Lippincott's Illustrated Reviews:

Pharmacology

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Chapter 31

Cell Wall Inhibitors

I. Overview

Some antimicrobial drugs selectively interfere with synthesis of the bacterial cell wallâ€”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 Î²-lactam antibiotics (named after the Î²-lactam ring that is essential to their activity) and *vancomycin*. Figure 31.1 shows the classification of agents affecting cell wall synthesis.

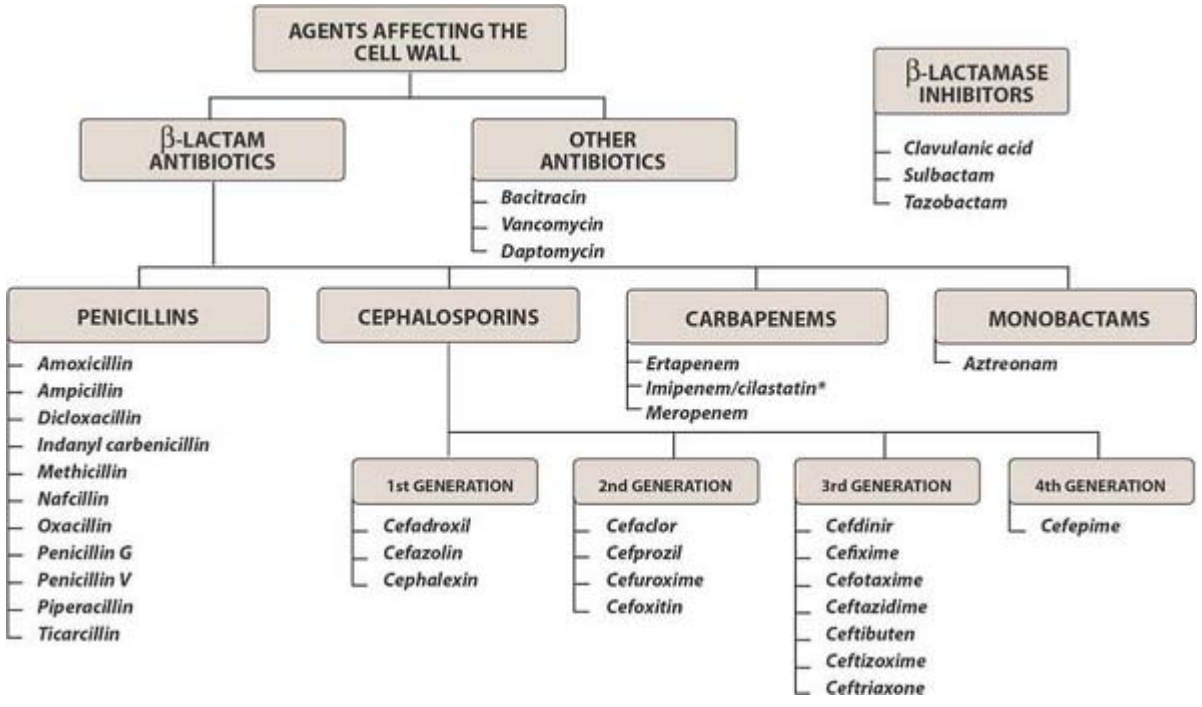


Figure 31.1 Summary of antimicrobial agents affecting cell wall synthesis. **Cilastatin* is not an antibiotic but a peptidase inhibitor that protects *imipenem* from degradation.

II. Penicillins

The penicillins are among the most widely effective antibiotics and also 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 31.2). The nature of this side chain affects the antimicrobial spectrum, stability to stomach acid, and susceptibility to bacterial degradative enzymes (Î²-lactamases).

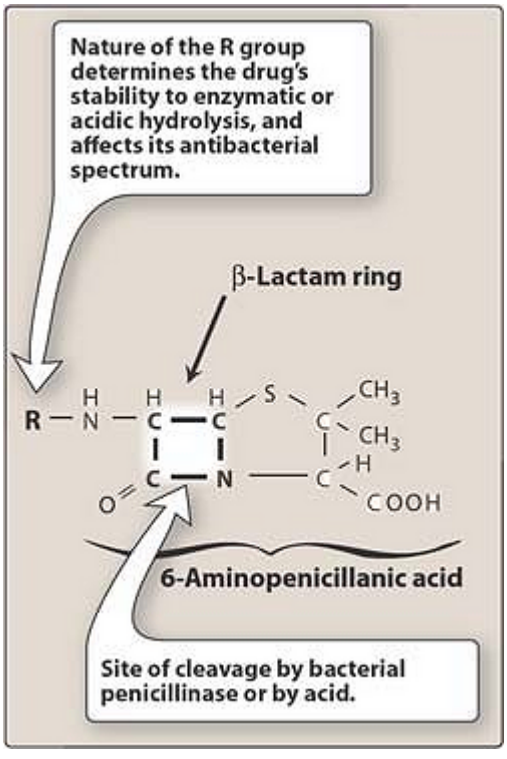


Figure 31.2 Structural features of Î²-lactam antibiotics.

A. Mechanism of action

The penicillins interfere with the last step of bacterial cell wall synthesis (transpeptidation or cross-linkage[1]), 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 thus bactericidal. The success of a penicillin antibiotic in causing cell death is related to the antibiotic's size, charge, and hydrophobicity. 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 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 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 target molecules provide the organism with resistance to the penicillins. [Note: *Methicillin*-resistant Staphylococcus aureus (MRSA) apparently arose because of such an alteration.]

2. **Inhibition of transpeptidase:** Some PBPs catalyze formation of the cross-linkages between peptidoglycan chains (Figure 31.3). Penicillins inhibit this transpeptidase-catalyzed reaction, thus hindering the formation of cross-links essential for cell wall integrity. As a result of this blockade of cell wall synthesis, the â€œPark nucleotideâ€ (formerly called the â€œPark peptideâ€), UDP-acetylmuramyl-l-Ala-D-Gln-L-Lys-D-Ala-D-Ala,

accumulates.

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. [Note: The exact autolytic mechanism is unknown, but it may be due to a disinhibition of the autolysins.] Thus, the antibacterial effect of a penicillin is the result of both inhibition of cell wall synthesis and destruction of existing cell wall by autolysins.

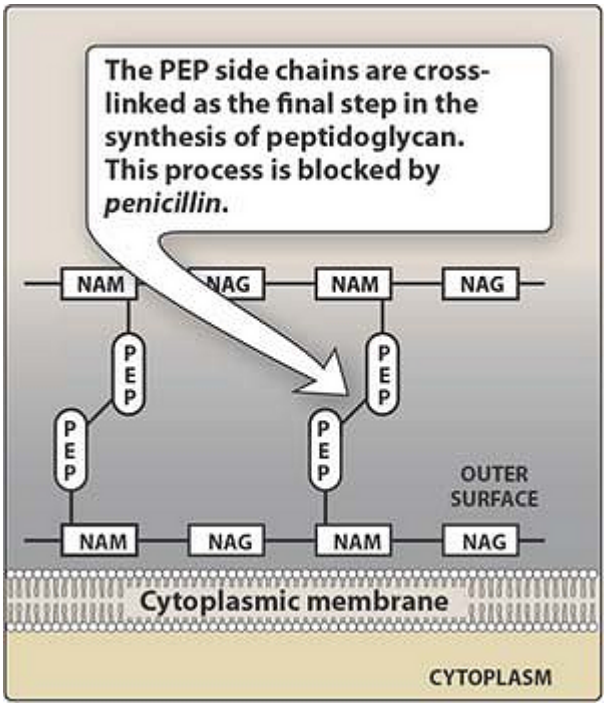


Figure 31.3 Bacterial cell wall of gram-positive bacteria. NAM = N-acetylmuramic acid; NAG = N-acetylglucosamine; PEP = cross-linking peptide.

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 Î²-lactam antibiotic. In general, gram-positive microorganisms have cell walls that are easily traversed by penicillins and, therefore, in the absence of resistance are susceptible to these drugs. Gram-negative microorganisms have an outer lipopolysaccharide membrane (envelope) 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. [Note: Pseudomonas aeruginosa lacks porins, making these organisms intrinsically resistant to many antimicrobial agents.]

1. **Natural penicillins:** These penicillins, which include those classified as antistaphylococcal, are obtained from fermentations of the mold Penicillium chrysogenum. Other penicillins, such as *ampicillin*, are called semisynthetic, because the different R groups are attached chemically to the 6-aminopenicillanic acid nucleus

obtained from fermentation broths of the mold. *Penicillin* [pen-i-SILL-in] *G* (*benzylpenicillin*) is the cornerstone of therapy for infections caused by a number of gram-positive and gram-negative cocci, gram-positive bacilli, and spirochetes (Figure 31.4). *Penicillin G* is susceptible to inactivation by Î²-lactamases (penicillinases). *Penicillin V* has a spectrum similar to that of penicillin G, but it is not used for treatment of bacteremia because of its higher minimum bactericidal concentration (the minimum amount of the drug needed to eliminate the infection; see p. 343). *Penicillin V* is more acid-stable than *penicillin G.* It is often employed orally in the treatment of infections, where it is effective against some anaerobic organisms.

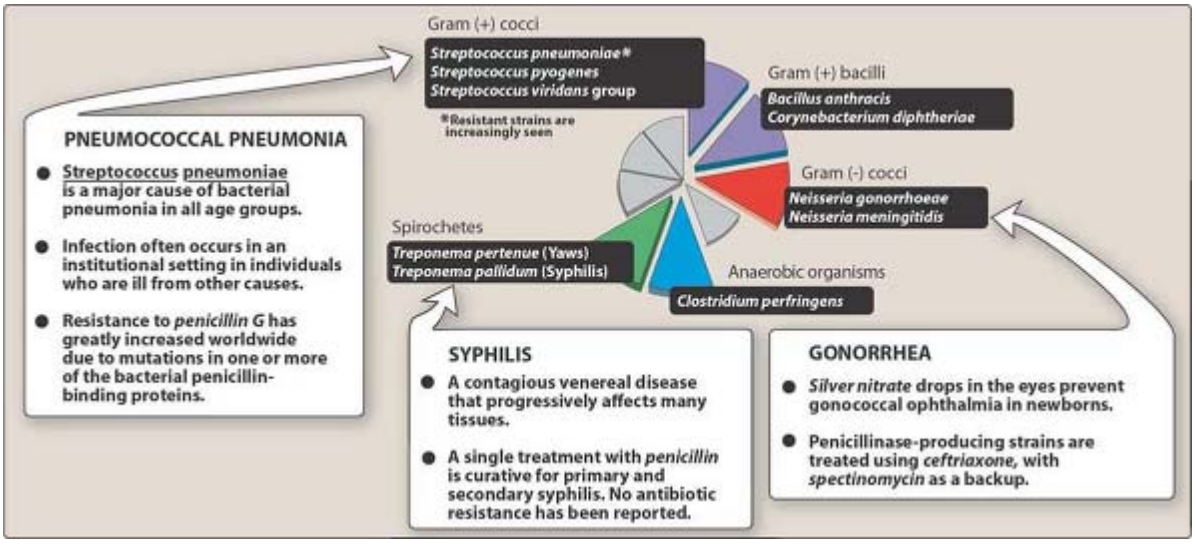


Figure 31.4 Typical therapeutic applications of *penicillin G*.

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 penicillinase-resistant penicillins. Their use is restricted to the treatment of infections caused by penicillinase-producing staphylococci. [Note: Because of its toxicity, *methicillin* is not used clinically except to identify resistant strains of S. aureus]. Currently a serious source of nosocomial (hospital-acquired) infections, MRSA is usually susceptible to *vancomycin* and, rarely, to *ciprofloxacin* or *rifampin.*

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. They are therefore referred to as extended-spectrum penicillins (Figure 31.5A). *Ampicillin* is the drug of choice for the gram-positive bacillus Listeria monocytogenes. These agents are also widely used in the treatment of respiratory infections, and *amoxicillin* is employed prophylactically by dentists for patients with abnormal heart valves who are to undergo extensive oral surgery. Resistance to these antibiotics is now a major clinical problem because of inactivation by plasmid-mediated penicillinase. [Note: Escherichia coli and Haemophilus influenzae are frequently resistant.] Formulation with a Î²-lactamase inhibitor, such as *clavulanic acid* or *sulbactam*, protects *amoxicillin* or *ampicillin*, respectively, from enzymatic hydrolysis and extends their antimicrobial spectrum.

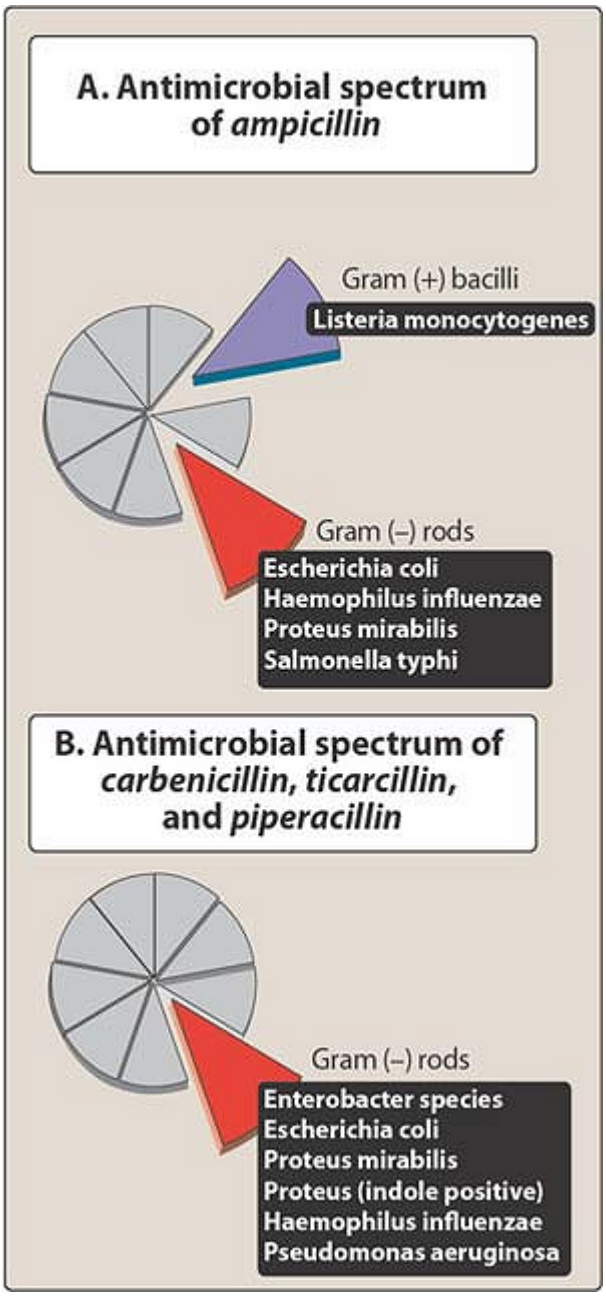


Figure 31.5 Typical therapeutic applications of *ampicillin* (A) and the antipseudomonal penicillins (B).

4. **Antipseudomonal penicillins:** *Carbenicillin* [kar-ben-i-SILL-in], *ticarcillin* [tye-kar-SILL-in], and *piperacillin* [pip-er-a-SILL-in] are called antipseudomonal penicillins because of their activity against P. aeruginosa (Figure 31.5B). *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. (Figure 31.6 summarizes of the stability of the penicillins to acid or the action of penicillinase.)

5. **Penicillins and aminoglycosides:** The antibacterial effects of all the Î²-lactam antibiotics are synergistic with the aminoglycosides. Because cell wall synthesis inhibitors alter the permeability of bacterial cells, these drugs

can facilitate the entry of other antibiotics (such as aminoglycosides) that might not ordinarily gain access to intracellular target sites. This can result in enhanced antimicrobial activity. [Note: Although the combination of a penicillin plus an aminoglycoside is used clinically, these drug types should never be placed in the same infusion fluid, because on prolonged contact, the positively charged aminoglycosides form an inactive complex with the negatively charged penicillins.]

C. Resistance

Natural resistance to the penicillins occurs in organisms that either lack a peptidoglycan cell wall (for example, mycoplasma) or have cell walls that are impermeable to the drugs. Acquired resistance to the penicillins by plasmid transfer has become a significant clinical problem, because an organism may become resistant to several antibiotics at the same

time due to acquisition of a plasmid that encodes resistance to multiple agents. Multiplication of such an organism will lead to increased dissemination of the resistance genes. By obtaining a resistance plasmid, bacteria may acquire one or more of the following properties, thus allowing it to withstand Î²-lactam antibiotics.

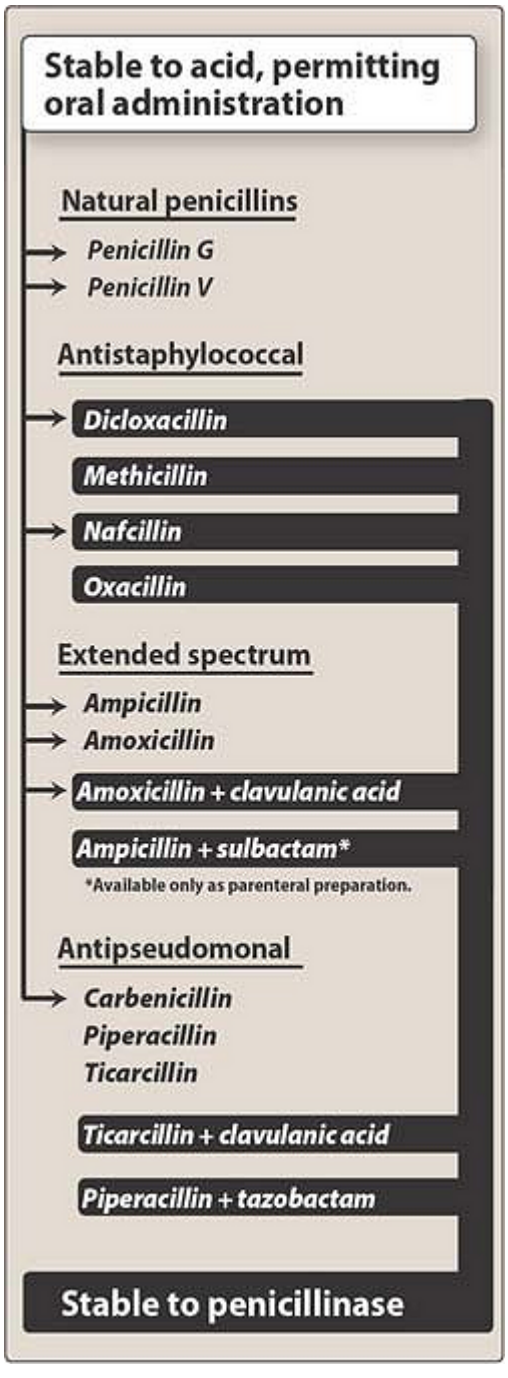


Figure 31.6 Stability of the penicillins to acid or the action of penicillinase.

1. **Î²-Lactamase activity:** This family of enzymes hydrolyzes the cyclic amide bond of the Î²-lactam ring, which results in loss of bactericidal activity (see Figure 31.2). They are the major cause of resistance to the penicillins and are an increasing problem. Î²-Lactamases are either constitutive or, more commonly, are acquired by the transfer of plasmids. Some of the Î²-lactam antibiotics are poor substrates for Î²-lactamases and resist cleavage, thus retaining their activity against Î²-lactamase producing organisms. [Note: Certain organisms may have chromosome-associated Î²-lactamases that are inducible by Î²-lactam antibiotics (for example, *cefoxitin*).] Gram-positive organisms secrete Î²-lactamases extracellularly, whereas gram-negative bacteria confine the

enzymes in the periplasmic space between the inner and outer membranes.

2. **Decreased permeability to the drug:** Decreased penetration of the antibiotic through the outer cell membrane prevents the drug from reaching the target PBPs. The presence of an efflux pump can also reduce the amount of intracellular drug.

3. **Altered PBPs:** Modified PBPs have a lower affinity for Î²-lactam antibiotics, requiring clinically unattainable concentrations of the drug to effect inhibition of bacterial growth. This mechanism may explain MRSA, although it does not explain its resistance to non-Î²-lactam antibiotics like *erythromycin*, to which they are also refractory.

D. Pharmacokinetics

1. **Administration:** The route of administration of a Î²-lactam antibiotic is determined by the stability of the drug to gastric acid and by the severity of the infection.

   a. **Routes of administration:** *Ticarcillin, carbenicillin, piperacillin*, and the combinations of *ampicillin* with *sulbactam, ticarcillin* with *clavulanic acid*, and *piperacillin* with *tazobactam,* must be administered intravenously (IV) or intramuscularly (IM). *Penicillin V, amoxicillin, amoxicillin* combined with *clavulanic acid*, and the indanyl ester of *carbenicillin* (for treatment of urinary tract infections) are available only as oral preparations. Others are effective by the oral, IV, or IM routes (see Figure 31.6).

   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. However, *amoxicillin* is almost completely absorbed. Consequently, it is not appropriate therapy for the treatment of shigella- or salmonella-derived enteritis, because therapeutically effective levels do not

reach the organisms in the intestinal crypts. Absorption of all the penicillinase-resistant penicillins is decreased by food in the stomach, because gastric emptying time is lengthened, and the drugs are destroyed in the acidic environment. Therefore, they must be administered 30 to 60 minutes before meals or 2 to 3 hours postprandially. Other penicillins are less affected by food.

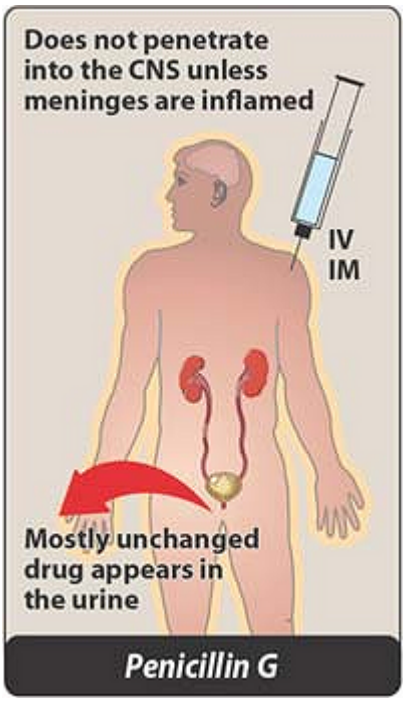


Figure 31.7 Administration and fate of *penicillin*.

3. **Distribution:** The Î²-lactam antibiotics distribute well throughout the body. All the penicillins cross the placental barrier, but none has been shown to be teratogenic. However, penetration into certain sites, such as bone or cerebrospinal fluid (CSF), is insufficient for therapy unless these sites are inflamed (Figures 31.7 and 31.8). [Note: During the acute phase of infection, the inflamed meninges are more permeable to the penicillins, resulting in an increased ratio of the amount of drug in the central nervous system compared to the amount in the serum. As the infection abates, inflammation subsides, and permeability barriers are reestablished.] *Penicillin* levels in the prostate are insufficient to be effective against infections.

4. **Metabolism:** Host metabolism of the Î²-lactam antibiotics is usually insignificant, but some metabolism of *penicillin G* has been shown to 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. Thus, the half-life of *penicillin G* can increase from a normal of between 30 minutes and 1 hour, to 10 hours in individuals with renal failure. *Probenecid* inhibits the secretion of penicillins by competing for active tubular secretion via the organic acid transporter and, thus, can increase blood levels. *Nafcillin* is eliminated primarily through the biliary route. [Note: This is also the preferential route for the acylureido penicillins in cases of renal failure.] The penicillins are also excreted into breast milk.

E. Adverse reactions

Penicillins are among the safest drugs, and blood levels are not monitored. However, the following adverse reactions may occur (Figure 31.9).

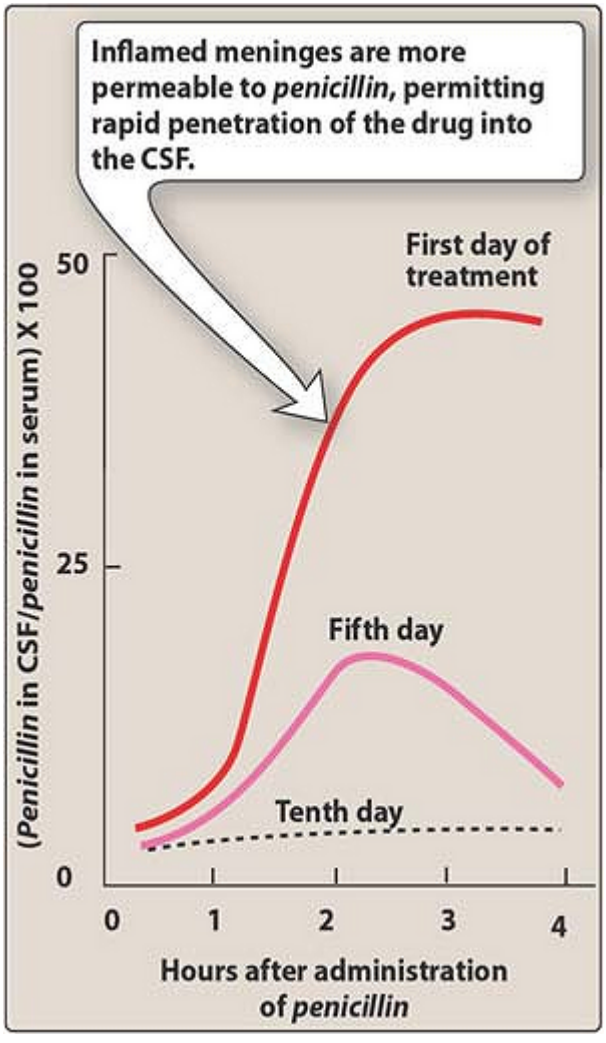


Figure 31.8 Enhanced penetration of *penicillin* into the cerebral spinal fluid (CSF) during inflammation.

1. **Hypersensitivity:** This is the most important adverse effect of the penicillins. The major antigenic determinant of penicillin hypersensitivity is its metabolite, penicilloic acid, which reacts with proteins and serves as a hapten to cause an immune reaction. Approximately five percent of patients have some kind of reaction, ranging from maculopapular rash (the most common rash seen with *ampicillin* hypersensitivity) to angioedema (marked swelling of the lips, tongue, and periorbital area) and anaphylaxis. Among patients with mononucleosis who are treated with *ampicillin*, the incidence of maculopapular rash approaches 100 percent. Cross-allergic reactions occur among the Î²-lactam antibiotics.

2. **Diarrhea:** This effect, which is caused by a disruption of the normal balance of intestinal microorganisms, is a common problem. It occurs to a greater extent with those agents that are incompletely

absorbed and have an extended antibacterial spectrum. As with some other antibiotics, pseudomembranous colitis[2] may occur.

3. **Nephritis:** All penicillins, but particularly *methicillin*, have the potential to cause acute interstitial nephritis. [Note: *Methicillin* is therefore no longer available.]

4. **Neurotoxicity:** The penicillins are irritating to neuronal tissue, and they can provoke seizures if injected

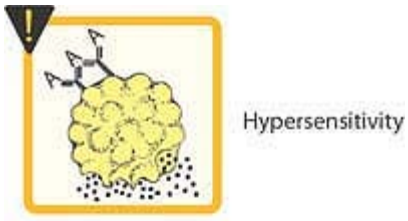
intrathecally or if very high blood levels are reached. Epileptic patients are particularly at risk.

5. **Hematologic toxicities:** Decreased coagulation may be observed with the antipseudomonal penicillins (*carbenicillin* and *ticarcillin*) and, to some extent, with *penicillin G.* It is generally a concern when treating patients who are predisposed to hemorrhage (for example, uremics) or those receiving anticoagulants. Additional toxicities include eosinophilia.

6. **Cation toxicity:** Penicillins are generally administered as the sodium or potassium salt. Toxicities may be caused by the large quantities of sodium or potassium that accompany the penicillin. Sodium excess may result in hypokalemia. This can be avoided by using the most potent antibiotic, which permits lower doses of drug and accompanying cations.

III. Cephalosporins

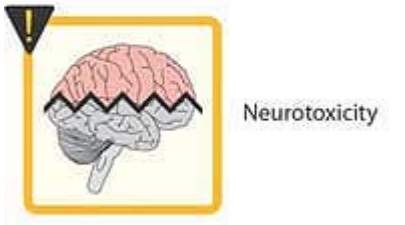
The cephalosporins are Î²-lactam antibiotics that are closely related both structurally and functionally to the penicillins. Most cephalosporins are produced semisynthetically by the chemical attachment of side chains to 7-aminocephalosporanic acid. Cephalosporins have the same mode of action as penicillins, and they are affected by the same resistance mechanisms. However, they tend to be more resistant than the penicillins to certain Î²-lactamases.



Hypersensitivity

Diarrhea

Nephritis



Neurotoxicity

Hematologic toxicities

Cation toxicity

Figure 31.9 Summary of the adverse effects of penicillin.

A. Antibacterial spectrum

Cephalosporins have been classified as first, second, third, or fourth generation, based largely on their bacterial susceptibility patterns and resistance to Î²-lactamases (Figure 31.10). [Note: Cephalosporins are ineffective against MRSA, L. monocytogenes, Clostridium difficile, and the enterococci.]

1. **First generation:** The first-generation cephalosporins act as *penicillin G* substitutes. They are resistant to the staphylococcal penicillinase and also have activity against Proteus mirabilis, E. coli, and Klebsiella pneumoniae (the acronym PEcK has been suggested).

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 (the acronym HENPEcK has been suggested with the second generation's

   increased coverage). [Note: The exception to this generalization is the structurally related cephamycin, *cefoxitin* [sef-OX-i-tin], which has little activity against H. influenzae yet is effective against the anaerobe Bacteroides fragilis [with some resistance occurring per 2007 antimicrobial guidelines.]

3. **Third generation:** These cephalosporins have assumed an important role in the treatment of infectious disease. Although inferior to first-generation cephalosporins in regard to their activity against gram-positive cocci, 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] or *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.

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, being active against streptococci and staphylococci (but only those that are *methicillin*-susceptible). *Cefepime* is also effective against aerobic gram-negative organisms, such as enterobacter, E. coli, K. pneumoniae, P. mirabilis, and P. aeruginosa.

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 penicillinase, cephalosporins may be susceptible to extended-spectrum Î²-lactamases.]

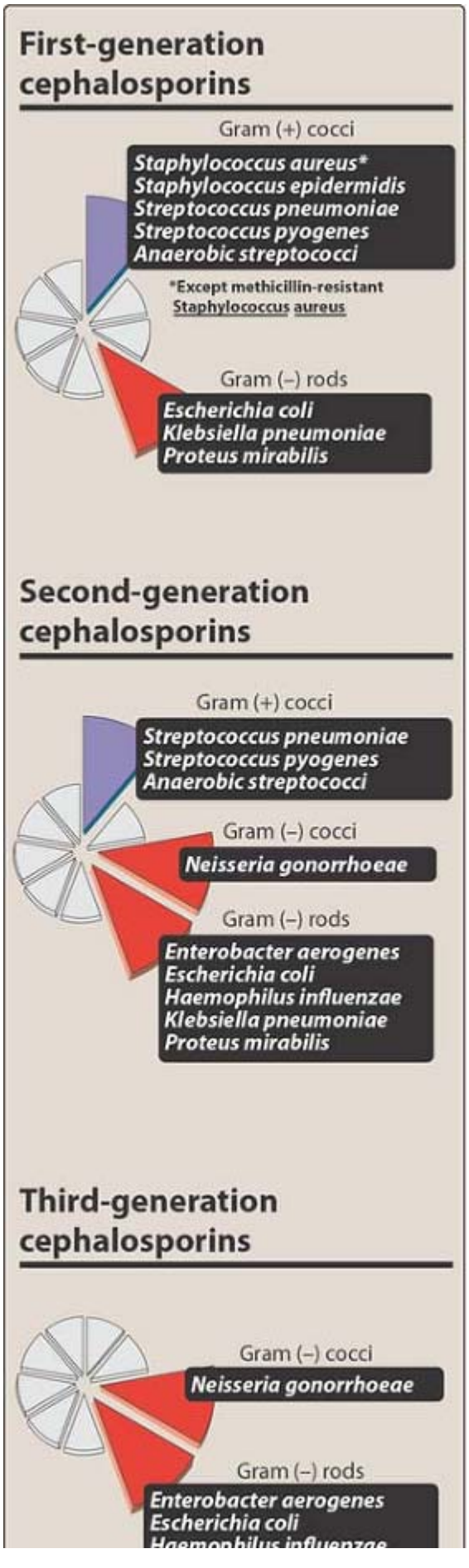

First-generation cephalosporins
Gram (+) cocci
Staphylococcus aureus*
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus pyogenes
Anaerobic streptococci
*Except methicillin-resistant Staphylococcus aureus
Gram (–) rods
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Second-generation cephalosporins
Gram (+) cocci
Streptococcus pneumoniae
Streptococcus pyogenes
Anaerobic streptococci
Gram (–) cocci
Neisseria gonorrhoeae
Gram (–) rods
Enterobacter aerogenes
Escherichia coli
Haemophilus influenzae
Klebsiella pneumoniae
Proteus mirabilis
Third-generation cephalosporins
Gram (–) cocci
Neisseria gonorrhoeae
Gram (–) rods
Enterobacter aerogenes
Escherichia coli

Figure 31.10 Summary of therapeutic applications of cephalosporins.

C. Pharmacokinetics

1. **Administration:** Many of the cephalosporins must be administered IV or IM (Figure 31.11) because of their poor oral absorption. Exceptions are noted in Figure 31.12.
2. **Distribution:** All cephalosporins distribute very well into body fluids. However, adequate therapeutic levels in the CSF, regardless of inflammation, are achieved only with the third-generation cephalosporins. For example, *ceftriaxone* or *cefotaxime* are effective in the treatment of neonatal and childhood meningitis caused by H. influenzae. *Cefazolin* [se-FA-zo-lin] finds application as a single prophylaxis dose prior to surgery because of its 1.8-hour half-life and its activity against penicillinase-producing S. aureus. However, additional intraoperative *cefazolin* doses may be required if the surgical procedure lasts longer than 3 hours. *Cefazolin* is effective for most surgical procedures, including orthopedic surgery because of its ability to penetrate bone. All cephalosporins cross the placenta.
3. **Fate:** Biotransformation of cephalosporins by the host is not clinically important. Elimination occurs through tubular secretion and/or glomerular filtration (see Figure 31.11). Therefore doses must be adjusted in cases of severe renal failure to guard against accumulation and toxicity. *Ceftriaxone* is excreted through the bile into the feces and, therefore, is frequently employed in patients with renal insufficiency.

D. Adverse effects

The cephalosporins produce a number of adverse affects, some of which are unique to particular members of the group.

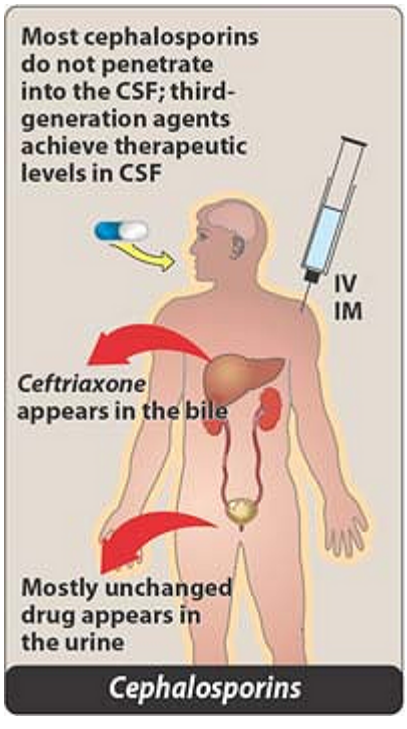


Figure 31.11 Administration and fate of the cephalosporins.

1. **Allergic manifestations:** Patients who have had an anaphylactic response to penicillins should not receive cephalosporins. The cephalosporins should be avoided or used with caution in individuals who are allergic to penicillins (about 5â€“15 percent show cross-sensitivity). In contrast, the incidence of allergic reactions to cephalosporins is one to two percent in patients without a history of allergy to penicillins.

IV. Other Î²-Lactam Antibiotics

A. Carbapenems

Carbapenems are synthetic Î²-lactam antibiotics that differ in structure from the penicillins in that the sulfur atom of the thiazolidine ring (see Figure 31.2) has been externalized and replaced by a carbon atom (Figure 31.13). *Imipenem* [i-mi-PEN-em], *meropenem* [mer-oh-PEN-em] and *ertapenem* [er-ta-PEN-em] are the only drugs of this group currently available. *Imipenem* is compounded with *cilastatin* to protect it from metabolism by renal dehydropeptidase.

1. **Antibacterial spectrum:** *Imipenem/cilastatin* and *meropenem* are the broadest-spectrum Î²-lactam antibiotic preparations currently available (Figure 31.14). *Imipenem* resists hydrolysis by most Î²-lactamases, but not the metallo-Î²-lactamases. The drug plays a role in empiric therapy because it is active against penicillinase-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* has antibacterial activity similar to that of *imipenem*. *Ertapenem* is not an alternative for P. aeruginosa coverage, because most strains exhibit resistance.
2. **Pharmacokinetics:** *Imipenem* and *meropenem* are administered IV and penetrate well into body tissues and fluids, including the CSF when the meninges are inflamed. 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. This allows the drug to be used in the treatment of urinary tract infections. *Meropenem* does not undergo metabolism. *Ertapenem* can be administered via IV or IM injection. [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 Î²-lactams. High levels of *imipenem* may provoke seizures, but *meropenem* is less likely to do so.

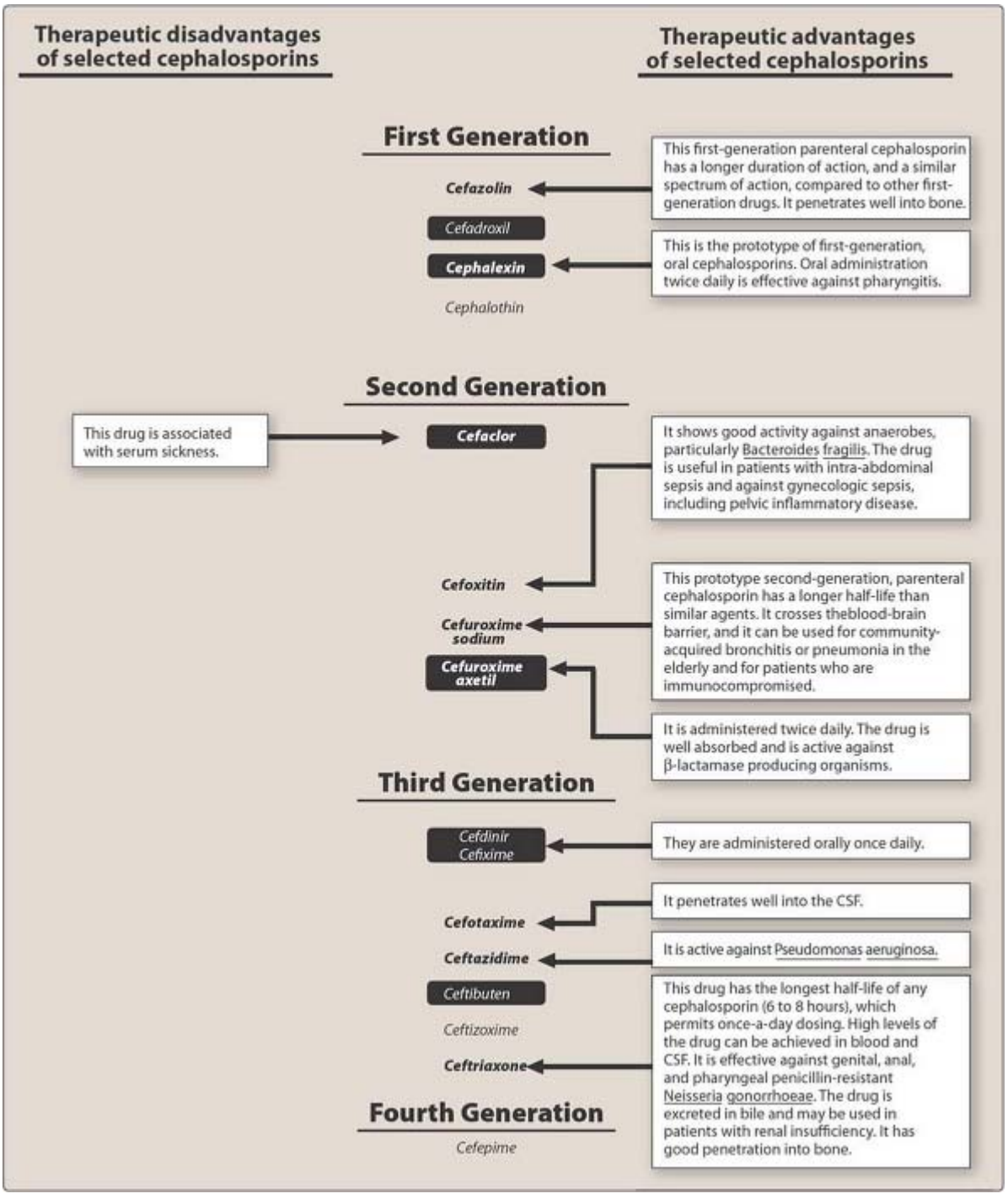


Figure 31.12 Characteristics of some clinically useful cephalosporins. [Note: Drugs that can be administered orally are shown in **reverse type**. More useful drugs shown in **bold**.] CSF = cerebrospinal fluid.

B. Monobactams

The monobactams, which also disrupt bacterial cell wall synthesis, are unique, because the Î²-lactam ring is not fused to another ring (see Figure 31.13). *Aztreonam* [az-TREE-oh-nam], which is the only commercially available

monobactam, has antimicrobial activity directed primarily against the enterobacteriaceae, but it also acts against aerobic gram-negative rods, including P. aeruginosa. It lacks activity against gram-positive organisms and anaerobes. This narrow antimicrobial spectrum precludes its use alone in empiric therapy (see p. 342). *Aztreonam* is resistant to the action of Î²-lactamases. It is administered either IV or IM and is excreted in the urine. It 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 Î²-lactams. Thus, this drug may offer a safe alternative for treating patients who are allergic to penicillins and/or cephalosporins.

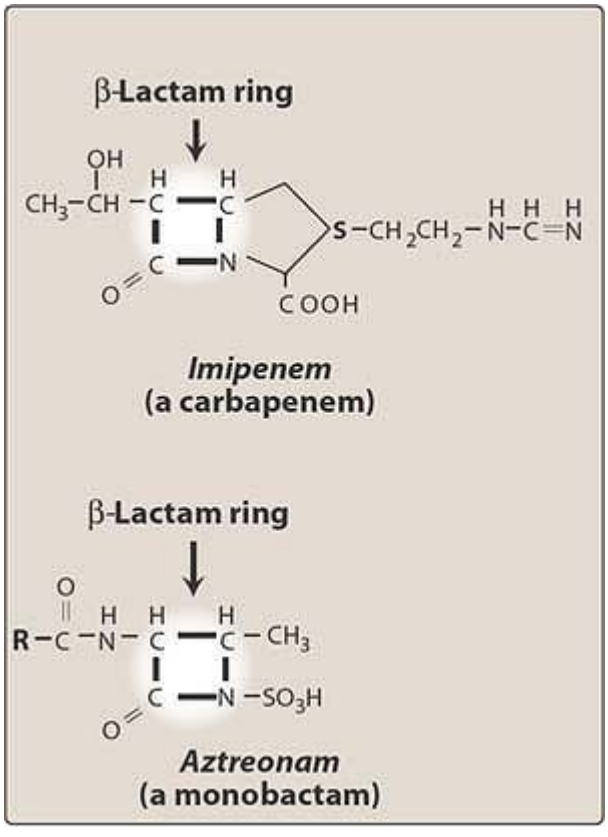


Figure 31.13 Structural features of *imipenem* and *aztreonam*.

V. Î²-Lactamase Inhibitors

Hydrolysis of the Î²-lactam ring, either by enzymatic cleavage with a Î²-lactamase or by acid, destroys the antimicrobial activity of a Î²-lactam antibiotic. Î²-Lactamase inhibitors, such as *clavulanic* [cla-vue-LAN-ick] *acid, sulbactam* [sul-BACK-tam], and *tazobactam* [ta-zoh-BACK-tam], contain a Î²-lactam ring but, by themselves, do not have significant antibacterial activity. Instead, they bind to and inactivate Î²-lactamases, thereby protecting the antibiotics that are normally substrates for these enzymes. The Î²-lactamase inhibitors are therefore formulated in combination with Î²-lactamase sensitive antibiotics. For example, Figure 31.15 shows the effect of *clavulanic acid* and *amoxicillin* on the growth of Î²-lactamase producing E. coli. [Note: *Clavulanic acid* alone is nearly devoid of antibacterial activity.]

VI. Vancomycin

Vancomycin [van-koe-MYE-sin] is a tricyclic glycopeptide that has become increasingly important because of its

effectiveness against multiple drug-resistant organisms, such as MRSA and enterococci. The medical community is presently concerned with emergence of *vancomycin* resistance in these organisms. [Note: *Bacitracin* [bass-i-TRAY-sin] is a mixture of polypeptides that also inhibits bacterial cell wall synthesis. It is active against a wide variety of gram-positive organisms. Its use is restricted to topical application because of its potential for nephrotoxicity with systemic use.]

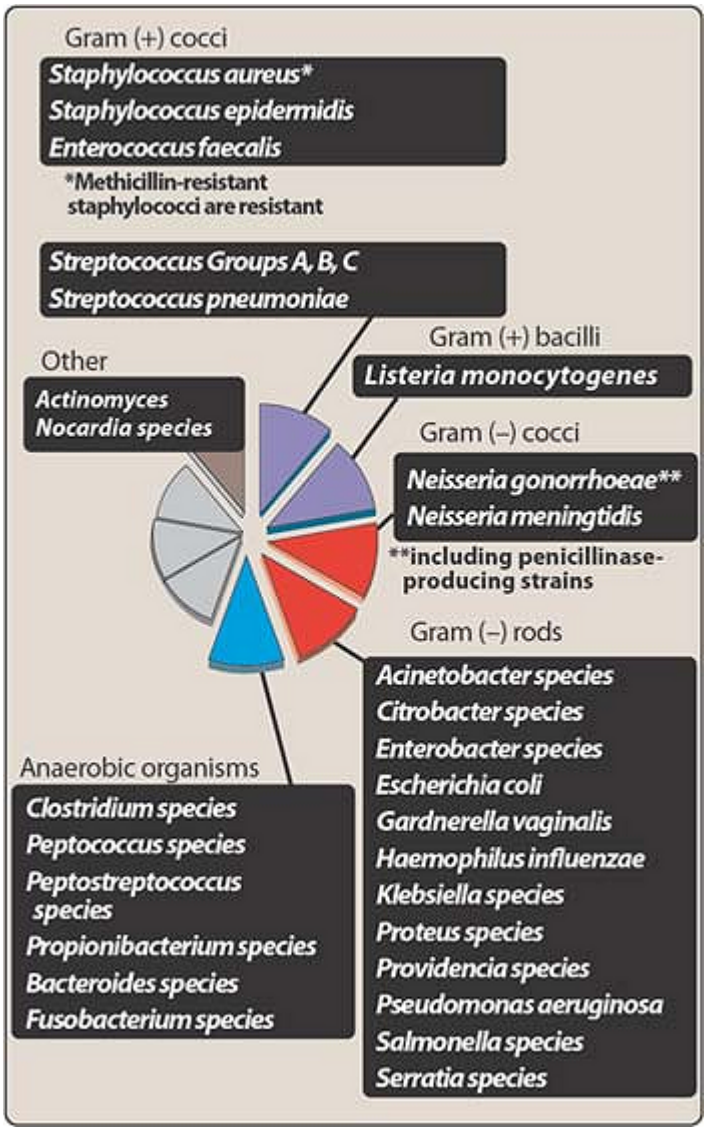


Figure 31.14 Antimicrobial spectrum of *imipenem*.

A. Mode of action

Vancomycin inhibits synthesis of bacterial cell wall phospholipids as well as peptidoglycan polymerization by binding to the D-Ala-D-Ala side chain of the precursor pentapeptide. This prevents the transglycosylation step in peptidoglycan polymerization, thus weakening the cell wall and damaging the underlying cell membrane.

B. Antibacterial spectrum

Vancomycin is effective primarily against gram-positive organisms (Figure 31.16). It has been lifesaving in the

treatment of MRSA and *methicillin*-resistant Staphylococcus epidermidis (MRSE) infections as well as enterococcal infections. 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 Î²-lactam resistant, gram-positive microorganisms or for patients with gram-positive infections who have a serious allergy to the Î²-lactams. Oral *vancomycin* is limited to treatment for potentially life-threatening, antibiotic-associated colitis due to C. difficile or staphylococci. *Vancomycin* is used in individuals with prosthetic heart valves and in patients undergoing implantation with prosthetic devices. [Note: The latter is of particular concern in those hospitals where there is a problem with MRSA or MRSE. *Daptomycin*, a cyclic lipopeptide antibiotic, and two protein synthesis inhibitorsâ€"*quinopristin/dalfopristin* and *linezolid*â€"are currently available for the treatment of *vancomycin*-resistant organisms.] *Vancomycin* acts synergistically with the aminoglycosides, and this combination can be used in the treatment of enterococcal endocarditis.

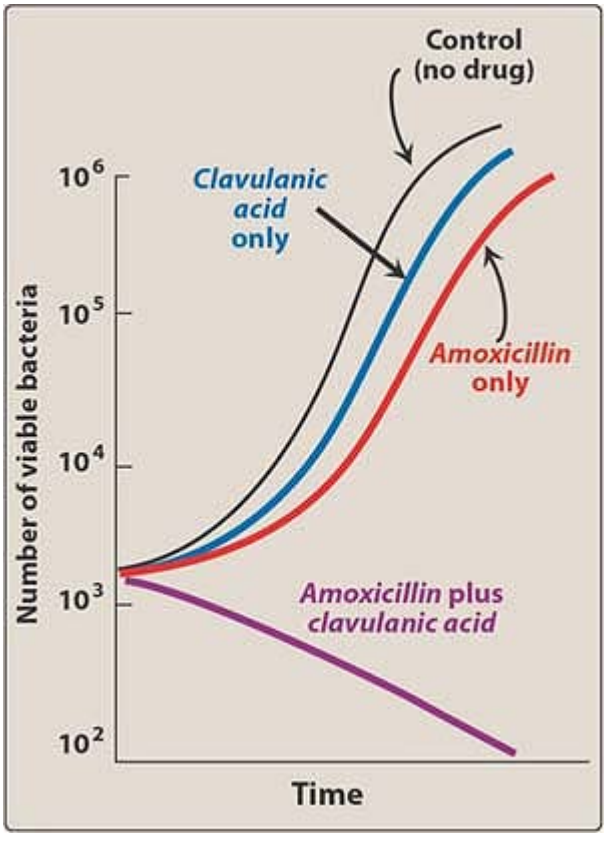


Figure 31.15 The in vitro growth of Escherichia coli in the presence of *amoxicillin*, with and without *clavulanic* acid.

C. Resistance

Vancomycin resistance can be caused by plasmid-mediated changes in permeability to the drug or by decreased binding of *vancomycin* to receptor molecules. [Note: An example of the latter is caused by the replacement of a D-Ala by D-lactate in resistant organisms.]

D. Pharmacokinetics

Slow IV infusion (60â€“90 minutes) is employed for treatment of systemic infections or for prophylaxis. Because *vancomycin* is not absorbed after oral administration, this route is employed only for the treatment of antibiotic-induced colitis due to C. difficile when *metronidazole* has proven to be ineffective. Inflammation allows penetration into the meninges. However, it is often necessary to combine *vancomycin* with other antibiotics, such as *ceftriaxone* for synergistic effects when treating menigits. Metabolism of the drug is minimal, and 90 to 100 percent is excreted by glomerular filtration (Figure 31.17). [Note: Dosage must be adjusted in renal failure, because the drug will accumulate. The normal half-life of *vancomycin* is 6 to 10 hours, compared to over 200 hours in end-stage renal disease.]

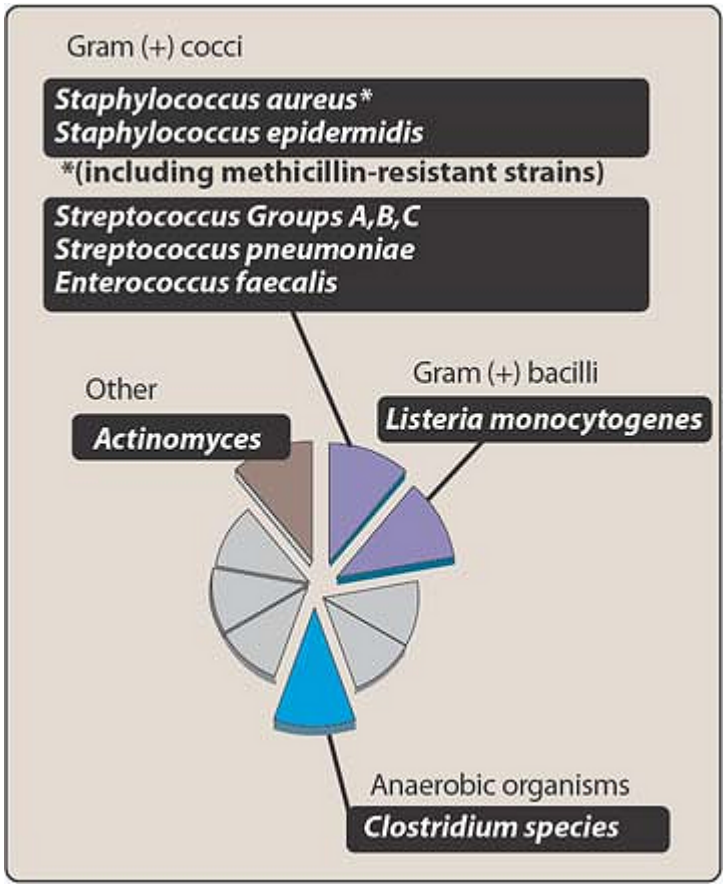


Figure 31.16 Antimicrobial spectrum of *vancomycin*.

E. Adverse effects

Side effects are a serious problem with *vancomycin* and include fever, chills, and/or phlebitis at the infusion site. Flushing (â€œred man syndromeâ€) and shock results from histamine release associated with a rapid infusion. If an infusion-related reaction occurs, slow the infusion rate to administer vancomycin over 2 hours, increase the dilution volume, or pretreat with an antihistamine 1 hour prior to administration. Additionally, reactions can be treated with antihistamines and steroids (Figure 31.18). Dose-related hearing loss has occurred in patients with renal failure who accumulate the drug. Ototoxicity and nephrotoxicity are more common when *vancomycin* is administered with another drug (for example, an aminoglycoside) that can also produce these effects.

VII. Daptomycin

Daptomycin [DAP-toe-mye-sin] is a 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).

A. Mode of action

Upon binding to the bacterial cytoplasmic membrane, *daptomycin* induces rapid depolarization of the membrane, thus disrupting multiple aspects of membrane function and inhibiting intracellular synthesis of DNA, RNA, and protein. *Daptomycin* is bactericidal, and bacterial killing is concentration dependent.

B. Antibacterial spectrum

Daptomycin has a spectrum of activity limited to gram-positive organisms, which includes methicillin-susceptible and methicillin-resistant S. aureus, penicillin-resistant Streptococcus pneumoniae, Streptococcus pyogenes, Corynebacterium jeikeium, E. faecalis, and E. faecium (including VRE). *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 is not indicated in the treatment of pneumonia.

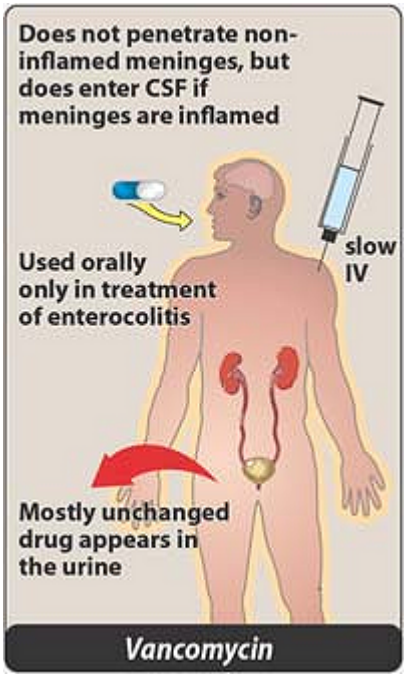


Figure 31.17 Administration and fate of *vancomycin*.

C. Pharmacokinetics

Daptomycin is 90 to 95 percent protein bound and does not appear to undergo hepatic metabolism; however, the dosing interval needs to be adjusted in patients with renal impairment (creatinine clearance less than 30 mL/minute). In skin and soft tissue infections, *daptomycin* is administered at 4 mg/kg IV daily via a 30-minute infusion. Nevertheless, when treating bacteremia and endocarditis, dose should be increased to 6 mg/kg.

D. Adverse effects

The most common adverse effects reported in clinical trials included constipation, nausea, headache, and insomnia. Increased hepatic transaminases and also elevations in creatin phosphokinases occurred, suggesting weekly monitoring while the patient is receiving *daptomycin*. Although no clinically significant interactions have been identified, it is recommended to temporarily discontinue 3-hydroxy-3-methylglutary coenzyme A reductase inhibitors (statins) while receiving *daptomycin* due to the potential for additive muscle toxicity.

Figure 31.18 Some adverse effects of *vancomycin*.

Study Questions

Choose the ONE best answer

31.1 An elderly diabetic patient is admitted to the hospital with pneumonia. The sputum culture stains for a

gram-negative rod. The patient is started on IV ampicillin. Two days later, the patient is not improving, and the microbiology laboratory reports the organism to be a Î²-lactamase producing H. influenzae. What course of treatment is indicated?

A. Continue with the IV ampicillin.

B. Switch to IV cefotaxime.

C. Switch to oral vancomycin.

D. Add gentamicin to the ampicillin therapy.

View Answer

31.2 A 70-year-old alcoholic male with poor dental hygiene is to have his remaining teeth extracted for subsequent dentures. He has mitral valve stenosis with mild cardiac insufficiency and is being treated with captopril, digoxin, and furosemide. The dentist decides that his medical history warrants prophylactic antibiotic therapy prior to the procedure and prescribes which of the following drugs?

A. Vancomycin.

B. Amoxicillin.

C. Tetracycline.

D. Cotrimoxazole.

E. Imipenem.

View Answer

31.3 A patient with degenerative joint disease is to undergo insertion of a hip prosthesis. To avoid complications due to postoperative infection, the surgeon will pretreat this patient with an antibiotic. This hospital has a significant problem with MRSA. Which of the following antibiotics should the surgeon select?

A. Ampicillin.

B. Imipenem/cilastatin.

C. Gentamicin/piperacillin.

D. Vancomycin.

E. Cefazolin

View Answer

31.4 A 25-year-old male returns home from a holiday in the Far East and complains of 3 days of dysuria and a purulent urethral discharge. You diagnose this to be a case of gonorrhea. Which of the following is appropriate treatment?

A. Ceftriaxone IM.

B. Penicillin G IM.

C. Gentamicin IM.

D. Piperacillin/tazobactam IV.

E. Vancomycin IV.

View Answer

Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
Title: *Lippincott's Illustrated Reviews: Pharmacology, 4th Edition*

Chapter 32

Protein SynthesisInhibitors

I. Overview

A number of antibiotics exert their antimicrobial effects by targeting the bacterial ribosome, which has components that differ structurally from those of the mammalian cytoplasmic ribosome. In general, the bacterial ribosome is smaller (70S) than the mammalian ribosome (80S) and is composed of 50S and 30S subunits (as compared to 60S and 40S subunits). The mammalian mitochondrial ribosome, however, more closely resembles the bacterial ribosome. Thus, although drugs that interact with the bacterial target usually spare the host cells, high levels of drugs such as *chloramphenicol* or the tetracyclines may cause toxic effects as a result of interaction with the host mitochondrial ribosomes. Figure 32.1 lists the drugs discussed in this chapter.

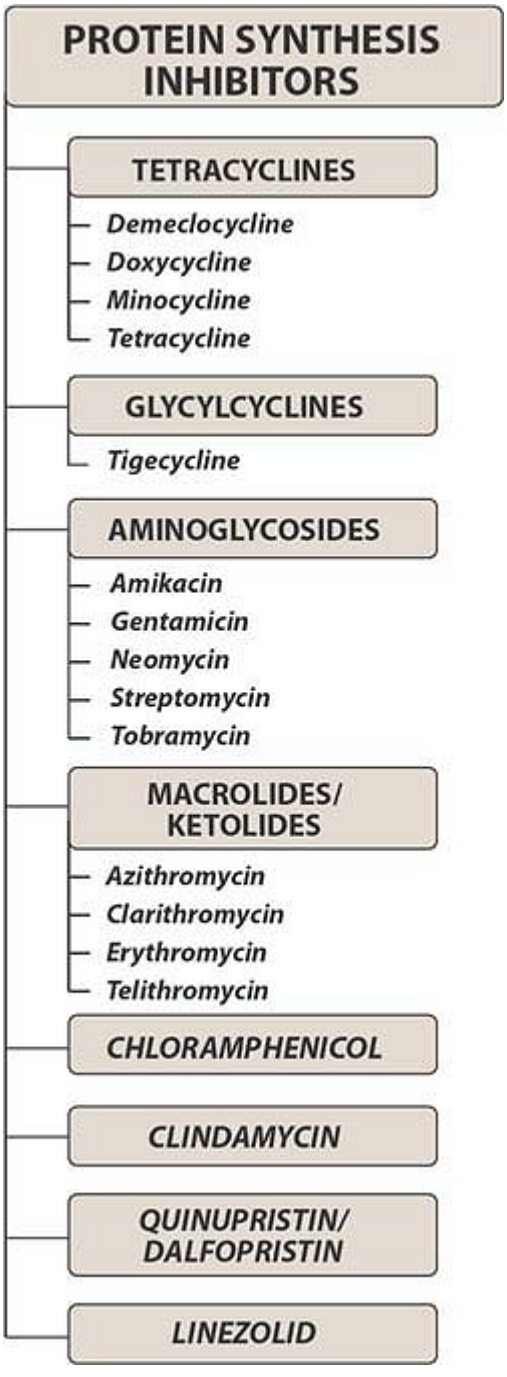


Figure 32.1 Summary of protein synthesis inhibitors.

II. Tetracyclines

The tetracyclines are a group of closely related compounds that, as the name implies, consist of four fused rings with a system of conjugated double bonds. Substitutions on these rings are responsible for variation in the drugs' individual pharmacokinetics, which cause small differences in their clinical efficacy.

A. Mechanism of action

Entry of these agents into susceptible organisms is mediated both by passive diffusion and by an energy-dependent transport protein mechanism unique to the bacterial inner cytoplasmic membrane. Nonresistant strains concentrate the tetracyclines intracellularly. The drug binds reversibly to the 30S subunit of the bacterial ribosome, thereby blocking access of the amino acyl-tRNA to the mRNA-ribosome complex at the acceptor site. By this mechanism, bacterial protein synthesis is inhibited (Figure 32.2).

B. Antibacterial spectrum

As broad-spectrum, bacteriostatic antibiotics, the tetracyclines are effective against gram-positive and gram-negative bacteria as well as against organisms other than bacteria. Tetracyclines are the drugs of choice for infections such as those shown in Figure 32.3.

C. Resistance

Widespread resistance to the tetracyclines limits their clinical use. The most commonly encountered, naturally occurring resistance

(â€œRâ€) factor confers an inability of the organism to accumulate the drug, thus producing resistance. This is accomplished by Mg^{2+}-dependent, active efflux of the drug, mediated by the plasmid-encoded resistance protein, TetA. Other less important mechanisms of bacterial resistance to tetracyclines include enzymatic inactivation of the drug and production of bacterial proteins that prevent tetracyclines from binding to the ribosome. Any organism resistant to one tetracycline is resistant to all. The majority of penicillinase-producing staphylococci are now insensitive to tetracyclines.

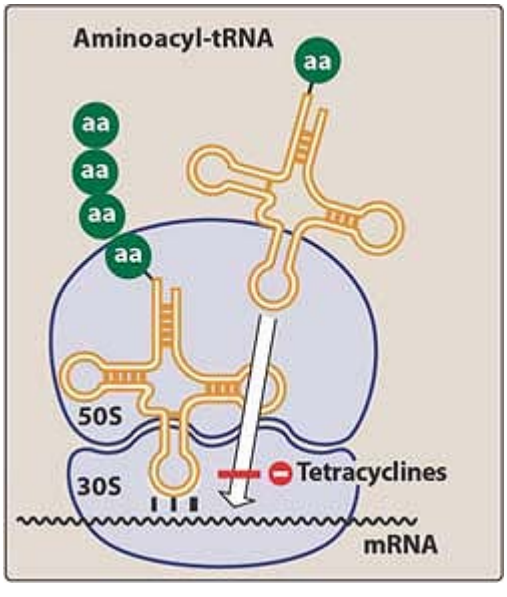


Figure 32.2 Tetracyclines binds to the 30S ribosomal subunit, thus preventing the binding of aminoacyl-tRNA to the ribosome. aa = amino acid.

D. Pharmacokinetics

1. **Absorption:** All tetracyclines are adequately but incompletely absorbed after oral ingestion (Figure 32.4). However, taking these drugs concomitantly with dairy foods in the diet decreases absorption due to the formation of nonabsorbable chelates of the tetracyclines with calcium ions. Nonabsorbable chelates are also

formed with other divalent and trivalent cations (for example, those found in magnesium and aluminum antacids and in iron preparations). [Note: This presents a problem if a patient self-treats the epigastric upsets caused by tetracycline ingestion with antacids (Figure 32.5).] *Doxycycline* [dox-i-SYE-kleen] and *minocycline* [min-oh-SYE-kleen] are almost totally absorbed on oral administration. Currently, *doxycycline* is the preferred tetracycline for parenteral administration.

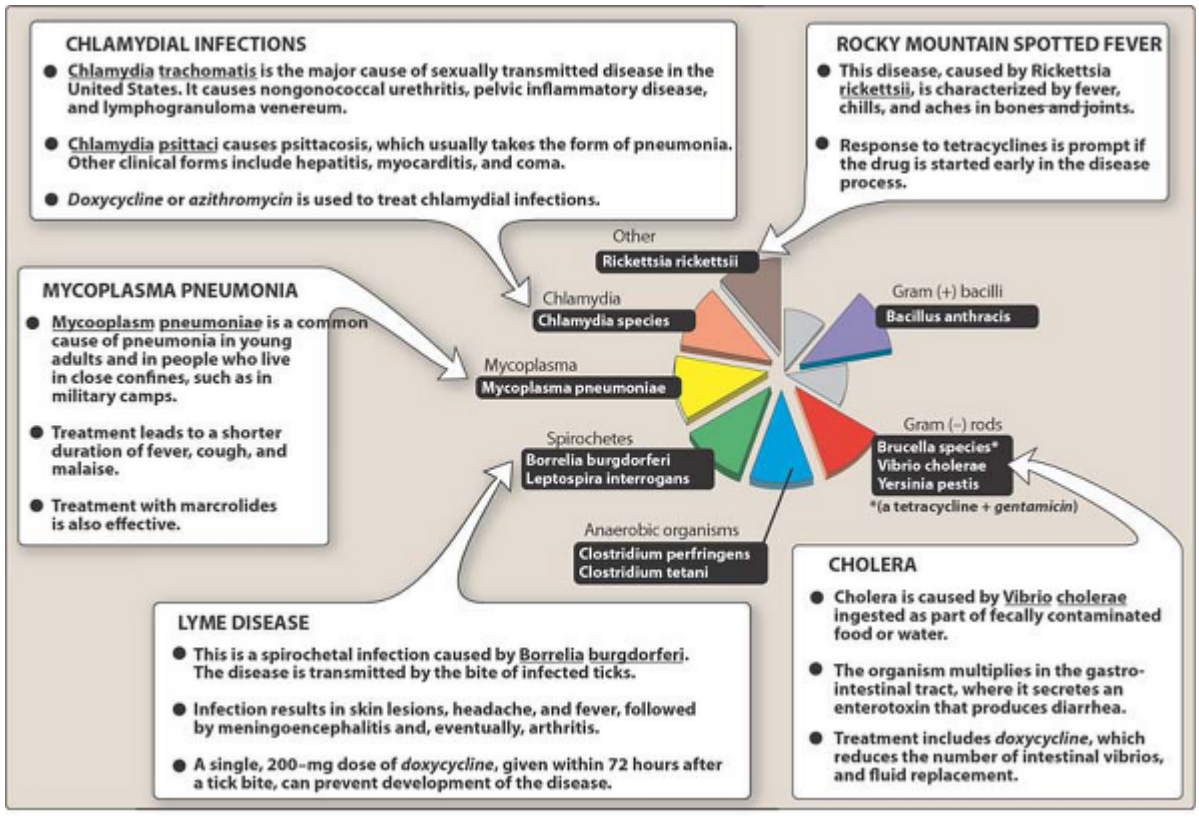


Figure 32.3 Typical therapeutic applications of tetracyclines.

2. **Distribution:** The tetracyclines concentrate in the liver, kidney, spleen, and skin, and they bind to tissues undergoing calcification (for example, teeth and bones) or to tumors that have a high calcium content (for example, gastric carcinoma). Penetration into most body fluids is adequate. Although all tetracyclines enter the cerebrospinal fluid (CSF), levels are insufficient for therapeutic efficacy, except for *minocycline*. *Minocycline* enters the brain in the absence of inflammation and also appears in tears and saliva. Although useful in eradicating the meningococcal carrier state, *minocycline* is not effective for central nervous system infections. All tetracyclines cross the placental barrier and concentrate in fetal bones and dentition.

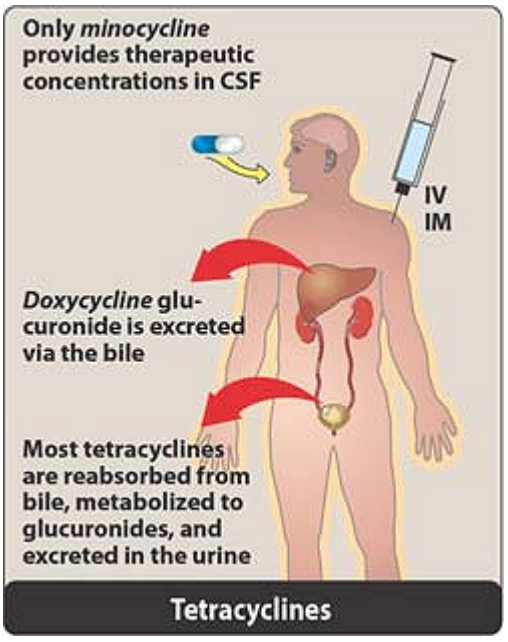


Figure 32.4 Administration and fate of tetracyclines.

3. **Fate:** All the tetracyclines concentrate in the liver, where they are, in part, metabolized and conjugated to form soluble glucuronides. The parent drug and/or its metabolites are secreted into the bile. Most tetracyclines are reabsorbed in the intestine via the enterohepatic circulation and enter the urine by glomerular filtration. Obstruction of the bile duct and hepatic or renal dysfunction can increase their half-lives. Unlike other tetracyclines, *doxycycline* can be employed for treating infections in renally compromised patients, because it is preferentially excreted via the bile into the feces. [Note: Tetracyclines are also excreted in breast milk.]

E. Adverse effects

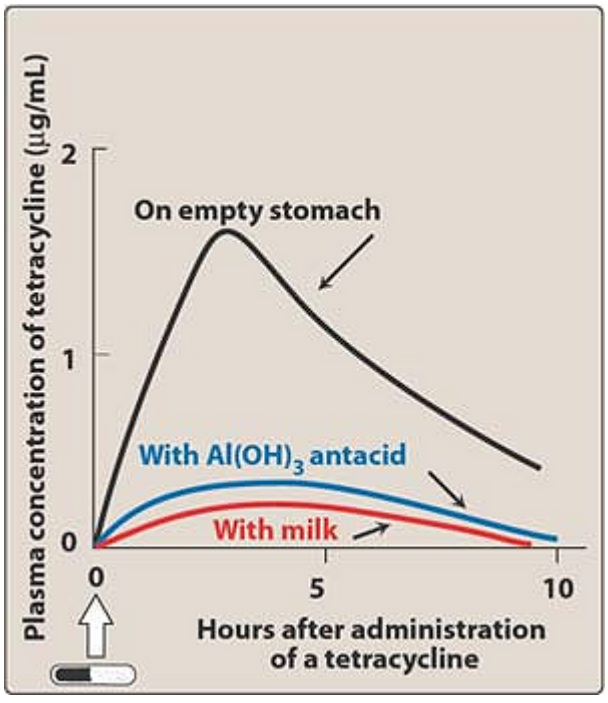


Figure 32.5 Effect of antacids and milk on the absorption of tetracyclines.

1. **Gastric discomfort:** Epigastric distress commonly results from irritation of the gastric mucosa (Figure 32.6) and is often responsible for noncompliance in patients treated with these drugs. The discomfort can be controlled if the drug is taken with foods other than dairy products.
2. **Effects on calcified tissues:** Deposition in the bone and primary dentition occurs during calcification in growing children. This causes discoloration and hypoplasia of the teeth and a temporary stunting of growth.
3. **Fatal hepatotoxicity:** This side effect has been known to occur in pregnant women who received high doses of tetracyclines, especially if they were experiencing pyelonephritis.
4. **Phototoxicity:** Phototoxicity, such as severe sunburn, occurs when a patient receiving a tetracycline is exposed to sun or ultraviolet rays. This toxicity is encountered most frequently with *tetracycline* [tet-rah-SYE-kleen], *doxycycline*, and *demeclocycline* [dem-e-kloe-SYE-kleen].
5. **Vestibular problems:** These side effects (for example, dizziness, nausea, and vomiting) occur particularly with *minocycline*, which concentrates in the endolymph of the ear and affects function. *Doxycycline* may also cause vestibular effects.
6. **Pseudotumor cerebri:** Benign, intracranial hypertension characterized by headache and blurred vision may occur rarely in adults. Although discontinuation of the drug reverses this condition, it is not clear whether permanent sequelae may occur.
7. **Superinfections:** Overgrowths of Candida (for example, in the vagina) or of resistant staphylococci (in the intestine) may occur. Pseudomembranous colitis due to an overgrowth of Clostridium difficile has also been reported.

8. **Contraindications:** Renally impaired patients should not be treated with any of the tetracyclines except *doxycycline.* Accumulation of tetracyclines may aggravate preexisting azotemia (a higher-than-normal level of

urea or other nitrogen-containing compounds in the blood)by interfering with protein synthesis, thus promoting amino acid degradation. The tetracyclines should not be employed in pregnant or breast-feeding women or in children less than 8 years of age.

III. Glycylcyclines

Tigecycline [tye-ge-SYE-kleen] is the first available member of a new class of antimicrobial agents called glycylcyclines. *Tigecycline*, a derivative of *minocycline*, is structurally similar to the tetracyclines and has a broad-spectrum activity against multidrug-resistant gram-positive pathogens, some gram-negative organisms, and anaerobic organisms. *Tigecycline* is indicated for treatment of complicated skin and soft tissue infections as well as complicated intra-abdominal infections.

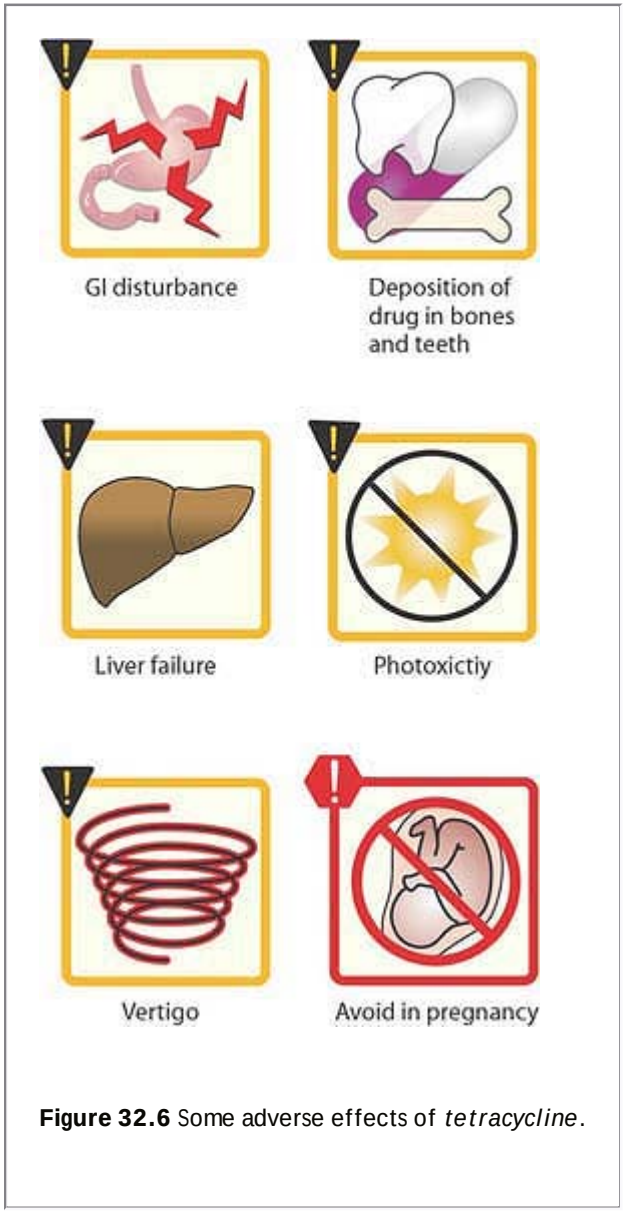


Figure 32.6 Some adverse effects of *tetracycline*.

A. Mechanism of action

Tigecycline exhibits bacteriostatic action by reversibly binding to the 30S ribosomal subunit and inhibiting protein translation.

B. Antibacterial spectrum

Tigecycline exhibits expanded broad-spectrum activity that includes methicillin-resistant staphylococci, multidrug-resistant Streptococcus pneumoniae, and other susceptible strains of streptococcal species, *vancomycin*-resistant enterococci, extended-spectrum Î²-lactamase producing gram-negative bacteria, Acinetobacter baumannii, and many anaerobic organisms. However, *tigecycline* is not active against Proteus, Providencia, and Pseudomonas species.

C. Resistance

Tigecycline was developed to overcome the recent emergence of tetracycline classâ€“resistant organisms that utilize efflux and ribosomal protection to infer resistance.

D. Pharmacokinetics

Following a 30- to 60-minute intravenous infusion every 12 hours, *tigecycline* is extensively distributed throughout plasma and body tissue. It does not undergo significant liver metabolism, but it is primarily eliminated via biliary/fecal excretion. No dose adjustment is necessary for patients who are renally impaired. However, dose adjustment is needed in severe hepatic dysfunction.

E. Adverse effects

Tigecycline is well tolerated, with the main adverse effects being similar to those of the tetracycline class. In clinical trials, the most commonly reported-class adverse effects were nausea and vomiting. Other similar tetracycline adverse effects that may occur with *tigecycline* include photosensitivity, pseudotumor cerebri, discoloration of permanent teeth when used during tooth development, and fetal harm when administered to a pregnant woman.

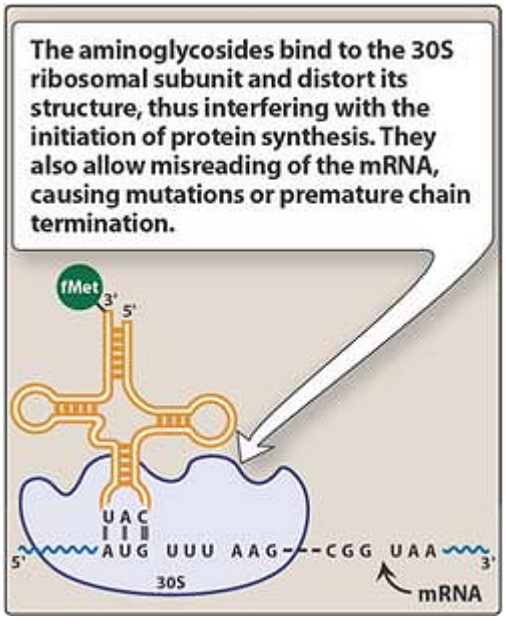


Figure 32.7 Mechanism of action of the aminoglycosides.

F. Drug interactions

The cytochrome P450 liver enzymes do not metabolize *tigecycline*; therefore, it will not be affected by medications

that induce or inhibit these enzymes. Although *tigecycline* does not affect prothrombin time significantly, it has been found to inhibit the clearance of *warfarin*. Therefore, it is recommended that anticoagulation be monitored closely when *tigecycline* is coadministered with *warfarin*. No dose adjustment of *digoxin* is necessary with concomitant use of *tigecycline* even though *digoxin* C_{max} is increased. However, another method of contraception is suggested when *tigecycline* and oral contraceptives are coadministered, because the oral contraceptives may become less effective.

IV. Aminoglycosides

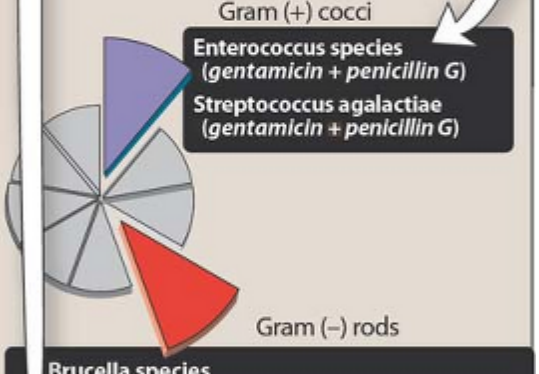
Aminoglycoside antibiotics had been the mainstays for treatment of serious infections due to aerobic gram-negative bacilli. However, because their use is associated with serious toxicities, they have been replaced to some extent by safer antibiotics, such as the third- and fourth-generation cephalosporins, the fluoroquinolones, and the carbapenems. Aminoglycosides that are derived from Streptomyces have -mycin suffixes, whereas those derived from Micromonospora end in -micin. The terms â€œaminoglycosideâ€ and â€œaminocyclitolâ€ stem from their structureâ€”two amino sugars joined by a glycosidic linkage to a central hexose (aminocyclitol) nucleus. Their polycationic nature precludes their easy passage across tissue membranes. All members of this family are believed to inhibit bacterial protein synthesis by the mechanism determined for *streptomycin* [strep-toe-MYE-sin] as described below.

TULAREMIA

- Tularemia is commonly acquired during rabbit-hunting season by hunters skinning infected animals.
- Pneumonic tularemia results from infection by the respiratory route or by bacteremic seeding of lung.
- *Gentamicin* is effective in treating this rare lymphoid disease.

INFECTIONS DUE TO ENTEROCOCCI

- Enterococci are intrinsically resistant to most antibiotic classes and require two synergistic antibiotics for effective therapy.
- Recommended therapy is with *gentamicin* or *streptomycin* plus *vancomycin* or a β-lactam, such as *penicillin G.*



Brucella species
(*gentamicin + doxycycline*)

Francisella tularensis
(*gentamicin*)

Klebsiella species
(*gentamicin* + an antipseudomonal penicillin)

Pseudomonas aeruginosa
(*tobramycin* + an antipseudomonal penicillin)

Yersinia pestis
(*streptomycin + doxycycline*)

INFECTIONS DUE TO PSEUDOMONAS AERUGINOSA

- Pseudomonas aeruginosa rarely attacks healthy individuals, but can cause infections under special circumstances, for example, in immunocompromised patients, and in burn victims.
- Treatment includes *tobramycin*

Figure 32.8 Typical therapeutic applications of aminoglycosides.

A. Mechanism of action

Susceptible gram-negative organisms allow aminoglycosides to diffuse through porin channels in their outer membranes. These organisms also have an oxygen-dependent system that transports the drug across the cytoplasmic membrane. The antibiotic then binds to the 30S ribosomal subunit prior to ribosome formation (Figure 32.7). There, it interferes with assembly of the functional ribosomal apparatus and/or can cause the 30S subunit of the completed ribosome to misread the genetic code. Polysomes become depleted, because the aminoglycosides interrupt the process of polysome disaggregation and assembly. [Note: The aminoglycosides synergize with Î²-lactam antibiotics because of the latter's action on cell wall synthesis, which enhances diffusion of the aminoglycosides into the bacterium.]

B. Antibacterial spectrum

The aminoglycosides are effective in the empirical treatment of infections suspected of being due to aerobic gram-negative bacilli, including Pseudomonas aeruginosa. To achieve an additive or synergistic effect, aminoglycosides are often combined with a Î²-lactam antibiotic, or *vancomycin*, or a drug active against anaerobic bacteria. All aminoglycosides are bactericidal. The exact mechanism of their lethality is unknown because other antibiotics that affect protein synthesis are generally bacteriostatic. [Note: The aminoglycosides are effective only against aerobic organisms because strict anaerobes lack the oxygen-requiring drug transport system.] Some therapeutic applications of four commonly used aminoglycosidesâ€"*amikacin* [am-i KAY-sin], *gentamicin* [jen-ta-MYE-sin], *tobramycin* [toe-bra-MYE-sin], and *streptomycin*â€"are shown in Figure 32.8.

C. Resistance

Resistance can be caused by 1) decreased uptake of drug when the oxygen-dependent transport system for aminoglycosides or porin channels are absent and 2) plasmid-associated synthesis of enzymes (for example, acetyl transferases, nucleotidyltransferases, and phosphotransferases) that modify and inactivate aminoglycoside antibiotics. Each of these enzymes has its own aminoglycoside specificity; therefore, cross-resistance is not an invariable rule. [Note: *Amikacin* is less vulnerable to these enzymes than are the other antibiotics of this group.]

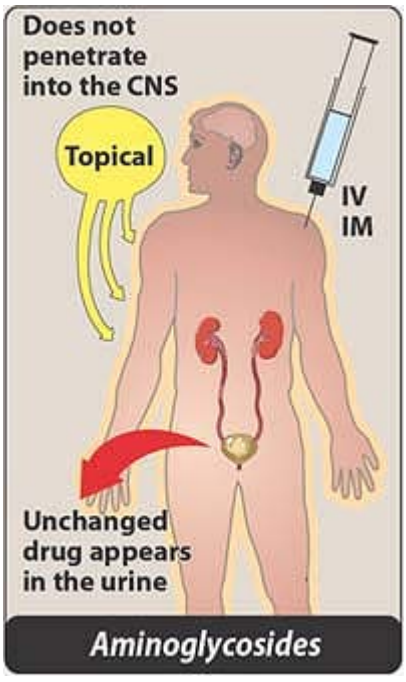


Figure 32.9 Administration and fate of aminoglycosides.

D. Pharmacokinetics

1. **Administration:** The highly polar, polycationic structure of the aminoglycosides prevents adequate absorption after oral administration (Figure 32.9). Therefore, all aminoglycosides (except *neomycin* [nee-oh-MYE-sin]) must be given parenterally to achieve adequate serum levels. [Note: The severe nephrotoxicity associated with *neomycin* precludes parenteral administration, and its current use is limited to topical application for skin infections or oral administration to prepare the bowel prior to surgery.] The bactericidal effect of aminoglycosides is concentration and time dependent; that is, the greater the concentration of drug, the greater the rate at which the organisms die. They also have a postantibiotic effect. Because of these properties, once-daily dosing with the aminoglycosides can be employed. This results in fewer toxicities and is less expensive to administer. The exceptions are pregnancy, neonatal infections, and bacterial endocarditis, in which these agents are administered in divided doses every 8 hours. [Note: The dose that is administered is calculated based on lean body mass, because these drugs do not distribute into fat.]

2. **Distribution:** All the aminoglycosides have similar pharmacokinetic properties. Levels achieved in most tissues are low, and penetration into most body fluids is variable. Concentrations in CSF are inadequate, even when the meninges are inflamed. Except for *neomycin*, the aminoglycosides may be administered intrathecally or intraventricularly. High concentrations accumulate in the renal cortex and in the endolymph and perilymph of the inner ear, which may account for their nephrotoxic and ototoxic potential. All aminoglycosides cross the placental barrier and may accumulate in fetal plasma and amniotic fluid.

3. **Fate:** Metabolism of the aminoglycosides does not occur in the host. All are rapidly excreted into the urine, predominantly by glomerular filtration (see Figure 32.9). Accumulation occurs in patients with renal failure and requires dose modification.

E. Adverse effects

It is important to monitor plasma levels of *gentamicin, tobramycin*, and *amikacin* to avoid concentrations that

cause dose-related toxicities (Figure 32.10). [Note: When the drugs are administered two to three times daily, both peak and trough levels are measured. Peak levels are defined as those obtained 30 minutes to 1 hour after infusion. Trough levels are obtained immediately before the next dose. When once-daily dosing is employed, only the trough concentrations are monitored.] Patient factors, such as old age, previous exposure to aminoglycosides, and liver disease, tend to predispose patients to adverse reactions. The elderly are particularly susceptible to nephrotoxicity and ototoxicity.

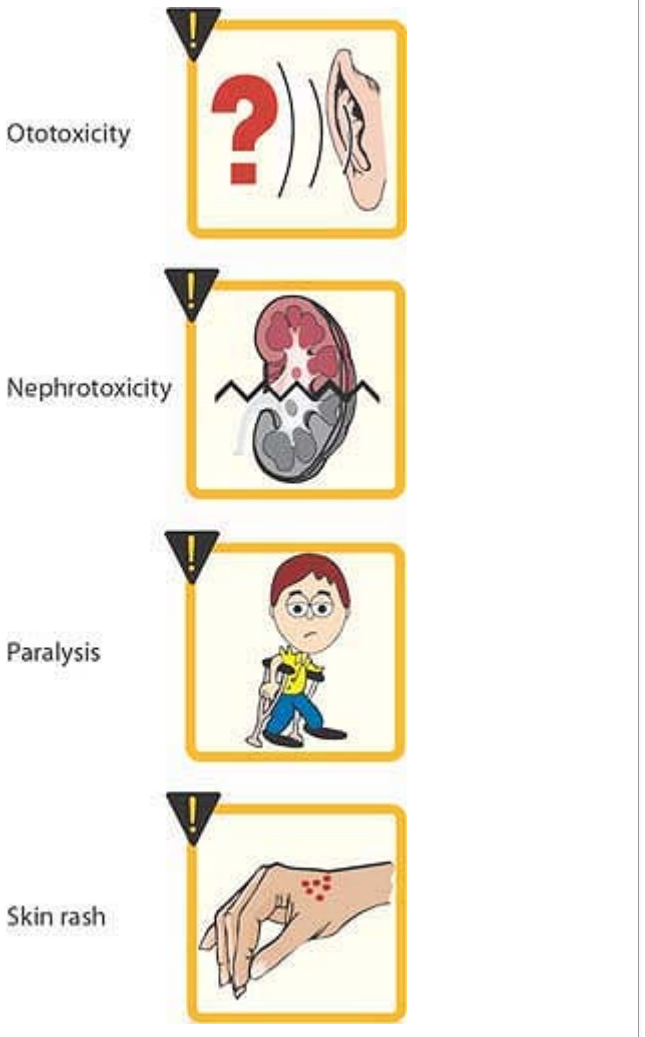


Figure 32.10 Some adverse effects of aminoglycosides.

1. **Ototoxicity:** Ototoxicity (vestibular and cochlear) is directly related to high peak plasma levels and the duration of treatment. The antibiotic accumulates in the endolymph and perilymph of the inner ear, and toxicity correlates with the number of destroyed hair cells in the organ of Corti. Deafness may be irreversible and has been known to affect fetuses in utero. Patients simultaneously receiving another ototoxic drug, such as *cisplatin* or the loop diuretics, *furosemide, bumetanide*, or *ethacrynic acid,* are particularly at risk. Vertigo and loss of balance (especially in patients receiving *streptomycin*) may also occur, because these drugs affect the vestibular apparatus.

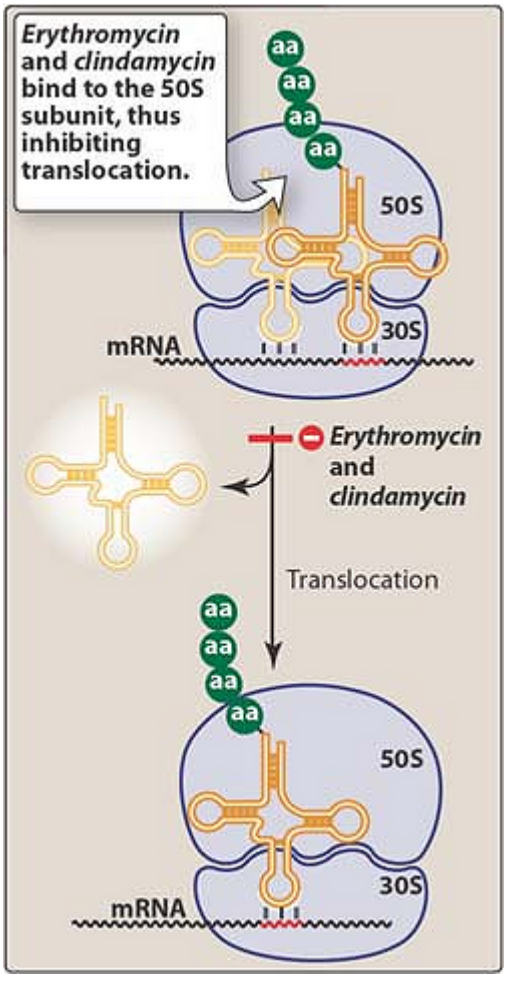


Figure 32.11 Mechanism of action of *erythromycin* and *clindamycin*.

2. **Nephrotoxicity:** Retention of the aminoglycosides by the proximal tubular cells disrupts calcium-mediated transport processes, and this results in kidney damage ranging from mild, reversible renal impairment to severe, acute tubular necrosis, which can be irreversible.

3. **Neuromuscular paralysis:** This side effect most often occurs after direct intraperitoneal or intrapleural application of large doses of aminoglycosides. The mechanism responsible is a decrease in both the release of acetylcholine from prejunctional nerve endings and the sensitivity of the postsynaptic site. Patients with myasthenia gravis are particularly at risk. Prompt administration of *calcium gluconate* or *neostigmine* can reverse the block.

4. **Allergic reactions:** Contact dermatitis is a common reaction to topically applied *neomycin*.

V. Macrolides

The macrolides are a group of antibiotics with a macrocyclic lactone structure to which one or more deoxy sugars are attached. *Erythromycin* [er-ith-roe-MYE-sin] was the first of these drugs to find clinical application, both as a drug of first choice and as an alternative to *penicillin* in individuals who are allergic to Î²-lactam antibiotics. The newer members of this family, *clarithromycin* [kla-rith-roe-MYE-sin] (a methylated form of *erythromycin*) and *azithromycin* [az-ith-roe-MYE-sin] (having a larger lactone ring), have some features in common with, and others

that improve on, *erythromycin*. *Telithromycin* [tel-ith-roe-MYE-sin], a semisynthetic derivative of *erythromycin*, is the first â€œketolideâ€ antimicrobial agent that has been approved and is now in clinical use. Ketolides and macrolides have very similar antimicrobial coverage. However, the ketolides are active against many macrolide-resistant gram-positive strains.

A. Mechanism of action

The macrolides bind irreversibly to a site on the 50S subunit of the bacterial ribosome, thus inhibiting the translocation steps of protein synthesis (Figure 32.11). They may also interfere at other steps, such as transpeptidation. Generally considered to be bacteriostatic, they may be bactericidal at higher doses. Their binding site is either identical or in close proximity to that for *clindamycin* and *chloramphenicol*.

B. Antibacterial spectrum

1. **Erythromycin:** This drug is effective against many of the same organisms as *penicillin G* (Figure 32.12); therefore, it is used in patients who are allergic to the penicillins.

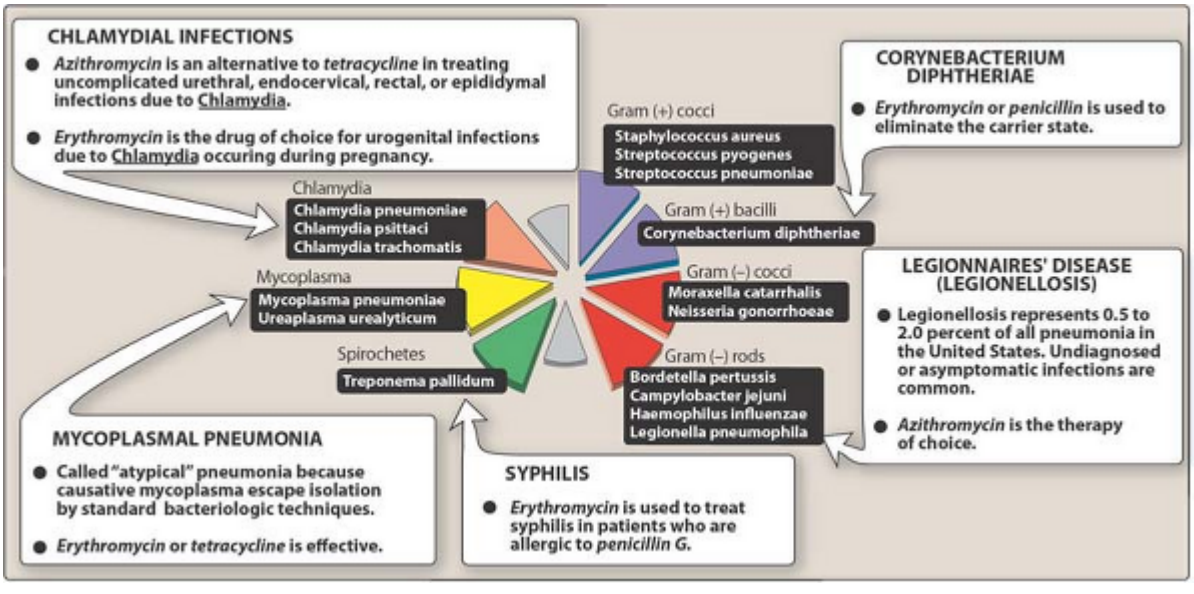


Figure 32.12 Typical therapeutic applications of macrolides.

2. **Clarithromycin:** This antibiotic has a spectrum of antibacterial activity similar to that of *erythromycin*, but it is also effective against Haemophilus influenzae. Its activity against intracellular pathogens, such as Chlamydia, Legionella, Moraxella, and Ureaplasma species and Helicobacter pylori, is higher than that of *erythromycin*.

3. **Azithromycin:** Although less active against streptococci and staphylococci than *erythromycin, azithromycin* is far more active against respiratory infections due to H. influenzae and Moraxella catarrhalis. *Azithromycin* is now the preferred therapy for urethritis caused by Chlamydia trachomatis. It also has activity against Mycobacterium avium-intracellulare complex in patients with acquired immunodeficiency syndrome and disseminated infections.

4. **Telithromycin:** This ketolide drug has an antibacterial spectrum similar to that of *azithromycin*. Moreover, the structural modification within ketolides neutralizes the most common resistance mechanisms (methylase-mediated and efflux-mediated) that make macrolides ineffective.

C. Resistance

Resistance to *erythromycin* is becoming a serious clinical problem. For example, most strains of staphylococci in hospital isolates are resistant to this drug. Several mechanisms have been identified: 1) the inability of the organism to take up the antibiotic or the presence of an efflux pump, both of which limit the amount of intracellular drug; 2) a decreased affinity of the 50S ribosomal subunit for the antibiotic, resulting from the methylation of an adenine in the 23S bacterial ribosomal RNA; and 3) the presence of a plasmid-associated *erythromycin* esterase. Both *clarithromycin* and *azithromycin* show cross-resistance with *erythromycin*, but *telithromycin* can be effective against macrolide-resistant organisms.

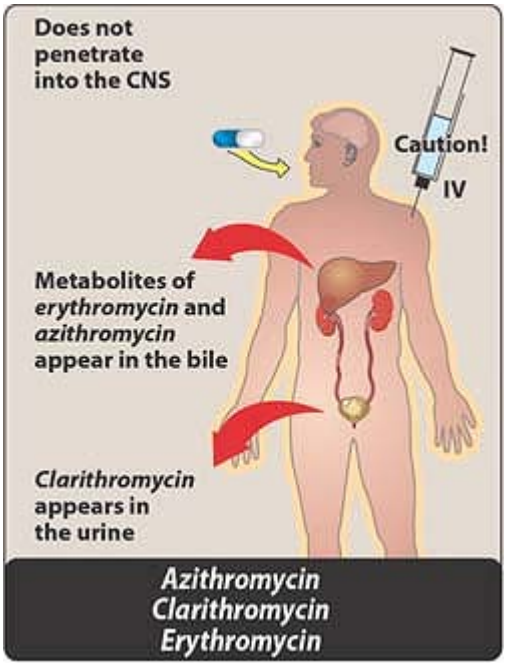


Figure 32.13 Administration and fate of the macrolide antibiotics.

D. Pharmacokinetics

	Erythro-mycin	*Clarithro-mycin*	*Azithro-mycin*	*Telithro-mycin*
Oral absorption	Yes	Yes	Yes	Yes
Half-life (hours)	2	3.5	>40	10
Conversion to an active metabolite	No	Yes	Yes	Yes
Percent excretion in urine	15	50	12	13

Figure 32.14 Some properties of the macrolide antibiotics.

1. **Administration:** The *erythromycin* base is destroyed by gastric acid. Thus, either enteric-coated tablets or esterified forms of the antibiotic are administered. All are adequately absorbed upon oral administration (Figure 32.13). *Clarithromycin, azithromycin*, and *telithromycin* are stable to stomach acid and are readily absorbed. Food interferes with the absorption of *erythromycin* and *azithromycin* but can increase that of *clarithromycin*. *Azithromycin* is available for intravenous infusion, but intravenous administration of *erythromycin* is associated with a high incidence of thrombophlebitis.
2. **Distribution:** *Erythromycin* distributes well to all body fluids except the CSF. It is one of the few antibiotics that diffuses into prostatic fluid, and it has the unique characteristic of accumulating in macrophages. All four drugs concentrate in the liver. Inflammation allows for greater tissue penetration. Similarly, *clarithromycin, azithromycin*, and *telithromycin* are widely distributed in the tissues. Serum levels of *azithromycin* are low; the drug is concentrated in neutrophils, macrophages, and fibroblasts. *Azithromycin* has the longest half-life and largest volume of distribution of the four drugs (Figure 32.14).
3. **Fate:** *Erythromycin* and *telithromycin* are extensively metabolized and are known to inhibit the oxidation of a number of drugs through their interaction with the cytochrome P450 system (see p. 14). Interference with the metabolism of drugs such as *theophylline* and *carbamazepine* has been reported for *clarithromycin* (see Figure 32.16). *Clarithromycin* is oxidized to the 14-hydroxy derivative, which retains antibiotic activity.
4. **Excretion:** *Erythromycin* and *azithromycin* are primarily concentrated and excreted in an active form in the bile (see Figure 32.13). Partial reabsorption occurs through the enterohepatic circulation. Inactive metabolites are excreted into the urine. In contrast, *clarithromycin* and its metabolites are eliminated by the kidney as well as the liver, and it is recommended that the dosage of this drug be adjusted in patients with compromised renal function.

E. Adverse effects

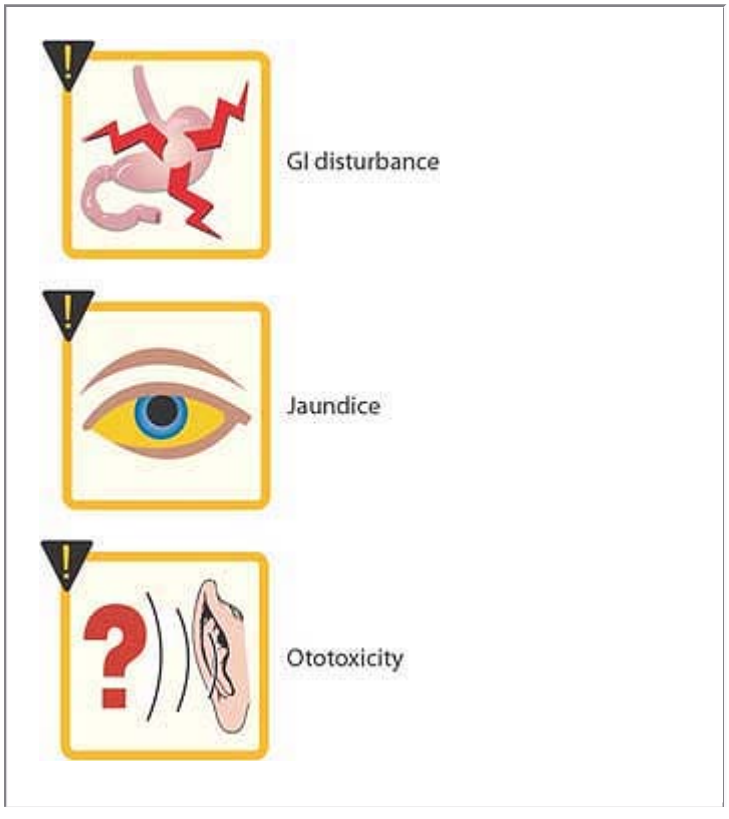


Figure 32.15 Some adverse effects of macrolide antibiotics.

1. **Epigastric distress:** This side effect is common and can lead to poor patient compliance for *erythromycin*. *Clarithromycin* and *azithromycin* seem to be better tolerated by the patient, but gastrointestinal problems are their most common side effects (Figure 32.15).
2. **Cholestatic jaundice:** This side effect occurs especially with the estolate form of *erythromycin*, presumably as the result of a hypersensitivity reaction to the estolate form (the lauryl salt of the propionyl ester of *erythromycin*). It has also been reported for other forms of the drug.
3. **Ototoxicity:** Transient deafness has been associated with *erythromycin*, especially at high dosages.
4. **Contraindications:** Patients with hepatic dysfunction should be treated cautiouslyâ€"if at allâ€"with *erythromycin, telithromycin*, or *azithromycin*, because these drugs accumulate in the liver. Recent cases of severe hepatotoxicity with *telithromycin* use have emphasized

the caution needed when utilizing this agent. Additionally, *telithromycin* has the potential to prolongate the QTc interval in some patients. Therefore, it should be avoided in patients with congenital prolongation of the QTc interval and in those patients with proarrhythmic conditions. Similarly, patients who are renally compromised should be given *telithromycin* with caution. *Telithromycin* is contraindicated in patients with myasthenia gravis.

5. **Interactions:** *Erythromycin, telithromycin*, and *clarithromycin* inhibit the hepatic metabolism of a number of drugs, which can lead to toxic accumulations of these compounds (Figure 32.16). An interaction with *digoxin* may occur in some patients. In this case, the antibiotic eliminates a species of intestinal flora that ordinarily inactivates *digoxin*, thus leading to greater reabsorption of the drug from the enterohepatic circulation. No interactions have been reported for *azithromycin*.

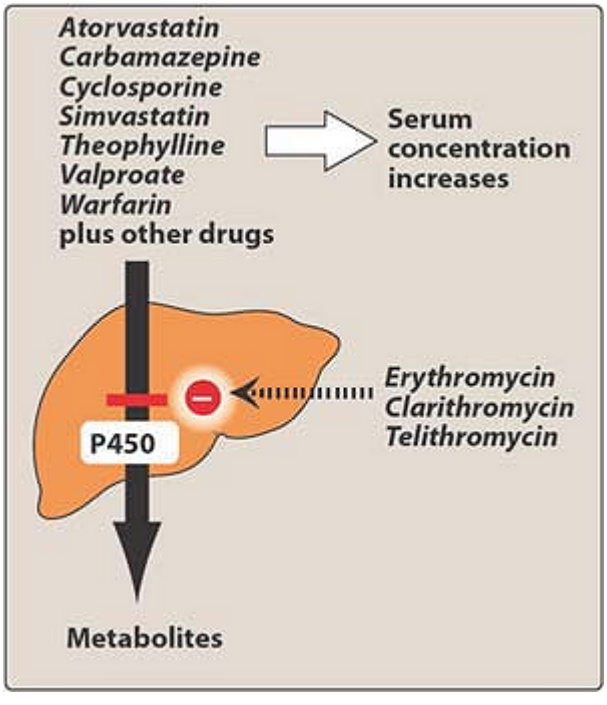


Figure 32.16 Inhibition of the cytochrome P450 system by *erythromycin, clarithromycin*, and *telithromycin*.

VI. Chloramphenicol

Chloramphenicol [klor-am-FEN-i-kole] is active against a wide range of gram-positive and gram-negative organisms. However, because of its toxicity, its use is restricted to life-threatening infections for which no alternatives exist.

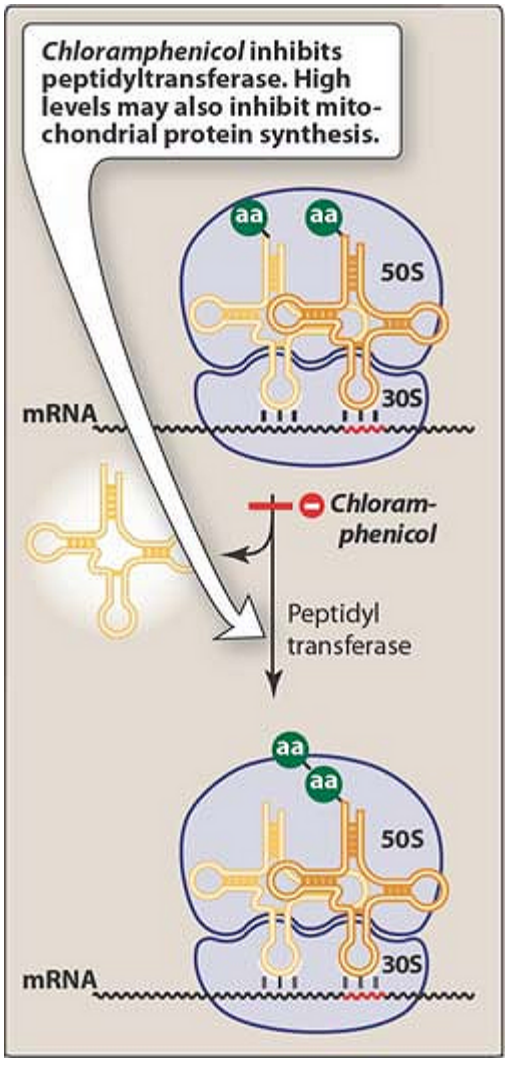


Figure 32.17 Mechanism of action of *chloramphenicol*.

A. Mechanism of action

The drug binds to the bacterial 50S ribosomal subunit and inhibits protein synthesis at the peptidyl transferase reaction (Figure 32.17). Because of the similarity of mammalian mitochondrial ribosomes to those of bacteria, protein synthesis in these organelles may be inhibited at high circulating *chloramphenicol* levels, producing bone

marrow toxicity.

B. Antimicrobial spectrum

Chloramphenicol, a broad-spectrum antibiotic, is active not only against bacteria but also against other microorganisms, such as rickettsiae. Pseudomonas aeruginosa is not affected, nor are the chlamydiae. *Chloramphenicol* has excellent activity against anaerobes. The drug is either bactericidal or (more commonly) bacteriostatic, depending on the organism.

C. Resistance

Resistance is conferred by the presence of an R factor that codes for an acetyl coenzyme A transferase. This enzyme inactivates *chloramphenicol.* Another mechanism for resistance is associated with an inability of the antibiotic to penetrate the organism. This change in permeability may be the basis of multidrug resistance.

D. Pharmacokinetics

Chloramphenicol may be administered either intravenously or orally (Figure 32.18). It is completely absorbed via the oral route because of its lipophilic nature, and is widely distributed throughout the body. It readily enters the normal CSF. The drug inhibits the hepatic mixed-function oxidases. Excretion of the drug depends on its conversion in the liver to a glucuronide, which is then secreted by the renal tubule. Only about 10 percent of the parent compound is excreted by glomerular filtration. *Chloramphenicol* is also secreted into breast milk.

E. Adverse effects

The clinical use of *chloramphenicol* is limited to life-threatening infections because of the serious adverse effects associated with its administration. In addition to gastrointestinal upsets, overgrowth of Candida albicans may appear on mucous membranes.

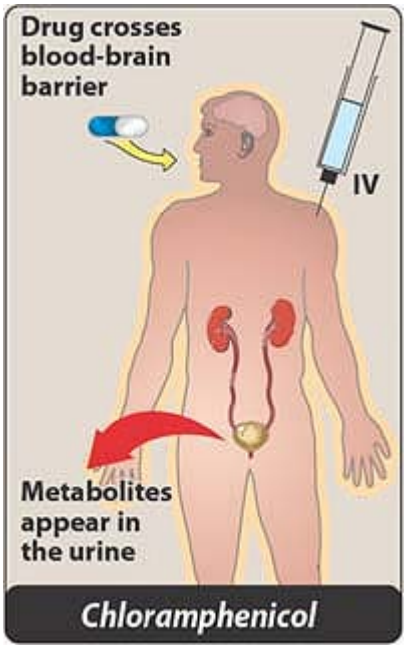


Figure 32.18 Administration and fate of *chloramphenicol*.

1. **Anemias:** Hemolytic anemia occurs in patients with low levels of glucose 6-phosphate dehydrogenase. Other types of anemia occurring as a side effect of *chloramphenicol* include reversible anemia, which is apparently dose-related and occurs concomitantly with therapy, and aplastic anemia, which although rare is idiosyncratic and usually fatal. [Note: Aplastic anemia is independent of dose and may occur after therapy has ceased.]

2. **Gray baby syndrome:** This adverse effect occurs in neonates if the dosage regimen of *chloramphenicol* is not properly adjusted. Neonates have a low capacity to glucuronylate the antibiotic, and they have underdeveloped renal function. Therefore, neonates have a decreased ability to excrete the drug, which accumulates to levels that interfere with the function of mitochondrial ribosomes. This leads to poor feeding, depressed breathing, cardiovascular collapse, cyanosis (hence the term â€œgray babyâ€), and death. Adults who have received very high doses of the drug can also exhibit this toxicity.

3. **Interactions:** *Chloramphenicol* is able to inhibit some of the hepatic mixed-function oxidases and, thus, blocks the metabolism of such drugs as *warfarin, phenytoin, tolbutamide,* and *chlorpropamide*, thereby elevating their concentrations and potentiating their effects (Figure 32.19).

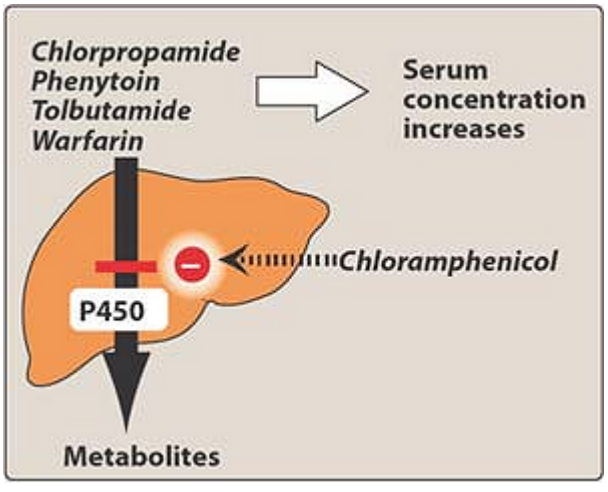


Figure 32.19 Inhibition of the cytochrome P450 system by *chloramphenicol*.

VII. Clindamycin

Clindamycin [klin-da-MYE-sin] has a mechanism of action that is the same as that of *erythromycin*. *Clindamycin* is employed primarily in the treatment of infections caused by anaerobic bacteria, such as Bacteroides fragilis, which often causes abdominal infections associated with trauma. However, it is also significantly active against nonenterococcal, gram-positive cocci. Resistance mechanisms are the same as those for *erythromycin,* and cross-resistance has been described. [Note: Clostridium difficile is always resistant to *clindamycin*.] *Clindamycin* is well absorbed by the oral route. It distributes well into all body fluids except the CSF. Adequate levels of *clindamycin* are not achieved in the brain, even when meninges are inflamed. Penetration into bone occurs even in the absence of inflammation. *Clindamycin* undergoes extensive oxidative metabolism to inactive products. The drug is excreted into the bile or urine by glomerular filtration, but therapeutically effective levels of the parent drug are not achieved in the urine (Figure 32.20). Accumulation has been reported in patients with either severely compromised renal function or hepatic failure. In addition to skin rashes, the most serious adverse effect is potentially fatal pseudomembranous colitis caused by overgrowth of C. difficile, which elaborates necrotizing toxins. Oral administration of either *metronidazole* or *vancomycin* is usually effective in controlling this serious problem. [Note: *Vancomycin* should be reserved for a condition that does not respond to *metronidazole*.] Impaired liver function has also been reported.

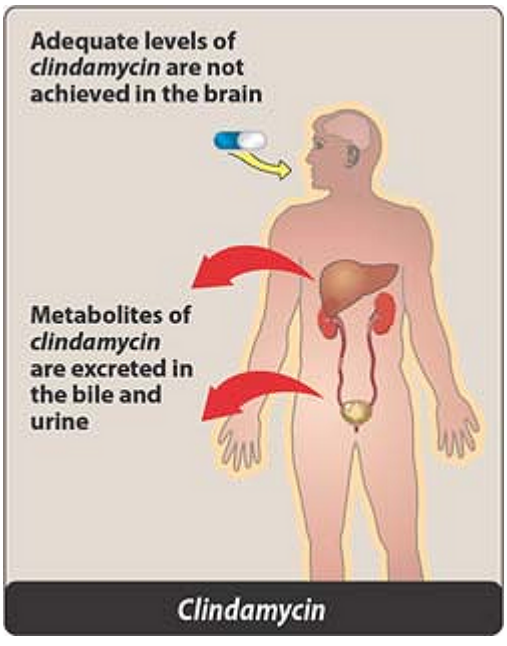


Figure 32.20 Administration and fate of *clindamycin*.

VIII. Quinupristin/Dalfopristin

Quinupristin/dalfopristin [KWIN-yoo-pris-tin/DAL-foh-pris-tin] is a mixture of two streptogramins in a ratio of thirty to seventy, respectively. They are derived from a streptomycete and then chemically modified. The drug is normally reserved for the treatment of *vancomycin*-resistant Enterococcus faecium (VRE).

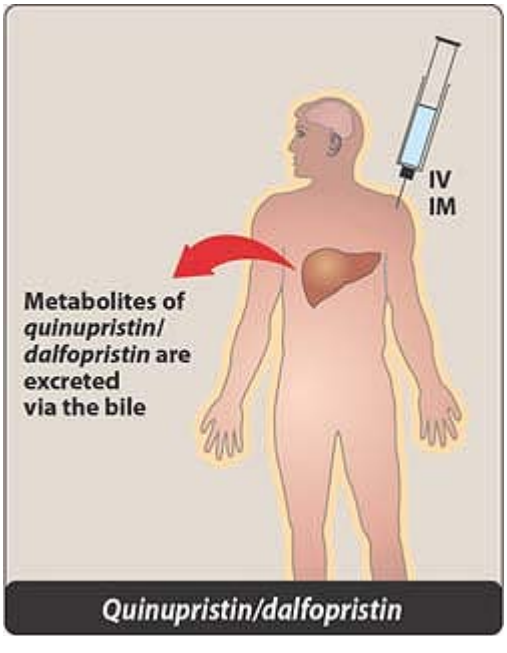


Figure 32.21 Administration and fate of *quinupristin/dalfopristin*.

A. Mechanism of action

Each component of this combination drug binds to a separate site on the 50S bacterial ribosome, forming a stable ternary complex. Thus, they synergistically interrupt protein synthesis. The combination drug is bactericidal and has a long postantibiotic effect.

B. Resistance

Enzymatic processes commonly account for resistance to these agents. For example, the presence of a ribosomal enzyme that methylates the target bacterial 23S ribosomal RNA site can interfere in *quinupristin* binding. In some cases, the enzymatic modification can change the action from bactericidal to bacteriostatic. Plasmid-associated acetyltransferase inactivates *dalfopristin.* An active efflux pump can also decrease levels of the antibiotics in bacteria.

C. Antibacterial spectrum

The combination drug is active primarily against gram-positive cocci, including those resistant to other antibiotics (for example, *methicillin*-resistant staphylococci). Its primary use is in the treatment of E. faecium infections, including VRE strains. [Note: In the latter case, the effect is bacteriostatic rather than bactericidal.] The drug is not effective against Enterococcus faecalis.

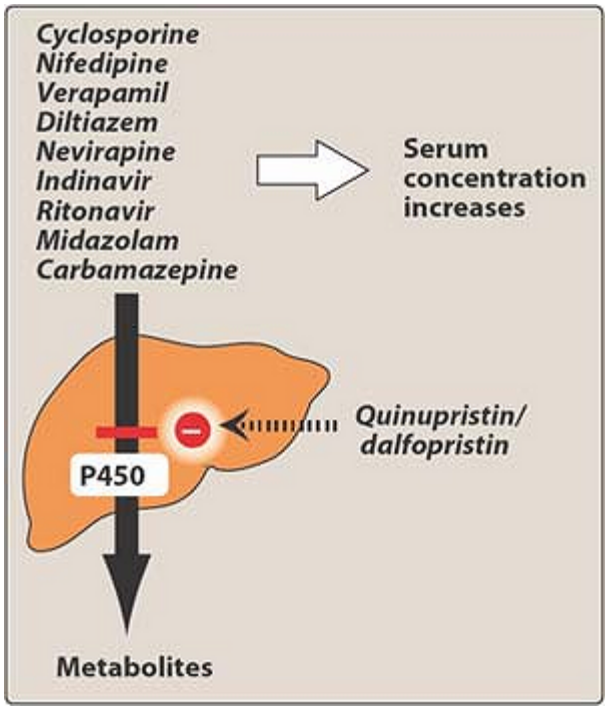


Figure 32.22 Inhibition of cytochrome P450 system by *quinupristin/dalfopristin*.

D. Pharmacokinetics

Quinupristin/dalfopristin is injected intravenously in a 5 percent dextrose solution (the drug is incompatible with a saline medium). The combination drug penetrates macrophages and polymorphonucleocytes, a property that is important, because VRE are intracellular. Levels in the CSF are low. Both compounds undergo metabolism. The products are less active than the parent in the case of *quinupristin* and are equally active in the case of *dalfopristin*. Most of the parent drugs and metabolites are cleared through the liver and eliminated via the bile into the feces (Figure 32.21). Urinary excretion is secondary.

E. Adverse effects

1. **Venous irritation:** This commonly occurs when *quinupristin/dalfopristin* is administered through a peripheral rather than a central line.
2. **Arthralgia and myalgia:** These have been reported when higher levels of the drugs are employed.
3. **Hyperbilirubinemia:** Total bilirubin is elevated in about 25 percent of patients, resulting from a competition with the antibiotic for excretion.

4. **Interactions:** Because of the ability of *quinupristin/dalfopristin* to inhibit the cytochrome P450 (CYP3A4) isozyme, concomitant administration with drugs that are metabolized by this pathway may lead to toxicities (Figure 32.22). A drug interaction with *digoxin* appears to occur by the same mechanism as that caused by *erythromycin*.

IX. Linezolid

Linezolid [lih-NEH-zo-lid] was introduced recently to combat resistant gram-positive organisms, such as *methicillin*- and *vancomycin*-resistant Staphylococcus aureus, v*ancomycin*-resistant E. faecium and E. faecalis, and *penicillin*-resistant streptococci. *Linezolid* is a totally synthetic oxazolidinone.

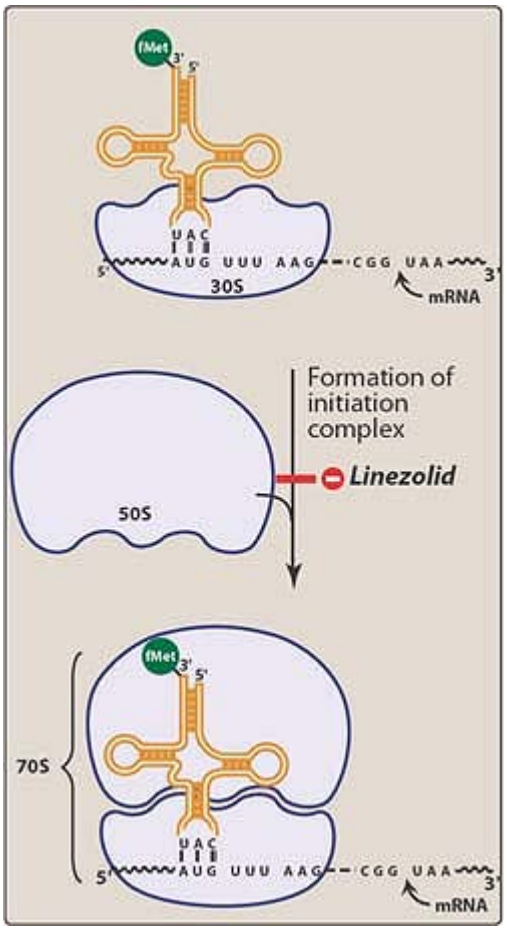


Figure 32.23 Mechanism of action of *linezolid*.

A. Mechanism of action

The drug inhibits bacterial protein synthesis by inhibiting the formation of the 70S initiation complex. *Linezolid* binds to a site on the 50S subunit near the interface with the 30S subunit (Figure 32.23).

B. Resistance

Decreased binding to the target site confers resistance on the organism. Cross-resistance with other antibiotics does not occur.

C. Antibacterial spectrum

The antibacterial action of *linezolid* is directed primarily against gram-positive organisms, such as staphylococci, streptococci, and enterococci, as well as Corynebacterium species and Listeria monocytogenes (Figure 32.24). It is also moderately active against Mycobacterium tuberculosis. However, its main clinical use is against the resistant organisms mentioned above. Like other agents that interfere with bacterial protein synthesis, *linezolid* is bacteriostatic. However, it is cidal against the streptococci and Clostridium perfringens.

D. Pharmacokinetics

Linezolid is completely absorbed on oral administration. An intravenous preparation is also available. The drug is

widely distributed throughout the body, having a volume of distribution of 40 to 50 liters. Two metabolites that are oxidation products have been identified, one of which has antimicrobial activity. However, cytochrome P450 enzymes are not involved in their formation. The drug is excreted both by renal and nonrenal routes. The metabolites rely on the kidney for elimination.

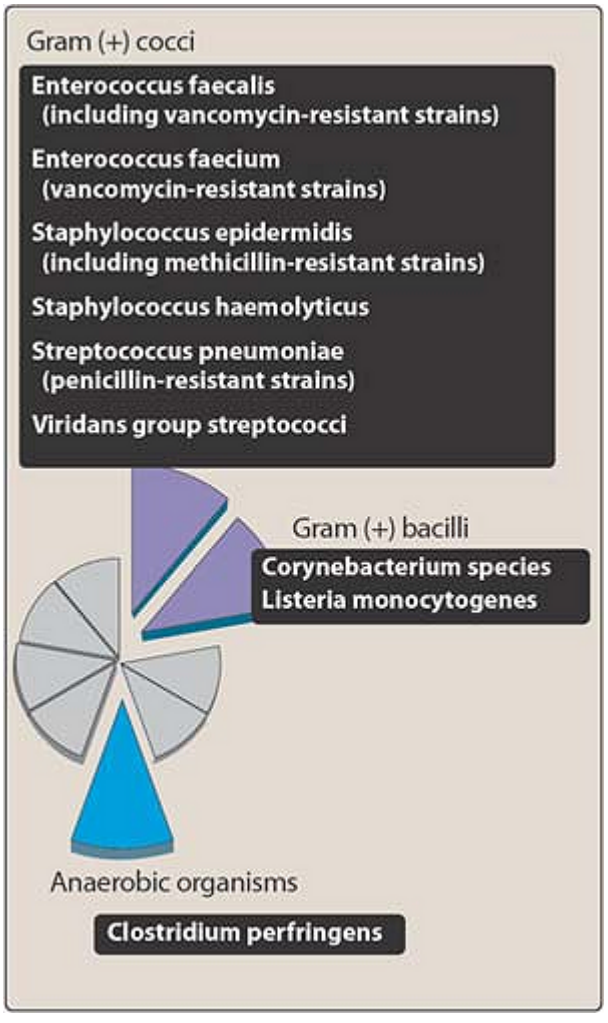


Figure 32.24 Antimicrobial spectrum of *linezolid*.

E. Adverse effects

Linezolid is well-tolerated, with some reports of gastrointestinal upset, nausea, and diarrhea, as well as headaches and rash. Thrombocytopenia was found to occur in about 2 percent of patients who were on the drug for longer than 2 weeks. Although no reports have appeared that *linezolid* inhibits monoamine oxidase activity, patients are cautioned not to consume large quantities of tyramine-containing foods. Early oxazolidinones had been shown to inhibit monoamine oxidase activity. The condition was reversible when the drug was suspended. Reversible enhancement of the pressor effects of *pseudoephedrine* was shown to occur.

Study Questions

Choose the ONE best answer.

32.1 A patient with a gunshot wound to the abdomen, which has resulted in spillage of intestinal contents, is brought to the emergency room. Which antibiotic would you select to effectively treat an infection due to Bacteroides fragilis?

A. Aztreonam.

B. Clindamycin.

C. Gentamicin.

D. Azithromycin.

E. Doxycycline.

View Answer

32.2 A pregnant woman was hospitalized and catheterized with a Foley catheter. She developed a urinary tract infection caused by Pseudomonas aeruginosa and was treated with gentamicin. Which of the following adverse effects was a risk to the fetus when the woman was on gentamicin?

A. Skeletal deformity.

B. Hearing loss.

C. Teratogenesis.

D. Blindness.

E. Mental retardation.

View Answer

32.3 Children younger than 8 years of age should not receive tetracyclines because these agents:

A. Cause rupture of tendons.

B. Do not cross into the CS.

C. Are not bactericidal.

D. Deposit in tissues undergoing calcification.

E. Can cause aplastic anemia.

View Answer

32.4 A 46-year-old woman is in the intensive care unit for treatment of a vancomycin-resistant strain of Enterococcus faeciumâ€“caused bacteremia. You want to limit the risk of drug interactions in this woman, who is receiving five other medications. Which one of the following antibiotics would you choose?

A. Azithromycin.

B. Clindamycin.

C. Doxycycline.

D. Linezolid.

E. Quinupristin/dalfopristin.

View Answer

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Chapter 33

Quinolones, Folic AcidAntagonists, and Urinary Tract Antiseptics

I. Fluoroquinolones

Introduction of the first fluorinated quinolone, *norfloxacin*, was rapidly followed by development of other members of this group, such as *ciprofloxacin*, which has had wide clinical application. Newer fluorinated quinolones offer greater potency, a broader spectrum of antimicrobial activity, greater in vitro efficacy against resistant organisms, and in some cases, a better safety profile than older quinolones and other antibiotics. Compared to *ciprofloxacin*, the new compounds are more active against gram-positive organisms, yet retain favor able activity against gram-negative microorganisms. It seems likely that the number of drugs in this class of antibiotics will increase due to its wide antibacterial spectrum, favorable pharmacokinetic properties, and relative lack of adverse reactions. Unfortunately, their overuse has already led to the emergence of resistant strains, resulting in limitations to their clinical usefulness. The fluoroquinolones and other antibiotics discussed in this chapter are listed in Figure 33.1.

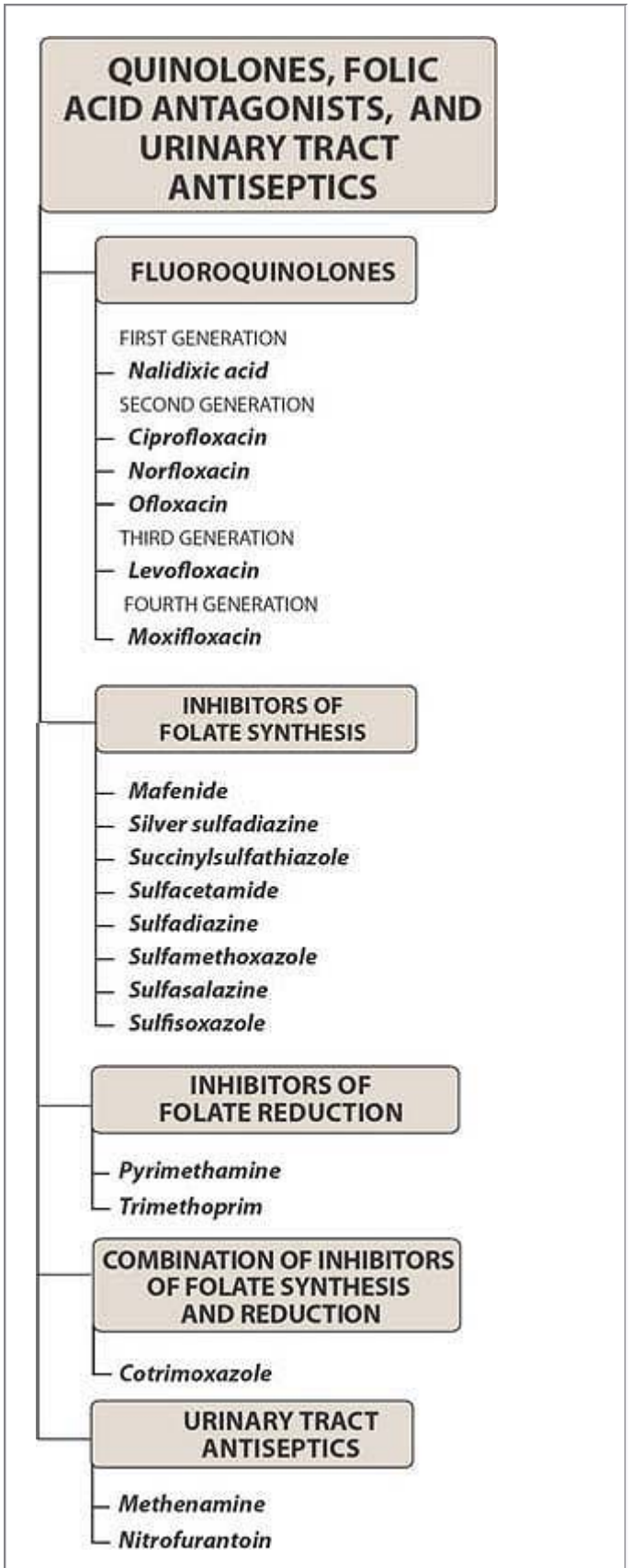

Figure 33.1 Summary of drugs described in this chapter.

A. Mechanism of action

The fluoroquinolones enter the bacterium by passive diffusion through water-filled protein channels (porins) in the outer membrane. Once inside the cell, they inhibit the replication of bacterial DNA by interfering with the action of DNA gyrase (topoisomerase II) and topoisomerase IV during bacterial growth and reproduction. [Note: Topoisomerases are enzymes that change the configuration or topology of DNA by a nicking, pass-through, and resealing mechanism. They do not change the DNA's primary sequence[1] (Figure 33.2).] Binding of the quinolone to both the enzyme and the DNA forms a ternary complex that inhibits the resealing step, and can cause cell death by inducing cleavage of the DNA. Because DNA gyrase is a bacteriospecific target for antimicrobial therapy, cross-resistance with other, more commonly used antimicrobial drugs is rare, but this is increasing in the case of multidrug-resistant organisms. The second site blocked by the fluoroquinolonesâ€"topoisomerase IVâ€"is required by bacteria for cell division. It has been implicated in the process of segregating newly replicated DNA. In gram-negative organisms (for example, Escherichia coli), the inhibition of DNA gyrase is more significant than that of topoisomerase IV, whereas in gram-positive organisms (for example, the staphylococci), the opposite is true.

B. Antimicrobial spectrum

All the fluoroquinolones are bactericidal. Like aminoglycosides, the quinolones exhibit concentration-dependent bacterial killing. Bactericidal activity becomes more pronounced as the serum drug concentration increases to approximately 30-fold the minimum inhibitory concentration. In general, they are effective against gram-negative organisms such as the Enterobacteriaceae, Pseudomonas species, Haemophilus influenzae, Moraxella catarrhalis, Legionellaceae, chlamydia, and mycobacteria (except for Mycobacterium avium-intracellulare complex). They are effective in the treatment of gonorrhea but not syphilis. The newer agents (for example, *levofloxacin* and *moxifloxacin*) also have good activity against some gram-positive organisms, such as Streptococcus pneumoniae. *Moxifloxacin* has activity against many anaerobes. If used prophylactically before transurethral surgery, fluoroquinolones lower the incidence of postsurgical urinary tract infections (UTIs). It has become common practice to classify the fluoroquinolones into â€œgenerations,â€ based on their antimicrobial targets (Figure 33.3). The nonfluorinated quinolone *nalidixic acid* is considered to be first generation, with a narrow spectrum of susceptible organisms usually confined to the urinary tract. *Ciprofloxacin* and *norfloxacin* are assigned to the second generation because of their activity against aerobic gram-negative and atypical bacteria. In addition, these fluoroquinolones exhibit significant intracellular penetration, allowing therapy for infections in which a bacterium spends part or all of its life cycle inside a host cell (for example, chlamydia, mycoplasma, and legionella). *Levofloxacin* is classified as third generation because of its increased activity against gram-positive bacteria. Lastly, the fourth generation includes only *moxifloxacin* because of its activity against anaerobic as well as gram-positive organisms.

C. Examples of clinically useful fluoroquinolones

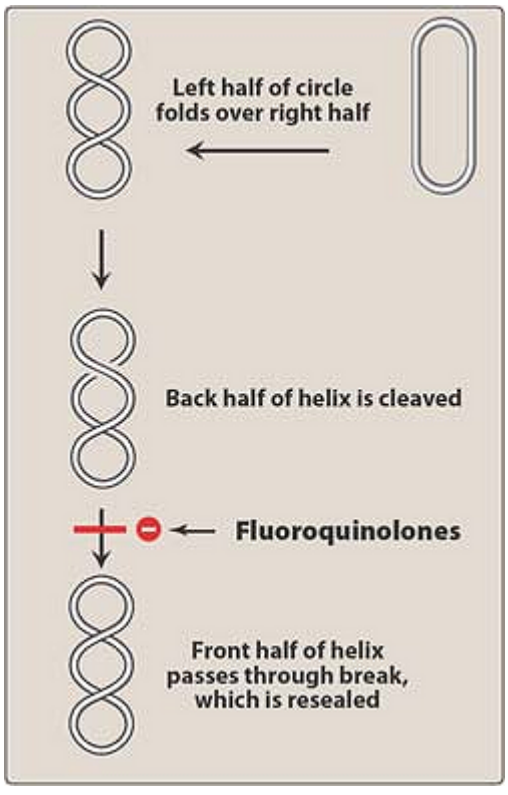

Figure 33.2 Action of Type II DNA topoisomerase.

1. **Ciprofloxacin:** This is the most frequently used fluoroquinolone in the United States (Figure 33.4). The serum levels of *ciprofloxacin* [sip-row-FLOX-a-sin] that are achieved are effective against many systemic infections, with the exception of serious infections caused by *methicillin*-resistant Staphylococcus aureus (MRSA), the enterococci, and pneumococci. *Ciprofloxacin* is also particularly useful in treating infections caused by many Enterobacteriaceae and other gram-negative bacilli. For example, traveler's diarrhea caused by E. coli can be effectively treated. *Ciprofloxacin* is also the drug of choice for prophylaxis and treatment of anthrax. It is the most potent of the fluoroquinolones for Pseudomonas aeruginosa infections and, therefore, is used in the treatment of pseudomonal infections associated with cystic fibrosis. The drug is also used as an alternative to more toxic drugs, such as the aminoglycosides. It may act synergistically with Î²-lactams and is also of benefit in treating resistant tuberculosis.

2. **Norfloxacin:** *Norfloxacin* (nor-FLOX-a-sin] is effective against both gram-negative (including P. aeruginosa) and gram-positive organisms in treating complicated and uncomplicated UTIs and prostatitis. It is not effective in systemic infections.

3. **Levofloxacin:** *Levofloxacin* [leave-oh-FLOX-a-sin] is an isomer of *ofloxacin* [oh-FLOX-a-sin] and has largely replaced it clinically. It can be used in the treatment of prostatitis due to E. coli and of sexually transmitted diseases, with the exception of syphilis. It may be used as alternative therapy in patients with gonorrhea. Additionally, due to its broad spectrum of activity, *levofloxacin* is utilized in a wide

range of infections, including skin infections, acute sinusitis, acute exacerbation of chronic bronchitis, community-acquired pneumonia, as well as nosocomial pneumonia. *Levofloxacin* has excellent activity against respiratory infections due to S. pneumoniae.

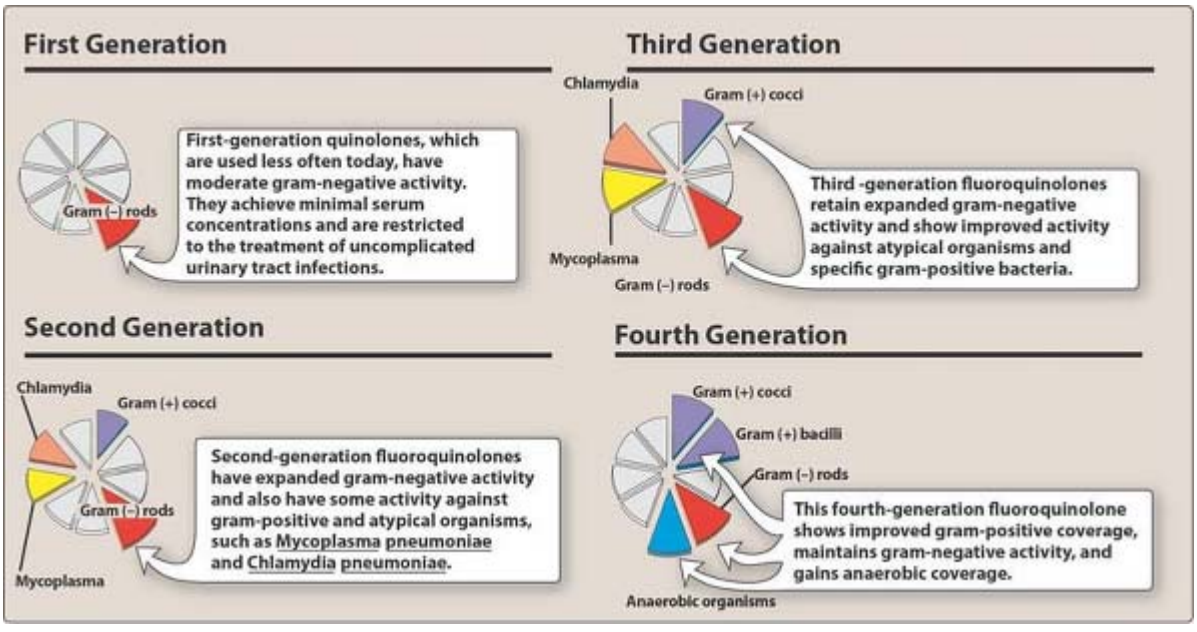

Figure 33.3 Summary of antimicrobial spectrum of quinolones. [Note: The antimicrobial spectrum of specific agents may differ from the generalizations shown in this figure.]

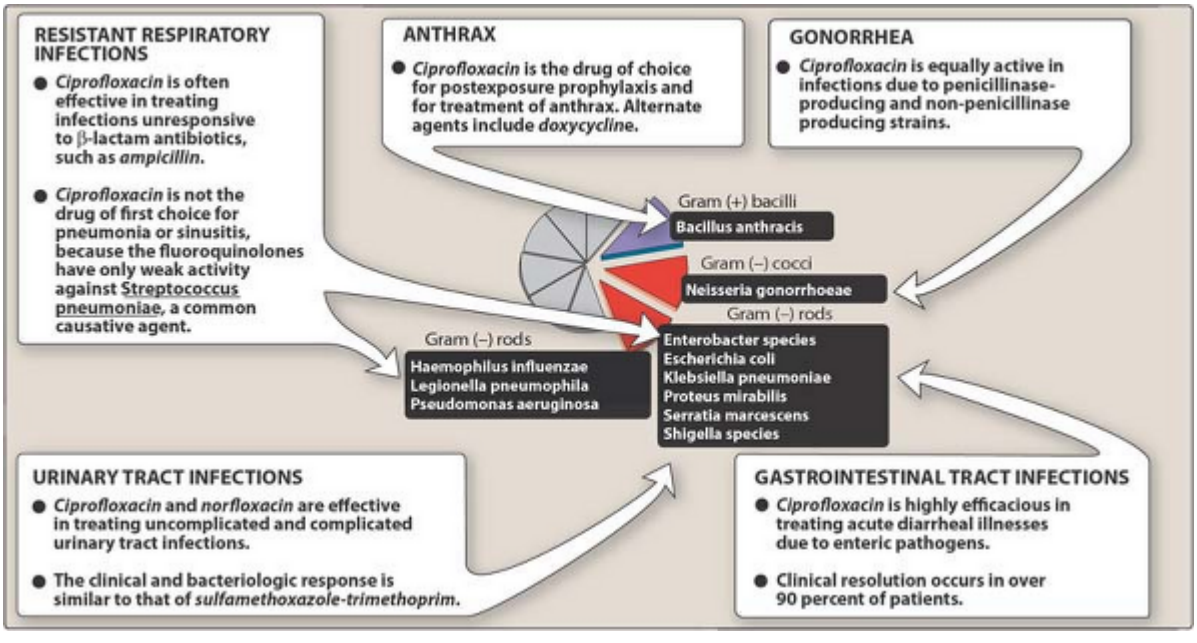

Figure 33.4 Typical therapeutic applications of *ciprofloxacin.*

4. **Moxifloxacin**: *Moxifloxacin* [moxie-FLOX-a-sin] not only has enhanced activity against gram-positive organisms

(for example, S. pneumoniae) but also has excellent activity against many anaerobes. It has very poor activity against P. aeruginosa.

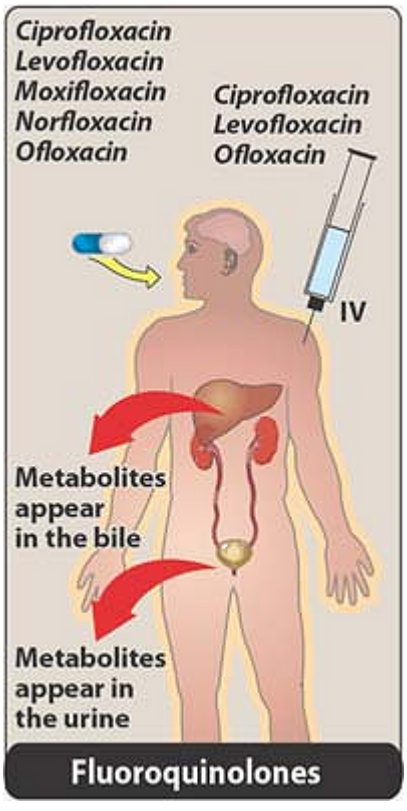

Figure 33.5 Administration and fate of the fluoroquinolones.

D. Resistance

When the fluoroquinolones were first introduced, there was optimism that resistance would not develop. Although no plasmid-mediated resistance has been reported, resistant MRSA, pseudomonas, coagulase-negative staphylococci, and enterococci have unfortunately emerged due to chromosomal mutations. Cross-resistance exists among the quinolones. The mechanisms responsible for this resistance include the following.

1. **Altered target:** Mutations in the bacterial DNA gyrase have been associated with a decreased affinity for fluoroquinolones. Topoisomerase IV also undergoes mutations. Resistance is frequently associated with mutations in both gyrase and topoisomerase IV.
2. **Decreased accumulation:** Reduced intracellular concentration of the drugs in the bacterial cell is linked to two mechanisms. One involves a decreased number of porin proteins in the outer membrane of the resistant cell, thereby impairing access of the drugs to the intracellular topoisomerases. The other mechanism is associated with an energy-dependent efflux system in the cell membrane.

E. Pharmacokinetics

1. **Absorption:** Only 35 to 70 percent of orally administered *norfloxacin* is absorbed, compared with 85 to 95 percent of the other fluoroquinolones (Figure 33.5). Intravenous preparations of *ciprofloxacin, levofloxacin*, and *ofloxacin* are available. Ingestion of the fluoroquinolones with *sucralfate*, antacids containing aluminum or

magnesium, or dietary supplements containing iron or zinc can interfere with the absorption of these antibacterial drugs. Calcium and other divalent cations have also been shown to interfere with the absorption of these agents (Figure 33.6). The fluoroquinolones with the longest half-lives (*levofloxacin* and *moxifloxacin*) permit once-daily dosing.

2. **Fate:** Binding to plasma proteins ranges from 10 to 40 percent. [Note: Achieved plasma levels of free *norfloxacin* are insufficient for treatment of systemic infections.] All the fluoroquinolones distribute well into all tissues and body fluids. Levels are high in bone, urine, kidney, and prostatic tissue (but not prostatic fluid), and concentrations in the lung exceed those in serum. Penetration into cerebrospinal fluid is low except for *ofloxacin*, for which concentrations can be as high as 90 percent of those in the serum. The fluoroquinolones also accumulate in macrophages and polymorphonuclear leukocytes, thus being effective against intracellular organisms such as Legionella pneumophila. They are excreted by the renal route.

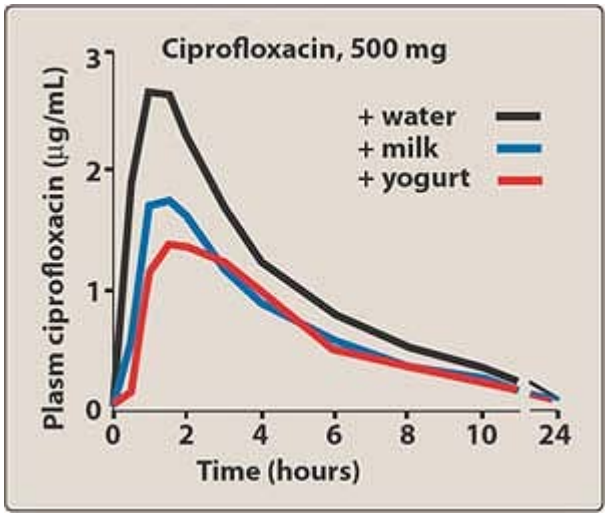

Figure 33.6 Effect of dietary calcium on the absorption of *ciprofloxaxin*.

F. Adverse reactions

In general, these agents are very well tolerated. Toxicities similar to those for *nalidixic acid* have been reported for the fluoroquinolones (Figure 33.7).

1. **Gastrointestinal:** The most common adverse effects of the fluoroquinolones are nausea, vomiting, and diarrhea, which occur in three to six percent of patients.

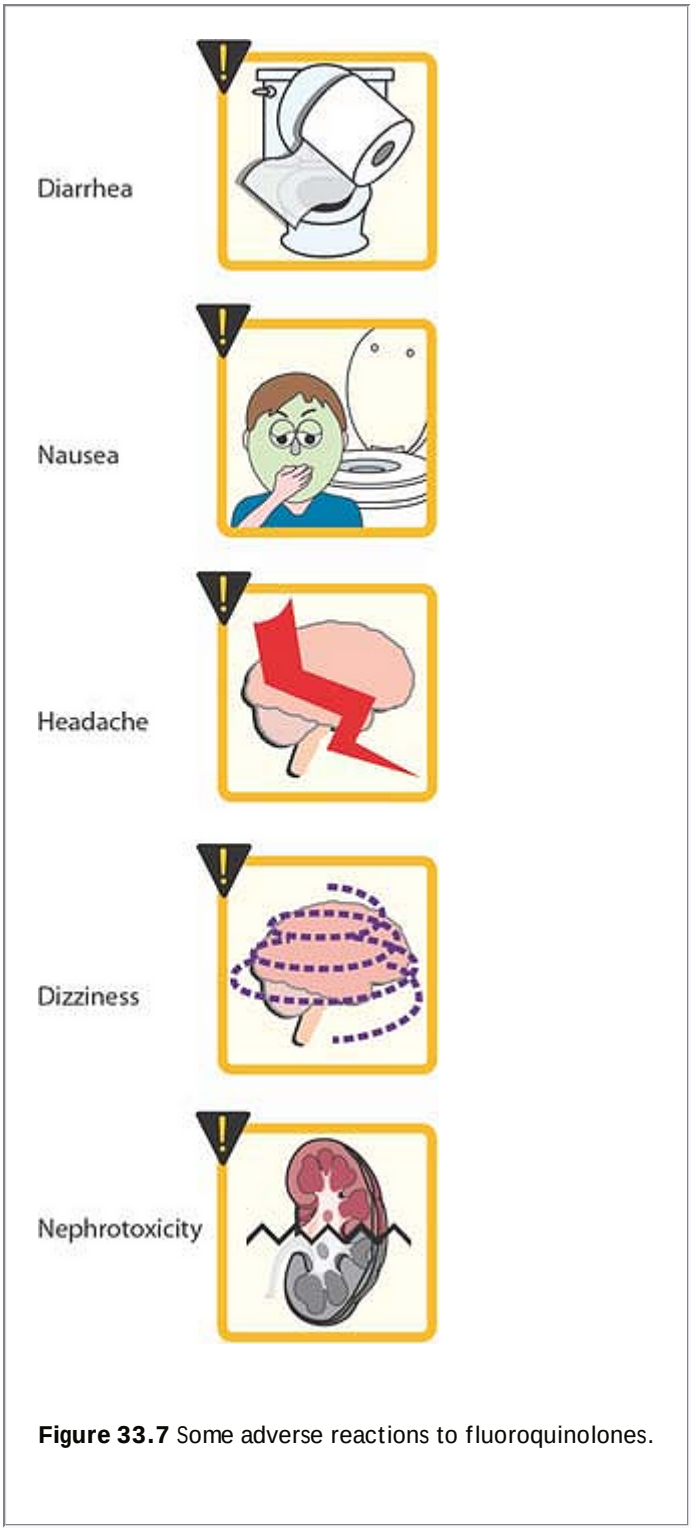

Figure 33.7 Some adverse reactions to fluoroquinolones.

2. **Central nervous system problems:** The most prominent central nervous system (CNS) effects of fluoroquinolone treatment are headache and dizziness or light-headedness. Thus, patients with CNS disorders, such as epilepsy, should be treated cautiously with these drugs. [Note: *Ciprofloxacin* interferes in the metabolism of *theophylline* and may evoke seizures.]
3. **Phototoxicity:** Patients taking fluoroquinolones are advised to avoid excessive sunlight and to apply sunscreens. However, the latter may not protect completely. Thus, it is advisable that the drug should be discontinued at the first sign of phototoxicity.
4. **Connective tissue problems:** Fluoroquinolones should be avoided in pregnancy, in nursing mothers, and in

children under 18 years of age, because articular cartilage erosion (arthropathy) occurs in immature experimental animals. [Note: Children with cystic fibrosis who receive *ciprofloxacin* have had few problems, but careful monitoring is indicated.] In adults, fluoroquinolones can infrequently cause ruptured tendons.

5. **Contraindications:** *Moxifloxacin* may prolong the QTc interval and, thus, should not be used in patients who are predisposed to arrhythmias or are taking antiarrhythmic medications.
6. **Drug interactions:** The effect of antacids and cations on the absorption of these agents was considered above. *Ciprofloxacin* and *ofloxacin* can increase the serum levels of *theophylline* by inhibiting its metabolism (Figure 33.8). This is not the case with the third- and fourth-generation fluoroquinolones, which may raise the serum levels of *warfarin, caffeine*, and *cyclosporine*.

II. Overview of the Folate Antagonists

Enzymes requiring folate-derived cofactors are essential for the synthesis of purines and pyrimidines[2] (precursors of RNA and DNA) and other compounds necessary for cellular growth and replication. Therefore, in the absence of folate, cells cannot grow or divide. To synthesize the critical folate derivative, tetrahydrofolic acid, humans must first obtain preformed folate in the form of folic acid as a vitamin from the diet. In contrast, many bacteria are impermeable to folic acid and other folates and, therefore, must rely on their ability to synthesize folate de novo. The sulfonamides (sulfa drugs) are a family of antibiotics that inhibit this de novo synthesis of folate. A second type of folate antagonistâ€"*trimethoprim*â€"prevents microorganisms from converting dihydrofolic acid to tetrahydrofolic acid, with minimal effect on a human cell's ability to make this conversion. Thus, both sulfonamides and *trimethoprim* interfere with the ability of an infecting bacterium to divide. Compounding the sulfonamide *sulfamethoxazole* with *trimethoprim* (the generic name for the combination is *cotrimoxazole*) provides a synergistic combination that is used as effective treatment of a variety of bacterial infections.

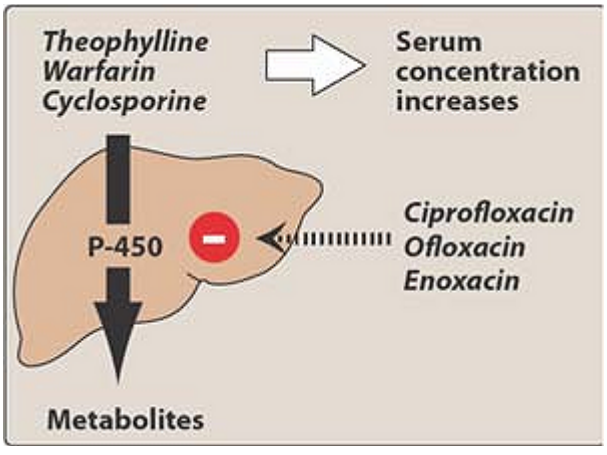

Figure 33.8 Drug interactions with fluoroquinolones.

III. Sulfonamides

The sulfa drugs are seldom prescribed alone except in developing countries, where they are still employed because of their low cost and their efficacy in certain bacterial infections, such as trachoma and those of the urinary tract. However, when *cotrimoxazole* was introduced in the mid-1970s, there was a renewed interest in the sulfonamides. Sulfa drugs differ from each other not only in their chemical and physical properties but also in their pharmacokinetics.

A. Mechanism of action

In many microorganisms, dihydrofolic acid is synthesized from *p*-aminobenzoic acid (PABA), pteridine, and glutamate (Figure 33.9). All the sulfonamides currently in clinical use are synthetic analogs of PABA.[3] Because of their structural similarity to PABA, the sulfonamides compete with this substrate for the bacterial enzyme, dihydropteroate synthetase. They thus inhibit the synthesis of bacterial dihydrofolic acid and, thereby, the formation of its essential cofactor forms.[4] The sulfa drugs, including *cotrimoxazole*, are bacteriostatic.

B. Antibacterial spectrum

Sulfa drugs are active against selected enterobacteria in the urinary tract and nocardia. In addition, *sulfadiazine* [sul-fa-DYE-a-zeen], in combination with the dihydrofolate reductase inhibitor *pyrimethamine* [py-ri-METH-a-meen], is the preferred form of treatment for toxoplasmosis and chloroquine-resistant malaria.

C. Resistance

Only organisms that synthesize their folate requirements de novo are sensitive to the sulfonamides. Thus, humans, who synthesize critical folate cofactors from dietary folic acid, are not affected, and bacteria that can obtain folates from their environment are naturally resistant to these drugs. Acquired bacterial resistance to the sulfa drugs can arise

from plasmid transfers or random mutations. [Note: Organisms resistant to one member of this drug family are resistant to all.] Resistance is generally irreversible and may be due to 1) an altered dihydropteroate synthetase, 2) decreased cellular permeability to sulfa drugs, or 3) enhanced production of the natural substrate, PABA.

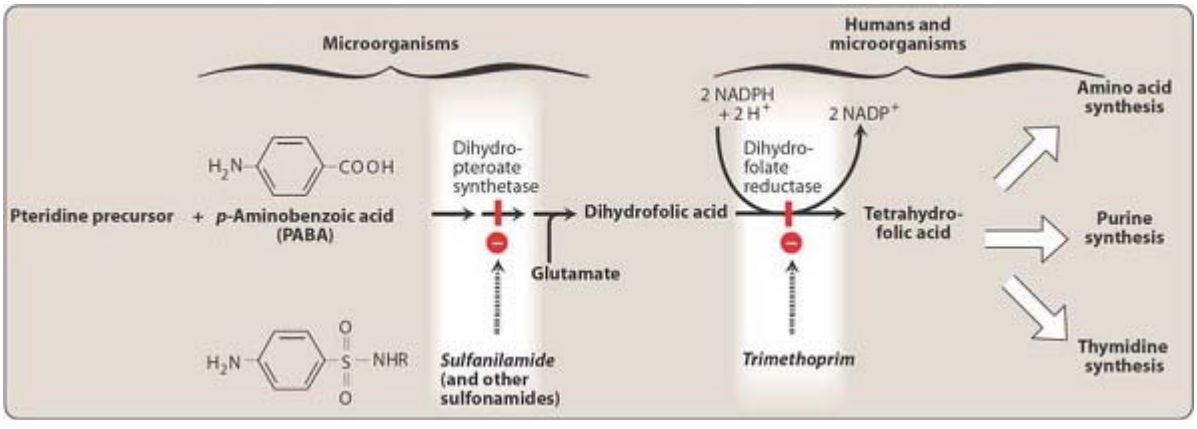

Figure 33.9 Inhibition of tetrahydrofolate synthesis by sulfonamides and *trimethoprim*.

D. Pharmacokinetics

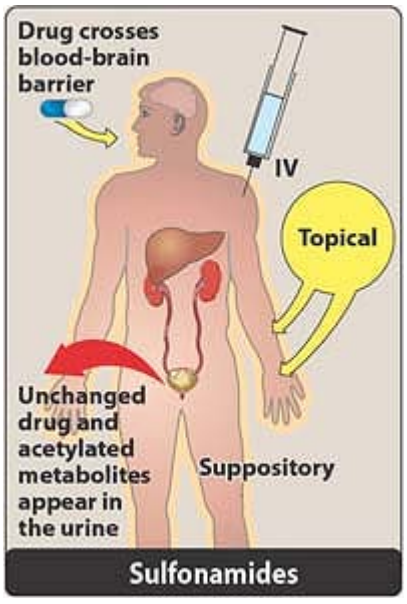

Figure 33.10 Administration and fate of the sulfonamides.

1. **Administration:** After oral administration, most sulfa drugs are well absorbed via the small intestine (Figure 33.10). An exception is *sulfasalazine* [sul-fa-SAL-a-zeen]. It is not absorbed when administered orally or as a suppository and, therefore, is reserved for treatment of chronic inflammatory bowel disease (for example, Crohn's disease or ulcerative colitis). [Note: Local intestinal flora split *sulfasalazine* into sulfapyridine and 5-aminosalicylate, with the latter exerting the anti-inflammatory effect. Absorption of the *sulfapyridine* can lead to toxicity in patients who are slow acetylators (see below).] Intravenous sulfonamides are generally reserved for patients who are unable to take oral preparations. Because of the risk of sensitization, sulfas are not usually applied topically. However, in burn units, creams of *silver sulfadiazine* or *mafenide* [mah-FEN-ide] *acetate* (*Î±-amino-p-toluene-sulfonamide*) have been effective in reducing burn-associated sepsis, because they prevent colonization of bacteria. Superinfections with resistant bacteria or fungi may still occur. [Note: *Silver sulfadiazine* is preferred, because *mafenide* produces pain on application. Furthermore, *mafenide* can be absorbed in burn patients, causing an increased risk of acid-base imbalance.]
2. **Distribution:** Sulfa drugs are bound to serum albumin in the circulation, where the extent of binding depends on the particular agent's pK_a. In general, the lower the pK_a, the greater the binding. Sulfa drugs distribute throughout the body's water and penetrate well into cerebrospinal fluidâ€”even in the absence of inflammation. They can also pass the placental barrier and enter fetal tissues.
3. **Metabolism:** The sulfa drugs are acetylated, primarily in the liver. The product is devoid of antimicrobial activity but retains the toxic potential to precipitate at neutral or acidic pH. This causes crystalluria (â€œstone formationâ€; see below) and, therefore, potential damage to the kidney.
4. **Excretion:** Sulfa drugs are eliminated by glomerular filtration. Therefore, depressed kidney function causes accumulation of both the parent compounds and their metabolites. The sulfonamides may also be eliminated in breast milk.

E. Adverse effects

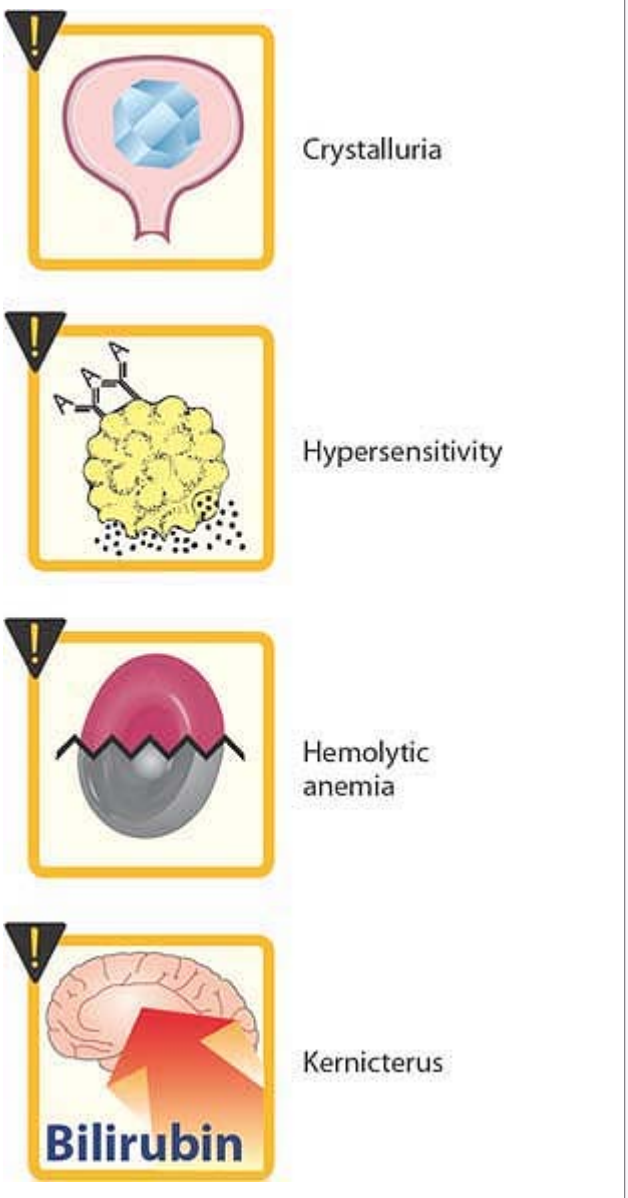

Figure 33.11 Some adverse reactions to sulfonamides.

1. **Crystalluria:** Nephrotoxicity develops as a result of crystalluria (Figure 33.11). Adequate hydration and alkalinization of urine prevent the problem by reducing the concentration of drug and promoting its ionization. Agents, such as *sulfisoxazole* [sul-fi-SOX-a-zole] and *sulfamethoxazole* [sul-fa-meth-OX-a-zole] are more soluble at urinary pH than are the older sulfonamides (for example, *sulfadiazine*) and are less liable to cause crystalluria .

2. **Hypersensitivity:** Hypersensitivity reactions, such as rashes, angioedema, and Stevens-Johnson syndrome, are fairly common. The latter occurs more frequently with the longer-acting agents.

3. **Hemopoietic disturbances:** Hemolytic anemia is encountered in patients with glucose 6-phosphate dehydrogenase deficiency.Granulocytopenia and thrombocytopenia can also occur.

4. **Kernicterus:** This disorder may occur in newborns, because sulfa drugs displace bilirubin from binding sites on

serum albumin. The bilirubin is then free to pass into the CNS, because the baby's blood-brain barrier is not fully developed (see below).

Figure 33.12 Contraindication for sulfonamide treatment.

5. **Drug potentiation:** Transient potentiation of the hypoglycemic effect of *tolbutamide* or the anticoagulant effect of *warfarin* results from their displacement from binding sites on serum albumin. Free *methotrexate* levels may also rise through displacement.
6. **Contraindications:** Due to the danger of kernicterus, sulfa drugs should be avoided in newborns and infants less than 2 months of age as well as in pregnant women at term. Because sulfonamides condense with formaldehyde, they should not be given to patients receiving *methenamine* for UTIs (Figure 33.12).

IV. Trimethoprim

Trimethoprim [trye METH-oh-prim], a potent inhibitor of bacterial dihydrofolate reductase, exhibits an antibacterial spectrum similar to that of the sulfonamides. *Trimethoprim* is most often compounded with *sulfamethoxazole*, producing the combination called *cotrimoxazole*.

A. Mechanism of action

The active form of folate is the tetrahydro-derivative that is formed through reduction of dihydrofolic acid by dihydrofolate reductase.[5] This enzymatic reaction (see Figure 33.9) is inhibited by *trimethoprim*, leading to a decreased availability of the tetrahydrofolate coenzymes required for purine, pyrimidine, and amino acid synthesis. The bacterial reductase has a much stronger affinity for *trimethoprim* than does the mammalian enzyme, which accounts for the drug's selective toxicity. [Note: Examples of other drugs that function as folate reductase inhibitors include *pyrimethamine*, which is used with sulfonamides in treating parasitic infections, and *methotrexate*, which is used in the treatment of cancer, rheumatoid arthritis, and psoriasis].

B. Antibacterial spectrum

The antibacterial spectrum of *trimethoprim* is similar to that of *sulfamethoxazole*. However, *trimethoprim* is 20- to 50-fold more potent than the sulfonamide. *Trimethoprim* may be used alone in the treatment of acute UTIs and in the treatment of bacterial prostatitis (although fluoroquinolones are preferred) and vaginitis.

C. Resistance

Resistance in gram-negative bacteria is due to the presence of an altered dihydrofolate reductase that has a lower

affinity for *trimethoprim*. Overproduction of the enzyme may also lead to resistance, because this can decrease drug permeability.

D. Pharmacokinetics

The half-life of *trimethoprim* is similar to that of *sulfamethoxazole.* However, because the drug is a weak base, higher concentrations of *trimethoprim* are achieved in the relatively acidic prostatic and vaginal fluids. The drug also penetrates the cerebrospinal fluid. *Trimethoprim* undergoes some O-demethylation, but most of it is excreted unchanged through the kidney.

E. Adverse effects

Trimethoprim can produce the effects of folic acid deficiency.[6] These effects include megaloblastic anemia, leukopenia, and granulocytopenia, especially in pregnant patients and those having very poor diets. These blood disorders can be reversed by the simultaneous administration of *folinic acid*, which does not enter bacteria.

V. Cotrimoxazole

The combination of *trimethoprim* with *sulfamethoxazole*, called *cotrimoxazole* [co-try-MOX-a-zole], shows greater antimicrobial activity than equivalent quantities of either drug used alone (see Figure 33.13). The combination was selected because of the similarity in the half-lives of the two drugs.

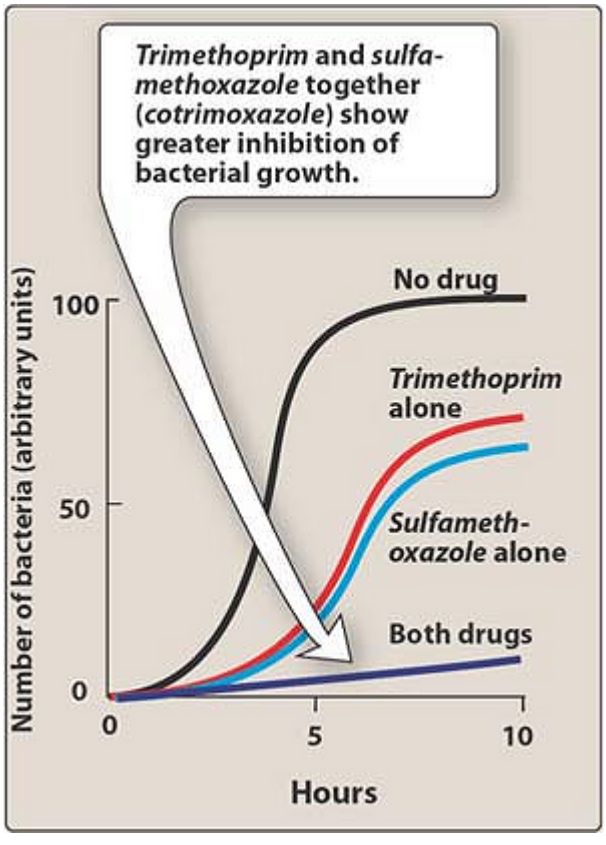

Figure 33.13 Synergism between *trimethoprim* and *sulfamethoxazole* on the inhibition of growth of Escherichia coli.

A. Mechanism of action

The synergistic antimicrobial activity of *cotrimoxazole* results from its inhibition of two sequential steps in the synthesis of tetrahydrofolic acid: *Sulfamethoxazole* inhibits the incorporation of PABA into dihydrofolic acid precursors, and *trimethoprim* prevents reduction of dihydrofolate to tetrahydrofolate (see Figure 33.9).

B. Antibacterial spectrum

Cotrimoxazole has a broader spectrum of antibacterial action than the sulfa drugs (Figure 33.14). It is effective in treating UTIs and respiratory tract infections as well as in Pneumocystis jiroveci pneumonia and *ampicillin*- or *chloramphenicol*-resistant systemic salmonella infections.

C. Resistance

Resistance to the *trimethoprim-sulfamethoxazole* combination is less frequently encountered than resistance to either of the drugs alone, because it would require that the bacterium have simultaneous resistance to both drugs.

D. Pharmacokinetics

Trimethoprim is more lipid soluble than *sulfamethoxazole* and has a greater volume of distribution. Administration of one part *trimethoprim* to five parts of the sulfa drug produces a ratio of the drugs in the plasma of twenty parts *sulfamethoxazole* to one part *trimethoprim*. This ratio is optimal for the antibiotic effect. *Cotrimoxazole* is generally administered orally (Figure 33.15). An exception involves intravenous administration to patients with severe pneumonia caused by P. jiroveci or to patients who cannot take the drug by mouth. Both agents distribute throughout the body. *Trimethoprim* concentrates in the relatively acidic

milieu of prostatic and vaginal fluids, and it accounts for the use of the *trimethoprim-sulfamethoxazole* combination in infections at these sites. Both parent drugs and their metabolites are excreted in the urine.

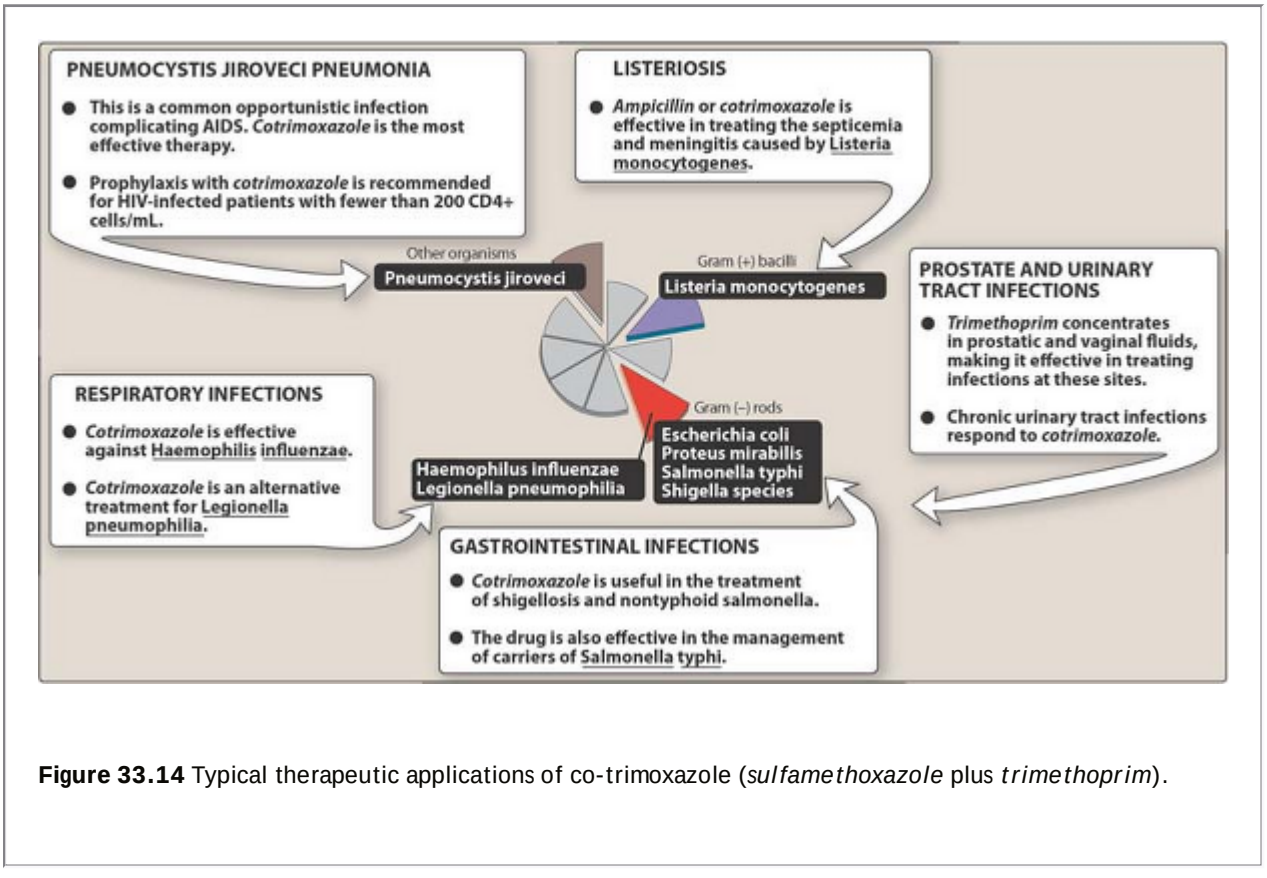

Figure 33.14 Typical therapeutic applications of co-trimoxazole (*sulfamethoxazole* plus *trimethoprim*).

E. Adverse effects

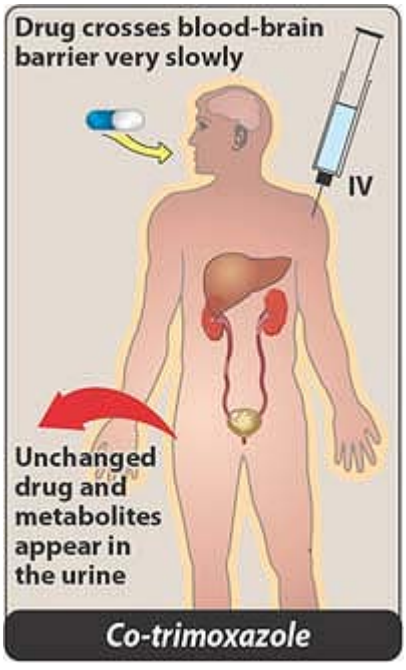

Figure 33.15 Administration and fate of the *cotrimoxazole.*

1. **Dermatologic:** Reactions involving the skin are very common and may be severe in the elderly (Figure 33.16).
2. **Gastrointestinal:** Nausea, vomiting, as well as glossitis and stomatitis are not unusual.
3. **Hematologic:** Megaloblastic anemia, leukopenia, and thrombocytopenia may occur. All these effects may be reversed by the concurrent administration of *folinic acid*, which protects the patient and does not enter the microorganism. Hemolytic anemia may occur in patients with glucose 6-phosphate dehydrogenase deficiency due to the *sulfamethoxazole*.
4. **Patients infected with human immunodeficiency virus:** Immuno-compromised patients with P. jiroveci pneumonia frequently show drug-induced fever, rashes, diarrhea, and/or pancytopenia.
5. **Drug interactions:** Prolonged prothrombin times in patients receiving both *trimethoprim* and *warfarin* have been reported. The plasma half-life of *phenytoin* may be increased due to an inhibition of its metabolism. *Methotrexate* levels may rise due to displacement from albumin-binding sites by *sulfamethoxazole*.

VI. Urinary Tract Antiseptics/Antimicrobials

Urinary tract infections (most commonly uncomplicated acute cystitis and pyelonephritis) in women of child-bearing age and in the elderly are one of the most common problems seen by primary care physicians. Escherichia coli is the most common pathogen, causing about 80 percent of uncomplicated upper and lower UTIs. Staphylococcus saprophyticus is the second most common bacterial pathogen causing UTIs, with other common causes including Klebsiella pneumoniae and Proteus mirabilis These infections may be treated with any one of a group of agents called urinary tract antiseptics, including *methenamine, nitrofurantoin*, and the quinolone *nalidixic acid*. These drugs do not achieve antibacterial levels in the circulation, but because they are concentrated in the urine,

microorganisms at that site can be effectively eradicated.

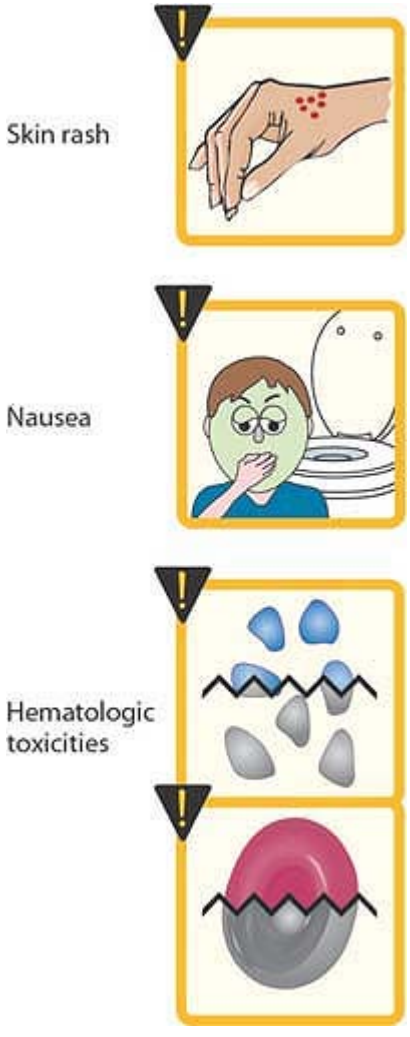

Figure 33.16 Some adverse reactions to *cotrimoxazole*.

A. Methenamine

1. **Mechanism of action:** To act, *methenamine* [meth-EN-a-meen] must decompose at an acidic pH of 5.5 or less in the urine, thus producing formaldehyde, which is toxic to most bacteria (Figure 33.17). The reaction is slow, requiring 3 hours to reach 90 percent decomposition. *Methenamine* should not be used in patients with indwelling catheters. Bacteria do not develop resistance to formaldehyde. [Note: *Methenamine* is frequently formulated with a weak acid, such as mandelic acid or hippuric acid.]

2. **Antibacterial spectrum:** *Methenamine* is primarily used for chronic suppressive therapy. Urea-splitting bacteria that alkalinize the urine, such as Proteus species, are usually resistant to the action of *methenamine*. *Methenamine* is used to treat lower UTIs but is not effective in upper UTIs.

3. **Pharmacokinetics:** *Methenamine* is administered orally. In addition to formaldehyde, ammonium ion is produced in the bladder. Because the liver rapidly metabolizes ammonia to form urea, *methenamine* is contraindicated in patients with hepatic insufficiency, in which elevated levels of circulating ammonium ions would be toxic to the CNS. *Methenamine* is distributed throughout the body fluids, but no decomposition of the

drug occurs at pH 7.4. Thus, systemic toxicity does not occur. The drug is eliminated in the urine.

4. **Adverse effects:** The major side effect of *methenamine* treatment is gastrointestinal distress, although at higher doses, albuminuria, hematuria, and rashes may develop. *Methenamine mandelate* is contraindicated in patients with renal insufficiency, because mandelic acid may precipitate. [Note: Sulfonamides react with formaldehyde and must not be used concomitantly with *methenamine*.]

B. Nitrofurantoin

Nitrofurantoin [nye-troe-FYOOR-an-toyn] is less commonly employed for treating UTIs because of its narrow antimicrobial spectrum and its toxicity. Sensitive bacteria reduce the drug to an active agent that inhibits various enzymes and damages DNA. Antibiotic activity is greater in acidic urine. The drug is bacteriostatic. It is useful against E. coli, but other common urinary tract gram-negative bacteria may be resistant. Gram-positive cocci are susceptible. Adverse effects include gastrointestinal disturbances, acute pneumonitis, and neurologic problems.

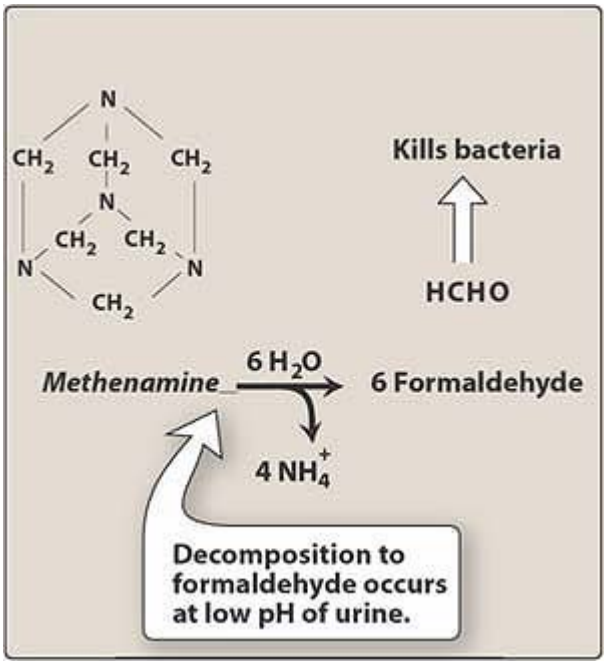

Figure 33.17 Formation of formaldehyde from *methenamine* at acid pH.

Study Questions

Choose the ONE best answer.

33.1 A 30-year-old male is diagnosed to be human immunodeficiency virus (HIV) positive. His CD4+ count is 200 cells/mm^3 and his viral load is 10,000 copies/mL. In addition to receiving antiviral therapy, which of the following is indicated to protect him against pneumonia due to Pneumocystis jiroveci?

A. Trimethoprim.

B. Ciprofloxacin.

C. Cotrimoxazole.

D. Clindamycin.

View Answer

33.2 A 26-year-old young man presents with the symptoms of gonorrhea. Because this condition is often associated with an infection due to Chlamydia trachomatis, which of the following quinolones would be the best choice for treating him?

A. Ciprofloxacin.

B. Nalidixic acid.

C. Norfloxacin.

D. Levofloxacin.

View Answer

33.3 In which one of the following infections is ciprofloxacin ineffective?

A. Urinary tract infections due to a Î²-lactamase producing strain of Klebsiella.

B. Pneumonia due to Streptococcus pneumoniae.

C. Exacerbation of chronic bronchitis due to Moraxella catarrhalis.

D. UTI due to Escherichia coli.

E. UTIs due to Pseudomonas aeruginosa.

View Answer

33.4 Sulfonamides increase the risk of neonatal kernicterus, because they:

A. Diminish the production of plasma albumin.

B. Increase the turnover of red blood cells.

C. Inhibit the metabolism of bilirubin.

D. Compete for bilirubin-binding sites on plasma albumin.

E. Depress the bone marrow.

View Answer

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Title: *Lippincott's Illustrated Reviews: Pharmacology, 4th Edition*

Chapter 34

Antimycobacterials

I. Overview

Mycobacteria are slender, rod-shaped bacteria with lipid-rich cell walls that stain poorly with the Gram stain, but once stained, the walls cannot be easily decolorized by treatment with acidified organic solvents. Hence, they are termed â€œacid-fast.â€ The most widely encountered mycobacterial infections is tuberculosisâ€”the leading cause worldwide of death from infection. Members of the genus Mycobacterium also cause leprosy as well as several tuberculosis-like human infections. Mycobacterial infections are intracellular and, generally, result in the formation of slow-growing granulomatous lesions that are responsible for major tissue destruction.[1] There are four currently recommended first-line agents utilized for antituberculosis therapy (Figure 34.1). Second-line medications are either less effective, more toxic, or have not been studied as extensively. They are useful in patients who cannot tolerate the first-line drugs or who are infected with myobacteria that are resistant to the first-line agents.

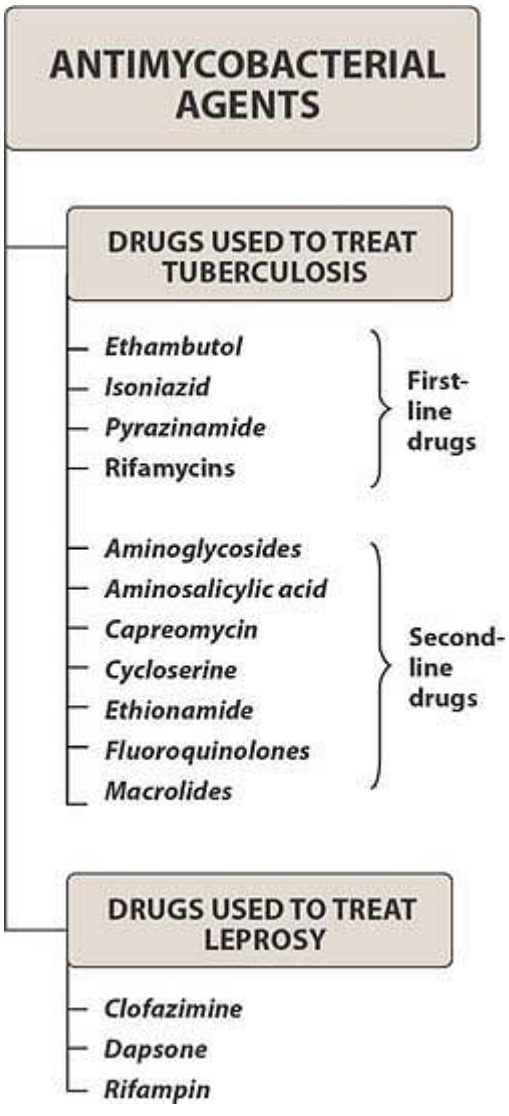

Figure 34.1 Summary of drugs used to treat mycobacterial infections.

II. Chemotherapy for Tuberculosis

Mycobacterium tuberculosis, one of a number of mycobacteria, can lead to serious infections of the lungs, genitourinary tract, skeleton, and meninges. Treating tuberculosis as well as other mycobacterial infections presents therapeutic problems. The organism grows slowly; thus, the disease may have to be treated for 6 months to 2 years. Resistant organisms readily emerge, particularly in patients who have had prior therapy or who fail to adhere to the treatment protocol. It is currently estimated that about one-third of the world's population is infected with M. tuberculosis, with 30 million people having active disease. Worldwide, 8 million new cases occur, and approximately 2 million people die of the disease each year.

A. Strategies for addressing drug resistance

Strains of M. tuberculosis that are resistant to a particular agent emerge during treatment with a single drug. For example, Figure 34.2 shows that resistance rapidly develops in patients given only *streptomycin*. Therefore, multidrug therapy is employed when treating tuberculosis in an effort to delay or prevent the emergence of

are the principal or so-called â€œfirst-lineâ€ drugs because of their efficacy and acceptable degree of toxicity. Today, however, because of poor patient compliance and other factors, the number of multidrug-resistant organisms has risen. Some bacteria have been identified that are resistant to as many as seven antitubercular agents. Therefore, although treatment regimens vary in duration and in the agents employed, they always include a minimum of two drugs, preferably with both being bactericidal (see p. 348). The combination of drugs should prevent the emergence of resistant strains. The multidrug regimen is continued well beyond the disappearance of clinical disease to eradicate any persistent organisms. For example, the initial short-course chemotherapy for tuberculosis includes *isoniazid, rifampin, ethambutol,* and *pyrazinamide* for 2 months and then *isoniazid* and *rifampin* for the next 4 months (the â€œcontinuation phaseâ€; Figure 34.3). Before susceptibility data are available, more drugs may be added to the first-line ones for patients who have previously had tuberculosis or those in whom multidrug-resistant tuberculosis is suspected. The added drugs normally include an aminoglycoside (*streptomycin, kanamycin,* or *amikacin*) or *capreomycin* (injectable agents), a fluoroquinolone, and perhaps a second-line antituberculosis agent such as *cycloserine, ethionamide,* or *para-aminosalicylic acid*. Once susceptibility data are available, the drug regimen can be individually tailored to the patient. Patient compliance is often low when multidrug schedules last for 6 months or longer. One successful strategy for achieving better treatment completion rates is â€œdirectly observed therapy,â€ also known as DOT, in which patients take their medication while being supervised and observed. DOT have been shown to decrease drug resistance as well as relapse and mortality rates and to improve cure rates. Most local and state health departments offer DOT services.

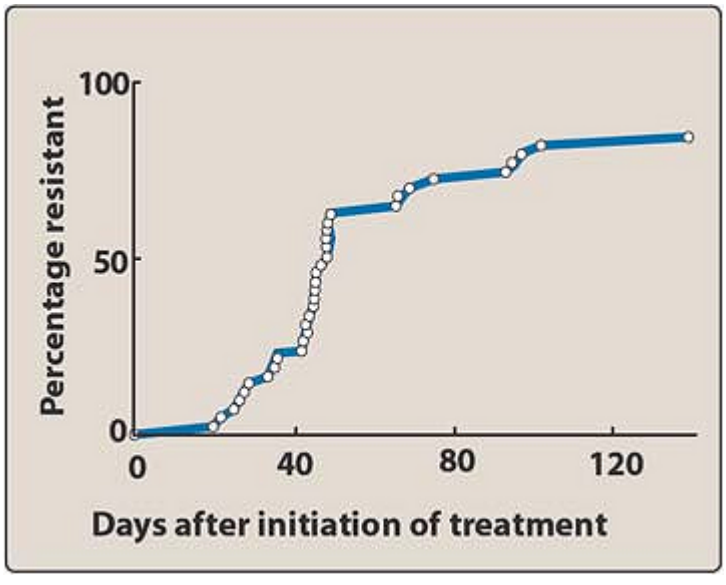

Figure 34.2 Cumulative percentage of strains of Mycobacterium tuberculosis showing resistance to streptomycin.

B. Isoniazid

Isoniazid [eye-soe-NYE-a-zid], the hydrazide of isonicotinic acid, is a synthetic analog of pyridoxine. It is the most potent of the antitubercular drugs but is never given as a single agent in the treatment of active tuberculosis. Its introduction revolutionized the treatment of tuberculosis.

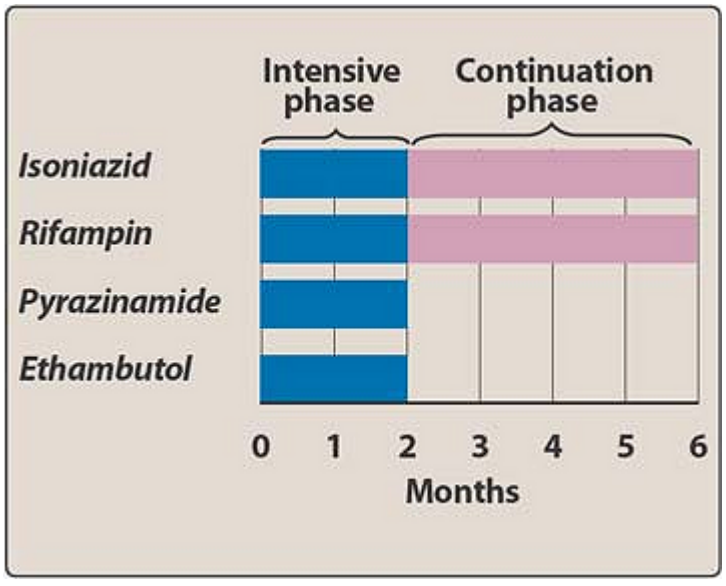

Figure 34.3 One of several recommended multidrug schedules for the treatment of tuberculosis.

1. **Mechanism of action:** *Isoniazid*, often referred to as *INH*, is a prodrug that is activated by a mycobacterial catalase-peroxidase (KatG). Genetic and biochemical evidence has implicated at least two different target enzymes for *isoniazid* within the unique Type II fatty acid synthase system involved in the production of mycolic acids. [Note: Mycolic acid is a unique class of very-long-chain, Î²-hydroxylated fatty acids found in mycobacterial cell walls. Decreased mycolic acid synthesis corresponds with the loss of acid-fastness after exposure to *isoniazid*.] The targeted enzymes are enoyl acyl carrier protein reductase (InhA) and a Î²-ketoacyl-ACP synthase (KasA). The activated drug covalently binds to and inhibits these enzymes, which are essential for the synthesis of mycolic acid.

2. **Antibacterial spectrum:** For bacilli in the stationary phase, *isoniazid* is bacteriostatic, but for rapidly dividing organisms, it is bactericidal. It is effective against intracellular bacteria. *Isoniazid* is specific for treatment of M. tuberculosis, although Mycobacterium kansasii (an organism that causes three percent of the clinical illness known as tuberculosis) may be susceptible at higher drug levels. When it is used alone, resistant organisms rapidly emerge.

3. **Resistance:** This is associated with several different chromosomal mutations, each of which results in one of the following: mutation or deletion of KatG (producing mutants incapable of prodrug activation), varying mutations of the acyl carrier proteins, or overexpression of InhA. Cross-resistance does not occur between *isoniazid* and other antitubercular drugs.

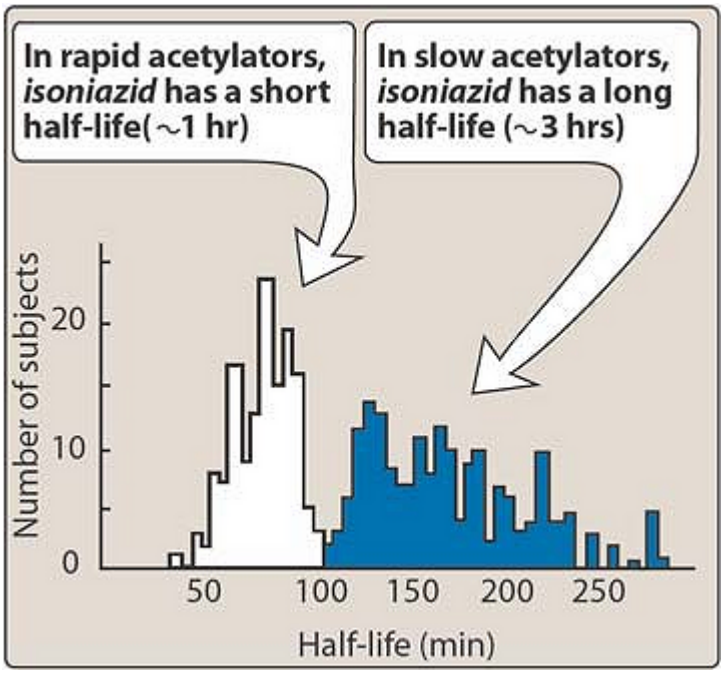

Figure 34.4 Bimodal distribution of *isoniazid* half-lives caused by rapid and slow acetylation of the drug.

4. **Pharmacokinetics:** Orally administered *isoniazid* is readily absorbed. Absorption is impaired if *isoniazid* is taken with food, particularly carbohydrates, or with aluminum-containing antacids. The drug diffuses into all body fluids, cells, and caseous material (necrotic tissue resembling cheese that is produced in tubercles). Drug levels in the cerebrospinal fluid (CSF) are about the same as those in the serum. The drug readily penetrates host cells and is effective against bacilli growing intracellularly. Infected tissue tends to retain the drug longer. *Isoniazid* undergoes N-acetylation and hydrolysis, resulting in inactive products. [Note: Acetylation is genetically regulated, with the fast acetylator trait being autosomally dominant. A bimodal distribution of fast and slow acetylators exists (Figure 34.4).] Chronic liver disease decreases metabolism, and doses must be reduced. Excretion is through glomerular filtration, predominantly as metabolites (Figure 34.5). Slow acetylators excrete more of the parent compound. Severely depressed renal function results in accumulation of the drug, primarily in slow acetylators.

5. **Adverse effects:** The incidence of adverse effects is fairly low. Except for hypersensitivity, adverse effects are related to the dosage and duration of administration.

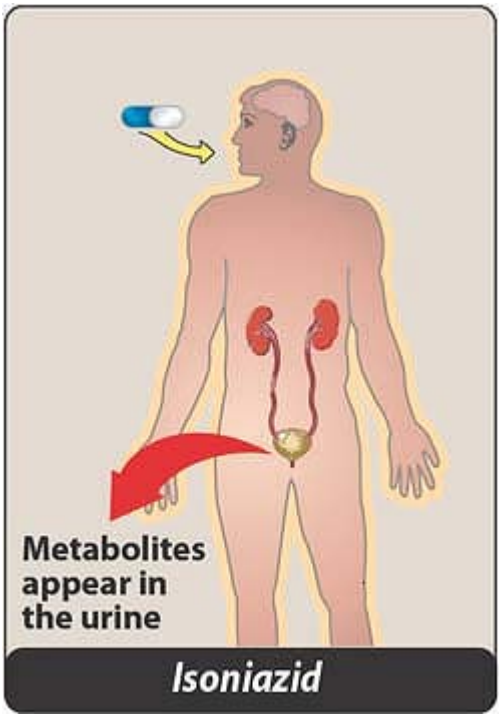

Figure 34.5 Administration and fate of *isoniazid*.

a. **Peripheral neuritis:** Peripheral neuritis (manifesting as paresthesias of the hands and feet), which is the most common adverse effect, appears to be due to a relative pyridoxine deficiency. Most of the toxic reactions are corrected by supplementation of 25 to 50 mg per day of pyridoxine (vitamin B_6). [Note: *Isoniazid* can achieve levels in breast milk that are high enough to cause a pyridoxine deficiency in the infant unless the mother is supplemented with the vitamin.[2]]

b. **Hepatitis and idiosyncratic hepatotoxicity:** Potentially fatal hepatitis is the most severe side effect associated with *isoniazid*. It has been suggested that this is caused by a toxic metabolite of monoacetylhydrazine, formed during the metabolism of *isoniazid*. Its incidence increases among patients with increasing age, among patients who also take *rifampin*, or among those who drink alcohol daily.

c. **Drug interactions:** Because *isoniazid* inhibits metabolism of *phenytoin* (Figure 34.6), *isoniazid* can potentiate the adverse effects of that drug (for example, nystagmus and ataxia). Slow acetylators are particularly at risk .

d. **Other adverse effects:** Mental abnormalities, convulsions in patients prone to seizures, and optic neuritis have been observed. Hypersensitivity reactions include rashes and fever.

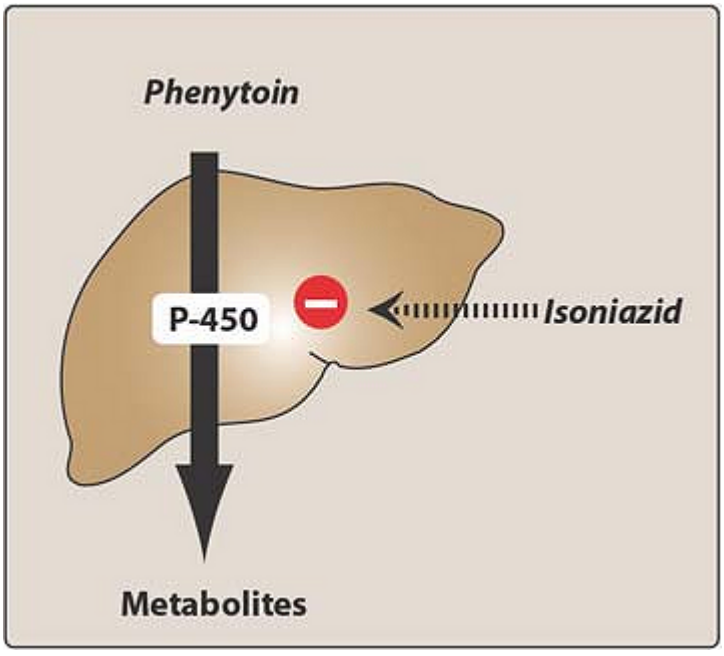

Figure 34.6 Isoniazid potentiates the adverse effects of *phenytoin*.

C. Rifamycins: Rifampin, rifabutin and rifapentine

Rifampin, rifabutin, and *rifapentine* are all considered to be rifamycins, a group of structurally similar macrocyclic antibiotics, which are first-line drugs for tuberculosis. Any of these rifamycins must always be used in conjunction with at least one other antituberculosis drug to which the isolate is susceptible.

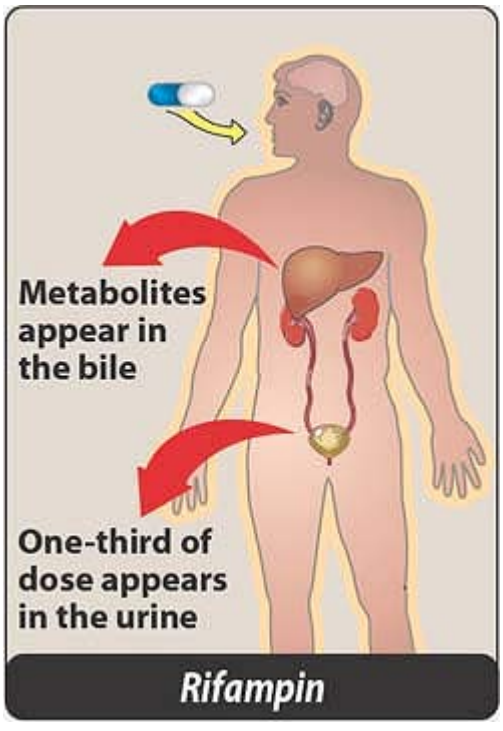

Figure 34.7 Administration and fate of *rifampin*. [Note: Patient should be warned that urine and tears may be orange-red in color.]

1. **Rifampin:** *Rifampin* [rif-AM-pin], which is derived from the soil mold Streptomyces, has a broader antimicrobial activity than *isoniazid* and has found application in the treatment of a number of different bacterial infections. Because resistant strains rapidly emerge during therapy, it is never given as a single agent in the treatment of active tuberculosis.

    a. **Mechanism of action:** *Rifampin* blocks transcription by interacting with the Î² subunit of bacterial but not human DNA-dependent RNA polymerase. [Note: The drug is thus specific for prokaryotes.] *Rifampin* inhibits mRNA synthesis by suppressing the initiation step.

    b. **Antimicrobial spectrum:** *Rifampin* is bactericidal for both intracellular and extracellular mycobacteria, including M. tuberculosis, and atypical mycobacteria, such as M. kansasii. It is effective against many gram-positive and gram-negative organisms and is frequently used prophylactically for individuals exposed to meningitis caused by meningococci or Haemophilus influenzae. *Rifampin* is the most active antileprosy drug at present, but to delay the emergence of resistant strains, it is usually given in combination with other drugs. *Rifabutin*, an analog of *rifampin*, has some activity against Mycobacterium avium-intracellulare complex but is less active against tuberculosis.

    c. **Resistance:** Resistance to *rifampin* can be caused by a mutation in the affinity of the bacterial DNA-dependent RNA polymerase for the drug or by decreased permeability.

    d. **Pharmacokinetics:** Absorption is adequate after oral administration. Distribution of *rifampin* occurs to all body fluids and organs. Adequate levels are attained in the CSF even in the absence of inflammation. The drug is taken up by the liver and undergoes enterohepatic cycling. *Rifampin* itself can induce the hepatic mixed-function oxidases (see p. 14), leading to a shortened half-life. Elimination of metabolites and the parent drug is via the bile into the feces or via the urine (Figure 34.7). [Note: Urine and feces as well as other secretions have an orange-red color; patients should be forewarned. Tears may permanently stain soft

contact lenses orange-red.]

e. **Adverse effects:** Rifampin is generally well tolerated. The most common adverse reactions include nausea, vomiting, and rash. Hepatitis and death due to liver failure is rare; however, the drug should be used judiciously in patients who are alcoholic, elderly, or have chronic liver disease due to the increased incidence of severe hepatic dysfunction when *rifampin* is administered alone or concomitantly with *isoniazid.* Often, when *rifampin* is dosed intermittently, or in daily doses of 1.2 grams or greater, a flu-like syndrome is associated with fever, chills, and myalgias

and sometimes is associated with acute renal failure, hemolytic anemia, and shock.

f. **Drug interactions:** Because *rifampin* can induce a number of cytochrome P450 enzymes (see p. 14), it can decrease the half-lives of other drugs that are coadministered and metabolized by this system (Figure 34.8). This may lead to higher dosage requirements for these agents.

2. **Rifabutin:** *Rifabutin* [rif-a-BYOO-tin], a derivative of *rifampin*, is the preferred drug for use in tuberculosis-infected with the human immunodeficiency virus (HIV) patients who are concomitantly treated with protease inhibitors or nonnucleoside reverse transcriptase inhibitors, because it is a less potent inducer of cytochrome P450 enzymes. *Rifabutin* has adverse effects similar to those of *rifampin* but can also cause uveitis, skin hyperpigmentation, and neutropenia.

3. **Rifapentine:** *Rifapentine* [rih-fa-PEN-teen] has activity comparable to that of *rifampin* but has a longer half-life than *rifampin* and *rifabutin*, which permits weekly dosing. However, for the intensive phase (initial 2 months) of the short-course therapy for tuberculosis, *rifapentine* is given twice weekly. In the subsequent phase, *rifapentine* is dosed once per week for 4 months. To avoid resistance issues, *rifapentine* should not be used alone but, rather, be included in a three to four-drug regimen.

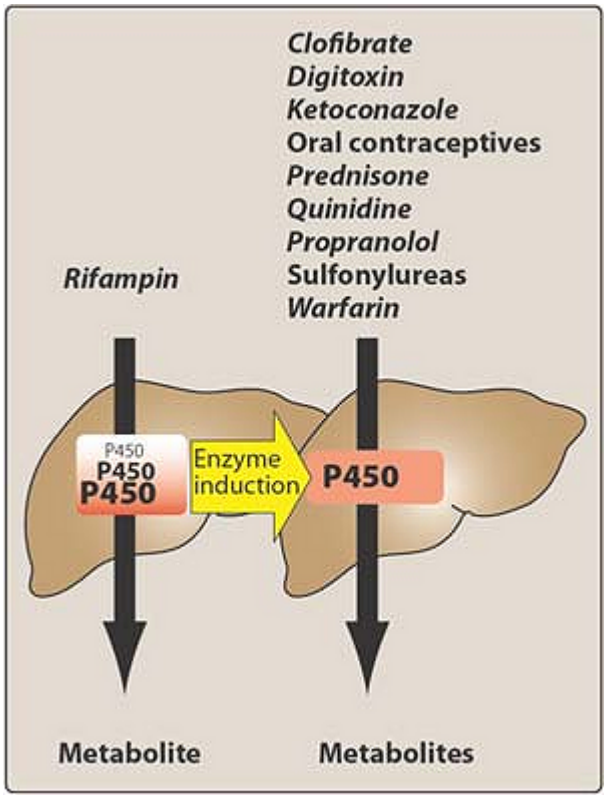

Figure 34.8 *Rifampin* induces cytochrome P450, which can decrease the half-lives of coadministered drugs

that are metabolized by this system.

D. Pyrazinamide

Pyrazinamide [peer-a-ZIN-a-mide] is a synthetic, orally effective, bactericidal, antitubercular agent used in combination with *isoniazid, rifampin,* and *ethambutol*. It is bactericidal to actively dividing organisms, but the mechanism of its action is unknown. *Pyrazinamide* must be enzymatically hydrolyzed to pyrazinoic acid, which is the active form of the drug. Some resistant strains lack the pyrazinamidase. *Pyrazinamide* is active against tubercle bacilli in the acidic environment of lysosomes as well as in macrophages. *Pyrazinamide* distributes throughout the body, penetrating the CSF. It undergoes extensive metabolism. About one to five percent of patients taking *isoniazid, rifampin*, and *pyrazinamide* may experience liver dysfunction. Urate retention can also occur and may precipitate a gouty attack (Figure 34.9).

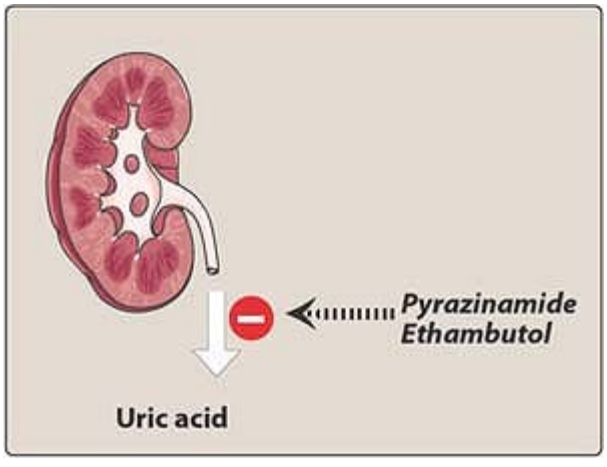

Figure 34.9 *Pyrazinamide and ethambutol* may cause urate retention and gouty attacks.

E. Ethambutol

Ethambutol [e-THAM-byoo-tole] is bacteriostatic and specific for most strains of M. tuberculosis and M. kansasii. *Ethambutol* inhibits arabinosyl transferaseâ€"an enzyme that is important for the synthesis of the mycobacterial arabinogalactan cell wall. Resistance is not a serious problem if the drug is employed with other antitubercular agents. *Ethambutol* can be used in combination with *pyrazinamide, isoniazid*, and *rifampin* to treat tuberculosis. Absorbed on oral administration, *ethambutol* is well distributed throughout the body. Penetration into the central nervous system (CNS) is therapeutically adequate in tuberculous meningitis. Both parent drug and metabolites are excreted by glomerular filtration and tubular secretion. The most important adverse effect is optic neuritis, which results in diminished visual acuity and loss of ability to discriminate between red and green. Visual acuity should be periodically examined. Discontinuation of the drug results in reversal of the optic symptoms. In addition, urate excretion is decreased by the drug; thus, gout may be exacerbated (see Figure 34.9). Figure 34.10 summarizes

some of the characteristics of first-line drugs. [Note: As with any drug, antitubercular drugs have a therapeutic margin, which is the difference between the minimum drug concentration required to inhibit the growth of M. tuberculosis and the maximum concentration that can be given without provoking drug toxicity.]

DRUG	ADVERSE EFFECTS	COMMENTS
Ethambutol	Optic neuritis with blurred vision, red-green color blindness	Establish baseline visual acuity and color vision; test monthly.
Isoniazid	Hepatic enzyme elevation, hepatitis, peripheral neuropathy	Take baseline hepatic enzyme measurements; repeat if abnormal or patient is at risk or symptomatic. Clinically significant interation with *phenytoin* and antifugal agents (azols).
Pyrazinamide	Nausea, hepatitis, hyperuricemia, rash, joint ache, gout (rare)	Take baseline hepatic enzymes and uric acid measurements; repeat if abnormal or patient is at risk or symptomatic.
Rifampin	Hepatitis, GI upset, rash, flu-like syndrome, significant interaction with several drugs	Take baseline hepatic enzyme measurements and CBC count; repeat if abnormal or patient is at risk or symptomatic. Warn patient that urine and tears may turn red-orange in color.

Figure 34.10 Some characteristics of first-line drugs used in treating tuberculosis. CBC = complete blood count.

F. Alternate second-line drugs

A number of drugsâ€"*streptomycin*, [strep-toe-MY-sin], *para-aminosalicylic acid* [a-mee-noe-sal-i-SIL-ik], *ethionamide* [e-thye-ON-am-ide], *cycloserine* [sye-kloe-SER-een], *capreomycin* [kap-ree-oh-MYE sin], fluoroquinolones, and macrolidesâ€"are considered to be second-line drugs, either because they are no more effective than the first-line agents and their toxicities are often more serious or because they are particularly active against atypical strains of mycobacteria.

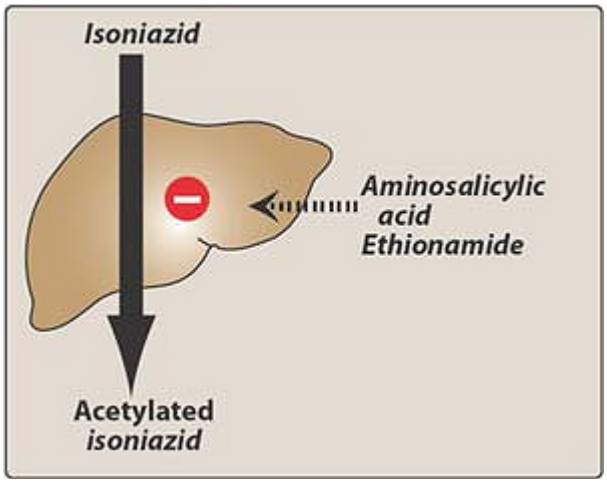

Figure 34.11 *Aminosalicylic acid* and *ethionamide* can inhibit the acetylation of isoniazid.

1. **Streptomycin:** This is the first antibiotic effective in the treatment of tuberculosis and is discussed with the aminoglycosides (see p. 377). Its action is directed against extracellular organisms. Infections due to *streptomycin*-resistant organisms may be treated with *kanamycin* or *amikacin*, to which these bacilli remain sensitive.

2. **Capreomycin:** This is a peptide that inhibits protein synthesis. It is administered parenterally. *Capreomycin* is primarily reserved for the treatment of multidrug-resistant tuberculosis. Careful monitoring of the patient is necessary to prevent its nephrotoxicity and ototoxicity.

3. **Cycloserine** is an orally effective, tuberculostatic agent that appears to antagonize the steps in bacterial cell wall synthesis involving D-alanine. It distributes well throughout body fluids, including the CSF. *Cycloserine* is metabolized, and both parent and metabolite are excreted in urine. Accumulation occurs with renal insufficiency. Adverse effects involve CNS disturbances, and epileptic seizure activity may be exacerbated. Peripheral neuropathies are also a problem, but they respond to pyridoxine.

4. **Ethionamide:** This is a structural analog of *isoniazid*, but it is not believed to act by the same mechanism. *Ethionamide* can inhibit acetylation of *isoniazid* (Figure 34.11). It is effective after oral administration and is widely distributed throughout the body, including the CSF. Metabolism is extensive, and the urine is the main route

of excretion. Adverse effects that limit its use include gastric irritation, hepatotoxicity, peripheral neuropathies, and optic neuritis. Supplementation with vitamin B_6 (pyridoxine) may lessen the severity of the neurologic side effects.

5. **Fluoroquinolones:** The fluoroquinolones, such as *moxifloxacin* and *levofloxacin,* have an important place in the treatment of multidrug-resistant tuberculosis. Some atypical strains of mycobacteria are also susceptible. These drugs are discussed in detail in Chapter 33.

6. **Macrolides:** The macrolides, such as *azithromycin* and *clarithromycin*, are part of the regimen that includes *ethambutol* and *rifabutin* used for the treatment of infections by M. avium-intracellulare complex. *Azithromycin* is preferred for HIV-infected patients because it is least likely to interfere with the metabolism of antiretroviral drugs. Details about the pharmacology of macrolides are found in Chapter 32.

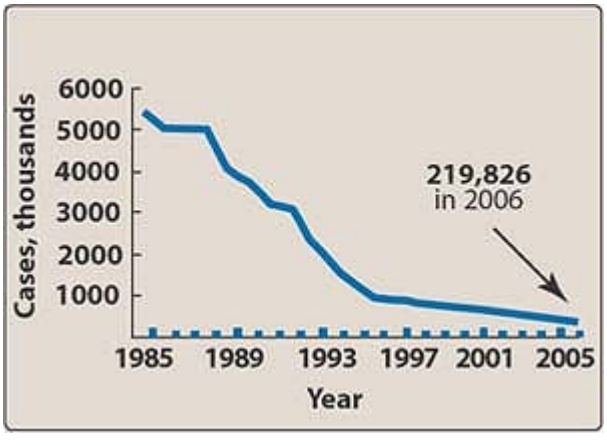

Figure 34.12 Reported prevalence of leprosy worldwide.

III. Chemotherapy for Leprosy

Leprosy (or, as it is specified by the U.S. Public Health Service, Hansen's disease) is rare in the United States, but a small number of cases, both imported and domestically acquired, are reported each year. Worldwide, it is a much larger problem (Figure 34.12). Approximately 70 percent of all cases in the world are located in India. Bacilli from skin lesions or nasal discharges of infected patients enter susceptible individuals via abraded skin or the respiratory tract. The World Health Organization recommends the triple-drug regimen of *dapsone, clofazimine*, and *rifampin*

for 6 to 24 months. Figure 34.13 shows the effects of multi-drug therapy.

A. Dapsone

Dapsone [DAP-sone] is structurally related to the sulfonamides and similarly inhibits folate synthesis via dihydropteroate synthetase inhibiton. It is bacteriostatic for Mycobacterium leprae, but resistant strains are encountered. *Dapsone* is also employed in the treatment of pneumonia caused by Pneumocystis jiroveci in patients infected with the HIV. The drug is well absorbed from the gastrointestinal tract and is distributed throughout the body, with high levels concentrated in the skin. The parent drug enters the enterohepatic circulation and undergoes hepatic acetylation. Both parent drug and metabolites are eliminated through the urine. Adverse reactions include hemolysis, especially in patients with glucose 6-phosphate dehydrogenase deficiency, as well as methemoglobinemia, peripheral neuropathy, and the possibility of developing erythema nodosum leprosum (a serious and severe skin complication of leprosy). [Note: The latter is treated with corticosteroids or *thalidomide*.]

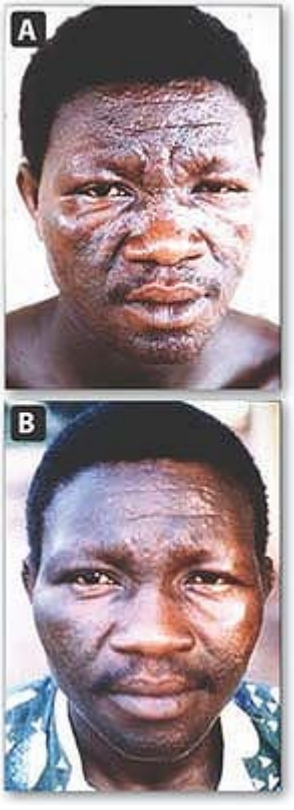

Figure 34.13 Leprosy patient. A. Before therapy. B. After 6 months of multidrug therapy.

B. Clofazimine

Clofazimine [kloe-FA-zi-meen] is a phenazine dye that binds to DNA and prevents it from serving as a template for future DNA replication. Its redox properties may lead to the generation of cytotoxic oxygen radicals that are also toxic to the bacteria. *Clofazimine* is bactericidal to M. leprae and has some activity against M. avium-intracellulare complex. Following oral absorption, the drug accumulates in tissues, allowing intermittent therapy, but it does not enter the CNS. Patients may develop a red-brown discoloration of the skin. Eosinophilic enteritis has been reported as an adverse effect. The drug also has some anti-inflammatory activity; thus, erythema nodosum leprosum does not develop.

Study Questions

Choose the ONE best answer.

34.1 A 31-year-old white intravenous drug user was admitted to the hospital with a 4-week history of cough and fever. A chest radiograph showed left upper lobe cavitary infiltrate. Cultures of sputum yielded M. tuberculosis susceptible to all antimycobacterial drugs. The patient received isoniazid, rifampin, and pyrazinamide. The patient's sputum remained culture-positive for the subsequent 4 months. Which one of the following is the most likely cause of treatment failure?

A. False-positive cultures.

B. Maladsorption of the medications.

C. Concomitant infection with HIV.

D. Noncompliance by the patient.

E. Drug resistance.

View Answer

34.2 A 40-year-old man has been on primary therapy for active pulmonary tuberculosis for the past 2 months. At his regular clinic visit, he complains of a â€œpins and needlesâ€ sensation in his feet. You suspect that he might be deficient in which one of the following vitamins?

A. Ascorbic acid.

B. Niacin.

C. Pyridoxine.

D. Calcitriol.

E. Folic acid.

View Answer

34.3 A 35-year-old male, formerly a heroin abuser, has been on methadone maintenance for the last 13 months. Two weeks ago, he had a positive tuberculosis skin test (PPD test), and a chest radiograph showed evidence of right upper lobe infection. He was started on standard antimycobacterial therapy. He has come to the emergency department complaining of â€œwithdrawal symptoms.â€ Which of the following antimycobacterial drugs is likely to have caused this patient's acute withdrawal reaction?

A. Ethambutol.

B. Isoniazid.

C. Pyrazinamide.

D. Rifampin.

E. Streptomycin.

View Answer

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Chapter 35

Antifungal Drugs

I. Overview

Infectious diseases caused by fungi are called mycoses, and they are often chronic in nature.[1] Many common mycotic infections are superficial and only involve the skin (cutaneous mycoses), but fungi may also penetrate the skin, causing subcutaneous infections. The fungal infections that are most difficult to treat are the systemic mycoses, which are often life-threatening. Unlike bacteria, fungi are eukaryotic. They have rigid cell walls composed largely of chitinâ€"a polymer of N-acetylglucosamineâ€"rather than peptidoglycan (a characteristic component of most bacterial cell walls). The fungal cell membrane contains ergosterol rather than the cholesterol found in mammalian membranes. These chemical characteristics are useful in targeting chemotherapeutic agents against fungal infections. Fungal infections are generally resistant to antibiotics used in the treatment of bacterial infections, and conversely, bacteria are resistant to the antifungal agents. The last two decades have seen a rise in the incidence of fungal infections so that candidemia is the fourth most common cause of septicemia. This increased incidence of fungal infections is associated with greater numbers of individuals who are on chronic immune suppression following organ transplant, undergoing chemotherapy for myelogenous and solid tumors, or infected with the human immunodeficiency virus (HIV). During this same period, there have been significant changes in the therapeutic options available to the clinician. For example, the ongoing development of new azole antifungal drugs offers effective therapy for all but the most serious mycotic infections. Clinically useful antifungal agents are listed in Figure 35.1.

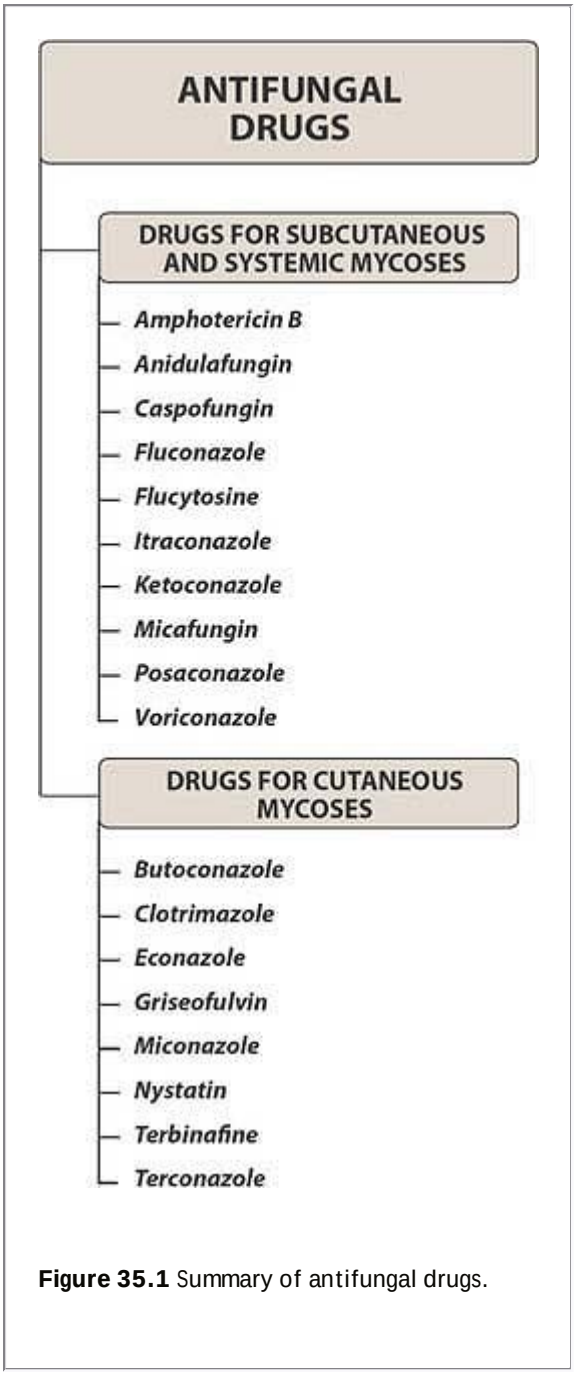

Figure 35.1 Summary of antifungal drugs.

II. Drugs for Subcutaneous and Systemic Mycotic Infections

The drugs used in the treatment of subcutaneous and systemic mycoses are listed in Figure 35.1. [Note: Additional azole drugs are effective in the topical treatment of candidiasis or dermatophytic infections.] The echinocandins are a new class of antifungal agents that exert their fungicidal activity by inhibiting 1,3-Î²-glucan synthesis for the fungal cell wall.

A. Amphotericin B

Amphotericin [am-foe-TER-i-sin] *B* is a naturally occurring, polyene macrolide antibiotic produced by Streptomyces nodosus. In spite of its toxic potential, *amphotericin B* is the drug of choice for the treatment

of life-threatening, systemic mycoses. [Note: Conventional *amphotericin* (*amphotericin B deoxycholate*, the

nonlipid formulation) has undergone several formulation improvements to reduce the incidence of side effects, particularly nephrotoxicity.] The drug is also sometimes used in combination with *flucytosine* so that lower (less toxic) levels of *amphotericin B* are possible.

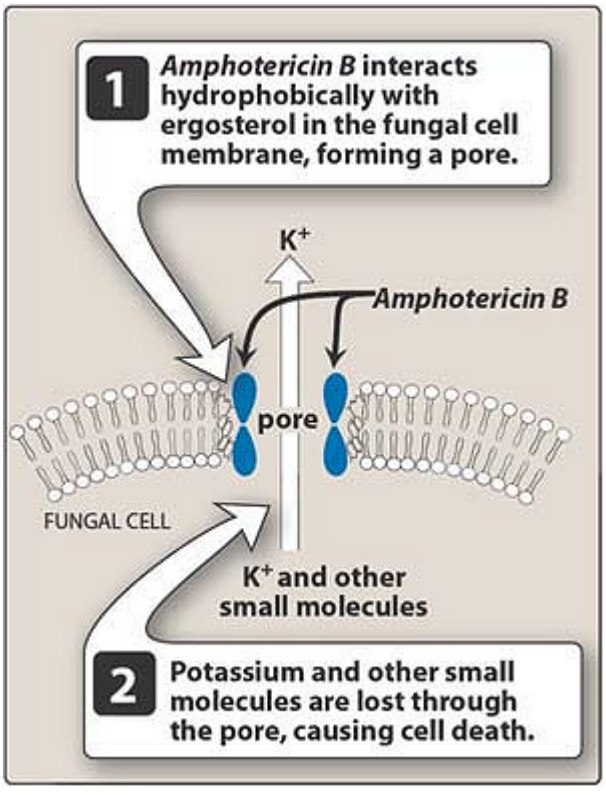

Figure 35.2 Model of a pore formed by *amphotericin B* in the lipid bilayer membrane.

1. **Mechanism of action:** Several *amphotericin B* molecules bind to ergosterol in the plasma membranes of sensitive fungal cells. There, they form pores (channels) that require hydrophobic interactions between the lipophilic segment of the polyene antibiotic and the sterol (Figure 35.2). The pores disrupt membrane function, allowing electrolytes (particularly potassium) and small molecules to leak from the cell, resulting in cell death. [Note: Because the polyene antibiotics bind preferentially to ergosterol rather than to cholesterolâ€"the sterol found in mammalian membranesâ€"a relative (but not absolute) specificity is conferred.]

2. **Antifungal spectrum:** *Amphotericin B* is either fungicidal or fungistatic, depending on the organism and the concentration of the drug. It is effective against a wide range of fungi, including Candida albicans, Histoplasma capsulatum, Cryptococcus neoformans, Coccidioides immitis, Blastomyces dermatitidis, and many strains of aspergillus. [Note: *Amphotericin B* is also used in the treatment of the protozoal infection, leishmaniasis.]

3. **Resistance:** Fungal resistance, although infrequent, is associated with decreased ergosterol content of the fungal membrane.

4. **Pharmacokinetics:** *Amphotericin B* is administered by slow, intravenous infusion (Figure 35.3). *Amphotericin B* is insoluble in water, and injectable preparations require the addition of sodium deoxycholate, which produces a soluble colloidal dispersion. The more dangerous intrathecal route is sometimes chosen for the treatment of meningitis caused by fungi that are sensitive to the drug. *Amphotericin B* has also been formulated with a variety of artificial lipids that form liposomes. The three *amphotericin B* lipid formulations marketed in the United States are *AmphotecÂ®, AbelcetÂ®*, and *AmBisomeÂ®*. For example, the simplest and smallest of the

liposome preparations, *AmBisomeÂ®*, is produced by the incorporation of *amphotericin B* into a single liposomal bilayer composed of phospholipids and cholesterol (Figure 35.4). These liposomal preparations have the primary advantage of reduced renal and infusion toxicity. However, because of their high cost, they are reserved mainly as salvage therapy for those individuals who cannot tolerate conventional *amphotericin B*. *Amphotericin B* is extensively bound to plasma proteins and is distributed throughout the body, becoming highly tissue bound. Inflammation favors penetration into various body fluids, but little of the drug is found in the cerebrospinal fluid (CSF), vitreous humor, or amniotic fluid. However, *amphotericin B* does cross the placenta. Low levels of the drug and its metabolites appear in the urine over a long period of time; some are also eliminated via the bile. Dosage adjustment is not required in patients with compromised hepatic function, but when renal dysfunction is due to the use of conventional *amphotericin B*, the total daily dose is decreased by 50% . Sodium loading with infusions of normal saline and the lipid-based *amphotericin B* products are alternatives utilized to minimize nephrotoxicity.

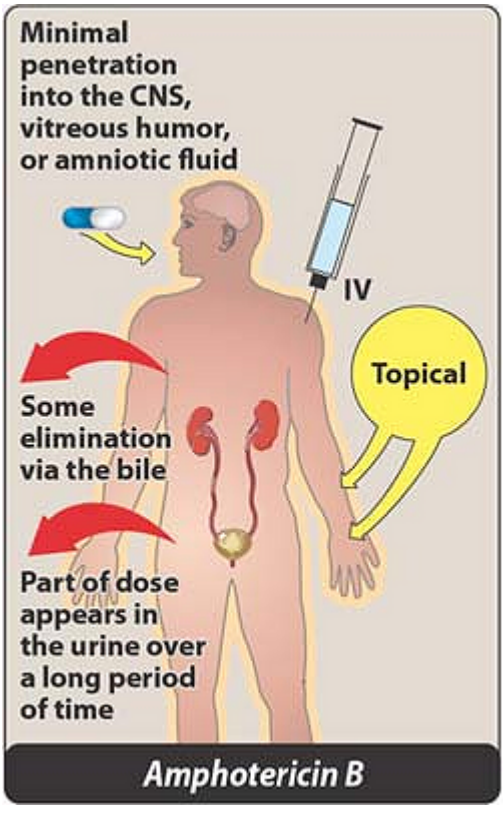

Figure 35.3 *Administration* and fate of *amphotericin B*.

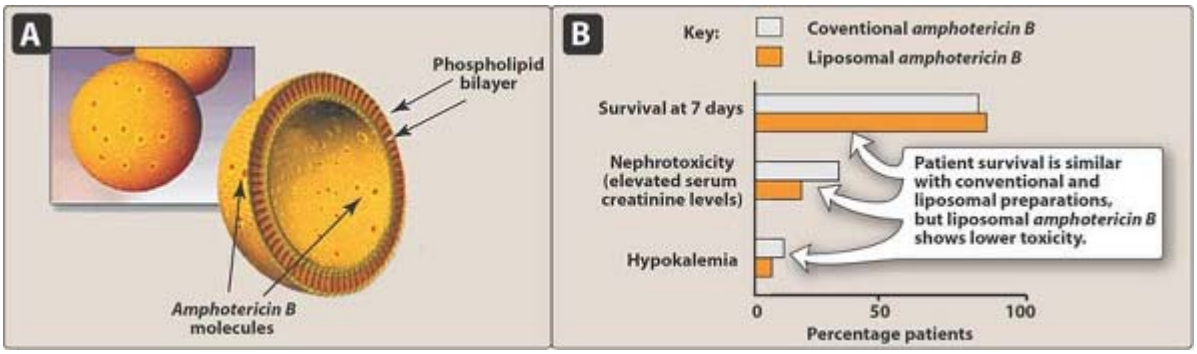

Figure 35.4 A. *Amphotericin B* intercalated between the phospholipids of a spherical liposome (AmBisomeÂ®). B. Outcomes of antifungal therapy in febrile, neutropenic cancer patients treated with conventional *amphotericin B* and liposomal *amphotericin B*.

5. **Adverse effects:** *Amphotericin B* has a low therapeutic index. A total adult daily dose should not exceed 1.5 mg/kg. Small test doses are usually administered to assess the degree of a patient's negative responses, such as anaphylaxis or convulsions. Other toxic manifestations include the following (Figure 35.5).

    a. **Fever and chills:** These occur most commonly 1 to 3 hours after starting the intravenous administration, but they usually subside with repeated administration of the drug. Premedication with a corticosteroid or an antipyretic helps to prevent this problem.

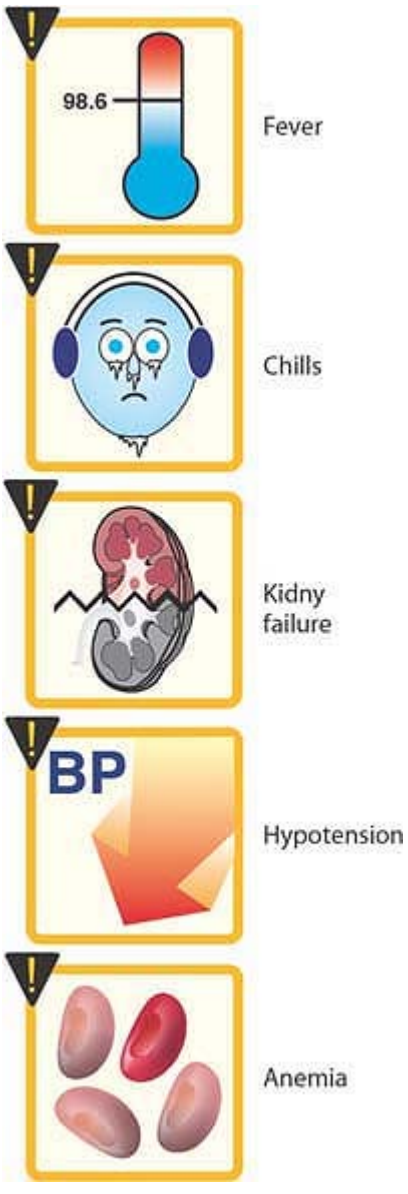

Figure 35.5 Adverse effects of *amphotericin B*.

b. **Renal impairment:** Despite the low levels of the drug excreted in the urine, patients may exhibit a decrease in glomerular filtration rate and renal tubular function. Creatinine clearance can drop, and potassium and magnesium are lost. [Note: Nephrotoxicity may be potentiated by sodium depletion; thus, a bolus infusion of normal saline before and after *amphotericin B* infusion may reduce the incidence of drug-induced nephrotoxicity.] Normal renal function usually returns on suspension of the drug, but residual damage is likely at high doses. Azotemia (elevated blood urea) is exacerbated by other nephrotoxic drugs, such as aminoglycosides, *cyclosporine*, or *pentamidine*, although adequate hydration can decrease its severity.

c. **Hypotension:** A shock-like fall in blood pressure accompanied by hypokalemia may occur, requiring potassium supplementation. Care must be exercised in patients taking *digoxin*.

d. **Anemia:** Normochromic, normocytic anemia caused by a reversible suppression of erythrocyte production may occur. This may be exacerbated in patients infected with HIV who are taking *zidovudine*.

e. **Neurologic effects:** Intrathecal administration can cause a variety of serious neurologic problems.

f. **Thrombophlebitis:** Adding *heparin* to the infusion can alleviate this problem.

B. Flucytosine

Flucytosine [floo-SYE-toe-seen] (*5-FC*) is a synthetic pyrimidine antimetabolite that is often used in combination with *amphotericin B.* This combination of drugs is administered for the treatment of systemic mycoses and for meningitis caused by Cryptococcus neoformans and Candida albicans.

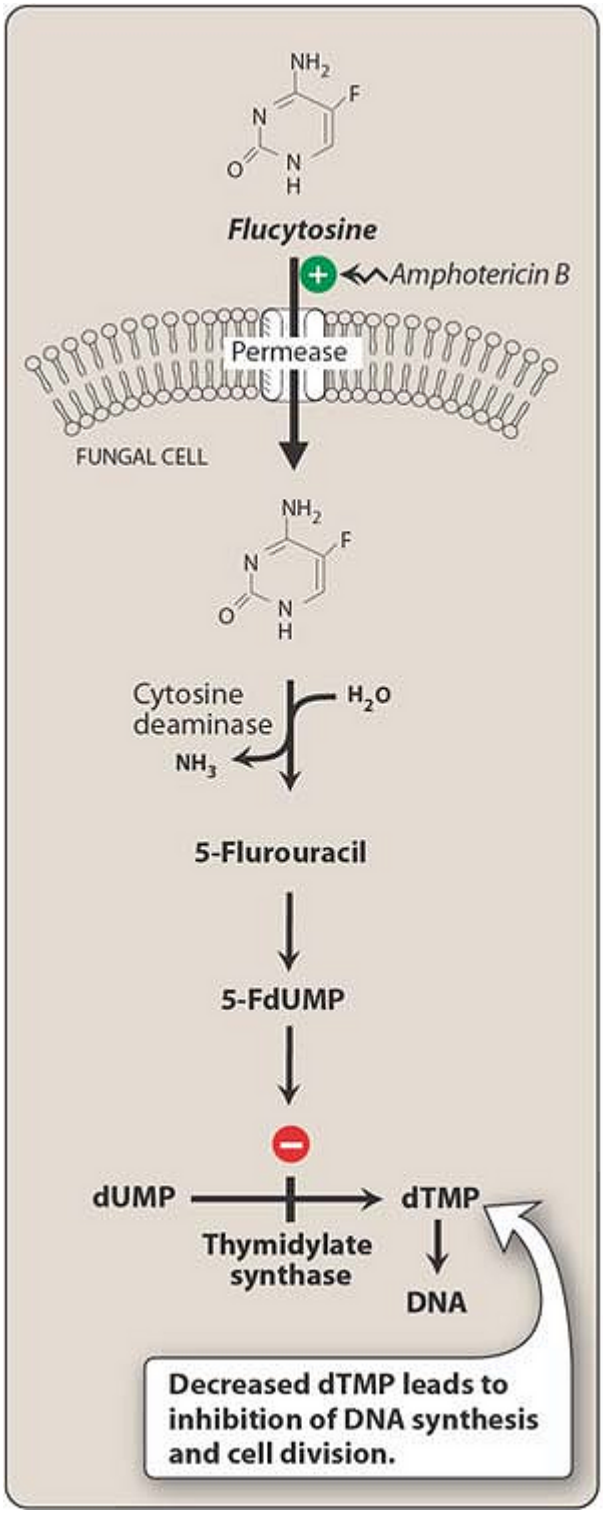

Figure 35.6 Mode of action of *flucytosine*. 5-FdUMP = 5-fluorodeoxyuridine 5'-monophosphate; dTMP = deoxythymidine 5'-monophosphate.

1. **Mechanism of action:** *5-FC* enters fungal cells via a cytosine-specific permeaseâ€”an enzyme not found in mammalian cells. *5-FC* is then converted by a series of steps to 5-fluorodeoxyuridine 5'-monophosphate. This

false nucleotide inhibits thymidylate synthase, thus depriving the organism of thymidylic acidâ€"an essential DNA component (Figure 35.6). The unnatural mononucleotide is further metabolized to a trinucleotide (5-fluorodeoxyuridine 5'-triphosphate) and is incorporated into fungal RNA, thus disrupting nucleic acid and protein synthesis. [Note: *Amphotericin B* increases cell permeability, allowing more *5-FC* to penetrate the cell. Thus, *5-FC* and *amphotericin B* are synergistic (Figure 35.7).]

2. **Antifungal spectrum:** *5-FC* is fungistatic. It is effective in combination with *itraconazole* for treating chromoblastomycosis and in combination with *amphotericin B* for treating candidiasis or cryptococcosis.

3. **Resistance:** Resistance due to decreased levels of any of the enzymes in the conversion of *5-FC* to *5-fluorouracil* (*5-FU*) and beyond, or increased synthesis of cytosine, can develop during therapy. This is the primary reason that *5-FC* is not used as a single antimycotic drug. The rate of emergence of resistant fungal cells is lower with a combination of *5-FC* plus a second antifungal agent than it is with *5-FC* alone.

4. **Pharmacokinetics:** *5-FC* is well absorbed by the oral route. It distributes throughout the body water and penetrates well into the CSF. *5-FU* is detectable in patients and is probably the result of metabolism of *5-FC* by intestinal bacteria. Excretion of both the parent drug and its metabolites is by glomerular filtration, and the dose must be adjusted in patients with compromised renal function.

5. **Adverse effects:** *5-FC* causes reversible neutropenia, thrombo-cytopenia, and dose-related bone marrow depression. Caution must be exercised in patients undergoing radiation or chemotherapy with drugs that depress bone marrow. Reversible hepatic dysfunction with elevation of serum transaminases and alkaline phosphatase may occur. Gastrointestinal disturbances, such as nausea, vomiting, and diarrhea, are common, and severe enterocolitis may occur. [Note: Some of these adverse effects may be related to *5-FU* formed by intestinal organisms from *5-FC*.]

C. Ketoconazole

Ketoconazole [kee-toe-KON-a-zole] was the first orally active azole available for the treatment of systemic mycoses.

Figure 35.7 Synergism between *flucytosine* and *amphotericin B*.

1. **Mechanism of action:** Azoles are predominantly fungistatic. They inhibit C-14 Î±-demethylase (a cytochrome P450 enzyme), thus blocking the demethylation of lanosterol to ergosterolâ€"the principal sterol of fungal membranes (Figure 35.8). This inhibition disrupts membrane structure and function and, thereby, inhibits fungal cell

growth. [Note: Unfortunately, as is often the case for the initial member of a class of drugs, the selectivity of *ketoconazole* toward its target is not as precise as those of later azoles. For example, in addition to blocking fungal ergosterol synthesis, the drug also inhibits human gonadal and adrenal steroid synthesis, leading to decreased testosterone and cortisol production. In addition, *ketoconazole* inhibits cytochrome P450â€"dependent hepatic drug-metabolizing enzymes.]

2. **Antifungal spectrum:** *Ketoconazole* is active against many fungi, including Histoplasma, Blastomyces, Candida, and Coccidioides, but not aspergillus species. Although *itraconazole* has largely replaced *ketoconazole* in the treatment of most mycoses because of its broader spectrum, greater potency, and fewer adverse effects, *ketoconazole*, as a second-line drug, is a less expensive alternative for the treatment of mucocutaneous candidiasis. Strains of several fungal species that are resistant to *ketoconazole* have been identified.

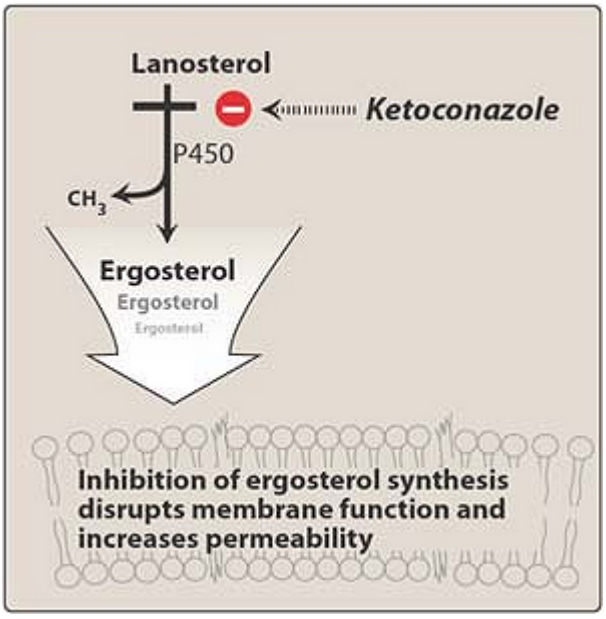

Figure 35.8 Mode of action of *ketoconazole*.

3. **Resistance:** This is becoming a significant clinical problem, particularly in the protracted therapy required for those with advanced HIV infection. Identified mechanisms of resistance include mutations in the C-14 Î±-demethylase gene, which cause decreased azole binding. Additionally, some strains of fungi have developed the ability to pump the azole out of the cell.

4. **Pharmacokinetics:** *Ketoconazole* is only administered orally (Figure 35.9). It requires gastric acid for dissolution and is absorbed through the gastric mucosa. Drugs that raise gastric pH, such as antacids, or that interfere with gastric acid secretion, such as H_2-histamine receptor blockers and proton-pump inhibitors, impair absorption. Administering acidifying agents, such as cola drinks, before taking the drug can improve absorption in patients with achlorhydria. *Ketoconazole* is extensively bound to plasma proteins. Although penetration into tissues is limited, it is effective in the treatment of histoplasmosis in lung, bone, skin, and soft tissues. The drug does not enter the CSF. Extensive metabolism occurs in the liver, and excretion is primarily through the bile. Levels of parent drug in the urine are too low to be effective against mycotic infections of the urinary tract.

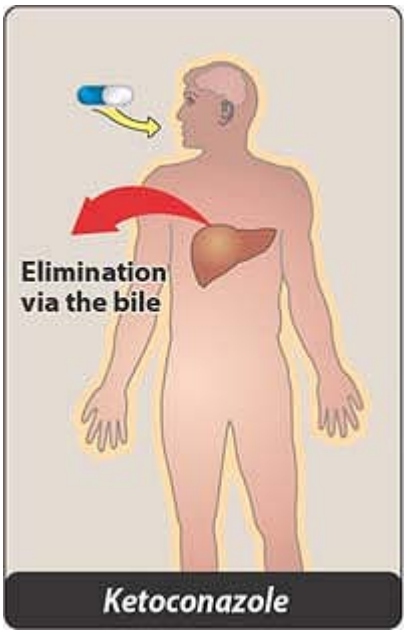

Figure 35.9 Administration and fate of *ketoconzole*.

5. **Adverse effects:** In addition to allergies, dose-dependent gastrointestinal disturbances, including nausea, anorexia, and vomiting, are the most common adverse effects of *ketoconazole* treatment. Endocrine effects, such as gynecomastia, decreased libido, impotence, and menstrual irregularities, result from the blocking of androgen and adrenal steroid synthesis by *ketoconazole.* Transient increases in serum transaminases are found in from 2 to 10 percent of patients. Frank hepatitis occurs rarely but requires immediate cessation of treatment. [Note: *Ketoconazole* may accumulate in patients with hepatic dysfunction. Plasma concentrations of the drug should be monitored in these individuals.]

6. **Drug interactions and contraindications:** By inhibiting cytochrome P450, *ketoconazole* can potentiate the toxicities of drugs such as *cyclosporine, phenytoin, tolbutamide*, and *warfarin*, among others (Figure 35.10). *Rifampin*, an inducer of the cytochrome P450 system, can shorten the duration of action of *ketoconazole* and the other azoles. Drugs that decrease gastric acidity, such as H_2-receptor

blockers, antacids, proton-pump inhibitors, and *sucralfate*, can decrease absorption of *ketoconazole*. *Ketoconazole* and *amphotericin B* should not be used together, because the decrease in ergosterol in the fungal membrane reduces the fungicidal action of *amphotericin B* (Figure 35.11). Finally, *ketoconazole* is teratogenic in animals, and it should not be given during pregnancy.

D. Fluconazole

Fluconazole [floo-KON-a-zole] is clinically important because of its lack of the endocrine side effects of *ketoconazole* and its excellent penetrability into the CSF of both normal and inflamed meninges. *Fluconazole* is employed prophylactically, with some success, for reducing fungal infections in recipients of bone marrow transplants. It inhibits the synthesis of fungal membrane ergosterol in the same manner as *ketoconazole* and is the drug of choice for Cryptococcus neoformans, for candidemia, and for coccidioidomycosis. *Fluconazole* is effective against all forms of mucocutaneous candidiasis. [Note: Treatment failures due to resistance have been reported in some HIV-infected patients.] *Fluconazole* is administered orally or intravenously. Its absorption is excellent and, unlike that of *ketoconazole*, is not dependent on gastric acidity. Binding to plasma proteins is minimal. Unlike

ketoconazole, fluconazole is poorly metabolized. The drug is excreted via the kidney, and doses must be reduced in patients with compromised renal function. The adverse effects caused by *fluconazole* treatment are less of a problem than those with *ketoconazole*. *Fluconazole* has no endocrinologic effects, because it does not inhibit the cytochrome P450 system responsible for the synthesis of androgens. However, it can inhibit the P450 cytochromes that metabolize other drugs listed in Figure 35.10. Nausea, vomiting, and rashes are a problem. Hepatitis is rare. *Fluconazole* is teratogenic, as are other azoles, and should not be used in pregnancy.

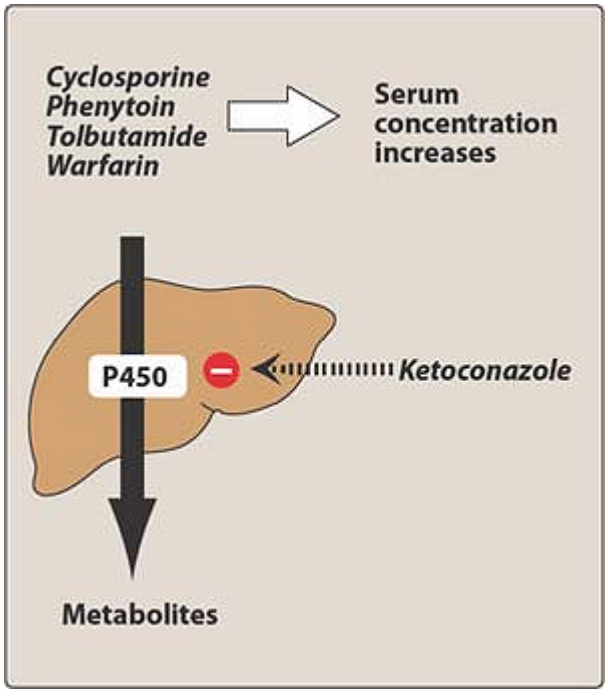

Figure 35.10 By inhibiting cytochrome P450, *ketoconazole* can potentiate the toxicities of other drugs.

E. Itraconazole

Itraconazole [it-ra-KON-a-zole] is an azole antifungal agent with a broad antifungal spectrum. Like *fluconazole*, it is a synthetic triazole and also lacks the endocrinologic side effects of *ketoconazole*. Its mechanism of action is the same as that of the other azoles. *Itraconazole* is now the drug of choice for the treatment of blastomycosis, sporotrichosis, paracoccidioidomycosis, and histoplasmosis. Unlike *ketoconazole*, it is effective in acquired immunodeficiency syndromeâ€“associated histoplasmosis. *Itraconazole* is well-absorbed orally, but it requires acid for dissolution. Food increases the bioavailability of some preparations. The drug is extensively bound to plasma proteins and distributes well throughout most tissues, including bone and adipose tissues. However, therapeutic concentrations are not attained in the CSF. Like *ketoconazole, itraconazole* is extensively metabolized by the liver, but it does not inhibit androgen synthesis. Its major metabolite, hydroxyitraconazole, is biologically active, with a similar antifungal spectrum. Little of the parent drug appears in the urine; thus, doses do not have to be reduced in renal failure. Adverse effects include nausea and vomiting, rash (especially in immunocompromised patients), hypokalemia, hypertension, edema, and headache. *Itraconazole* should be avoided in pregnancy. *Itraconazole* inhibits the metabolism of many drugs, including oral anticoagulants, statins, and *quinidine*. Inducers of the cytochrome P450 system increase the metabolism of *itraconazole*.

Figure 35.11 *Ketoconazole* and *amphotericin B* should not be used together.

F. Voriconazole

Voriconazole [vor-i-KON-a-zole] has the advantage of being a broad-spectrum antifungal agent. It is available for intravenous administration and also for oral administration and is approximately 96% bioavailable. *Voriconazole* is approved for the treatment of invasive aspergillosis and seems to have replaced *amphotericin B* as the treatment of choice for this indication. *Voriconazole* is also approved for treatment of serious infections caused by Scedosporium apiospermum and Fusarium species. *Voriconazole* penetrates tissues well, including the CNS. Elimination is primarily by metabolism through the cytochrome P450 2C19, 2C9, and 3A4 enzymes. The significant number of drug interactions due to its metabolism through the various hepatic enzymes may limit its use. Side effects are similar to those of the other azoles. One unique problem is a transient visual disturbance that occurs within 30 minutes of dosing.

G. Posaconazole

Posaconazole [poe-sa-kon-a-zole] is a new oral, broad-spectrum antifungal agent with a chemical structure similar to that of *itraconazole*. It was approved in 2006 to prevent *Candida* and *Aspergillus* infections in severely immunocompromised patients and for the treatment of oropharyngeal candidiasis. Due to its spectrum of activity, *posaconazole* could possibly be used in the treatment of fungal infections caused by *Mucor* species and other zygomycetes. To date, *amphotericin B* formulations are the only other antifungal agents available for treatment of zygomycete infections. Overall, *posaconazole* is relatively well tolerated. The most common side effects observed were gastrointestinal issues (nausea, vomiting, diarrhea, and abdominal pain) and headaches. Like other azoles, *posaconazole* can cause an elevation of liver function tests aspartate aminotransferase and alanine aminotransferase. Additionally, in patients who are receiving concomitant *cyclosporine* or *tacrolimus* for management of transplant rejection, rare cases of hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and pulmonary embolus have been reported. Due to its inhibition of cytochrome P450 3A4 enzyme, *posaconazole* may increase the effect and toxicity of many drugs, including *cyclosporine, tacrolimus,* and *sirolumus*. Concomitant use of *posaconazole* with ergot alkaloids, *pimozide,* and *quinidine* is contraindicated. To be effective, *posaconazole* must be administered with a full meal or nutritional supplement. For treatment of oropharyngeal

candidiasis, dosing is daily. However, for prophylaxis of *Candida* and *Aspergillus* infections, *posaconazole* must be dosed three times a day. Figure 35.12 summarizes the azole antifungal agents.

	KETOCONAZOLE	FLUCONAZOLE	VORICONAZOLE	POSACONAZOLE
SPECTRUM	Narrow	Expanded	Expanded	Expanded
ROUTE(S) OF ADMINISTRATION	Oral	Oral, IV	Oral, IV	Oral
$t_{1/2}$ (HOURS)	6–9	30	6–24	20–66
CSF PENETRATION	No	Yes	Yes	Yes
RENAL EXCRETION	No	Yes	No	No
INTERACTION WITH OTHER DRUGS	Frequent	Occasional	Frequent	Frequent
INHIBITION OF MAMMALIAN STEROL SYNTHESIS	Dose-dependent inhibitory effect	No inhibition	No inhibition	No inhibition

Figure 35.12 Summary of some azole fungistatic drugs.

H. Echinocandins: Caspofungin, micafungin, and anidulafungin

1. **Caspofungin:** *Caspofungin* [kas-poh-FUN-jin] is the first approved member of the echinocandins class of antifungal drugs. Echinocandins interfere with the synthesis of the fungal cell wall by inhibiting the synthesis of Î²(1,3)-D-glucan, leading to lysis and cell death. This drug's spectrum is limited to Aspergillus and Candida species. *Caspofungin* is not active by the oral route. The drug is highly bound to serum proteins and has a half-life of 9 to 11 hours. It is slowly metabolized by hydrolysis and N-acetylation. Elimination is approximately equal between the urinary and fecal routes. Adverse effects include fever, rash, nausea, and phlebitis. Flushing occursâ€"probably due to the release of histamine from mast cells. *Caspofungin* should not be coadministered with *cyclosporine*. *Caspofungin* is a second-line antifungal for those who have failed or cannot tolerate *amphotericin B* or an azole.

2. **Micafungin and anidulafungin:** *Micafungin* (mi-ka-FUN-gin) and *anidulafungin* (ay-nid-yoo-la-FUN-jin) are the newer members of the echinocandins class of antifungal drugs. Like *caspofungin*, they are not orally active, are only available via intravenous infusion, and have histamine-mediated side effects. *Micafungin* and *anidulafungin* have similar efficacy against *Candida* species, but the efficacy for treatment of other fungal infections has not been established. Also, they are not substrates for cytochrome P450 enzymes and do not have any associated drug interactions.

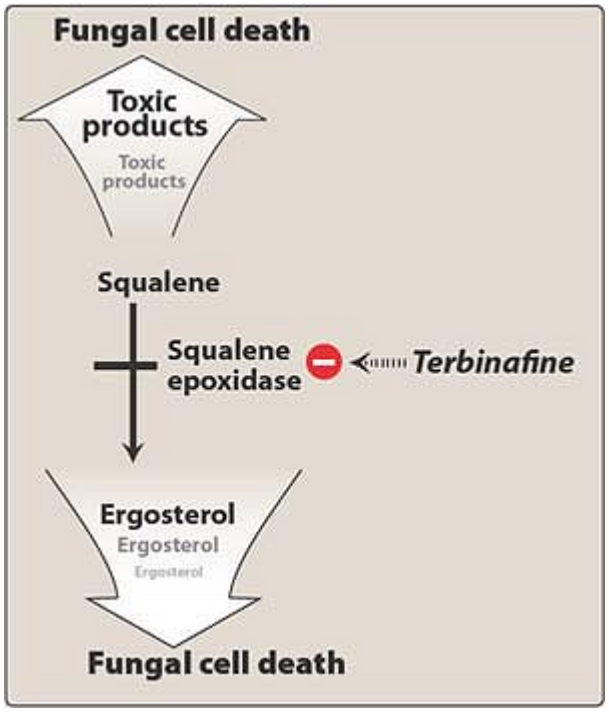

Figure 35.13 Mode of action of *terbinafine*.

III. Drugs for Cutaneous Mycotic Infections

Fungi that cause superficial skin infections are called dermatophytes. Common dermatomycoses, such as tinea infections, are often referred to as â€œringworm.â€ This is a misnomer, because fungi rather than worms cause the disease.

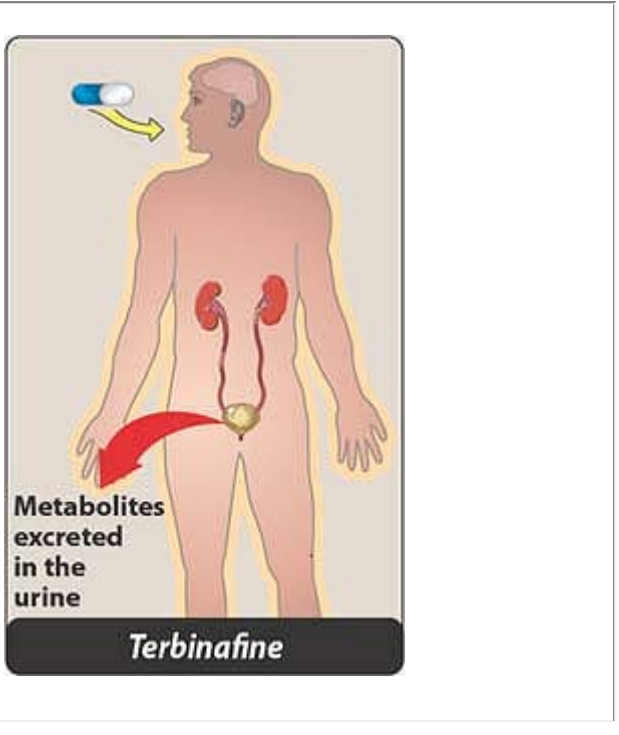

Figure 35.14 Administration and fate of *terbinafine*.

A. Terbinafine

Terbinafine [TER-bin-a-feen] is the drug of choice for treating dermatophytoses and, especially, onychomycoses (fungal infections of nails). It is better tolerated, requires shorter duration of therapy, and is more effective than either *itraconazole* or *griseofulvin*.

1. **Mechanism of action:** *Terbinafine* inhibits fungal squalene epoxidase, thereby decreasing the synthesis of ergosterol (Figure 35.13). This plus the accumulation of toxic amounts of squalene result in the death of the fungal cell. [Note: Significantly higher concentrations of *terbinafine* are needed to inhibit human squalene epoxidase, an enzyme required for the cholesterol synthetic pathway.]

2. **Antifungal spectrum:** The drug is primarily fungicidal. Antifungal activity is limited to dermatophytes and Candida albicans. Therapy is prolongedâ€"usually about 3 monthsâ€"but considerably shorter than that with *griseofulvin*.

3. **Pharmacokinetics:** *Terbinafine* is orally active, although its bioavailability is only 40 percent due to first-pass metabolism. Absorption is not significantly enhanced by food. *Terbinafine* is greater than 99 percent bound to plasma proteins. It is deposited in the skin, nails, and

fat. *Terbinafine* accumulates in breast milk and, therefore, should not be given to nursing mothers. A prolonged terminal half-life of 200 to 400 hours may reflect the slow release from these tissues. *Terbinafine* is extensively metabolized prior to urinary excretion (Figure 35.14). Patients with either moderate renal impairment or hepatic cirrhosis have reduced clearance.

4. **Adverse effects:** The most common adverse effects due to *terbinafine* are gastrointestinal disturbances (diarrhea, dyspepsia, and nausea), headache, and rash. Taste and visual disturbances have been reported as well as transient elevations in serum liver enzyme levels. All adverse effects resolve upon drug discontinuation. Rarely, *terbinafine* may cause hepatotoxicity and neutropenia. Although *terbinafine* is extensively metabolized, there does not seem to be a significant risk of reduced clearance of other drugs. *Rifampin* decreases blood levels of *terbinafine*, whereas *cimetidine* increases blood levels of *terbinafine*.

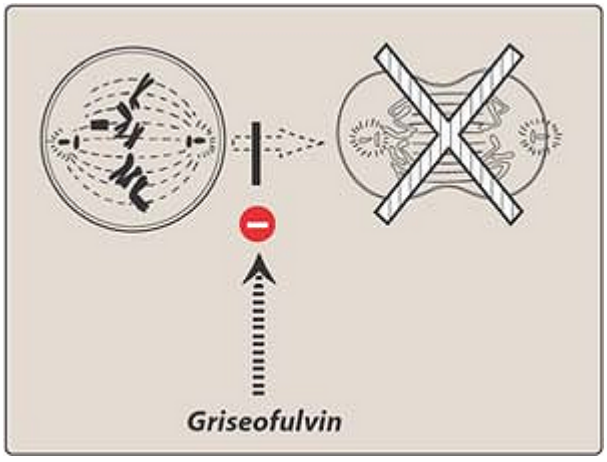

Figure 35.15 Inhibition of mitosis by *griseofulvin*.

B. Griseofulvin

Griseofulvin [gris-e-oh-FUL-vin] has been largely replaced by *terbinafine* for the treatment of dermatophytic infections of the nails. *Griseofulvin* requires treatment of 6 to 12 months in duration. It is only fungistatic, and it causes a number of significant drug interactions. *Griseofulvin* accumulates in newly synthesized, keratin-containing tissue, where it causes disruption of the mitotic spindle and inhibition of fungal mitosis (Figure 35.15). Duration of therapy is dependent on the rate of replacement of healthy skin or nails. Ultrafine crystalline preparations are absorbed adequately from the gastrointestinal tract; absorption is enhanced by high-fat meals. *Griseofulvin* induces hepatic cytochrome P450 activity (Figure 35.16). It also increases the rate of metabolism of a number of drugs, including anticoagulants. It may exacerbate intermittent porphyria. Patients should not drink alcoholic beverages during therapy, because griseofulvin potentiates the intoxicating effects of alcohol.

C. Nystatin

Nystatin [nye-STAT-in] is a polyene antibiotic, and its structure, chemistry, mechanism of action, and resistance resemble those of *amphotericin B*. Its use is restricted to topical treatment of Candida infections because of its systemic toxicity. The drug is negligibly absorbed from the gastrointestinal tract, and it is never used parenterally. It is administered as an oral agent (â€œswish and swallowâ€ or â€œswish and spitâ€) for the treatment of oral candidiasis. Excretion in the feces is nearly quantitative. Adverse effects are rare because of its lack of absorption, but nausea and vomiting occasionally occur.

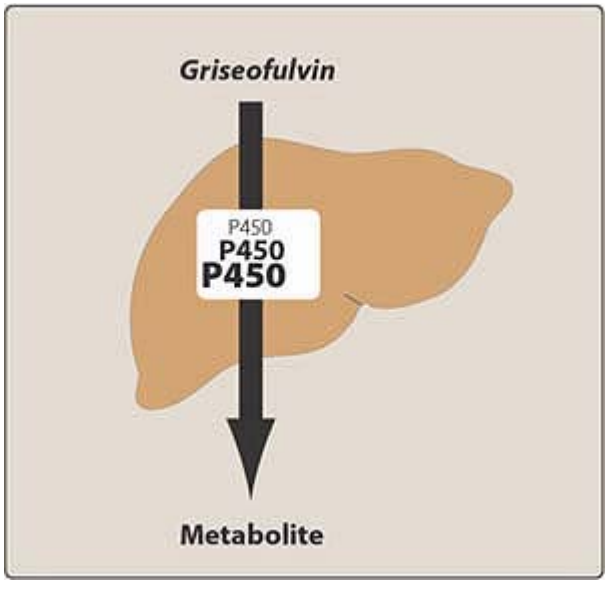

Figure 35.16 Induction of hepatic cytochrome P450 activity by *griseofulvin*.

D. Miconazole and other topical agents

Miconazole [my-KON-a-zole], *clotrimazole* [kloe-TRIM-a-zole], *butoconazole* [byoo-toe-KON-a-zole], and *terconazole* [ter-KON-a-zole] are topically active drugs that are only rarely administered parenterally because of their severe toxicity. Their mechanism of action and antifungal spectrum are the same as those of *ketoconazole.* Topical use is associated with contact dermatitis, vulvar irritation, and edema. *Miconazole* is a potent inhibitor of *warfarin* metabolism and has produced bleeding in warfarin-treated patients even when *miconazole* is applied topically. No significant difference in clinical outcomes is associated with any azole or *nystatin* in the treatment of vulvar candidiasis.

Study Questions

Choose the ONE best answer.

35.1 A 25-year-old male patient with acquired immunodeficiency syndrome has a fever of 102Â°F and complains of severe headaches during the past week. Staining of his CSF with India ink reveals Cryptococcus neoformans. The patient is admitted to the hospital and is treated with:

A. Intravenous amphotericin B plus flucytosine.

B. Oral ketoconazole.

C. Intrathecal amphotericin B.

D. Oral fluconazole.

E. Intravenous amphotericin B plus ketoconazole.

View Answer

35.2 A 30-year-old male has had a heart transplant and is being maintained on the immunosuppressant

cyclosporine. He develops a Candida infection and is treated with ketoconazole. Why is this poor therapy?

A. Ketoconazole is not effective against Candida species.

B. Ketoconazole reacts with cyclosporine to inactivate it.

C. Ketoconazole has a potential for cardiotoxicity.

D. Ketoconazole inhibits cytochrome P450 enzymes that inactivate cyclosporine.

E. Ketoconazole causes gynecomastia and decreased libido in the male.

View Answer

35.3 A 22-year-old male has been treating his â€œathlete's footâ€ with an over-the-counter drug without much success. Upon examination, it is found that the nail bed of both great toes is infected. Which one of the following antifungal agents would be most appropriate for this patient?

A. Caspofungin.

B. Fluconazole.

C. Griseofulvin.

D. Nystatin.

E. Terbinafine.

View Answer