Inhibitors of Cell Wall Synthesis

30

I. OVERVIEW

Some antimicrobial drugs selectively interfere with the synthesis of the bacterial cell wall. Unique to bacteria, this structure is not found in mammalian cells. It is a polymer of glycan units joined to each other by peptide cross-links, hence, the designation of peptidoglycan cell wall. To be maximally effective, these agents require actively proliferating microorganisms; they have little or no effect on bacteria that are not growing. The most important members of the group are the β-lactam antibiotics, named after the β-lactam ring, which is essential to their activity (Figure 30.1).

II. PENICILLINS

The penicillins [pen i SILL in] are the most widely effective antibiotics and are among the least toxic drugs known; the major adverse reaction to penicillins is hypersensitivity. The members of this family differ from one another in the R substituent attached to the 6-aminopenicillanic acid residue. The nature of this side chain affects their antimicrobial spectrum, stability to stomach acid, and susceptibility to bacterial degradative enzymes (β-lactamases). Figure 30.1 shows the main structural features of the penicillins. Figure 30.2 shows the classification of agents affecting cell wall synthesis.

A. Mechanism of action

The penicillins interfere with the last step of bacterial cell wall synthesis (transpeptidation or cross-linkage), thus exposing the osmotically less stable membrane. Cell lysis can then occur, and these drugs are therefore bactericidal. The success of a penicillin antibiotic in causing cell death is related to its size, charge, and hydrophobicity (see p. 300). Penicillins are, of course, 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.

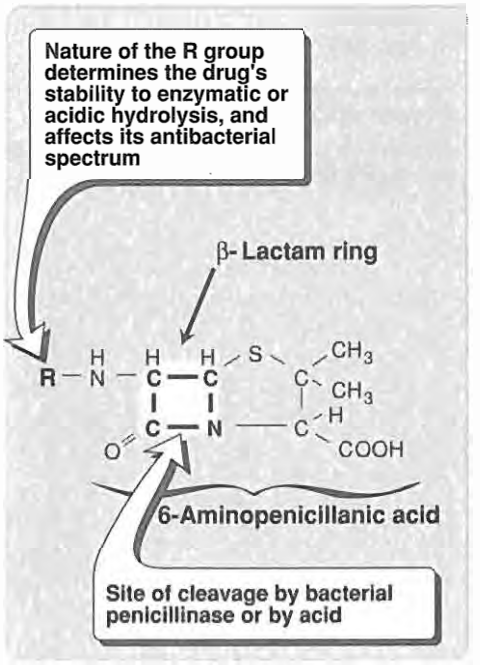


Figure 30.1
Structural features of β-lactam antibiotics.

Lippincott's Illustrated Reviews: Pharmacology, Second Edition.
by Mary Mycek, Richard A. Harvey and Pamela C. Champe.
Lippincott–Raven Publishers, Philadelphia, PA © 1997.

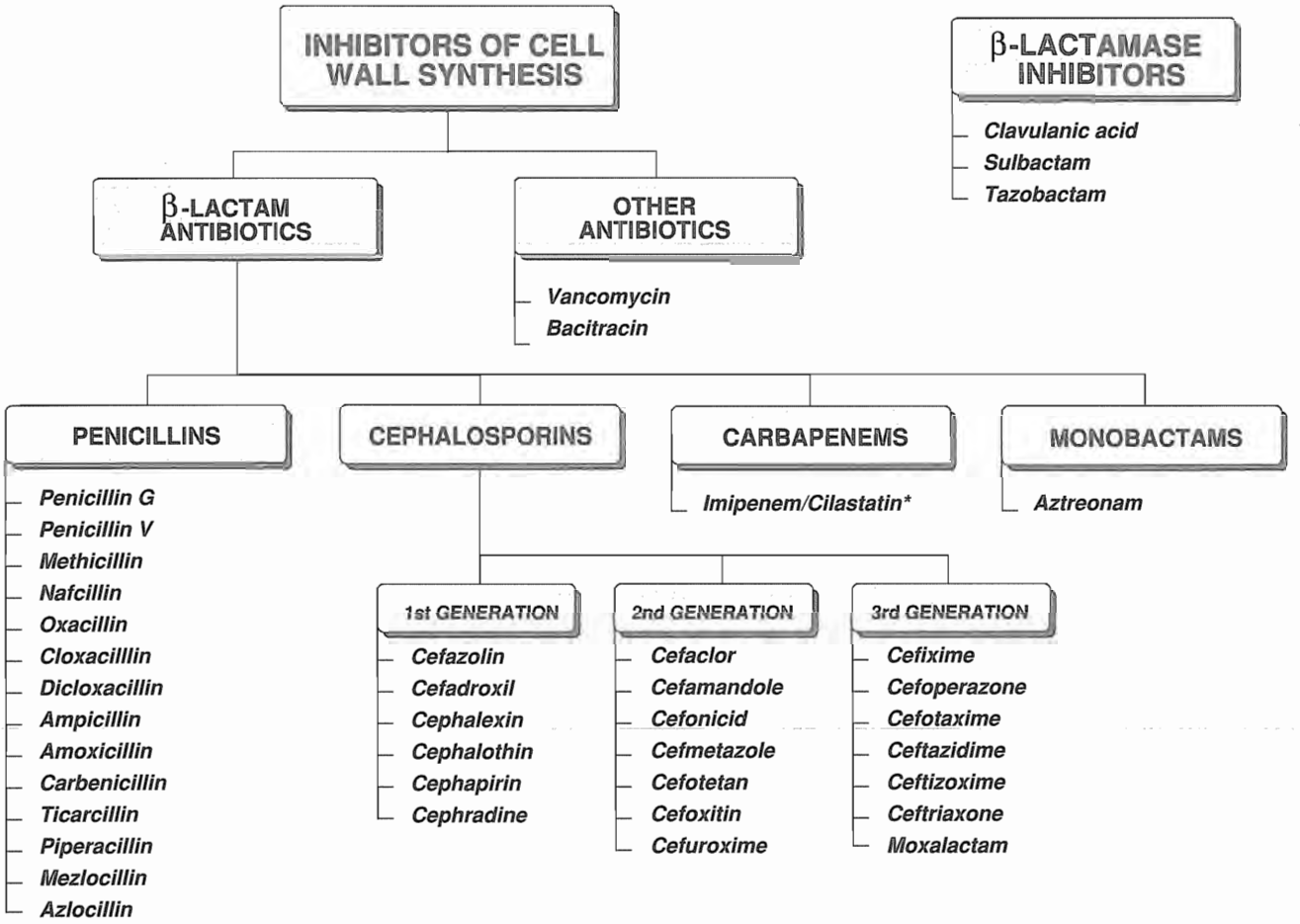


Figure 30.2
Summary of antimicrobial agents affecting cell wall synthesis *[Note: Cilastatin is not an antibiotic but a peptidase inhibitor that protects *imipenem* from degradation.]

1. **Penicillin binding proteins:** Penicillins inactivate proteins present 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 vary with the type of organism. Alterations in some of these target molecules confer resistance on the organism. [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. Penicillins inhibit this transpeptidase-catalyzed reaction, thus hindering the formation of crosslinks essential for cell wall integrity. As a result of this blockade of cell wall synthesis, the "Park peptide", UDP-acetylmuramyl-L-Ala-D-Gln-L-Lys-D-Ala-D-Ala, accumulates.

3. **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 *penicillin*, the degradative action of the autolysins proceeds in the absence of cell wall synthesis. The exact autolytic mechanism is unknown but may be due to a disinhibition of the autolysins. Thus, the antibacterial effect of *penicillin* is the result of both inhibition of cell wall synthesis and destruction of existing cell wall by autolysins.

B. Antibacterial spectrum

The antibacterial spectrum of the various penicillins is determined, in part, by their ability to cross the bacterial peptidoglycan cell wall and to reach the penicillin-binding proteins that are located in the periplasmic space. 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 surrounding the cell wall that presents a barrier to the water-soluble penicillins. [Note: For this reason, penicillins have little use in the treatment of intracellular pathogens.] Gram-negative bacteria have

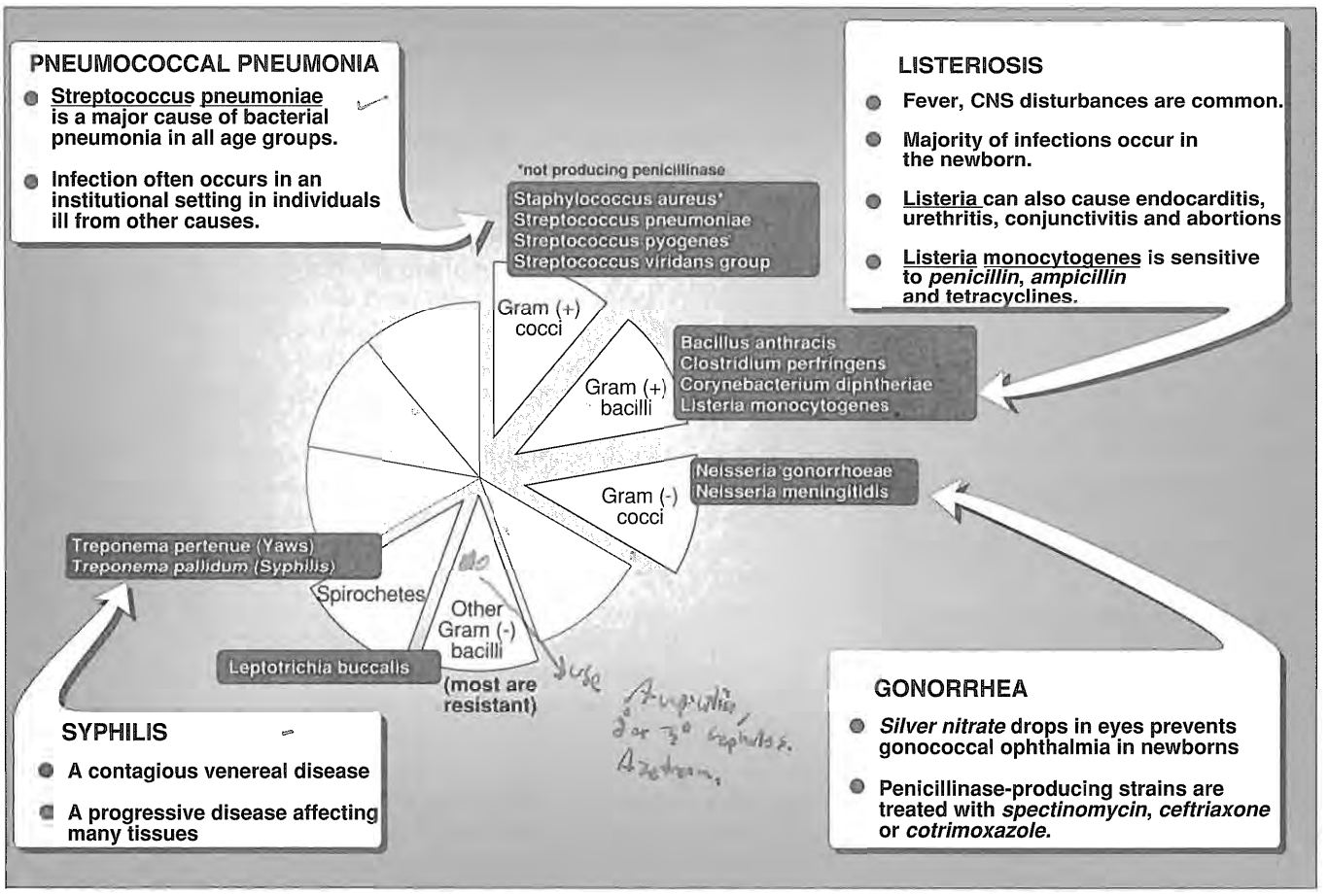


Figure 30.3
Typical therapeutic applications of penicillin G.

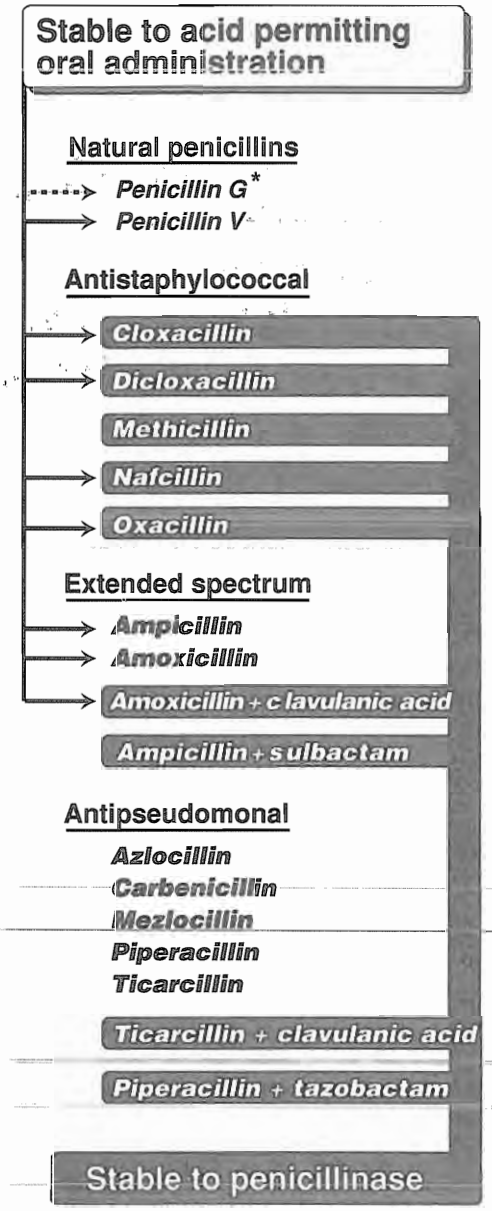


Figure 30.4
Stability of the penicillins to acid or the action of penicillinase
*[Note: *Penicillin G* is largely inactived by stomach acid, but doses can be adjusted so that adequate serum levels are achieved.]

proteins inserted in the lipopolysaccharide layer that act as water-filled channels (also called porins) and permit transmembrane entry. Factors that determine their susceptibility to these antibiotics include the size, charge and hydrophobicity of the particular β-lactam.

1. Natural penicillins

These penicillins, which include those listed as antistaphylococcal, are obtained from fermentations of the mold Penicillium chrysogenum. Other penicillins are called semi-synthetic because the different R groups are attached chemically to the 6-aminopenicillanic acid nucleus obtained from fermentation broths of the mold.

a. Penicillin 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 30.3). *Penicillin G* is susceptible to inactivation by β-lactamases (penicillinases, Figure 30.4).

b. Penicillin V has a spectrum similar to *penicillin G*, but it is not used for treatment of bacteremia because of its higher minimum lethal concentration (MLC, the minimum amount of the drug needed to eliminate the infection). *Penicillin V* is more acid-stable than *penicillin G*. It is often employed in the treatment of oral infections where it is effective against some anaerobic organisms.

2. Antistaphylococcal penicillins: *Methicillin* [meth i SILL in], *nafcillin* [naf SILL in], *oxacillin* [ox a SILL in], *cloxacillin* [klox 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. Because of its toxicity, *methicillin* is rarely used. *Methicillin*-resistant strains of Staphylococcus aureus (MRSA), currently a serious source of nosocomial (hospital-acquired) infections, are usually susceptible to *vancomycin*, and rarely to *ciprofloxacin* or *rifampin*.

3. Extended spectrum penicillins: *Ampicillin* [am pi SIL in] and *amoxicillin* [a mox i SIL 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 30.5). *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 β-lactamase inhibitor, such as *clavulanic acid* or *sulbactam*, protects *amoxicillin* or *ampicillin*, respectively, from enzymatic hydrolysis, and extends their antimicrobial spectrum. (See p. 307 for a discussion of these inhibitors.)

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 Pseudomonas aeruginosa. *Piperacillin* is the most potent. These antibiotics are effective against many gram-negative bacilli but not against Klebsiella, because of its constitutive penicillinase (Figure 30.5B). Formulation of *ticarcillin* or *piperacillin* with *clavulanic acid* or *tazobactam*, respectively (see p. 307) extends the antimicrobial spectrum of these antibiotics to include penicillinase-producing organisms. *Mezlocillin* [mez loe SILL in] and *azlocillin* [az loe SILL in] (sometimes referred to as *acylureido penicillins*) are also effective against Pseudomonas aeruginosa, and a large number of gram-negative organisms. They are susceptible to β-lactamase breakdown. (see Figure 30.4).

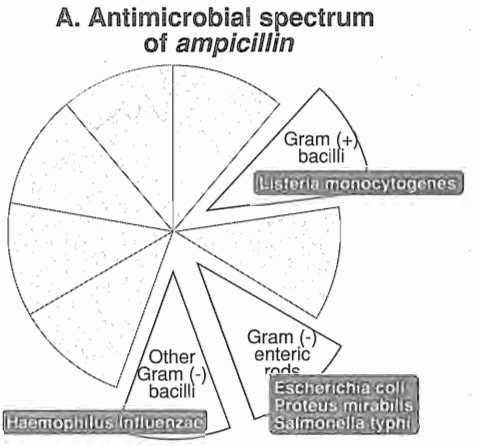
6. **Penicillins and aminoglycosides:** The antibacterial effects of all the β-lactam antibiotics are synergistic with the aminoglycosides. The ability of penicillins (and other agents that inhibit cell wall synthesis) to alter permeability of the bacterial cell can facilitate entry of antibiotics that might not ordinarily gain access to target sites, thus resulting in enhanced antimicrobial activity. Although the combination is employed 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 that have cell walls that are impermeable to the drugs. **Acquired resistance** to the penicillins by plasmid transfer has become a significant clinical problem, since an organism may become resistant to several antibiotics due to acquisition of a plasmid that encodes resistance for 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 both of the following properties, thus allowing it to withstand β-lactam antibiotics.

1. **β-lactamase activity:** This family of enzymes hydrolyzes the cyclic amide bond of the β-lactam ring, which results in loss of bactericidal activity (see Figure 30.1). β-Lactamases are either constitutive or, more commonly, are acquired by the transfer of plasmids. Some of the β-lactam antibiotics are poor substrates for β-lactamases and resist cleavage; thus they retain their activity against β-lactamase-producing organisms. [Note: Certain organisms may have chromosome-associated β-lactamases that are inducible by β-lactam antibiotics (for example, *cefoxitin*).]

2. **Decreased permeability to drug**: Decreased penetration of the antibiotic through the outer cell membrane prevents the drug from reaching the target penicillin-binding proteins (PBPs).



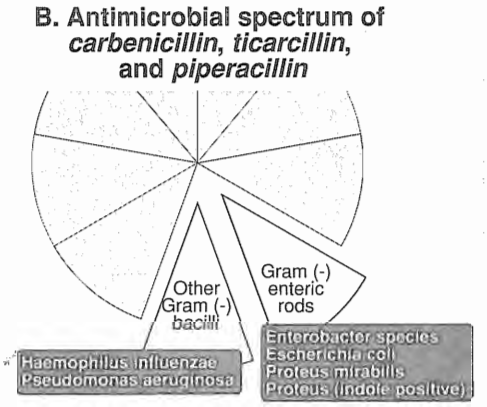


Figure 30.5
Typical therapeutic applications of *ampicillin* (A) and the antipseudomonal penicillins (B).

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

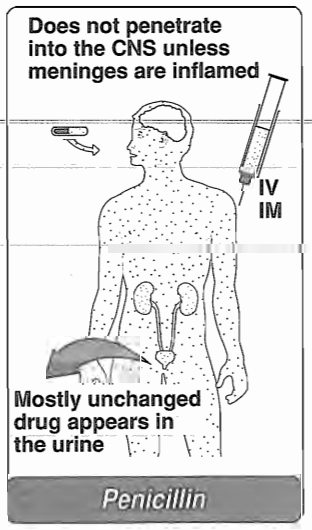
D. Pharmacokinetics

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

   a. **Routes of administration:** *Methicillin*, *ticarcillin*, *carbenicillin*, *mezlocillin*, *piperacillin*, *azlocillin*, 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*, and *amoxicillin* combined with *clavulanic acid* are only available as oral preparations. Others are effective by the oral, IV, or IM routes (see Figure 30.4).

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

2. **Absorption:** Most of the penicillins are incompletely absorbed after oral administration and 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, since therapeutically effective levels do not reach the organisms in the intestinal crypts. Absorption of *penicillin G* and all the penicillinase-resistant penicillins is decreased by food in the stomach since gastric emptying time is reduced and the drugs are destroyed in the acidic environment. Therefore, they must be administered 30-60 minutes before meals or 2-3 hours postprandially. Other penicillins are less affected by food.



3. **Distribution:** Distribution of the free drug throughout the body is good. All the penicillins cross the placental barrier, but none have been shown to be teratogenic. However, penetration into certain sites such as bone or cerebrospinal fluid is insufficient for therapy, unless these sites are inflamed (Figure 30.6). During the acute phase (first day), the inflamed meninges are more permeable to penicillins, resulting in an increased ratio in 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.

4. **Metabolism:** Metabolism of these drugs by the host 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 (see p. 224), as well as by glomerular filtration. Patients with impaired renal function must have dosage regimens adjusted. Thus the $t_{1/2}$ of *penicillin G* can increase from a normal of $^1/_2$ -1 hour to 10 hours in individuals with renal failure. *Probenecid* inhibits the secretion of penicillins. *Nafcillin* is primarily eliminated through the biliary route. [Note: This is also the preferential route for the *acylureido penicillins* in cases of renal failure.]

E. Adverse reactions

Penicillins are among the safest drugs, and blood levels are not monitored, although adverse reactions do occur.

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 5% of patients have some kind of reaction, ranging from maculopapular rash to angioedema (marked swelling of lips, tongue, periorbital area) and anaphylaxis. Cross-allergic reactions do occur among the β-lactam antibiotics. Although rashes can develop with all the penicillins, maculopapular rashes are most common with *ampicillin*. Among patients with mononucleosis who are treated with *ampicillin*, the incidence of maculopapular rash approaches 100%.

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.

3. **Nephritis:** All penicillins, but particularly *methicillin*, have the potential to cause acute interstitial nephritis.

4. **Neurotoxicity**: The penicillins are irritating to neuronal tissue and can provoke seizures if injected intrathecally or if very high blood levels are reached. Epileptic patients are especially at risk.

5. **Platelet dysfunction**: This side effect, which involves decreased agglutination, is observed with the antipseudomonal penicillins (*carbenicillin* and *ticarcillin*) and, to some extent, with *penicillin G*. It is generally a concern when treating patients predisposed to hemorrhage or those receiving anticoagulants.

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.

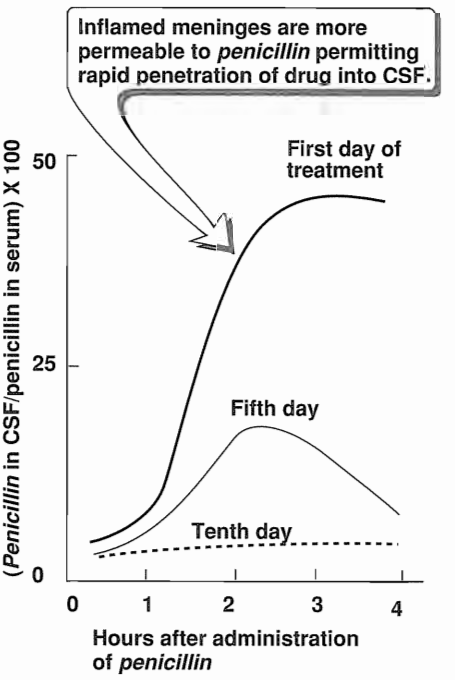


Figure 30.6
Enhanced penetration of *penicillin* into the cerebral spinal fluid (CSF) during inflammation.

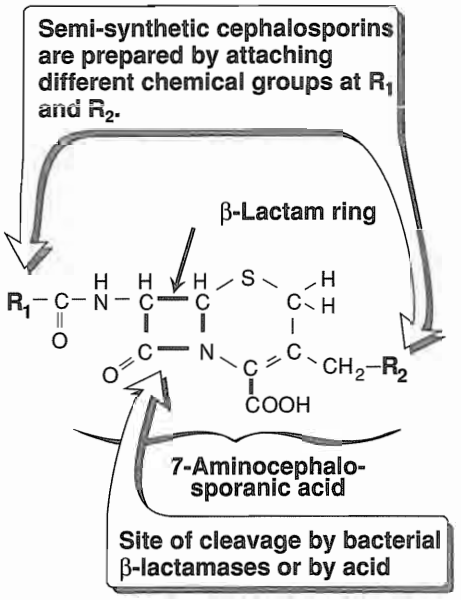


Figure 30.7
Structural features of cephalosporins.

III. CEPHALOSPORINS

The cephalosporins and their 7-methoxy analogs, the cephamycins such as *cefoxitin* (se FOX i tin), *cefotetan* (se foe TEE tan) and *cefmetazole* (sef MET a zol), are β-lactam antibiotics that are closely related both structurally (Figure 30.7) and functionally to the penicillins. Most cephalosporins are produced semi-synthetically by the chemical attachment of side chains to 7-aminocephalosporanic acid. Cephalosporins and cephamycins have the same mode of action as the penicillins and are affected by the same resistance mechanisms, but they tend to be more resistant than the penicillins to β-lactamases.

A. Antibacterial spectrum

Cephalosporins have been classified as first, second or third generation, largely on the basis of bacterial susceptibility patterns and resistance to β-lactamases (Figure 30.8). [Note: They are ineffective against *methicillin*-resistant Staphylococcus aureus (MRSA), Listeria monocytogenes, Clostridium difficile and the enterococci.]

1. **First generation:** Cephalosporins designated first generation (Figure 30.8) act as *penicillin G* substitutes that are resistant to the staphylococcal penicillinase. They also have activity against **P**roteus mirabilis, **E**scherichia **c**oli, and **K**lebsiella pneumoniae (the acronym **PEcK** has been suggested).

2. **Second generation:** The second generation cephalosporins display greater activity against three additional gram-negative organisms, **H**aemophilus influenzae, some **E**nterobacter aerogenes and some **N**eisseria species (**HENPEcK**), whereas activity against gram-positive organisms is weaker. [Note: The cephamycins are effective against Bacteroides fragilis; *cefoxitin* is the most potent.]

3. **Third generation:** These cephalosporins have assumed an important role in the treatment of infectious disease. Though greatly 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 plus most other enteric organisms and Serratia marcescens. *Ceftriaxone* (sef tree AKS own) or *cefotaxime* [sef oh TAKS eem] have become agents of choice in the treatment of meningitis. *Ceftazidime* (sef TAZ id eem) has activity against Pseudomonas aeruginosa.

B. Resistance

Mechanisms of bacterial resistance to the cephalosporins are essentially the same as those described for the penicillins (see p. 301).

C. Pharmacokinetics

1. **Administration:** All the cephalosporins (except for those highlighted in Figure 30.8) must be administered intravenously because of their poor oral absorption.

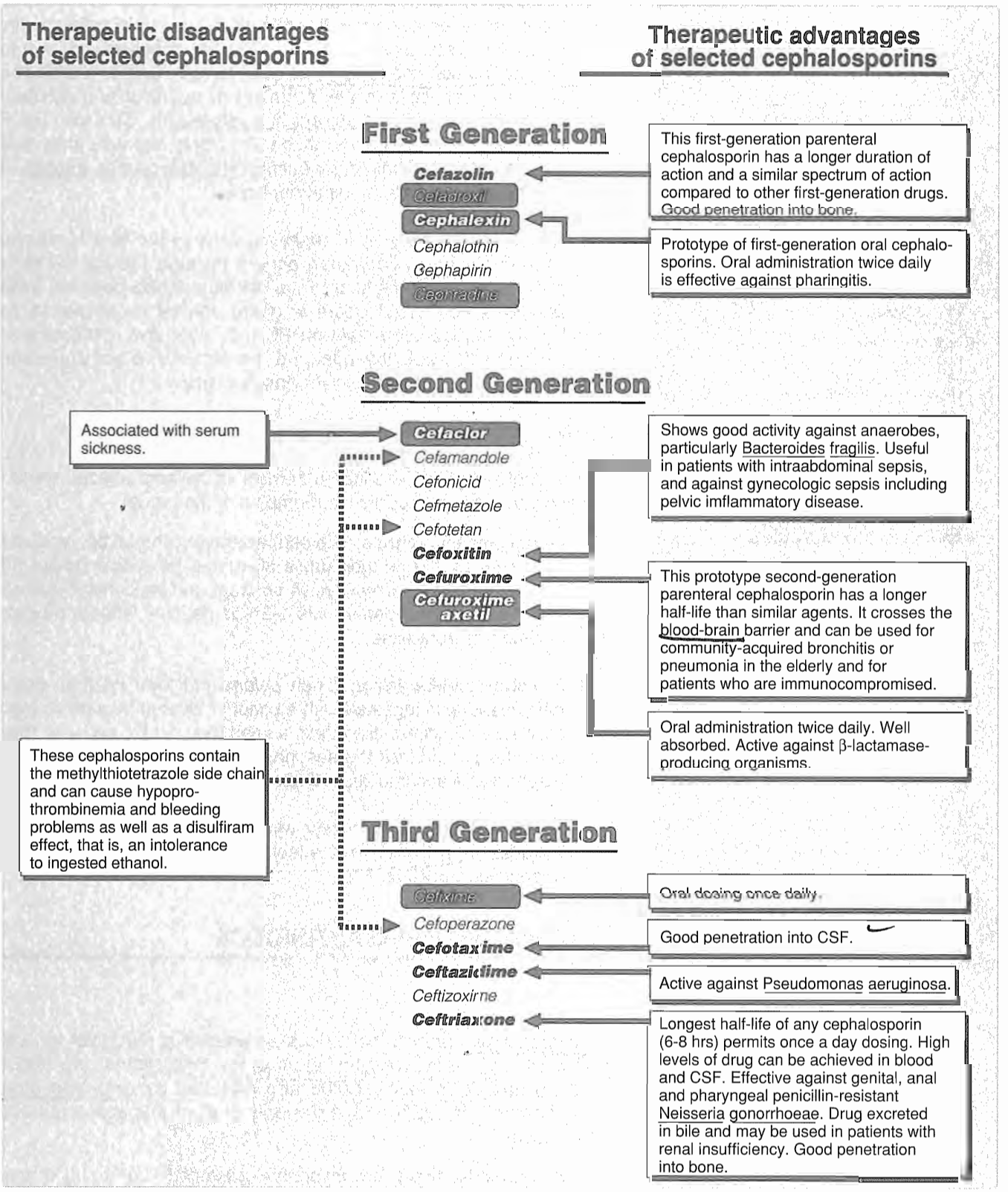
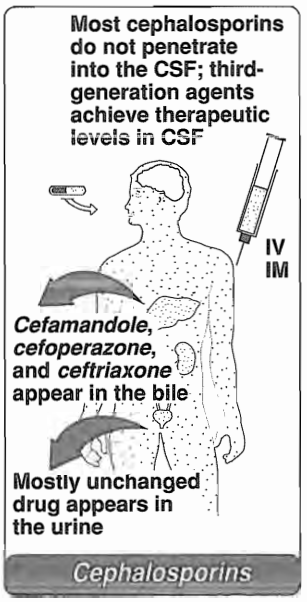


Figure 30.8
Characteristic of some clinically useful cephalosporins. Note: Drugs that can be administered orally are shown in reverse type. More useful drugs shown in **bold**.



2. **Distribution:** All of these antibiotics distribute very well into body fluids. However, adequate therapeutic levels in the cerebrospinal fluid (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 Haemophilus influenzae). *Cefazolin* (se FA zo lin) finds application in orthopedic surgery because of its activity against penicillinase-producing Staphylococcus aureus, its half-life and its ability to penetrate bone.

3. **Fate:** Biotransformation of cephalosporins by the host is not clinically important. Elimination occurs through tubular secretion and/or glomerular filtration; thus doses must be adjusted in the case of severe renal failure to guard against accumulation and toxicity. *Cefoperazone* (sef oh PER az own) and *ceftriaxone* are excreted through the bile into the feces and are 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.

1. **Allergic manifestations**: The cephalosporins should be avoided or used with caution in individuals allergic to penicillins (about 5 to 15% show cross-sensitivity). In contrast, the incidence of allergic reactions to cephalosporins is 1-2% in patients without a history of allergy to penicillins.

2. **A disulfiram-like effect:** When *cefamandole* [se FAM an dol] or *cefoperazone* is ingested with alcohol or alcohol-containing medications, a disulfiram-like effect is seen (see p. 96), because these cephalosporins block the second step in alcohol oxidation, which results in the accumulation of acetaldehyde[1].

3. **Bleeding:** Bleeding can occur with *cefamandole* or *cefoperazone*, because of anti-vitamin K effects; administration of the vitamin corrects the problem.

IV. OTHER β-LACTAM ANTIBIOTICS

A. Carbapenems

Carbapenems are synthetic β-lactam antibiotics that differ from the penicillins in that the sulfur atom of the thiazolidine ring (Figure 30.9) has been externalized and replaced by a carbon atom. *Imipenem* [i mi PEN em] is the only drug of this group currently available.

1. **Antibacterial spectrum:** *Imipenem/cilastatin* is the broadest spectrum β-lactam antibiotic preparation currently available. *Imipenem* resists hydrolysis by most β-lactamases. The drug plays a role in empiric therapy since it is active against penicillinase-producing gram-positive and gram-negative organisms, anaerobes, and

[1]See p. 310 for Infolink references to other books in this series.

Pseudomonas aeruginosa, although other pseudomonas strains are resistant. [Note: Resistant strains of Pseudomonas aeruginosa have been reported to arise during therapy.]

2. **Pharmacokinetics:** *Imipenem* is administered intravenously and penetrates well into body tissues and fluids including cerebral spinal fluid when the meninges are inflamed. It is excreted by glomerular filtration and undergoes cleavage by a dehydropeptidase found in the brush border of the proximal renal tubule to form an inactive metabolite that is potentially nephrotoxic. Compounding the *imipenem* with *cilastatin*, a dehydropeptidase inhibitor, protects the parent drug from cleavage and thus prevents the formation of a toxic metabolite. This allows the drug to be active in the treatment of urinary tract infections. [Note: The dose 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. High levels of this agent may provoke seizures.

B. Monobactams

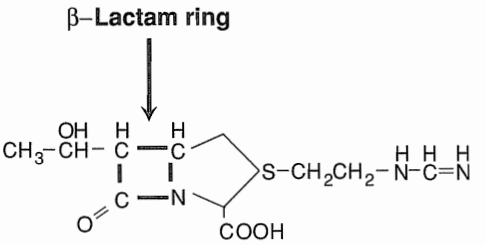
G(−) Aerobic Rods

The monobactams, of which *aztreonam* [az TREE oh nam] is the only commercially available example, are unique because the β-lactam ring is not fused to another ring (Figure 30.9). Monobactams also disrupt cell wall synthesis. The drug's narrow antimicrobial spectrum precludes its use alone in empiric therapy (p. 279). *Aztreonam* is resistant to the action of β-lactamases.

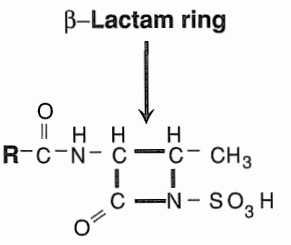
1. **Antibacterial spectrum:** The antibacterial activity of *aztreonam* is primarily directed against the enterobacteria. *Aztreonam* is useful because of its action against aerobic gram-negative rods. It lacks activity against gram-positive organisms and anaerobes.

2. **Pharmacokinetics:** *Aztreonam* is administered via IV or IM routes. It is excreted in the urine and can accumulate in patients with renal failure.

3. **Adverse effects:** *Aztreonam* is relatively nontoxic, but it may cause phlebitis, skin rash, and occasionally, abnormal liver function tests. *Aztreonam* has a low immunogenic potential and shows little cross-reactivity with antibodies induced by other β-lactams. Thus *aztreonam* may offer a safe alternative for treating patients allergic to penicillins and/or cephalosporins.



Imipenem
(a carbapenem)



Aztreonam
(a monobactam)

Figure 30.9
Structural features of *imipenem* and *aztreonam*.

V. β-LACTAMASE INHIBITORS

Hydrolysis of the β-lactam ring, either by enzymatic cleavage via a β-lactamase or by acid, destroys antimicrobial activity. β-Lactamase inhibitors, such as *clavulanic acid* [cla vue LA nick], *sulbactam* [sul BACK tam] and *tazobactam* [ta zoh BACK tam], contain a β-lactam ring, but they do not have significant antibacterial activity. Instead, they bind to and inactivate β-lactamases, thereby protecting the antibiotics that are normally substrates for these enzymes. The β-lactamase inhibitors are formulated with the penicillin derivatives to protect the latter from enzymatic inactiva-

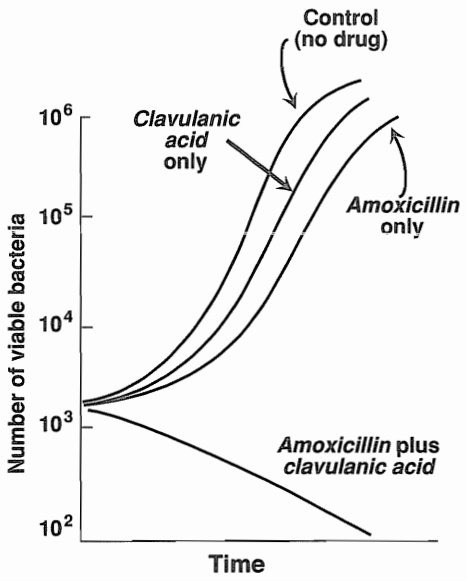


Figure 30.10
The growth of Escherichia coli in the presence of *amoxicillin*, with and without *clavulanic acid*.

tion. Figure 30.10 shows the effect of *clavulanic acid* and *amoxicillin* on the growth of β-lactamase-producing Escherichia coli. Note that *clavulanic acid* alone is nearly devoid of antibacterial activity.

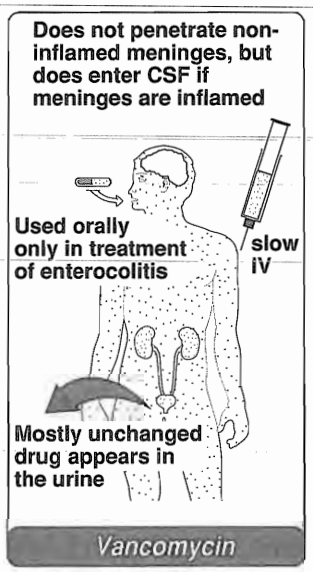
VI. OTHER AGENTS AFFECTING THE CELL WALL

A. 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 *methicillin*-resistant staphylococci. The medical community is presently concerned about reports of emergence of *vancomycin* resistance in these strains as well as the enterococci.

1. **Mode of action:** *Vancomycin* inhibits synthesis of bacterial cell wall phospholipids as well as peptidoglycan polymerization at a site earlier than that inhibited by the β-lactam antibiotics.

2. **Antibacterial spectrum:** In order to curtail the increase in *vancomycin*-resistant bacteria (for example, the Enterococcus faecium and Enterococcus faecalis), it is important to restrict its use to the treatment of serious infections caused by β-lactam-resistant gram-positive microorganisms, or for patients with gram-positive infections who have a serious allergy to the β-lactams. It is also used for potentially life-threatening antibiotic-associated colitis due to Clostridium difficile or staphylococci. It is used prophylactically in dental patients. *Vancomycin* is used in individuals with prosthetic heart valves or in patients being implanted with prosthetic devices. The latter is of particular concern in those hospitals where there is a problem with *methicillin*-resistant Staphylococcus aureus (MRSA) or Staphylococcus epidermidis (MRSE). *Vancomycin* acts synergistically with the aminoglycosides and this combination can be used in the treatment of enterococcal endocarditis.



3. **Resistance:** Occurring rarely, *vancomycin* resistance is due to plasmid-mediated changes in permeability to the drug and is also due to decreased binding of *vancomycin* to receptor molecules.

4. **Pharmacokinetics:** Slow intravenous infusion is employed for treatment of systemic infections or for prophylaxis. Because *vancomycin* is not absorbed after oral administration, this route is only employed for the treatment of antibiotic-induced colitis due to C. difficile. Inflammation allows penetration into the meninges. Metabolism is minimal; 90-100 % is excreted by glomerular filtration. [Note: Dosage must be adjusted in renal failure since the drug will accumulate. Normal half-life is 6-10 hours compared to over 200 hours in end-stage renal disease.]

5. **Adverse effects:** Side effects are a serious problem with *vancomycin* and include fever, chills, and/or phlebitis at the infusion site. Shock has occurred as a result of rapid administration.

Flushing ("red man syndrome") and shock result due to histamine release caused by rapid infusion. Dose-related hearing loss has occurred in patients with renal failure who accumulate the drug.

B. Bacitracin

Bacitracin [bass i TRAY sin] is a mixture of polypeptides that 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.

Study Questions

Choose the ONE best answer.

30.1 Which one of the following drugs is both penicillinase-resistant and effective by oral administration?

A. Methicillin.
B. Carbenicillin.
C. Penicillin V.
D. Amoxicillin plus clavulanic acid.
E. Piperacillin.

Correct answer = D. Amoxicillin plus clavulanic acid is an extended spectrum formulation that is penicillinase resistant because of the presence of a β-lactamase inhibitor, and is stable in acid. Methicillin, an antistaphylococcal penicillin, is penicillinase resistant but is not stable in acid. Carbenicillin and piperacillin, antipseudomonal penicillins, are neither penicillinase resistant nor stable in acid. Penicillin V is a narrow spectrum antibiotic that is not penicillinase resistant but is stable in acid.

30.2 Which one of the following antibiotics is INCORRECTLY matched with an appropriate clinical indication?

A. Penicillin G: Pneumonia caused by Klebsiella pneumoniae
B. Carbenicillin: Urinary tract infection caused by Pseudomonas aeruginosa (β-lactamase negative)
C. Ampicillin: Bacterial meningitis caused by Haemophilus influenzae (β-lactamase negative)
D. Penicillin G: Syphilis caused by Treponema pallidum
E. Cefazolin: Staphyloccocal osteomyelitis

Correct choice = A. Cephalosporins, not penicillins, are effective against Klebsiella.

30.3 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:

A. Vancomycin
B. Amoxicillin
C. Tetracycline
D. Co-trimoxazole
E. Imipenem

Answer: B (Amoxicillin). The multiple extractions can lead to bacteremia while the mitral valve stenosis and cardiac insufficiency place him at risk for developing endocarditis. The present American Heart Association guidelines indicate amoxicillin (3 gm 1 hour prior to procedure and 1.5 gm 6 hours after original dose.) Vancomycin would only be appropriate if the patient was allergic to penicillins. Tetracycline and cotrimoxazole are bacteriostatic and not effective against the viridans group of Streptococci, the usual causative organism. Imipenem is also inappropriate since its spectrum is too broad.

30.4 All of the following statements about penicillin G are correct EXCEPT:

A. It is excreted from the body primarily via the hepatobiliary route.
B. Administered orally, it is variably absorbed because of its degradation by stomach acid.
C. It is more effective in killing growing bacteria than microorganisms in the stationary phase.
D. It can act synergistically with aminoglycosides.
E. Levels in the blood can be increased by administration of probenecid.

Correct choice = A. The primary route of excretion of penicillin G is via the kidney. Oral administration of penicillin G is unreliable, in part because the β-lactam ring is cleaved in acid. Penicillin G is bactericidal to growing microorganisms when they are actively making new cell wall material, and it facilitates the entry of the aminoglycosides into the cell, leading to synergistic antimicrobial effects. Administration of probenecid interferes with the secretion of penicillins and results in higher blood levels of penicillin and a prolonged half-life of the antibiotic.

30.5 Which one of the following statements about inhibitors of cell wall synthesis is INCORRECT?

A. The concentration of penicillin in the cerebrospinal fluid is higher when administered to patients with meningococcal meningitis than it is when given to normal patients.

B. First generation cephalosporins are more effective against staphylococcal infections than are third generation cephalosporins.

C. Cefoxitin is less likely to cause an allergic reaction in a patient that is hypersensitive to penicillin G than is penicillin V.

D. The half-life of procaine penicillin administered intramuscularly is greater than the half-life of penicillin G administered orally.

E. Third-generation cephalosporins are susceptible to β-lactamase activity.

Correct choice = E. Unlike the penicillins, cephalosporins are less sensitive to β-lactamase activity. Inflammation does increase penetration of penicillin into the CSF. All penicillin derivatives, including penicillin V, can potentially trigger an allergic reaction in patients sensitive to penicillin G. Cefoxitin can often be used in these patients. However, caution should be exercised, since there is about 5 to 15% cross-reactivity.

30.6 A 25-year-old male returns home from a holiday in the Far East and complains of three 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

Correct answer = A. Most gonoccocal infections are now resistant to penicillin, the previous drug of choice. The other antibiotics are inappropriate.

30.7 An eight-month pregnant medical student complains of lower abdominal pain and a 48-hour history of dysuria. She does not have any fever; an analysis of her urine shows protein, but no blood or glucose. A culture is taken. Which of the following is useful for treating this urinary tract infection orally without causing risks to the fetus?

A. Cefadroxil (first generation cephalosporin)

B. Cotrimoxazole (TMP/SM)

C. Penicillin V

D. Ceftriaxone (third generation cephalosporin)

E. Tetracycline

Correct answer = A. Most urinary tract infections are due to E. coli and can usually be treated with cotrimoxazole. However, this patient is near term and the sulfa in the cotrimoxazole might put the infant at risk due to kernicterus. Thus, the first generation cephalosporin, cefadroxil, is appropriate since it would be effective orally against penicillinase producing E. coli. Ceftriaxone, while it would be effective, would have to be administered parenterally. Penicillin V is not effective against E. coli. Tetracycline deposits in teeth and skeleton of the fetus and is contraindicated.

30.8 A patient with degenerative joint disease is to undergo insertion of a hip prosthesis. In order to avoid complications due to post-operative infection, the surgeon will pretreat this patient with an antibiotic. This hospital has a significant problem with methicillin-resistant Staphylococcus aureus. Which of the following antibiotics should the surgeon select?

A. Ampicillin

B. Imipenem/cilastatin

C. Gentamicin/piperacillin

D. Vancomycin

E. Cefazolin

Correct answer = D. The only antibiotic which is effective against methicillin-resistant Staphylococcus aureus is vancomycin.

[1]See p. 279 in **Biochemistry** (2nd ed.) for a discussion of ethanol metabolism.

Protein Synthesis Inhibitors

31

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. 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[1]. The mammalian mitochondrial ribosome, however, more closely resembles the bacterial ribosome. Thus, although drugs that interact with the bacterial site usually spare the host cells, high levels of drugs like *chloramphenicol* or the tetracyclines may cause toxic effects as a result of interaction with the mitochondrial ribosomes. Figure 31.1 lists the drugs discussed in this chapter

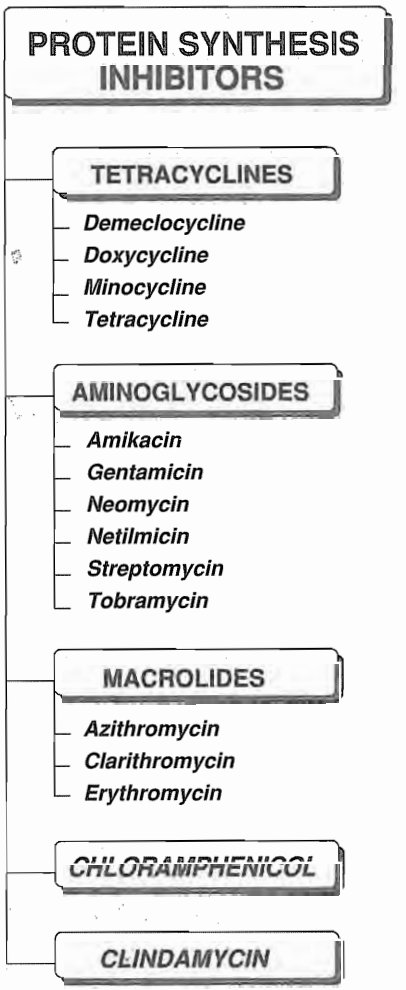


Figure 31.1
Summary of protein synthesis inhibitors.

II. TETRACYCLINES

Tetracyclines [tet ra SYE kleen] are a group of closely related compounds that, as the name implies, consist of 4 fused rings with a system of conjugated double bonds. Their small differences in clinical efficacy reflect a variation in their individual pharmacokinetics due to substitutions on these rings.

A. Mode of action

Entry of these agents into susceptible organisms is mediated by transport proteins unique to the bacterial inner cytoplasmic membrane. Binding of the drug to the 30S subunit of the bacterial ribosome is believed to block access of the amino acyl-tRNA to the mRNA-ribosome complex at the acceptor site, thus inhibiting bacterial protein synthesis[2].

B. Antibacterial spectrum

As broad spectrum antibiotics, the tetracyclines are also effective against organisms other than bacteria. Tetracyclines are generally bacteriostatic and are the drugs of choice for infections shown in Figure 31.2.

[1,2]See p. 322 for Infolink references to other books in this series.

Lippincott's Illustrated Reviews: Pharmacology, Second Edition.
by Mary Mycek, Richard A. Harvey and Pamela C. Champe.
Lippincott–Raven Publishers, Philadelphia, PA © 1997

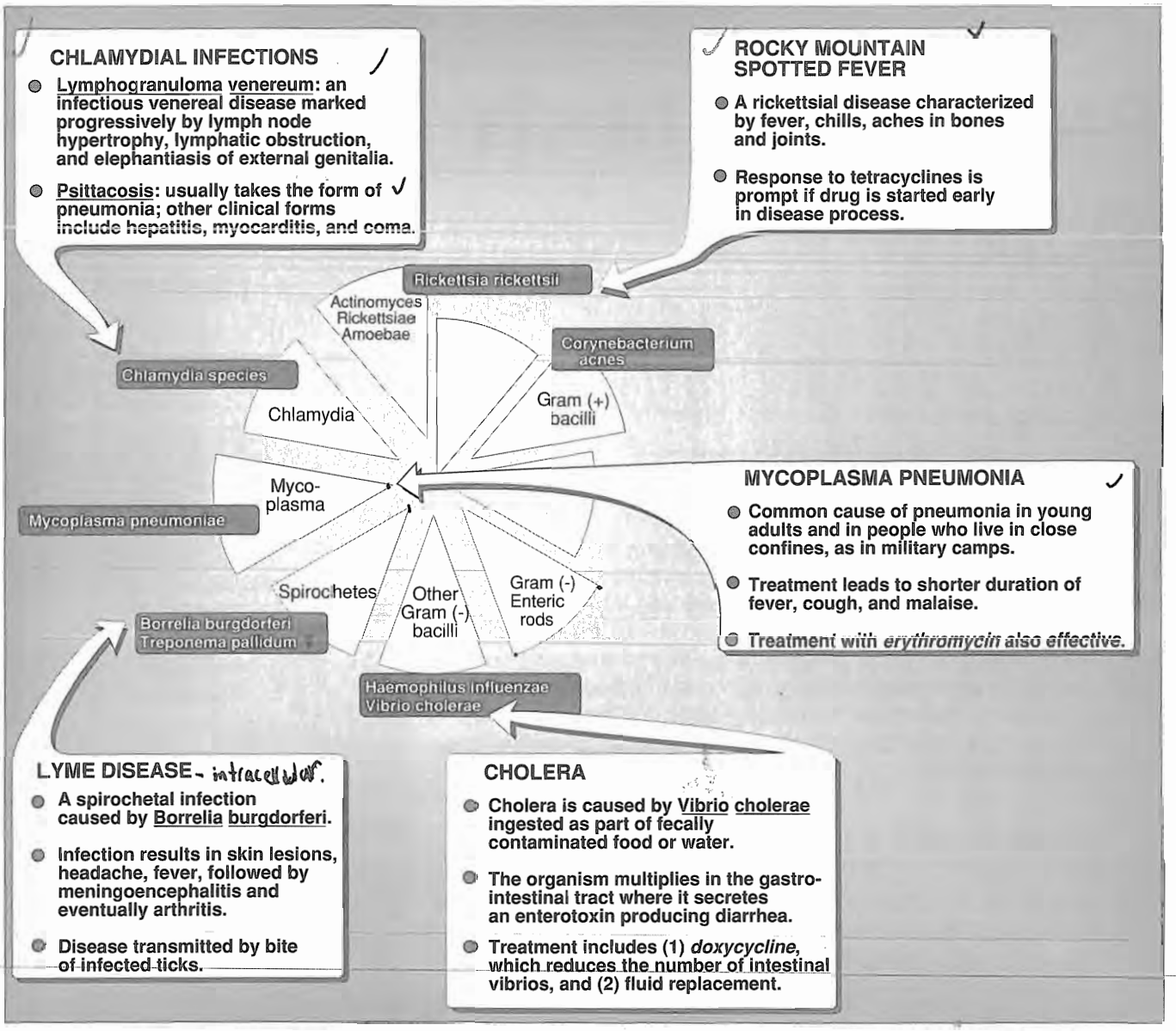


Figure 31.2
Typical therapeutic applications of tetracyclines.

C. Resistance

Widespread resistance to tetracyclines limits their clinical use. The most commonly encountered naturally occurring R factor confers an inability of the organism to accumulate the drug, thus producing resistance. This is accomplished by a Mg^{++}-dependent active efflux of the drug mediated by the resistance protein TetA. Other mechanisms such as possible modification of the tetracycline binding site have also been reported. Any organism resistant to one tetracycline is resistant to all. The majority of penicillinase-producing staphylococci are now also insensitive to tetracyclines.

D. Pharmacokinetics

1. **Absorption:** All tetracyclines are adequately but incompletely absorbed after oral ingestion. However, taking these drugs concomitantly with dairy foods in the diet decreases absorption because of the formation of nonabsorbable chelates of the tetracyclines with calcium ions. This is less of a problem with *doxycycline* [dox i SYE kleen]. 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 the patient self-treats the epigastric upsets caused by tetracycline ingestion with antacids (Figure 31.3).]

2. **Distribution:** The tetracyclines concentrate in the liver, kidney, spleen, and skin and 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, levels are insufficient for therapeutic efficacy, except for *minocycline* [mi noe SYE kleen]. *Minocycline* enters the brain in the absence of inflammation, and also appears in tears and saliva. Though useful in eradicating the meningococcal carrier state, *minocycline* is not effective for central nervous system (CNS) infections. All tetracyclines cross the placental barrier and concentrate in fetal bones and dentition.

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 and enter the urine by glomerular filtration. *Doxycycline* is an exception, since its metabolite is preferentially excreted via the bile into the feces. Thus, unlike other tetracyclines, *doxycycline* can be employed in treating infections in renally compromised patients.

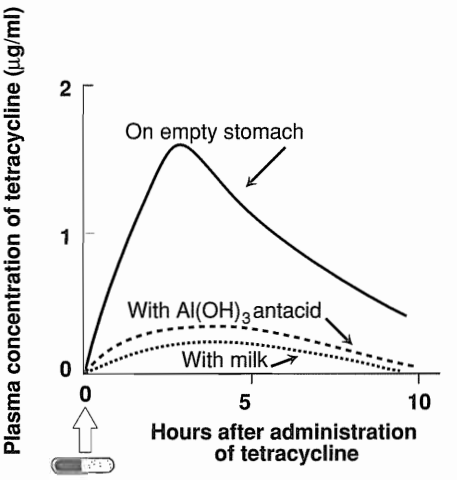
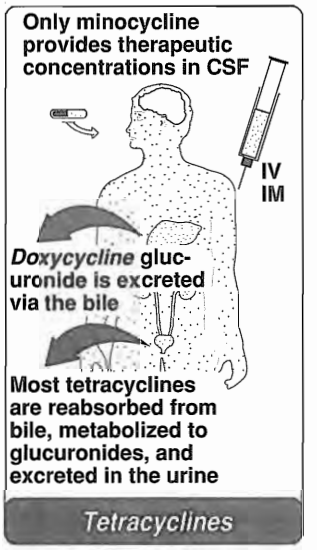


Figure 31.3
Effect of antacids and milk on the absorption of tetracyclines.



E. Adverse effects

1. **Gastric discomfort:** Epigastric distress commonly results from irritation of the gastric mucosa (Figure 31.4) and is often responsible for non-compliance 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 are experiencing pyelonephritis.

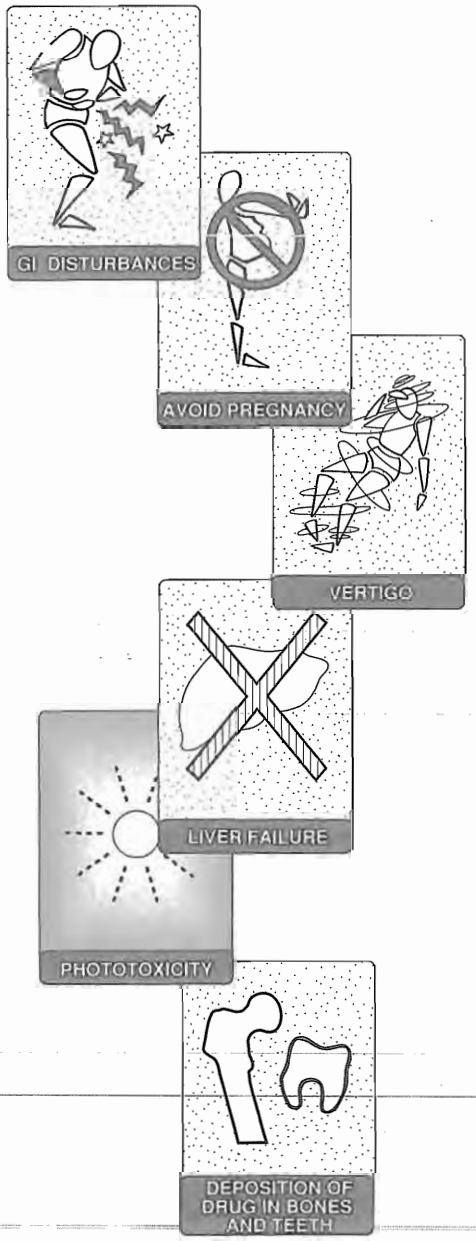


Figure 31.4
Some adverse effects of tetracycline.

4. **Phototoxicity:** Phototoxicity, for example, severe sunburn, occurs when the patient receiving a tetracycline is exposed to sun or ultraviolet rays. This toxicity is encountered most frequently with *tetracycline*, *doxycycline*, and *demeclocycline* [dem e kloe SYE kleen].

5. **Vestibular problems:** These side effects (for example, dizziness, nausea, vomiting) occur with *minocycline*, which concentrates in the endolymph of the ear and affects function.

6. **Pseudotumor cerebri:** Benign intracranial hypertension characterized by headache and blurred vision may occur in adults. Though discontinuation of the drug reverses the 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.

8. **Contraindications:** Renally-impaired patients should not be treated with any of the tetracyclines except *doxycycline*. Accumulation of tetracyclines may aggravate pre-existing azotemia 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 under 8 years of age.

III. AMINOGLYCOSIDES

Aminoglycoside antibiotics had been the mainstays of treatment of serious infections due to aerobic gram-negative bacilli. However, since their use was limited by serious toxicities, they have been replaced to some extent by safer antibiotics such as the third generation cephalosporins (see p. 304), the fluoroquinolones (see p. 323), and *imipenem/cilastatin* (see p. 306). Aminoglycosides that are derived from Streptomyces have "mycin" suffixes, whereas those from Micromonospora end in "micin." The terms "aminoglycoside" and "aminocyclitol" stem from their structure — two amino sugars joined in glycosidic linkage to a central hexose (aminocyclitol) nucleus.

A. Mode of action

All members of this family are believed to inhibit bacterial protein synthesis by the mechanism determined for *streptomycin* [strep toe MYE sin]. Susceptible organisms have an oxygen-dependent system that transports the antibiotic across the cell membrane. The antibiotic then binds to the separated 30S ribosomal subunit, interfering with assembly of the functional ribosomal apparatus, or causing the 30S subunit of the complete 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 β-lactam antibiotics because of the latters' action on cell wall synthesis, which enhances diffusion of the aminoglycosides into the bacterium (see p. 301).].

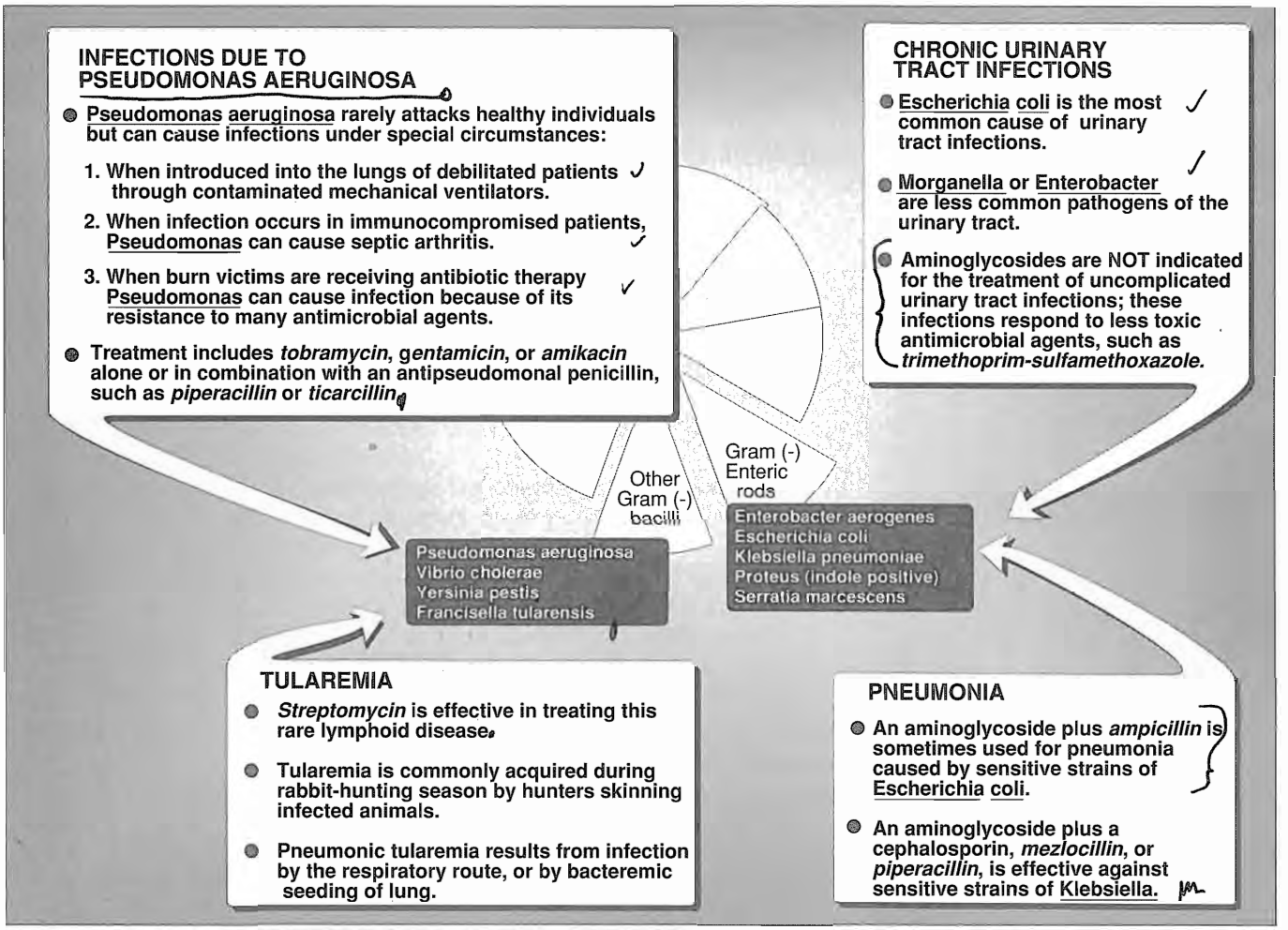


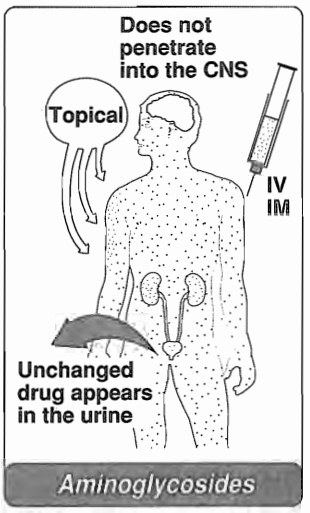
Figure 31.5
Typical therapeutic applications of *gentamicin*, *tobramycin*, *streptomycin* and *amikacin*.

B. Antibacterial spectrum

All aminoglycosides are bactericidal. They are effective only against aerobic organisms, since anaerobes lack the oxygen-requiring transport system. *Streptomycin* is used to treat tuberculosis, plague, tularemia, and in combination with *penicillin*, endocarditis caused by viridans group streptococci. Some therapeutic applications of four commonly used aminoglycosides, *amikacin* [am i KAY sin], *gentamicin* [jen ta MYE sin], *tobramycin* [toe bra MYE sin] and *streptomycin* are shown in Figure 31.5.

C. Resistance

Resistance can be caused by 1) decreased uptake of drug when the oxygen-dependent transport system for aminoglycosides is absent; an altered receptor where the 30S ribosomal subunit binding site has a lowered affinity for aminoglycosides; plasmid-associated synthesis of enzymes (for example, acetyltransferases, nucleotidyltransferases, and phosphotransferases) that modify and inactivate aminoglycoside



antibiotics. Each type of enzyme has its own specificity as to substrate antibiotic; therefore, cross-resistance is not an invariable rule. *Netilmicin* [ne TIL mye sin] and *amikacin* are less vulnerable to these enzymes than are the other antibiotics of this group.

D. Pharmacokinetics

1. **Administration:** The highly polar, polycationic structure of the aminoglycosides prevents adequate absorption after oral administration. 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 or oral treatment in hepatic coma to reduce the intestinal bacterial population.]

2. **Distribution:** All of the aminoglycosides have similar pharmacokinetic properties. Levels achieved in most tissues are low, and penetration into most body fluids is variable. Concentrations in cerebrospinal fluid are inadequate even when the meninges are inflamed. Except for *neomycin*, the aminoglycosides may be administered intrathecally. 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 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. Accumulation occurs in patients with renal failure, and requires dose modification (Figure 31.6).

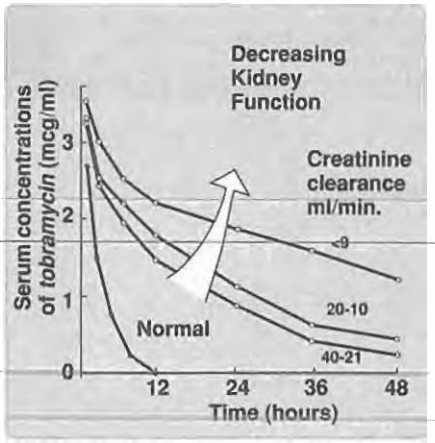


Figure 31.6
Serum concentrations of *tobramycin* following administration of the same dose of drug to normal and azotemic patients.

E. Adverse effects

It is important to monitor peak and trough plasma levels (see p. 20) of *gentamicin*, *tobramycin*, *netilmicin*, and *amikacin* to avoid concentrations that cause dose-related toxicities (Figure 31.7). [Note: Peak levels are defined as those obtained ½ to 1 hour after infusion. Trough levels are obtained immediately before the next dose.] Patient factors, such as old age, previous exposure to aminoglycosides, gender, and liver disease, tend to predispose patients to adverse reactions. The elderly are particularly susceptible to nephrotoxicity and ototoxicity.

1. **Ototoxicity:** Ototoxicity (vestibular and cochlear) is directly related to high peak plasma levels and duration of treatment. Deafness may be irreversible and has been known to affect fetuses in utero. Patients simultaneously receiving another ototoxic drug such as the loop diuretics *furosemide*, *bumetanide*, *ethacrynic acid* (see p. 227) or *cisplatin* (see p. 396), are particulary at risk. Vertigo and loss of balance may also occur because these drugs affect the vestibular apparatus.

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

3. **Neuromuscular paralysis:** This side effect most often results 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*.

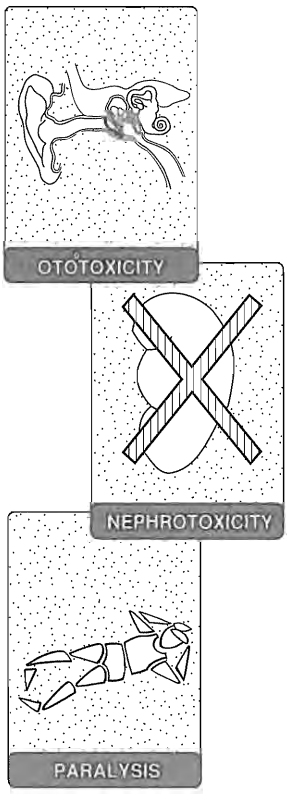


Figure 31.7
Some adverse effects of aminoglycosides.

IV. MACROLIDES

The macrolides are a group of antibiotics with a macrocyclic lactone structure. *Erythromycin* [er ith roe MYE sin] was the first of these to find clinical application both as the drug of first choice, and as an alternative to *penicillin* in individuals who are allergic to β-lactam antibiotics. The new members of this family, *clarithromycin* (a methylated form of *erythromycin*) and *azithromycin* (having a larger lactone ring) have some features in common with and others that improve on, *erythromycin*. Recently, *dirithromycin* [di rith roe MYE sin], a macrolide similar to erythromycin in antibacterial spectrum, but with the advantage of one-daily dosage, has been approved.

A. Mode 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. Generally considered to be bacteriostatic, they may be cidal at higher doses. The binding site is either identical to or in close proximity to that for *lincomycin*, *clindamycin*, and *chloramphenicol*.

B. Antibacterial spectrum

1. **Erythromycin** is effective against the same organisms as *penicillin G*; therefore, it is used in patients allergic to the penicillins. In addition, it is the drug of choice for the treatment of the infections shown in Figure 31.8.

2. **Clarithromycin** has a spectrum of antibacterial activity similar to that of *erythromycin*, but is also effective against Haemophilus influenzae. Its activity against intracellular pathogens such as Chlamydia, Legionella and Ureaplasma is higher than that of *erythromycin* (Figure 31.9).

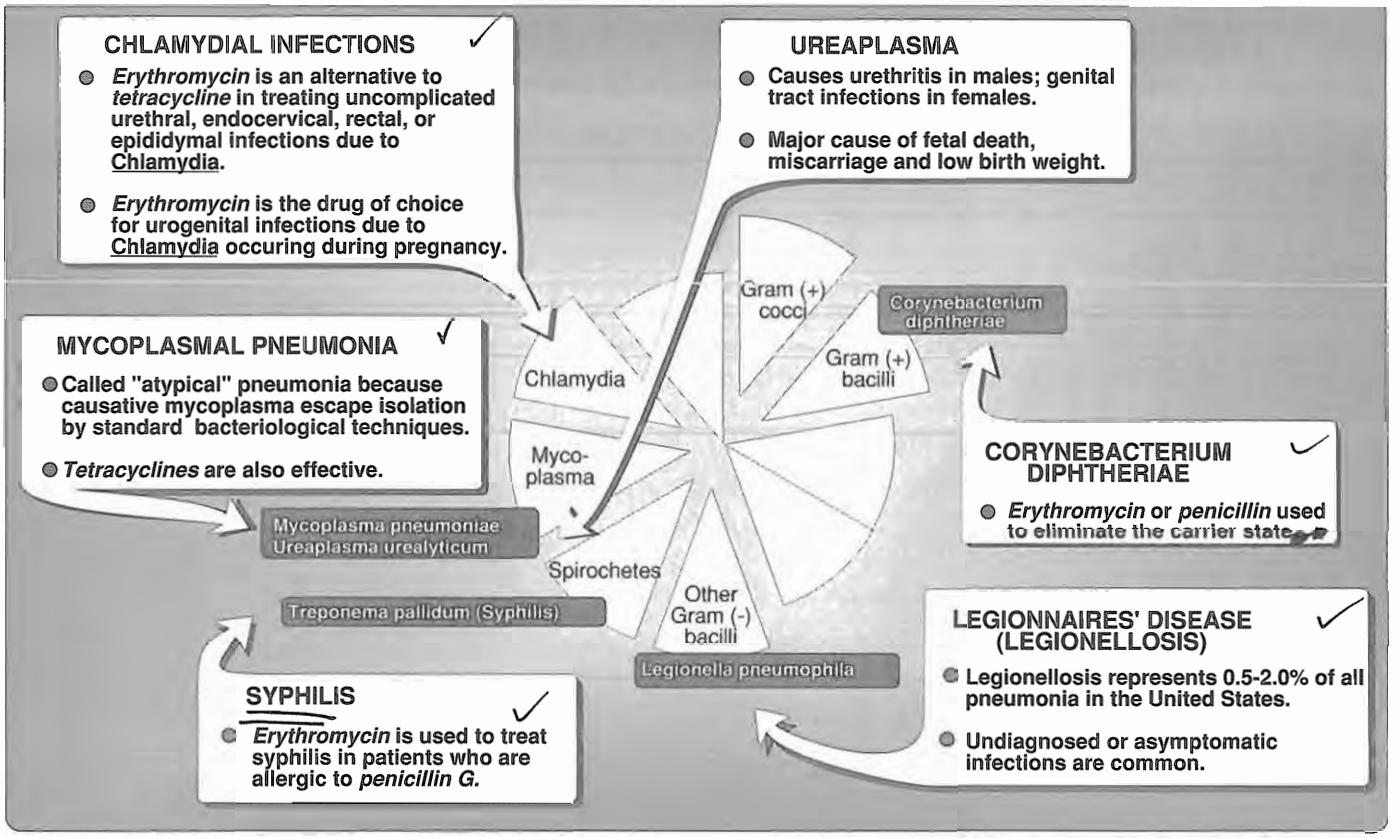
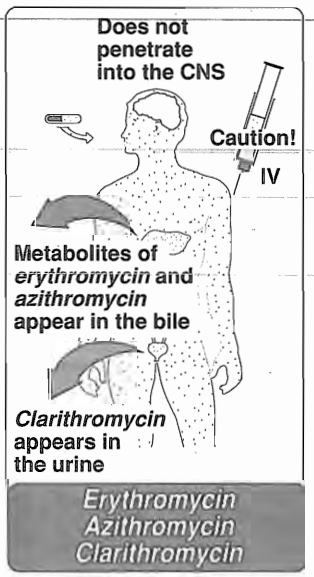


Figure 31.8
Typical therapeutic applications of *erythromycin*.



3. **Azithromycin,** though less active against streptococci and staphylococci than *erythromycin*, is far more active against respiratory infections due to Haemophilus influenzae and Moraxella catarrhalis. Except for its cost, it is now the preferred therapy for urethritis caused by Chlamydia trachomatis. Its activity against Mycobacterium avium intracellulare complex has not proven to be clinically important, except in AIDS patients with disseminated infections.

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; (2) a decreased affinity of the 50S ribosomal subunit for the antibiotic resulting from the methylation of an adenine of the 23S bacterial ribosomal RNA; and (3) presence of a plasmid-associated *erythromycin* esterase. Both *clarithromycin* and *azithromycin* show cross-resistance with *erythromycin*.

D. Pharmacokinetics

1. **Administration:** The *erythromycin* base is destroyed by gastric acid; thus either enteric coated tablets or esterified forms are administered. All are adequately absorbed on oral administration. *Clarithromycin* and *azithromycin* are stable to stomach acid and are readily absorbed. Food interferes with the absorption of *erythromycin* and *azithromycin* but can increase that of *clarithromycin*. Intravenous administration of *erythromycin* is associated with a high incidence of thrombophlebitis.

2. **Distribution:** *Erythromycin* distributes well to all body fluids except the cerebrospinal fluid (CSF). It is one of the few antibiotics that diffuses into prostatic fluid and has the unique characteristic of accumulating in macrophages. It concentrates in the liver. Inflammation allows for greater tissue penetration. Similarly, *clarithromycin* and *azithromycin* are widely distributed in tissues. Serum levels of *azithromycin* are low; the drug is concentrated in neutrophils, macrophages, and fibroblasts.

3. **Metabolism:** *Erythromycin* is extensively metabolized and is known to inhibit the oxidation of a number of drugs through its interaction with the cytochrome P-450 system (see p. 14). *Clarithromycin* is oxidized to the 14-hydroxy derivative, which retains antibiotic activity; interference with the metabolism of drugs such as *theophylline* and *carbamazepine* has been reported. *Azithromycin* does not undergo metabolism.

4. **Excretion:** *Erythromycin* and *azithromycin* are primarily concentrated and excreted in an active form in the bile. Partial reabsorption occurs through the enterohepatic circulation. In contrast, *clarithromycin* and its metabolites are eliminated by the kidney as well as the liver and it is recommended that dosage be adjusted in patients with compromised renal function.

E. Adverse effects

1. **Epigastric distress:** This side effect is common and can lead to poor patient compliance for *erythromycin*. The new macrolides seem to be better tolerated by the patient; gastrointestinal problems are their most common side effects.

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 not be treated with *erythromycin*, since the drug accumulates in the liver.

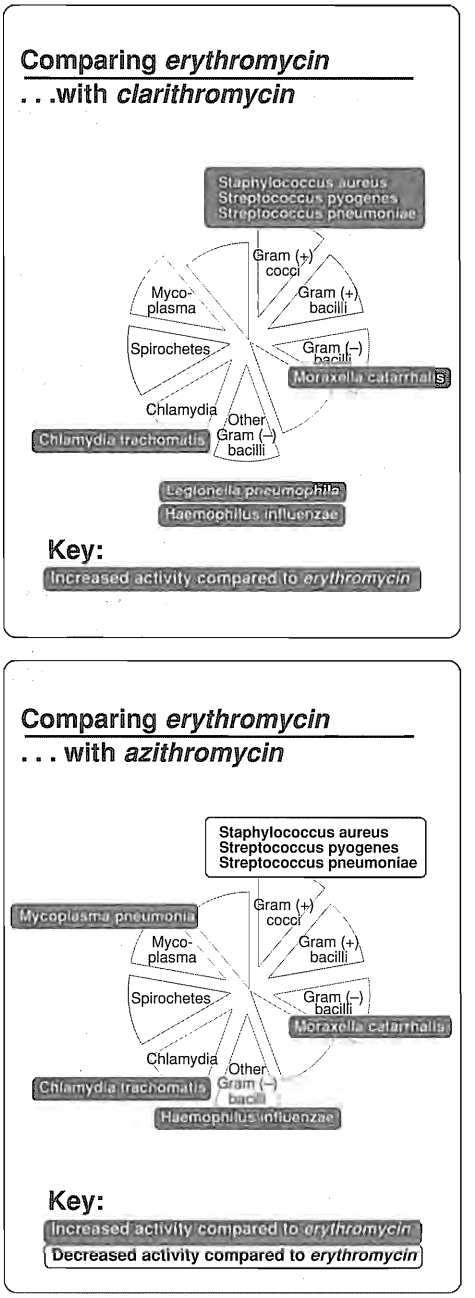
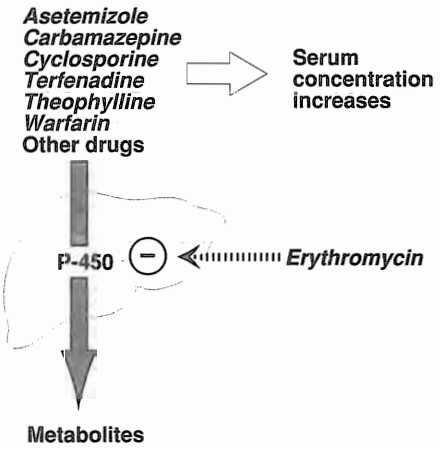


Figure 31.9
Antimicrobial activity of two new macrolides compared with that of *erythromycin*.

5. **Interactions:** *Erythromycin* and *clarithromycin* inhibit the hepatic metabolism of *theophylline*, *warfarin*, *terfenadine*, *astemizole*, *carbamazepine* and *cyclosporine* which can lead to toxic accumulations of these drugs. 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 *digoxin* from the enterohepatic circulation.



V. CHLORAMPHENICOL

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

A. Mode of action

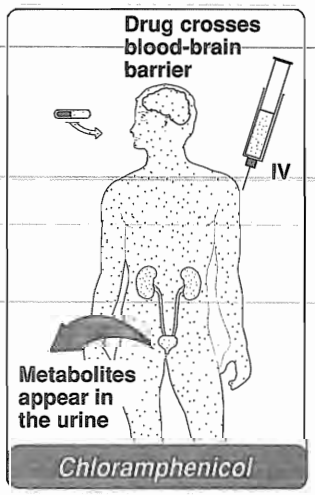
The drug binds to the bacterial 50S ribosomal subunit and inhibits protein synthesis at the peptidyl transferase reaction. Because of the similarity of mammalian mitochondrial ribosomes to those of bacteria, protein synthesis in these organelles may be inhibited at high circulating *chloramphenicol* 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. *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, which codes for an acetyl coenzyme A transferase that 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. 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 that is then secreted by the renal tubule. Only about 10% of the parent compound is excreted by glomerular filtration.

E. Adverse effects

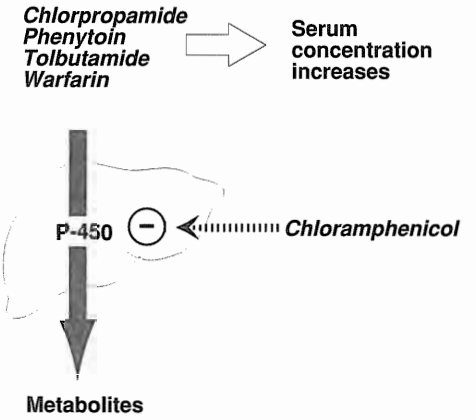
The clinical use of *chloramphenicol* is limited because of the serious

adverse effects associated with its administration. In addition to gastrointestinal upsets, overgrowth of Candida may appear on the mucuous membranes.

1. **Anemias:** Hemolytic anemia occurs in patients with low levels of glucose 6-phosphate dehydrogenase[3] (see p. 351). 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 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 glucuronidate the antibiotic and they have underdeveloped renal function. They therefore 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 "gray baby") and death.

3. **Interactions:** *Chloramphenicol* is able to inhibit some of the hepatic mixed function oxidases and thus can block the metabolism of such drugs as *warfarin*, *phenytoin*, *tolbutamide* and *chlorpropamide*, thus elevating their concentrations and potentiating their effects.



VI. CLINDAMYCIN

Clindamycin's [klin da MYE sin] mode of action is the same as that of *erythromycin* (see p. 317). *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 non-enterococcal gram-positive cocci. Resistance mechanisms are the same as those for *erythromycin*, but cross-resistance is not a problem. [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. 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 Clostridium difficile, which elaborates necrotizing toxins. Oral administration of either *metronidazole* (see p. 347) or *vancomycin* (see p. 308) is usually effective in controlling this serious problem. Impaired liver function has also been reported.

[3]See p. 322 for Infolink references to other books in this series.

Choose the ONE best answer.

31.1 Which one of the following diseases is NOT treated with a tetracycline?

A. Cholera.
B. Lyme disease.
C. Rocky Mountain spotted fever.
D. Mycoplasma pneumonia.
E. Streptococcal infection.

Correct choice = E. Most strains of streptococci are resistant to tetracycline.

31.2 Which one of the following statements about tetracycline is INCORRECT?

A. Its use is rarely contraindicated because of resistant strains.
B. It is contraindicated in pregnancy.
C. It is effective in treating infections caused by Chlamydiae.
D. It can form poorly absorbable complexes with calcium ions.
E. It can lead to discoloration of teeth if given to children.

Correct choice = A. Widespread resistance to tetracycline limits the clinical uses of this drug. Deposition of tetracycline in calcifying tissues of the fetus and growing children can occur. The drug has the potential for causing hepatic toxicity in the mother. Dairy foods in the diet decrease absorption because of the formation of nonabsorbable chelates of tetracycline with calcium ions.

31.3 Which one of the following statements about tetracyclines is INCORRECT?

A. Accumulation of tetracyclines by susceptible organisms is mediated by transport proteins located in the bacterial membrane.
B. Tetracyclines, even at high concentrations, do not affect mammalian cell metabolism.
C. Tetracyclines bind to the 30S subunit of the bacterial ribosome and block protein synthesis.
D. Phototoxicity is encountered most frequently with demeclocycline and doxycycline.
E. Doxycycline is the only tetracycline that may be used in treating patients with renal failure.

Correct choice = B. At high concentrations, tetracycline enters mammalian cells by diffusion and interacts with mitochondrial ribosomes, blocking access of the amino acyl-tRNA to the mRNA-ribosome complex at the acceptor site. Severe photosensitive dermatitis occurs when the patient receiving tetracycline is exposed to sun or ultraviolet rays.

31.4 All of the following properties are exhibited by aminoglycosides EXCEPT:

A. They are poorly absorbed from gastrointestinal tract.
B. They have bactericidal properties.
C. They can achieve adequate serum levels after oral administration.
D. They bind to the 30S ribosomal subunit.
E. They are not accumulated by anaerobic microorganisms.

Correct choice = C. All aminoglycosides are poorly absorbed from the gastrointestinal tract. All aminoglycosides are given parenterally and are rapidly bactericidal. They interfere with assembly of the functional ribosomal apparatus or cause the 30S subunit of the complete ribosome to misread the genetic code. Anaerobes lack the oxygen-dependent system that is responsible for transporting the antibiotics across the cytoplasmic membrane, therefore, strictly anaerobic organisms are resistant to aminoglycosides.

31.5. A patient being treated for springtime allergies with terfenadine develops an upper respiratory problem. He receives an antibiotic and develops a cardiac arrhythmia. What was the likely antibiotic?

A. Ampicillin
B. Cefaclor
C. Erythromycin
D. Doxycycline
E. Cotrimoxazole

The correct answer is C. Erythromycin and clarithromycin inhibit the metabolism of terfenadine giving rise to cardiac arrhythmias (torsade de pointe). None of the other antibiotics have this effect.

[1]See p. 393 in **Biochemistry** (2nd ed.) for a discussion of structure of ribosomes.

[2]See p. 396 in **Biochemistry** (2nd ed.) for a discussion of drug binding to ribosomes.

[3]See p. 115 in **Biochemistry** (2nd ed.) for a discussion of hemolytic anemia that occurs in patients with low levels of glucose 6-phosphate dehydrogenase.

Quinolones and Urinary Tract Antiseptics

32

I. OVERVIEW

Introduction of the first fluorinated quinolone, *norfloxacin* [nor FLOX a sin], has been rapidly followed by new members of this class. These agents are totally synthetic and are closely related structurally to an earlier quinolone, *nalidixic acid* [nal i DIX ik]. The principal member of this group is *ciprofloxacin* [sip ro FLOX a sin], which has the widest clinical application. Other antibiotics in this group available in the United States are primarily employed to treat urinary infections (Figure 32.1). It seems likely that the size of 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.

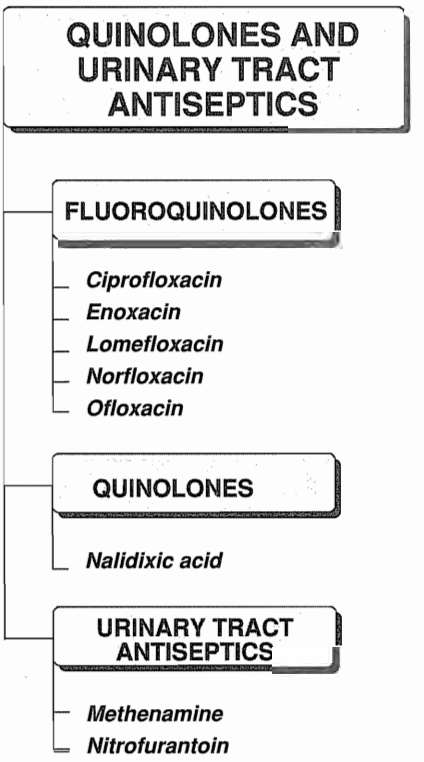


Figure 32.1
Summary of drugs described in this chapter.

II. FLUOROQUINOLONES

The older drug, *nalidixic acid*, is a nonfluorinated quinolone, and is not effective against systemic infections. Its use in the treatment of urinary tract infections (UTIs) is limited due to the rapid emergence of resistant strains. It will be considered in a separate section below. Unless care is taken to employ these drugs in appropriate infective states, it is possible that their value will be lost.

A. Mechanism of action

The fluoroquinolones enter the cell by passive diffusion through water-filled protein channels (porins) in the outer membrane. Intracellularly, they uniquely inhibit the replication of bacterial DNA by interfering with the action of DNA gyrase (topoisomerase II) during bacterial growth and reproduction. [Note: Topoisomerases are enzymes that change the configuration or topology of DNA by a nicking, pass-through and re-sealing mechanism without changing its primary structure (Figure 32.2).][1] Binding of the quinolone to both the enzyme and the DNA to form a ternary complex inhibits the rejoining

[1] See p. 330 for Infolink references to other books in this series.

Lippincott's Illustrated Reviews: Pharmacology, Second Edition.
by Mary Mycek, Richard A. Harvey and Pamela C. Champe.
Lippincott–Raven Publishers, Philadelphia, PA © 1997.

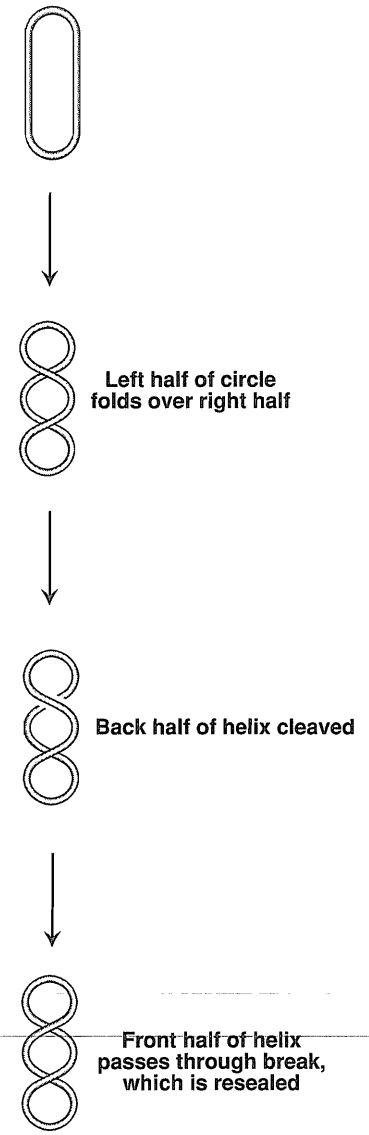


Figure 32.2
Action of type II DNA topoisomerase.

step and can cause cell death by inducing cleavage of the DNA. Since DNA gyrase is a distinct target for antimicrobial therapy, cross-resistance with other more commonly used antimicrobial drugs is rare but increasing in the case of multi-drug resistant organisms.

B. Antimicrobial spectrum

All of the fluoroquinolones are bactericidal. In general, they are effective against gram-negative organisms such as the enterobacteria, pseudomonas organisms, Haemophilus influenzae, Moraxella catarrhalis, Legionella, Chlamydia and mycobacteria except for M. avium intracellulare complex. They are effective in the treatment of gonorrhea but not syphilis. Though active against some gram-positive organisms, they should be avoided in the treatment of pneumoccal or enterococcal infections. Their activity against anaerobes is poor. If used prophylactically before transurethral surgery, they lower the incidence of postsurgical UTIs.

1. **Ciprofloxacin:** This is the most potent of the fluoroquinolones and has an antibacterial spectrum similar to that of *norfloxacin* (Figure 32.3). *Ciprofloxacin* finds use in the treatment of pseudomonas infections associated with cystic fibrosis. The serum levels 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 particularly useful in treating infections caused by many Enterobacteraceae and other gram-negative bacilli. *Ciprofloxacin* is an alternative to more toxic drugs, such as the aminoglycosides (p. 314). It may act synergistically with β-lactams (p. 297).

2. **Norfloxacin:** This agent is effective against both gram-negative (including Pseudomonas aeruginosa) and gram-positive organisms in treating complicated and uncomplicated UTIs and prostatitis, but not in systemic infections.

3. **Ofloxacin:** Like *norfloxacin*, *ofloxacin* [oh FLOX a sin] is primarily used in the treatment of prostatitis due to E. coli and of sexually transmitted diseases (STDs) with the exception of syphilis. It may be used as alternative therapy in patients with gonorrhea. It has some benefit in the treatment of skin and lower respiratory tract infections.

4. **Lomefloxacin:** *Lomefloxacin* [loh me FLOX a sin] and *enoxacin* [ee NOX a sin] are useful in the treatment of UTIs and bronchitis caused by Haemophilus influenzae or Moraxella catarrhalis. *Lomefloxacin* is not effective against pseudomonal bacteremia.

C. Resistance

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

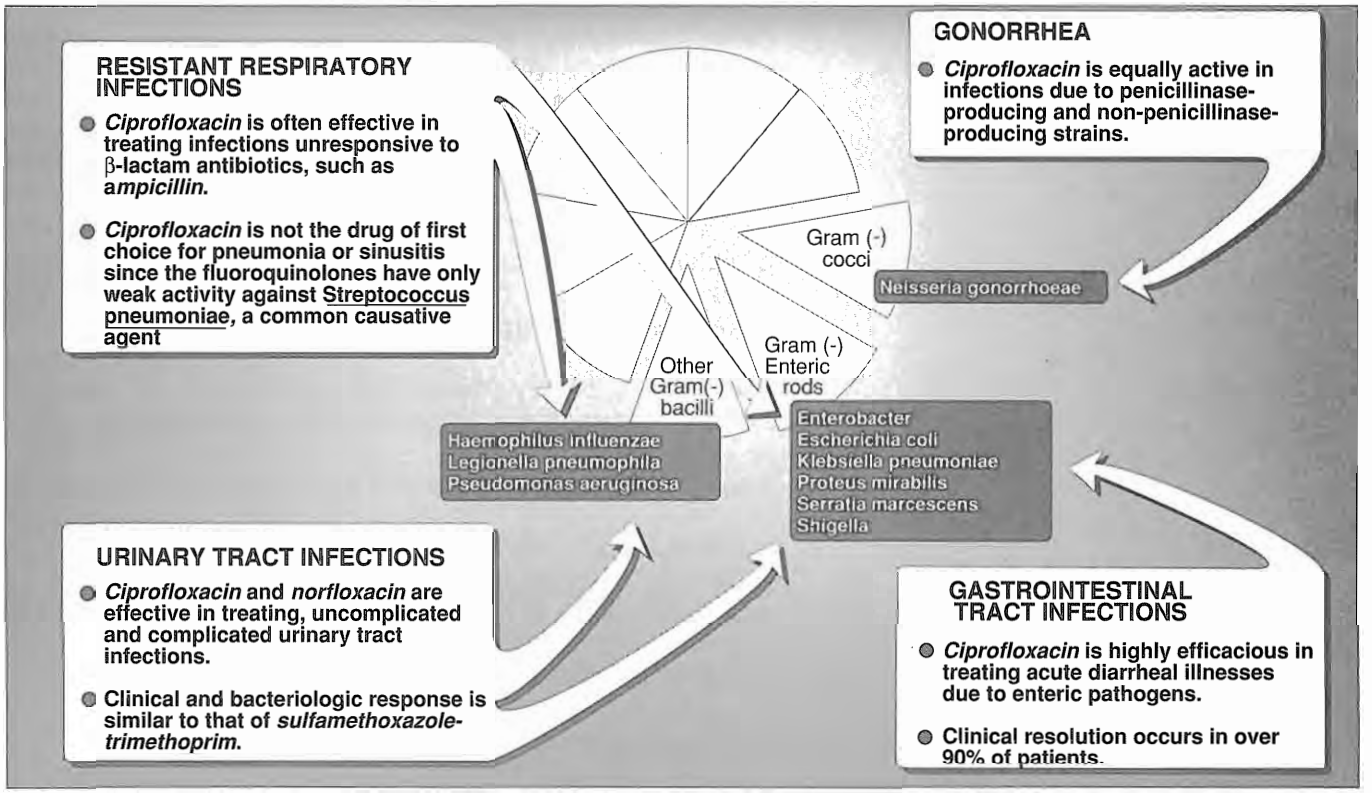
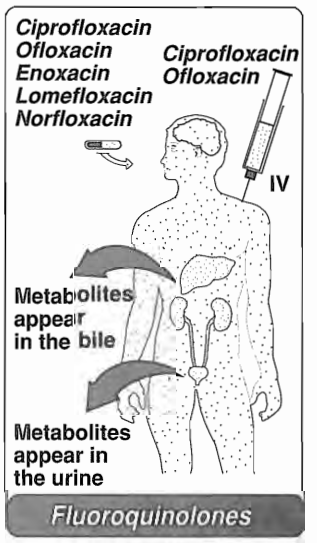


Figure 32.3
Typical therapeutic applications of *ciprofloxacin*.

1. **Altered target:** Modifications in the bacterial DNA gyrase, especially in amino acids at the N-terminus of the A subunit, have been associated with a decreased affinity for the fluoroquinolone. The B subunit of the gyrase is rarely mutated.

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 gyrase. The other mechanism is associated with an energy-dependent efflux system in the cytoplasmic membrane.



D. Pharmacokinetics

1. **Absorption:** Only 35-70% of oral *norfloxacin* is absorbed. However, 70-90% of the other fluoroquinolones are absorbed after oral administration. Bioavailability is greatest for *ofloxacin* and *lomefloxacin*. Intravenous preparations of *ciprofloxacin* 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 agents.

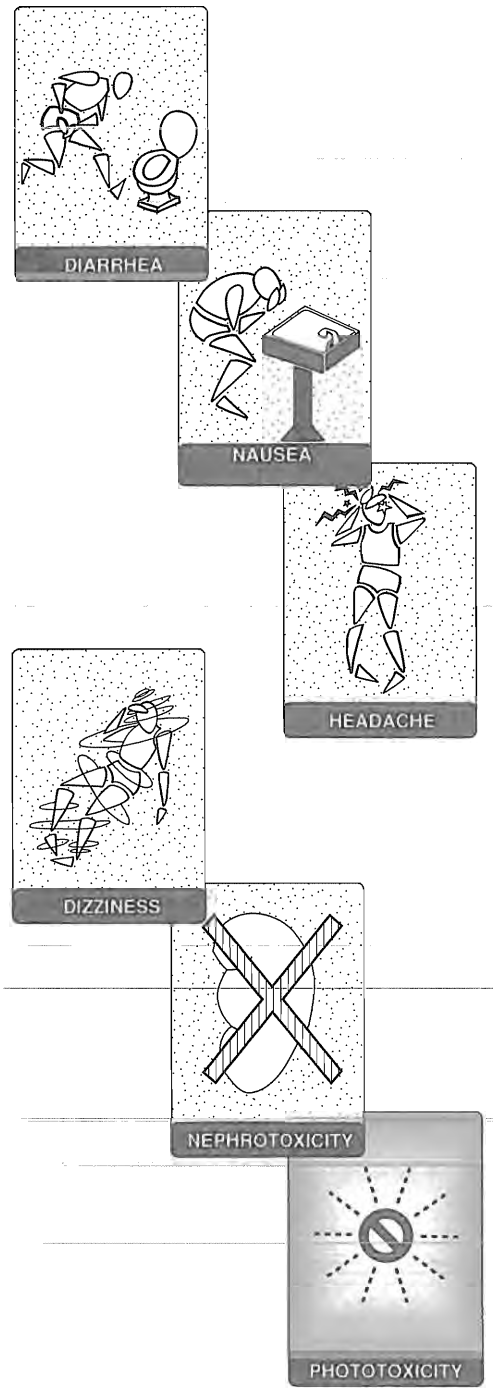


Figure 32.4
Some adverse reactions to fluoroquinolones.

2. **Distribution:** Binding to plasma proteins ranges from 10 to 40%. [Note: 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* where concentrations can be as high as 90% of those in the serum. The fluoroquinolones also accumulate in macrophages and polymorphonuclear leukocytes, thus being effective against intracellular organisms such as Legionella.

3. **Metabolism:** Except for *ofloxacin* and *lomefloxacin*, these agents are partially metabolized to compounds with less antimicrobial activity.

4. **Excretion:** The parent drugs and their metabolites are excreted into the urine where high levels can occur. This is the major excretory route for *ofloxacin*. Renal failure prolongs the half-life of each drug. The other fluoroquinolones undergo hepatic as well as renal clearance; this route assumes importance in renal failure. The half-lives of the fluoroquinolones range from 3-5 hours, except for *lomefloxacin* which has a half-life of 8 hours.

E. Adverse reactions

Toxicities similar to those for *nalidixic acid* (p. 327) have been reported for the fluoroquinolones (Figure 32.4). Besides diarrhea, the following adverse reactions may be encountered.

1. **CNS problems:** The most prominent side effects are nausea, headache, and dizziness or lightheadedness. Thus, patients with CNS disorders, such as epilepsy, should be treated cautiously with these drugs.

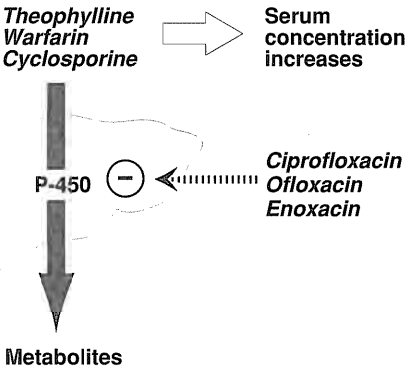
2. **Nephrotoxicity:** Crystalluria has been reported in patients receiving excessive doses (3-4 times normal).

3. **Phototoxicity:** Patients are advised to avoid excessive sunlight and to use sunscreen. However, even sunscreens or sunblocks may not protect against the phototoxicity and the drug should be discontinued at the first sign of this toxicity.

4. **Contraindications:** Fluoroquinolones should be avoided in pregnancy, in nursing mothers and in children under 18 years of age, since articular cartilage erosion (arthropathy) occurs in immature experimental animals.

5. **Drug interactions:** The effect of antacids and cations on the absorption of these agents was considered above. *Ciprofloxacin*, *ofloxacin* and *enoxacin* can increase the serum levels of *theophylline* by inhibiting its metabolism. They also may raise levels of *warfarin*, *caffeine* and *cyclosporine*. *Cimetidine* interferes with the

elimination of the fluoroquinolones. *Enoxacin* when administered concurrently with anti-inflammatory *fenoprofen* has been reported to cause seizures.



III. QUINOLONES

Nalidixic acid is a nonfluorinated quinolone with the same mechanism of action as that of the fluoroquinolones. It is effective against most of the gram-negative bacteria that commonly cause UTIs but gram-positive organisms are resistant. Its clinical usefulness is limited by the rapid emergence of resistant strains. Well-absorbed, most (>90%) of the drug is protein bound and levels of free drug are therefore inadequate for treatment of systemic infections. Hydroxylation leads to the more potent bactericidal compound, 7-hydroxynalidixic acid, which is excreted in the urine along with the parent drug. Among the adverse effects are nausea, vomiting and abdominal pain. Photosensitivity, urticaria and fever can occur. CNS problems ranging from headache and malaise to visual disturbances are rare. Therapy lasting longer than 2 weeks can adversely affect liver function.

IV. URINARY TRACT ANTISEPTICS

Urinary tract infections (UTI, most commonly uncomplicated acute cystitis and pyleonephritis) 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% of uncomplicated upper and lower UTI. Staphylococcus saprophyticus is the second most common bacterial pathogen causing UTI; other common causes include Klebsiella pneumoniae and Proteus mirabilis infections. In addition, UTI may be treated with any one of a group of agents called urinary tract antiseptics, including *methenamine* and *nitrofurantoin*. 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.

A. Methenamine

1. **Mechanism of action:** In order 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 32.5). The reaction is slow, requiring 3 hours to reach 90% decomposition. *Methenamine* should not be used in patients with indwelling catheters. Bacterial resistance to formaldehyde does not develop. [Note: *Methenamine* is frequently formulated with a weak acid such as mandelic acid, which lowers the pH of the urine thus aiding decomposition of the drug.]

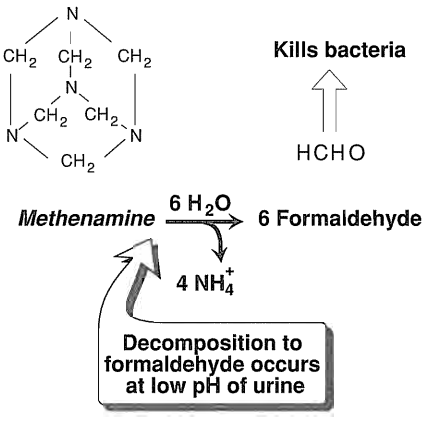


Figure 32.5
Formation of formaldehyde from *methenamine* at acid pH.

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

3. **Pharmacokinetics:** *Methenamine* is orally administered. 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 side effects include gastrointestinal distress. At higher doses, albuminuria, hematuria and rashes may develop. *Methenamine mandelate* is contraindicated in treating patients with renal insufficiency, because mandelic acid may precipitate. Sulfonamides react with formaldehyde and must not be used concomitantly with *methenamine*.

C. Nitrofurantoin

Nitrofurantoin [nye troe FYOOR an toyn] is less commonly employed for treating UTIs because of its narrow antimicrobial spectrum and its toxicity.

1. **Mechanism of action**: Sensitive bacteria reduce the drug to an active agent that inhibits various enzymes and damages DNA. Activity is greater in acidic urine.

2. **Antimicrobial Spectrum:** The drug is bacteriostatic. It is useful against Escherichia coli, but other common urinary tract gram-negative bacteria may be resistant. Gram-positive cocci are susceptible.

3. **Resistance:** Resistance is constitutive. It is associated with an inability to reduce the nitrogen group in the presence of oxygen. Resistance does not develop during therapy.

4. **Pharmacokinetics:** Absorption is complete after oral administration. The drug is rapidly excreted by glomerular filtration. The presence of the drug turns the urine brown, a surprise for unsuspecting patients.

5. **Adverse effects:**

   a. **Gastrointestinal disturbances:** These side effects include nausea, vomiting, and diarrhea. The macrocrystalline form is better tolerated. Ingestion with food or milk ameliorates these symptoms.

   b. **Acute pneumonitis**: This is a serious complication. Other pul-

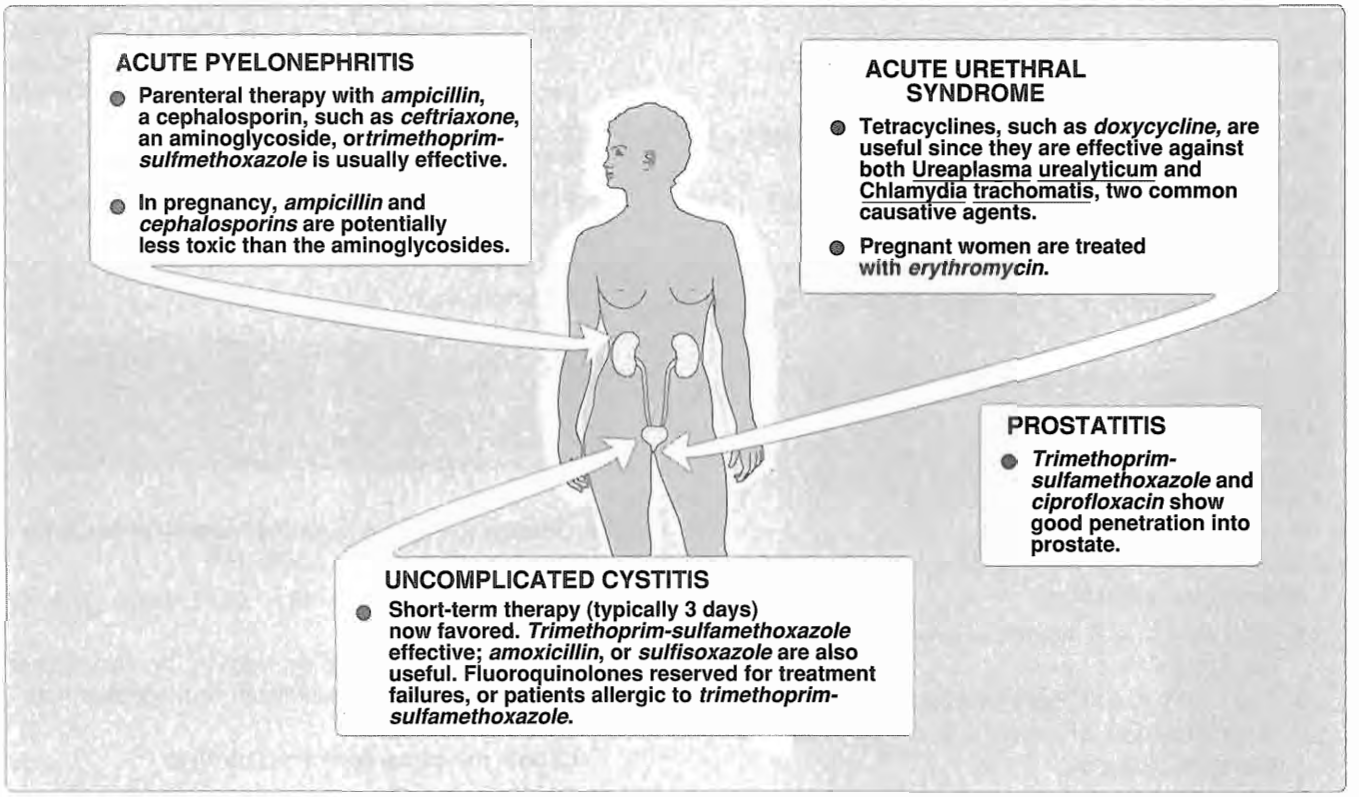


Figure 32.6
Antimicrobial drugs commonly used in treating urinary tract infections.

monary effects, such as interstitial pulmonary fibrosis, can occur in patients being chronically treated.

c. **Neurological problems:** Neurological side effects such as headache, nystagmus, and polyneuropathies with demyelination (sometime leading to footdrop) may develop.

d. **Hemolytic anemia:** The drug is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency, neonates, and pregnant women.

Agents commonly used in uncomplicated UTI are summarized in Figure 32.6).

Choose the ONE best answer:

32.1 All of the following statements about methenamine are true EXCEPT:

A. It is used in chronic suppressive therapy of urinary tract infections.
B. It has its major antibacterial effect at alkaline pH.
C. It is contraindicated in renal insufficiency.
D. It may cause gastric disturbances.
E. Its antimicrobial activity is confined to the urinary tract.

Correct choice = B. Methenamine has its maximum effect at acidic pH—this is the reason that the drug is often formulated with a weak acid such as mandelic acid

32.2. In which one of the following infections are the fluoroquinolones ineffective?

A. UTIs due to a β-lactamase-producing strain of Klebsiella.
B. Pneumonia due to Streptococcus pneumoniae.
C. Exacerbation of chronic bronchitis due to Moraxella catarrhalis.
D. Urinary tract infection due to E. coli.
E. UTIs due to Pseudomonas aeruginosa.

Correct answer = B. The fluoroquinolones do not have sufficient activity against S. pneumoniae to be effective. Since they are not β-lactams, the fluoroquinolones are effective in treating UTIs caused by β-lactamase-producing organisms. Fluoroquinolones are also indicated for treatment of the other infections listed.

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

A. Ciprofloxacin
B. Nalidixic acid
C. Norfloxacin
D. Ofloxacin
E. Lomefloxacin

Correct answer = D. Ofloxacin has the best activity of all the quinolones against both gonorrheal and chlamydial infections. Nalidixic acid is without activity in these conditions.

32.4 Ciprofloxacin and tetracycline have all of the following properties in common EXCEPT:

A. Resistant organisms have an increased ability to pump out the drugs.
B. Absorption can be decreased by concurrent administration with aluminum or magnesium containing antacids.
C. Both can cause severe phototoxicity.
D. Both accumulate with decreased renal function.
E. Both are deposited in developing bones and teeth.

Correct choice = E. Only tetracycline is deposited in bone and thus is contraindicated in children under age 8. Ciprofloxacin damages developing articular cartilage in young experimental animals, which is why it is contraindicated in children under 18 years of age. All the other statements pertain to both antibiotics.

[1]See p. 365 in **Biochemistry** (2nd ed.) for a discussion of topoisomerases and the topology of DNA.

Antimycobacterial Drugs

33

I. OVERVIEW

The modern era of tuberculosis therapy began with the introduction of *streptomycin*, *isoniazid*, and *p-aminosalicylic acid* and today multidrug therapy includes drugs listed in Figure 33.1. The number of cases of tuberculosis waned and there was hope of complete eradication. Indeed, predictions were made that tuberculosis would be almost nonexistent in the United States by the year 2002. However, in the past decade, tuberculosis cases have significantly increased, chiefly among AIDS patients and the homeless (Figure 33.2). Today tuberculosis is still the leading cause of death by infectious disease throughout the world.

II. CHEMOTHERAPY OF TUBERCULOSIS

Mycobacterium tuberculosis, one of a number of mycobacteria, can lead to serious infections of the lungs, the genitourinary tract, skeleton, and meninges. The mycobacteria are classified on the basis of their staining properties. [Note: Though difficult to stain because of the presence of an outer coat of mycolic acid, once stained they hold the stain even in the presence of destaining agents such as acid. Thus they are referred to as "acid-fast".] Treating tuberculosis as well as other mycobacterial infections presents therapeutic problems. The organism grows slowly, and thus the disease may have to be treated for up to 2 years, especially if it is caused by a resistant organism.

A. Strategies for addressing drug resistance

Because strains of the organism resistant to a particular agent emerge during treatment, multiple drug therapy is employed to delay or prevent their emergence. *Isoniazid*, *rifampin*, *ethambutol*, *streptomycin*, and *pyrazinamide* are the principal or so-called "first line" drugs because of their efficacy and acceptable degree of toxicity. However today, 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

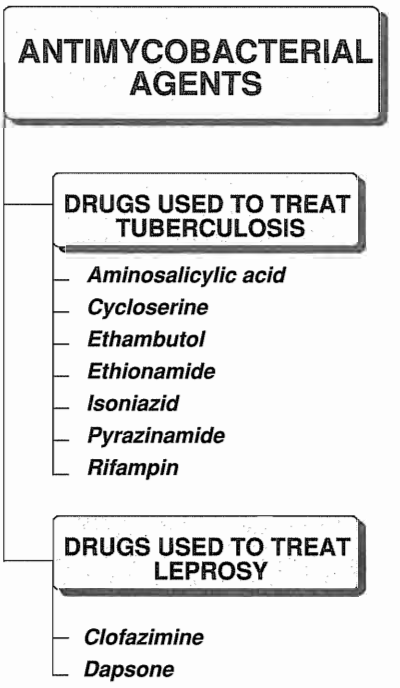


Figure 33.1
Summary of drugs used to treat mycobacterial infections.

Lippincott's Illustrated Reviews: Pharmacology, Second Edition.
by Mary Mycek, Richard A. Harvey and Pamela C. Champe.
Lippincott–Raven Publishers, Philadelphia, PA © 1997.

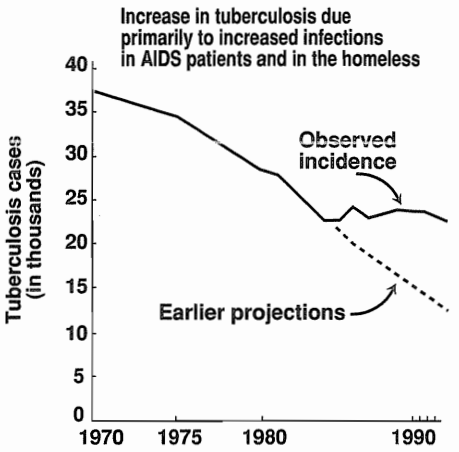


Figure 33.2
Incidence of new cases of tuberculosis.

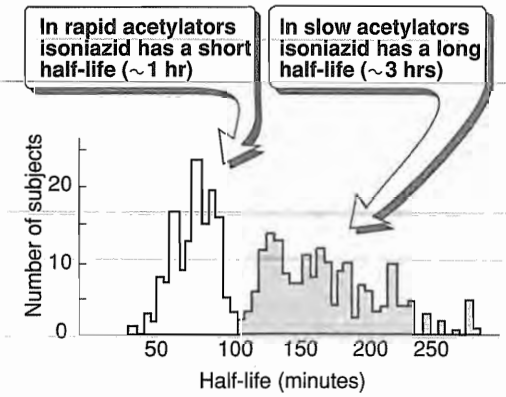


Figure 33.3
Bimodal distribution of *isoniazid* half-lives caused by rapid and slow acetylation of drug.

antitubercular agents. Therefore, although treatment regimens vary in duration and in agents employed, they always include a minimum of two drugs, preferably both cidal (see p. 283). Together they should prevent the emergence of resistant strains. The regimen is continued well beyond the disappearance of clinical disease so as to eradicate any persistent organisms. For example, the short course chemotherapy for tuberculosis includes *isoniazid*, *rifampin* and *pyrazinamide* for 2 months, and *isoniazid* and *rifampin* for the next 4 months. *Ethambutol* may also be added to this regimen.

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 anti-tubercular drugs, but is never given as a single agent in the treatment of active tuberculosis. Its introduction revolutionized the treatment of tuberculosis.

1. **Mechanism of action:** *Isoniazid*, often referred to as INH, is believed to target the enzyme responsible for assembly of mycolic acids into the outer layer of the mycobacteria, a structure unique to these organisms. Mycolic acids account for the acid-fastness of the mycobacteria; this property is lost after exposure to *isoniazid*.

2. **Antibacterial spectrum:** For bacilli in the stationary phase, the drug 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 may be susceptible at higher drug levels. When it is used alone, resistant organisms rapidly emerge.

3. **Resistance** is associated with the constitutive inability of the organism to accumulate the drug. There is also suggestive evidence that the target enzyme may be altered so as not to bind the *isoniazid*, or that excessive amounts of the enzyme may be produced so that the drug is overwhelmed. No cross-resistance exists between *isoniazid* and other anti-tubercular drugs.

4. **Pharmacokinetics:** The drug is readily absorbed orally. Absorption is impaired if taken with food, particularly carbohydrates, or with aluminum-containing antacids. *Isoniazid* diffuses into all body fluids, cells, and caseous material (necrotic tissue resembling cheese); levels in the cerebrospinal fluid (CSF) are about the same as those in the serum. Infected tissue tends to retain the drug longer. The drug readily penetrates host cells and is effective against bacilli growing intracellularly. *Isoniazid* undergoes N-acetylation and hydrolysis, resulting in inactive products. Acetylation is genetically regulated; the fast acetylator trait is autosomally dominant. A bimodal distribution of fast and slow acetylators exists (Figure 33.3). Chronic liver disease will decrease metabolism, and doses must be reduced. Excretion is through glomerular filtration, predominantly as metabolites. Slow acetylators excrete more of the parent compound. Severely depressed renal function results in accumulation of the drug, primarily in slow acetylators. The drug is also excreted into the

saliva, sputum, and milk.

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

   a. **Peripheral neuritis:** Peripheral neuritis (manifest as paresthesia) is the most common adverse effect, which appears to be due to a relative pyridoxine deficiency. This has been attributed to a competition of *isoniazid* with pyridoxal phosphate for the enzyme apotryptophanase. Most of the toxic reactions are corrected by pyridoxine (vitamin B_6) supplementation. [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.]

   b. **Hepatitis and Idiosyncratic hepatotoxicity:** Potentially fatal hepatitis is the most severe side effect associated with *isoniazid*. It has been suggested that it 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 imbibe alcohol daily.

   c. **Drug interactions:** *Isoniazid* can potentiate the adverse effects of *phenytoin* (for example, nystagmus, ataxia, see p. 146) because the *isoniazid* inhibits metabolism of *phenytoin* (Figure 33.4). 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.

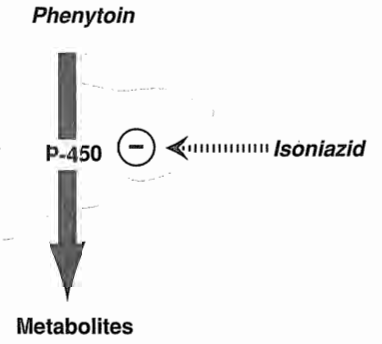


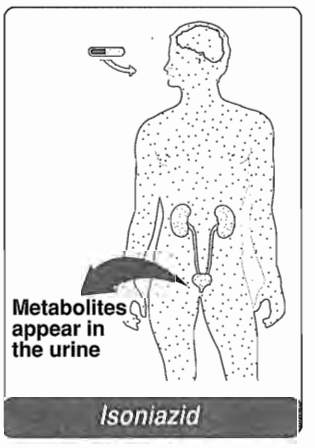
Figure 33.4
Isoniazid potentiates adverse effects of *phenytoin*.

C. Rifampin

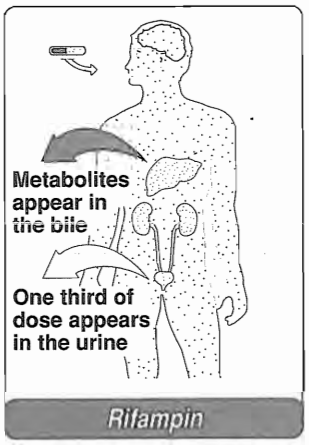
Rifampin [RIF am pin], derived from the soil mold Streptomyces, has a broader antimicrobial activity than *isoniazid* and has found application in the treatment of other bacterial infections. Because resistant strains rapidly emerge during therapy, it is never given as a single agent in the treatment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

1. **Mechanism of action:** *Rifampin* blocks transcription by interacting with the β-subunit of bacterial DNA-dependent RNA polymerase[1], thus inhibiting RNA synthesis by suppressing the initiation step. The drug is specific for prokaryotes.

2. **Antimicrobial spectrum:** *Rifampin* is bactericidal for both intracellular and extracellular mycobacteria, including M. tuberculosis, atypical mycobacteria, and Mycobacterium leprae. It is effective against many gram (+) and gram (-) organisms and is frequently used prophylactically for household members exposed to meningitis caused by meningococci or Haemophilus influenzae. *Rifampin* is the most active antileprosy drug at present, but to delay emergence of resistant strains it is usually given in combination with other drugs. *Rifabutin*, an analog of *rifampin*, has



[1]See p. 336 for Infolink references to other books in this series.



some activity against Mycobacterium avium intracellulare complex, but is less active against tuberculosis.

3. **Resistance:** Resistance may be caused by a change in the affinity of the DNA-dependent RNA polymerase for the drug, or by decreased permeability.

4. **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 is via the bile into the feces and the urine as metabolites and parent drug. Urine and feces as well as other secretions have an orange-red color; patients should be forewarned. [Note: Tears may permantly stain contact lenses orange-red.]

5. **Adverse effects:** Adverse effects are a minor problem with *rifampin.* but can include nausea and vomiting, rash, and fever. The drug should be used judiciously in patients with hepatic failure because of the jaundice that occurs in patients with chronic liver disease, alcoholics, or in the elderly.

6. **Drug interactions:** Because *rifampin* can induce the cytochrome P-450 enzymes (see p. 14), it can decrease the half-lives of other drugs that are coadministered and metabolized by this system (Figure 33.5) This may lead to higher dosage requirements for these agents.

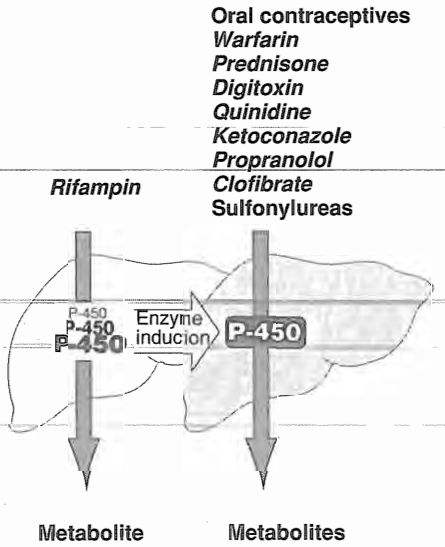


Figure 33.5
Rifampin induces P-450, which can decrease half-life of coadministered drugs that are metabolized by this system.

C. Pyrazinamide

Pyrazinamide [peer a ZIN a mide] is a synthetic orally effective bactericidal anti-tubercular agent used along with *isoniazid* and *rifampin*. It is bactericidal to actively dividing organisms. *Pyrazinamide* must be enzymatically hydrolyzed to pyrazinoic acid which is the active form of the drug. Some resistant strains lack the pyrazinamidase. However, the mechanism of its action is unknown. It is active against tubercle bacilli in the acid environment of lysosomes as well as in macrophages. *Pyrazinamide* distributes throughout the body penetrating the CSF; it also undergoes extensive metabolism. About 1-5% of patients taking *isoniazid*, *rifampin*, and *pyrazinamide* may experience liver dysfunction. Urate retention can also occur and may precipitate a gouty attack (Figure 33.6).

D. Ethambutol

Ethambutol [e THAM byoo tole] is bacteriostatic and specific for most strains of M. tuberculosis and M. kansasii. Resistance is not a serious problem if the drug is employed with other antituberculous 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 toxic symptoms. In addition, urate excretion is decreased by the drug, thus gout may be exacerbated (Figure 33.6).

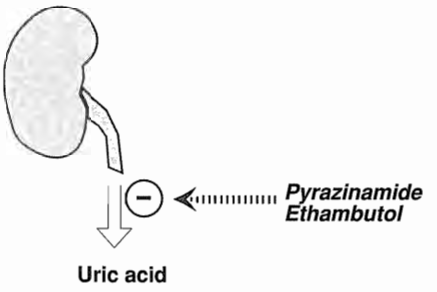


Figure 33.6
Pyrazinamide and *ethambutol* may cause urate retention and gouty attacks.

E. Alternate second-line drugs

A number of drugs—*aminosalicylic acid* [a mee noe sal i SIL ik], *ethionamide* [e thye on AM ide], *cycloserine* [sye kloe SER een]—are considered second-line drugs because they are no more effective than the first-line agents and their toxicities are often more serious. *Streptomycin*, the first antibiotic effective in the treatment of tuberculosis, has been discussed wth the aminoglycosides (see p. 314). Its action is directed against extracellular organisms.

1. **Aminosalicylic acid:** Because it is poorly tolerated, *aminosalicylic acid* [a mee noe sal i SIL ik] is infrequently used today. It is a bacteriostatic agent that acts as a competitive inhibitor for p-aminobenzoic acid (PABA) in folate biosynthesis[2].

2. **Ethionamide:** This structural analog of *isoniazid* is believed not to act by the same mechanism. It is effective after oral administration, and is widely distributed throughout the body, including the CSF. Metabolism is extensive. *Ethionamide* [e thye on AM ide] can inhibit acetylation of *isoniazid* (Figure 33.7). The urine is the main route of excretion. Adverse effects that limit its use include gastric irritation, hepatotoxicity, peripheral neuropathies, and optic neuritis.

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

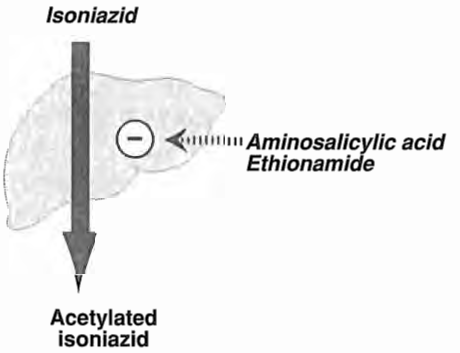


Figure 33.7
Aminosalicylic acid and *ethionamide* can inhibit the acetylation of *isoniazid*.

III. CHEMOTHERAPY OF LEPROSY

Leprosy (Hansen's disease) is caused by M. leprae. Bacilli from skin lesions or nasal discharges of infected patients enter susceptible individuals via the skin or respiratory tract. The World Health Organization recommends the triple drug regimen, *dapsone*, *clofazimine*, and *rifampin* (see p. 333) for 6 to 24 months.

A. Dapsone

Dapsone [DAP sone] is structurally related to the sulfonamides. It is

[2]See p. 336 for Infolink references to other books in this series.

bacteriostatic for M. leprae, but resistant strains are encountered. *Dapsone* is also employed in the treatment of Pneumocystis pneumonia in human immunodeficiency virus (HIV) patients. It acts as a PABA antagonist to inhibit folate biosynthesis. The drug is well absorbed from the gastrointestinal tract and is distributed throughout the body. The parent drug enters the enterohepatic circulation and undergoes heptic acetylation. Both parent drug and metabolites are eliminated through the urine. Adverse reactions include hemolysis, especially in patients with glucose-6-phosphate dehydrogenase deficiency[3], methemoglobinemia, peripheral neuropathy, and the possibility of developing erythema nodosum leprosum. [Note: The latter is treated with corticosteroids (see p. 272) or *thalidomide*.]

B. Clofazimine

Clofazimine [kloe FA zi meen] is a phenazine dye that binds to DNA and inhibits template function. 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. On oral absorption, it accumulates in tissues, allowing for 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

Study Questions

Choose the ONE best answer.

33.1 All of the following statements about rifampin are correct EXCEPT:

A. It is frequently used prophylactically for household members exposed to meningitis caused by meningococci or Haemophilus influenzae.
B. It colors body secretions orange-red.
C. It disrupts bacterial lipid metabolism as its major mechanism of action.
D. Although rare, it can cause serious hepatotoxicity.
E. When used alone, there is a high risk of the emergence of resistant strains of mycobacteria.

Correct choice = C. Rifampin interacts with the β-subunit of bacterial DNA-dependent RNA polymerase and thereby inhibits RNA synthesis. Because of the rapid emergence of resistant strains, rifampin is never given as a single agent.

33.2 All of the following statements about isoniazid are correct EXCEPT:

A. It produces age-dependent hepatotoxicity.
B. It readily penetrates into infected cells.
C. It inhibits mycolic acid synthesis in susceptible mycobacteria.
D. It may induce the symptoms of cyanocobalamin (vitamin B_{12}) deficiency.
E. It potentiates the adverse effects of phenytoin when the patient receives both medications concurrently.

Correct choice = D. Isoniazid reacts with pyridoxine (vitamin B_6), which can cause a deficiency of this vitamin. Isoniazid readily penetrates into infected cells and therefore is effective against bacilli growing intracellularly. Isoniazid inhibits the metabolism of phenytoin.

[1]See p. 379 in **Biochemistry** (2nd ed.) for a discussion of DNA-dependent RNA polymerase.

[2]See p. 325 in **Biochemistry** (2nd ed.) for a discussion of the role of p-aminobenzoic acid in folate biosynthesis.

[3]See p. 115 in **Biochemistry** (2nd ed.) for a discussion of glucose-6-P dehydrogenase deficiency.

Antifungal Drugs

34

I. OVERVIEW

Infectious diseases caused by fungi are called mycoses and are often chronic in nature. Many common mycotic infections are superficial and only involve the skin, 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 containing chitin as well as polysaccharides, and a cell membrane composed of ergosterol. Thus, fungal infections are generally resistant to antibiotics used in the treatment of bacterial infections. Conversely, bacteria are resistant to the antifungal agents. The incidence of fungal infections has escalated as the number of immunosuppressed individuals (e.g. cancer, transplant patients) as well as those debilitated by AIDS, has risen. These patients often suffer from so-called opportunistic fungal infections such as cryptococcal meningitis or aspergillosis. Endemic mycoses, such as blastomycosis, coccidioidomycosis and histoplasmosis, have always been a problem in some geographic locations. The availability of the azole antifungal drugs has been a major advance in the treatment of systemic infections since they are less toxic than *amphotericin B*. Figure 34.1 shows the clinically useful antifungal agents.

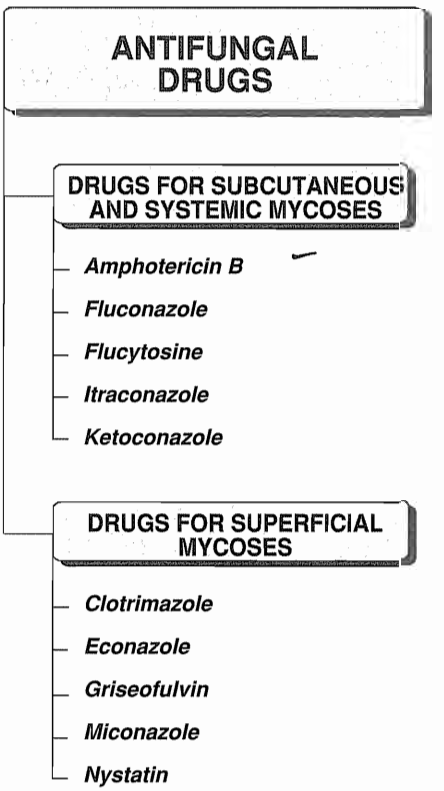


Figure 34.1
Summary of antifungal drugs.

II. DRUGS FOR SUBCUTANEOUS AND SYSTEMIC MYCOTIC INFECTIONS

The drugs used in the treatment of subcutaneous and systemic mycoses are *amphotericin B*, *flucytosine*, and the new group of azoles, *ketoconazole*, *fluconazole* and *itraconazole*.

A. Amphotericin B

Amphotericin B [am foe TER i sin] is a naturally occurring polyene macrolide antibiotic, produced by Streptomyces nodosus. In spite of its toxic potential, *amphotericin B* is the drug of choice used in the treatment of the systemic mycoses. It is sometimes used in combination with *flucytosine* so that lower (less toxic) levels of *amphotericin* are possible.

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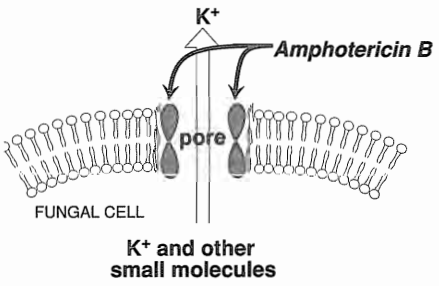


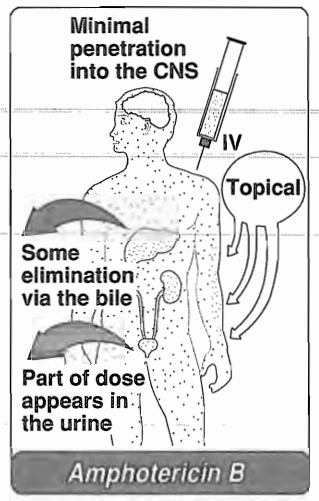
Figure 34.2
Model of pore formed by *amphotericin* in lipid bilayer membrane.

1. **Mode of action:** Several polyene molecules bind to ergosterol present in cell membranes of sensitive fungal cells to form pores or channels that involve hydrophobic bonds between the lipophilic segment of the polyene antibiotic and the sterol (Figure 34.2). This disrupts membrane function, allowing electrolytes (particularly potassium) and small molecules to leak from the cell, resulting in cell death. Since the polyene antibiotics bind preferentially to ergosterol rather than cholesterol, the sterol found in mammalian membranes, 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, such as Candida albicans, Histoplasma capsulatum, Cryptococcus neoformans, Coccidioides immitis, many strains of aspergillus, and Blastomyces dermatitidis.

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

4. **Pharmacokinetics:** *Amphotericin B* is administered by intravenous infusion. The intrathecal route is sometimes chosen for the treatment of meningitis caused by fungi that are sensitive to *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 is found in the cerebrospinal fluid, vitreous humor, or amniotic fluid. However, *amphotericin B* does cross the placenta. Low levels of the drug, mostly metabolites, appear in the urine over a long period of time; some is also eliminated via the bile. Adjustment of dose is not required in patients with compromised renal or hepatic function. Liposomal preparations of *amphotericin B* are available and have shown therapeutic efficacy.



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

   a. **Fever and chills:** These appear with intravenous administration but usually subside with repeated administration of the drug. Premedication with a steroid or an anitpyretic helps prevent this problem. *Meperidine* (see p. 138) can abort fever and chills that have already started.

   b. **Renal impairment:** Despite the low levels of the drug excreted in the urine, patients may exhibit impaired renal function (decrease in glomerular filtration rate and tubular function). Creatinine clearance drops and potassium is lost. The nephrotoxicity may be potentiated by sodium depletion. Normal renal function usually returns on suspension of the drug, but residual damage is likely at high doses. Azotemia is exacerbated by other nephrotoxic drugs such as *aminoglycosides* (see 314),

cyclosporine, or *pentamidine* (see p. 353), 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 *digitalis.*

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

e. **Neurological effects:** Intrathecal administration can cause a variety of 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 used only in combination with *amphotericin* for the treatment of systemic mycoses and meningitis caused by Cryptococcus neoformans and Candida.

1. **Mode of action:** The drug enters fungal cells via a cytosine-specific permease, an enzyme not found in mammalian cells. *5-FC* is then converted by a series of steps to 5-fluorodeoxyuridylic acid (5-FdUMP); this false nucleotide inhibits thymidylate synthetase, thus depriving the organism of thymidylic acid, an essential DNA component (Figure 34.3). The unnatural pyrimidine is also metabolized to the nucleotide (5-FUTP) and incorporated into fungal RNA, to disrupt nucleic acid and protein synthesis. The combination of *flucytosine* and *amphotericin B* is synergistic. [Note: The *amphotericin B* affects cell permeability, allowing more of the *flucytosine* to penetrate the cell.]

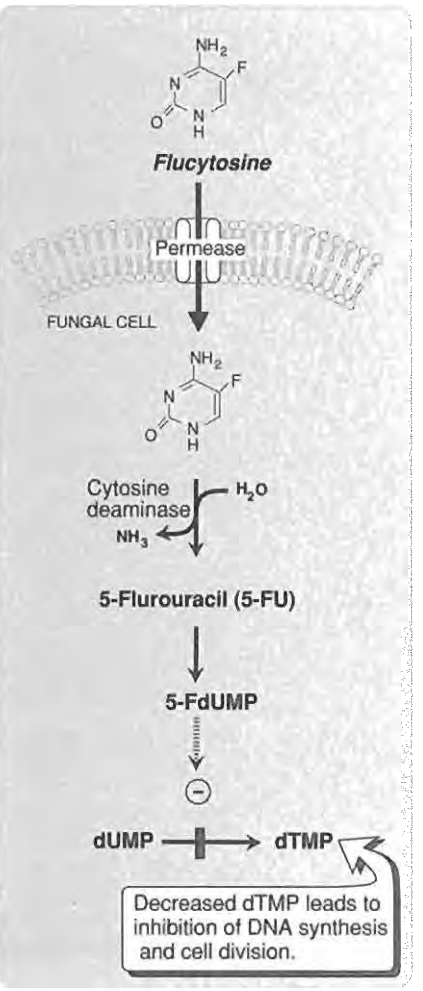
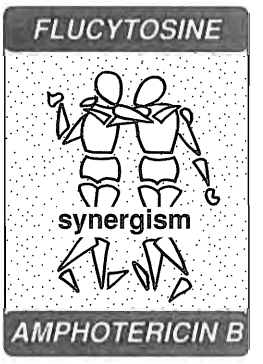


Figure 34.3
Mode of action of *flucytosine.*

2. **Antifungal spectrum:** *Flucytosine* is fungistatic and effective in treating chromoblastomycosis and in combination for candidiasis, and cryptococcosis.

3. **Resistance:** Resistance can develop during therapy and is the reason that *flucytosine* is not used as a single antimycotic drug except for chromoblastomycosis. The rate of emergence of resistant fungal cells is lower with the combination of *amphotericin B* and *flucytosine* than it is with *flucytosine* alone. Decreased levels of any of the enzymes in the conversion of *5-FC* to 5-FU and beyond, or increased synthesis of cytosine, can confer resistance.

4. **Pharmacokinetics:** *Flucytosine* is well absorbed by the oral route, distributes throughout the body water, and penetrates well into cerebrospinal fluid (CSF). 5-Fluorouracil is detectable in patients and probably is due to 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:** Some of these adverse effects may be related to 5-FU formed by intestinal organisms from *5-FC*.

   a. **Hematologic toxicity:** *Flucytosine* causes reversible neutropenia, thrombocytopenia, and occasional bone marrow depression. Caution must be exercised in patients undergoing radiation or chemotherapy with drugs that depress bone marrow.

   b. **Hepatic dysfunction:** Reversible hepatic dysfunction with elevation of serum transaminases and alkaline phosphatase may occur.

   c. **Gastrointestinal disturbances:** Nausea, vomiting, and diarrhea are common, and severe enterocolitis may occur.

C. Ketoconazole

Ketoconazole [kee toe KON a zole], a substituted imidazole, is one of a family of azoles useful in treating systemic mycoses. In addition to its antifungal activity, *ketoconazole* also inhibits gonadal and adrenal steroid synthesis in humans by blocking C17-20 lyase, 11β-hydroxylase, and cholesterol side-chain cleavage; thus, it suppresses *testosterone* and *cortisol* synthesis.

1. **Mode of action:** *Ketoconazole* interacts with C-14 α-demethylase (a cytochrome P-450 enzyme) to block demethylation of lanosterol to ergosterol, the principal sterol of fungal membranes Figure 34.4). This inhibition disrupts membrane function and increases permeability. *Ketoconazole* acts in an additive manner with *flucytosine* against Candida, but antagonizes *amphotericin B*'s antifungal activity.

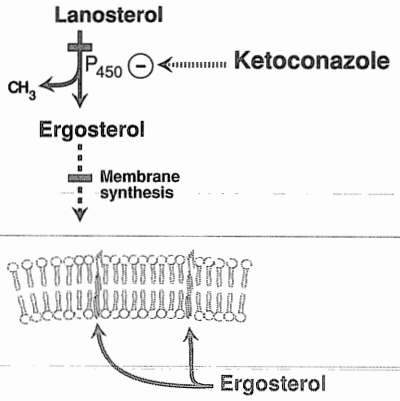


Figure 34.4
Mode of action of *ketoconazole*.

2. **Antifungal spectrum:** *Ketoconazole* is either fungistatic or fungicidal, depending on the dose. Although active against the same fungi as *amphotericin B*, it is most useful in the treatment of histoplasmosis. *Ketoconazole* is also effective against nonmeningeal coccidiomycosis and blastomycosis. Candida, and various dermatophytic infections, including those resistant to *griseofulvin* are also susceptible.

3. **Resistance:** No resistance has been observed.

4. **Pharmacokinetics:** *Ketoconazole* is only administered orally. It dissolves in the acidic gastric contents and is absorbed through the gastric mucosa. Food, antacids, *cimetidine*, and *rifampin* impair absorption. Coca-Cola being acidic has been shown to improve absorption of *ketoconazole*. The drug is highly 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. It does not enter the CSF. Extensive metabolism occurs in the liver. Induction of the cytochrome P-450 system enzymes (see p. 14) in the liver shortens the half-life of *ketoconazole,* but the drug can also inhibit certain cytochromes P-450 to potentiate the effects of some drugs (see p. 341). Excretion is primarily through the bile. Levels of parent drug in the urine are too low to be effective against urinary tract mycotic infections.

5. **Adverse effects:** These effects are primarily gastrointestinal. In addition to allergies, other toxicities include the following effects:

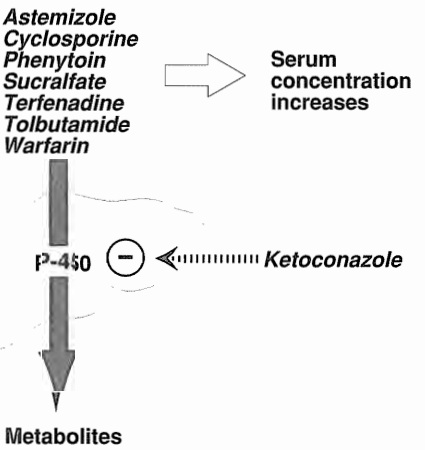
   a. **Gastrointestinal distress** is a common side effect.

   b. **Endocrine effects:** These result from the blocking of androgen and adrenal steroid synthesis by *ketoconazole*. Among the effects are gynecomastia, decreased libido, impotence, and menstrual irregularities.

   c. **Hepatic dysfunction:** Although the incidence is low, hepatic dysfunction, with elevation of serum transaminase levels, is a serious toxic manifestation. *Ketoconazole* may accumulate in patients with hepatic dysfunction. Plasma concentrations of the drug should be monitored in these individuals.

   d. **Contraindications:** *Ketoconazole* and *amphotericin B* should not be used together.

   e. **Drug interactions:** By inhibiting cytochrome P-450, *ketoconazole* can potentiate the toxicities of *cyclosporine*, *phenytoin*, and the H_1-histamine antagonists, *terfenadine* and *astemizole*. It can also increase the levels of *sucralfate, tolbutamide* and *warfarin*. *Rifampin*, an inducer of the cytochrome P-450 system, can shorten the duration of *ketoconazole* and the other azoles (see Figure 33.5, p. 334). Drugs that decrease gastric acidity such as H_2-receptor blockers and antacids also can decrease absorption of *ketoconazole*.



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. *Fluconazole* is employed prophylactically, with some success, for reducing fungal infections in recipients of bone marrow transplants.

1. **Mode of action:** It inhibits the synthesis of fungal membrane ergosterol in the same manner as *ketoconazole*.

2. **Antifungal spectrum:** It is the drug of choice for Cryptococcus neoformans, for candidemia, and for coccidioidomycosis. *Fluconazole* has also been shown to be useful in the treatment of blastomycosis, candidiasis, and histoplasmosis. These infections are characterized by a high rate of relapse, and *fluconazole* has proved effective in chronic ambulatory treatment.

3. **Resistance:** Treatment failures have been reported in some HIV-infected patients.

4. **Pharmacokinetics:** *Fluconazole* is administered orally or intravenously. Its absorption is excellent and, unlike *ketoconazole*, is not dependent on gastric acidity. Binding to plasma proteins is minimal. Its importance lies in its ability to penetrate the CSF of

Oral or IV

normal and inflamed meninges. Unlike *ketoconazole*, *fluconazole* is poorly metabolized. The drug is excreted via the kidney, and doses must be reduced in patients with compromised renal function.

5. **Adverse effects:** Its adverse effects are less of a problem than with *ketoconazole*. *Fluconazole* has no endocrinologic effects because it does not inhibit the cytochrome P-450 responsible for the synthesis of androgens. However, it can inhibit the cytochromes P-450 that metabolize the other drugs listed on p. 341 under *ketoconazole*. Besides nausea and vomiting, rashes are a problem. Hepatitis is rare. Recent reports indicate that *fluconazole* is a potent teratogen and suggest that other of the azoles may also be teratogenic.

E. Itraconazole

Itraconazole [it ra KON a zole] is a recent addition to the azole family of antifungal agents. Like fluconazole it is a synthetic triazole, and it also lacks the endocrinologic side effects of *ketoconazole*. Its mode of action is the same as that of the other azoles. *Itraconazole* is now the drug of choice for the treatment of blastomycosis. Unlike *ketoconazole*, it is effective in AIDS-associated histoplasmosis. However, current studies show that it may also be effective in the treatment of aspergillosis, candidemia, coccidioidomycosis, and cryptococcosis. Thus it has a broad antifungal spectrum.

	Ketoconazole	*Fluconazole*	*Itraconazole*
Spectrum	Narrow	Expanded	Expanded
Route(s) of administration	Oral	Oral, IV	Oral
$t_{1/2}$ (hours)	6-9	30	30-40
CSF penetration	No	Yes	No
Renal excretion	No	Yes	No
Interaction with other drugs	Frequent	Occasional	Occasional
Inhibition of mammalian sterol synthesis	Dose-dependent inhibitory effect	No inhibition	No inhibition

Figure 34.5
Summary of azole fungistatic drugs.

1. **Pharmacokinetics:** *Itraconazole* is well-absorbed orally and food increases its bioavailability. It is extensively bound to plasma proteins and distributes well throughout most tissues, including bone, sputum and adipose tissues. However, therapeutic concentrations are not attained in the CSF. Like *ketoconazole* it is extensively metabolized in the liver but does not inhibit androgen synthesis. Little of the parent drug appears in the urine and thus doses do not have to be reduced in renal failure.

2. **Adverse effects**: Adverse effects include nausea and vomiting, rash (especially in immunocompromised patients), hypokalemia, hypertension, edema, and headache. Drug interactions listed above are also possible with *itraconazole*. Figure 34.5 summarizes the azole antifungal agents.

III. DRUGS FOR SUPERFICIAL MYCOTIC INFECTIONS

Fungi that cause superficial skin infections are called dermatophytes. Common dermatomycoses, such as tinea infections, are often referred to as ringworm, which is a misnomer, since fungi rather than worms cause the disease.

A. Griseofulvin

1. **Mode of action:** *Griseofulvin* [gri see oh FUL vin] enters susceptible fungal cells by an energy-dependent process. It is believed to

interact with the microtubules within the fungus to disrupt the mitotic spindle and inhibit mitosis (Figure 34.6). It accumulates in the infected, newly synthesized, keratin-containing tissues, making them unsuitable for the growth of the fungi. Therapy must be continued until normal tissue replaces infected tissue. This usually requires weeks to months of therapy.

2. **Antifungal spectrum:** The drug is principally fungistatic. It is effective only against the dermatophytes—Trichophyton, Microsporum, and Epidermophyton. It is used in the treatment of severe tinea infections that do not respond to other antifungal agents.

3. **Resistance:** Resistance is due to the lack of the energy-dependent uptake system.

4. **Pharmacokinetics:** Ultra-fine crystalline preparations are absorbed adequately from the gastrointestinal tract. Absorption is promoted if ingested with a high fat diet. *Phenobarbital* can interfere with the absorption of *griseofulvin*. The drug is ineffective topically. *Griseofulvin* distributes chiefly to infected keratinized tissue where it becomes bound; therefore, it is uniquely suited for the treatment of dermatophytic infections. Concentrations in other tissues and body fluids are much lower. *Griseofulvin* is extensively metabolized to the demethylated and glucuronidated forms. *Griseofulvin* induces hepatic cytochrome P-450 activity, and can increase the rate of metabolism of a number of drugs including oral anticoagulants (see p. 199). Excretion of the drug occurs via the kidney, primarily as metabolites.

5. **Adverse effects:** Toxicity is not generally a clinical problem although allergic reactions and a number of adverse effects (e.g., headache, nausea) have been reported. *Griseofulvin* may cause hepatotoxicity and is contraindicated in patients with acute intermittent porphyria. The drug potentiates the intoxicating effects of alcohol. *Griseofulvin* is teratogenic in laboratory animals.

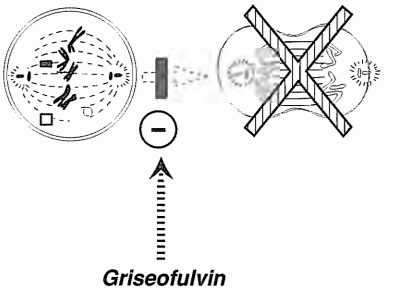


Figure 34.6
Inhibition of mitosis by *griseofulvin*.

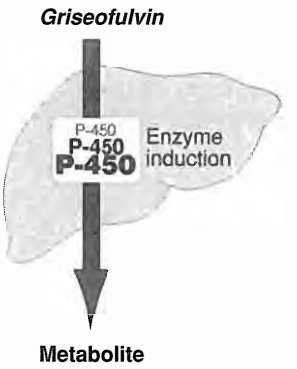


Figure 34.7
Induction of hepatic cytochrome P-450 activity by *griseofluvin.*

B. Nystatin

Nystatin [nye STAT in] is a polyene antibiotic; its structure, chemistry, mode 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 ("swish and swallow") for the treatment of oral candidiasis. Excretion in the feces is nearly quantitative. Adverse effects are rare because of its lack of absorption, but occasionally nausea and vomiting occur.

C. Miconazole and other topical agents

Miconazole [my KON a zole], *clotrimazole* [kloe TRIM a zole], and *econazole* [e KON a zole] are topically active drugs and are only rarely administered parenterally because of their severe toxicity. Their mechanism of action, antifungal spectrum, distribution, and type of metabolism are the same as *ketoconazole*.

Choose the ONE best answer.

Questions 34.1 - 34.3: For each numbered phrase, select the ONE drug (A-E) that is most closely associated with it. Each drug may be selected once, more than once, or not at all.

A. Flucytosine
B. Griseofulvin
C. Penicillin G
D. Amphotericin-B
E. Ketoconazole

34.1 Binds to ergosterol present in cell membranes of sensitive fungal cells, thereby disrupting membrane function.

The correct answer = D. (Amphotericin B).

34.2 Blocks lanosterol demethylation to ergosterol, thus disrupting fungal membrane integrity.

The correct answer = E. (Ketoconazole).

34.3 Is metabolized to a product that inhibits thymidylate synthetase and thus prevents fungal DNA synthesis.

The correct answer = A. (Flucytosine).

Choose the ONE best answer:

34.4 Which one of the following drugs is not used for the treatment of systemic fungal infections?

A. Amphotericin B.
B. Flucytosine.
C. Ketoconazole.
D. Griseofulvin.
E. Fluconazole.

Correct answer = D. Griseofulvin use is restricted to the treatment of superficial mycotic infections.

34.5 All of the following statements correctly describe ketoconazole EXCEPT:

A. It inhibits the conversion of lanosterol to ergosterol.
B. It may produce gastrointestinal upsets.
C. It can cause gynecomastia in males.
D. It penetrates into the cerebrospinal fluid.
E. It should not be combined with amphotericin B.

Correct answer = D. Ketoconazole does not enter the CSF.

34.6 All of the following statements concerning griseofulvin are correct EXCEPT:

A. It is only effective against dermatophytic infections.
B. It exacerbates acute intermittent porphyria.
C. It induces the hepatic cytochrome P-450 system.
D. It enhances CNS depressant effects of ethanol.
E. Its use in therapy for superficial mycotic infections is usually short term (several days).

Correct answer = E. Griseofulvin accumulates in the infected, newly synthesized keratin-containing tissues making them unsuitable for the growth of the fungi. Therapy must be continued until normal tissue replaces infected tissue. This usually requires long-term therapy.

34.7 A 25-year-old male AIDS patient has a fever of 102°F and complains of severe headaches during the past week. Staining of his cerebrospinal fluid 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.

The correct answer = C. Intrathecal administration of amphotericin B is indicated as the most effective way to treat cryptococcal meningitis. Although intravenous amphotericin B may be useful, the addition of flucytosine with its potential for bone marrow toxicity would not be appropriate therapy. Oral ketoconazole is also wrong because of its inability to cross into the CSF. Although fluconazole is very effective against Cryptococcus neoformans and does enter the CSF, the oral route is only used for chronic suppressive therapy and not meningitis. The combination of amphotericin B and ketoconazole is a poor one since ketoconazole disrupts fungal membrane function and thus interferes with the action of amphotericin B.

34. 8 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.
B. Ketoconazole reacts with cyclosporine to inactivate it.
C. Ketoconazole has a potential for cardiotoxicity.
D. Ketoconazole inhibits cytochrome P-450 enzymes that inactivate cyclosporine.
E. Ketoconazole causes gynecomastia and decreased libido in the male.

The correct answer = D. Ketoconazole is effective against Candida, but it does not react with cyclosporine nor is it cardiotoxic. Ketoconazole inhibits the hepatic cytochrome P-450 enzymes that inactivate cyclosporine. Thus in this instance the patient would be in danger of increased cyclosporine toxicity. Though ketoconazole does cause gynecomastia and decreased libido, this would not be of primary concern.

Antiprotozoal Drugs

35

I. OVERVIEW

Protozoal infections are common among people in underdeveloped tropical and subtropical countries where sanitary conditions, hygienic practices, and control of the vectors of transmission are inadequate. However, with increased world travel, protozoal diseases such as malaria, amebiasis, leishmaniasis, trypanosomiasis, trichomoniasis, and giardiasis are no longer confined to specific geographic locales. Because they are eukaryotes, the unicelluar protozoal cells have metabolic processes closer to those of the human host than to prokaryotic bacterial pathogens. Protozoal diseases are thus less easily treated than bacterial infections, and many of the antiprotozoal drugs cause serious toxic effects in the host, particularly on cells showing high metabolic activity—neuronal, renal tubular, intestinal and bone marrow stem cells. Most antiprotozoal agents have not proved safe for pregnant patients. Drugs used to treat protozoan infections are summarized in Figure 35.1.

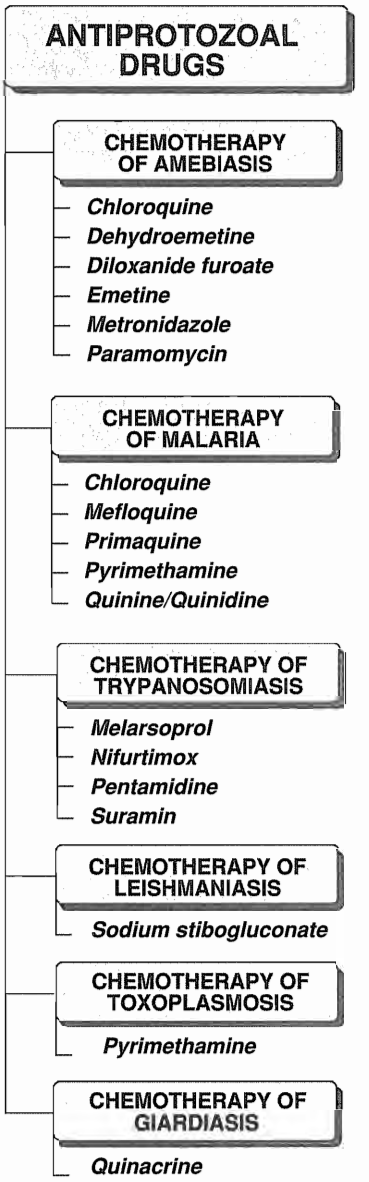


Figure 35.1
Summary of antiprotozoal agents.

II. CHEMOTHERAPY OF AMEBIASIS

Amebiasis (also called amebic dysentery) is an infection of the intestinal tract caused by Entamoeba histolytica. The disease can be acute or chronic with patients showing varying degrees of illness, from no symptoms to mild diarrhea to fulminating dysentery. Diagnosis is made by isolating E. histolytica in fresh feces. Therapy is aimed not only at the acutely ill patient but also at those who are asymptomatic carriers since dormant E. histolytica may cause future infections in the carrier and may be a potential source of infection of others.

A. Life cycle of E. histolytica

E. histolytica exists in two forms: cysts that can survive outside the body, and labile but invasive trophozoites that do not persist outside the body. Cysts, ingested through feces-contaminated food or water, pass into the intestine where trophozoites are liberated. The trophozoites multiply, and either invade and ulcerate the mucosa of the large intestine, or simply feed on intestinal bacteria. [Note: One strategy for treating luminal amebiasis is to add antibiotics, such as *tetra-*

Lippincott's Illustrated Reviews: Pharmacology, Second Edition.
by Mary Mycek, Richard A. Harvey and Pamela C. Champe.
Lippincott–Raven Publishers , Philadelphia, PA © 1996.

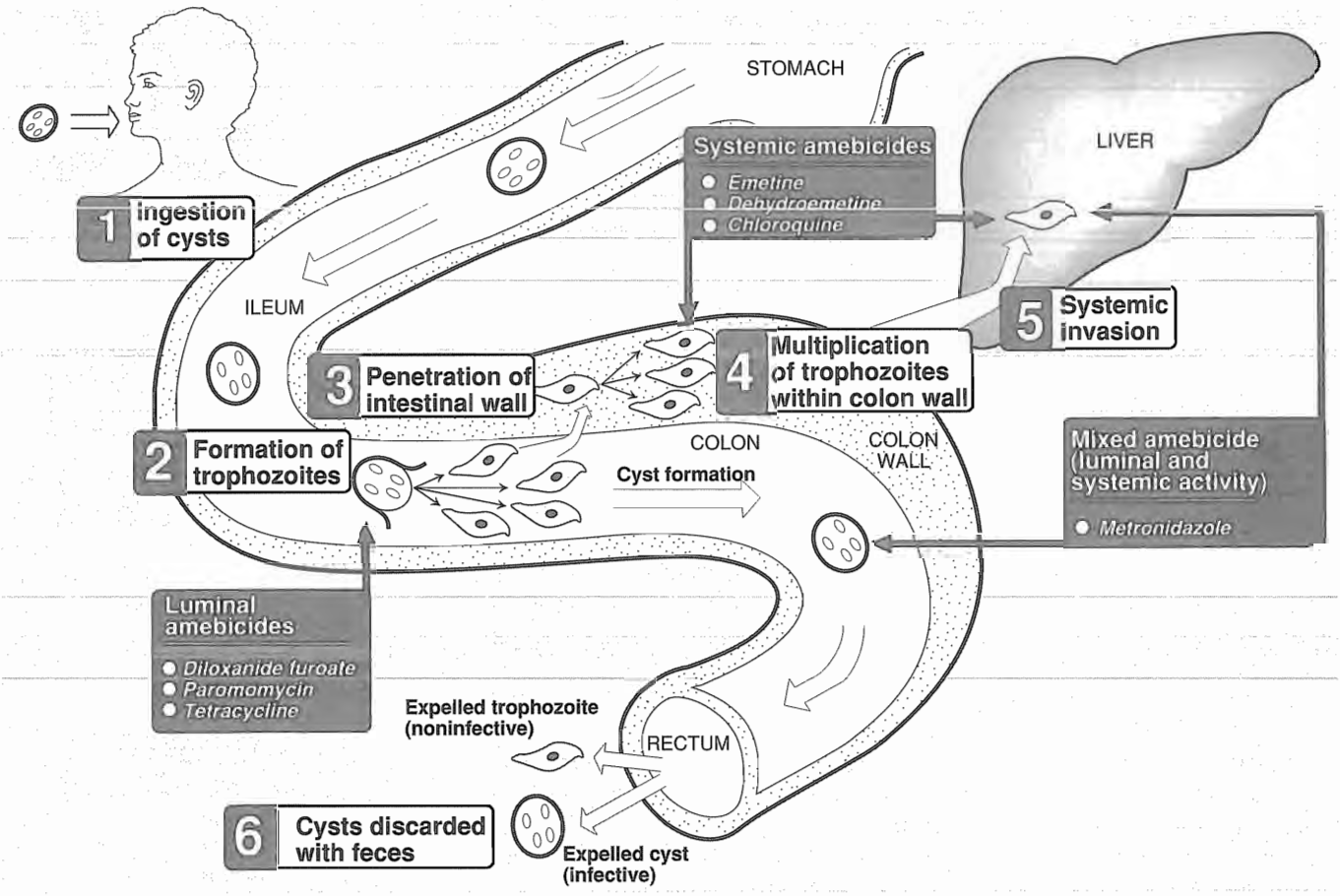


Figure 35.2
Life cycle of Entamoeba histolytica showing sites of action of amebicidic drugs.

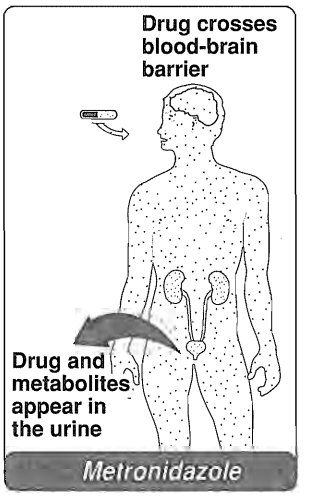
cycline, to the treatment regimen resulting in a reduction in intestinal flora, the amebae's major food source.] Large numbers of trophozoites within the colon wall can lead to systemic invasion. The trophozoites within the intestine are slowly carried toward the rectum where they return to the cyst form and are excreted in feces. A summary of the life cycle of this organism is presented in Figure 35.2.

B. Classification of antiprotozal drugs

Therapeutic agents are classified as mixed, luminal, or systemic amebicides according to the site where the drug is effective (see Figure 35.2). For example, mixed amebicides are effective against both the luminal and systemic forms of the disease, though luminal concentrations are too low for single drug treatment. Luminal amebicides act on the parasite in the lumen of the bowel, whereas systemic agents are effective against amebae in the intestine wall and the liver.

C. Mixed amebicide: metronidazole

Amebiasis is generally treated with a combination of *metronidazole* [me troe NYE da zole] plus a luminal amebicidal drug, such as *diloxanide furoate*. This combination provides cure rates of greater than 90%. *Metronidazol* also has important antibacterial activity.



1. **Mode of action:** *Metronidazole* is selectively toxic not only for amebae but also for anaerobic organisms (including bacteria), and for anoxic or hypoxic cells. Some anaerobic protozoan parasites (including amebae) possess ferrodoxin-like, low-redox potential, electron transport proteins that participate in metabolic electron removal reactions. The nitro group of *metronidazole* is able to serve as an electron acceptor, forming reduced cytotoxic compounds that bind to proteins and DNA to result in cell death.

2. **Antimicrobial spectrum:** *Metronidazole* is the agent of choice for treating infections caused by E. histolytica in which it kills the E. histolytica trophozoites, Giardia lamblia, and Trichomonas vaginalis in both males and females. *Metronidazole* also finds extensive use in the treatment of infections caused by anaerobic cocci and anaerobic gram-negative bacilli (for example, bacteroides species). Anaerobic gram-positive bacilli, such as Clostridia, which cause pseudomembranous colitis, are also sensitive. The drug is effective in the treatment of brain abscesses caused by these organisms.

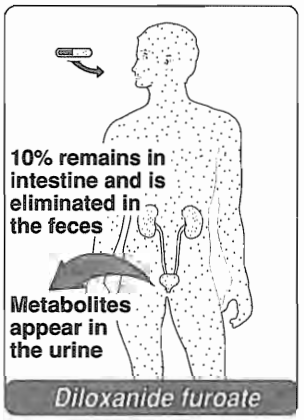
3. **Resistance:** Resistance is not a therapeutic problem, although strains of trichomonads resistant to *metronidazole* have been reported.

4. **Pharmacokinetics**

   a. **Administration and distribution:** *Metronidazole* is completely and rapidly absorbed after oral administration and for the treatment of amebiasis, is usually administered with a luminal amebicide, such as *diloxanide furoate*. It distributes well throughout body tissues and fluids. Therapeutic levels can be found in vaginal and seminal fluids, saliva, breast milk and cerebrospinal fluid (CSF).

   b. **Fate:** Metabolism depends on hepatic oxidation of the *metronidazole* side-chain by mixed function oxidase, followed by glucuronidation (see p. 14). Therefore, concomitant treatment with inducers of this enzymatic system, such as *phenobarbital* (see p. 94), enhances the rate of metabolism. Conversely, those that inhibit this system, such as *cimetidine* (see p. 236), prolong the plasma half-life ($t_{1/2}$). The drug accumulates in patients with severe hepatic disease. The parent drug and metabolites are excreted in the urine.

5. **Adverse effects:** The most common adverse effects are those associated with the gastrointestinal tract—nausea, vomiting, epigastric distress, and abdominal cramps. An unpleasant metallic taste is often experienced. Other effects include oral moniliasis



(yeast infection of the mouth) and rarely, neurotoxicologic problems, such as dizziness, vertigo, and numbness or paresthesias in the peripheral nervous system. [Note: The latter are reasons for discontinuing the drug.] If taken with alcohol, a *disulfiram*-like effect occurs (see p. 96).

D. Luminal amebicide: Diloxanide furoate

Diloxanide furoate [dye LOX a nide] is useful in the treatment of asymptomatic passers of cysts. Its only indication is in the treatment of intestinal amebiasis. After oral administration, *diloxanide furoate* is hydrolyzed in the intestinal mucosa, and the diloxanide is about 90% absorbed. However, the unabsorbed drug is the active amebicide. Adverse effects are mild. They include flatulence, dryness of the mouth, pruritus, and urticaria. The drug is contraindicated in pregnant women and children under 2 years of age.

E. Luminal amebicide: Paromomycin

Paromomycin [par oh moe MYE sin], an aminoglycoside antibiotic, is only effective against the intestinal (luminal) forms of E. histolytica and tapeworm, since it is not significantly absorbed from the gastrointestinal tract. It is an alternative agent for cryptosporidiosis. Although directly amebicidal, *paromomycin* also exerts its antiamebic actions by reducing the population of the intestinal flora. Its direct amebicidal action is probably due to the effects it has on cell membranes to cause leakage. Very little of the drug is absorbed on oral ingestion; that which is, is excreted in the urine. Gastrointestinal distress and diarrhea are the principal adverse effects.

F. Systemic amebicide: Chloroquine

Chloroquine [KLOR oh kwin] is used in conjunction with *metronidazole* and *diloxanide furoate* to treat and prevent amebic liver abscesses. It eliminates trophozoites in liver abscesses, but it is not useful in treating luminal amebiasis. *Chloroquine* is also effective in the treatment of malaria and is more fully described in the malaria section (see p. 349).

G. Systemic amebicides: Emetine and dehydroemetine

Emetine [EM e teen] and *dehydroemetine* [de hye dro EM e teen] are alternate agents for the treatment of amebiasis. They inhibit protein synthesis by blocking chain elongation[1]. Intramuscular injection is the preferred route. *Emetine* is concentrated in the liver where it persists for a month after a single dose. It is slowly metabolized and excreted and can accumulate. Its $t_{1/2}$ is 5 days. The use of these ipecac alkaloids is limited by their toxicities. *Dehydroemetine* is probably less toxic than *emetine*. Close clinical observation is necessary when these drugs are used. Among the untoward effects are pain at the site of injection, transient nausea, cardiotoxicity (e.g., arrhythmias, congestive heart failure), neuromuscular weakness, dizziness, and rashes.

[1]See p. 358 for Infolink references to other books in this series.

III. CHEMOTHERAPY OF MALARIA

Malaria is an acute infectious disease caused by four species of the protozoal genus plasmodium. The parasite is transmitted to humans through the bite of female anopheles mosquito, which thrives in humid, swampy areas. Plasmodium falciparum is the most dangerous species, causing an acute, rapidly fulminating disease characterized by persistent high fever, orthostatic hypotension and massive erythrocytosis (swollen and reddish condition of the limbs). Plasmodium falciparum infection can lead to capillary obstruction and death if treatment is not instituted promptly. Plasmodium vivax causes a milder form of the disease. P. malariae is common to many tropical regions but Plasmodium ovale is rarely encountered. Resistance acquired by the mosquito to insecticides, and by the parasite to drugs, has led to new therapeutic challenges, particularly in the treatment of P. falciparum.

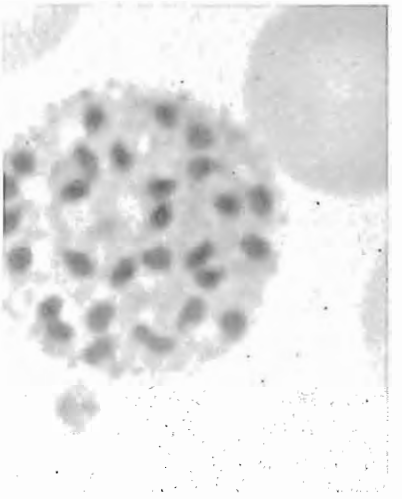


Figure 35.3
Red blood cells containing Plasmodium vivax.

A. Life cycle of the malaria parasite

When an infected mosquito bites, it injects Plasmodium sporozoites into the blood stream. The sporozoites migrate through the blood to the liver where they form cyst-like structures containing thousands of merozoites. [Note: Diagnosis depends on laboratory identification of the parasites in red blood cells of peripheral blood smears (Figure 35.3).] Upon release, each merozoite invades red blood cells, using hemoglobin as a nutrient. Eventually the infected cell ruptures, releasing heme and merozoites that can enter other erythrocytes. The effectiveness of a drug treatment is related to the particular species of infecting plasmodium and the stage of its life cycle. A summary of the life cycle of the parasite and the sites of therapeutic interventions are presented in Figure 35.4.

B. Tissue schizonticide: Primaquine

Primaquine [PRIM a kwin] is an 8-aminoquinoline that eradicates primary exoerythrocytic forms of P. falciparum and P. vivax and the secondary exoerythrocytic forms of recurring malarias (P. vivax and P. ovale). In addition, the sexual (gametocytic) forms of all four plasmodia are destroyed in the blood or are prevented from maturing later in the mosquito. Because of its lack of activity against the erythrocytic schizonts, *primaquine* is often used in conjunction with a schizonticide.

1. **Mode of action:** This is not completely understood. Intermediates are believed to act as oxidants that are responsible for the schizonticidal action as well as for hemolysis and methemoglobinemia encountered as toxicities.

2. **Antimicrobial spectrum:** In spite of structural similarity to the 4-aminoquinolines (for example, *chloroquine*), the 8-aminoquinolines are effective only against the exoerythrocytic (tissue) stages and not the erythrocytic stage of malaria. It is the only agent that can lead to radical cures of the P. vivax and P. ovale malarias, which may remain in the liver after the erythrocytic form of the disease is

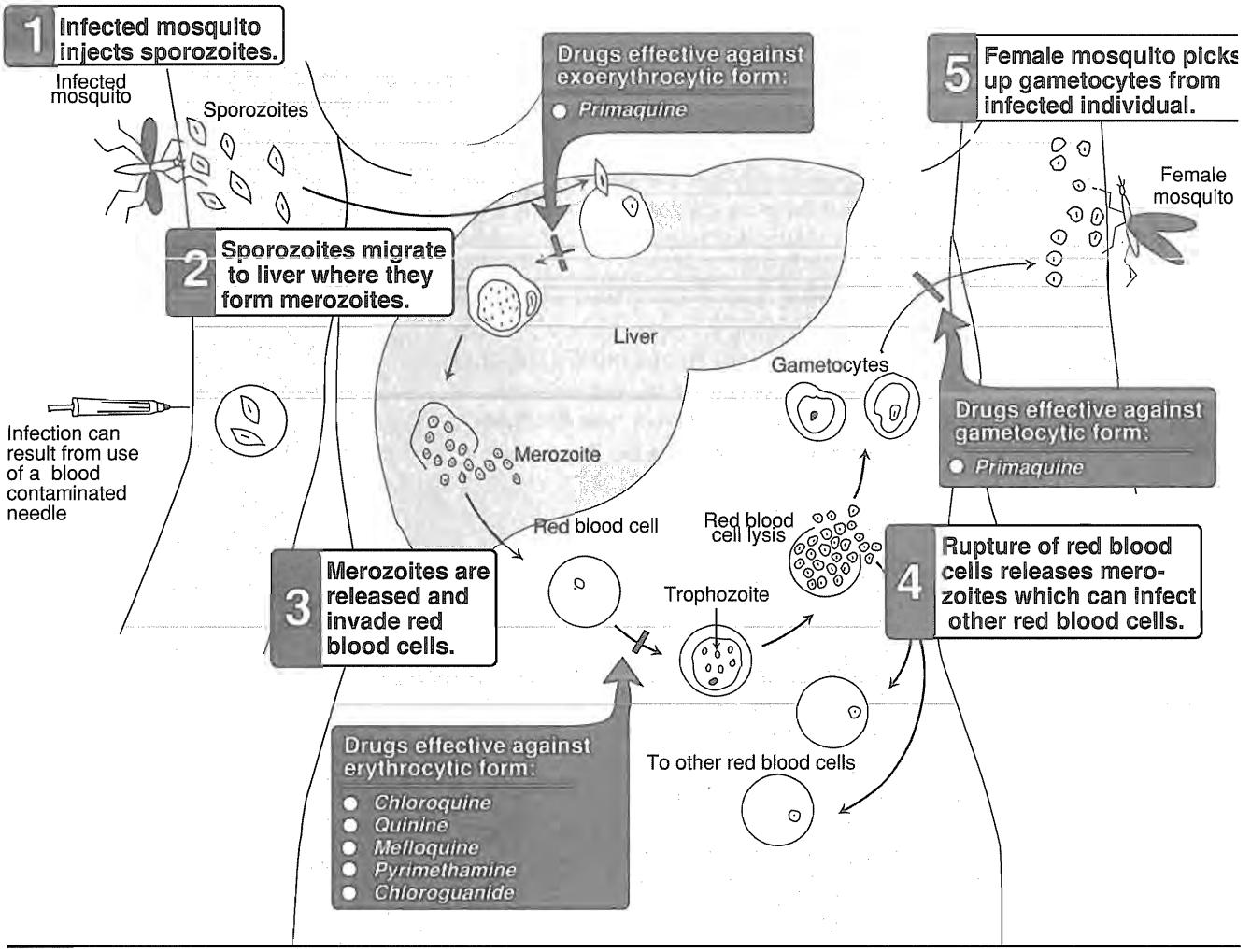


Figure 35.4
Life cycle of the malarial parasite showing the sites of action of antimalarial drugs.

eliminated. Because *primaquine* is also gametocidal for all four plasmodia species, transmission of the disease can be interrupted.

3. **Pharmacokinetics:** *Primaquine* is well absorbed on oral administration and is not concentrated in tissues. It is rapidly oxidized to many compounds, the major one being the deaminated drug. It has not been established which compound possesses the schizonticidal activity. Metabolites appear in urine.

4. **Adverse effects:** *Primaquine* has a low incidence of adverse effects except for drug-induced hemolytic anemia in patients with genetically low levels of glucose-6-phosphate dehydrogenase (Figure 35.5).[2] Other toxic manifestations observed after large doses of the drug include abdominal discomfort, especially in combination with *chloroquine*, (which may affect patient compliance), and occasional methemoglobinemia; granulocytopenia and agranulocytosis are rarely seen except in patients with lupus or arthritis, in whom the drug aggravates both these conditions.

[2]See p. 358 for Infolink references to other books in this series.

C. Blood schizonticide: Chloroquine

Chloroquine [KLOR oh kwin] is a synthetic 4-aminoquinoline that has been the mainstay of antimalarial therapy until the recent appearance of drug resistant strains of P. falciparum.

1. **Mode of action:** Several mechanisms have been identified by which *chloroquine* kills the organism after accumulating in the organism.

   a. **Damage mediated by accumulated heme:** *Chloroquine* enters the red blood cells and interferes with a unique enzyme that is essential to the survival of the parasites in the red blood cells. The parasites digest the host cell's hemoglobin to get essential amino acids and iron. However, this process also releases large amounts of soluble heme that is toxic to the parasites. To protect itself, the parasite ordinarily polymerizes the heme to hemozoin (a pigment) that is sequestered in the parasite's food vacuole. *Chloroquine* inhibits the polymerase and thus soluble heme kills the organism by inhibiting proteinases in the food vacuole. *Chloroquine* also binds to ferriprotoporphyrin IX, which is formed from the breakdown of hemoglobin in infected erythrocytes. The resulting complex damages the membranes and leads to lysis of both the parasite and the red blood cell.

   b. **Alkalinization of food vacuole:** *Chloroquine* is taken up into the parasite's food vacuole by an active transport system. Inside the acidic vacuole the drug, which is very basic, combines with a proton and is trapped, resulting in alkalinization of this organelle. This causes an inability of the parasite to carry out hemoglobin digestion.

   c. **Decreased DNA synthesis:** The drug can also decrease DNA synthesis in the parasite by disrupting the tertiary structure of the nucleic acid.

2. **Resistance:** Resistance of plasmodia to available drugs has become a serious medical problem throughout Asia and some areas of Central and South America. *Chloroquine*-resistant P. falciparum contain membrane-associated P-glycoprotein (see p. 377) that extrudes the drug from the organism.

3. **Antimicrobial spectrum:** *Chloroquine* is the drug of choice in the treatment of erythrocytic falciparum malaria, except in resistant strains. *Chloroquine* is less effective against vivax malaria. It is highly specific for the asexual form of P. vivax and P. falciparum. It is also effective in the treatment of extraintestinal amebiasis (see p. 346). The anti-inflammatory action of *chloroquine* explains its occasional use in rheumatoid arthritis and discoid lupus erythematosus.

4. **Pharmacokinetics**

   a. **Administration and distribution:** *Chloroquine* is rapidly and completely absorbed following oral administration. Usually 4

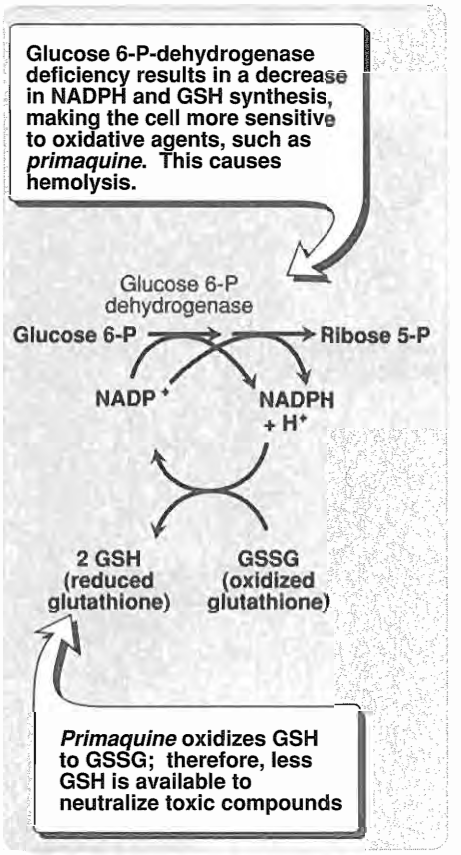


Figure 35.5
Mechanism of *primaquine*-induced hemolytic anemia. GSH, reduced glutathione; GSSG, oxidized glutathione; NADPH, reduced nicotinamide adenine dinucleotide phosphate.

days of therapy suffice to cure the disease. The drug concentrates in erythrocytes, liver, spleen, kidney, lung, and melanin-containing tissues as well as leukocytes. Thus it has a very large volume of distribution. It persists in erythrocytes (see mode of action above). The drug also penetrates into the central nervous system and traverses the placenta.

b. **Fate:** *Chloroquine* is dealkylated by the hepatic mixed function oxidases (see p. 14), but some metabolic products retain antimalarial activity. Both parent drug and metabolites are excreted predominantly in the urine. Excretion rate is enhanced as urine is acidified.

5. **Adverse effects:** Side effects are minimal at low doses used in the chemosuppression of malaria. At higher doses, many more toxic effects occur, such as gastrointestinal upset, pruritus, headaches (Figure 35.6), and visual disturbances (an ophthalmological examination should be routinely performed). Discoloration of the nail beds and mucous membranes may be seen on chronic administration. *Chloroquine* should be used cautiously in patients with hepatic dysfunction or severe gastrointestinal problems, or in patients with neurologic or blood disorders. *Chloroquine* can cause electrocardiographic changes, since it has a *quinidine*-like effect (see p. 167). It may also exacerbate dermatitis produced by *gold* (see p. 414) or *phenylbutazone* (see p. 411) therapy. [Note: Patients with psoriasis or porphyria should not be treated with *chloroquine* because an acute attack may be provoked.]

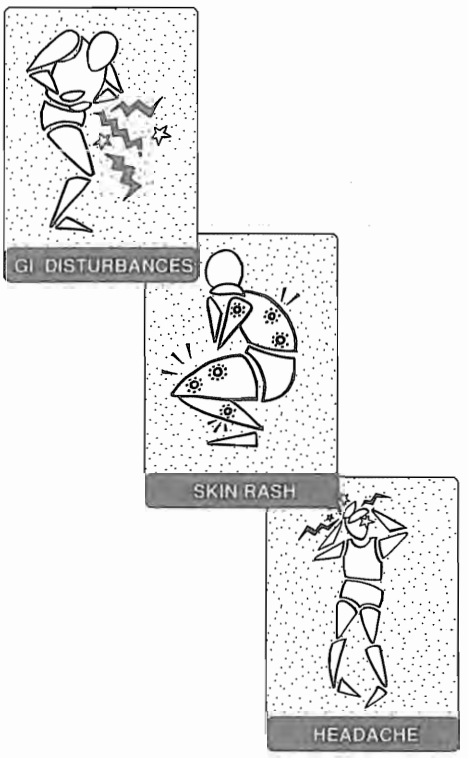


Figure 35. 6
Some adverse effects commonly associated with *chloroquine*.

D. Blood schizonticide: Quinine

Quinine [KWYE nine] is now reserved for malarial strains resistant to other agents. The drug can affect DNA synthesis.

1. **Pharmacokinetics:** When a *chloroquine*-resistant organism is encountered, therapy usually consists of a combination of *quinine*, *pyrimethamine*, and a *sulfonamide*. All are administered orally. [Note: FANSIDAR, a combination of *pyrimethamine* and *sulfadoxime* is used.] Taken orally, *quinine* is well distributed throughout the body and can reach the fetus across the placenta. Alkalinization of the urine decreases its excretion.

2. **Adverse effects:** The major adverse effect of *quinine* is cinchonism, a syndrome causing nausea, vomiting, tinnitus, and vertigo. These effects are reversible and are not considered reason to suspend therapy. However, *quinine* should be suspended if a positive result to a Coombs' test for hemolytic anemia occurs. Among the drug interactions are 1) retardation of absorption when *quinine* is taken with aluminum-containing antacids, 2) potentiation of neuromuscular blocking agents, and 3) elevation of *digoxin* (see p. 158) levels if taken concurrently with *quinine*. *Quinine* is fetotoxic.

E. Blood schizonticide: Mefloquine:

Mefloquine [MEF lo kween] appears promising as an effective single agent for suppressing and curing multidrug-resistant forms of P. -

falciparum. Its exact mechanism of action remains to be determined, but it apparently can damage the parasite's membrane like *quinine* does. Resistant strains have been identified. *Mefloquine* is absorbed well after oral administration and concentrates in the liver and lung. It has a long half-life (17 days) because of concentration in various tissues and because of its continuous circulation through the enterohepatic and enterogastric systems. The drug undergoes extensive metabolism. Its major excretory route is the feces. Adverse reactions at high doses range from nausea, vomiting, and dizziness to disorientation, hallucinations, and depression. Electrocardiographic abnormalities and cardiac arrest are possible if *mefloquine* is taken concurrently with *quinine*, or *quinidine* or β-blockers.

F. Blood schizonticide and sporontocide: Pyrimethamine

The antifolate agent, *pyrimethamine*, is frequently employed as a blood schizonticide to effect a radical cure. It also acts as a strong sporonticide in the mosquito's gut when the mosquito ingests it with the blood of the human host. *Pyrimethamine* inhibits plasmodial dihydrofolate reductase[3] at much lower concentrations than those that inhibit the mammalian enzyme. The inhibition deprives the protozoan of tetrahydrofolate, a cofactor required in the de novo biosynthesis of purines and pyrimidines, and interconversions of certain amino acids. *Pyrimethamine* alone is effective against P. falciparum. In combination with a sulfonamide, it is also used against P. malariae and Toxoplasma gondii. If megaloblastic anemia occurs, it may be reversed with *leucovorin* (see p. 379)

IV. CHEMOTHERAPY OF TRYPANOSOMIASIS

Trypanosomiasis refers to two chronic and eventually fatal diseases caused by species of Trypanosoma: African sleeping sickness and American sleeping sickness (Figure 35.7). In African sleeping sickness, the causative organisms, Trypanosoma brucei gambiense and Trypanosoma brucei rhodiense, initially live and grow in the blood. The parasite invades the CNS, causing an inflammation of the brain and spinal cord that produces the characteristic lethargy and eventually continuous sleep. Chagas' disease (American sleeping sickness) caused by Trypanosoma cruzi occurs in South America.

A. Melarsoprol

Melarsoprol [me LAR soe prole] is a derivative of *mersalyl oxide*, a trivalent arsenical.

1. **Mode of action:** The drug reacts with sulfhydryl groups of various substances including enzymes in both the organism and host. Parasitic enzymes may be more sensitive than are those of the host. There is evidence that mammalian cells may be less permeable to the drug and thus protected from its toxic effects.

2. **Antimicrobial spectrum:** *Melarsoprol* is limited to the treatment of trypanosomal infections, usually in the late stage with CNS involvement, and is lethal for these parasites.

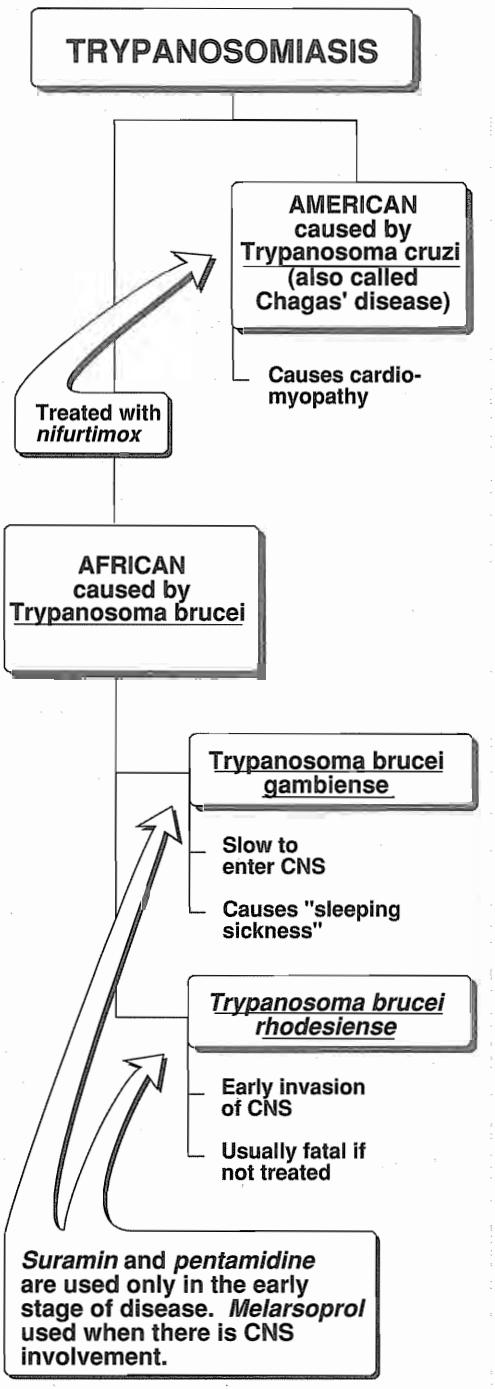
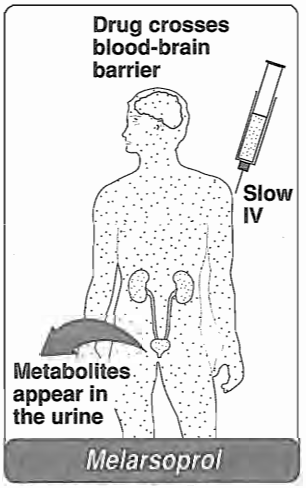


Figure 35.7
Summary of trypanosomiasis.

[3]See p. 358 for Infolink references to other books in this series.



3. **Resistance:** may be due to decreased permeability to the drug.

4. **Pharmacokinetics:**

   a. **Administration and distribution:** *Melarsoprol* is usually slowly administered intravenously through a fine needle, even though it is absorbed from the gastrointestinal tract. Because it is very irritating, care should be taken not to infiltrate surrounding tissue. Adequate trypanocidal concentrations appear in the cerebrospinal fluid, which contrasts with *pentamidine* (see p. 355), which does not enter the cerebrospinal fluid. *Melarsoprol* is therefore the agent of choice in the treatment of T. brucei rhodesiense, which rapidly invades the CNS, as well as for meningoencephalitis caused by T.brucei gambiense.

   b. **Fate:** The host readily oxidizes the drug to the relatively nontoxic pentavalent arsenic compound. The drug has a very short half-life and is rapidly excreted into the urine.

5. **Adverse effects**

   a. **Central nervous system toxicities:** These side effects are the most serious. Encephalopathy may appear soon after the first course of treatment but usually subsides. It may, however, be fatal.

   b. **Hypersensitivity reactions:** Such reactions may also occur. Fever may follow injection.

   c. **Gastrointestinal disturbance:** Severe vomiting and abdominal pain can be minimized if the patient is in the fasting state during drug administration and for several hours thereafter.

   d. **Contraindications:** *Melarsoprol* is contraindicated in patients with influenza. Hemolytic anemia has been seen in patients with glucose 6-phosphate dehydrogenase deficiency.

B. Pentamidine isethionate

Pentamidine [pen TAM i deen] is active against protozoal infections, as well as those caused by Pneumocystis carinii. [Note: P. carinii is now considered to be a fungus, but it is not susceptible to antifungal drugs.] Because of the increased incidence of pneumonia caused by this organism in immunocompromised patients such as those infected with human immunodeficiency virus (HIV), *pentamidine* has assumed an important place in chemotherapy. *Pentamidine* is one of the drugs for the prevention and treatment of the hematologic stage of T. brucei gambiense.

1. **Mode of action:** T. brucei concentrates the drug by an energy-dependent, high-affinity uptake system. Although its mode of action has not been defined, evidence exists that the drug binds to the parasite's DNA, and interferes in the synthesis of RNA, DNA, phospholipid and protein of the parasite.

2. **Antimicrobial spectrum:** *Pentamidine* is not effective against all trypanosomes, for example, T. cruzi is resistant. However, it is effective in the treatment of systemic blastomycosis. *Pentamidine* is also effective against P. carinii, but *trimethoprim-sulfamethoxazole* (see p. 293) is preferred. *Pentamidine* is the drug of choice in treating patients with pneumonia caused by P. carinii who have failed to respond to *trimethoprim-sulfamethoxazole*, or in treating individuals who are allergic to sulfonamides. It is an alternative drug to *stibogluconate* in the treatment of leishmaniasis.

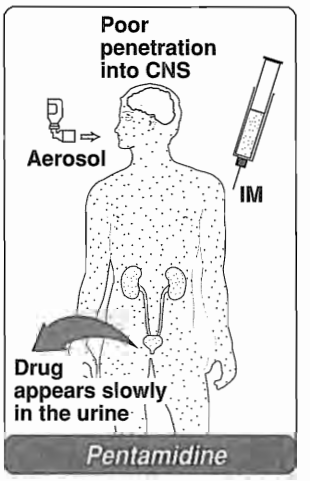
3. **Resistance:** Resistance is associated with an inability of the trypanosome to concentrate the drug.

4. **Pharmacokinetics**

   a. **Administration and distribution:** Fresh solutions are administered intramuscularly or as an aerosol. [Note: The intravenous route is avoided because of severe adverse reactions such as a sharp fall in blood pressure and tachycardia.] The drug is concentrated and stored in the liver and kidney for a long period of time. Because it does not enter the CSF, it is ineffective against the meningoencephalitic stage of trypanosomiasis.

   b. **Fate:** The drug is not metabolized and is excreted very slowly into the urine. Its $t_{1/2}$ is about 5 days.

5. **Adverse effects:** Serious renal dysfunction may occur, which reverses on discontinuation of the drug. Other adverse reactions are hypotension, dizziness, rash and toxicity to β-cells of pancreas.



C. Nifurtimox

Nifurtimox [nye FOOR ti mox] has found use only in the treatment of acute T. cruzi infections (Chagas' disease) although treatment of the chronic stage of such infections has led to variable results. [Note: *Nifurtimox* is suppressive not curative.] Being a nitroaromatic compound, *nifurtimox* undergoes reduction and eventually generates intracellular oxygen radicals, such as superoxide radicals and hydrogen peroxide, in both the amastigote and trypomastigote of T. cruzi. These highly reactive radicals are toxic to the organism, which lacks catalase[4]. Mammalian cells are partially protected from such substances by the presence of enzymes such as catalase, glutathione peroxidase, and superoxide dismutase. The drug is administered orally and is rapidly absorbed and metabolized to unidentified products, which are excreted in the urine. Adverse effects are common following chronic administration, particularly among the elderly. Major toxicities include immediate hypersensitivity reactions, such as anaphylaxis; delayed hypersensitivity reactions, for example dermatitis and icterus; and gastrointestinal problems that may be so severe as to cause weight loss. Peripheral neuropathy is relatively common, and disturbances in the CNS may also occur. In addition, cell-mediated immune reactions may be suppressed.

[4]See p. 358 for Infolink references to other books in this series.

D. Suramin

Suramin [SOO ra min] is used primarily in the early treatment and especially in the prophylaxis of African trypanosomiasis. It is very reactive and inhibits many enzymes, among them, those involved in energy metabolism (e.g., glycerol phosphate dehydrogenase) which appears to be the mechanism most closely correlated with trypanocidal activity. *Suramin* is also the drug of choice in treatment of patients with the adult forms of the filarial parasite, Onchocerca volvulus. The drug must be injected intravenously. It binds to plasma proteins and remains in the plasma for a long time, accumulating in the liver and in the proximal tubular cells of the kidney. The severity of the adverse reactions demands that the patient be carefully followed, especially if debilitated. Although infrequent, these reactions include nausea and vomiting (which causes further debilitation of the patient), shock and loss of consciousness, acute urticaria, and neurologic problems that include paresthesia, photophobia, palpebral edema, and hyperesthesia of the hands and feet. Albuminuria tends to be common, but when cylindruria (the presence of renal casts in the urine) and hematuria occur, treatment should cease.

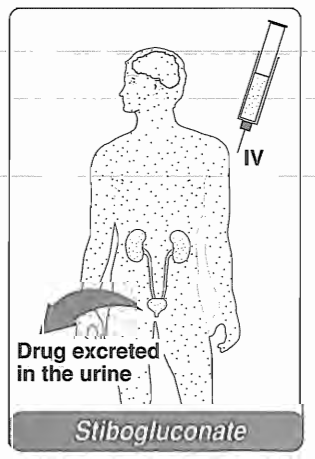
Figure 35.8
Mucocutaneous leishmaniasis.

V. CHEMOTHERAPY OF LEISHMANIASIS

There are three types of leishmaniasis: the cutaneous, mucocutaneous (Figure 35.8), and visceral. [Note: In the visceral type (liver and spleen), the parasite is in the bloodstream and can cause very serious problems.] Leishmaniasis is transmitted from animal to humans (and between humans) by the bite of infected sandflies. The treatments of leishmaniasis and trypanosomiasis (see p. 337), are difficult, because the effective drugs are limited by their toxicities and failure rates. Pentavalent antimonials, such as *sodium stibogluconate*, are the conventional therapy used in the treatment of leishmaniasis, with *pentamidine* (see p. 354) and *amphotericin B* (see p. 357) as back-up agents. *Allopurinol* (see p. 417) has also been reported to be effective. The drug is converted to a toxic metabolite by the amastigote form. The diagnosis is made by demonstrating the organism in biopsy material and skin lesions.

A. Life cycle of the causative organism, Leishmania

The sandfly transfers the flagellated promastigote form of the protozoa, which is rapidly phagocytized by macrophages. In the macrophage, the promastigotes rapidly change to nonflagellated amastigotes and multiply, killing the cell. The newly released amastigotes are again phagocytized, and the cycle continues.



B. Sodium stibogluconate

Stibogluconate [stib o GLOO koe nate] is not effective in vitro; therefore it has been proposed that reduction to the trivalent antimony compound is essential for activity. The exact mechanism of action has not been determined. Evidence for inhibition of glycolysis in the parasite at the phosphofructokinase reaction[5] has been found.

[5]See p. 358 for Infolink references to other books in this series.

Because it is not absorbed on oral administration, *sodium stibogluconate* must be administered parenterally. It is distributed in the extravascular compartment. Metabolism is minimal and the drug is excreted into the urine. Adverse effects include pain at the injection site, gastrointestinal upsets, and cardiac arrhythmias. Renal and hepatic function should be periodically monitored.

VI. CHEMOTHERAPY OF TOXOPLASMOSIS

One of the most common infections in man is caused by the protozoan, Toxoplasma gondii, which is transmitted to humans when they consume raw or inadequately cooked, infected meat. Infected pregnant women can transmit the organism to the fetus. Cats are the only animals that shed oocysts that can infect other animals as well as man. The treatment of choice for this condition is the antifolate drug, *pyrimethamine* [peer i METH a meen] (see p. 353). A combination of *sulfadiazine* (see p. 289) and *pyrimethamine* is also efficacious. *Leucovorin* is often administered to protect against folate deficiency. Other inhibitors of folate biosynthesis, such as *trimethoprim* (see p. 293) and *sulfamethoxazole* (see p. 289) are without therapeutic efficacy in toxoplasmosis. [Note: At the first appearance of a rash, *pyrimethamine* should be discontinued since hypersensitivity to this drug can be severe.]

VII. CHEMOTHERAPY OF GIARDIASIS

Giardia lamblia is the most commonly diagnosed intestinal parasite in the United States. It has only two life-cycle stages: the binucleate trophozoite with 4 flagellae, and the drug-resistant 4-nucleate cyst. Ingestion, usually from contaminated drinking water, leads to infection. The trophozoites exist in the small intestine and divide by binary fission. Occasionally, cysts are formed that pass out in the stool. Though some infections are asymptomatic, severe diarrhea can occur which can be very serious in immune-suppressed patients. The treatment is usually either *quinacrine* or *metronidazole* (see p. 347).

A. Quinacrine

Quinacrine is an acridine derivative that is primarily used in the treatment of giardiasis, but is also effective against tapeworm and malaria, and topically, against leishmaniasis. It binds to membrane phospholipids, blocking phospholipase A_2 activity. *Quinacrine* also binds to the acetylcholine receptor. Given orally, *quinacrine* concentrates in the liver. Because it crosses the placenta, it should be avoided in pregnant women. Adverse effects range from the more common dizziness, headaches, and vomiting to more serious psychosis, urticaria, exfoliative dermatitis and pigmentation of the skin. *Quinacrine* and *primaquine* should not be given together because of increased toxicity.

Questions 35.1 - 35.3: For each numbered phrase, select the ONE drug (A-E) that is most closely associated with it. Each drug (A-E) may be selected once, more than once, or not at all.

A. Sodium stibogluconate
B. Diloxanide furoate
C. Pyrimethamine
D. Emetine
E. Metronidazole

35.1 A systemic amebicide.

Correct answer = D (emetine).

35.2 Used in the treatment of toxoplasmosis.

Correct answer = C (pyrimethamine).

35.3 Used in the treatment of leishmaniasis.

Correct answer = A (sodium stibogluconate).

Choose the ONE best answer.

35.4 All of the following statements about chloroquine are true EXCEPT:

A. It blocks protozoal DNA and RNA synthesis.
B. Infected cells can concentrate the drug to a greater extent than can uninfected cells.
C. It is the drug of choice for the treatment of an acute attack of falciparum or vivax malaria.
D. Chronic administration may cause discoloration of nail beds and mucous membranes.
E. Only exoerythrocytic forms of plasmodium are susceptible.

Correct choice = E. Only the erythrocytic form of the parasite is susceptible to chloroquine.

35.5 All of the following statements about metronidazole are true EXCEPT:

A. It is administered intravenously because it is poorly absorbed after oral administration.
B. It is effective against a wide variety of anaerobic bacteria.
C. It produces a disulfiram-like effect on the ingestion of alcohol.
D. Dosage should be reduced in patients with hepatic dysfunction.
E. Therapeutic levels can be found in the cerebral spinal fluid.

Correct choice = A. Metronidazole is rapidly and nearly completely absorbed after oral administration.

35.6 All of the following statements about melarsoprol are true EXCEPT:

A. It reacts with sulfhydryl groups of various cellular substances, including enzymes.
B. It is equally effective against African and American trypanosomiasis.
C. Adequate trypanocidal concentrations of the drug appear in the cerebral spinal fluid.
D. It can cause serious encephalopathy.
E. It has a very short half-life in the body.

Correct choice = B. American trypanosomiasis, which is caused by T. cruzi, is not successfully treated with melarsoprol.

35.7 Which one of the following statements about primaquine is correct?

A. It is effective against erythrocytic forms of malaria.
B. It is ineffective in treating relapsing vivax malaria.
C. High (toxic) doses may produce corneal opacities.
D. Glucose 6-phosphate dehydrogenase deficient individuals are at risk for hemolytic anemia.
E. It is administered only by intravenous route.

Correct choice = D. See mechanism on p. 351 (Figure 35.5)

[1]See p. 398 in **Biochemistry** (2nd ed.) for a discussion of inhibitors of protein elongation.

[2]See p. 115 in **Biochemistry** (2nd ed.) for a discussion of glucose 6-phosphate dehydrogenase deficiency.

[3]See p. 250 in **Biochemistry** (2nd ed.) for a discussion of metabolic roles of tetrahydrofolate.

[4]See p. 114 in **Biochemistry** (2nd ed.) for a discussion of catalase and reactive oxygen intermediates.

[5]See p. 90 in **Biochemistry** (2nd ed.) for a discussion of phosphofructokinase reaction