceptibility results from the wound culture return. The *S. aureus* is found to be susceptible to methicillin, oxacillin, cefazolin, piperacillin/tazobactam, clindamycin, TMP/SMX, and vancomycin. It is resistant to penicillin, ampicillin, tetracycline, and levofloxacin. Because the isolate from TR's wound is methicillin-sensitive *Staphylococcus aureus* (MSSA), the clinician discontinues vancomycin and initiates *definitive therapy* with oxacillin.

Note how in TR's case we began empiric therapy with a broad-spectrum regimen of vancomycin and piperacillin/tazobactam to cover the Gram-positive and Gram-negative aerobes and anaerobes that tend to cause diabetic foot infections but narrowed that therapy gradually as Gram stain and culture data returned. Eventually we were able to choose a highly effective, narrow-spectrum, inexpensive, and safe choice of definitive therapy that was driven by microbiology results. Both vancomycin and piperacillin/tazobactam were active against TR's *Staphylococcus aureus* as well, but both are broader in spectrum than oxacillin and represent less-ideal therapy choices.

Antibiotic Pharmacodynamics

3

The term *antibiotic pharmacodynamics* refers to the manner in which antibiotics interact with their target organisms to exert their effects: Does the antibiotic kill the organism or just prevent its growth? Is it better to give a high dose of antibiotics all at once or to achieve lower concentrations for a longer time? Clinicians increasingly recognize such considerations as important in maximizing the success of therapy, especially for difficult-to-treat infections or in immunocompromised patients.

Susceptibility Testing

Typically, one judges the susceptibility of a particular organism to an antibiotic based on the minimum inhibitory concentration (MIC) for the organism-antibiotic combination. The microbiology laboratory determines the MIC by mixing a standard concentration of the organism that the patient has grown with increasing concentrations of the antibiotic in a broth solution. Classically this was done in test tubes (see **Figure 3–1**), but today it is done more commonly on microdilution plates. The mixture is incubated for about a day, and the laboratory technician examines the tubes or plates (with the naked eye or with a computer) for signs of cloudiness, indicating growth of the organism. The mixture with the

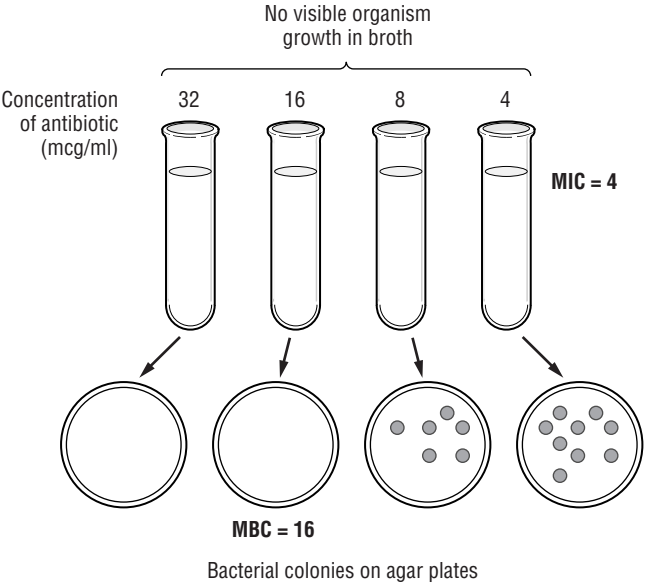
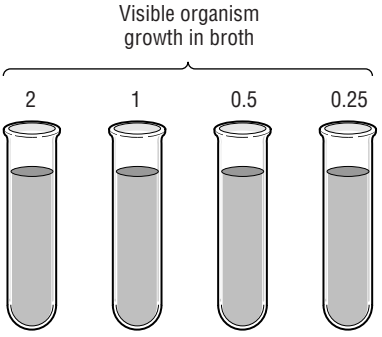


Figure 3–1
Susceptibility Testing of Antibiotics

lowest concentration of antibiotic where there is no visible growth is deemed to be the MIC. For each organism-antibiotic pair there is a particular cutoff MIC that is considered susceptible. This particular MIC is called the breakpoint. **Table 3–1** provides examples of how breakpoints differ for various organism/pathogen combinations and even based on the site of infection. Note that just because an antibiotic has the lowest MIC for a pathogen, that does not mean it is the best choice—different antibiotics achieve different concentrations in the body in different places. Thus, antibiotic MICs for a single organism generally should not be compared across different drugs in selecting therapy. Finally, be



aware that other methods of susceptibility testing exist, including disk diffusion and E-tests, but that broth dilution methods are generally considered the gold standard.

Static Versus Cidal

At the MIC the antibiotic is inhibiting growth, but it may or may not actually be killing the organism. Antibiotics that inhibit growth of the organism without killing it are termed bacteriostatic (or fungistatic in the case of fungi). If antibiotics are removed, the organisms can begin growing again. However, bacteriostatic antibiotics are usually successful in treating infections because they allow the

TABLE 3–1
Examples of Antibiotic Susceptibility Breakpoints

Organism Antibiotics	Susceptible	Intermediate	Resistant
E. coli			
Cefepime	≤ 8 mcg/ml	16 mcg/ml	≥ 32 mcg/ml
Levofloxacin	≤ 2 mcg/ml	4 mcg/ml	≥ 8 mcg/ml
Trimethoprim/ sulfamethoxazole	≤ 2/38 mcg/ml	—	≥ 4/76 mcg/ml
Streptococcus pneumoniae			
Cefepime (meningitis)	≤ 0.5 mcg/ml	1 mcg/ml	≥ 2 mcg/ml
(Non-meningeal)	≤ 1 mcg/ml	2 mcg/ml	≥ 4 mcg/ml
Levofloxacin	≤ 2 mcg/ml	4 mcg/ml	≥ 8 mcg/ml
Trimethoprim/ sulfamethoxazole	≤ 0.5/9.5 mcg/ml	1–2/19–38 mcg/ml	≥ 4/76 mcg/ml

patient's immune system to catch up and kill off the organisms. Other antibiotics are considered bactericidal; their action kills the organisms without any help from the immune system.

For most infections, outcomes using appropriate bacteriostatic versus bactericidal drugs are similar; however, for certain infections bactericidal drugs are preferred. Such infections include endocarditis, meningitis, infections in neutropenic patients, and possibly osteomyelitis. The immune system may not be as effective in fighting these infections because of the anatomic location or- the immunosuppression of the patient. Bactericidal activity is determined by taking a sample of the broth at various concentrations and below and spreading the broth on agar plates (Figure 3–1). The bacterial colonies on the plates are counted, and the concentration corresponding to a 99.9% reduction in the original bacterial in-

oculum is considered to be the minimum bactericidal concentration (MBC). When the MBC is 4 times or less the MIC, the drug is considered to be bactericidal; if the MBC/MIC ratio is greater than 4, it is considered bacteriostatic. MIC testing is standard in most laboratories; MBC testing is more difficult and is not commonly done. **Table 3–2** lists drugs and indicates whether they are generally considered bacteriostatic or bactericidal; however, it should be noted that this activity can vary based on the pathogen being treated, the achievable dose, and the growth phase of the organism.

Pharmacokinetic/ Pharmacodynamic Relationships

Besides differing in whether they kill microorganisms or merely inhibit their growth, antibiotics also differ in how they manifest their effects over time. Careful studies have revealed that for certain antibiotics, activity against microorganisms correlates with the duration of time that the concentration of

TABLE 3–2
Antibacterial Activity of Antibiotics

Antibiotic	Antibacterial Activity	Predictive PK/PD Parameter
Penicillins Cephalosporins Carbapenems Monobactams	Bactericidal	Time > MIC
Vancomycin	Bactericidal (slowly)	AUC/MIC
Fluoroquinolones Aminoglycosides Metronidazole Daptomycin	Bactericidal	Peak:MIC
Macrolides Tetracyclines Linezolid	Bacteriostatic	AUC/MIC

the drug remains above the MIC (time-dependent activity). For other antibiotics, antibacterial activity correlates not with the time above the MIC but with the ratio of the peak concentration of the drug to the MIC (concentration-dependent or time-independent activity). For some antibiotics, the best predictor of activity is the ratio of the area under the concentration-time curve to the MIC. **Figure 3–2** illustrates these pharmacokinetic/pharmacodynamic (PK/PD) parameters schematically, and Table 3-2 shows which parameter is most predictive of efficacy for antibiotic classes. The practical implications of these findings are in the design of antibiotic dosing schedules: aminoglycosides are now frequently given as a single large dose daily to leverage the concentration-dependent activity, while some clinicians are administering beta-lactam drugs such as ceftazidime as continuous or prolonged infusions because of their time-dependent activity. As target values for these parameters that predict efficacy are found, there may be an increase in the individualization of dosing of antibiotics to achieve these target values.

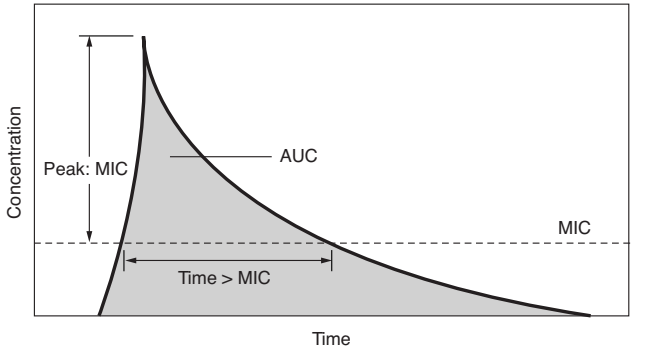


Figure 3–2
Pharmacokinetic/Pharmacodynamic Relationships

Adverse Consequences of Antibiotic Use

4

Although antibiotics are undoubtedly one of the most beneficial discoveries of science, their use does carry risks. They can adversely affect patients by eliciting allergic reactions, causing direct toxicity, or altering the normal bacterial flora, leading to superinfections with other organisms. Antibiotic use is the primary driving force in the development of antibiotic resistance, which can affect not only the treated patients but other patients by transmission of resistant organisms. It is important to keep in mind all of these potential adverse consequences when using antibiotics.

Antibiotic Allergy

Through formation of complexes with human proteins, antibiotics can trigger immunologic reactions. These reactions may manifest immediately (such as anaphylaxis or hives) or be delayed (rashes, serum sickness, drug fever). Because of their highly reactive chemical structure and frequent use, beta-lactam drugs are the most notorious group of drugs for causing allergic reactions. It is difficult to determine how likely it is that a patient with an allergy to a particular antibiotic agent will have a similar reaction to another agent within that class. While some (highly debated) estimates of the degree of cross-reactivity

are available for beta-lactam drugs, estimates for cross-reactivity within other classes (for example, between fluoroquinolones) are essentially nonexistent. Because labeling a patient with an allergy to a particular antibiotic can limit future treatment options severely and possibly lead to the selection of inferior drugs, every effort should be made to clarify the exact nature of a reported allergy.

Antibiotic Toxicities

Despite being designed to affect the physiology of microorganisms rather than humans, antibiotics can have direct toxic effects on patients. In some cases this is an extension of their mechanism of action when selectivity for microorganisms is not perfect. For example, the hematologic adverse effects of trimethoprim stem from its inhibition of folate metabolism in humans, which is also its mechanism of antibiotic effect. In other cases, antibiotics display toxicity through unintended physiologic interactions, such as when vancomycin stimulates histamine release, leading to its characteristic red man syndrome. Some of these toxicities may be dose related and can be attenuated by dose reduction; this often occurs when doses are not adjusted properly for renal dysfunction and thus accumulate to a toxic level.

Superinfection

As Appendix 1 illustrates, the human body is colonized by a variety of bacteria and fungi. These organisms are generally considered commensals, in that they benefit from living on or in the body but do not cause harm (within their ecologic niches). Colonization with commensal organisms can be

beneficial, given that they compete with and crowd out more pathogenic organisms. When administration of antibiotics kills off the commensal flora, pathogenic drug-resistant organisms can flourish because of the absence of competition. This is considered a superinfection (i.e., an infection on top of another infection). For example, administration of antibiotics can lead to the overgrowth of the gastrointestinal (GI) pathogen *Clostridium difficile*, which is often resistant to most antibiotics. *C. difficile* can cause diarrhea and life-threatening bowel inflammation. Similarly, administration of broad-spectrum antibacterial drugs can select for the overgrowth of fungi, most commonly yeasts of the genus *Candida*. Disseminated *Candida* infections carry a high risk of mortality. To reduce the risk of superinfection, antibiotics should be administered only to patients with proven or probable infections, using the most narrow-spectrum agents appropriate to the infection for the shortest effective duration.

Antibiotic Resistance

Thousands of studies have documented the relationship between antibiotic use and resistance, both at a patient level (if you receive an antibiotic, you are more likely to become infected with a drug-resistant organism) and a society level (the more antibiotics a hospital, region, or country uses, the greater the antibiotic resistance). The development of antibiotic resistance leads to a vicious spiral where resistance necessitates the development of broader-spectrum antibiotics, leading to evolution of bacteria resistant to those new antibiotics, requiring ever broader-spectrum drugs, and so on. This is particularly problematic because antibiotic

development has slowed down greatly. Although we can see clearly the broad relationship between antibiotic use and resistance, many of the details of this relationship are not clear. Why do some bacteria develop resistance rapidly and others never develop resistance? What is the proper duration of treatment to maximize the chance of cure and minimize the risk of resistance?

Guidelines

Until we develop a more sophisticated understanding of the relationship between antibiotic use and resistance on a micro level, we are left with some general guidelines for minimizing the potential for development of resistance:

Avoid Using Antibiotics to Treat Colonization or Contamination

A substantial percentage of all antibiotic use is directed toward patients who are not truly infected, but in whom organisms are recovered from culture. Isolation of *Staphylococcus epidermidis* from a single blood culture or *Candida* species from a urinary culture in a catheterized patient are common situations in which patients should be scrutinized to determine whether an infection is truly present. A proper diagnosis is key.

Use the Most Narrow-Spectrum Agent Appropriate for the Patient's Infection

Broader-spectrum agents multiply the number of bacteria affected by the drug, increasing the chances both for development of resistance and superinfection. "Broader" and "newer" are not synonymous with "better": for example, good old penicillin

kills susceptible organisms more rapidly than almost any drug on the market. The treating clinician's goal always should be definitive, narrow-spectrum therapy.

Use the Proper Dose

Bacteria that are exposed to low concentrations of antibiotics are more likely to become resistant than those exposed to effective doses. After all, dead bugs don't mutate! Further research in pharmacodynamics should make it easier to determine the proper dose for each patient and thus to reduce the likelihood that resistance will develop.

Use the Shortest Effective Duration of Therapy

Unfortunately, duration of therapy is one of the least-studied areas of infectious diseases. Examination of standard treatment durations says much more about how humans think than about how antibiotics and bacteria truly interact—durations are typically 5, 7, 10, or 14 days, more in line with our decimal system and the days in a week than with anything studied precisely. New studies are showing that shorter durations of therapy are often just as effective as prolonged courses and possibly less likely to select for resistance. As studies progress and determine additional factors that indicate when infections are sufficiently treated, it should be possible to define more accurately the length of therapy on a patient-by-patient basis. Many clinicians find that "old habits die hard," however, and should remember that learning new evidence about duration of therapy is important as it emerges.

PART
2

Antibacterial Drugs

5 Beta-Lactams

Introduction to Beta-Lactams

Beta-lactams include a wide variety of antibiotics that seem to exist only to confuse students and clinicians. Penicillins, cephalosporins, and carbapenems are all beta-lactams. Monobactams (aztreonam) are structurally similar, but they lack one of the two rings that other beta-lactams have and have little to no cross-allergenicity with other beta-lactams. To make matters more confusing, not all beta-lactams end in *-cillin* or *-penem* or start with *ceph-*.

We believe the best approach to keeping beta-lactams straight is to group them into classes and learn the characteristics of each class. If you work in a hospital, you will likely have only one or two drugs of each class to worry about. Fortunately, all beta-lactams have a few things in common.

- All beta-lactams can cause hypersensitivity reactions, ranging from mild rashes to drug fever to acute interstitial nephritis (AIN) to anaphylaxis. There is some cross-sensitivity among classes, but there is no way to predict exactly how often that will occur. Studies on the matter differ greatly in their conclusions.
- Seizures can result from very high doses of any beta-lactam. Some are more notorious for this

adverse effect than others. Accumulation to toxic levels can occur when the dose of a beta-lactam is not properly adjusted for a patient's renal function. Did you check your patient's renal function?

- All beta-lactams share a mechanism of action—inhibition of transpeptidases (that is, penicillin-binding proteins) in the bacterial cell wall. Thus, giving two beta-lactams in combination for the same infection is generally not useful. There are a few exceptions to this rule, but not many.
- All beta-lactams lack activity against atypical organisms such as *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*. Add another drug to your regimen if you are concerned about these bugs, as in cases of community-acquired pneumonia.
- Nearly all currently available beta-lactams lack activity against MRSA. Add vancomycin or another agent if this bug is suspected. Among the available beta-lactams, only the recently approved cephalosporin ceftaroline has anti-MRSA activity.

Once you know the similarities among beta-lactams, it is easier to learn the differences among them.

Penicillins

Introduction to Penicillins

Penicillins are one of the largest and oldest classes of antimicrobial agents. Since the development of the natural penicillins in the 1930s, further penicillin development has been directed by the need to combat increasing antimicrobial resistance. Classes of penicillins with expanded Gram-negative spectra overcome the shortfalls of natural penicillins, and they can be grouped fairly easily by spectrum of activity.

Penicillins have several things in common:

- Penicillins have very short half-lives (< 2 hours) and must be dosed multiple times per day. The half-lives of most of them are prolonged in the presence of renal dysfunction.
- Like other beta-lactams, penicillins can cause hypersensitivity reactions. If a patient has a true hypersensitivity reaction to a penicillin, other penicillins should be avoided, even if they are from different subclasses of penicillins. If the reaction is not severe, cephalosporins or carbapenems may be useful.
- Many penicillins are relatively poorly absorbed, even those available as oral formulations. This can lead to diarrhea when oral therapy is

needed. Pay attention to the dosing of oral versus intravenous (IV) penicillins—often, a conversion from IV to oral therapy means there will be a substantial decrease in the amount of active drug in the body.

Many penicillins were developed after the natural penicillins became available. Until researchers developed beta-lactamase inhibitors, development primarily focused on *either* improved activity against staphylococci (MSSA) or GNRs (**Figure 5–1**).

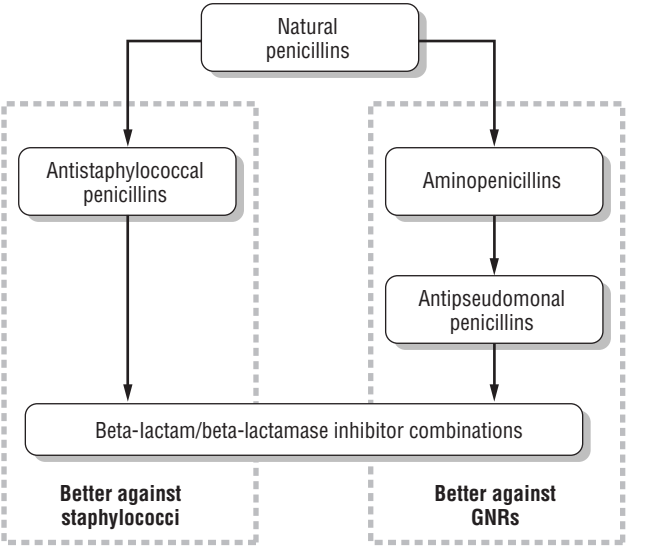


Figure 5–1
Penicillin Drug Development

Natural Penicillins

Agents: penicillin G, penicillin V

All of us have heard of the discovery of penicillin by Sir Alexander Fleming in 1929. Once penicillin was isolated years later, it had a major impact on society, particularly in the treatment of wound infections. The importance of this discovery became apparent during World War II, when the Allies had access to penicillin and the Axis did not. Unfortunately, staphylococci quickly became resistant to penicillin, initiating the search for new beta-lactams and leading to the confusing array of these drugs available today. The development of resistance has narrowed the spectrum of effectiveness of natural penicillins considerably over the past 60 years, such that staphylococci are almost universally resistant to them. Occasionally we still see an isolate of *Staphylococcus aureus* that is susceptible to penicillin.

Spectrum

Good: *Treponema pallidum*, most streptococci
Moderate: *Streptococcus pneumoniae*, enterococci
Poor: almost everything else

Adverse Effects

Similar to those of other beta-lactams.

Important Facts

- Natural penicillins have a very short half-life and must be dosed frequently or given by continuous infusion. Long-acting depot formulations (procaine, benzathine) are available for intramuscular administration. It is important to know the differences among these formulations because the doses vary considerably. It is even more important not to give procaine or benzathine products intravenously, which can be fatal.
- Penicillin V is the oral form of penicillin G. Other drugs have supplanted it in most, but not all, uses.
- Penicillin G remains the drug of choice for syphilis.
- Because of resistance, penicillin is a poor empiric choice for most infections. Not all textbooks and references have been updated to reflect the changes in penicillin use that have resulted from widespread resistance.

What They're Good For

Syphilis, particularly neurosyphilis. During penicillin shortages, hospitals often reserve its use for this indication. Penicillin is also used in susceptible streptococcal infections such as pharyngitis or endocarditis.

Don't Forget!

Other, more conveniently dosed narrow-spectrum beta-lactams are available for bugs treatable with penicillin.

Antistaphylococcal Penicillins

Agents: nafcillin, oxacillin, dicloxacillin, methicillin, cloxacillin

It did not take long for *Staphylococcus* species to become resistant to penicillin. Within a few years of penicillin becoming widely available, staphylococcal strains began to produce beta-lactamases, rendering penicillin useless in these infections. The basic structure of penicillin was modified to resist these destructive enzymes, leading to the antistaphylococcal penicillins. This modification gave these drugs activity against staphylococci that produce penicillinases (beta-lactamases active against penicillins), but did not add to the poor Gram-negative activity of the natural penicillins.

Spectrum

Good: MSSA, streptococci
Poor: GNRs, enterococci, anaerobes, MRSA

Adverse Effects

Similar to those of other beta-lactams, with a possibly higher incidence of AIN.

Important Facts

- Antistaphylococcal penicillins have a short half-life and must be dosed frequently. This

presents a problem, because they cause phlebitis. Does your patient have phlebitis? Try a first-generation cephalosporin instead.

- Most antistaphylococcal penicillins are eliminated from the body in large part by the liver and do not need to be adjusted in cases of renal dysfunction.
- These drugs are interchangeable therapeutically. Therefore, *Staphylococcus aureus* that is susceptible to methicillin (which is no longer used) is susceptible to oxacillin, nafcillin, and the rest. That is, MSSA = OSSA = NSSA, etc.

What They're Good For

Infections caused by MSSA, such as endocarditis and skin and soft-tissue infections.

Don't Forget!

Beta-lactams kill staphylococci more quickly than vancomycin, so patients with MSSA infections who lack serious beta-lactam allergies should be switched to beta-lactams, such as antistaphylococcal penicillins.

Aminopenicillins

Agents: amoxicillin, ampicillin

Though the antistaphylococcal penicillins improve on the Gram-positive coverage of natural penicillins, they do not add to their Gram-negative coverage. Aminopenicillins are more water-soluble and pass through porin channels in the cell wall of some Gram-negative organisms. However, they are susceptible to beta-lactamases, and resistance to them has become fairly common in many institutions. Aminopenicillins are rarely active against staphylococci, because these almost always produce penicillinases. Also, remember that these drugs do not have useful activity against *Pseudomonas aeruginosa*.

Spectrum

Good: streptococci, enterococci
Moderate: enteric GNRs, *Haemophilus*
Poor: staphylococci, anaerobes

Adverse Effects

Similar to those of other beta-lactams. Aminopenicillins have a high incidence of diarrhea when given orally.

Important Facts

- Though ampicillin can be given orally, amoxicillin is a better choice. It is more bioavailable, better tolerated, and administered less frequently. Use ampicillin for IV therapy, and amoxicillin for oral therapy. Europeans disagree; they use amoxicillin intravenously also.
- Ampicillin is a drug of choice for susceptible enterococci.

What They're Good For

Infections caused by susceptible GNRs, enterococci, and streptococci. Because resistance among GNRs is prevalent, aminopenicillins are used only infrequently in complicated nosocomial infections. Amoxicillin is frequently prescribed for infections of the upper respiratory tract, including streptococcal pharyngitis (strep throat) and otitis media (ear infection).

Don't Forget!

To achieve bactericidal activity against enterococci, ampicillin (or any other beta-lactam) has to be combined with an aminoglycoside. This should be done in serious infections such as endocarditis.

Antipseudomonal Penicillins

Agents: piperacillin, mezlocillin, carbenicillin, **ticarcillin**

None of the penicillins we have discussed thus far offer appreciable activity against *Pseudomonas aeruginosa*, a common nosocomial pathogen that is often resistant to multiple antibiotics. Enter the antipseudomonal penicillins. These agents are active against *Pseudomonas aeruginosa* and other more drug-resistant GNRs. However, they are just as susceptible to beta-lactamases as penicillin and ampicillin, so they are not antistaphylococcal. Also, strains of GNRs that produce beta-lactamases are resistant to them. They do have activity against streptococci and enterococci.

Spectrum

Good: *Pseudomonas aeruginosa,* streptococci, enterococci
Moderate: enteric GNRs, *Haemophilus*
Poor: staphylococci, anaerobes

Adverse Effects

Similar to those of other beta-lactams.

Important Facts

- These drugs retain the Gram-positive activity of penicillin and are active against many streptococci and enterococci.
- Antipseudomonal penicillins can be used by themselves or, more commonly, in combination with a beta-lactamase inhibitor (see the next section).
- Piperacillin is the most frequently prescribed of these agents. It has stronger antipseudomonal activity than ticarcillin. Carbenicillin may be administered orally, but it does not achieve useful concentrations for the treatment of anything except UTIs. Mezlocillin is not commonly used.

What They're Good For

Infections caused by susceptible *Pseudomonas* or other GNRs. If a Gram-positive organism is susceptible to an antipseudomonal penicillin, it will be susceptible to at least one narrower-spectrum penicillin as well, and the narrower-spectrum drug should generally be used.

Don't Forget!

These drugs are useful step-down agents in the treatment of infections caused by *Pseudomonas aeruginosa*. However, they are not good empiric therapeutic choices, because other GNRs that cause nosocomial infections may be resistant to them (such as *E. coli*). Start with a beta-lactamase-resistant agent, then change your therapy to an antipseudomonal penicillin if susceptibilities allow.

Beta-Lactam/Beta-Lactamase Inhibitor Combinations

Agents: ampicillin/sulbactam, amoxicillin/clavulanate, piperacillin/tazobactam, ticarcillin/clavulanate

Though the aminopenicillins and antipseudomonal penicillins have good intrinsic activity against GNRs, they remain just as susceptible to beta-lactamases as penicillin G. This means that they are not useful against the vast majority of staphylococci or many GNRs and anaerobes, because these organisms have learned to produce beta-lactamase. In other words, it seemed we learned either how to make a penicillin resistant to beta-lactamase, or how to make it more active against GNRs, but not both. Beta-lactamase inhibitors counter beta-lactamases; these drugs mimic the structure of beta-lactams but have little antimicrobial activity on their own. They bind to beta-lactamases irreversibly, preventing the beta-lactamase from destroying any beta-lactams that are co-administered and enabling the therapeutic beta-lactam to be effective.

When considering the activity of the beta-lactam/beta-lactamase inhibitor combination, remember that the beta-lactamase inhibitor only frees up the beta-lactam to kill the organism—it doesn't

enhance the activity. Therefore, the combination products are active only against the bacteria that the beta-lactam in the combination has intrinsic activity against. For example, ampicillin/sulbactam is active against beta-lactamase producing *E. coli*, because ampicillin alone is active against non-beta-lactamase producing *E. coli*. However, it has no useful activity against *Pseudomonas aeruginosa,* because ampicillin lacks activity against this organism. In contrast, piperacillin/tazobactam is active against *P. aeruginosa* because piperacillin alone is useful. Though these drugs have very broad spectra of activity, there are differences among the agents. Keep in mind the rule that beta-lactamase inhibitors restore activity, not add to it, to set them straight.

Spectrum

Good: MSSA, streptococci, enterococci, many anaerobes, enteric GNRs, *Pseudomonas aeruginosa* (only piperacillin/ tazobactam and ticarcillin/clavulanate)

Moderate: GNRs with advanced beta-lactamases

Poor: MRSA, extended-spectrum beta-lactamase (ESBL) producing GNRs

Adverse Effects

Similar to those of other beta-lactams.

Important Facts

- Unlike the other members of this class, amoxicillin/clavulanate is available orally. Various doses are available, but higher doses are associated with more diarrhea.
- The beta-lactamase inhibitors packaged in these combinations are not active against all

beta-lactamases. New beta-lactamases with the ability to destroy many types of beta-lactams are continually being discovered and are becoming more prevalent.

- Except for study purposes, beta-lactamase inhibitors are not available outside of the combination products.
- Sulbactam has good activity against *Acinetobacter baumannii*, a highly drug-resistant GNR that causes nosocomial infections. For this reason, high doses of ampicillin/sulbactam can be used in the treatment of infections caused by this organism.

What They're Good For

Empiric therapy of nosocomial infections, particularly nosocomial pneumonia (not aminopenicillin-based combinations). Because they have activity against aerobes and anaerobes, they are a good empiric choice for mixed infections, such as intra-abdominal infections, diabetic ulcers, and aspiration pneumonia.

Don't Forget!

Narrow your coverage once culture results return. These are good choices of empiric therapy, but poor choices of definitive therapy if alternatives are available. Be sure you know which drugs are antipseudomonal and which are not—this is a major difference among these agents that drives their use. Ampicillin/sulbactam is a poor choice for nosocomial pneumonia, and piperacillin/tazobactam is overkill for community-acquired pneumonia.

Cephalosporins

Introduction to Cephalosporins

The cephalosporins are probably the most confusing group of antibiotics. For convenience, they have been grouped into "generations" that largely correlate with their spectrum of activity, with some notable exceptions. Although there are many different individual agents, the good news is that most hospitals use only a few of them, so, in practice, learning your institution's cephalosporins of choice is easy. In general, it is best to learn the characteristics of each generation and then learn the quirks about the individual agents.

Cephalosporins have several elements in common:

- All have some cross-allergenicity with penicillins, though there are differences among generations. Estimates about the likelihood of cross-reactivity between penicillin and cephalosporin allergies differ. It is likely very low, below the oft-quoted 10%. A reasonable estimate is no more than 3% to 5%, though some publications support even lower numbers, particularly for later-generation agents. However, using any cephalosporin in a patient with a penicillin allergy is a matter of balancing risks

and benefits. Assess the validity of the patient's allergy through interview and consider the level of risk associated with cephalosporin administration. Be skeptical of nausea, but be sure to take hives and any signs of anaphylaxis very seriously! Use alternative classes of antibiotics when practical.

- The cephalosporins are generally more resistant to beta-lactamases than penicillins are. Beta-lactamases that are active against penicillins but inactive against cephalosporins are called *penicillinases*. Beta-lactamases that inactivate cephalosporins (*cephalosporinases*) also exist and are increasing in prevalence.
- None of the currently available cephalosporins have useful activity against enterococci.

First-Generation Cephalosporins

Agents: cefazolin, cephalexin, cefadroxil, cephalothin

First-generation cephalosporins are the most commonly used class of antibiotics in the hospital. Why? They are used immediately prior to surgery to prevent surgical site infections. Their spectrum of activity, inexpensive cost, and low incidence of adverse effects make them ideal for this purpose.

Spectrum

Good: MSSA, streptococci
Moderate: some enteric GNRs
Poor: enterococci, anaerobes, MRSA, *Pseudomonas*

Adverse Effects

Similar to those of other beta-lactams.

Important Facts

- First-generation cephalosporins are good alternatives to antistaphylococcal penicillins. They cause less phlebitis and are infused less frequently. Unlike antistaphylococcal penicillins, however, they do not cross the blood-brain barrier and should not be used in central nervous system (CNS) infections.

- Cephalexin and cefadroxil are available orally; the others are parenteral.

What They're Good For

Skin and soft-tissue infections, surgical prophylaxis, staphylococcal endocarditis (MSSA).

Don't Forget!

Surgical prophylaxis is the most common indication for first-generation cephalosporins in the hospital. Be sure to limit the duration of therapy for this use; administering more than one dose of antibiotics should be uncommon, and giving more than 24 hours of antibiotics is rarely justified. Such use does not lower infection rates, but it can select for more resistant organisms later in the hospital stay.

Second-Generation Cephalosporins

Agents: cefuroxime, cefoxitin, cefotetan, cefprozil, loracarbef, cefmetazole, cefonicid, cefamandole, cefaclor

Compared with first-generation cephalosporins, second-generation agents have better Gram-negative activity and somewhat weaker Gram-positive activity, though they are still used for these organisms. They are more stable against Gram-negative beta-lactamases and are particularly active against *Haemophilus influenzae* and *Neisseria gonorrheae*. Though the second-generation agents are the most numerous cephalosporins, they are probably the least utilized in U.S. hospitals.

Spectrum

Good: some enteric GNRs, *Haemophilus*, *Neisseria*
Moderate: streptococci, staphylococci, anaerobes (only cefotetan, cefoxitin, cefmetazole)
Poor: enterococci, MRSA, *Pseudomonas*

Adverse Effects

Similar to those of other beta-lactams. Cephalosporins with the N-methylthiotetrazole (MTT) side chain—cefamandole, cefmetazole, and cefotetan—

can inhibit vitamin K production and prolong bleeding. These MTT cephalosporins can also cause a disulfuram-like reaction when co-administered with ethanol. While most people in the hospital do not have access to alcoholic beverages while being treated for infections, outpatients need to be counseled on this interaction. The interaction is a common question on board exams.

Important Facts

- Cefoxitin, cefotetan, and cefmetazole are cephamycins. They are grouped with the second-generation cephalosporins because they have similar activity, with one important exception: anaerobes. Cephamycins have activity against many anaerobes in the GI tract, and cefoxitin and cefotetan are often used for surgical prophylaxis in abdominal surgery.
- Loracarbef is technically a carbacepham. You should immediately forget this to allow room for more important facts.
- Cefaclor, cefprozil, and loracarbef are available only orally. Cefuroxime is available in both IV and oral formulations, and the others are IV only.
- Like first-generation cephalosporins, second-generation agents do not cross the blood-brain barrier well enough to be useful to treat CNS infections.

What They're Good For

Upper respiratory tract infections, community-acquired pneumonia, gonorrhea, surgical prophylaxis (cefotetan, cefoxitin, cefuroxime).

Don't Forget!

The cephamycins have good intrinsic anaerobic activity, but resistance to them is increasing in *Bacteroides fragilis* group infections. When using them for surgical prophylaxis, limit the duration of antibiotic exposure after surgery. If an infection does develop, use alternative agents such as beta-lactamase inhibitor combinations or another Gram-negative agent with metronidazole.

Third-Generation Cephalosporins

Agents: ceftriaxone, cefotaxime, ceftazidime, cefdinir, cefpodoxime, cefixime, ceftibuten

Third-generation cephalosporins have greater Gram-negative activity than the first- and second-generation drugs. They also have good streptococcal activity, but generally lesser staphylococcal activity than previous generations of cephalosporins. These are broad-spectrum agents that have many different uses.

Spectrum

Good: streptococci, enteric GNRs, *Pseudomonas* (ceftazidime only)
Moderate: MSSA (except ceftazidime, which is poor)
Poor: enterococci, *Pseudomonas* (except ceftazidime), anaerobes, MRSA

Adverse Effects

Similar to those of other beta-lactams. Third-generation cephalosporins have been shown to be one of the classes of antibiotics with the strongest association with *Clostridium difficile*–associated diarrhea. Cefpodoxime has the MTT side chain that can inhibit vitamin K production (see section on second-generation cephalosporins for details).

Important Facts

- Ceftazidime is the exception to the spectrum of activity rule for third-generation agents. Unlike the others, it is antipseudomonal and lacks clinically useful activity against Gram-positive organisms.
- Ceftriaxone, cefotaxime, and ceftazidime cross the blood-brain barrier effectively and are useful for the treatment of CNS infections. However, their differences in spectrum lead clinicians to use them for different types of infections. Ceftazidime would be a poor choice for community-acquired meningitis, in which *Streptococcus pneumoniae* predominates.
- Third-generation cephalosporins are notorious for inducing resistance among GNRs. Though they can be useful in nosocomial infections, too much broad-spectrum utilization can result in harder-to-treat organisms.
- Ceftriaxone has the characteristic of having dual modes of elimination via both renal and biliary excretion. It does not need to be adjusted for renal dysfunction.
- Ceftriaxone has two problems that make its use in neonates problematic: it interacts with calcium-containing medications to form crystals that can precipitate in the lungs and kidneys, which has led to fatalities, and it can also lead to biliary sludging with resultant hyperbilirubinemia. Cefotaxime is a safer drug for these young patients.

What They're Good For

Lower respiratory tract infections, pyelonephritis, nosocomial infections (ceftazidime), Lyme disease

(ceftriaxone), meningitis, skin and soft-tissue infections, febrile neutropenia (ceftazidime).

Don't Forget!

Ceftriaxone is a once-daily drug for almost all indications *except* meningitis. Make sure your meningitis patients receive the full 2 gram IV q12h dose and also use vancomycin and ampicillin (if indicated).

Fourth-Generation Cephalosporins

Agent: cefepime

There is only one fourth-generation cephalosporin, cefepime. Cefepime is the broadest-spectrum cephalosporin, with activity against both Gram-negative organisms, including *Pseudomonas,* and Gram-positive organisms. One way to remember its spectrum is to think that cefazolin + ceftazidime = cefepime.

Spectrum

Good: MSSA, streptococci, *Pseudomonas*, enteric GNRs
Moderate: Acinetobacter
Poor: enterococci, anaerobes, MRSA

Adverse Effects

Similar to those of other beta-lactams.

Important Facts

- Cefepime is a broad-spectrum agent. It is a good empiric choice for many nosocomial infections, but overkill for most community-acquired infections. Be sure to de-escalate therapy if possible when you treat empirically with cefepime.

- For monotherapy of febrile neutropenia, cefepime is a better choice than ceftazidime because of its better Gram-positive activity. It may also induce less resistance in GNRs than third-generation cephalosporins, but it is still not a good drug to overuse.
- Cefepime briefly had a bad reputation after a meta-analysis showed increased mortality with its use compared with other drugs. Many clinicians were skeptical, however, and a more thorough FDA analysis exonerated cefepime.

What It's Good For

Febrile neutropenia, nosocomial pneumonia, post-neurosurgical meningitis, other nosocomial infections.

Don't Forget!

Cefepime is used primarily for nosocomial infections. Although it is indicated for infections of the urinary tract and lower respiratory tract, it is overkill for most community-acquired sources of these infections.

Fifth-Generation Cephalosporins

Agents: ceftaroline, ceftobiprole

Two new cephalosporins have recently been developed with unique characteristics. We are anticipating that they will be marketed as "fifth-generation" cephalosporins, although there is no consensus on the issue yet. What makes these agents unique is their activity against MRSA. Their structures have been engineered to bind to the penicillin-binding protein 2a of MRSA that has low affinity for other beta-lactams. Unlike other cephalosporins, these agents also have modest activity against *Enterococcus faecalis* (but not *Enterococcus faecium*). They lose some of the Gram-negative potency of cefepime; their Gram-negative activity is closer to that of ceftriaxone. In an era of high MRSA prevalence, these agents offer intriguing possibilities for therapy, but because they are so new their role is not yet defined.

Spectrum

Good: MSSA, MRSA, streptococci, enteric GNRs
Moderate: Acinetobacter, Enterococcus faecalis
Poor: Pseudomonas aeruginosa, Enterococcus faecium, anaerobes

Adverse Effects

Information available to date from clinical trials suggests adverse effects of these agents are similar to those of other beta-lactams.

Important Facts

- As is typical for new antimicrobials coming to market, the initial indications for these agents are "low-hanging fruit": skin and soft tissue infections and community-acquired pneumonia. These are indications for which there are already a great many agents available. The challenge will be to determine what the role of these drugs is for hospital-acquired pneumonia and other severe diseases often caused by drug-resistant pathogens.

What They're Good For

Ceftaroline is approved (in the United States) for treatment of complicated skin and soft tissue infections and community-acquired pneumonia. Ceftobiprole is approved for treatment of complicated skin and soft tissue infections in Canada but has not been approved in the United States at this time.

Don't Forget!

If you want to think about these drugs as fifth-generation agents, just don't forget that their Gram-negative activity is less compared to the fourth generation, especially as regards *Pseudomonas aeruginosa*.

Carbapenems

Agents: imipenem/cilastatin, meropenem, ertapenem, doripenem

Carbapenems are among our most broad-spectrum antibacterial drugs, particularly imipenem, doripenem, and meropenem. They possess a beta-lactam ring and share the same mechanism of action of beta-lactams, but they are structurally unique and differ from both penicillins and cephalosporins. Their broad spectrum makes them both appealing and unappealing for empiric therapy, depending on the infection being treated and the risk factors of the patient for a resistant organism. Imipenem, doripenem, and meropenem have similar spectra of activity; ertapenem has important deficiencies in its spectrum that must be learned.

Spectrum

Good: MSSA, streptococci, anaerobes, enteric GNRs, *Pseudomonas* (not ertapenem), *Acinetobacter* (not ertapenem), ESBL-producing GNRs
Moderate: enterococci (not ertapenem)
Poor: MRSA, penicillin-resistant streptococci

Adverse Effects

Similar to those of other beta-lactams, but with a higher propensity to induce seizures. This is partic-

ularly problematic with imipenem. Minimize the risk by calculating appropriate doses for patients with renal dysfunction and avoiding imipenem use in patients with meningitis, because it can cross the blood-brain barrier more readily.

Important Facts

- Imipenem is metabolized in the kidney to a nephrotoxic product. Cilastatin blocks the renal dehydropeptidase that catalyzes this reaction and prevents this metabolism from occurring. It is always co-administered with imipenem for this reason.
- Carbapenems are very broad-spectrum agents. Imipenem, doripenem, and meropenem are particularly broad and should not be used empirically for most community-acquired infections. They are good choices for many types of nosocomial infections, particularly in patients who have received many other classes of antibiotics during their hospital stay.
- Although ertapenem has weaker activity than the other carbapenems for a few organisms, this activity is significant enough to change the utility of the drug. Ertapenem is a poor choice for many nosocomial infections, particularly nosocomial pneumonia in which both *Pseudomonas* and *Acinetobacter* are important pathogens. However, it is administered only once a day and thus more convenient than the other carbapenems, so it may be a better choice for home infusion therapy for susceptible infections.
- Carbapenems may elicit an allergic reaction in patients with a history of penicillin allergy. One study showed the incidence of such reactions to

be as high as 50% with a proven penicillin allergy (keep in mind that many penicillin allergies are unproven), but more recent and better-performed studies have shown this number to be much lower (close to 1%). Nevertheless, take the possibility of cross-reactivity seriously. Keep in mind that even if the cross-reactivity is very low between these agents, patients with a history of allergy to any drug are more likely to react to another one.

What They're Good For

All: mixed aerobic/anaerobic infections, infections caused by ESBL-producing organisms, intra-abdominal infections

Imipenem, doripenem, meropenem: nosocomial pneumonia, febrile neutropenia, other nosocomial infections

Don't Forget!

Check your dosing in patients with renal dysfunction to minimize the risk of carbapenem-induced seizures.

Monobactams

Agent: aztreonam

Aztreonam is the only monobactam available. Structurally, aztreonam contains only the four-membered ring of the basic beta-lactam structure, hence the name *monobactam*. Aztreonam's quirk is that it seems to be safe to administer to patients with allergies to other beta-lactams, except patients who have a specific allergy to ceftazidime. This cross-reactivity seems to be a result of the fact that ceftazidime and aztreonam share an identical side chain. Ceftazidime and aztreonam also share virtually the same spectrum of activity. It is reasonably safe to remember the utility of aztreonam by thinking of it as ceftazidime without allergic cross-reactivity with other beta-lactams.

Spectrum

Good: *Pseudomonas*, most GNRs
Moderate: *Acinetobacter*
Poor: Gram-positive organisms, anaerobes

Adverse Effects

Similar to those of other beta-lactams, but with a low incidence of hypersensitivity.

Important Facts

- Aztreonam shares a mechanism of action and pharmacodynamic profile with other beta-lactams. Because it is a Gram-negative drug that is often used in patients with penicillin allergies, it is often confused with aminoglycosides. It is chemically unrelated to aminoglycosides and does not share their toxicities.
- Aztreonam can be administered via inhalation to patients with cystic fibrosis to prevent exacerbations of infection.
- Aztreonam is a type of beta-lactam, and combination therapy with it and other beta-lactams against the same organism is unwarranted. Try adding a non-beta-lactam drug to your empiric regimen for serious nosocomial infections instead.

What It's Good For

Gram-negative infections, including *Pseudomonas*, particularly in patients with a history of beta-lactam allergy.

Don't Forget!

Before using aztreonam in your patients with beta-lactam allergies, investigate whether the reaction was specifically to ceftazidime. If you cannot determine this and the reaction was serious, proceed with caution or use an alternative agent.

6 Glycopeptides

Agents: vancomycin, telavancin

To date, there are three glycopeptides in clinical use: vancomycin, teicoplanin, and telavancin. Teicoplanin is not used in the United States, and telavancin was only recently approved. At least two more glycopeptides are in late stages of clinical development: oritavancin and dalbavancin.

Vancomycin is invaluable, because it has activity against all things Gram-positive that have not learned to become resistant to it. Many enterococci (especially *E. faecium*) have figured this out—we call them vancomycin-resistant enterococci (VRE). A few staphylococci have learned vancomycin-resistance from the enterococci, but these staphylococci are currently very rare. In general they are susceptible.

Telavancin is a somewhat different agent. It is a lipoglycopeptide that was modified from vancomycin's structure. It has some unique properties that may be advantageous compared with vancomycin, such as improved activity against MRSA that is less susceptible to vancomycin, but its place in therapy is still being determined.

Spectrum

Good: MSSA, MRSA, streptococci, *Clostridium difficile*
Moderate: enterococci
Poor: anything Gram-negative

Adverse Effects

Ototoxicity and nephrotoxicity are adverse effects classically assigned to vancomycin. Although the historical evidence linking these with vancomycin is poor, recent studies have shown that it may be nephrotoxic in high doses. The early formulation of vancomycin was brown, and clinicians trying to amuse themselves dubbed it "Mississippi mud." The current formulation is clear and lacks those potentially toxic excipients. A histamine-mediated reaction called red man syndrome can occur; the patient may feel warm, flushed, and can be hypotensive. This reaction can be prevented by slowing the infusion rate and is not a true allergy. Antihistamines can also ameliorate the reaction.

Telavancin has renal toxicity issues as well. Taste disturbances and foamy urine are more common. Telavancin should not be given to pregnant women because of problems seen in animal studies. Because telavancin is a modification of vancomycin, red man syndrome may also occur with telavancin.

Dosing Issues

Vancomycin is often pharmacokinetically monitored, but the evidence that these concentrations mean anything is lacking, particularly for peak concentrations. Trough concentrations can be used to ensure that the drug is not being eliminated too quickly or slowly, and different indications have

different preferred trough ranges. Recent data indicate that higher troughs may be associated with nephrotoxicity.

Important Facts

- Oral vancomycin is absorbed poorly. Its only use is for the treatment of *Clostridium difficile*–associated disease. Also, IV vancomycin does not reach intracolonic concentrations high enough to kill *C. difficile*, so oral is the only way to go.
- Do not overreact if your vancomycin trough is too high. Was it drawn correctly? If so, increase your dosing interval.
- Although vancomycin is active against staphylococci, it does not kill MSSA as quickly as beta-lactams do. Does your patient have MSSA? Use nafcillin or cefazolin instead.
- Recently, a phenomenon described as "MIC creep" has been seen with staphylococci and vancomycin. MICs have been rising to vancomycin in many institutions, and while they have not yet reached the level of resistance, they are increasing within the range labeled as susceptible, that is, ≤ 2 mcg/ml. However, patients receiving vancomycin for serious infections caused by staphylococci with an MIC = 2 mcg/ml to vancomycin have been shown to have worse outcomes than those with lower MICs. This issue warrants careful attention.
- Telavancin is more rapidly bactericidal than vancomycin. This activity may be an advantage in the treatment of some infections, but clinical evidence that shows a benefit is lacking at this point.

What They're Good For

Vancomycin is a drug of choice for MRSA infections and for empiric use when MRSA is a concern, such as for nosocomial pneumonia. It is also useful in other Gram-positive infections when the patient has a severe beta-lactam allergy. Telavancin is indicated only for skin and skin structure infections at this time. It has activity against organisms with decreased vancomycin susceptibility, but its role is still being defined.

Don't Forget!

Are you *sure* that vancomycin trough concentration was drawn correctly?

7 Fluoroquinolones

Agents: ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin

Many of the fluoroquinolones are near-ideal antibiotics: they have broad-spectrum activity that includes Gram-positive, Gram-negative, and atypical organisms; display excellent oral bioavailability; and have a relatively low incidence of adverse effects. Unfortunately, these characteristics have led to overprescribing and the inevitable rise in resistance, despite recommendations to reserve this class. In particular, although activity against enteric Gram-negative organisms (such as *E. coli* and *Klebsiella*) has historically been excellent, in certain geographical regions or patient populations these drugs have lost much of their potency. The newer drugs (moxifloxacin, gemifloxacin) gain increasing Gram-positive (mostly pneumococcal) activity at the expense of some Gram-negative (mostly *Pseudomonas*) activity. Significant differences among the agents are in **bold**.

Spectrum: Ciprofloxacin

Good: enteric GNRs (*E. coli*, *Proteus*, *Klebsiella*, etc.), *H. influenzae*

Moderate: Pseudomonas, atypicals (*Mycoplasma*, *Chlamydia*, *Legionella*)
Poor: staphylococci, *S. pneumoniae*, anaerobes, enterococci

Spectrum: Levofloxacin/Moxifloxacin/ Gemifloxacin

Good: enteric Gram negatives, ***S. pneumoniae,*** atypicals, *H. influenzae*
Moderate: Pseudomonas (**levofloxacin only**), MSSA
Poor: anaerobes (**except moxifloxacin,** which has moderate activity), enterococci

Adverse Effects

GI side effects, headache, and photosensitivity are most common. Rare but serious side effects usually occur in patients with underlying conditions: hyper- or hypoglycemia (diabetes), seizures (seizure disorder), prolongation of the QT interval (underlying arrhythmia or proarrhythmic medications). These effects are dose related, so carefully review dosing in patients with renal dysfunction and the elderly. Arthralgias (uncommonly) and Achilles tendon rupture (very rarely) may occur. Fluoroquinolones also can cause CNS adverse reactions, including dizziness, confusion, and hallucinations. Elderly patients are particularly susceptible to these. Younger patients may develop insomnia.

Because of toxicities seen in juvenile beagle dogs, fluoroquinolones are absolutely contraindicated in pregnant women and relatively contraindicated in children, although experience with use in children suggests they may be used safely.

Dosing Issues

While ciprofloxacin and levofloxacin have activity against *Pseudomonas*, MICs are typically higher than with other susceptible organisms (e.g., *E. coli*). Thus, when using these drugs to treat documented or possible *Pseudomonas* infections, give them at higher, antipseudomonal doses: 400 mg IV q8h or 750 mg PO q12h for ciprofloxacin; 750 mg IV/PO daily for levofloxacin.

Important Facts

- Bioavailability of all fluoroquinolones is 80–100%, so oral dose = IV dose (**except ciprofloxacin**: PO = 1.25 times IV dose).
- Fluoroquinolones chelate cations, and their oral bioavailability is *significantly decreased* when administered with calcium, iron, antacids, milk, or multivitamins. Separate these agents by at least 2 hours or have your patient take a week off of the supplements, if possible. Administration with tube feedings is also problematic. This problem is unique to the oral formulations—IV forms avoid it.
- Most fluoroquinolones are cleared renally and require dose reduction in renal dysfunction. **Moxifloxacin is the exception;** because it is not excreted into the urine, it is also not approved for treatment of UTIs. Gemifloxacin has dual elimination, and its utility in treating UTIs is not yet established, though it does require dose adjustment in renal failure. It is probably best to avoid using gemifloxacin for UTIs until there is evidence that supports its use.

- The FDA has recently added a black box warning to all fluoroquinolone package inserts regarding the possibility of tendon rupture.

What They're Good For

Not everything, despite the temptation. Remember, the longer you want to be able to use these drugs, the more restraint should be exercised now. Indications for the fluoroquinolones are listed in **Table 7–1**.

Don't Forget!

When using the oral forms of fluoroquinolones, be especially careful to avoid co-administering with chelating agents (calcium, magnesium, aluminum, etc.). Also be cautious of using these drugs in patients with conditions or drugs that prolong the QT interval.

TABLE 7–1
Indications for Fluoroquinolones

Indication	Cipro	Levo	Moxi	Gemi
CAP, sinusitis, AECB	–	+	+	+
UTI	+	+	–	?
Intra-abdominal infection	+	+	+	?
Systemic Gram-negative infections	+	+	+	?
Skin/soft tissue infection	–	+	+	+
Single-dose treatment of gonorrhea	+	+	?	?
Pseudomonas infections (+/- beta-lactam)	+	+	–	–
Treatment/prophylaxis in bioterrorism scenarios (active vs. anthrax, plague, tularemia)	+	+	?	?

+ = approved/studied/makes sense for this indication.
? = should work, no clinical data.
– = suboptimal.

8

Aminoglycosides

Agents: gentamicin, tobramycin, amikacin, streptomycin, spectinomycin

The aminoglycosides as a class dispel the notion that antibiotics are largely nontoxic. These drugs have a narrow therapeutic window, and improper dosing carries the risk of inflicting significant toxicity (primarily nephro- and ototoxicity) on your patients. Because of this, there has been a reduction in their use as primary therapy for most infections. That being said, they retain good activity against many problem pathogens (such as *Pseudomonas* and *Acinetobacter*) that have developed resistance to the more benign drug classes. They are also excellent at synergizing with the beta-lactams and glycopeptides to improve the efficiency of bacterial killing. Gentamicin and tobramycin are the most widely used drugs, amikacin is generally reserved for pathogens resistant to the first two, and streptomycin (*Enterococcus*, tuberculosis [TB], and plague) and spectinomycin (gonorrhea) are niche drugs.

Spectrum: Gentamicin/tobramycin/amikacin

Good: Gram-negatives (*E. coli*, *Klebsiella*, *Pseudomonas*, *Acinetobacter*, most others)

Moderate: in combination with a beta-lactam or glycopeptide: staphylococci (including MRSA), viridans streptococci, enterococci

Poor: atypicals, anaerobes, Gram-positive organisms (as monotherapy)

Adverse Effects

Nephrotoxicity: Oliguric acute renal failure, preceded by a rising serum creatinine, is a dose-related adverse effect of aminoglycosides. Risk can be reduced by correct dosing (including the use of extended-interval dosing), as well as avoidance of co-administration of other nephrotoxins (cyclosporin, cisplatin, foscarnet, etc.).

Ototoxicity: Aminoglycosides cause dose-related cochlear and vestibular toxicity. For patients anticipated to receive long-term (> 2 weeks) aminoglycosides, baseline and follow-up audiology are necessary. It is important to monitor patients closely for any hearing loss or balance problems, because these are not reversible and can significantly affect quality of life.

Neuromuscular blockade can occur when aminoglycosides are given, particularly in high doses in patients who are receiving therapeutic paralysis.

Important Facts

- Once-daily or extended-interval aminoglycoside dosing leverages the concentration-dependent killing of the drugs to create an equally effective, more convenient, and possibly safer dosing regimen. However, there are many populations in which once-daily dosing has had minimal study, including the pregnant,

the critically ill, those with significant renal dysfunction, and the morbidly obese. Use this dosing method with caution, if at all, in these populations. Aminoglycosides are pregnancy category D and should be avoided if possible in pregnant women anyway.

- Aminoglycoside serum levels can help guide appropriate dosing and reduce the risk of toxicity, but they must be drawn correctly to have meaningful interpretations. For traditional dosing methods, a peak level should be drawn half an hour after the end of the infusion, while trough levels should be drawn within 30 minutes of the next dose. For once-daily dosing there are a number of potential monitoring points.
- Aminoglycosides have relatively poor distribution into many tissues, including the lungs. They have minimal nervous system penetration. This makes them less than optimal as monotherapy for many severe infections. It also means that a dose should be based on the patient's ideal or adjusted body weight, rather than his or her total body weight. Given the high prevalence of morbid obesity, serious overdosing of patients can occur if the patient's total body weight is used.
- Some older drug references and textbooks list streptomycin as a first-line treatment for tuberculosis. While it was the first anti-tuberculosis drug available, it has been supplanted by safer and more effective first-line drugs (see later chapters). It is still an alternative in resistant tuberculosis infections—these should be treated by an expert in their management.

What They're Good For

In combination with a beta-lactam agent, treatment of serious infections with documented or suspected Gram-negative pathogens, including febrile neutropenia, sepsis, exacerbations of cystic fibrosis, and ventilator-associated pneumonia. Aminoglycosines are also used in combination with a beta-lactam or glycopeptide for treatment of serious Gram-positive infections, including endocarditis, osteomyelitis, and sepsis. In combination with other antimycobacterials, they are used for treatment of drug-resistant infections with *M. tuberculosis* or other mycobacteria (streptomycin and amikacin).

Don't Forget!

Most aminoglycoside toxicity is dose related, so get the dose right from the start by adjusting for renal dysfunction and using ideal or adjusted body weight. Pharmacokinetic concentrations are useful for monitoring and dosing aminoglycosides if they are drawn correctly.

Tetracyclines and Glycylcyclines

9

Agents: doxycycline, minocycline, tetracycline, **tigecycline** (a glycylcycline)

Once considered broad-spectrum antibiotics, the relentless advance of bacterial resistance and the off-patent status of the drugs have reduced the use of tetracyclines to niche indications. They are useful (but not highly studied) alternatives for the treatment of common respiratory tract infections and drugs of choice for a variety of uncommon infections. Doxycycline is preferred in most situations over tetracycline and minocycline. This class may see a revival with the introduction of the glycylcyclines (starting with tigecycline), which evade most tetracycline resistance mechanisms and have a broad spectrum of activity.

Spectrum: Tetracycline/doxycycline/ minocycline

Good: atypicals, rickettsia, spirochetes (e.g., *B. burgdorferi*, *H. pylori*), *Plasmodium* species (malaria)

Moderate: staphylococci (including MRSA), *S. pneumoniae*

Poor: most GNRs, anaerobes, enterococci

Spectrum: Tigecycline

Good: atypicals, enterococci (including VRE), staphylococci (including MRSA), *S. pneumoniae*
Acceptable: most GNRs, anaerobes
Poor: *Pseudomonas*, *Proteus*, *Providencia*

Adverse Effects

GI side effects (nausea, diarrhea) and photosensitivity are most common. Tigecycline, though an IV drug, can cause severe nausea, vomiting, and diarrhea. Tetracyclines can cause esophageal irritation, and patients should take the drug with water, while standing up if possible. Minocycline may cause dizziness and vertigo. All tetracyclines can cause discoloration of developing teeth and are contraindicated in pregnant women and children younger than 8 years old.

Important Facts

- Doxycycline and minocycline bioavailability is approximately 100%. Tigecycline is IV only.
- Tetracyclines chelate cations, and their oral bioavailability is *decreased significantly* when administered with calcium, iron, antacids, or multivitamins. Have patients separate these agents by at least 2 hours or take a week off from the supplements, if possible. Food decreases the absorption of tetracycline substantially, but of minocycline and doxycycline minimally.
- Doxycycline does not need to be adjusted in renal or hepatic dysfunction; tetracycline is eliminated renally and should not be used in cases of renal insufficiency (it can worsen renal dysfunction).

- Tigecycline has a very large volume of distribution, indicating that it distributes highly into many tissues. However, it is eliminated hepatically, achieves low urinary concentrations, and should probably not be used for UTIs. Its extensive distribution also leads to low bloodstream concentrations, and it is not an ideal choice for treating primary bloodstream infections.

What They're Good For

Uncomplicated respiratory tract infections: acute exacerbations of chronic bronchitis, sinusitis, community-acquired pneumonia. They are the drugs of choice for many tick-borne diseases. Use as alternative drugs for skin or soft-tissue infections, syphilis, pelvic inflammatory disease (with cefoxitin). Use as an alternative to ciprofloxacin in bioterrorism scenarios (they are active against anthrax, plague, tularemia). Use for malaria prophylaxis and treatment. Tigecycline may have a role in the treatment of complicated polymicrobial infections, such as intra-abdominal infections and complicated skin and skin structure infections.

Don't Forget!

Ask patients if they take mineral supplements (like calcium and iron) at home. Just because supplements are not on a patient's medication profile does not mean they do not take them. A patient who washes down a tetracycline with a calcium supplement or even a glass of milk may completely negate an otherwise brilliant therapeutic plan.

Macrolides and Ketolides

10

Agents: clarithromycin, azithromycin, erythromycin, **telithromycin** (a ketolide)

Macrolides are among the antibiotics used most frequently in the outpatient setting because of their broad coverage of respiratory pathogens. Though their coverage is broad, it is not particularly deep, because there is increasing resistance to these agents (especially in *Streptococcus pneumoniae*). To combat this resistance, the ketolide derivatives (including telithromycin) have been introduced with better coverage of resistant *S. pneumoniae.* Unfortunately, telithromycin appears to have a significant risk of hepatotoxicity. Although erythromycin is the class patriarch, because of its adverse effects, drug interactions, and frequent dosing, it has little use except as a GI stimulant.

Spectrum

Good: atypicals, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Helicobacter pylori*, *Mycobacterium avium*

Moderate: S. pneumoniae (telithromycin > macrolides), *S. pyogenes*

Poor: staphylococci, enteric GNRs (azithromycin > clarithromycin), anaerobes, enterococci

Adverse Effects

Gastrointestinal: Significant GI adverse effects (nausea, vomiting, diarrhea) have been associated with the macrolides. Erythromycin is the worst offender—it is employed as a pro-kinetic agent for patients with impaired GI motility.

Hepatic: Rare but serious adverse hepatic events have been associated with the macrolides. Telithromycin has been associated with hepatic failure leading to death or the need for transplantation.

Cardiac: Prolongation of the QT interval has been seen with the macrolides, again most commonly with erythromycin. Use with caution in patients with preexisting heart conditions, those on antiarrhythmic drugs, or those taking interacting drugs (see below).

Important Facts

- ***Drug interaction alert!*** These drugs (with the exception of azithromycin) are potent inhibitors of drug-metabolizing cytochrome P450 enzymes. Be sure to screen your patient's regimen with a computerized drug interaction checker or a drug information resource before starting these agents.
- Azithromycin has a prolonged half-life such that a 3- to 5-day course may be adequate for most infections, instead of 7–10 days with other drugs. This makes use of the Z-pak® and the newer Z-max® possible.
- Macrolides are bacteriostatic drugs and are not appropriate for infections in which cidal activity is usually required (meningitis, endocarditis, etc.).

- Prevpac® is a combination of drugs prescribed for eradication of *H. pylori* and the treatment of peptic ulcer disease. In addition to clarithromycin and lansoprazole, it contains amoxicillin. Be sure to screen patients for beta-lactam allergies and drug interactions before administering it.

What They're Good For

Upper and lower respiratory tract infections, chlamydia, atypical mycobacterial infections, and traveler's diarrhea (azithromycin). Clarithromycin is a key component in the treatment of *H. pylori*–induced GI ulcer disease in combination with other drugs and acid-suppressive agents.

Don't Forget!

Sure, macrolides are good respiratory tract drugs and are relatively benign, but do you really need to be treating your patient's nonspecific (possibly viral) cough and cold with any antibiotic? Besides causing possible adverse reactions and wallet toxicity, overuse of these drugs has contributed to increasing resistance. How about some decongestants, acetaminophen, and chicken soup instead?

11 Oxazolidinones

Agent: linezolid

Currently, linezolid is the only available member of the oxazolidinone class. Thanks to its broad Gram-positive activity and excellent oral bioavailability, linezolid has become a useful (albeit expensive) antibiotic for the treatment of various resistant Gram-positive infections. Its use is likely to increase as MRSA becomes more prevalent in the community, but remember that other drugs can combat MRSA infections as well.

Spectrum

Good: MSSA, MRSA, streptococci (including multidrug-resistant *S. pneumoniae*), enterococci (including VRE), *Nocardia*
Moderate: some atypicals
Poor: all Gram-negatives, anaerobes

Adverse Effects

Linezolid is generally well tolerated, but it can cause bone marrow suppression, most commonly thrombocytopenia. Bone marrow suppression tends to occur after 2 or more weeks of therapy and warrants monitoring. Peripheral neuropathy may occur after even more prolonged therapy (months) because of toxicity to mitochondria.

Important Facts

- Linezolid has bioavailability approaching 100%, and its oral formulation greatly increases its utility.
- Linezolid is also an inhibitor of monoamine oxidase and can cause serotonin syndrome when given concurrently with serotonergic agents such as selective serotonin reuptake inhibitors (SSRIs)—avoid concurrent use if possible. Recent evidence has shown this reaction to be uncommon, but it does occur. The interaction is listed as a contraindication in linezolid's package insert.
- Linezolid has dual hepatic and renal elimination, and doses do not need to be adjusted in cases of renal or hepatic dysfunction.
- Both oral and IV formulations are very expensive, but the oral formulation is less expensive than home-infusion vancomycin and a nurse.

What It's Good For

Infections caused by resistant Gram-positive organisms such as MRSA and VRE, including nosocomial pneumonia and skin and soft-tissue infections.

Don't Forget!

Monitor patients for bone marrow suppression, particularly during long-term therapy with linezolid. Avoid concurrent serotonergic drug use if possible. Remember that many SSRIs have long half-lives, so simply discontinuing SSRI use does not avoid a potential interaction. Monitor patients for signs and symptoms of serotonin syndrome if the interaction cannot be avoided.

12 Nitroimidazoles

Agents: metronidazole, tinidazole

Nitroimidazoles are around to clean up organisms that the big drug classes—penicillins, cephalosporins, fluoroquinolones, macrolides, etc.—for the most part miss. Worried about gut anaerobes? Metronidazole is there for you. Thinking about parasites in your patient with diarrhea? Try metronidazole or its newer cousin tinidazole, which has a spectrum of activity similar to that of metronidazole but is approved only for parasitic infections. And of course, if you have gone overboard with the antibiotics and your patient has *C. difficile* colitis, turn to metronidazole as your first-line therapy. Just remember the limitations of these drugs: they do not have adequate activity against aerobic bacteria—staphylococci, streptococci, *E. coli,* and such.

Spectrum: metronidazole

Good: Gram-negative and Gram-positive anaerobes, including *Bacteroides*, *Fusobacterium*, and *Clostridium* species; protozoa, including *Trichomonas*, *Entamoeba*, and *Giardia*

Moderate: Helicobacter pylori

Poor: aerobic Gram-negative and Gram-positive organisms, anaerobes that reside in the mouth

(*Peptostreptococcus, Actinomyces, Propionibacterium*)

Adverse Effects

Gastrointestinal: Nausea, vomiting, and diarrhea, along with a metallic taste, are not uncommon with metronidazole. More severe adverse reactions such as hepatitis and pancreatitis are rare.

Neurologic: Dose-related, reversible peripheral neuropathy is occasionally reported with metronidazole, as have very rare cases of confusion and seizures.

Important Facts

- Metronidazole has a reputation for causing a disulfiram-like reaction with the consumption of alcohol, because of its inhibition of aldehyde dehydrogenase. It is prudent to have patients abstain from alcohol while taking metronidazole. Much more considerable is the interaction with warfarin, whose anticoagulant properties are significantly potentiated by inhibition of warfarin metabolism. Careful monitoring is necessary, because possible warfarin dose reduction may be required.
- Metronidazole has excellent (~100%) bioavailability and none of the drug-chelating concerns of the fluoroquinolones; thus patients should be switched from IV to oral metronidazole as soon as they are tolerating oral medications.
- Resistance to metronidazole among isolates of *C. difficile* is uncommon, but treatment failure with this infection is not. The organism can exist as an antibiotic-resistant spore and cause

relapses after the end of treatment. Re-treatment with metronidazole is reasonable in most cases of mild or moderate relapsing *C. difficile* infection, although treatment with oral vancomycin is an alternative. Alternatives are currently being developed for *C. difficile* infection.

What They're Good For

Infections with documented or suspected abdominal anaerobic bacteria, with adjunctive coverage of aerobes by a second drug when necessary. They are also used for treatment of vaginal trichomoniasis and GI infections caused by susceptible protozoa (amebiasis, giardiasis, etc.). Metronidazole is also a component of therapy for *H. pylori* GI ulcer disease in combination with other antibacterials and acid-suppressive drugs. It is also a drug of choice for mild to moderate *C. difficile* infections.

Don't Forget!

The GI flora of humans is a delicate ecosystem—disturb it at your patient's peril. Metronidazole's effect on the normal (primarily anaerobic) GI flora can set up your patients for colonization with nasty bugs such as VRE; determine whether you really need anaerobic coverage.

13 Nitrofurans

Agent: nitrofurantoin

With the rise in resistance among common urinary tract pathogens (primarily *E. coli*), first among TMP/SMX and more recently among the fluoroquinolones, clinicians are left searching for an alternative to treat their patients with uncomplicated cystitis. Nitrofurantoin fits nicely into this niche, because it has retained excellent activity against *E. coli* (> 90% in most studies) and also has adequate coverage of other common community-acquired urinary tract pathogens. Its utility is limited to infections of the lower urinary tract, however, because of its pharmacokinetic limitations. Thus, nitrofurantoin should not be used for more severe infections such as pyelonephritis and urosepsis.

Spectrum

Good: *E. coli, Staphylococcus saprophyticus*
Moderate: *Citrobacter, Klebsiella*, enterococci
Poor: *Pseudomonas, Proteus, Acinetobacter, Serratia*

Adverse Effects

Gastrointestinal: Nausea and vomiting are occasionally reported. Taking the drug with food may decrease these effects.

Pulmonary: Nitrofurantoin can cause very rare but serious pulmonary toxicity of two forms. First is an acute pneumonitis manifesting as cough, fever, and dyspnea. This form typically resolves soon after drug discontinuation. A chronic pulmonary fibrosis can occur, most commonly with prolonged nitrofurantoin therapy; recovery of lung function is limited after drug discontinuation.

Peripheral neuropathy may also occur.

Important Facts

- It bears repeating: nitrofurantoin is ineffective for infections outside of the lower urinary tract. The drug requires high concentrations for antimicrobial activity, and these are reached only where it concentrates in the urine. Note this also means that in patients who have significant renal dysfunction (e.g., a creatinine clearance of less than 50 ml/min), there is insufficient accumulation of the drug in the urine for activity.
- Nitrofurantoin comes in two formulations: a crystalline form (Macrodantin®) and a macrocrystalline/monohydrate form (Macrobid®). The former is dosed 4 times daily, the latter BID. Guess which one patients prefer?
- A recent study of nitrofurantoin showed that it can be used for 5 days instead of the traditional 7-day regimen. This shorter regimen may make nitrofurantoin therapy more palatable for pa-

tients who are used to 3-day courses of other UTI drugs (TMP/SMX and fluoroquinolones).

What It's Good For

Treatment of uncomplicated cystitis in patients with adequate renal function and prophylaxis against recurrent uncomplicated lower UTI.

Don't Forget!

To repeat: do not use this drug in anything but uncomplicated cystitis. Nitrofurantoin use in pyelonephritis or urosepsis is a treatment failure waiting to happen.

14 Streptogramins

Agent: quinupristin/dalfopristin

The increase in resistance to antibiotics among staphylococci and enterococci led to pharmaceutical companies increasing the development of drugs to combat these resistant infections. One of the first of the newer drugs to treat VRE and MRSA infections was quinupristin/dalfopristin. These drugs are two different streptogramins given in a combined formulation. Though each separate streptogramin is bacteriostatic, when given together they act *synergistically* to give bacteri*cid*al activity against some Gram-positive cocci; hence the brand name of this drug: Synercid®. Quinupristin/dalfopristin initially enjoyed frequent use, particularly to treat VRE infections, but its use has lessened as other agents have come on the market. Other streptogramins have been developed and are used in animals as growth promoters, a questionable but common practice in modern agriculture.

Spectrum

Good: MSSA, MRSA, streptococci, *Enterococcus faecium* (including vancomycin-resistant strains)

Poor: *Enterococcus faecalis*, anything Gram-negative

Adverse Effects

Quinupristin/dalfopristin can cause phlebitis and ideally should be administered via a central line. It is also associated with a high incidence of myalgias and arthralgias that can limit tolerance to therapy. Quinupristin/dalfopristin also inhibits cytochrome P450 3A4, so clinicians need to be aware of potential drug interactions.

Important Facts

- Quinupristin/dalfopristin must be mixed and administered with 5% dextrose in water (D5W) solutions only. When mixed with normal saline, the drug becomes insoluble and can crystallize, even when a patient's IV line is flushed with saline. Be sure that your patient's nurses know to flush the line with D5W or another saline-free diluent. The drug is not available orally.
- The arthralgias and myalgias associated with quinupristin/dalfopristin are significant and should not be underestimated. It may be possible to decrease their severity by decreasing the dose, but this could compromise efficacy.

What It's Good For

Infections caused by *E. faecium* or MRSA in patients not responding to or intolerant of other medications.

Don't Forget!

Quinupristin/dalfopristin is not active against *Enterococcus faecalis*. Between the two most common clinical species of *Enterococcus* (*E. faecalis* and *E. faecium*), *E. faecalis* is more common in most hospitals, but it is less likely to be resistant to vanco-

mycin. For this reason, quinupristin/dalfopristin is better employed as a definitive therapy than an empiric one for enterococci unless you strongly suspect *E. faecium* infection.

15 Cyclic Lipopeptides

Agent: daptomycin

Daptomycin is the only cyclic lipopeptide that has made its way onto the market. It has a unique mechanism of action and target compared with other antibiotics. Daptomycin binds to the cell membrane of Gram-positive bacteria, weakening it and allowing essential ions to leak out of the organism. This leads to a rapid depolarization of the membrane potential and cessation of needed cell processes, leading to cell death. Interestingly, instead of blowing the bacteria apart as beta-lactams do, daptomycin leaves the dead bacteria intact.

Spectrum

Good: MSSA, MRSA, streptococci
Moderate to Good: enterococci, including VRE
Poor: anything Gram-negative

Adverse Effects

Daptomycin has effects on skeletal muscle that can manifest as muscle pain or weakness, or possibly rhabdomyolysis. To monitor for this effect, creatine kinase (CK) concentrations should be checked weekly while on therapy. This toxicity can be decreased by administering the drug no more than

once daily and by adjusting the interval in renal dysfunction. Drug fever is also a possibility. Recently, eosinophilic pneumonia has been reported in patients on daptomycin therapy.

Important Facts

- Daptomycin is active against many resistant Gram-positive organisms, including VRE and MRSA. It has been proven effective in staphylococcal endocarditis (specifically right-sided endocarditis), an indication that few antibiotics have.
- Resistance to daptomycin is very rare, but it is reported occasionally. Before using daptomycin for your patient, ensure that the lab tests the isolate for daptomycin susceptibility. Because a standard MIC for resistance has not yet been defined, labs may report isolates as "nonsusceptible" or, worse, not report them at all if they do not fall into the susceptible range. Ask your lab for specifics on its procedures.
- Though it penetrates lung tissue very well, daptomycin cannot be used to treat pneumonia. Human pulmonary surfactant binds to daptomycin, rendering it inactive. Early clinical trials showed poor outcomes in daptomycin-treated pneumonia patients.

What It's Good For

Skin and soft-tissue infections caused by resistant Gram-positive organisms and staphylococcal bacteremia, including right-sided endocarditis. Daptomycin also has utility in enterococcal bacteremia, though it is not indicated or as well studied for this use.

Don't Forget!

Monitor CK concentrations and renal function for patients taking daptomycin, particularly if they are on other drugs toxic to skeletal muscle, like HMG-CoA reductase inhibitors.

16 Folate Antagonists

Agents: trimethoprim/sulfamethoxazole (TMP/SMX), dapsone, pyrimethamine, sulfadiazine, sulfadoxine

These drugs inhibit steps in the folate-synthesis pathway, ultimately leading to inhibition of DNA synthesis in susceptible organisms. In this class of drugs, the combination drug TMP/SMX is the most widely used, for both bacterial and parasitic/fungal infections. TMP/SMX was once considered a broad-spectrum drug that has since fallen victim to the relentless march of antibiotic resistance; however, it is still a drug of choice for a number of indications. Resistance varies considerably by geographic region, so consider your local antibiogram before using TMP/SMX as empiric therapy. The other agents are used against parasitic/fungal infections. The information below refers to TMP/SMX except where noted.

Spectrum

Good: *Staphylococcus aureus* (including many MRSA strains), *H. influenzae*, *Stenotrophomonas maltophilia, Listeria, Pneumocystis jirovecii* (formerly known as *P. carinii*), *Toxoplasma gondii* (pyrimethamine and sulfadiazine)

Moderate: enteric GNRs, *S. pneumoniae, Salmonella, Shigella, Nocardia*

Poor: Pseudomonas, enterococci, *S. pyogenes*, anaerobes

Adverse Effects

Dermatologic: TMP/SMX frequently causes rash, usually because of the sulfamethoxazole component. Rash is much more common in HIV/AIDS patients. Although these rashes are usually not severe, life-threatening dermatologic reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome have been documented.

Hematologic: A primarily dose-dependent bone-marrow suppression can be seen with TMP/SMX, especially at the higher doses used to treat *Pneumocystis* infections.

Renal: Confusingly, TMP/SMX can cause both true and pseudo-renal failure. Crystalluria and AIN caused by the SMX component can lead to acute renal failure; however, the blockade of creatinine secretion by TMP can cause an increase in serum creatinine without a true decline in glomerular filtration rate. TMP can also cause hyperkalemia in a fashion similar to the potassium-sparing diuretics (e.g., triamterene).

Important Facts

- For years, TMP/SMX was standard first-line therapy for treatment of acute uncomplicated cystitis in women. Guidelines suggest, however, that in areas with local resistance rates of less than 15–20% in *E. coli*, an alternative drug

(e.g., ciprofloxacin or nitrofurantoin) should be used. This recommendation is somewhat controversial because of the increasing rate of fluoroquinolone resistance. Certainly, at a minimum TMP/SMX should not be used for empiric therapy of complicated UTI (pyelonephritis or urosepsis).

- TMP/SMX comes in a fixed 1:5 ratio of the two components. Dosing is based on the TMP component. The oral form comes in two strengths: single-strength (80:400 mg TMP:SMX) and double-strength (160:800 mg TMP:SMX). TMP/SMX has excellent oral bioavailability, allowing for conversion to oral therapy when patients are tolerating oral medications.
- TMP/SMX has a significant drug interaction with warfarin, leading to higher-than-anticipated prothrombin times. TMP/SMX should be avoided in patients on warfarin if possible. If co-administration is absolutely necessary, careful monitoring of the patient's international normalized ratio is required.
- TMP/SMX is fairly insoluble in IV solutions, and relatively large volumes of diluent are needed for it to go into solution. Be aware that this fluid may be considerable, particularly for volume-overloaded patients such as those with heart failure.

What They're Good For

Treatment of uncomplicated lower UTIs (in areas with low local resistance), prophylaxis against recurrent UTIs, treatment of listerial meningitis, treatment of and prophylaxis for *Pneumocystis jirovecii* pneumonia, and treatment of *Toxoplasma*

encephalitis. TMP/ SMX is also an alternative therapy for bacterial prostatitis, typhoid fever, and methicillin-resistant *Staphylococcus aureus* infections.

Don't Forget!

Patients allergic to TMP/SMX may have cross-reactions to other drugs containing sulfonamide moieties, such as furosemide, sulfadiazine, acetazolamide, hydrochlorothiazide, and glipizide.

17 Lincosamides

Agent: clindamycin

Clindamycin can be considered a mix of vancomycin and metronidazole; it has attributes of each drug, but it is not quite as good as either one alone. Clindamycin is an alternative when treatment requires Gram-positive activity (as with beta-lactam allergies), but it has more variable activity than vancomycin against such pathogens as MRSA and *S. pyogenes*. Clindamycin also covers many anaerobic organisms, but there is a higher level of resistance among the Gram-negative anaerobes (such as *B. fragilis*) than with metronidazole. Because of these limitations and clindamycin's tendency to cause GI toxicity, it is best used empirically for nonsevere infections of the skin and oral cavity, or as definitive therapy when susceptibilities are known.

Spectrum: clindamycin

Good: many Gram-positive anaerobes, *Plasmodium* species (malaria)

Moderate: Staphylococcus aureus (including some MRSA), *Streptococcus pyogenes*, Gram-negative anaerobes, *Chlamydia trachomatis, Pneumocystis jirovecii, Actinomyces, Toxoplasma*

Poor: enterococci, *Clostridium difficile*, Gram-negative aerobes

Adverse Effects

Gastrointestinal: Diarrhea is one of the most common adverse effects associated with clindamycin. Clindamycin itself can cause relatively benign, self-limiting diarrhea or can result in more severe diarrhea resulting from superinfection with *Clostridium difficile. C. difficile*–associated diarrhea and colitis can occur during or after clindamycin therapy and can be life threatening. Patients with diarrhea need evaluation for *C. difficile* disease, especially if it is severe, associated with fever, or persists after the end of clindamycin therapy.

Dermatologic: Rash may occur with clindamycin, very rarely with severe manifestations such as Stevens-Johnson syndrome.

Important Facts

- Clindamycin is a reasonable alternative drug for the treatment of staphylococcal infections; however, care must be taken in interpreting the antibiotic susceptibility of these isolates. A significant proportion of organisms that are reported as clindamycin-susceptible but erythromycin-resistant may harbor a gene for resistance that may lead to high-level clindamycin resistance during therapy. Erythromycin-resistant, clindamycin-susceptible strains should be screened with a D-test (the microbiology lab will know what you mean) before using clindamycin. If the D-test

is positive, then inducible clindamycin resistance is present and clindamycin should not be used.

- Clindamycin's inhibition of protein synthesis and activity against organisms in stationary-phase growth has been utilized in the treatment of necrotizing fasciitis and other toxin-mediated diseases. Consider the addition of clindamycin to beta-lactam-based therapy when treating these types of infections.
- Clindamycin is nearly 100% orally bioavailable, but oral doses are generally lower than IV doses in order to improve GI tolerance.

What It's Good For

Treatment of skin and soft-tissue infections, infections of the oral cavity, and anaerobic intra-abdominal infections. It is used topically in the treatment of acne. Clindamycin is a second-line agent (in combination with primaquine) in the treatment of *P. jirovecii* pneumonia. It is also used to treat malaria in combination with other drugs, to treat bacterial vaginosis, and in the prophylaxis of bacterial endocarditis.

Don't Forget!

Almost all antibiotics have been associated with an increased risk of *C. difficile* disease; however, some studies suggest that clindamycin may confer an especially high risk (note that this is a popular board exam question). Although it is a convenient and relatively well-tolerated drug, clindamycin should not be used lightly because of this risk.

18 Polymyxins

Agents: colistin (colistimethate sodium), polymyxin B

Polymyxins are an older class of antibiotics that had nearly vanished from systemic use years ago in favor of the "safer" aminoglycosides. Unfortunately, the continuous evolution of bacterial resistance has re-invigorated the use of colistin and polymyxin B in the treatment of resistant Gram-negative infections. This is problematic because these drugs have not been evaluated with the rigor of the modern drug approval process, and pharmacokinetic and efficacy data on their use are limited. However, they have been found to be useful in the treatment of infections caused by highly resistant Gram-negative organisms such as *Acinetobacter baumannii* and carbapenemase-producing *Klebsiella pneumoniae*.

Spectrum

Good: many GNRs, including multi-drug resistant *Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Klebsiella pneumoniae*

Moderate: Stenotrophomonas maltophilia

Poor: All Gram-positive organisms, anaerobes, *Proteus*, *Providencia*, *Burkholderia*, *Serratia*, Gram-negative cocci

Adverse Effects

Renal: The most common adverse effect is nephrotoxicity because of acute tubular necrosis. Nephrotoxicity is common in clinical use, though the incidence is hard to estimate because most recent studies of polymyxins are non-comparative evaluations of last-line indications in very ill patients.

Neurological: Neurotoxicity is less common. It can manifest as dizziness, weakness, paresthesias, or mental status changes. Neuromuscular blockade can also occur and may lead to fatal respiratory arrest.

Important Facts

- Colistin and polymyxin B are very similar drugs. Colistin may be more active, but to be given systemically it is administered as colistimethate sodium. Colistimethate is then converted into active colistin in the body. Colistimethate is renally cleared, and only the proportion that is not cleared is converted to colistin. It is dosed as milligrams of active colistin (360 mg colistimethate = 150 mg of base colistin). Colistin itself is not used systemically. When most references refer to "colistin" (including this one), they are referring to "colistimethate".
- To further confound colistin use, different standards of dosing are used by different countries. The U.S. formulation is dosed in milligrams, while Europe and many other countries dose in international units. When comparing, it is important to know that 1 mg = 12,500 units.

- Because polymyxin drugs are generally last-line antibiotics, they are sometimes used in combination with other drugs. Various combinations of colistin and other drugs such as rifampin may be better than colistin use alone; this is an area of active study.
- The oral formulation of colistin is given only for bowel decontamination, such as before GI surgery. Don't try to convert someone from IV to PO colistin to treat a systemic infection.

What They're Good For

Polymyxins are useful in the treatment of multidrug resistant Gram-negative infections including pneumonia, bacteremia, sepsis, and complicated UTIs. Because polymyxins are poorly studied in many of these disease states, other drugs should be used if pathogens are susceptible.

Don't Forget!

While estimates of polymyxin nephrotoxicity vary, the incidence is substantial, particularly in critically ill patients who may not be able to tolerate the renal insult. Monitor renal function closely in patients receiving polymyxins.

PART 3

Antimycobacterial Drugs

Antimycobacterial Drugs

19

Introduction to Antimycobacterial Drugs

Tuberculosis, the disease caused by *Mycobacterium tuberculosis*, is one of the world's most formidable infections. Tuberculosis and other mycobacterial diseases are difficult to treat for several reasons. Mycobacteria replicate more slowly than "typical" bacteria such as *E. coli* or *Staphylococcus aureus*. This may seem to make the disease easier to control, but it makes pharmacotherapy more difficult because rapidly dividing cells are most metabolically active and therefore susceptible to antibiotic chemotherapy.

Mycobacteria can also exist in a dormant state, making them resistant to nearly all antibiotics. They are intracellular organisms, and therefore drugs that do not work within cells are ineffective. Mycobacteria also have cell walls that are structurally different from typical Gram-positive and Gram-negative bacteria. The outermost layer of mycobacteria consists of phospholipids and mycolic acids that make a waxy layer that resists penetration from antibiotics. Arabinogalactan and peptidoglycan are polysaccharide components of the cell wall, but the peptidoglycan is not accessible to beta-lactam antibiotics, and they are largely inactive. **Figure 19–1** shows the basic structure of mycobacteria.

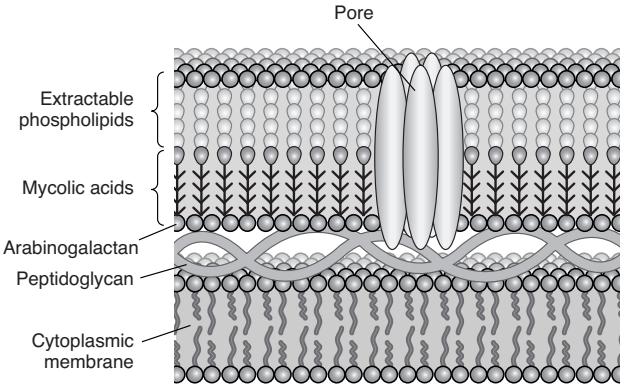


Figure 19–1
Mycobacterial Cell Wall

The pharmacotherapy of mycobacterial disease is complex. Combinations of drugs are always given for patients with active disease to minimize the development of resistance and shorten the duration of therapy. These combinations interact with each other and often with other medications that the patient is on, because immunocompromised patients are particularly vulnerable to mycobacterial disease. Because mycobacteria grow slowly, susceptibility testing takes weeks instead of days to perform, so empiric regimens are often given for extended durations. For tuberculosis, the standard of care for patients with active infections is to start with a 4-drug regimen, so compliance and careful watching for drug interactions are important.

First-line drugs for tuberculosis and MAC are discussed in this section. Many second-line drugs are available for tuberculosis; however, because the treatment of multidrug-resistant tuberculosis

requires the management of an infectious diseases specialist, we omit them from this text. The following antimycobacterial drugs are listed in the antibacterial chapters: fluoroquinolones (moxifloxacin is particularly active), macrolides, and aminoglycosides. It is particularly important to know the toxicities of the first-line agents for tuberculosis, because they each have a characteristic one. You can expect questions about these characteristics to pop up on a lot of exams, both in school and for licensure.

20 Rifamycins

Agents: rifampin, rifabutin, rifapentine, rifaximin (not used for mycobacterial disease)

The rifamycins are cornerstones of therapy for both tuberculosis and MAC. They are protein synthesis inhibitors that inhibit transcription of DNA to bacterial mRNA. Rifampin (or rifampicin, as it is known in European literature) is one of the two most important drugs in tuberculosis pharmacotherapy. The rifamycins are potent inducers of the cytochrome P450 system, and patients receiving them should *always* be screened for drug interactions. In addition to their activity against mycobacteria, rifamycins are active against many "typical" bacteria as well and are sometimes added to other therapies, particularly to treat difficult MRSA infections.

Spectrum

Good: Most mycobacteria

Moderate: *Staphylococcus*, *Acinetobacter*, Enterobacteraciae

Poor: "Typical" bacteria as monotherapy, some very rare mycobacteria

Adverse Effects

Rifamycins are generally well-tolerated drugs that are most notorious for their potent CYP450-inducing effects. Their potent induction of metabolism can lead to subtherapeutic concentrations of other drugs that can manifest with devastating clinical consequences, such as loss of seizure control (anticonvulsants) or organ rejection (antirejection agents). Rifampin characteristically colors secretions (urine, tears, etc.) orange-red and can actually stain contact lenses, which should not be worn during rifampin therapy. Otherwise, this effect is nonpermanent and not harmful, which patients appreciate knowing. Rifamycins can also cause hepatotoxicity. Less serious side effects include rash, nausea, vomiting, and hypersensitivity (often fever).

Important Facts

- Rifampin is a drug of choice for tuberculosis, while rifabutin is a drug of choice for MAC, although both drugs have activity against both pathogens. MAC infections are most common in patients with HIV, who are often taking antiretroviral therapy that is metabolized by CYP450. Because rifabutin has somewhat fewer CYP450-inducing effects than rifampin does, it is more commonly used in MAC infections to minimize the impact of drug interactions in this population.
- Rifampin (or rifabutin) is one of the two most important drugs in the treatment of tuberculosis (the other being isoniazid). If an isolate of *M. tuberculosis* is rifampin-resistant, then the likelihood of successful pharmacotherapy is lower

and more complicated regimens must be used for a longer duration.

- All rifamycins induce CYP450 enzymes and can induce the metabolism of drugs through other hepatic pathways as well. Always screen for drug interactions when starting a rifamycin.
- Rifabutin induces CYP450 metabolism less potently than rifampin does, but it is still a potent inducer.
- Rifapentine is a second-line drug that is given once weekly. It shares susceptibility with rifampin and rifabutin, meaning that if an isolate is resistant to one drug, it is resistant to all of them.
- Rifaximin is a nonabsorbed rifamycin used only in the treatment or prevention of GI conditions. It is not used for mycobacterial diseases and is listed here only for completeness.
- Rifamycins should not be used as monotherapy for treatment of active tuberculosis, but they can be used as monotherapy to treat latent tuberculosis infection. They are second-line drugs for this use.

What They're Good For

Treatment of active tuberculosis and MAC, in combination with other agents; latent tuberculosis; and selected bacterial infections (most notably endocarditis of a prosthetic valve in combination with another antibiotic).

Don't Forget!

Ensure that patients are informed that their urine and other secretions may turn orange or red. That's a surprise that most people don't want.

21 Isoniazid

Agent: isoniazid

Isoniazid is active only against *M. tuberculosis* and the related *M. kansasii*, but it is one of the two most important drugs in tuberculosis pharmacotherapy (the other being rifampin). It works by preventing the synthesis of mycolic acids in the cell wall, and it is effective against both actively growing and dormant mycobacteria. It is used in the treatment of both active and latent tuberculosis.

Spectrum

Active only against *M. tuberculosis* and *M. kansasii.*

Adverse Effects

Isoniazid's classic adverse reaction is peripheral neuropathy. This can be prevented by administering pyridoxine (vitamin B6), which is recommended for patients at risk for developing neuropathy (e.g., diabetics, pregnant women, alcohol abusers). Other neurotoxicities that are less common include optic neuritis and, rarely, seizures. Drug-induced lupus can also occur; this abates with the cessation of therapy. Like other tuberculosis medications, hepatotoxicity is also possible. Hypersensitivity can be seen, most commonly as rash or drug fever.

Important Facts

- Isoniazid is the drug of choice for the treatment of latent tuberculosis. It can be given as monotherapy for latent disease because the burden of organisms is much lower than in active tuberculosis, where resistance can develop to monotherapy.
- Isoniazid is a classic example of a drug with variable pharmacogenomic metabolism. "Rapid acetylators" of isoniazid metabolize it more quickly than "slow acetylators," but the clinical significance of this is unknown. Genetic testing is not routinely performed before starting isoniazid.
- Isoniazid is bactericidal against growing mycobacteria, but bacteriostatic against dormant mycobacteria.
- Patients should be advised not to drink alcohol while taking isoniazid. This has nothing to do with the common myth that alcohol decreases antibiotic effectiveness; it is to prevent an additive risk of hepatotoxicity.

What It's Good For

Isoniazid is the drug of choice for both active and latent tuberculosis. For treatment of active tuberculosis, it must be combined with other medications. The combination of isoniazid and rifampin is common for the consolidation phase of non-multidrug-resistant tuberculosis.

Don't Forget!

Although guidelines require adding pyridoxine for preventing neuropathy only in high-risk patients,

there's no downside in recommending it to all your patients receiving isoniazid. Don't confuse pyridoxine with pyrazinamide (discussed in the next section) and assume that your patient is receiving both drugs when he or she is not. Most patients with tuberculosis should be taking both pyridoxine and pyrazinamide.

22 Pyrazinamide

Agent: pyrazinamide

Pyrazinamide is a first-line drug for the treatment of tuberculosis. It is added to the initial 4-drug regimen to shorten the overall duration of therapy from 9 months to 6 months. Pyrazinamide has bactericidal activity against even slow-growing *M. tuberculosis* by inhibiting fatty acid synthesis at a different step than isoniazid does. It is generally used only in the first 2 months of tuberculosis therapy.

Spectrum

Active only against *M. tuberculosis.*

Adverse Effects

The key adverse effects for pyrazinamide are hyperuricemia and hepatotoxicity. Hepatotoxicity (chiefly hepatitis) is dose-dependent and less common at the lower doses given today than the higher ones previously used. Hyperuricemia is predictable and can rarely precipitate gout, leading to withdrawal of pyrazinamide from the regimen and an extension of the duration of tuberculosis therapy. Arthralgias also occur and are separate from hyperuricemia; these can be managed with over-the-counter pain medications.

Important Facts

- Interestingly, pyrazinamide is active only in acidic environments (pH < 6). This would be problematic for some diseases, but it is perfect for the caseous granulomas that active tuberculosis forms. It also works intracellularly in phagocytes.
- Pyrazinamide is no longer used in combination with rifampin as an alternative for latent tuberculosis because of high rates of hepatitis.
- Be careful not to confuse this drug with pyridoxine, which most patients with tuberculosis should also be taking.

What It's Good For

Pyrazinamide's only use is in the initial phase of active tuberculosis treatment.

Don't Forget!

Tell your patients to report any signs of hepatitis (dark urine, abdominal pain, loss of appetite) when they are on pyrazinamide or any first-line tuberculosis therapy.

23 Ethambutol

Agent: ethambutol (EMB)

Ethambutol is a first-line drug for the treatment of both active tuberculosis and MAC infections. It inhibits production of arabinogalactan, a component of the mycobacterial cell wall. Like pyrazinamide, ethambutol is principally used in the initial 4-drug phase of active tuberculosis, but it is usually given for the duration of MAC therapy.

Spectrum

M. tuberculosis, *M. avium-intracellulare* complex, *M. kansasii.*

Adverse Effects

The characteristic adverse effect of ethambutol is optic neuritis, often manifesting as decreased visual acuity and the inability to differentiate red from green. It is dependent on both the dose and duration of therapy and generally reversible, and monitoring is required to detect this problem. Use of ethambutol in children younger than 5 years is not recommended, because these children are generally not able to reliably perform the vision tests needed for monitoring. Rash and drug fever occur uncommonly.

Important Facts

- Ethambutol is very well tolerated, and it is one of the few tuberculosis drugs that is not associated with hepatotoxicity.
- Ethambutol can be used as a substitute for rifampin in patients who are unable to take this medication during the continuation phase (after 2 months) of active tuberculosis therapy. However, the duration of therapy has to be extended relative to what it would be with rifampin and isoniazid.
- Ethambutol is one of the primary first-line drugs (along with a macrolide and rifabutin) for treating MAC infections.

What It's Good For

First-line therapy for both active tuberculosis and MAC infections. Second-line therapy in patients unable to tolerate rifampin during the continuation phase.

Don't Forget!

Want an easy way to remember that ethambutol causes optic neuritis? Just remember: for **E**thambutol, the **E**yes have it!

PART 4

Antifungal Drugs

24 Antifungal Drugs

Introduction to Antifungal Drugs

Fungi rule their own kingdom. There are thousands of species of these saprophytic and parasitic organisms, but, as with bacteria, only a small minority are pathogens. Most pathogenic fungi are opportunistic and require a compromised host or disrupted barrier in order to cause infection in humans. In a way, the increase of systemic fungal infections can be seen as a medical advance, because improvements in transplantation, oncology, rheumatology, neonatology, geriatrics, and other fields have created more hosts for fungi. The practice of medical mycology has expanded greatly.

Fungi exist in two basic forms: yeasts and moulds. **Table 24–1** highlights some of the medically important fungi. Yeasts are solitary forms of fungi that reproduce by budding. When they are left to grow in colonies, they have a moist, shiny appearance. Moulds are multicellular fungi that consist of many branching hyphae and can reproduce either by translocation of existing hyphae to a new area, or through spore formation and spread (hence, one bad apple really does spoil a bunch). They have a familiar fuzzy appearance, such as the *Rhizopus* that you have undoubtedly seen on bread.

TABLE 24–1
Common Clinical Fungi

Yeasts	Dimorphic Fungi	Moulds
Candida	*Histoplasma*	*Aspergillus*
Cryptococcus	*Blastomyces*	*Fusarium*
	Coccidioides	*Scedosporium*
	Paracoccidioides	*Zygomycetes*

In addition to these two basic forms, there are dimorphic fungi that can exist in either form. These fungi are often mould-like at room temperature, but yeast-like at body temperature. They are also called endemic fungi, because they cause infections endemic to certain regions of the world; for example, *Coccidioides immitis* causes an infection in the southwestern United States and central California that is sometimes called valley fever.

Yeasts, particularly *Candida* species, have become the fourth leading cause of nosocomial bloodstream infections. This makes them important infectious agents that are worthy of our attention. Unfortunately, specific diagnostic criteria for invasive *Candida* infections are lacking. Moulds generally cause invasive disease only in immunocompromised hosts, but they should be considered in patients with various levels of immune system suppression, not just those in the most severe category. Dimorphic fungi usually cause mild, self-limited disease, but some can also cause fatal disseminated disease, particularly in patients with suppressed immunity.

Antifungal pharmacotherapy has several problems that often make fungal infections more diffi-

cult to treat than bacterial infections. One is that fungal disease often presents no differently than bacterial disease, but the pathogens can be more difficult to isolate on culture. This makes the prompt initiation of empiric therapy important when invasive fungal infections are suspected. Prophylaxis is also used in highly susceptible populations to prevent fungal infections from developing.

Another concern with the treatment of fungal disease is that most centers do not conduct antifungal susceptibility testing. This forces clinicians to guess at likely susceptibility patterns based on speciation rather than test results. Further, the capabilities of the host significantly affect the likelihood of success in treating an invasive fungal infection. For neutropenic patients with mycoses, neutrophil recovery is a significant predictor of success, and patients with a prolonged immunocompromised status have a much worse prognosis. Therefore, while the selection of an appropriate antifungal is important, control of patient risk factors for fungal infection is perhaps more so, whether it is the need to remove a central venous catheter or to decrease doses of immunosuppressants.

Compared with the abundance of drugs available to kill bacteria, the number of systemic antifungal drugs is much lower. Selective toxicity is more difficult to achieve with eukaryotic fungi than with prokaryotic bacteria. Several newly marketed agents have changed the way fungal infections are treated. The chapters that follow introduce these agents in more detail.

25 Polyenes

Agents: amphotericin B, lipid formulations of amphotericin B, nystatin (topical)

For many years, amphotericin B deoxycholate was the standard of care for many systemic fungal infections, for both its broad antifungal spectrum and a lack of available alternatives. Polyenes work by binding to ergosterol in the cell membrane of fungi, disrupting its function. Amphotericin B is notable for its toxicities, principally nephrotoxicity and infusion-related reactions. To attenuate these toxicities, three lipid forms were developed: amphotericin B colloidal dispersion (ABCD), amphotericin B lipid complex, and liposomal amphotericin B (LAmB).

Amphotericin B formulations have seen considerably less use since the introduction of the echinocandins and broad-spectrum azoles, but they still have utility. Activity against yeasts and many moulds, proven efficacy in understudied disease states, and a long history of use help maintain their place in the antifungal armamentarium.

Spectrum

Good: most species of *Candida* and *Aspergillus*, *Cryptococcus neoformans*, dimorphic fungi, many moulds

Moderate: Zygomycetes
Poor: *Candida lusitaniae, Aspergillus terreus*

Adverse Effects

Nephrotoxicity and infusion-related reactions are the most common adverse effects. Both direct effects on the distal tubule and indirect effects through vasoconstriction of the afferent arteriole cause the nephrotoxicity, and nephrotoxicity also leads to wasting of magnesium and potassium, which thus need supplementation. Infusion-related reactions include fever, chills, and rigors and can be impressive. Less common adverse effects include increased transaminases and rash.

Dosing Issues

The multiple formulations of amphotericin B can lead to confusion over their dosing. Amphotericin B deoxycholate is generally dosed between 0.5 and 1.5 mg/kg/day, where the lipid formulations are dosed at 3–6 mg/kg/day. Whether the lipid formulations are equivalent is a matter of debate, but most clinicians dose them as if they are. Fatal overdoses of amphotericin B deoxycholate have been given when dosed as the lipid forms are—generally a 5× overdose. Mind your formulation.

Important Facts

- Amphotericin B nephrotoxicity can be attenuated by the process of sodium loading: administered boluses of normal saline before and after the amphotericin infusion. Sodium loading is an inexpensive and easy way of protecting the kidneys.

- Many practitioners administer such drugs as acetaminophen, diphenhydramine, and hydrocortisone to decrease the incidence and severity of infusion-related reactions of amphotericin B. Meperidine is often given to treat rigors when they develop, but be wary of using this drug in patients who develop renal dysfunction because it has a neurotoxic metabolite that is eliminated renally.
- Whether differences in efficacy exist between the lipid formulations of amphotericin B is a matter of debate, but differences in safety do exist. In terms of infusion-related reactions, ABCD seems to have the worst, while LAmB has the least. All of them have less nephrotoxicity than amphotericin B deoxycholate, but LAmB seems to have the least of all.
- Nystatin is used only topically because of poor tolerance when given systemically.

What They're Good For

Amphotericin B formulations remain the drugs of choice for cryptococcal meningitis and serious forms of some other fungal infections, such as dimorphic fungi and some mould infections. Because of their broad spectrum, they are also a reasonable choice if fungal infection is suspected but the infecting organism is not known, as in febrile neutropenia. Their use in candidiasis and aspergillosis has declined with the availability of newer, safer agents.

Don't Forget!

Double-check that dose of amphotericin B; which formulation are you using?

26 Antimetabolites

Agent: flucytosine (5-FC)

Flucytosine has a mechanism of action that is distinct from that of other antifungals in that it has an antimetabolite that interferes with DNA synthesis. Flucytosine was originally investigated as an oncology drug, but it was found to be significantly more active against fungi than against human cancer cells. The primary role of flucytosine is in combination therapy with amphotericin B formulations for cryptococcal disease. Because of its toxicity and relative lack of efficacy, it is rarely used for other infections.

Spectrum

Good: in combination with amphotericin B: *Cryptococcus neoformans*, most species of *Candida*
Moderate: monotherapy: *Cryptococcus neoformans*, most species of *Candida*
Poor: moulds, *Candida krusei*

Adverse Effects

Flucytosine, which is also called 5-FC, is fluorouracil for fungi. When this fact is considered, the adverse effects are predictable. Flucytosine is only relatively

selective for fungi and can cause considerable bone marrow suppression, particularly in higher doses or during prolonged courses. GI complaints are more common, but they are less severe.

Important Facts

- Drug concentration monitoring is available for flucytosine: check a peak concentration about 2 hours after the dose is given. However, do not rely on flucytosine concentrations alone to monitor for toxicity—hematology values are more important than drug levels.
- Flucytosine generally should not be used as monotherapy for invasive candidiasis because of the potential emergence of resistance *in vivo*.
- The most common use for flucytosine is in combination with an amphotericin B formulation for cryptococcal meningitis. Though this combination is recommended in guidelines and very common, some clinicians question the value of flucytosine. In the main clinical study for this indication, flucytosine use was associated with more rapid sterility of cerebrospinal fluid cultures but showed no obvious clinical benefit.

What It's Good For

As stated above, most flucytosine use is in combination with an amphotericin B formulation for treatment of cryptococcal meningitis. This combination may also be used to treat other forms of cryptococcal infection and, uncommonly, to treat *Candida* infection. It may be an acceptable option for the clearance of candiduria in patients who cannot receive fluconazole because of allergy or resistance,

but the number of patients who require this therapy is small.

Don't Forget!

Follow your patient's cell counts closely and reconsider the value of flucytosine therapy if hematologic toxicity develops.

27 Azoles

Introduction to Azoles

Agents: ketoconazole, **fluconazole, itraconazole, voriconazole, posaconazole,** multiple topical formulations

The azoles are a broad class of antifungal agents whose drug development has recently been expanding. They work by inhibiting fungal cytochrome P450, decreasing ergosterol production. One might expect that this mechanism of action would lead to issues with drug interactions, and this is indeed a significant problem with these drugs.

Azoles have become mainstays of antifungal pharmacotherapy. As they have been developed, agents of variable antifungal spectrums and toxicity profiles have been introduced. These differences are fundamental and are among the most important characteristics to know if you use them clinically. Because they are so different, we will discuss the commonly used systemic agents individually.

Fluconazole

The introduction of fluconazole in 1990 was a breakthrough in antifungal pharmacotherapy. Fluconazole is highly bioavailable, available in both oral and IV formulations, and highly active against many species of *Candida*. Before this, clinicians were faced with the toxicity and inconvenience of amphotericin B for serious forms of candidiasis. Fluconazole has a low incidence of serious adverse reactions, and converting from IV to oral therapy is simple. Though a shift toward non-*albicans* species of *Candida* has affected the use of fluconazole, it remains an important, frequently utilized agent.

Spectrum

Good: *Candida albicans, Candida tropicalis, Candida parapsilosis, Candida lusitaniae, Cryptococcus neoformans, Coccidioides immitis*

Moderate: *Candida glabrata* (can be susceptible dose-dependent, or resistant)

Poor: moulds, many dimorphic fungi, *Candida krusei*

Adverse Effects

Though fluconazole is generally well tolerated, it can cause hepatotoxicity or rash. It has a lower propensity for serious drug interaction than many

other azoles, but interactions still occur with many drugs metabolized by the cytochrome P450 system. QTc prolongation is also possible.

Dosing Issues

Fluconazole doses for systemic fungal infections have been escalated, particularly for the treatment of *Candida glabrata*. Be sure to adjust dosing with regard to renal function, because the drug is eliminated through the urine. Vulvovaginal candidiasis requires only a one-time dose of 150 mg of fluconazole.

Important Facts

- Fluconazole is poorly active against all *Candida krusei* and some *Candida glabrata*. If you are using it for the latter infection, it is best to check susceptibilities and give 800 mg per day of fluconazole. If your lab does not do susceptibility testing of fungi, consider an alternative agent such as an echinocandin.
- Fluconazole is often given as prophylaxis against *Candida* infections in susceptible populations like intensive care unit patients. Are you treating a patient who was receiving it and now has yeast in the blood? Try an echinocandin instead.
- The high bioavailability of fluconazole makes it an excellent therapy to transition to as patients tolerate oral medications.

What It's Good For

Fluconazole remains a drug of choice for many susceptible fungal infections, including invasive and noninvasive candidiasis and cryptococcal disease.

It is also used for some dimorphic fungal infections, such as coccidioidomycosis.

Don't Forget!

Not all species of *Candida* are fluconazole-susceptible. Ensure that you check your patient's isolate before committing to a definitive course of therapy with it.

Itraconazole

Itraconazole is a broader-spectrum azole than fluconazole that could probably have a bigger place in antifungal pharmacotherapy today if it were not for pharmacokinetic issues that have hampered its greater use. It has activity against *Aspergillus* and other mould species and was once commonly used as a step-down therapy in aspergillosis, but this use has declined since voriconazole became available.

Spectrum

Good: *Candida albicans, Candida tropicalis, Candida parapsilosis, Candida lusitaniae, Cryptococcus neoformans, Aspergillus* species, many dimorphic fungi

Moderate: *Candida glabrata* and *Candida krusei* (can be susceptible dose-dependent, or resistant)

Poor: Zygomycetes, many other moulds

Adverse Effects

Itraconazole's adverse effect profile causes more concerns than that of fluconazole. In addition to causing hepatotoxicity, itraconazole is a negative ionotrope and is contraindicated in patients with heart failure. The oral solution is associated with

diarrhea. It is also a stronger inhibitor of cytochrome P450 enzymes and has a long list of drug interactions. QTc prolongation can also occur.

Important Facts

- Itraconazole comes in two different formulations with different bioavailabilities and requirements. The capsules have lower bioavailability than the solution and are less preferred for systemic fungal infections.
- The oral formulations of itraconazole have different instructions with regard to taking them with meals. Capsules should always be taken with a full meal, whereas the solution should be taken on an empty stomach. Absorption can also be lowered by agents that decrease gastric acidity, such as proton-pump inhibitors; try having your patients take their itraconazole with a soda.
- Because itraconazole absorption is so erratic and unpredictable, concentrations are often monitored. Consider checking a trough concentration on your patient if he or she is taking it for a serious fungal infection and/or for a long time.
- Itraconazole was once available in an IV formulation, but this has been discontinued by the manufacturer. Ignore older references that suggest using it.

What It's Good For

Itraconazole remains a drug of choice for some dimorphic fungal infections, like histoplasmosis. It once had a larger role in the management and prophylaxis of aspergillosis and other mould infections, but it has been largely replaced by voriconazole.

Don't Forget!

Watch for those drug interactions, and be sure to counsel your patients on how to take their itraconazole formulation.

Voriconazole

The introduction of voriconazole represented a significant improvement in the treatment of mould infections. It is also a broad-spectrum antifungal like itraconazole, with good activity against *Candida* species and many moulds. Unlike itraconazole, voriconazole is well absorbed and available in both highly bioavailable oral formulations and an IV admixture. Perhaps most important, voriconazole was shown to be superior to amphotericin B deoxycholate for invasive aspergillosis and has become the drug of choice for that disease.

Spectrum

Good: *Candida albicans, Candida lusitaniae, Candida parapsilosis, Candida tropicalis, Candida krusei, Cryptococcus neoformans, Aspergillus* species, many other moulds

Moderate: *Candida glabrata* (can be susceptible dose-dependent, or resistant), *Candida albicans* that are fluconazole-resistant, *Fusarium* species

Poor: Zygomycetes

Adverse Effects

In addition to the hepatotoxicity, rash, and drug interactions that are common with this class, voriconazole has some agent-specific adverse effects

worth watching. Visual effects such as seeing wavy lines or flashing are very common and dose-related; they tend to go away with continued use. Visual hallucinations can also occur but are less common.

Dosing Issues

Voriconazole has highly variable interpatient pharmacokinetics and nonlinear elimination, making it difficult to dose correctly. Some centers monitor voriconazole trough concentrations, but tests are not yet widely available. If you are committing your patient to an extended course of therapy for voriconazole, consider checking a trough.

Important Facts

- Voriconazole is active against many fluconazole-resistant strains of *Candida albicans*, but it is less active against them than fluconazole-susceptible strains. An echinocandin is a better choice, but consider susceptibility testing if you need to use voriconazole for an oral option.
- Voriconazole is a potent inhibitor and a substrate of the cytochrome P450 system. The list of drugs that interact with voriconazole is long and varied. Some of them are contraindicated, such as rifampin, while others, such as calcineurin inhibitors (e.g., cyclosporine), require dose adjustments. This is significant, because many of the patients who require voriconazole are immunosuppressed.
- The IV form of voriconazole contains a cyclodextrin vehicle that accumulates in renal dysfunction and may be nephrotoxic. It is contraindicated with a creatinine clearance of less

than 50 ml/min. The oral formulations avoid this issue.

- Voriconazole is eliminated hepatically and is unlikely to be useful in the treatment of candiduria.

What It's Good For

Voriconazole is the drug of choice for invasive aspergillosis and is frequently used in the treatment of infections caused by other moulds. It can be used for candidiasis as well, but fluconazole and echinocandins are more frequently used for these infections. Some clinicians use voriconazole in the empiric treatment of febrile neutropenia.

Don't Forget!

Watch for drug interactions with voriconazole, and consider checking drug concentrations if you are using it for an extended course of therapy.

Posaconazole

Posaconazole is the newest extended-spectrum azole. It is an analog of itraconazole that is substantially more active against many fungi. Currently, it is indicated only for the prophylaxis of fungal infections in neutropenic patients and the treatment of oropharyngeal candidiasis. It is unique among the azoles in that it has good activity against the Zygomycetes, a difficult-to-treat class of moulds that most antifungals (voriconazole included) do not treat.

Spectrum

Good: *Candida albicans, Candida lusitaniae, Candida parapsilosis, Candida tropicalis, Candida krusei*, *Aspergillus* species, Zygomycetes, many other moulds, dimorphic fungi

Moderate: *Fusarium* species, *Candida glabrata*

Though posaconazole is active against these organisms, clinical data are lacking for many of them.

Adverse Reactions

Posaconazole seems to be well tolerated, though it can cause hepatotoxicity, nausea, and rash. It has the same propensity to cause drug interactions via cytochrome P450 as the other azoles. We will learn

more about the adverse effect spectrum of posaconazole as clinical experience with it grows.

Dosing Issues

Posaconazole is available only as an oral suspension. It should always be administered with food to increase its absorption; foods with a high fat concentration improve absorption the most. An IV formulation is in development.

Important Facts

- Posaconazole's primary use is in the prophylaxis of fungal infections in high-risk patients. As with voriconazole, many of these patients are taking immunosuppressants that interact with posaconazole, so keep close tabs on those drug concentrations.
- Clinical data with posaconazole for Zygomycete infections are growing, and posaconazole is emerging as a drug of choice for these infections.
- Posaconazole has issues with absorption. High-fat meals boost absorption substantially and may be required for adequate absorption in some patients. Posaconazole drug concentrations are not standardly tested for in many labs, but tests are becoming available and may be a way to ensure that patients are absorbing enough of the drug for it to be effective.

What It's Good For

Posaconazole is most commonly used as prophylaxis against fungal infections in susceptible hosts, but it can also be used in zygomycosis, oropharyngeal candidiasis, and fungal infections refractory to other agents.

Don't Forget!

Have your patients take posaconazole with meals to ensure adequate absorption. This is not always possible with neutropenic patients with mucositis.

28 Echinocandins

Agents: caspofungin, micafungin, anidulafungin

The echinocandins are the latest class of antifungal agents to be introduced in clinical practice and are slowly changing the way some fungal diseases are treated. They work by inhibiting the synthesis of beta-1,3-glucan, a component of the fungal cell wall. This mechanism of action is distinct from that of other antifungals and gives clinicians a new area of fungi to target. The three available echinocandins are similar drugs with virtually indistinguishable spectra. They are very well tolerated and have excellent activity against *Candida*, but they all suffer from the same pharmacokinetic setback: lack of an oral formulation. They have considerably fewer drug interactions than azoles, are safer than polyenes, and have great activity against fluconazole-resistant yeasts.

Spectrum

Good: *Candida albicans, Candida glabrata, Candida lusitaniae, Candida parapsilosis, Candida tropicalis, Candida krusei, Aspergillus* species

Moderate: *Candida parapsilosis*, some dimorphic fungi

Poor: Zygomycetes and most non-*Aspergillus* moulds, *Cryptococcus neoformans*

Adverse Effects

Echinocandins have an excellent safety profile. They can cause mild histamine-mediated infusion-related reactions, but these are not common and can be ameliorated by slowing the infusion rate. Hepatotoxicity is also possible with any of these agents, but this is not common.

Important Facts

- Differences among the echinocandins are minor and mostly pharmacokinetic. Caspofungin and micafungin are eliminated hepatically by non–cytochrome P450 metabolism, while anidulafungin degrades in the plasma and avoids hepatic metabolism. Despite this unique method of elimination, it is not completely devoid of hepatotoxicity.
- Echinocandins have excellent fungicidal activity against *Candida*, but against *Aspergillus* species they exhibit activity that is neither classically cidal nor static. Instead, they cause aberrant, nonfunctional hyphae to be formed by the actively growing mould.
- All of the echinocandins are less active against *Candida parapsilosis* than the other common clinical species. It has yet to be determined whether this is likely to result in clinical failure, because this organism has been successfully treated with these drugs. If your patient is infected with this organism, be sure to change any IV catheters your patient has and consider fluconazole therapy instead.

- Though drug interactions with the echinocandins are minor, there are some of which you should be aware, particularly with caspofungin and micafungin. Be careful when you use them with the immunosuppressants cyclosporine (caspofungin) and sirolimus (micafungin).

What They're Good For

Echinocandins are becoming drugs of choice for invasive candidiasis, particularly in patients who are clinically unstable. They are also useful in the treatment of invasive aspergillosis but do not have the level of supporting data that voriconazole and the polyenes do for this indication. All of them are used for esophageal candidiasis, and some are used in prophylaxis or empiric therapy of fungal infections in neutropenic patients.

Don't Forget!

Echinocandins are great drugs for invasive candidiasis, but they are not cheap. After beginning empiric therapy with an echinocandin, transition your patient to fluconazole if he or she has a susceptible strain of *Candida* and no contraindication to fluconazole.

Antiviral Drugs

PART 5

29 Antiviral Drugs

Introduction to Antiviral Drugs

The term *virus* has interesting meanings in popular culture: it is commonly used to describe something that has or can spread quickly from person to person, such as a computer virus or a "viral" video, a video that gains quick popularity through Internet or e-mail sharing. This usage represents a basic understanding of the high transmissibility of many respiratory viruses, such as influenza and the rhinoviruses that cause the common cold. However, many less-understood viruses, particularly those that cause chronic disease, can be confusing.

The world of viruses is very different from that of prokaryotes and eukaryotes. Viruses are dependent on cells to replicate and cannot perpetuate without them. They are considerably smaller than eukaryotes and even much smaller than most prokaryotes, though they vary widely in size (see Figure 1–2). They are relatively simple organisms compared with prokaryotes or eukaryotes, but they outnumber all life forms on earth. Scientists have debated for many years about whether viruses are life forms or not, and no clear consensus yet exists. The understanding of how they interact with and shape the existence of living cells, however, has

increased greatly since they were described by Louis Pasteur in the late nineteenth century.

An in-depth discussion of the structure of viruses is beyond the scope of this text, but a basic understanding of viruses will help you understand the actions of antiviral drugs. Viruses are highly diverse, though nearly all of them share a few common characteristics. Many are covered by a viral *envelope* as their outmost layer, composed of elements of the host cell membrane, endoplasmic reticulum, or nuclear envelope. This layer covers the *capsid*, a shell composed of identical building blocks of *capsomeres*. The capsid protects the viral *nucleic acid*, which is either DNA or RNA but not both (as in cells). The DNA or RNA can be either single- or double-stranded. Finally, many viruses contain enzymes that catalyze reactions that lead to their replication or cell entry. Viruses cannot synthesize their own components to replicate—they are dependent on host cellular processes for all synthetic functions. Individual complete particles of virus are termed *virions*.

The specific steps of the viral life cycle differ from virus to virus, but they follow the same basic pathway. Viruses spread from host to host through various means, some through direct inhalation, some through direct fluid exchange, some through vectors such as mosquitoes. Once a virus reaches its target cell, it has to penetrate the cell membrane. Specific receptors on the cell and viral surfaces often facilitate this process. The virus then uncoats and releases its genetic information from the capsule into the host cell. The host cell reads the genetic material and begins to translate it into viral proteins. How exactly this proceeds depends

on the form in which the genetic material exists in the virus. In some cases, the genetic material is encoded as RNA. In the group of viruses known as retroviruses, the RNA genetic material is first translated into DNA (via an enzyme known as reverse transcriptase) before integrating into the host genome. For these viruses or those viruses whose genome is already encoded as DNA, transcription into messenger RNA occurs, followed by translation into protein. Once the pieces of the puzzle are built, the viral enzymes assemble them into complete virions and they are finally released from the cell. The available antiviral drugs are aimed at various steps in this cycle. Some are aimed at specific receptors against specific viruses (such as influenza), and some are aimed at more general steps to attack multiple viruses.

The pharmacotherapy of viral infections is different from that of bacterial infections. Patient-specific susceptibility results are rarely available, leaving practitioners to choose therapies based upon general patterns of susceptibility for viral infections (HIV is a notable exception). While viruses can be cultured, many viral illnesses are diagnosed through genetic testing for viral antigens or nucleic acids. These tests can be followed quantitatively to see if an infection improves, but symptoms are usually followed instead. Most common viral infections have no effective pharmacotherapeutic remedy, which is a fancy way of saying that there is still "no cure for the common cold."

Anti-Herpes Simplex Virus and Varicella-Zoster Virus Agents

30

Agents: acyclovir, valacyclovir, famciclovir

These agents are primarily used in the treatment of infections caused by herpes simplex virus (HSV) and varicella-zoster virus (VZV), though they are active against some other viruses as well. All of these agents are nucleoside analogs that prevent viral DNA replication. Acyclovir is poorly absorbed and must be given up to 5 times daily when administered orally; valacyclovir and famciclovir are pro-drugs that are absorbed better and can be administered less frequently. Only acyclovir can be administered intravenously, and it is the agent of choice for serious HSV infections such as encephalitis.

Spectrum

Good: HSV-1 and HSV-2
Moderate: VZV
Poor: Epstein-Barr virus (EBV), cytomegalovirus (CMV), HIV

Adverse Effects

These drugs are generally well tolerated with few adverse effects. The most concerning adverse effect is nephrotoxicity through either crystallization or AIN, most commonly associated with IV acyclovir in higher

doses. Crystallization is preventable through hydration and correct dosing in renally impaired patients. Seizures, tremors, or other CNS effects can also occur. Nausea, diarrhea, and rash are more common. Thrombotic thrombocytopenic purpura has been reported with valacyclovir in HIV patients.

Important Facts

- Valacyclovir is a pro-drug of acyclovir with substantially improved bioavailability and less-frequent dosing. Its disadvantage is higher cost. Famciclovir is a pro-drug of penciclovir, an agent that is available only as a topical preparation.
- Acyclovir dosing varies widely by indication and host status. Be sure to double-check that it is appropriate for your patients.
- Acyclovir is most nephrotoxic in combination with diuretics or other nephrotoxins. Keep your patients hydrated during acyclovir therapy, particularly if it is given in higher IV doses.

What They're Good For

Acyclovir is the drug of choice for severe or difficult-to-treat HSV infections, such as encephalitis or severe HSV outbreaks among HIV patients. Any of these agents can be used to treat HSV-2 infections (genital herpes) to prevent outbreaks or decrease symptom duration. They are all also effective in treating VZV infection.

Don't Forget!

Make sure your patient can afford valacyclovir or famciclovir before prescribing either one. Oral acyclovir is less convenient, but much less expensive.

Anti-Cytomegalovirus Agents

31

Agents: ganciclovir, valganciclovir, foscarnet, cidofovir

The common virus known as cytomegalovirus (CMV) causes infections that are usually asymptomatic in immunocompetent patients but can be devastating in immunocompromised patients. Approximately 60% of Americans become seropositive for CMV by adulthood, and infection is lifelong. If a patient becomes immunocompromised, the infection can reactivate and the patient will need pharmacotherapy. Anti-cytomegalovirus agents work by preventing viral replication. They also all have appreciable toxicity that must be respected and monitored.

Spectrum

Good: CMV, HSV-1, HSV-2, VZV, EBV
Poor: HIV

Adverse Effects

Ganciclovir and valganciclovir are the same active drug and have the same adverse reactions. They both have dose-dependent myelosuppression that is relatively common, particularly when used in higher doses or in renally impaired patients without dose adjustment. Foscarnet is nephrotoxic and

neurotoxic, and it is reserved for patients who have failed other therapy. Nausea, vomiting, and diarrhea can occur from any of these agents. Foscarnet can also cause penile ulcers. Cidofovir is an uncommonly used agent that also exhibits nephrotoxicity.

Important Facts

- Oral ganciclovir has been replaced by valganciclovir, which has much better bioavailability.
- Ganciclovir must be carefully dosed by patient weight and renal function. Monitor patients closely for changes in renal function when they are on therapy.
- The package insert for valganciclovir specifies dose adjustment for renal dysfunction but not weight. It comes in two strengths: 900 mg and 450 mg. The dose of 900 mg BID is considered to be equivalent to 5 mg/kg q12h of IV ganciclovir, but it may be much more than that for an underweight patient because it is approximately 60% bioavailable. Consider this example for a 50-kg patient:
  - Ganciclovir dose = 50 kg × 5 mg/kg = 250 mg ganciclovir
  - Valganciclovir dose = 900 mg × 0.60 bioavailability = 540 mg of active ganciclovir

  This patient would receive more than double the amount of active ganciclovir if 900 mg BID of valganciclovir are used. It may be worth considering dose reduction in underweight patients, particularly if they are at high risk of toxicity.
- Foscarnet has significant nephrotoxicity. This can be somewhat attenuated through hydra-

tion with normal saline. Cidofovir is also nephrotoxic.

- Even if a patient's isolate of CMV is resistant to both ganciclovir and foscarnet, it may still be susceptible to the combination.

What They're Good For

Ganciclovir and valganciclovir are first-line drugs for the treatment and prevention of CMV infections. Valganciclovir is often given to prevent CMV infection after transplant. Foscarnet is a second-line agent for CMV that can also be used for severe or resistant HSV infections. Cidofovir is a second-line agent for CMV.

Don't Forget!

Although valganciclovir is oral, it is highly bioavailable and has adverse effects similar to those of ganciclovir. Valganciclovir use requires monitoring for toxicity that is just as rigorous as that for ganciclovir.

Neuramidase Inhibitors

32

Agents: oseltamivir, zanamivir

The neuramidase inhibitors are anti-influenza virus drugs that have activity against influenza A and B strains, unlike amandatine and rimantidine, older drugs that are active only against influenza A strains. They work by preventing the viral neuramidase enzyme from releasing new virions from the host cell, preventing further replication. The two drugs differ in their form of delivery—oseltamivir is an oral pro-drug, while zanamivir is inhaled. They can be used in either the treatment of influenza or as prophylaxis for patients who cannot take the influenza vaccine.

Spectrum

Good: Influenza A and B
Poor: other viruses

Adverse Effects

Both oseltamivir and zanamivir are well-tolerated drugs. Oseltamivir can cause nausea, vomiting, and abdominal pain, but these tend to be transient effects. Headache and fatigue can also occur, particularly during prophylactic use when the drug is given for a longer period of time. Zanamivir has

mostly pulmonary adverse effects, including cough and bronchospasm. Avoid using it in patients with asthma or other reactive pulmonary diseases.

Important Facts

- Resistance to the neuramidase inhibitors can occur. Their utility is dictated by the degree of resistance that exists in the dominant influenza strains of the season. Currently, zanamivir is active against the vast majority of oseltamivir-resistant strains, but these resistance patterns may change.
- Neuramidase inhibitors are most effective when started early in the course of infection, because viral replication peaks early (48–72 hours after infection). The package inserts for these drugs state they should be started in patients who have been symptomatic for no more than 2 days and should be given for 5 days, but clinicians do not always follow these guidelines. In severe influenza infections such as those that require hospitalization, it may be worth extending the duration of treatment.
- Both of these drugs are highly effective at preventing influenza infection when the predominant strains in the community are susceptible, but they are not substitutes for a vaccination strategy. Adverse effects are more common with the prolonged use seen with prophylactic use than with the shorter durations of therapeutic use.

What They're Good For

Oseltamivir and zanamivir are both effective at treating and preventing influenza infections if the

circulating strains are susceptible. The desired route of administration dictates the choice of agent.

Don't Forget!

If your patient's flu has peaked and he or she is improving, then it's probably not the time to utilize one of these drugs. It may, however, be a good time to counsel on the utility of the influenza vaccine for *next* season.

33 Antiretroviral Drugs

Introduction to Antiretroviral Drugs

Despite the decades-long stall in antimicrobial drug development, one area that has seen substantial growth is the development of antiretroviral drugs targeting the HIV virus. Only a single active drug (zidovudine) was available near the beginning of the epidemic in the mid-1980s, and today more than two dozen drugs and drug combinations are available with more in the pipeline. Some antiretroviral drug classes are in their second or third generation of agents, leaving some of the earlier agents essentially obsolete. The development and proper usage of these agents have moved HIV infection toward the realm of a chronic disease rather than a short-term "death sentence." More than any other antimicrobial group, however, the antiretrovirals come with the challenges of taking complex multidrug regimens for years: drug adherence, resistance, toxicities, and interactions. The full scope of these issues is beyond this text; instead, we will highlight key aspects of the drug classes and unique properties of individual agents, especially as related to toxicities. The latest information on drugs and regimens is available at http://aidsinfo.nih.gov. Important note: we present the commonly

used abbreviations for these agents so that you may recognize them in practice, but it is *not* acceptable to use these abbreviations in prescriptions and not recommended to use them in patient documentation.

Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

Agents: tenofovir (TDF), emtricitabine (FTC), lamivudine (3TC), zidovudine (ZDV, AZT), abacavir (ABC), stavudine (d4T), didanosine (ddI)

Combinations: emtricitabine/tenofovir (Truvada), **abacavir/lamividune** (Epzicom), lamivudine/zidovudine (Combivir), abacavir/lamivudine/zidovudine (Trizivir)

The nucleoside reverse transcriptase inhibitors (NRTIs) are the oldest class of antiretrovirals (tenofovir is technically a nucleotide but is grouped with these agents). A combination of two of these drugs typically forms the "backbone" of most anti-HIV regimens.

Spectrum

In addition to being used to treat the HIV virus, several of these drugs (tenofovir, emtricitabine, lamivudine) have clinically useful activity against hepatitis B virus (HBV).

Adverse Effects

Extremities: Peripheral neuropathy is seen as a delayed, slowly progressive adverse effect in

some patients taking didanosine or stavudine (and especially in combination).

Gastrointestinal: NRTIs tend to have less GI toxicity (nausea, vomiting, diarrhea) than many antiretrovirals, but zidovudine and didanosine may be problematic.

Hematologic: Bone marrow suppression (anemia, neutropenia) occurs frequently with zidovudine, and rarely with other NRTIs.

Hypersensitivity: In a minority of patients, abacavir use is associated with a hypersensitivity reaction manifesting with fever, rash, and flulike symptoms days to weeks after starting therapy. Continuation of or rechallenge with abacavir in patients experiencing this syndrome can be fatal. Patients at highest risk for this toxicity can be identified by a genetic test for the HLA B*5701 allele before starting therapy; patients testing positive should not be offered abacavir.

Metabolic: Lactic acidosis, hepatic steatosis, and pancreatitis are part of a complex of toxicities suspected to be of mitochondrial origin that are a classwide adverse effect of NRTIs. Mortality can be high if symptoms are not recognized early—which is a problem because symptoms are typically delayed (for months) in onset and may be nonspecific in initial presentation. Agents with a higher propensity for this toxicity include stavudine, didanosine, and zidovudine. Didanosine and zidovudine may also contribute to hyperlipidemia, insulin resistance, and lipoatrophy (loss of fat causing changes in appearance, primarily in the face and buttocks).

Renal: Nephrotoxicity, evidenced by increased serum creatinine and renal electrolyte and protein wasting, is a well-documented adverse effect of tenofovir and requires regular monitoring of renal function.

Important Facts

- Most of the NRTIs require dosage adjustment in renal dysfunction. This may require avoiding the fixed-dose combination preparations to give more dose flexibility.
- NRTIs have minimal metabolic drug interactions compared with the other antiretroviral drug classes. Tenofovir has interactions with didanosine and atazanavir that require dosage adjustment.
- Didanosine, stavudine, and zidovudine tend to have the most toxicity and are now mostly used as second-line treatment for resistant cases.
- Various patterns of cross-resistance among the NRTIs occur. Expert interpretation of antiviral susceptibility is required, and in some cases NRTIs may confer a therapeutic benefit even for resistant viruses.

What They're Good For

NRTIs are used as components of a combination antiretroviral regimen for HIV. For treatment-naive patients, two NRTIs are typically combined with a drug from another class. For treatment-experienced patients, three or more NRTIs may be part of a salvage regimen. As noted, certain NRTIs are also used to manage HBV infections. Use of these drugs in management of HIV/HBV co-infected

patients requires accounting for the overlap in activity between the viruses to ensure that resistance doesn't emerge because of suboptimal activity against one of the viruses.

Don't Forget!

If there aren't two NRTIs (taking into account combination preparations as well) as part of a patient's anti-HIV regimen, something is weird. The patient may be on an unusual salvage regimen (hopefully under the care of an HIV expert), but it's best to check to make sure something didn't get left out.

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Agents: efavirenz (EFV), nevirapine (NVP), etravirine (ETR), delavirdine (DLV)

Combinations: efavirenz/tenofovir/emtricitabine (Atripla)

The non-nucleoside reverse transcriptase inhibitors (NNRTIs) inhibit the same enzyme as the NRTIs but work through a different mechanism and have greatly different pharmacologic properties. That extra *N* makes a big difference: it's very important to keep the two drug classes straight.

Spectrum

Only current clinical use is for HIV.

Adverse Effects

CNS: Efavirenz can cause a broad spectrum of CNS effects; common effects include dizziness, drowsiness (or sometimes insomnia), and abnormal (and especially vivid) dreams. Less common effects include depression, psychosis, and suicidal ideation. The onset of effects is usually very rapid (with the first few doses) and often subsides after several weeks of therapy. These effects may be minimized by taking the drug on an empty stomach and by taking at

bedtime or 2–3 hours prior. A history of mental illness or depression is a relative contraindication to the use of efavirenz.

Dermatologic: Rashes can occur with all NNRTIs, although the nevirapine appears to be the biggest offender. Though some mild forms can be treated with antihistamines, any lesions involving the mucous membranes (suggesting Stevens-Johnson syndrome or similar eruptions) must be managed urgently and represent an absolute contraindication to rechallenge.

Hepatotoxicity: All NNRTIs can cause a spectrum of hepatotoxicity, from asymptomatic transaminase elevations, to clinical hepatitis, to fulminant hepatic failure. Nevirapine-induced hepatotoxicity may occur in the context of a hypersensitivity reaction (see below). Monitoring of signs and symptoms of hepatitis and liver enzymes is important for all these agents.

Hypersensitivity: Nevirapine can cause a hypersensitivity reaction characterized by flulike symptoms, fever, jaundice, and abdominal pain, with or without a rash. Fulminant hepatic failure and severe rash (e.g., toxic epidermal necrolysis) are the most feared manifestations of nevirapine hypersensitivity reactions. Interestingly, this syndrome appears to be more frequent in patients who are less immunocompromised (have higher CD4 counts) when starting nevirapine. The risk of nevirapine hypersensitivity syndrome may be reduced by using a "reverse taper" upon drug initiation: start with a lower dose and escalate to full dose over 2 weeks, when the risk is highest.

Metabolic: Lipohypertrophy, manifesting as a gradual accumulation of fat in the abdomen, chest, and neck (as a "buffalo hump"), may occur with the NNRTIs. Efavirenz and nevirapine have also been linked to hyperlipidemia.

Pregnancy/Lactation: Efavirenz is a pregnancy category D agent and should not be offered to pregnant women or those trying to conceive or not using effective birth control. Other NNRTIs are pregnancy category C.

Important Facts

- A key limitation of NNRTIs has been the low "genetic barrier" to resistance. A single point mutation can lead to high-level resistance to the entire class of drugs. Thus, even stricter adherence may be necessary to NNRTI-based regimens to prevent the emergence of resistance. The advanced-generation agent etravirine possesses activity against viruses with the most common NNRTI mutations, and it may have a role for patients who have failed other NNRTIs.
- NNRTIs have a much broader drug interaction profile than the NRTIs (remember, one *N* makes a lot of difference!). Generally, nevirapine and etravirine are inducers of drug metabolism, delavirdine is an inhibitor, and efavirenz shows mixed inducing and inhibitory properties. Thus, careful screening of these drugs against all other agents in a patient's regimen is warranted.

What They're Good For

A combination regimen of efavirenz with the NRTIs tenofovir and emtricitabine is one of the preferred

regimens for treatment-naive patients with HIV. Co-formulated as Atripla, this regimen represents the long-sought one-pill, once-daily antiretroviral regimen. Of course, this doesn't mean it is necessarily the best choice for any individual patient. The other NNRTIs tend to be used as second-line therapy in treatment-experienced patients.

Don't Forget!

When initiating an NNRTI, the first few weeks are key. Patients must be counseled carefully about recognizing adverse effects, especially skin reactions and symptoms of hepatotoxicity. The need for strict adherence to prevent resistance, the dose titration schedule for nevirapine, and the CNS effects of efavirenz need to be fully explained to patients. There's really only one shot to get it right with these very valuable drugs!

Protease Inhibitors

Agents: atazanavir (ATV), darunavir (DRV), ritonavir (boosting dose: /r), fosamprenavir (FPV), saquinavir (SQV), indinavir (IDV), nelfinavir (NFV), tipranavir (TPV), ritonavir (full dose: RTV)

Combinations: lopinavir/ritonavir (LPV/r, Kaletra)

The introduction of the protease inhibitors (PIs) was a major advance in antiretroviral therapy. Combination regimens with PIs were the beginning of the era of "highly active antiretroviral therapy" (HAART) and have had a major impact on prolonging lifespan among HIV-infected individuals. (Note: the term *HAART* has largely fallen out of favor.) PIs are now entering their third generation, with more-potent agents with fewer acute toxicities; however, long-term toxicities are arising as a concern. A key advance has been the introduction of "boosting": using the (normally undesirable) potent inhibition of drug-metabolizing enzymes displayed by ritonavir to increase the serum concentrations and half-lives of other PIs. Boosting is now routine for essentially all PIs: patients take an additional pill of a low dose of ritonavir along with

their PI (typically indicated as "/r", as in ATV/r). The drug Kaletra (lopinavir/ritonavir) is the only agent where the boosted ritonavir is co-formulated into the same pill.

Spectrum

Only current clinical use is for HIV.

Adverse Effects

Cardiovascular: That patients with HIV were living long enough to suffer from heart attacks and strokes was viewed (somewhat perversely) as a sign of the success of potent antiretroviral therapy, particularly PIs. However, the possibility of cardiovascular adverse effects is now recognized as a substantial problem. PIs appear to interact with conventional cardiovascular risk factors to increase risk for myocardial infarction and stroke beyond that expected from just prolonging lifespan. Atazanavir and darunavir may confer somewhat lower risk compared with other PIs. Management is with all the mainstays of cardiovascular risk prevention (diet, exercise, drugs).

Gastrointestinal: All PIs are pretty hard on the GI tract (nausea, vomiting, diarrhea). Taking the drugs with food may reduce the symptoms somewhat. Many patients find the effects more tolerable with time. Severe cases may require administration with anti-emetics or antidiarrheals.

Hepatotoxicity: The potential for hepatotoxicity exists with all PIs, ranging from asymptomatic transaminase elevations to clinical hepatitis. Risk may be highest with boosted tipranavir.

Metabolic: One means by which PIs increase cardiovascular risk is through adverse effects on the lipid profile. The PIs are also associated with lipohypertrophy (fat accumulation in abdomen, breasts, and neck).

Nephrotoxicity: Renal toxicity caused by certain PIs precipitating in the kidneys or ureters has been reported. This toxicity is most common with the now infrequently used agent indinavir, and it is reported rarely with atazanavir and fosamprenavir. Adequate fluid intake is recommended for prevention.

Important Facts

- Compared with the NNRTIs, PIs are more robust to antiviral resistance. Typically, several mutations in the target enzyme are required to confer high-level resistance. Thus, PI-based regimens may be slightly more "forgiving" of less than perfect adherence—although, of course, that's probably not the message to convey to your patients.
- The PIs pose tremendous drug interaction challenges. They are all substrates of the common drug-metabolizing enzymes and thus can have their concentrations substantially increased or decreased by drugs that inhibit or induce these enzymes. Ritonavir is one of the most potent inhibitors of the cytochrome P450 enzyme system; hence its use in boosting levels of the other PIs (at the boosting doses used, it has minimal direct antiviral effect). Generally, co-administering other drugs that are P450 substrates (such as statins, macrolides, benzodiazepines, and calcium channel blockers) with ritonavir

leads to increased serum concentrations of these drugs. However, more unpredictable effects can occur, perhaps as a result of shunting to alternative pathways or mixed inhibition/induction, leading to the reduction in serum levels of P450 substrates (as can be seen with voriconazole and methadone). The bottom line: for patients on PIs, carefully screen all of their medications for drug interactions using the most up-to-date references.

What They're Good For

Several PI-based combinations are among the preferred regimens for treatment of initial HIV infection. They are also often used in salvage regimens for patients with resistant virus. Their durable viral suppression needs to be balanced against their long-term toxicities (particularly cardiovascular effects), and patients should be prepared to make appropriate lifestyle changes.

Don't Forget!

Only atazanavir and fosamprenavir can be used unboosted (and this is generally not recommended). If there's not a little ritonavir in the regimen, something is probably wrong.

Entry and Integrase Inhibitors

Agents: maraviroc (MVC), raltegravir (RAL), enfuvirtide (T20)

The three newest classes of antiretrovirals focus on preventing the HIV virus from binding to target cells (maraviroc), fusion of the viral particle with the cell membrane and entry into the cell (enfuvirtide), or integration of the intracellular virus into the chromosomal DNA (raltegravir). Enfuvirtide is administered as a subcutaneous injection associated with substantial injection site reactions; thus, it is generally reserved for patients with the most difficult-to-treat, multidrug-resistant strains of virus.

Spectrum

Only current clinical use is for HIV.

Adverse Effects

Dermatologic: Injection site reactions, including pain, erythema, pruritis, and nodule formation, occur in essentially all patients using subcutaneous enfuvirtide.

Hepatotoxicity: Maraviroc has a black box warning regarding hepatotoxicity, based on case reports from healthy subjects who received the drug in

early clinical trials. The effect seems to be rare in patients treated with maraviroc.

Musculoskeletal: Raltegravir has been associated with increases in creatine phosphokinase. Most of these cases have been asymptomatic; clinically evident myositis or rhabdomyolysis is rare.

Important Facts

- Maraviroc has a unique mechanism of action—binding to and blocking one of the host cell receptors (known as CCR5) that the HIV virus attaches to. Thus, its target is a human protein, not a viral one. HIV can also use another host cell receptor (CXCR4) to attach to, and different strains of HIV have different "preferences" for CCR5 versus CXCR4. Thus, before a patient is started on maraviroc, a tropism test must be performed to see whether the patient's virus "prefers" CCR5 (in which case maraviroc may be useful) or CXCR4 (thus ruling out maraviroc use).
- Maraviroc is a substrate of P450 drug-metabolizing enzymes, and thus there are different dosage recommendations depending on which other potentially interacting drugs the patient is taking. Enfuvirtide and raltegravir have minimal drug interactions.

What They're Good For

These drugs are mainly for use in treatment-experienced patients, although raltegravir in particular may become a standard initial drug for therapy.

Don't Forget!

Pretty much the only drug raltegravir has an interaction with is the anti-TB drug rifampin. Rifampin is a potent inducer of drug-metabolizing enzymes, and its co-administration with many HIV drugs reduces their serum levels below the effective range. Thus, seeing rifampin on the profile of a patient receiving antiretrovirals is a huge red flag and warrants investigation to make sure the patient's antiretroviral therapy is adequate.

PART 6

Antiparasitic Drugs

34 Antiparasitic Drugs

Introduction to Antiparasitic Drugs

There is a tremendously unequal variation in the human burden of parasitic disease, based on geography, industrialization/hygiene, and immune status. It is estimated that up to half of the world's population is chronically infected with parasites. The extent of parasite-related morbidity and mortality depends on parasite burden, preexisting immunity, and patient comorbidities. We will focus on parasitic diseases primarily affecting inhabitants of industrialized nations. Parasites causing human disease can be broadly grouped into two main categories, the unicellular protozoa and the multicellular helminthes (**Table 34–1**). The protozoa have many subgroups, but we present them as primarily intestinal or primarily extraintestinal pathogens. The helminthes are subdivided into nematodes (roundworms), trematodes (flukes), and cestodes (tapeworms). Examples of common pathogens for each group are given along with some of the agents used in their treatment. Although not technically considered parasites, two other organisms that are susceptible to antiparasitic drugs will also be addressed: *Pneumocystis jirovecii* (technically a

TABLE 34–1
Grouping of Parasites with Commonly Encountered Pathogens and Commonly Used Antiparasitic Agents

Group	Subgroup	Examples	Antiparasitics*
Protozoa	Extraintestinal	*Plasmodium* (malaria)	**Quinolines**
			Doxycycline
			Clindamycin
			Atovaquone-proguanil
		Toxoplasma	Pyrimethamine/sulfadiazine
			TMP/SMX
		Trypansoma	**Pentamidine**
	Intestinal	*Entamoeba*	Metronidazole
		Giardia	Tinidazole
		Cryptosporidium	*Paromomycin*
Helminths	Nematodes	*Ascaris*	**Albendazole**
		Strongyloides	**Ivermectin**
	Trematodes	*Schistosoma*	*Praziquantel*
	Cestodes	*Echinococcus*	**Albendazole**
		Taenia	*Praziquantel*
Other organisms	Fungus	*Pneumocystis*	TMP/SMX
			Clindamycin/**primaquine**
			Atovaquone
			Pentamidine
	Ectoparasites	Scabies	**Ivermectin**

*Agents in **bold** are discussed in this section; agents in normal type are covered in other chapters; agents in *italics* are not discussed in this book.

fungus) and *Sarcoptes scabei* (the scabies mite, technically an Arachnid).

Drugs with antiparasitic activity range from everyday antibacterial drugs (metronidazole, doxy-

cycline), to mildly exciting agents seen occasionally in routine practice (chloroquine, pentamidine), to the most exotic agents that can be obtained only from the Centers for Disease Control and Prevention (CDC) in the United States (diethylcarbamezapine, sodium stibogluconate). In this Part we will focus on the middle category, leaving the details of antibacterial drugs to their own chapters and the exotic agents to those with a keen interest.

35 Quinolines

Agents: chloroquine, mefloquine, quinidine, quinine, primaquine, amodiaquine, hydroxychloroquine

The quinoline agents are among the oldest antiinfective agents used by humans, with recorded use of the bark of the *Cinchona* tree (imported from Peru) to treat fever in malarious areas of Europe dating back to the seventeenth century. The primary component of this remedy was quinine, the first antimalarial agent to be widely used. Although malaria is no longer endemic to most industrialized countries, it is considered to be the most important cause of fever in returning travelers, especially those not native to endemic areas, because of the potential for severe illness. There are important differences between the quinolines in activity based on both the species of *Plasmodium* and the geographic area; readers are advised to consult their updated national guidelines when managing suspected malaria cases.

Spectrum

Protozoa (activity variable by region): Plasmodium falciparum, P. malariae, P. ovale, P. vivax

Like-a-parasite-but-technically-a-fungus: *Pneumocystis jirovecii* (primaquine)

Adverse Effects

Cardiovascular: The quinolines can cause dose-related cardiovascular toxicity, including QT interval prolongation, hypotension, and potentially fatal ventricular arrhythmias. Quinidine is a class IA antiarrhythmic, and it is also used therapeutically in the treatment of some arrhythmias (however, like many antiarrhythmics, it can be pro-arrhythmic). Cardiovascular effects are most likely with IV quinidine; less common with quinine, mefloquine, and chloroquine; and rare with primaquine.

Hematologic: Primaquine can cause hemolysis in patients deficient in glucose-6-phosphate dehydrogenase (G6PD); testing for G6PD deficiency is required before use.

Metabolic: Quinidine and quinine can cause profound hypoglycemia resulting from the stimulated release of insulin.

Psychiatric: Mefloquine is associated with a range of psychiatric disturbances ranging from insomnia, vivid dreams, and mood swings to depression, psychosis, and suicide. Although mefloquine is well tolerated by the vast majority of patients taking the drug, patients with a history of psychiatric issues, including depression, should avoid taking mefloquine.

Systemic: The syndrome of "cinchonism" (tinnitus, headache, nausea, and visual disturbances) is common in patients receiving therapeutic doses of quinine. These effects can lead to discontinuation of therapy because of intolerance, but they resolve after drug discontinuation.

Important Facts

- In the United States, quinidine is the only quinoline available intravenously. It is used in combination regimens for treatment of severe malaria. Intensive monitoring, including continuous monitoring of blood pressure and electrocardiogram (ECG) and serial monitoring of blood glucose, is required. The dosing of quinidine is altered in renal failure, which is not uncommon in severe malaria.
- Unlike other antimalarial drugs, primaquine is active against the "hypnozoite" forms of *P. vivax* and *P. ovale* that can lay dormant in the liver and cause relapsing infections. Thus, a 2-week course of primaquine is added to the antimalarial regimen when infection with these species is documented.

What They're Good For

Chloroquine: Treatment of uncomplicated malaria acquired in chloroquine-sensitive areas (only a few regions) and prophylaxis against malaria in travelers to those regions.

Mefloquine: Treatment of uncomplicated malaria acquired in mefloquine-sensitive areas (most of world except Southeast Asia) and prophylaxis against malaria in travelers to those regions.

Quinine/quinidine: Treatment of uncomplicated malaria (quinine) or severe malaria (quinidine) in combination with doxycycline, tetracycline, or clindamycin; not used for prophylaxis.

Primaquine: Treatment of uncomplicated malaria because of *P. vivax* or *P. ovale* in combination with a second agent, prophylaxis against malaria in travelers where *P. vivax* is the principal

species, in combination with clindamycin, and in treatment of mild to moderate *Pneumocystis* pneumonia.

Don't Forget!

As with bacterial infections, the progression of antimicrobial resistance makes treatment of and prophylaxis against malaria difficult. Because most clinicians deal with malaria infrequently, there is no shame in double-checking national guidelines to make sure you are using the most appropriate regimen for your patient. The CDC even has a malaria hotline to help clinicians deal with treatment of cases.

36 Atovaquone

Agents: atovaquone, atovaquone/proguanil

Atovaquone is an antiparasitic agent with activity against several important protozoans. Its activity against the malaria parasite is enhanced when given in combination with the drug proguanil (this co-formulated tablet is known as Malarone). Atovaquone tends to be better tolerated than comparator drugs but is limited by the lack of an IV formulation (for severe disease), high cost, and somewhat lower efficacy (for *Pneumocystis* disease).

Spectrum

Like-a-parasite-but-technically-a-fungus: *Pneumocystis jirovecii*

Protozoa: *Plasmodium* species, *Toxoplasma gondii*, *Babesia* species

Adverse Effects

Both atovaquone and atovaquone/proguanil are very well tolerated. The most common adverse effects are gastrointestinal (nausea/vomiting, diarrhea, abdominal pain).

Important Facts

- Atovaquone is available as a suspension, while atovaquone/proguanil is formulated as a tablet. Bioavailability is rather low with both, but it is enhanced substantially when given with food, especially high-fat meals. Both agents should be administered with food.
- In clinical trials of atovaquone in treating mild to moderate *Pneumocystis* pneumonia in patients intolerant of TMP/SMX, atovaquone was slightly less effective than its comparators (dapsone or pentamidine) but better tolerated, leading to similar overall success rates. Atovaquone should not be used in patients with severe *Pneumocystis* pneumonia or in patients whose GI absorption is thought to be poor.
- Other than its cost, atovaquone/proguanil is a favorable drug for malaria prophylaxis for travelers. It is highly effective, well tolerated, active against chloroquine-resistant *Plasmodium*, and requires administration only 1–2 days prior to travel, while in the malaria-endemic area, and for 7 days after return. Many other agents used for malaria prophylaxis require beginning the medication 2 weeks before travel and continuing for 4 weeks afterward.

What They're Good For

Atovaquone: Treatment of mild to moderate *Pneumocystis* pneumonia and prophylaxis against *Pneumocystis* in patients intolerant of first-line therapy.

Atovaquone/proguanil: Treatment of uncomplicated malaria and prophylaxis against malaria.

Don't Forget!

Make sure your patients take their atovaquone with food (or at the very least a glass of milk); the bioavailability of atovaquone is increased approximately 5 times when administered with food compared with the fasting state.

37 Benzimidazoles

Agents: albendazole, mebendazole, thiabendazole

These drugs are used primarily to treat infections caused by helminthes (worms), ranging from the common pinworms found in children to pathogens causing massive cystic lesions in the brain. Most intestinal worm infections can be cured with a single dose of these drugs; for tissue-invasive disease, prolonged courses are necessary.

Spectrum

Nematodes (roundworms): *Ascaris lumbricoides* (roundworm), *Enterobius vermicularis* (pinworm), *Necator americanus* (hookworm), *Strongyloides stercoralis* (threadworm)

Cestodes (tapeworms): *Echinococcus* (liver abscess), *Taenia solium* (neurocysticercosis)

Adverse Effects

Albendazole and mebendazole are very well tolerated, especially when used as single-dose therapy in treatment of intestinal worm infection. With multidose regimens, adverse effects are primarily gastrointestinal, although hepatotoxicity and neutropenia are rarely reported. Thiabendazole is the

most toxic and can cause CNS adverse effects. These drugs should generally be avoided in pregnancy, although some data suggest that they may be safe after the first trimester.

Important Facts

- Although data are limited, these drugs appear to be substrates of the cytochrome P450 system. Thus, it is possible that co-administration with strong inducers of drug-metabolizing enzymes such as phenytoin and rifampin may lower serum levels. Oral absorption of albendazole and mebendazole is limited, which generally does not pose a problem for treatment of intestinal nematode infections, and thus drug interactions would not be of concern. However, in treatment of systemic infections, caution is advised with co-administration of enzyme-inducing agents because of the potential for subtherapeutic drug levels.

What They're Good For

Single-dose therapy of most intestinal nematode infections, as an alternative for treatment of *Strongyloides* infection, and as treatment for tissue-invasive *Echinococcus* or *Taenia* infection.

Don't Forget!

For some parasitic infections, drug-induced killing of the parasite releases antigens that can cause allergic reactions. Corticosteroids are sometimes administered to mitigate this effect. Know which infections this applies to before using antiparasitics for invasive infections.

38 Pentamidine

Agent: pentamidine

Pentamidine is the primary alternative to TMP/SMX for patients with *Pneumocystis* pneumonia, which was once extremely common but is becoming less so with effective anti-HIV therapy. It is also very toxic, so familiarity with its extensive adverse effects is required. It can be given either intravenously or by inhalation, and the route depends upon its indication.

Spectrum

Like-a-parasite-but-technically-a-fungus: *Pneumocystis jirovecii*
Protozoa: *Trypanosoma, Leishmania*

Adverse Effects (IV pentamidine)

Cardiovascular: Hypotension can occur with rapid infusion of pentamidine; the drug should be infused over at least an hour. Cases of QT prolongation with ventricular arrhythmia have also been reported.

Metabolic: Pentamidine is toxic to the pancreas, leading to dysglycemias in up to 25% of patients. The course of this toxicity may initially manifest as hypoglycemia because

pentamidine-induced pancreatic injury causes release of insulin from islet cells. Later, continuing injury can cause a decrease in pancreatic function, with hypoinsulinemia and hyperglycemia. Continued use may lead to irreversible damage, leaving patients with diabetes mellitus. Other manifestations of pancreatitis may also occur.

Renal: Nephrotoxicity is common with pentamidine, although it is generally reversible upon drug discontinuation. Electrolyte disturbances, including hypokalemia and hypocalcemia, may also occur.

Respiratory: Administration of pentamidine as an inhalation may induce bronchoconstriction, especially in patients with asthma. Pretreatment with an inhaled bronchodilator may attenuate these effects.

Important Facts

- In clinical trials of pentamidine as treatment for *Pneumocystis* pneumonia, pentamidine appears to be equal in efficacy to TMP/SMX; however, only about half of patients could tolerate a full course of IV pentamidine without discontinuing the drug or decreasing the dose. Careful monitoring (ECG, metabolic panel) and supportive care interventions (electrolyte replacement, glucose, or insulin as appropriate) are necessary. Also, dosage adjustment in patients with renal insufficiency is recommended.
- Once-monthly inhaled pentamidine has reasonable efficacy as a second-line agent for prophylaxis against *Pneumocystis* pneumonia. However, unlike TMP/SMX prophylaxis, cases

of extrapulmonary *Pneumocystis* infection have been reported in patients on inhaled pentamidine. Inhaled pentamidine also does not protect against *Toxoplasma* disease or bacterial pneumonia as TMP/SMX does.

What It's Good For

IV pentamidine is an alternative drug for treatment of severe *Pneumocystis* pneumonia; inhaled pentamidine is an alternative for prophylaxis against *Pneumocystis* pneumonia. IV pentamidine is an alternative drug for treatment for leishmaniasis and trypanosomiasis.

Don't Forget!

Watch out for overlapping toxicities with pentamidine and other drugs the patient may be on. Patients receiving pentamidine are often severely ill and may be on drugs like insulin, furosemide, aminoglycosides, and antiarrhythmics that may exacerbate pentamidine's myriad adverse effects.

39 Ivermectin

Agent: ivermectin

If you practice in a healthcare institution, you will likely be treated to at least one scabies outbreak over your career, if not one each year. While scabies is most often treated with permethrin cream, patients or their healthcare providers who are unable or unwilling to baste themselves in the cream will receive oral ivermectin. Ivermectin is also given to patients with the highly contagious "Norwegian scabies" (an unwarranted aspersion on Scandinavian hygiene). In addition to scabies, ivermectin is also effective in treating several diseases that may be endemic in tropical settings, such as the causative agents of river blindness, strongyloidiasis, and cutaneous larva migrans, the latter two occurring infrequently in the United States. It can also be used for treatment of *Strongyloides* hyperinfection syndrome, an increasingly recognized cause of life-threatening illness in immunocompromised patients.

Spectrum

Ectoparasites: *Sarcoptes scabei* (scabies mite), *Pediculus humanus* (lice)

Nematodes (roundworms): *Onchocerca vovulus* (river blindness), *Strongyloides stercoralis* (strongyloidiasis), *Ancylostoma brazilense* (cutaneous larva migrans), other nematodes

Adverse Effects

In treatment of scabies, ivermectin is very well tolerated. Severe adverse reactions, including fever, myalgia, and hypotension, have been reported when ivermectin is used for management of nematode infections in endemic settings. These effects are thought to be a result of the host's immune response to antigens released from killed parasites. These effects are more severe in patients with higher worm burdens, and they generally resolve soon after drug administration.

Important Facts

- Yes, ivermectin is the same drug you use to treat your dog's heartworms. It's also at the center of a heart*worming* story: after ivermectin was shown to be effective as a once-yearly treatment for river blindness, the pharmaceutical company Merck offered to donate, free of charge, as much ivermectin as was needed to treat the disease. It's estimated that 200 million free treatments have been provided to date, avoiding more than half a million cases of blindness. Hey, at this point in the book, we figured you could use some good news (and bad puns).

What It's Good For

Ivermectin is used as an alternative to topical permethrin for scabies infection, to topical therapies

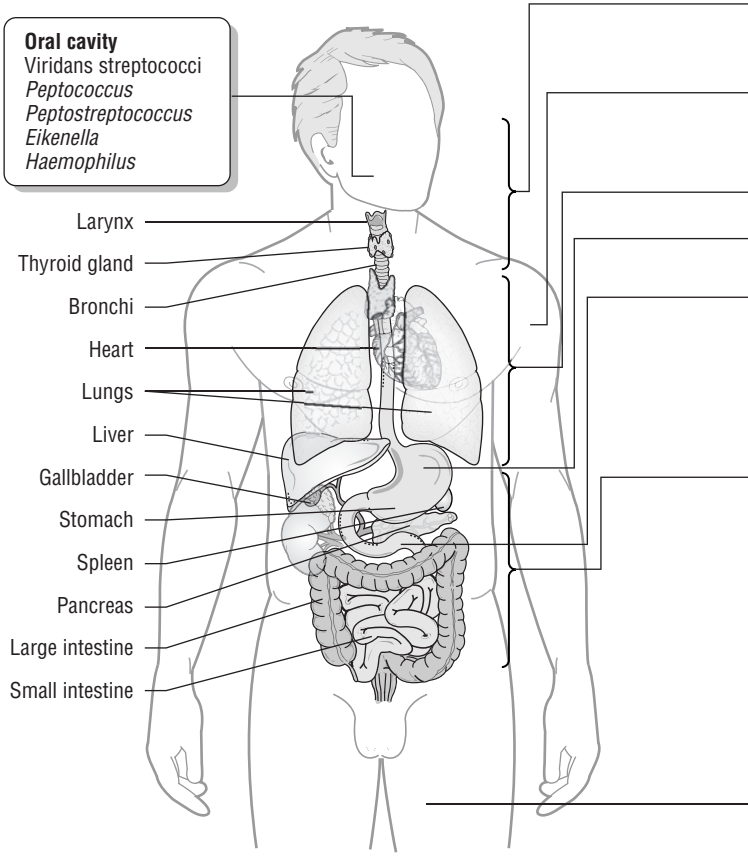
for treatment of head or body louse infestation, and for treatment of *Ancyclostoma* infections. It is also a drug of choice for infection caused by *Strongyloides* or *Onchocerca*.

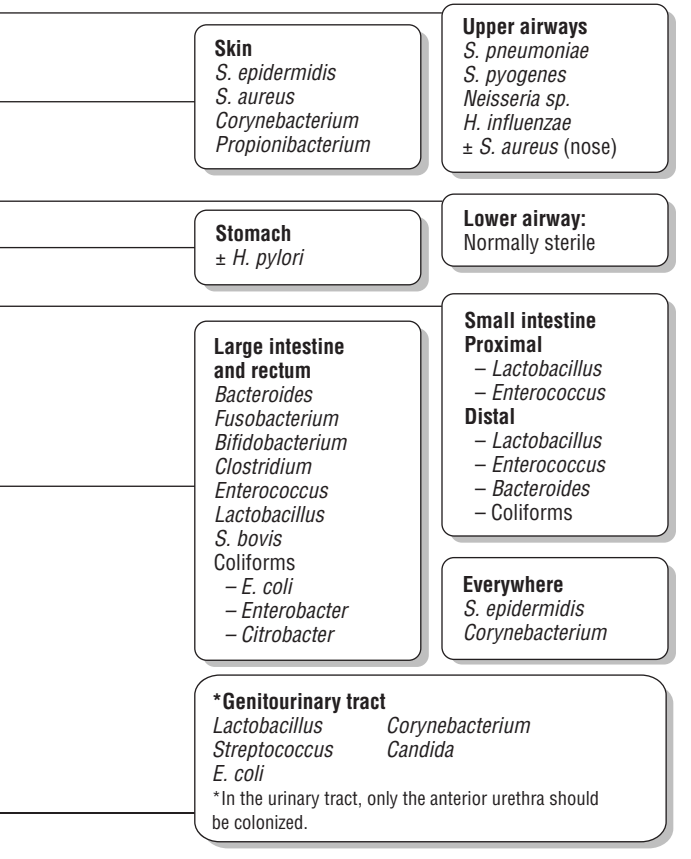
Don't Forget!

For treatment of ectoparasitic (scabies or lice) infestation, ivermectin should be administered as 2 doses, approximately one week apart. Administration of a single dose increases the risk of relapse.

APPENDIX
1

Selected Normal Human Flora




Skin
S. epidermidis
S. aureus
Corynebacterium
Propionibacterium
Upper airways
S. pneumoniae
S. pyogenes
Neisseria sp.
H. influenzae
± S. aureus (nose)
Stomach
± H. pylori
Lower airway:
Normally sterile
Large intestine and rectum
Bacteroides
Fusobacterium
Bifidobacterium
Clostridium
Enterococcus
Lactobacillus
S. bovis
Coliforms
– E. coli
– Enterobacter
– Citrobacter
Small intestine
Proximal
– Lactobacillus
– Enterococcus
Distal
– Lactobacillus
– Enterococcus
– Bacteroides
– Coliforms
Everywhere
S. epidermidis
Corynebacterium
*Genitourinary tract
Lactobacillus
Streptococcus
E. coli
Corynebacterium
Candida
*In the urinary tract, only the anterior urethra should be colonized.

APPENDIX 2 Clinically Useful Spectra of Activity

	MSSA	MRSA	Strep	Enterococci	GNR	Pseudo	Anaerobes*	Atypicals
Penicillin G			++	+				
Piperacillin			++	+	+	++		
Amp/Sulb	++		++	++	+		++	
Pip/Tazo	++		++	++	++	++	++	
Cefazolin	++		++		+			
Cefuroxime	+		+		++			
Cefotetan	+		+		++		++	
Ceftriaxone	+		++		++			
Ceftazidime					++	++		
Cefepime	+		++		++	++		
Aztreonam					++	++		
Imipenem	++		++	+	++	++	++	
Ertapenem	++		++		++		++	
Gentamicin	+(synt)		+(synt)	+(synt)	++	++		
Ciprofloxacin	+/-				++	++		+
Levofloxacin	++		++	+/-	++	++		++
Moxifloxacin	++		++	+/-	++		++	++
Doxycycline	+	+/-	+	+/-	+			++
Tigecycline	++	++	++	++	++		++	++
Clindamycin	++	+/-	++				++	

Vancomycin	++	++	++	++		
Azithromycin	+		++		+	++
Metronidazole						++
Telithromycin	+		++		+	++
Daptomycin	++	++	++	++		
Linezolid	++	++	++	++		+
Quin/Dalf	++	++	++	++		
Nitrofurantoin				+	+	
TMP/SMX	++	+/-	+/-		+	

Key: ++ = good activity; + = some activity; +/- = variable activity

*Anaerobes here include GI anaerobes except *Clostridium difficile*, for which the only antibiotics with good clinical activity on this list are vancomycin and metronidazole.

†Aminoglycosides have synergistic activity versus Gram-positive cocci only when paired with a cell-wall active agent (e.g., beta-lactams, vancomycin).

MSSA = methicillin-sensitive *Staphylococcus aureus*

MRSA = methicillin-resistant *Staphylococcus aureus*

Strep = streptococci

GNR = aerobic Gram-negative rods (in general, and not including *P. aeruginosa*)

Pseudo = *Pseudomonas aeruginosa*

Amp/sulb = ampicillin/sulbactam

Pip/tazo = piperacillin/tazobactam

Quin/dalf = Quinupristin/dalfopristin

TMP/SMX = trimethoprim/sulfamethoxazole

APPENDIX 3

Empiric Regimens for Common Infections

Infection	Common Pathogens	Patient/Infection Factors	Initial Empiric Therapy Options
Community-acquired pneumonia	*Streptococcus pneumoniae* *Haemophilus influenzae* *Mycoplasma pneumoniae* *Chlamydophilia pneumoniae* *Legionella pneumophila*	Outpatient, otherwise healthy, no recent antibiotic exposure	Doxycycline or Azithromycin or Clarithromycin
		Outpatient, comorbidities, and/or recent antibiotic exposure	Levofloxacin or Moxifloxacin or Gemifloxacin -OR- Amoxicillin or Amoxicillin/clavulanate or Cefuroxime *-Plus-* Azithromycin or Clarithromycin or Doxycycline
		Inpatient, non-ICU	Levofloxacin or Moxifloxacin -OR- Ceftriaxone or Cefotaxime or Ampicillin or Ertapenem *-Plus-* Azithromycin or Clarithromycin or Doxycycline
		Inpatient, ICU	Ceftriaxone or Cefotaxime or Ampicillin/sulbactam *-Plus-* Azithromycin or Levofloxacin or Moxifloxacin

Healthcare-associated pneumonia	*Streptococcus pneumoniae* *Haemophilus influenzae* *Staphylococcus aureus (MSSA)* *Escherichia coli* *Klebsiella pneumoniae*	Early-onset (within 5 days of hospitalization) and no recent antibiotic exposure	Ceftriaxone or Ampicillin/sulbactam or Ertapenem or Levofloxacin or Moxifloxacin or Ciprofloxacin
	As above plus: *Staphylococcus aureus* (MRSA) *Enterobacter* species *Proteus* species *Serratia* species *Pseudomonas aeruginosa*	Late-onset (after 5 days of hospitalization) and/or recent antibiotic exposure	Cefepime or Ceftazidime or Imipenem or Meropenem or Piperacillin/tazobactam or Aztreonam *-Plus-* Ciprofloxacin or Levofloxacin or Gentamicin or Tobramycin or Amikacin *-Plus-* Vancomycin or Linezolid
Otitis media	*Streptococcus pneumoniae* *Haemophilus influenzae* *Moraxella catarrhalis*	Mild-moderate otalgia with temperature $\leq$ 39 C Severe otalgia and/or temperature $\geq$ 39 C	Amoxicillin or Cefuroxime or Cefpodoxime or Azithromycin Amoxicillin/clavulanate or Ceftriaxone
Pharyngitis	Viruses *Streptococcus pyogenes*	Documented or high-risk for *Streptococcus pyogenes*	Penicillin VK or Cephalexin or Azithromycin

continues

Infection	Common Pathogens	Patient/Infection Factors	Initial Empiric Therapy Options
Urinary tract infections	*Escherichia coli* *Proteus* species *Klebsiella pneumoniae* *Staphylococcus saphrophyticus* *Enterococcus* species	Uncomplicated community-acquired lower urinary tract infection in healthy women < 50 years old	TMP/SMX or Ciprofloxacin or Levofloxacin or Nitrofurantoin or Fosfomycin
		Community-acquired complicated urinary tract infection or pyelonephritis	Ciprofloxacin or Levofloxacin or Ceftriaxone or Ertapenem
	As above plus: *Enterobacter* species *Pseudomonas aeruginosa*	Nosocomial complicated urinary tract infection or pyelonephritis	Ceftazidime or Piperacillin/tazobactam or Cefepime or Meropenem or Imipenem
Skin/soft tissue infections	*Streptococcus pyogenes* *Staphylococcus aureus*	Low risk for MRSA	Cefazolin or Nafcillin or Cephalexin or Dicloxacillin
		High risk for MRSA	Vancomycin or Linezolid or Clindamycin -OR- Cephalexin or Dicloxacillin *-Plus-* Doxycycline or TMP/SMX

	As above plus: *Escherichia coli* *Proteus* species *Klebsiella pneumoniae* *Bacteroides fragilis* *Enterococcus* species *Pseudomonas aeruginosa*	Diabetic foot infection, moderate to severe	Ceftriaxone or Ampicillin/sulbactam or Piperacillin/tazobactam or Ertapenem -OR- Levofloxacin or Ciprofloxacin *-Plus-* Clindamycin All WITH or WITHOUT Vancomycin
Intra-abdominal infections	*Escherichia coli* *Proteus* species *Klebsiella pneumoniae* *Bacteroides fragilis* *Enterococcus* species viridans *Streptococcus* As above plus: *Pseudomonas aeruginosa* *Enterobacter* species *Serratia* species	Community-acquired, mild-moderate severity Community-acquired, high severity, or high-risk patient -OR- Nosocomial (any severity or patient)	Ertapenem or Moxifloxacin or Tigecycline -OR- Cefazolin or Ceftriaxone or Levofloxacin or Ciprofloxacin *-Plus-* Metronidazole Piperacilin/tazobactam or Imipenem or Meropenem -OR- Ceftazidime or Cefepime *-Plus-* Metronidazole All WITH or WITHOUT Vancomycin

continues

Infection	Common Pathogens	Patient/Infection Factors	Initial Empiric Therapy Options
Community-acquired meningitis	*Streptococcus pneumoniae* *Neisseria meningitidis*	Otherwise healthy, 2–50 years of age	Ceftriaxone *-Plus-* Vancomycin
	As above plus: *Listeria monocytogenes*	> 50 years of age or immunocompromised	Ceftriaxone *-Plus-* Vancomycin *-Plus-* Ampicillin
Clostridium difficile infection	*Clostridium difficile*	Mild to moderate infection	Metronidazole (oral)
		Severe infection	Vancomycin (oral)
		Severe, complicated infection (e.g., ileus)	Vancomycin (oral) + intravenous metronidazole
Infectious diarrhea	*Shigella* *Salmonella* *E. coli* *Campylobacter*	Community-acquired	Fluoroquinolone or TMP/SMX

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