Principles of Antimicrobial Therapy

37

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I. OVERVIEW

Antimicrobial therapy takes advantage of the biochemical differences that exist between microorganisms and human beings. Antimicrobial drugs are effective in the treatment of infections because of their selective toxicity; that is, they have the ability to injure or kill an invading microorganism without harming the cells of the host. In most instances, the selective toxicity is relative rather than absolute, requiring that the concentration of the drug be carefully controlled to attack the microorganism, while still being tolerated by the host.

II. SELECTION OF ANTIMICROBIAL AGENTS

Selection of the most appropriate antimicrobial agent requires knowing 1) the organism's identity, 2) the organism's susceptibility to a particular agent, 3) the site of the infection, 4) patient factors, 5) the safety of the agent, and 6) the cost of therapy. However, some patients require empiric therapy (immediate administration of drug(s) prior to bacterial identification and susceptibility testing).

A. Identification of the infecting organism

Characterizing the organism is central to selection of the proper drug. A rapid assessment of the nature of the pathogen can sometimes be made on the basis of the Gram stain, which is particularly useful in identifying the presence and morphologic features of microorganisms in body fluids that are normally sterile (blood, serum, cerebrospinal fluid [CSF], pleural fluid, synovial fluid, peritoneal fluid, and urine). However, it is generally necessary to culture the infective organism to arrive at a conclusive diagnosis and determine the susceptibility to

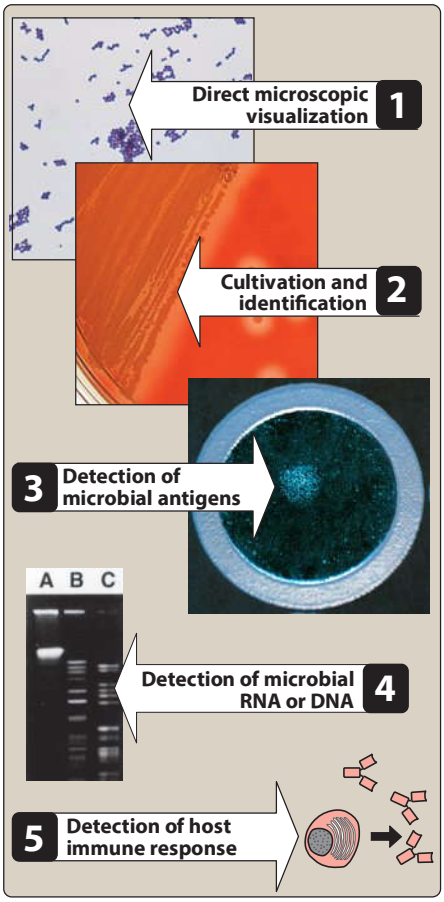


Figure 37.1
Some laboratory techniques that are useful in the diagnosis of microbial diseases.

antimicrobial agents. Thus, it is essential to obtain a sample culture of the organism prior to initiating treatment. Otherwise, it is impossible to differentiate whether a negative culture is due to the absence of organisms or is a result of antimicrobial effects of administered antibiotic. Definitive identification of the infecting organism may require other laboratory techniques, such as detection of microbial antigens, DNA, or RNA, or an inflammatory or host immune response to the microorganism (Figure 37.1).

B. Empiric therapy prior to identification of the organism

Ideally, the antimicrobial agent used to treat an infection is selected after the organism has been identified and its drug susceptibility established. However, in the critically ill patient, such a delay could prove fatal, and immediate empiric therapy is indicated.

1. **Timing:** Acutely ill patients with infections of unknown origin—for example, a neutropenic patient (one who is predisposed to infections due to a reduction in neutrophils) or a patient with meningitis (acute inflammation of the membranes covering the brain and spinal cord)—require immediate treatment. If possible, therapy should be initiated after specimens for laboratory analysis have been obtained but before the results of the culture and sensitivity are available.

2. **Selecting a drug:** Drug choice in the absence of susceptibility data is influenced by the site of infection and the patient's history (for example, previous infections, age, recent travel history, recent antimicrobial therapy, immune status, and whether the infection was hospital- or community-acquired). Broad-spectrum therapy may be indicated initially when the organism is unknown or polymicrobial infections are likely. The choice of agent(s) may also be guided by known association of particular organisms in a given clinical setting. For example, gram-positive cocci in the spinal fluid of a newborn infant is unlikely to be Streptococcus pneumoniae and most likely to be Streptococcus agalactiae (a group B streptococci), which is sensitive to *penicillin G*. By contrast, gram-positive cocci in the spinal fluid of a 40-year-old patient are most likely to be S. pneumoniae. This organism is frequently resistant to *penicillin G* and often requires treatment with a high-dose third-generation cephalosporin (such as *ceftriaxone*) or *vancomycin*.

C. Determining antimicrobial susceptibility of infective organisms

After a pathogen is cultured, its susceptibility to specific antibiotics serves as a guide in choosing antimicrobial therapy. Some pathogens, such as Streptococcus pyogenes and Neisseria meningitidis, usually have predictable susceptibility patterns to certain antibiotics. In contrast, most gram-negative bacilli, enterococci, and staphylococcal species often show unpredictable susceptibility patterns and require susceptibility testing to determine appropriate antimicrobial therapy. The minimum inhibitory and bactericidal concentrations of a drug can be experimentally determined (Figure 37.2).

1. **Bacteriostatic versus bactericidal drugs:** Antimicrobial drugs are classified as either bacteriostatic or bactericidal. Bacteriostatic drugs arrest the growth and replication of bacteria at serum

(or urine) levels achievable in the patient, thus limiting the spread of infection until the immune system attacks, immobilizes, and eliminates the pathogen. If the drug is removed before the immune system has scavenged the organisms, enough viable organisms may remain to begin a second cycle of infection. Bactericidal drugs kill bacteria at drug serum levels achievable in the patient. Because of their more aggressive antimicrobial action, bactericidal agents are often the drugs of choice in seriously ill and immunocompromised patients. Figure 37.3 shows a laboratory experiment in which the growth of bacteria is arrested by the addition of a bacteriostatic agent. Note that viable organisms remain even in the presence of the bacteriostatic drug. In contrast, addition of a bactericidal agent kills bacteria, and the total number of viable organisms decreases. Although practical, this classification may be too simplistic because it is possible for an antibiotic to be bacteriostatic for one organism and bactericidal for another. For example, *linezolid* is bacteriostatic against Staphylococcus aureus and enterococci but is bactericidal against most strains of S. pneumoniae.

2. **Minimum inhibitory concentration:** The minimum inhibitory concentration (MIC) is the lowest antimicrobial concentration that prevents visible growth of an organism after 24 hours of incubation. This serves as a quantitative measure of in vitro susceptibility and is commonly used in practice to streamline therapy. Computer automation has improved the accuracy and decreased the turnaround time for determining MIC results and is the most common approach used by clinical laboratories.

3. **Minimum bactericidal concentration:** The minimum bactericidal concentration (MBC) is the lowest concentration of antimicrobial agent that results in a 99.9% decline in colony count after overnight broth dilution incubations (Figure 37.2). [Note: The MBC is rarely determined in clinical practice due to the time and labor requirements.]

D. Effect of the site of infection on therapy: the blood–brain barrier

Adequate levels of an antibiotic must reach the site of infection for the invading microorganisms to be effectively eradicated. Capillaries with varying degrees of permeability carry drugs to the body tissues. Natural barriers to drug delivery are created by the structures of the capillaries of some tissues, such as the prostate, testes, placenta, the vitreous body of the eye, and the central nervous system (CNS). Of particular significance are the capillaries in the brain, which help to create and maintain the blood–brain barrier. This barrier is formed by the single layer of endothelial cells fused by tight junctions that impede entry from the blood to the brain of virtually all molecules, except those that are small and lipophilic. The penetration and concentration of an antibacterial agent in the CSF are particularly influenced by the following:

1. **Lipid solubility of the drug:** The lipid solubility of a drug is a major determinant of its ability to penetrate into the brain. Lipid-soluble drugs, such as *chloramphenicol* and *metronidazole*, have significant penetration into the CNS, whereas β-lactam

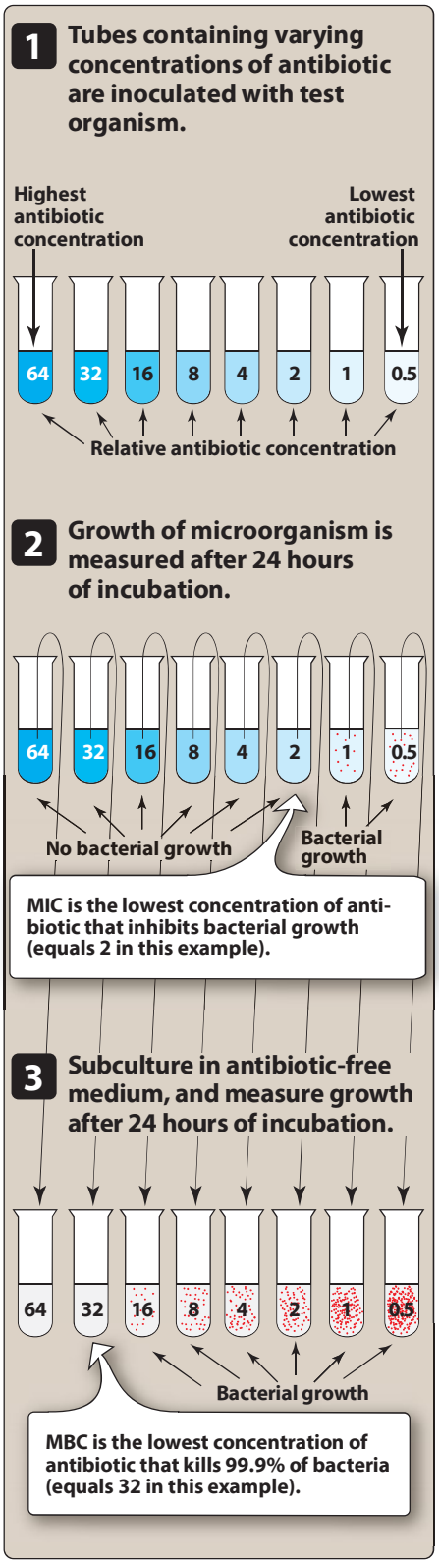


Figure 37.2
Determination of minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of an antibiotic.

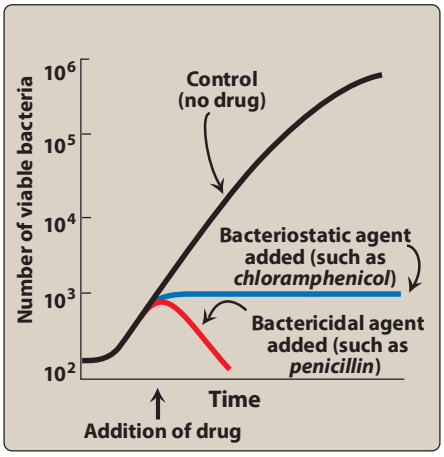


Figure 37.3
Effects of bactericidal and bacteriostatic drugs on the growth of bacteria in vitro.

antibiotics, such as *penicillin*, are ionized at physiologic pH and have low solubility in lipids. They therefore have limited penetration through the intact blood–brain barrier under normal circumstances. In infections such as meningitis in which the brain becomes inflamed, the barrier does not function as effectively, and local permeability is increased. Some β-lactam antibiotics can enter the CSF in therapeutic amounts when the meninges are inflamed.

2. **Molecular weight of the drug:** A compound with a low molecular weight has an enhanced ability to cross the blood–brain barrier, whereas compounds with a high molecular weight (for example, *vancomycin*) penetrate poorly, even in the presence of meningeal inflammation.

3. **Protein binding of the drug:** A high degree of protein binding of a drug restricts its entry into the CSF. Therefore, the amount of free (unbound) drug in serum, rather than the total amount of drug present, is important for CSF penetration.

E. Patient factors

In selecting an antibiotic, attention must be paid to the condition of the patient. For example, the status of the patient's immune system, kidneys, liver, circulation, and age must be considered. In women, pregnancy or breast-feeding also affects selection of the antimicrobial agent.

1. **Immune system:** Elimination of infecting organisms from the body depends on an intact immune system, and the host defense system must ultimately eliminate the invading organisms. Alcoholism, diabetes, HIV infection, malnutrition, autoimmune diseases, pregnancy, or advanced age can affect a patient's immunocompetence, as can immunosuppressive drugs. High doses of bactericidal agents or longer courses of treatment may be required to eliminate infective organisms in these individuals.

2. **Renal dysfunction:** Poor kidney function may cause accumulation of certain antibiotics. Dosage adjustment prevents drug accumulation and therefore adverse effects. Serum creatinine levels are frequently used as an index of renal function for adjustment of drug regimens. However, direct monitoring of serum levels of some antibiotics (for example, *vancomycin*, aminoglycosides) is preferred to identify maximum and/or minimum values to prevent potential toxicities. [Note: The number of functional nephrons decreases with age. Thus, elderly patients are particularly vulnerable to accumulation of drugs eliminated by the kidneys.]

3. **Hepatic dysfunction:** Antibiotics that are concentrated or eliminated by the liver (for example, *erythromycin* and *doxycycline*) must be used with caution when treating patients with liver dysfunction.

4. **Poor perfusion:** Decreased circulation to an anatomic area, such as the lower limbs of a diabetic patient, reduces the amount of antibiotic that reaches that area, making these infections difficult to treat.

5. **Age:** Renal or hepatic elimination processes are often poorly developed in newborns, making neonates particularly vulnerable to the toxic effects of *chloramphenicol* and sulfonamides. Young children should not be treated with tetracyclines or quinolones, which affect bone growth and joints, respectively. Elderly patients may have decreased renal or liver function, which may alter the pharmacokinetics of certain antibiotics.

6. **Pregnancy and lactation:** Many antibiotics cross the placental barrier or enter the nursing infant via the breast milk. Figure 37.4 summarizes the U.S. Food and Drug Administration (FDA) risk categories of antibiotic use during pregnancy. The drug examples listed in Figure 37.4 are not all inclusive but merely represent an example from each category. Although the concentration of an antibiotic in breast milk is usually low, the total dose to the infant may be sufficient to produce detrimental effects.

7. **Risk factors for multidrug-resistant organisms:** Infections with multidrug-resistant pathogens need broader antibiotic coverage when initiating empiric therapy. Common risk factors for infection with these pathogens include prior antimicrobial therapy in the preceding 90 days, hospitalization for greater than 2 days within the preceding 90 days, current hospitalization exceeding 5 days, high frequency of resistance in the community or local hospital unit (assessed using hospital antibiograms), and immunosuppressive diseases and/or therapies.

CATEGORY	DESCRIPTION	DRUG
A	No human fetal risk or remote possibility of fetal harm	
B	No controlled studies show human risk; animal studies suggest potential toxicity	β-Lactams β-Lactams with β inhibitors Cephalosporins *Aztreonam* *Clindamycin* *Erythromycin* *Azithromycin* *Metronidazole* *Nitrofurantoin* Sulfonamides
C	Animal fetal toxicity demonstrated; human risk undefined	*Chloramphenicol* Fluoroquinolones *Clarithromycin* *Trimethoprim* *Vancomycin* *Gentamicin* *Trimethoprim-sulfamethoxazole*
D	Human fetal risk present, but benefits may outweigh risks	Tetracyclines Aminoglycosides (except *gentamicin*)
X	Human fetal risk clearly outweighs benefits; contraindicated in pregnancy	

Figure 37.4
FDA categories of antimicrobials and fetal risk.

F. Safety of the agent

Antibiotics such as the penicillins are among the least toxic of all drugs because they interfere with a site or function unique to the growth of microorganisms. Other antimicrobial agents (for example, *chloramphenicol*) have less specificity and are reserved for life-threatening infections because of the potential for serious toxicity to the patient. [Note: Safety is related not only to the inherent nature of the drug but also to patient factors that can predispose to toxicity.]

G. Cost of therapy

Often several drugs may show similar efficacy in treating an infection but vary widely in cost. For example, treatment of *methicillin*-resistant Staphylococcus aureus (MRSA) generally includes one of the following: *vancomycin*, *clindamycin*, *daptomycin*, or *linezolid*. Although choice of therapy usually centers on the site of infection, severity of the illness, and ability to take oral medications, it is also important to consider the cost of the medication. Figure 37.5 illustrates the relative cost of commonly used drugs for staphylococcal infections.

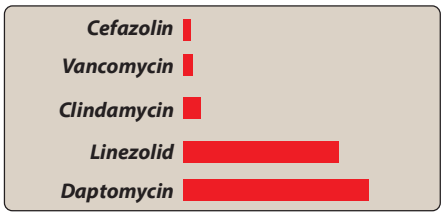


Figure 37.5
Relative cost of some drugs used for the treatment of Staphylococcus aureus.

III. ROUTE OF ADMINISTRATION

The oral route of administration is appropriate for mild infections that can be treated on an outpatient basis. In addition, economic pressures have prompted the use of oral antibiotic therapy in all but the most serious

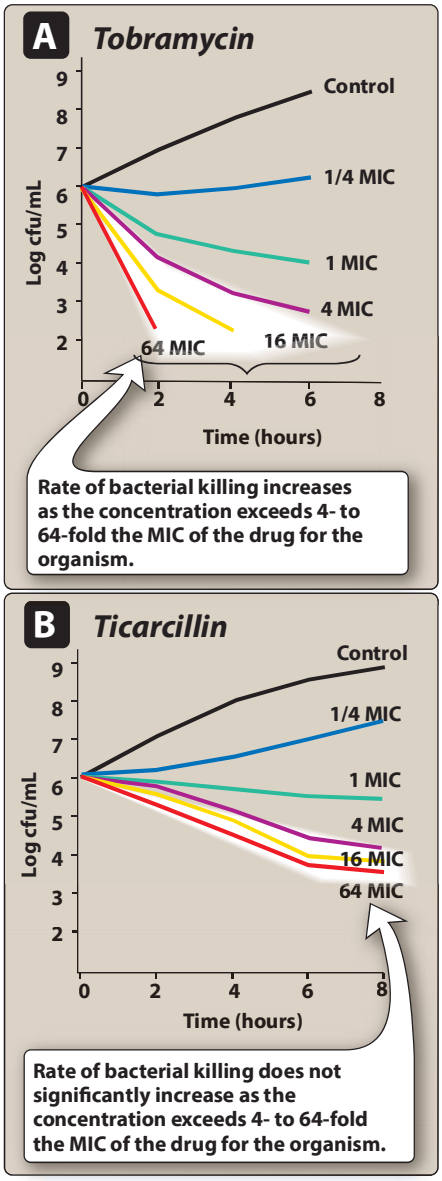


Figure 37.6
A. Significant dose-dependent killing effect shown by *tobramycin*. **B.** Nonsignificant dose-dependent killing effect shown by *ticarcillin*. (cfu = colony-forming units; MIC = minimum inhibitory concentration.)

infectious diseases. In hospitalized patients requiring intravenous therapy initially, the switch to oral agents should occur as soon as possible. However, some antibiotics, such as *vancomycin*, the aminoglycosides, and *amphotericin B* are so poorly absorbed from the gastrointestinal (GI) tract that adequate serum levels cannot be obtained by oral administration. Parenteral administration is used for drugs that are poorly absorbed from the GI tract and for treatment of patients with serious infections, for whom it is necessary to maintain higher serum concentrations of antimicrobial agents.

IV. DETERMINANTS OF RATIONAL DOSING

Rational dosing of antimicrobial agents is based on their pharmacodynamics (the relationship of drug concentrations to antimicrobial effects) and pharmacokinetic properties (the absorption, distribution, metabolism, and elimination of the drug). Three important properties that have a significant influence on the frequency of dosing are concentration-dependent killing, time-dependent killing, and postantibiotic effect (PAE). Utilizing these properties to optimize antibiotic dosing regimens can improve clinical outcomes and possibly decrease the development of resistance.

A. Concentration-dependent killing

Certain antimicrobial agents, including aminoglycosides and *daptomycin*, show a significant increase in the rate of bacterial killing as the concentration of antibiotic increases from 4- to 64-fold the MIC of the drug for the infecting organism (Figure 37.6A). Giving drugs that exhibit this concentration-dependent killing by a once-a-day bolus infusion achieves high peak levels, favoring rapid killing of the infecting pathogen.

B. Time-dependent (concentration-independent) killing

In contrast, β-lactams, glycopeptides, macrolides, *clindamycin*, and *linezolid* do not exhibit concentration-dependent killing (Figure 37.6B). The clinical efficacy of these antimicrobials is best predicted by the percentage of time that blood concentrations of a drug remain above the MIC. This effect is sometimes called concentration-independent or time-dependent killing. For example, dosing schedules for the penicillins and cephalosporins that ensure blood levels greater than the MIC for 50% and 60% of the time, respectively, provide the most clinical efficacy. Therefore, extended (generally 3 to 4 hours) or continuous (24 hours) infusions can be utilized instead of intermittent dosing (generally 30 minutes) to achieve prolonged time above the MIC and kill more bacteria.

C. Postantibiotic effect

The PAE is a persistent suppression of microbial growth that occurs after levels of antibiotic have fallen below the MIC. Antimicrobial drugs exhibiting a long PAE (for example, aminoglycosides and fluoroquinolones) often require only one dose per day, particularly against gram-negative bacteria.

V. CHEMOTHERAPEUTIC SPECTRA

In this book, the clinically important bacteria have been organized into eight groups based on Gram stain, morphology, and biochemical or other characteristics. They are represented as a color-coded list (Figure 37.7A). The ninth section of the list is labeled "Other," and it is used to represent any organism not included in one of the other eight categories. In this chapter, the list is used to illustrate the spectra of bacteria for which a particular class of antibiotics is therapeutically effective.

A. Narrow-spectrum antibiotics

Chemotherapeutic agents acting only on a single or a limited group of microorganisms are said to have a narrow spectrum. For example, *isoniazid* is active only against Mycobacterium tuberculosis (Figure 37.7B).

B. Extended-spectrum antibiotics

Extended spectrum is the term applied to antibiotics that are modified to be effective against gram-positive organisms and also against a significant number of gram-negative bacteria. For example, *ampicillin* is considered to have an extended spectrum because it acts against gram-positive and some gram-negative bacteria (Figure 37.7C).

C. Broad-spectrum antibiotics

Drugs such as *tetracycline*, fluoroquinolones and carbapenems affect a wide variety of microbial species and are referred to as broad-spectrum antibiotics (Figure 37.7D). Administration of broad-spectrum antibiotics can drastically alter the nature of the normal bacterial flora and precipitate a superinfection due to organisms such as Clostridium difficile, the growth of which is normally kept in check by the presence of other colonizing microorganisms.

VI. COMBINATIONS OF ANTIMICROBIAL DRUGS

It is therapeutically advisable to treat patients with a single agent that is most specific to the infecting organism. This strategy reduces the possibility of superinfections, decreases the emergence of resistant organisms, and minimizes toxicity. However, some situations require combinations of antimicrobial drugs. For example, the treatment of tuberculosis benefits from drug combinations.

A. Advantages of drug combinations

Certain combinations of antibiotics, such as β-lactams and aminoglycosides, show synergism; that is, the combination is more effective than either of the drugs used separately. Because such synergism among antimicrobial agents is rare, multiple drugs used in combination are only indicated in special situations (for example, when an infection is of unknown origin or in the treatment of enterococcal endocarditis).

B. Disadvantages of drug combinations

A number of antibiotics act only when organisms are multiplying. Thus, coadministration of an agent that causes bacteriostasis plus a second

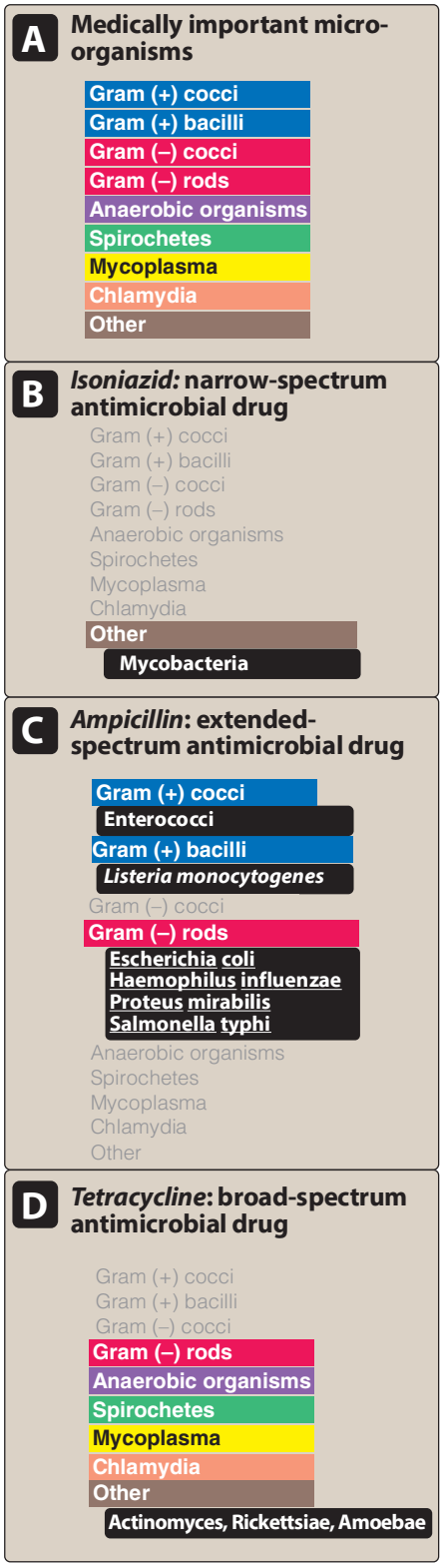


Figure 37.7
A. Color-coded representation of medically important microorganisms. **B.** *Isoniazid*, a narrow-spectrum antimicrobial agent. **C.** *Ampicillin*, an extended-spectrum antimicrobial agent. **D.** *Tetracycline*, a broad-spectrum antimicrobial agent.

agent that is bactericidal may result in the first drug interfering with the action of the second. For example, bacteriostatic tetracycline drugs may interfere with the bactericidal effects of penicillins and cephalosporins. Another concern is the risk of selection pressure and the development of antibiotic resistance by giving unnecessary combination therapy.

VII. DRUG RESISTANCE

Bacteria are considered resistant to an antibiotic if the maximal level of that antibiotic that can be tolerated by the host does not halt their growth. Some organisms are inherently resistant to an antibiotic. For example, most gram-negative organisms are inherently resistant to *vancomycin*. However, microbial species that are normally responsive to a particular drug may develop more virulent or resistant strains through spontaneous mutation or acquired resistance and selection. Some of these strains may even become resistant to more than one antibiotic.

A. Genetic alterations leading to drug resistance

Acquired antibiotic resistance requires the temporary or permanent gain or alteration of bacterial genetic information. Resistance develops due to the ability of DNA to undergo spontaneous mutation or to move from one organism to another (Figure 37.8).

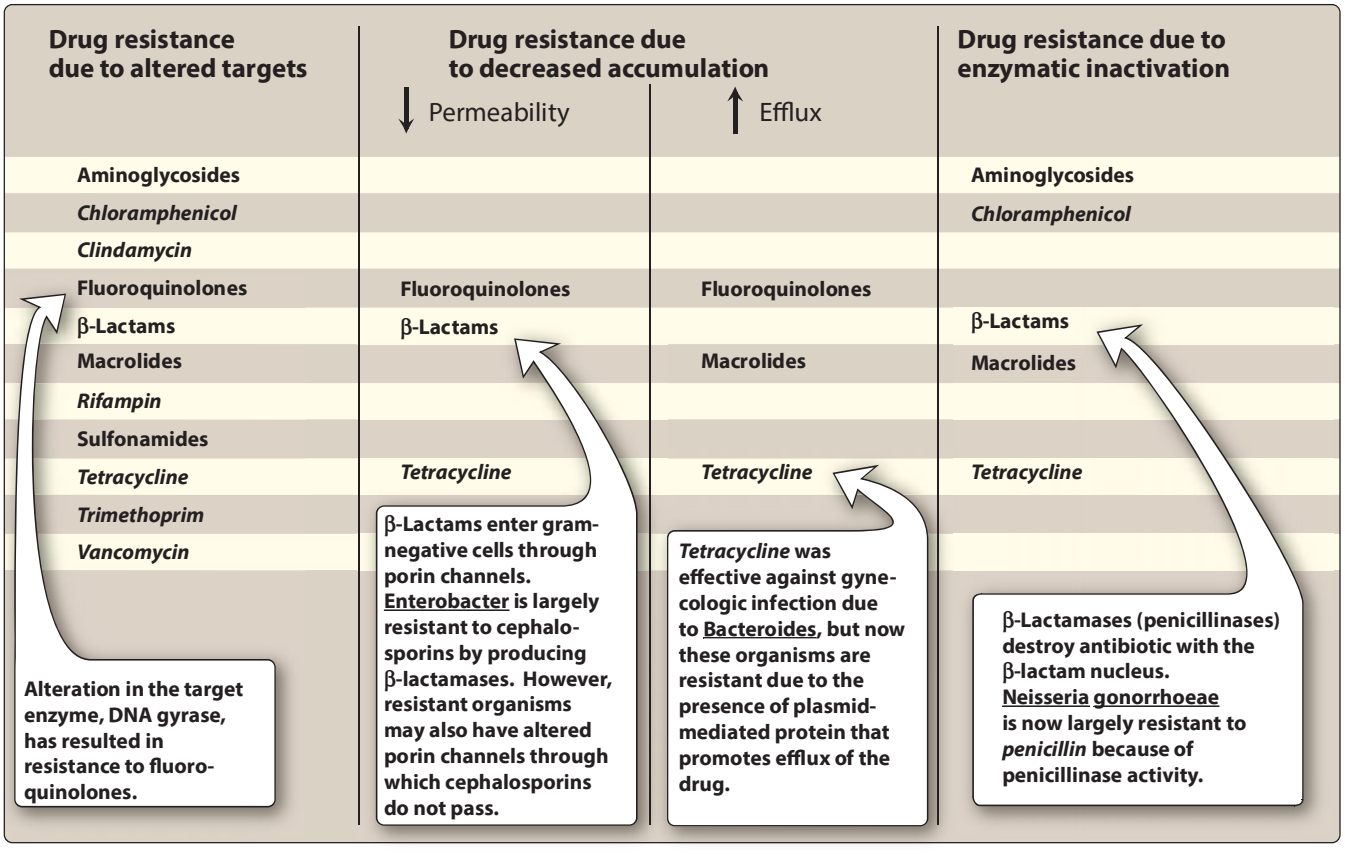


Figure 37.8
Some mechanisms of resistance to antibiotics.

B. Altered expression of proteins in drug-resistant organisms

Drug resistance is mediated by a variety of mechanisms, such as an alteration in an antibiotic target site, lowered penetrability of the drug due to decreased permeability, increased efflux of the drug, or presence of antibiotic-inactivating enzymes (Figure 37.8).

1. **Modification of target sites:** Alteration of an antibiotic's target site through mutation can confer resistance to one or more related antibiotics. For example, S. pneumoniae resistance to β-lactam antibiotics involves alterations in one or more of the major bacterial penicillin-binding proteins, resulting in decreased binding of the antibiotic to its target.

2. **Decreased accumulation:** Decreased uptake or increased efflux of an antibiotic can confer resistance because the drug is unable to attain access to the site of its action in sufficient concentrations to injure or kill the organism. For example, gram-negative organisms can limit the penetration of certain agents, including β-lactam antibiotics, as a result of an alteration in the number and structure of porins (channels) in the outer membrane. Also, the presence of an efflux pump can limit levels of a drug in an organism, as seen with tetracyclines.

3. **Enzymatic inactivation:** The ability to destroy or inactivate the antimicrobial agent can also confer resistance on microorganisms. Examples of antibiotic-inactivating enzymes include 1) β-lactamases ("penicillinases") that hydrolytically inactivate the β-lactam ring of penicillins, cephalosporins, and related drugs; 2) acetyltransferases that transfer an acetyl group to the antibiotic, inactivating *chloramphenicol* or aminoglycosides; and 3) esterases that hydrolyze the lactone ring of macrolides.

VIII. PROPHYLACTIC USE OF ANTIBIOTICS

Certain clinical situations, such as dental procedures and surgeries, require the use of antibiotics for the prevention rather than for the treatment of infections (Figure 37.9). Because the indiscriminate use of antimicrobial agents can result in bacterial resistance and superinfection, prophylactic use is restricted to clinical situations in which the benefits outweigh the potential risks. The duration of prophylaxis should be closely observed to prevent the unnecessary development of antibiotic resistance.

IX. COMPLICATIONS OF ANTIBIOTIC THERAPY

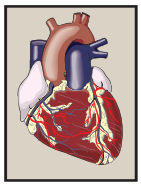
Even though antibiotics are selectively toxic to an invading organism, it does not protect the host against adverse effects. For example, the drug may produce an allergic response or may be toxic in ways unrelated to the antimicrobial activity.

A. Hypersensitivity

Hypersensitivity or immune reactions to antimicrobial drugs or their metabolic products frequently occur. For example, the penicillins, despite their almost absolute selective microbial toxicity, can cause serious hypersensitivity problems, ranging from urticaria (hives) to anaphylactic

1

Pretreatment may prevent streptococcal infections in patients with a history of rheumatic heart disease. Patients may require years of treatment.

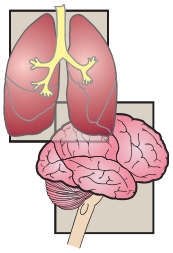


2

Pretreating of patients undergoing dental extractions who have implanted prosthetic devices, such as artificial heart valves, prevents seeding of the prosthesis.

3

Pretreatment may prevent tuberculosis or meningitis among individuals who are in close contact with infected patients.



4

Treatment prior to most surgical procedures can decrease the incidence of infection afterwards. Effective prophylaxis is directed against the most likely organism, not eradication of every potential pathogen.

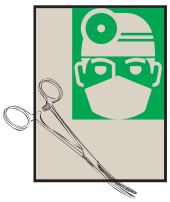


Figure 37.9
Some clinical situations in which prophylactic antibiotics are indicated.

shock. Patients with a documented history of Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis reaction to an antibiotic should *never* be rechallenged, not even for antibiotic desensitization.

B. Direct toxicity

High serum levels of certain antibiotics may cause toxicity by directly affecting cellular processes in the host. For example, aminoglycosides can cause ototoxicity by interfering with membrane function in the auditory hair cells.

C. Superinfections

Drug therapy, particularly with broad-spectrum antimicrobials or combinations of agents, can lead to alterations of the normal microbial flora of the upper respiratory, oral, intestinal, and genitourinary tracts, permitting the overgrowth of opportunistic organisms, especially fungi or resistant bacteria. These infections usually require secondary treatments using specific anti-infective agents.

X. SITES OF ANTIMICROBIAL ACTIONS

Antimicrobial drugs can be classified in a number of ways: 1) by their chemical structure (for example, β-lactams or aminoglycosides), 2) by their mechanism of action (for example, cell wall synthesis inhibitors), or 3) by their activity against particular types of organisms (for example, bacteria, fungi, or viruses). Chapters 37 through 40 are organized by the mechanisms of action of the drug (Figure 37.10), and Chapters 41 through 45 are organized according to the type of organisms affected by the drug.

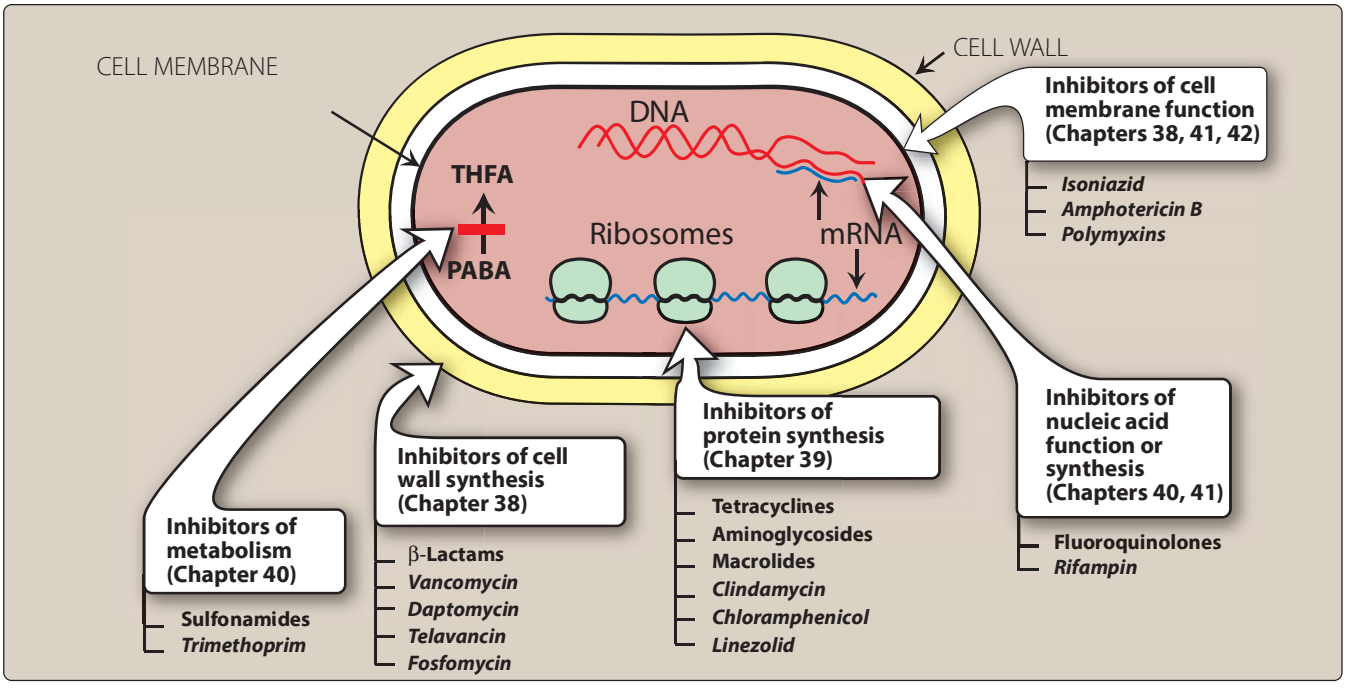


Figure 37.10
Classification of some antimicrobial agents by their sites of action. (THFA = tetrahydrofolic acid; PABA = *p*-aminobenzoic acid.)

Study Questions

Choose the ONE best answer.

37.1 A 24-year-old pregnant female presents to the urgent care clinic with fever, frequency, and urgency. She is diagnosed with a urinary tract infection (UTI). Based on potential harm to the fetus, which of the following medications should be avoided in treating her UTI?

A. Nitrofurantoin.
B. Amoxicillin.
C. Cephalexin.
D. Tobramycin.

Correct answer = D. Tobramycin (an aminoglycoside) is considered a pregnancy risk category D drug which means there is chance for potential harm to the fetus. Nitrofurantoin, amoxicillin (a penicillin), and cephalexin (a cephalosporin) are considered category B.

37.2 Which of the following is the primary method of β-lactam resistance with Streptococcus pneumoniae?

A. Modification of target site.
B. Decreased drug levels due to changes in permeability.
C. Decreased drug levels due to an efflux pump.
D. Enzymatic inactivation.

Correct answer = A. S. pneumoniae resistance to β-lactam antibiotics involves alteration in one or more of the major penicillin-binding proteins.

37.3 Which of the following agents is considered a narrow-spectrum antibiotic?

A. Ceftriaxone.
B. Ciprofloxacin.
C. Isoniazid.
D. Imipenem.

Correct answer = C. Isoniazid is only active against Mycobacterium tuberculosis, while ceftriaxone, ciprofloxacin, and imipenem are considered broad spectrum due to their activity against multiple types of bacteria and risk for developing a superinfection.

37.4 Which of the following antibiotics exhibits concentration-dependent killing?

A. Clindamycin.
B. Linezolid.
C. Vancomycin.
D. Daptomycin.

Correct answer = D. Clindamycin, linezolid, and vancomycin exhibit time-dependent killing, while daptomycin works best in a concentration-dependent fashion.

37.5 Which of the following antibiotics exhibits a long post-antibiotic effect that permits once-daily dosing?

A. Gentamicin.
B. Penicillin G.
C. Vancomycin.
D. Aztreonam.

Correct answer = A. Aminoglycosides, including gentamicin, possess a long post-antibiotic effect, especially when given as a high dose every 24 hours. Penicillin G, clindamycin, and vancomycin have a relatively short postantibiotic effect and require frequent dosing to maintain activity.

37.6 A 58-year-old male with a history of hepatitis C, cirrhosis, and ascites presents with spontaneous bacterial peritonitis. Which of the following antibiotics requires close monitoring and dosing adjustment in this patient given his liver disease?

A. Penicillin G.
B. Tobramycin.
C. Erythromycin.
D. Vancomycin.

Correct answer = C. Erythromycin is metabolized by the liver and should be used with caution in patients with hepatic impairment. Penicillin G, tobramycin, and vancomycin are primarily eliminated by the kidneys.

37.7 Which of the following antibiotics is considered safe to use in neonates?

A. Chloramphenicol.
B. Sulfamethoxazole/trimethoprim.
C. Tetracycline.
D. Penicillin G.

Correct answer = D. Chloramphenicol and sulfonamides (sulfamethoxazole) can cause toxic effects in newborns due to poorly developed renal and hepatic elimination processes. Tetracycline can have effects on bone growth and development and should be avoided in newborns and young children. Penicillin G is safe and effective in this population.

37.8 All of the following factors influence the penetration and concentration of an antibacterial agent in the cerebrospinal fluid except:

A. Lipid solubility of the drug.
B. Minimum inhibitory concentration of the drug.
C. Protein binding of the drug.
D. Molecular weight of the drug.

Correct answer = B. Although the minimum inhibitory concentration will impact the effectiveness of the drug against a given bacteria, it does not affect the ability of a drug to penetrate into the brain. The lipid solubility, protein binding, and molecular weight all determine the likelihood of a drug to penetrate the blood–brain barrier and concentrate in the brain.

37.9 A 72-year-old male presents with fever, cough, malaise, and shortness of breath. His chest x-ray shows bilateral infiltrates consistent with pneumonia. Bronchial wash cultures reveal Pseudomonas aeruginosa sensitive to cefepime. Which of the following is the best dosing scheme for cefepime based on the drug's time-dependent bactericidal activity?

A. 1 g every 6 hours given over 30 minutes.
B. 2 g every 12 hours given over 3 hours.
C. 4 g every 24 hours given over 30 minutes.
D. 4 g given as continuous infusion over 24 hours.

Correct answer = D. The clinical efficacy of cefepime is based on the percentage of time that the drug concentration remains above the MIC. A continuous infusion would allow for the greatest amount of time above the MIC compared to intermittent (30 minutes) and prolonged infusions (3 to 4 hours).

37.10 Which of the following adverse drug reactions precludes a patient from being rechallenged with that drug in the future?

A. Itching/rash from penicillin.
B. Stevens-Johnson syndrome from sulfamethoxazole–trimethoprim.
C. Gastrointestinal (GI) upset from clarithromycin.
D. Clostridium difficile superinfection from moxifloxacin.

Correct answer = B. Stevens-Johnson syndrome is a severe idiosyncratic reaction that can be life threatening, and these patients should never be rechallenged with the offending agent. Itching/rash is a commonly reported reaction in patients receiving penicillins but is not life threatening. A patient may be rechallenged if the benefits outweigh the risk (for example, pregnant patient with syphilis) or the patient could be exposed through a desensitization procedure. GI upset is a common side effect of clarithromycin but is not due to an allergic reaction. Moxifloxacin is a broad-spectrum antibiotic that can inhibit the normal flora of the GI tract, increasing the risk for the development of superinfections like C. difficile. This is not an allergic reaction, and the patient can be rechallenged; however, the patient might be at risk for developing C. difficile infection again.

Cell Wall Inhibitors

38

Jamie Kisgen

I. OVERVIEW

Some antimicrobial drugs selectively interfere with synthesis of the bacterial cell wall—a structure that mammalian cells do not possess. The cell wall is composed of a polymer called peptidoglycan that consists of glycan units joined to each other by peptide cross-links. To be maximally effective, inhibitors of cell wall synthesis require actively proliferating microorganisms. They have little or no effect on bacteria that are not growing and dividing. The most important members of this group of drugs are the β-lactam antibiotics (named after the β-lactam ring that is essential to their activity), *vancomycin*, and *daptomycin.* Figure 38.1 shows the classification of agents affecting cell wall synthesis.

II. PENICILLINS

The penicillins are among the most widely effective and the least toxic drugs known, but increased resistance has limited their use. Members of this family differ from one another in the R substituent attached to the 6-aminopenicillanic acid residue (Figure 38.2). The nature of this side chain affects the antimicrobial spectrum, stability to stomach acid, cross-hypersensitivity, and susceptibility to bacterial degradative enzymes (β-lactamases).

A. Mechanism of action

The penicillins interfere with the last step of bacterial cell wall synthesis (transpeptidation or cross-linkage), resulting in exposure of the osmotically less stable membrane. Cell lysis can then occur, either through osmotic pressure or through the activation of autolysins. These drugs are bactericidal and work in a time-dependent fashion. Penicillins are only effective against rapidly growing organisms that synthesize a peptidoglycan cell wall. Consequently, they are inactive against organisms devoid of this structure, such as mycobacteria, protozoa, fungi, and viruses.

1. **Penicillin-binding proteins:** Penicillins also inactivate numerous proteins on the bacterial cell membrane. These penicillin-binding proteins (PBPs) are bacterial enzymes involved in the synthesis of the cell wall and in the maintenance of the morphologic features of the bacterium. Exposure to these antibiotics can therefore not only

PENICILLINS
Amoxicillin AMOXIL
Ampicillin PRINCIPEN
Dicloxacillin DYNAPEN
Nafcillin
Oxacillin
Penicillin G PFIZERPEN
Penicillin V
Piperacillin
Ticarcillin

CEPHALOSPORINS
Cefaclor CECLOR
Cefadroxil DURACEF
Cefazolin KEFZOL
Cefdinir OMNICEF
Cefepime MAXIPIME
Cefixime SUPRAX
Cefotaxime CLAFORAN
Cefotetan CEFOTAN
Cefoxitin MEFOXIN
Cefprozil CEFZIL
Ceftaroline TEFLARO
Ceftazidime FORTAZ
Ceftibuten CEDAX
Ceftizoxime CEFIZOX
Ceftriaxone ROCEPHIN
Cefuroxime CEFTIN
Cephalexin KEFLEX

CARBAPENEMS
Doripenem DORIBAX
Ertapenem INVANZ
Imipenem/cilastatin PRIMAXIN
Meropenem MERREM

MONOBACTAMS
Aztreonam AZACTAM

Figure 38.1
Summary of antimicrobial agents affecting cell wall synthesis. (Figure continues on next page.)

β-LACTAMASE INHIBITOR + ANTIBIOTIC COMBINATIONS

Clavulanic acid + amoxicillin AUGMENTIN
Clavulanic acid + ticarcillin TIMENTIN
Sulbactam + ampicillin UNASYN
Tazobactam + piperacillin ZOSYN

OTHER ANTIBIOTICS

Colistin COLOMYCIN, COLY-MYCIN M
Daptomycin CUBICIN
Fosfomycin MONUROL
Polymyxin B AEROSPORIN
Telavancin VIBATIV
Vancomycin VANCOCIN

Figure 38.1 (Continued)
Summary of antimicrobial agents affecting cell wall synthesis.

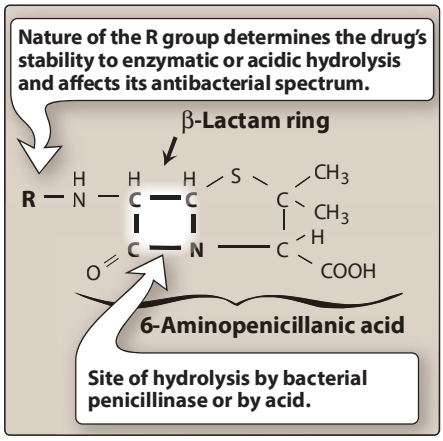


Figure 38.2
Structure of β-lactam antibiotics.

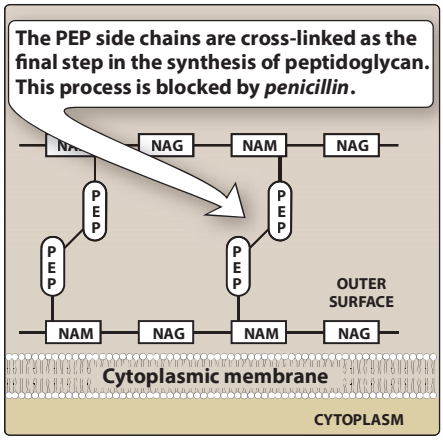


Figure 38.3
Bacterial cell wall of gram-positive bacteria. (NAM = *N*-acetylmuramic acid; NAG = *N*-acetylglucosamine; PEP = cross-linking peptide.)

prevent cell wall synthesis but also lead to morphologic changes or lysis of susceptible bacteria. The number of PBPs varies with the type of organism. Alterations in some of these PBPs provide the organism with resistance to the penicillins. [Note: *Methicillin*-resistant Staphylococcus aureus (MRSA) arose because of such an alteration.]

2. **Inhibition of transpeptidase:** Some PBPs catalyze formation of the cross-linkages between peptidoglycan chains (Figure 38.3). Penicillins inhibit this transpeptidase-catalyzed reaction, thus hindering the formation of cross-links essential for cell wall integrity.

3. **Production of autolysins:** Many bacteria, particularly the gram-positive cocci, produce degradative enzymes (autolysins) that participate in the normal remodeling of the bacterial cell wall. In the presence of a penicillin, the degradative action of the autolysins proceeds in the absence of cell wall synthesis. Thus, the antibacterial effect of a penicillin is the result of both inhibition of cell wall synthesis and destruction of the existing cell wall by autolysins.

B. Antibacterial spectrum

The antibacterial spectrum of the various penicillins is determined, in part, by their ability to cross the bacterial peptidoglycan cell wall to reach the PBPs in the periplasmic space. Factors that determine the susceptibility of PBPs to these antibiotics include the size, charge, and hydrophobicity of the particular β-lactam antibiotic. In general, gram-positive microorganisms have cell walls that are easily traversed by penicillins, and, therefore, in the absence of resistance, they are susceptible to these drugs. Gram-negative microorganisms have an outer lipopolysaccharide membrane surrounding the cell wall that presents a barrier to the water-soluble penicillins. However, gram-negative bacteria have proteins inserted in the lipopolysaccharide layer that act as water-filled channels (called porins) to permit transmembrane entry.

1. **Natural penicillins:** Natural penicillins (*penicillin G* and *penicillin V*) are obtained from fermentations of the fungus Penicillium chrysogenum. Semisynthetic penicillins, such as *amoxicillin* and *ampicillin* (also known as aminopenicillins), are created by chemically attaching different R groups to the 6-aminopenicillanic acid nucleus. *Penicillin* [pen-i-SILL-in] *G* (*benzyl-penicillin*) is the cornerstone of therapy for infections caused by a number of gram-positive and gram-negative cocci, gram-positive bacilli, and spirochetes (Figure 38.4). Penicillins are susceptible to inactivation by β-lactamases (penicillinases) that are produced by the resistant bacteria. Despite widespread use and increase in resistance to many types of bacteria, *penicillin* remains the drug of choice for the treatment of gas gangrene (Clostridium perfringens) and syphilis (Treponema pallidum). *Penicillin V* has a similar spectrum to that of *penicillin G*, but it is not used for treatment of bacteremia because of its poor oral absorption. *Penicillin V* is more acid stable than *penicillin G* and is often employed orally in the treatment of infections.

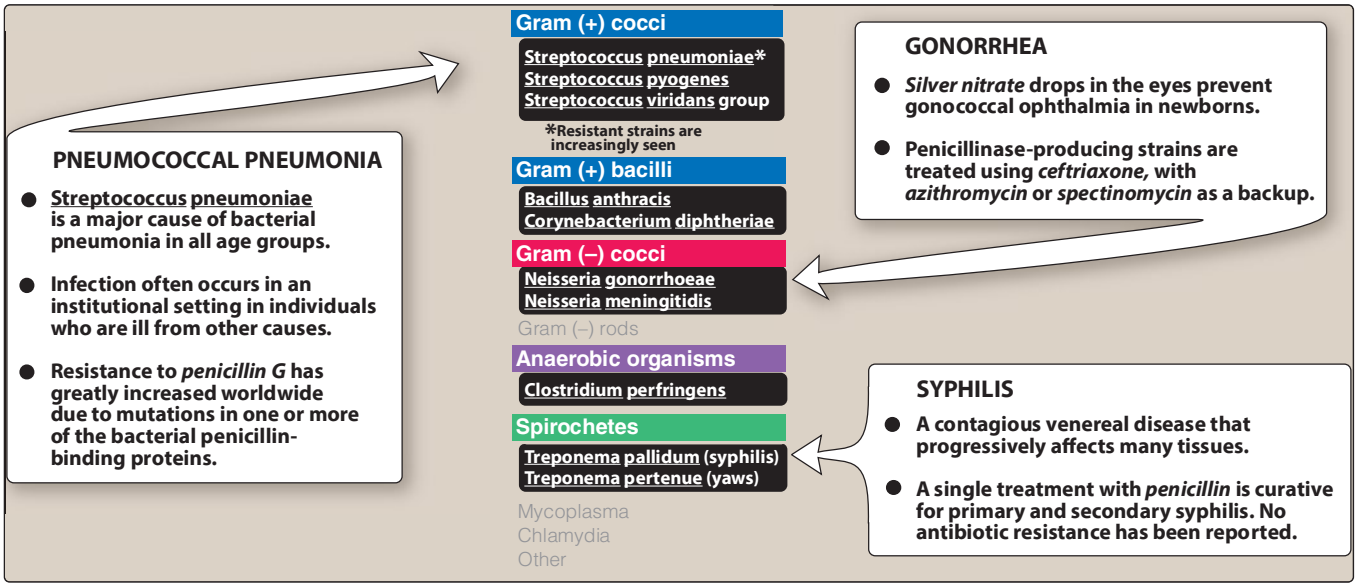


Figure 38.4
Typical therapeutic applications of *penicillin G.*

2. **Antistaphylococcal penicillins:** *Methicillin* [meth-i-SILL-in], *nafcillin* [naf-SILL-in], *oxacillin* [ox-a-SILL-in], and *dicloxacillin* [dye-klox-a-SILL-in] are β-lactamase (penicillinase)-resistant penicillins. Their use is restricted to the treatment of infections caused by penicillinase-producing staphylococci, including *methicillin*-sensitive Staphylococcus aureus (MSSA). [Note: Because of its toxicity (interstitial nephritis), *methicillin* is not used clinically in the United States except in laboratory tests to identify resistant strains of S. aureus. MRSA is currently a source of serious community and nosocomial (hospital-acquired) infections and is resistant to most commercially available β-lactam antibiotics.] The penicillinase-resistant penicillins have minimal to no activity against gram-negative infections.

3. **Extended-spectrum penicillins:** *Ampicillin* [am-pi-SILL-in] and *amoxicillin* [a-mox-i-SILL-in] have an antibacterial spectrum similar to that of *penicillin G* but are more effective against gram-negative bacilli (Figure 38.5A). *Ampicillin* (with or without the addition of *gentamicin*) is the drug of choice for the gram-positive bacillus Listeria monocytogenes and susceptible enterococcal species. These extended-spectrum agents are also widely used in the treatment of respiratory infections, and *amoxicillin* is employed prophylactically by dentists in high-risk patients for the prevention of bacterial endocarditis. Resistance to these antibiotics is now a major clinical problem because of inactivation by plasmid-mediated penicillinases. [Note: Escherichia coli and Haemophilus influenzae are frequently resistant.] Formulation with a β-lactamase inhibitor, such as *clavulanic acid* or *sulbactam*, protects *amoxicillin* or *ampicillin,* respectively, from enzymatic hydrolysis and extends their antimicrobial spectra. For example, without the β-lactamase inhibitor, MSSA is resistant to *ampicillin* and *amoxicillin.*

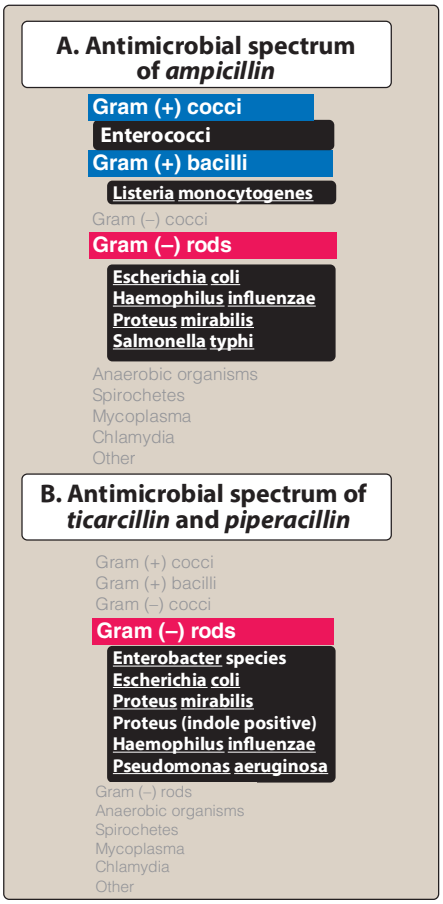


Figure 38.5
Antimicrobial activity of *ampicillin* **(A)** and the antipseudomonal penicillins **(B)**.

4. **Antipseudomonal penicillins:** *Piperacillin* [pip-er-a-SILL-in] and *ticarcillin* [tye-kar-SILL-in] are called antipseudomonal penicillins because of their activity against Pseudomonas aeruginosa (Figure 38.5B). These agents are available in parenteral formulations only. *Piperacillin* is the most potent of these antibiotics. They are effective against many gram-negative bacilli, but not against Klebsiella because of its constitutive penicillinase. Formulation of *ticarcillin* or *piperacillin* with *clavulanic acid* or *tazobactam*, respectively, extends the antimicrobial spectrum of these antibiotics to include penicillinase-producing organisms (for example, most Enterobacteriaceae and Bacteroides species). Figure 38.6 summarizes the stability of the penicillins to acid or the action of penicillinase.

C. Resistance

Natural resistance to the penicillins occurs in organisms that either lack a peptidoglycan cell wall (for example, Mycoplasma pneumoniae) or have cell walls that are impermeable to the drugs. Acquired resistance to the penicillins by plasmid-mediated β-lactamases has become a significant clinical problem. Multiplication of resistant strains leads to increased dissemination of the resistance genes. By obtaining resistance plasmids, bacteria may acquire one or more of the following properties, thus allowing survival in the presence of β-lactam antibiotics.

1. **β-Lactamase activity:** This family of enzymes hydrolyzes the cyclic amide bond of the β-lactam ring, which results in loss of bactericidal activity (Figure 38.2). They are the major cause of resistance to the penicillins and are an increasing problem. β-Lactamases either are constitutive, mostly produced by the bacterial chromosome or, more commonly, are acquired by the transfer of plasmids. Some of the β-lactam antibiotics are poor substrates for β-lactamases and resist hydrolysis, thus retaining their activity against β-lactamase–producing organisms. [Note: Certain organisms may have chromosome-associated β-lactamases that are inducible by β-lactam antibiotics (for example, second and third generation cephalosporins).] Gram-positive organisms secrete β-lactamases extracellularly, whereas gram-negative bacteria inactivate β-lactam drugs in the periplasmic space.

2. **Decreased permeability to the drug:** Decreased penetration of the antibiotic through the outer cell membrane of the bacteria prevents the drug from reaching the target PBPs. The presence of an efflux pump can also reduce the amount of intracellular drug (for example, Klebsiella pneumoniae).

3. **Altered PBPs:** Modified PBPs have a lower affinity for β-lactam antibiotics, requiring clinically unattainable concentrations of the drug to effect inhibition of bacterial growth. This explains MRSA resistance to most commercially available β-lactams.

D. Pharmacokinetics

1. **Administration:** The route of administration of a β-lactam antibiotic is determined by the stability of the drug to gastric acid and by the severity of the infection.

a. Routes of administration: The combination of *ampicillin* with *sulbactam, ticarcillin* with *clavulanic acid,* and *piperacillin* with *tazobactam*, and the antistaphylococcal penicillins *nafcillin* and *oxacillin* must be administered intravenously (IV) or intramuscularly (IM). *Penicillin V*, *amoxicillin*, and *dicloxacillin* are available only as oral preparations. Others are effective by the oral, IV, or IM routes (Figure 38.6). [Note: The combination of *amoxicillin* with *clavulanic acid* is only available in an oral formulation in the United States].

b. Depot forms: *Procaine penicillin G* and *benzathine penicillin G* are administered IM and serve as depot forms. They are slowly absorbed into the circulation and persist at low levels over a long time period.

2. Absorption: Most of the penicillins are incompletely absorbed after oral administration, and they reach the intestine in sufficient amounts to affect the composition of the intestinal flora. Food decreases the absorption of all the penicillinase-resistant penicillins because as gastric emptying time increases, the drugs are destroyed by stomach acid. Therefore, they should be taken on an empty stomach.

3. Distribution: The β-lactam antibiotics distribute well throughout the body. All the penicillins cross the placental barrier, but none have been shown to have teratogenic effects. However, penetration into bone or cerebrospinal fluid (CSF) is insufficient for therapy unless these sites are inflamed (Figures 38.7 and 38.8). [Note: Inflamed meninges are more permeable to the penicillins, resulting in an increased ratio of the drug in the CSF compared to the serum.] Penicillin levels in the prostate are insufficient to be effective against infections.

4. Metabolism: Host metabolism of the β-lactam antibiotics is usually insignificant, but some metabolism of *penicillin G* may occur in patients with impaired renal function.

5. Excretion: The primary route of excretion is through the organic acid (tubular) secretory system of the kidney as well as by glomerular filtration. Patients with impaired renal function must have dosage regimens adjusted. *Nafcillin* and *oxacillin* are exceptions to the rule. They are primarily metabolized in the liver and do not require dose adjustment for renal insufficiency. *Probenecid* inhibits the secretion of penicillins by competing for active tubular secretion via the organic acid transporter and, thus, can increase blood levels. The penicillins are also excreted in breast milk.

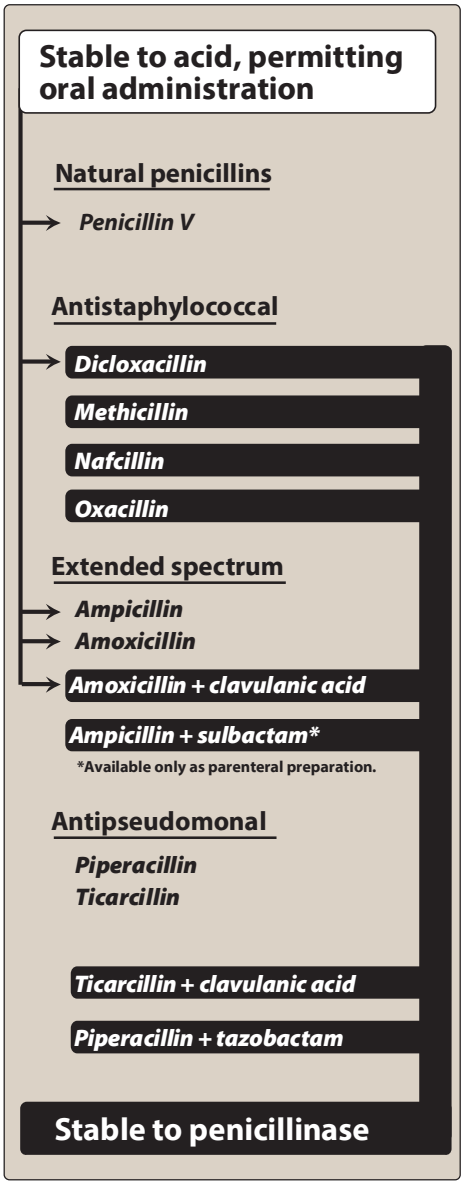


Figure 38.6
Stability of the penicillins to acid or the action of penicillinase.

E. Adverse reactions

Penicillins are among the safest drugs, and blood levels are not monitored. However, adverse reactions may occur (Figure 38.9).

1. Hypersensitivity: Approximately 5% percent of patients have some kind of reaction, ranging from rashes to angioedema (marked swelling of the lips, tongue, and periorbital area) and anaphylaxis. Cross-allergic reactions occur among the β-lactam antibiotics.

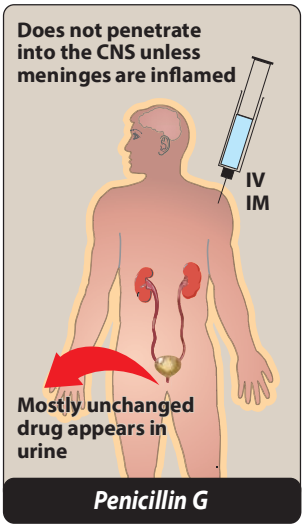


Figure 38.7
Administration and fate of *penicillin.* (CNS = central nervous system.)

To determine whether treatment with a β-lactam is safe when an allergy is noted, patient history regarding severity of previous reaction is essential.

2. **Diarrhea:** Diarrhea is a common problem that is caused by a disruption of the normal balance of intestinal microorganisms. It occurs to a greater extent with those agents that are incompletely absorbed and have an extended antibacterial spectrum. Pseudomembranous colitis from Clostridium difficile and other organisms may occur with penicillin use.

3. **Nephritis:** Penicillins, particularly *methicillin*, have the potential to cause acute interstitial nephritis. [Note: *Methicillin* is therefore no longer used clinically.]

4. **Neurotoxicity:** The penicillins are irritating to neuronal tissue, and they can provoke seizures if injected intrathecally or if very high blood levels are reached. Epileptic patients are particularly at risk due to the ability of penicillins to cause GABAergic inhibition.

5. **Hematologic toxicities:** Decreased coagulation may be observed with high doses of *piperacillin*, *ticarcillin*, and *nafcillin* (and, to some extent, with *penicillin G*). Cytopenias have been associated with therapy of greater than 2 weeks, and therefore, blood counts should be monitored weekly for such patients.

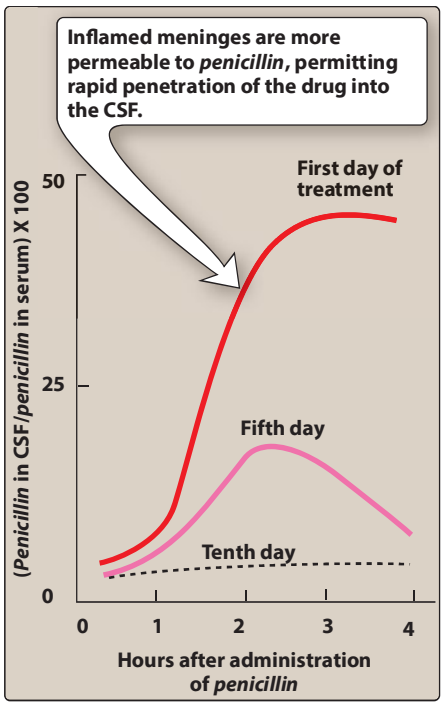


Figure 38.8
Enhanced penetration of *penicillin* into the cerebral spinal fluid (CSF) during inflammation.

III. CEPHALOSPORINS

The cephalosporins are β-lactam antibiotics that are closely related both structurally and functionally to the penicillins. Most cephalosporins are produced semisynthetically by the chemical attachment of side chains to 7-aminocephalosporanic acid. Cephalosporins have the same mode of action as penicillins, and they are affected by the same resistance mechanisms. However, they tend to be more resistant than the penicillins to certain β-lactamases.

A. Antibacterial spectrum

Cephalosporins have been classified as first, second, third, fourth, and advanced generation, based largely on their bacterial susceptibility patterns and resistance to β-lactamases (Figure 38.10). [Note: Commercially available cephalosporins are ineffective against MRSA, L. monocytogenes, C. difficile, and the enterococci.]

1. **First generation:** The first-generation cephalosporins act as *penicillin G* substitutes. They are resistant to the staphylococcal penicillinase (that is, they cover MSSA) and also have activity against Proteus mirabilis, E. coli, and K. pneumoniae.

2. **Second generation:** The second-generation cephalosporins display greater activity against three additional gram-negative organisms: H. influenzae, Enterobacter aerogenes, and some Neisseria species, whereas activity against gram-positive organisms is weaker. Antimicrobial coverage of the cephamycins (*cefotetan*

[sef-oh-TEE-tan] and *cefoxitin* [sef-OX-i-tin]) also includes anaerobes (for example, Bacteroides fragilis). They are the only cephalosporins commercially available with appreciable activity against gram-negative anaerobic bacteria. However, neither drug is first line because of the increasing prevalence of resistance among B. fragilis to both agents.

3. **Third generation:** These cephalosporins have assumed an important role in the treatment of infectious diseases. Although they are less potent than first-generation cephalosporins against MSSA, the third-generation cephalosporins have enhanced activity against gram-negative bacilli, including those mentioned above, as well as most other enteric organisms plus Serratia marcescens. *Ceftriaxone* [sef-trye-AKS-own] and *cefotaxime* [sef-oh-TAKS-eem] have become agents of choice in the treatment of meningitis. *Ceftazidime* [sef-TA-zi-deem] has activity against P. aeruginosa; however, resistance is increasing and use should be evaluated on a case-by-case basis. Third-generation cephalosporins must be used with caution, as they are associated with significant "collateral damage," essentially meaning the induction and spread of antimicrobial resistance. [Note: Fluoroquinolone use is also associated with collateral damage.]

4. **Fourth generation:** *Cefepime* [SEF-eh-peem] is classified as a fourth-generation cephalosporin and must be administered parenterally. *Cefepime* has a wide antibacterial spectrum, with activity against streptococci and staphylococci (but only those that are *methicillin* susceptible). *Cefepime* is also effective against aerobic gram-negative organisms, such as Enterobacter species, E. coli, K. pneumoniae, P. mirabilis, and P. aeruginosa. When selecting an antibiotic that is active against P. aeruginosa, clinicians should refer to their local antibiograms (laboratory testing for the sensitivity of an isolated bacterial strain to different antibiotics) for direction.

5. **Advanced generation:** *Ceftaroline* [sef-TAR-oh-leen] is a broad-spectrum, advanced-generation cephalosporin that is administered IV as a prodrug, *ceftaroline fosamil*. It is the only commercially available β-lactam in the United States with activity against MRSA and is indicated for the treatment of complicated skin and skin structure infections and community-acquired pneumonia. The unique structure allows *ceftaroline* to bind to PBP2a found with MRSA and PBP2x found with Streptococcus pneumoniae. In addition to its broad gram-positive activity, it also has similar gram-negative activity to the third-generation cephalosporin *ceftriaxone*. Important gaps in coverage include P. aeruginosa, extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, and Acinetobacter baumannii. The twice-daily dosing regimen also limits its use outside of an institutional setting.

B. Resistance

Mechanisms of bacterial resistance to the cephalosporins are essentially the same as those described for the penicillins. [Note: Although they are not susceptible to hydrolysis by the staphylococcal

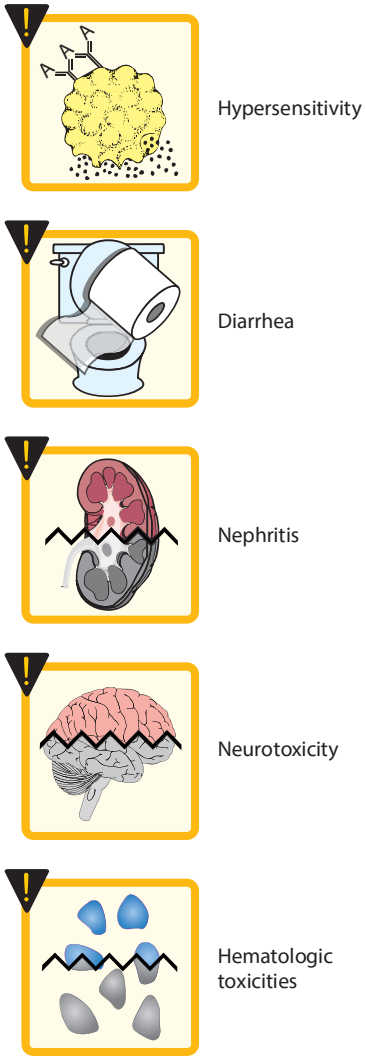


Figure 38.9
Summary of the adverse effects of *penicillin.*

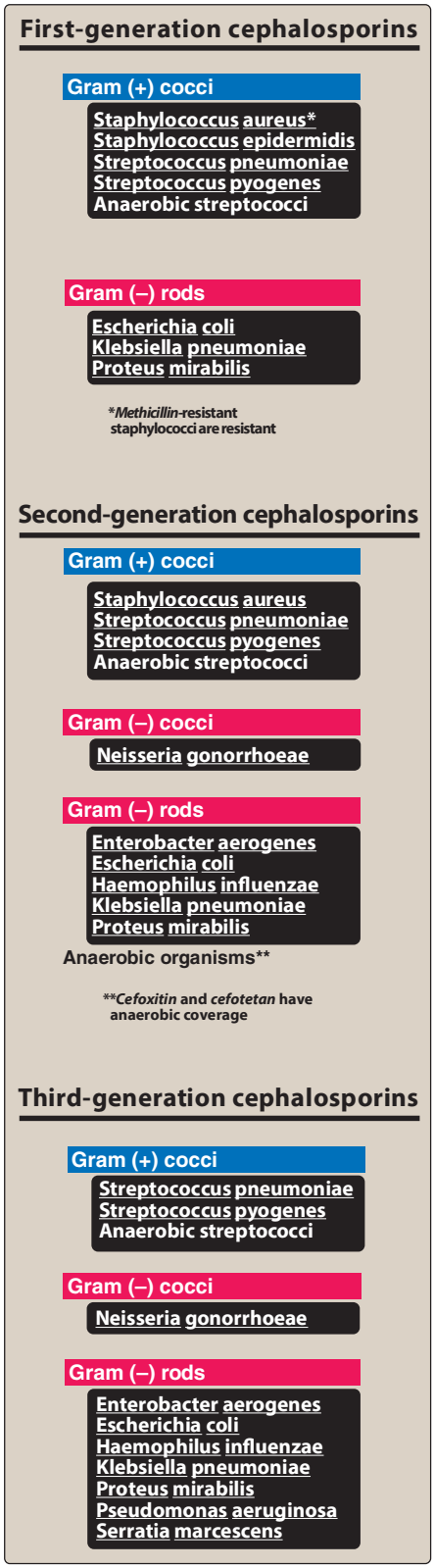


Figure 38.10
Summary of therapeutic applications of cephalosporins.

penicillinase, cephalosporins may be susceptible to ESBLs. Organisms such as E. coli and K. pneumoniae are particularly associated with ESBLs.]

C. Pharmacokinetics

1. **Administration:** Many of the cephalosporins must be administered IV or IM (Figure 38.11) because of their poor oral absorption. Exceptions are noted in Figure 38.12.

2. **Distribution:** All cephalosporins distribute very well into body fluids. However, adequate therapeutic levels in the CSF, regardless of inflammation, are achieved with only a few cephalosporins. For example, *ceftriaxone* and *cefotaxime* are effective in the treatment of neonatal and childhood meningitis caused by H. influenzae. *Cefazolin* [se-FA-zo-lin] is commonly used as a single prophylaxis dose prior to surgery because of its 1.8-hour half-life and its activity against penicillinase-producing S. aureus. *Cefazolin* is effective for most surgical procedures, including orthopedic surgery because of its ability to penetrate bone. All cephalosporins cross the placenta.

3. **Elimination:** Cephalosporins are eliminated through tubular secretion and/or glomerular filtration (Figure 38.11). Therefore, doses must be adjusted in cases of renal dysfunction to guard against accumulation and toxicity. One exception is *ceftriaxone*, which is excreted through the bile into the feces and, therefore, is frequently employed in patients with renal insufficiency.

D. Adverse effects

Like the penicillins, the cephalosporins are generally well tolerated. However, allergic reactions are a concern. Patients who have had an anaphylactic response, Stevens-Johnson syndrome, or toxic epidermal necrolysis to penicillins should not receive cephalosporins. Cephalosporins should be avoided or used with caution in individuals with penicillin allergy. Current data suggest that the cross-reactivity between penicillin and cephalosporins is around 3% to 5% and is determined by the similarity in the side chain, not the β-lactam structure. The highest rate of allergic cross-sensitivity is between penicillin and first-generation cephalosporins.

IV. OTHER β-LACTAM ANTIBIOTICS

A. Carbapenems

Carbapenems are synthetic β-lactam antibiotics that differ in structure from the penicillins in that the sulfur atom of the thiazolidine ring (Figure 38.2) has been externalized and replaced by a carbon atom (Figure 38.13). *Imipenem* [i-mi-PEN-em], *meropenem* [mer-oh-PEN-em], *doripenem* [dore-i-PEN-em], and *ertapenem* [er-ta-PEN-em] are the drugs of this group currently available. *Imipenem* is compounded with *cilastatin* to protect it from metabolism by renal dehydropeptidase.

1. **Antibacterial spectrum:** *Imipenem* resists hydrolysis by most β-lactamases, but not the metallo-β-lactamases. This drug plays a role in empiric therapy because it is active against β-lactamase–producing gram-positive and gram-negative organisms, anaerobes, and P. aeruginosa (although other pseudomonal strains are resistant and resistant strains of P. aeruginosa have been reported to arise during therapy). *Meropenem* and *doripenem* have antibacterial activity similar to that of *imipenem* (Figure 38.14). Unlike other carbapenems, *ertapenem* lacks coverage against P. aeruginosa, Enterococcus species, and Acinetobacter species.

2. **Pharmacokinetics:** *Imipenem/cilastatin* and *meropenem* are administered IV and penetrate well into body tissues and fluids, including the CSF when the meninges are inflamed. *Meropenem* is known to reach therapeutic levels in bacterial meningitis even without inflammation. They are excreted by glomerular filtration. *Imipenem* undergoes cleavage by a dehydropeptidase found in the brush border of the proximal renal tubule. This enzyme forms an inactive metabolite that is potentially nephrotoxic. Compounding the *imipenem* with *cilastatin* protects the parent drug and, thus, prevents the formation of the toxic metabolite. The other carbapenems do not require coadministration of *cilastatin. Ertapenem* can be administered via IV or IM injection once

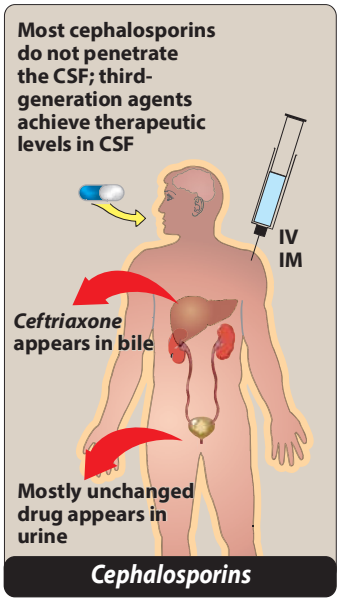


Figure 38.11
Administration and fate of the cephalosporins. (CSF = cerebrospinal fluid.)

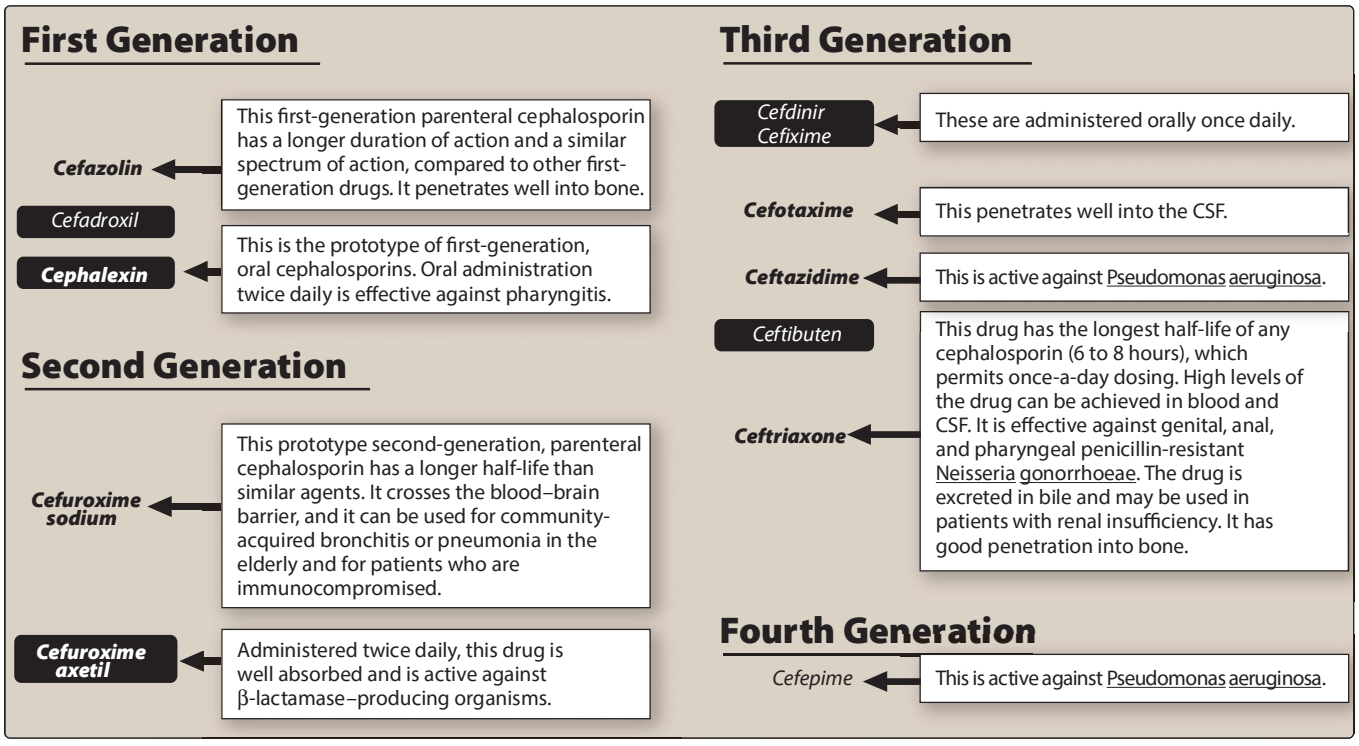


Figure 38.12
Therapeutic advantages of some clinically useful cephalosporins. [Note: Drugs that can be administered orally are shown in reverse type. More useful drugs shown in **bold**.]. **(**CSF = cerebrospinal fluid.)

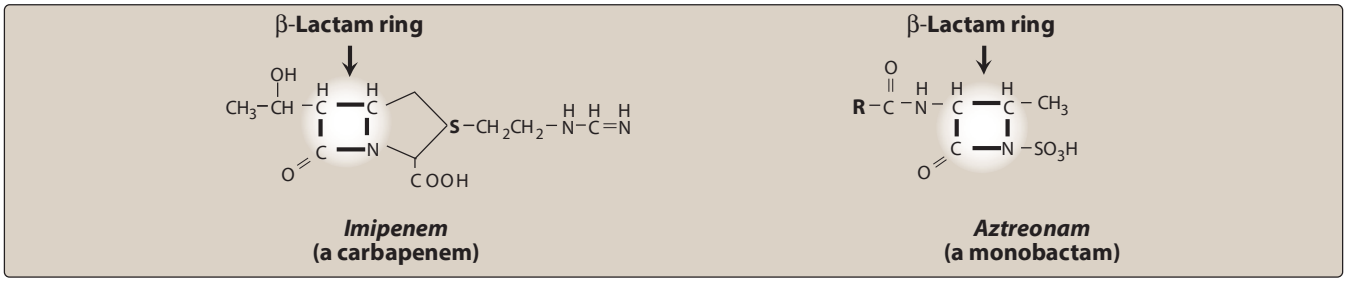


Figure 38.13
Structural features of *imipenem* and *aztreonam.*

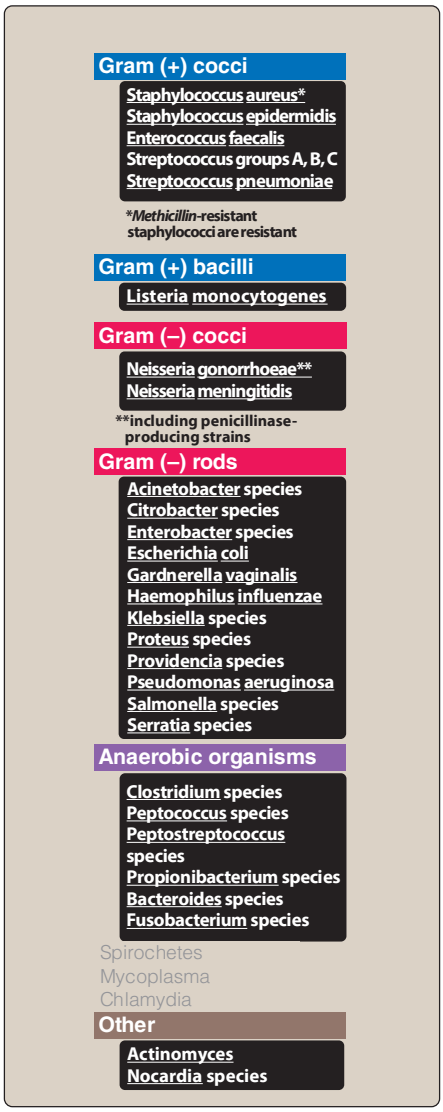


Figure 38.14
Antimicrobial spectrum of *imipenem.*

daily. [Note: Doses of these agents must be adjusted in patients with renal insufficiency.]

3. **Adverse effects:** *Imipenem/cilastatin* can cause nausea, vomiting, and diarrhea. Eosinophilia and neutropenia are less common than with other β-lactams. High levels of *imipenem* may provoke seizures; however, the other carbapenems are less likely to do so.

B. Monobactams

The monobactams, which also disrupt bacterial cell wall synthesis, are unique because the β-lactam ring is not fused to another ring (Figure 38.13). *Aztreonam* [az-TREE-oh-nam], which is the only commercially available monobactam, has antimicrobial activity directed primarily against gram-negative pathogens, including the Enterobacteriaceae and P. aeruginosa. It lacks activity against gram-positive organisms and anaerobes. *Aztreonam* is resistant to the action of most β-lactamases, with the exception of the ESBLs. It is administered either IV or IM and can accumulate in patients with renal failure. *Aztreonam* is relatively nontoxic, but it may cause phlebitis, skin rash and, occasionally, abnormal liver function tests. This drug has a low immunogenic potential, and it shows little cross-reactivity with antibodies induced by other β-lactams. Thus, this drug may offer a safe alternative for treating patients who are allergic to other penicillins, cephalosporins, or carbapenems.

V. β-LACTAMASE INHIBITORS

Hydrolysis of the β-lactam ring, either by enzymatic cleavage with a β-lactamase or by acid, destroys the antimicrobial activity of a β-lactam antibiotic. β-Lactamase inhibitors, such as *clavulanic* [cla-vue-LAN-ick] *acid, sulbactam* [sul-BACK-tam], and *tazobactam* [ta-zoh-BACK-tam], contain a β-lactam ring but, by themselves, do not have significant antibacterial activity or cause any significant adverse effects. Instead, they bind to and inactivate β-lactamases, thereby protecting the antibiotics that are normally substrates for these enzymes. The β-lactamase inhibitors are therefore formulated in combination with β-lactamase–sensitive

antibiotics. For example, Figure 38.15 shows the effect of *clavulanic acid* and *amoxicillin* on the growth of β-lactamase–producing E. coli. [Note: *Clavulanic acid* alone is nearly devoid of any antibacterial activity.]

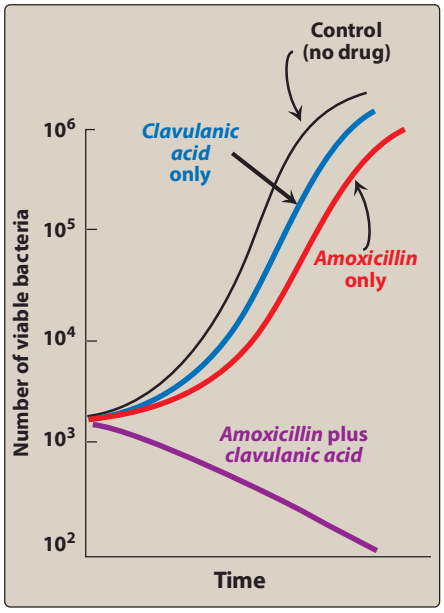


Figure 38.15
The in vitro growth of Escherichia coli in the presence of *amoxicillin,* with and without *clavulanic acid.*

VI. VANCOMYCIN

Vancomycin [van-koe-MYE-sin] is a tricyclic glycopeptide that has become increasingly important in the treatment of life-threatening MRSA and *methicillin*-resistant Staphylococcus epidermidis (MRSE) infections, as well as enterococcal infections (Figure 38.16). With the emergence of resistant strains, it is important to curtail the increase in *vancomycin*-resistant bacteria (for example, Enterococcus faecium and Enterococcus faecalis) by restricting the use of *vancomycin* to the treatment of serious infections caused by β-lactam resistant, gram-positive microorganisms or gram-positive infections in patients who have a serious allergy to the β-lactams. Intravenous *vancomycin* is used in individuals with prosthetic heart valves and in patients undergoing implantation with prosthetic devices, especially in those hospitals where there are high rates of MRSA or MRSE. Serum drug concentrations (troughs) are commonly measured to monitor and adjust dosages for safety and efficacy. *Vancomycin* is not absorbed after oral administration, so the use of the oral formulation is limited to the treatment of severe antibiotic-associated C. difficile colitis.

VII. DAPTOMYCIN

Daptomycin [DAP-toe-mye-sin] is a bactericidal concentration-dependent cyclic lipopeptide antibiotic that is an alternative to other agents, such as *linezolid* and *quinupristin/dalfopristin,* for treating infections caused by resistant gram-positive organisms, including MRSA and *vancomycin*-resistant enterococci (VRE) (Figure 38.17). *Daptomycin* is indicated for the treatment of complicated skin and skin structure infections and bacteremia caused by S. aureus, including those with right-sided infective endocarditis. Efficacy of treatment with *daptomycin* in left-sided endocarditis has not been demonstrated. Additionally, *daptomycin* is inactivated by pulmonary surfactants; thus, it should *never* be used in the treatment of pneumonia.

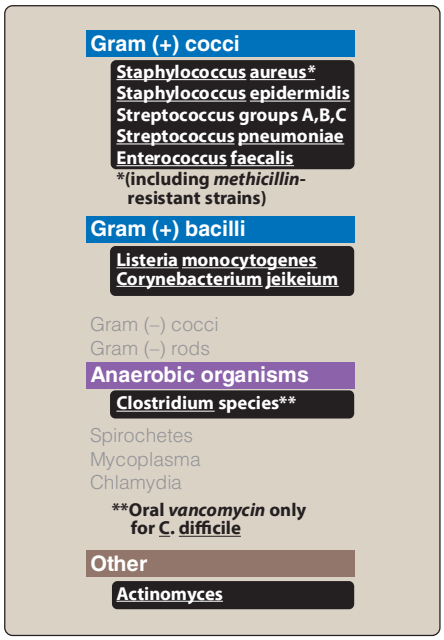


Figure 38.16
Antimicrobial spectrum of *vancomycin.*

VIII. TELAVANCIN

Telavancin [tel-a-VAN-sin] is a bactericidal concentration-dependent semisynthetic lipoglycopeptide antibiotic that is a synthetic derivative of *vancomycin.* Like *vancomycin, telavancin* inhibits bacterial cell wall synthesis. Moreover, *telavancin* exhibits an additional mechanism of action similar to that of *daptomycin,* which involves disruption of the bacterial cell membrane due to the presence of a lipophilic side chain moiety. It is an alternative to *vancomycin, daptomycin,* and *linezolid,* in treating complicated skin and skin structure infections caused by

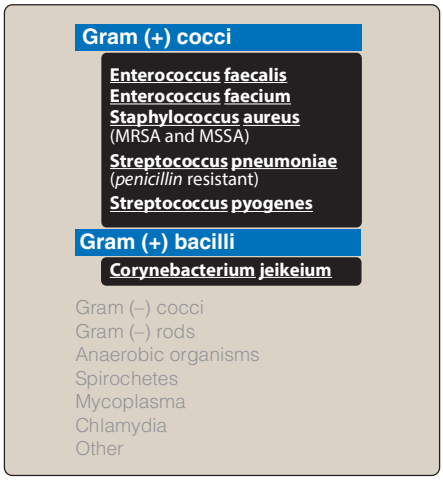


Figure 38.17
Antimicrobial spectrum of *daptomycin.* MRSA = *methicillin* resistant S. aureus; MSSA = *methicillin* susceptible S. aureus.

resistant gram-positive organisms (including MRSA). It is also an agent of last choice for hospital-acquired and ventilator-associated bacterial pneumonia when alternative treatments are not suitable. The use of *telavancin* in clinical practice is limited by significant adverse effects (for example, renal impairment), interaction with anticoagulation laboratory assays, risk of fetal harm in pregnant women, and interaction with medications that can prolong the QT_c interval (for example, fluoroquinolones, azole antifungals, macrolides). Figure 38.18 provides a comparison of important characteristics of *vancomycin*, *daptomycin*, and *telavancin*.

IX. FOSFOMYCIN

Fosfomycin [fos-foe-MYE-sin] is a bactericidal synthetic derivative of phosphonic acid. It blocks cell wall synthesis by inhibiting the enzyme UDP-*N*-acetylglucosamine enolpyruvyl transferase, which catalyzes the first step in peptidoglycan synthesis. It is indicated for urinary tract infections caused by E. coli or E. faecalis. Due to its unique structure and mechanism of action, cross resistance with other antimicrobial agents is unlikely. *Fosfomycin* is rapidly absorbed after oral administration and distributes well to the kidneys, bladder, and prostate. The drug is excreted in its active form in the urine and feces. It maintains high concentrations in the urine over several days, allowing for a one-time dose for the treatment of urinary tract infections. [Note: A parenteral formulation is available in select countries and has been used for the treatment of systemic infections.] The most commonly reported adverse effects include diarrhea, vaginitis, nausea, and headache.

X. POLYMYXINS

The polymyxins are cation polypeptides that bind to phospholipids on the bacterial cell membrane of gram-negative bacteria. They have a detergent-like effect that disrupts cell membrane integrity, leading to leakage of cellular components and ultimately cell death. Polymyxins are concentration-dependent bactericidal agents with activity against most clinically important gram-negative bacteria, including P. aeruginosa, E. coli, K. pneumoniae, Acinetobacter species, and Enterobacter species. However, alterations in the cell membrane lipid polysaccharides allow many species of Proteus and Serratia to be intrinsically resistant. Only two forms of polymyxin are in clinical use today, *polymyxin B* and *colistin* (*polymyxin E*). *Polymyxin B* is available in parenteral, ophthalmic, otic, and topical preparations. *Colistin* is only available as a prodrug, *colistimethate sodium*, which is administered IV or inhaled via a nebulizer. The use of these drugs has been limited for a long time, due to the increased risk of nephrotoxicity and neurotoxicity (for example, slurred speech, muscle weakness) when used systemically. However, with the increase in gram-negative resistance, they have seen a resurgence in use and are now commonly used as salvage therapy for patients with multidrug-resistant infections. Careful dosing and monitoring of adverse effects are important to maximize the safety and efficacy of these agents.

	VANCOMYCIN	DAPTOMYCIN	TELAVANCIN
Mechanism of Action	Inhibits synthesis of bacterial cell wall phospholipids as well as peptidoglycan polymerization	Causes rapid depolarization of the cell membrane, inhibits intracellular synthesis of DNA, RNA, and protein	Inhibits bacterial cell wall synthesis; disrupts cell membrane
Pharmacodynamics	Time dependent Bactericidal	Concentration dependent Bactericidal	Concentration dependent Bactericidal
Common Antibacterial Spectrum	Activity limited to gram-positive organisms: Staphylococcus aureus (including MRSA), Streptococcus pyogenes, S. agalactiae, penicillin-resistant S. pneumoniae, Corynebacterium jeikeium, *vancomycin*-susceptible Enterococcus faecalis, and E. faecium		
Unique Antibacterial Spectrum	Clostridium difficile (oral only)	*Vancomycin*-resistant E. faecalis and E. faecium (VRE)	Some isolates of *vancomycin*-resistant enterococci (VRE)
Route	IV/PO	IV	IV
Typical Administration Time	60- to 90-minute IV infusion	2-minute IV push 30-minute IV infusion	60-minute IV infusion
Pharmacokinetics	Renal elimination Normal half-life: 6–10 hours Dose is adjusted based on renal function and serum trough levels	Renal elimination Normal half-life: 7–8 hours Dose is adjusted based on renal function	Renal elimination Normal half-life: 7–9 hours Dose is adjusted based on renal function
Unique Adverse Effects	Infusion related reactions due to histamine release: Fever, chills, phlebitis, flushing (red man syndrome); dose-related ototoxicity and nephrotoxicity	Myalgias, elevated hepatic transaminases and creatine phosphokinases (check weekly), and rhabdomyolysis (consider holding HMG-CoA reductase inhibitors [statins] while on therapy)	Taste disturbances, foamy urine, QTc prolongation, interferes with coagulation labs (PT/INR, aPTT, ACT), not recommended in pregnancy (box warning recommends pregnancy test prior to initiation)
Key Learning Points	Drug of choice for severe MRSA infections; oral form only used for C. difficile infection; resistance can be caused by plasmid-mediated changes in permeability to the drug or by decreased binding of *vancomycin* to receptor molecules; monitor serum trough concentrations for safety and efficacy	*Daptomycin* is inactivated by pulmonary surfactants and should never be used in the treatment of pneumonia	Use with caution in patients with baseline renal dysfunction (CrCl < 50 mL/min) due to higher rates of treatment failure and mortality in clinical studies; any necessary coagulation labs should be drawn just prior to the *telavancin* dose to avoid interaction

Figure 38.18
Side-by-side comparison of *vancomycin*, *daptomycin*, and *telavancin.*

Study Questions

Choose the ONE best answer.

38.1 A 45-year-old male presented to the hospital 3 days ago with severe cellulitis and a large abscess on his left leg. Incision and drainage were performed on the abscess, and cultures revealed methicillin-resistant Staphylococcus aureus. Which of the following would be the most appropriate treatment option for once-daily outpatient intravenous therapy?

A. Ertapenem.
B. Ceftaroline.
C. Daptomycin.
D. Piperacillin/tazobactam.

Correct answer = C. Daptomycin is approved for skin and skin structure infections caused by MRSA and is given once daily. A and D are incorrect because they do not cover MRSA. Ceftaroline covers MRSA, but it must be given twice daily.

38.2 Which of the following adverse effects is associated with daptomycin?

A. Ototoxicity.
B. Red man syndrome.
C. QT_c prolongation.
D. Rhabdomyolysis.

Correct answer = D. Ototoxicity and red man syndrome are associated with vancomycin. QTc prolongation is associated with telavancin. Myalgias and rhabdomyolysis have been reported with daptomycin therapy and require patient education and monitoring.

38.3 A 72-year-old male is admitted to the hospital from a nursing home with severe pneumonia. He was recently discharged from the hospital 1 week ago after open heart surgery. The patient has no known allergies. Which of the following regimens is most appropriate for empiric coverage of methicillin-resistant Staphylococcus aureus and Pseudomonas aeruginosa in this patient?

A. Vancomycin + cefepime + ciprofloxacin.
B. Vancomycin + cefazolin + ciprofloxacin.
C. Telavancin + cefepime + ciprofloxacin.
D. Daptomycin + cefepime + ciprofloxacin.

Correct answer = A. Vancomycin provides adequate coverage against MRSA, and cefepime and ciprofloxacin provide adequate empiric coverage of *Pseudomonas*. B is incorrect because cefazolin does not have activity against *Pseudomonas.* C is incorrect because telavancin should be avoided if possible with drugs that prolong the QTc interval, in this case ciprofloxacin. Daptomycin is inactivated by pulmonary surfactant and should not be used for pneumonia.

38.4 A 23-year-old male presents with acute appendicitis that ruptures shortly after admission. He is taken to the operating room for surgery, and postsurgical cultures reveal Escherichia coli and Bacteroides fragilis, susceptibilities pending. Which of the following provides adequate empiric coverage of these two pathogens?

A. Cefepime.
B. Piperacillin/tazobactam.
C. Aztreonam.
D. Ceftaroline.

Correct answer = B. While all of these agents cover most strains of E. coli, piperacillin/tazobactam is the only drug on this list that provides coverage against *Bacteroides* species.

38.5 A 68-year-old male presents from a nursing home with fever, increased urinary frequency and urgency, and mental status changes. He has a penicillin allergy of anaphylaxis. Which of the following β-lactams is the most appropriate choice for gram-negative coverage of this patient's urinary tract infection?

A. Cefepime.
B. Ertapenem.
C. Aztreonam.
D. Ceftaroline.

Correct answer = C. Based on the severity of the allergic reaction, aztreonam is the choice of all the β-lactams. Although cross-reactivity with cephalosporins and carbapenems is low, the risk rarely outweighs the benefit in these cases.

38.6 A 25-year-old male presents to the urgent care center with a painless sore on his genitals that started 1 to 2 weeks ago. He reports unprotected sex with a new partner about a month ago. A blood test confirms the patient has Treponema pallidum. Which of the following is the drug of choice for the treatment of this patient's infection as a single dose?

A. Benzathine penicillin G.
B. Ceftriaxone.
C. Aztreonam.
D. Vancomycin.

Correct answer = A. A single treatment with penicillin is curative for primary and secondary syphilis. No antibiotic resistance has been reported, and it remains the drug of choice unless the patient has a severe allergic reaction.

38.7 A 20-year-old female presents to the emergency room with headache, stiff neck, and fever for 2 days and is diagnosed with meningitis. Which of the following agents is the best choice for the treatment of meningitis in this patient?

A. Cefazolin.
B. Cefdinir.
C. Cefotaxime.
D. Cefuroxime axetil.

Correct answer = C. Cefotaxime is the only drug on this list with adequate CSF penetration to treat meningitis. Cefdinir and cefuroxime axetil are only available orally, and cefazolin CSF penetration and spectrum of coverage against S. pneumoniae are not likely adequate to treat meningitis.

38.8 Which of the following cephalosporins has activity against gram-negative anaerobic pathogens like Bacteroides fragilis?

A. Cefoxitin.
B. Cefepime.
C. Ceftriaxone.
D. Cefazolin.

Correct answer = A. The cephamycins (cefoxitin and cefotetan) are the only cephalosporins with in vitro activity against anaerobic gram-negative pathogens. Cefepime, ceftriaxone, and cefazolin have no appreciable activity against Bacteroides fragilis.

38.9 In which of the following cases would it be appropriate to use telavancin?

A. A 29-year-old pregnant female with ventilator-associated pneumonia.
B. A 76-year-old male with hospital-acquired pneumonia also receiving amiodarone for atrial fibrillation.
C. A 36-year-old male with cellulitis and abscess growing MRSA.
D. A 72-year-old female with a diabetic foot infection growing MRSA who has moderate renal dysfunction.

Correct answer = C. A is not a good option due to the potential of telavancin harming the fetus. Option B is not a good choice because the patient is on amiodarone, and telavancin can cause QT_c prolongation. Option D is not an appropriate choice because the patient has baseline renal dysfunction and telavancin should be avoided unless benefit outweighs the risk. Option C is the best choice in this case since it is approved for skin and skin structure infections, and the patient has no apparent contraindication.

38.10 An 18-year-old female presents to the urgent care clinic with urinary frequency, urgency, and fever for the past 3 days. Based on symptoms and a urinalysis, she is diagnosed with a urinary tract infection. Cultures reveal Enterococcus faecalis that is pan sensitive. Which of the following is an appropriate oral option to treat the urinary tract infection in this patient?

A. Cephalexin.
B. Vancomycin.
C. Cefdinir.
D. Amoxicillin.

Correct answer = D. Option A and C are incorrect because enterococci are inherently resistant to all cephalosporins. Option B is incorrect because oral vancomycin is not absorbed and would not reach the urinary tract in sufficient quantities to treat a urinary tract infection. Option D is the best choice, as amoxicillin is well absorbed orally and concentrates in the urine.