Principles of Antimicrobial Therapy

OVERVIEW

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

SELECTION OF ANTIMICROBIAL AGENTS

Selection of the most appropriate antimicrobial agent requires knowing

A. The organism's identity.

B. The organism's susceptibility to a particular agent.

C. The site of the infection.

D. Patient factors.

E. The safety of the agent.

F. The cost of therapy.

- However, some patients require empiric therapy (immediate administration of drug(s) prior to bacterial identification and susceptibility testing).

A. Identification of the infecting organism

- Characterizing the organism is central to selection of the proper drug. A rapid assessment of the nature of the pathogen can sometimes be made on the basis of the **Gram stain**, which is particularly useful in identifying the presence and morphologic features of microorganisms in body fluids that are normally sterile (blood, serum, cerebrospinal fluid [CSF], pleural fluid, synovial fluid, peritoneal fluid, and urine).
- However, it is generally necessary to culture the infective organism to arrive at a conclusive diagnosis and determine the susceptibility to the organism prior to initiating treatment. Otherwise, it is impossible to differentiate whether a negative culture is due to the absence of organisms or is a result of antimicrobial effects of administered antibiotic.

Empiric therapy prior to identification of the organism

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

1. Timing: Acutely ill patients with infections of unknown origin—for example, a patient with meningitis (acute inflammation of the membranes covering the brain and spinal cord)—require immediate treatment. If

possible, therapy should be initiated after specimens for laboratory analysis have been obtained but before the results of the culture and sensitivity are available.

2. Selecting a drug: Drug choice in the absence of susceptibility data is influenced by the **site of infection** and **the patient's history** (for example, previous infections, age, recent travel history, recent antimicrobial therapy, immune status, and whether the infection was hospital- or community-acquired).

- Broad-spectrum therapy may be indicated initially when the organism is unknown.
- The choice of agent(s) may also be guided by **known association of particular organisms in a given clinical setting**. For example, gram-positive cocci in the spinal fluid of a newborn infant is **unlikely** to be Streptococcus pneumonia and most likely to be Streptococcus agalactiae (a group B streptococci), which is **sensitive to *penicillin G***. By contrast, gram-positive cocci in the spinal fluid of a 40-year-old patient are most likely to be S. pneumoniae. This organism is frequently **resistant to *penicillin G*** and often requires treatment with a high-dose third generation **cephalosporin (such as *ceftriaxone*) or *vancomycin*.**

B. Determining antimicrobial susceptibility of infective organisms

After a pathogen is cultured, its susceptibility to specific antibiotics serves as a guide in choosing antimicrobial therapy.

- Some pathogens, such as Streptococcus pyogenes and Neisseria meningitidis, usually have **predictable susceptibility** patterns to certain antibiotics. In contrast, most gram-negative bacilli, enterococci, and staphylococcal species often show **unpredictable susceptibility** patterns and require susceptibility testing to determine appropriate antimicrobial therapy.

Bacteriostatic versus bactericidal drugs:

- Antimicrobial drugs are classified as either bacteriostatic or bactericidal.
- Bacteriostatic drugs **arrest the growth and replication of bacteria at serum** (or urine) levels achievable in the patient, thus limiting the spread of infection until the immune system attacks, immobilizes, and eliminates the pathogen. If the drug is removed **before** the immune system has scavenged the organisms, enough viable organisms may remain to begin a second cycle of infection.

- Bactericidal drugs **<u>kill bacteria at drug serum levels achievable in the patient</u>**. Because of their more aggressive antimicrobial action, bactericidal agents are often the drugs of choice in seriously ill and immunocompromised patients.

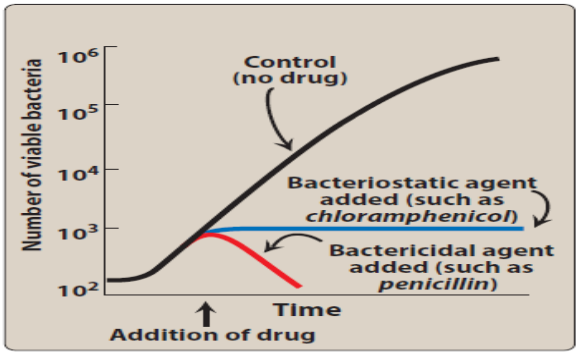


Figure 37.3
Effects of bactericidal and bacteriostatic drugs on the growth of bacteria in vitro.

Note that viable organisms remain even in the presence of the bacteriostatic drug.

- In contrast, addition of a bactericidal agent kills bacteria, and the total number of viable organism's decreases. Although practical, this classification may be too simplistic because it is possible for an antibiotic to be bacteriostatic for one organism and bactericidal for another.

Minimum inhibitory concentration: The minimum inhibitory concentration (MIC) is the lowest antimicrobial concentration that prevents visible growth of an organism after 24 hours of incubation.

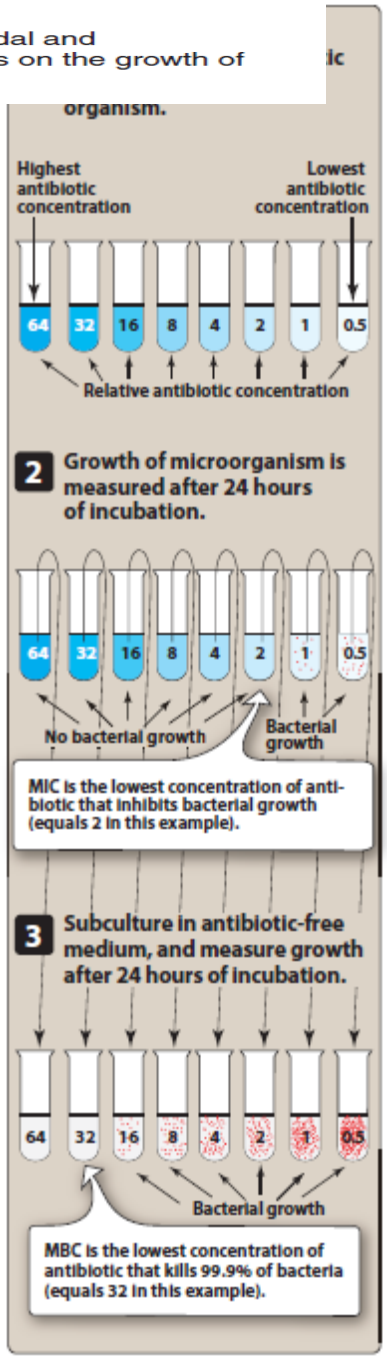


Figure 37.2
Determination of minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of an antibiotic.

Minimum bactericidal concentration: The minimum bactericidal concentration (MBC) is the lowest concentration of antimicrobial agent that results in a **99.9%** decline in colony count after overnight broth dilution incubations.

D. Effect of the site of infection on therapy:

The blood–brain barrier

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

1. **Lipid solubility of the drug:** The lipid solubility of a drug is a major determinant of its ability to penetrate into the brain.

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

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

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

E. Patient factors

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

1. **Immune system:** Elimination of infecting organisms from the body depends on an intact immune system, and the host defense system must ultimately eliminate the invading organisms.

- Alcoholism, diabetes, HIV infection, malnutrition, autoimmune diseases, pregnancy, or advanced age can affect a patient's immune-competence, as can immunosuppressive drugs.
- High doses of bactericidal agents or longer courses of treatment may be required to eliminate infective organisms in these individuals.

2. **Renal dysfunction:** Poor kidney function may cause accumulation of certain antibiotics. Dosage adjustment prevents drug accumulation and therefore adverse effects.

- Serum creatinine levels are frequently used as an index of renal function for adjustment of drug regimens. However, direct monitoring of serum levels of some antibiotics (for example, *vancomycin*, aminoglycosides) is preferred to identify maximum and/or minimum values to prevent potential toxicities.

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

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

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

6. Pregnancy and lactation: Many antibiotics cross the placental barrier or enter the nursing infant via the breast milk.

The drug examples listed in the table are not all inclusive but merely represent an example from each category. Although the concentration of an antibiotic in breast milk is usually low, the total dose to the infant may be sufficient to produce detrimental effects.

Category	Definition	Explanation
A	Generally acceptable	Controlled studies in pregnant women show no evidence of fetal risk.
B	May be acceptable	Either animal studies show no risk but human studies not available or animal showed minor risks and human studies were done and showed no risk.
C	Use with caution if benefits outweigh risks	Animal studies show risk and human studies not available or neither animal nor human studies were done.
D	Use in life-threatening emergencies when no safer drug is available	Positive evidence of human fetal risk.
X	Do not use in pregnancy	Risks involved outweigh potential benefits. Safer alternatives exist.

7. Risk factors for multidrug-resistant organisms: Infections with multidrug-resistant pathogens need broader antibiotic coverage when initiating empiric therapy. Common risk factors for infection with these pathogens include

a) prior antimicrobial therapy in the preceding 90 days

b) hospitalization for greater than 2 days within the preceding 90 days

c) current hospitalization exceeding 5 days

F. Safety of the agent

Antibiotics such as the penicillins are among the **least toxic of all drugs** because they interfere with a site or function unique to the growth of

microorganisms. Other antimicrobial agents (for example, *chloramphenicol*) have **less specificity** and are reserved for life-threatening infections because of the potential for serious toxicity to the patient.

G. Cost of therapy

Often several drugs may show similar efficacy in treating an infection but vary widely in cost. Although choice of therapy usually centers on the site of infection, severity of the illness, and ability to take oral medications, it is also important to consider the cost of the medication.

III. ROUTE OF ADMINISTRATION

-The oral route of administration is appropriate for mild infections that can be treated on an outpatient basis. In addition, economic pressures have prompted the use of oral antibiotic therapy in all but the most serious infectious diseases. In hospitalized patients requiring intravenous therapy initially, the switch to oral agents should occur as soon as possible.

- However, some antibiotics, such as *vancomycin*, the aminoglycosides, and *amphotericin B* are so poorly absorbed from the gastrointestinal (GI) tract that adequate serum levels cannot be obtained by oral administration.

-Parenteral administration is used for drugs that are poorly absorbed from the GI tract and for treatment of patients with serious infections, for whom it

is necessary to maintain higher serum concentrations of antimicrobial agents.

IV. DETERMINANTS OF RATIONAL DOSING

Rational dosing of antimicrobial agents is based on their **pharmacodynamics** (the relationship of drug concentrations to antimicrobial effects) and **pharmacokinetic properties** (the absorption, distribution, metabolism, and elimination of the drug).

-Three important properties that have a significant influence on the frequency of dosing are **concentration dependent killing**, **time-dependent killing**, and **post-antibiotic effect (PAE)**. Utilizing these properties to optimize antibiotic dosing regimens can improve clinical outcomes and possibly decrease the development of resistance.

A. Concentration-dependent killing

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

B. Time-dependent (concentration-independent) killing

In contrast, β-lactams, *clindamycin*, and *linezolid* do not exhibit concentration-dependent killing. The clinical efficacy of these antimicrobials is best predicted by the percentage of time that blood concentrations of a drug remain above the MIC. This effect is sometimes called concentration-independent or time-dependent killing.

-For example, dosing schedules for the penicillin's and cephalosporin's that ensure blood levels greater than the MIC for 50% and 60% of the time, respectively, provide the most clinical efficacy. Therefore, extended (generally 3 to 4 hours) or continuous (24 hours) infusions can be utilized instead of intermittent dosing (generally 30 minutes) to achieve prolonged time above the MIC and kill more bacteria.

C. Post-antibiotic effect

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

V. CHEMOTHERAPEUTIC SPECTRA

A. Narrow-spectrum antibiotics

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

B. Extended-spectrum antibiotics

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

C. Broad-spectrum antibiotics

-Drugs such as tetracycline, fluoroquinolones and carbapenems affect a wide variety of microbial species and are referred to as broad-spectrum antibiotics. -Administration of broad spectrum antibiotics can drastically alter the nature of the normal bacterial flora and precipitate a super-infection due to organisms

VI. COMBINATIONS OF ANTIMICROBIAL DRUGS

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

A. Advantages of drug combinations

Certain combinations of antibiotics, such as β-lactams and aminoglycosides, show synergism; that is, the combination is more effective than either of the drugs used separately. Because such synergism among antimicrobial agents is rare, multiple drugs used in combination are only indicated in special situations.

B. Disadvantages of drug combinations

A number of antibiotics act only when organisms are multiplying. Thus, co-administration of an agent that causes bacteriostatic plus a second agent that is bactericidal may result in the first drug interfering with the action of the second.

-For example, bacteriostatic tetracycline drugs may interfere with the bactericidal effects of penicillins and cephalosporins.

-Another concern is the risk of selection pressure and the development of antibiotic resistance by giving unnecessary combination therapy.

VII. DRUG RESISTANCE

Bacteria are considered resistant to an antibiotic if the maximal level of that antibiotic that can be tolerated by the host does not halt their growth.

A. Genetic alterations leading to drug resistance

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

B. Altered expression of proteins in drug-resistant organisms

Drug resistance is mediated by a variety of mechanisms, such as

1. an alteration in an antibiotic target site
2. lowered penetrability of the drug due to decreased permeability
3. increased efflux of the drug
4. Presence of antibiotic-inactivating enzymes.

1. Modification of target sites: Alteration of an antibiotic's target site through mutation can confer resistance to one or more related antibiotics.

2. Decreased accumulation: Decreased uptake or increased efflux of an antibiotic can confer resistance because the drug is unable to attain access to

the site of its action in sufficient concentrations to injure or kill the organism.

3. Enzymatic inactivation: The ability to destroy or inactivate the antimicrobial agent can also confer resistance on microorganisms. Examples of antibiotic-inactivating enzymes include

1) β-lactamases (penicillinase) that hydrolytically inactivate the β-lactam ring of penicillin, cephalosporin, and related drugs.

2) acetyl-transferees that transfer an acetyl group to the antibiotic, inactivating chloramphenicol or aminoglycosides.

3) Esterase that hydrolyze the lactone ring of macrolides.

VIII. PROPHYLACTIC USE OF ANTIBIOTICS

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

IX. Complications of Antibiotic Therapy

A. Hypersensitivity

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

B. Direct toxicity

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

C. Super-infections

Drug therapy, particularly with broad-spectrum antimicrobials or combinations of agents, can lead to alterations of the normal microbial flora of the upper respiratory, oral, intestinal, and genitourinary tracts, permitting the overgrowth of opportunistic organisms, especially fungi or resistant bacteria.

X. SITES OF ANTIMICROBIAL ACTIONS

Antimicrobial drugs can be classified in a number of ways:

1) By their chemical structure (for example, β-lactams or aminoglycosides),

2) By their mechanism of action (for example, cell wall synthesis inhibitors),

3) By their activity against particular types of organisms (for example, bacteria, fungi, or viruses).

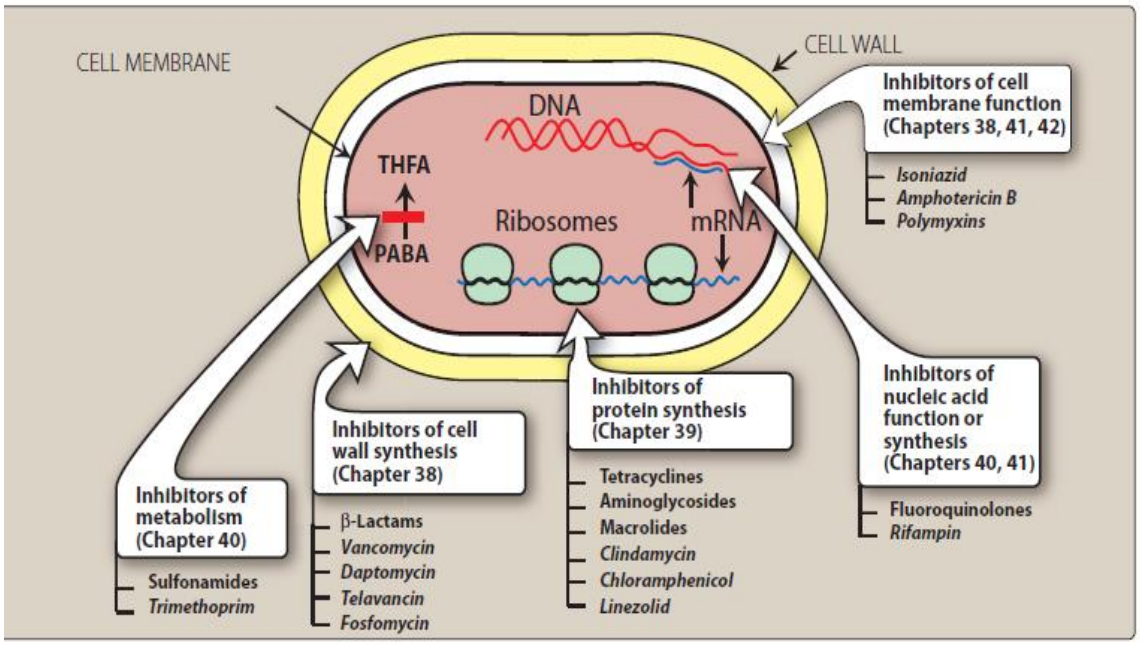
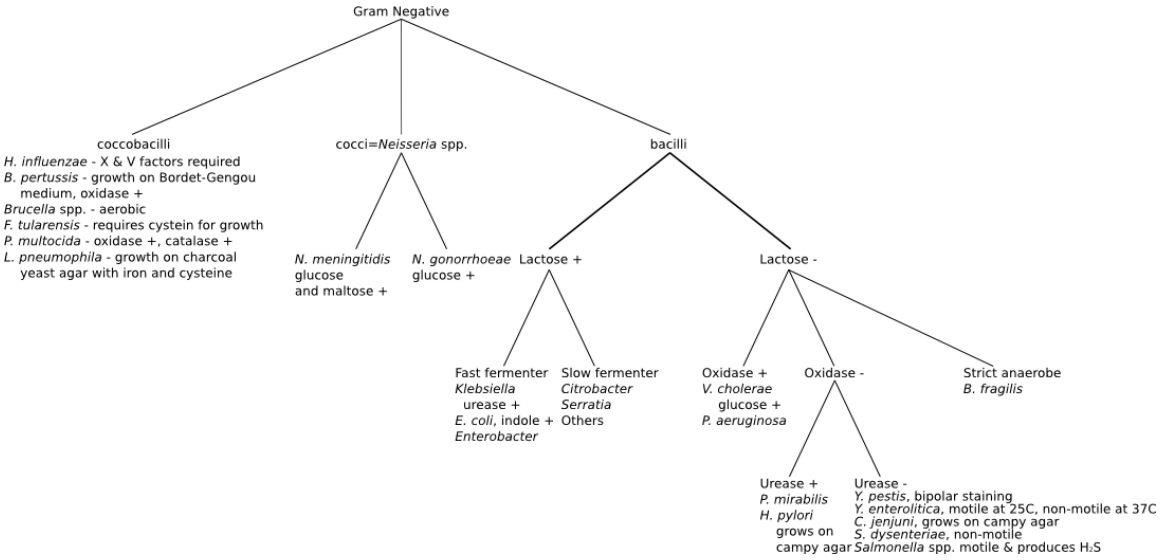
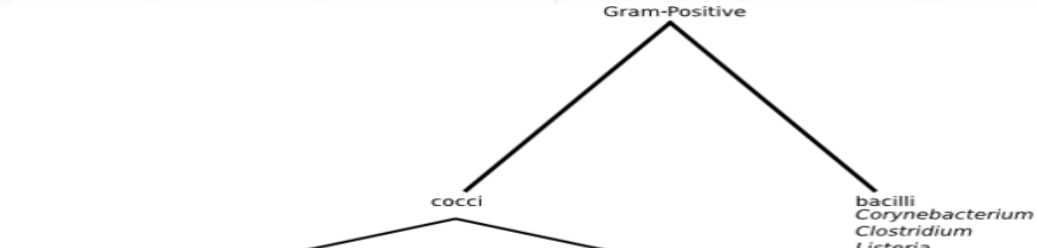


Figure 37.10
Classification of some antimicrobial agents by their sites of action. (THFA = tetrahydrofolic acid; PABA = *p*-aminobenzoic acid.)

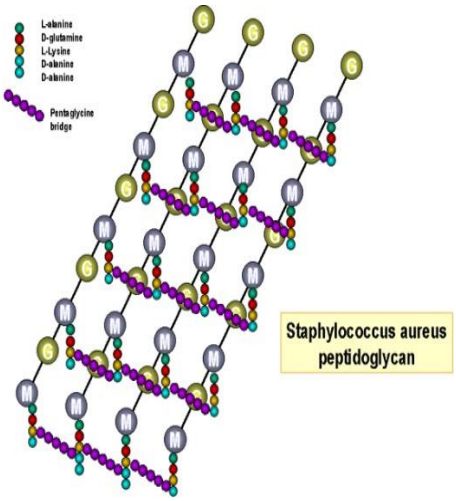


Gram-Positive			Gram-negative		
Bacteria	**Commonly found in**	**Common treatment**	**Bacteria**	**Commonly found in**	**Common treatment**
Staphylococci & streptococci	Skin and wound infections	**Vancomycin, Teicoplanin, Gentamicin (staphylococci only).** Resistant to: Cephalosporins, metronidazole **(except clostridia)**	**The Coliform bacteria;** *E. Coli, Klebsiella, enterobacter, salmonella*	The Gut! UTI, also can cause ventilator assisted pneumonia, wound infection, biliary tract infection, septicaemia	Cephalosporins, gentamicin, ciprofloxacin, tazocin, imipenem, trimethoprim Resistant to: amoxicillin,
Staph, Enterococci, corynebacteria	Line related infection		Pseudomonas	Moist environments – **chronic leg ulcers.** Catheters, pneumonia, septicaemia, CF/bronchiectasis	Aminoglycosides, cipro, tazocin, imipenem Resistant to: Most other AB's
Clostridia	Gangrenous wound infections, **abdominal infections**		**Bacteroids** – anaerobic bacteria	Intra-abdominal infections, soft tissue infection below the waist	Metronidazole, co-amoxiclav, imipenem, Tazocin, clindamycin Resistant to: Benzylpenicillin, amoxicillin, cefuroxime, gentamicin, quinolones, macrolides



Cell Wall Inhibitors

Overview



- Some antimicrobial drugs selectively interfere with synthesis of the bacterial cell wall—a structure that mammalian cells do not possess.
- The cell wall is composed of a polymer called peptidoglycan that consists of glycan units joined to each other by peptide cross-links.

PENICILLINS

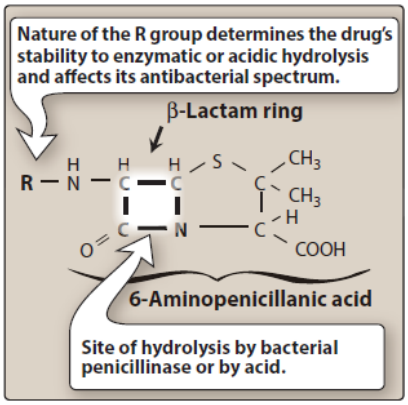


Figure 38.2
Structure of β-lactam antibiotics.

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

A. Mechanism of action

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

1. Penicillin-binding proteins(PBP):

- Penicillin also inactivate numerous proteins on the bacterial cell membrane. These penicillin-binding proteins (PBPs) are bacterial enzymes involved in the synthesis of the cell wall and in the maintenance of the morphologic features of the bacterium.
- Exposure to these antibiotics can therefore **not only prevent cell wall synthesis but also lead to morphologic changes or lysis of susceptible bacteria**.

- The number of PBPs varies with the type of organism.

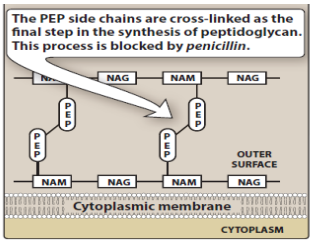


Figure 38.3
Bacterial cell wall of gram-positive bacteria. (NAM = *N*-acetylmuramic acid; NAG = *N*-acetylglucosamine; PEP = cross-linking peptide.)

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 cross-links essential for cell wall integrity.

3. **Production of autolysins:** Many bacteria, particularly the gram positive cocci, produce degradative enzymes (autolysins) that participate in the normal remodeling of the bacterial cell wall.

- In the presence of a penicillin, the degradative action of the autolysins proceeds in the absence of cell wall synthesis. Thus, the antibacterial effect of a penicillin is the result of both inhibition of cell wall synthesis and destruction of the existing cell wall by autolysins.

B. Antibacterial spectrum

- The antibacterial spectrum of the various penicillin is determined, in part, by their ability to cross the bacterial peptidoglycan cell wall to reach the PBPs in the periplasmic space.
- Factors that determine the susceptibility of PBPs to these antibiotics include the size, charge, and hydrophobicity of the particular β-lactam antibiotic.

- In general, gram-positive microorganisms have cell walls that are easily traversed by penicillin, and, therefore, in the absence of resistance, they are susceptible to these drugs.
- Gram-negative microorganisms have an outer lipopolysaccharide membrane surrounding the cell wall that presents a barrier to the water-soluble penicillin.
- However, gram-negative bacteria have proteins inserted in the lipopolysaccharide layer that act as water-filled channels (called porins) to permit transmembrane entry.

1. Natural penicillins:

- Natural penicillins (*penicillin G* and *penicillin V*) are obtained from fermentations of the fungus *Penicilliu chrysogenum*.
- Semisynthetic penicillins, such as *amoxicillin* and *ampicillin*
- *Penicillin* G (*benzyl-penicillin*) is the ***cornerstone*** of therapy for infections caused by a number of gram positive and gram-negative Bactria
- Penicillin are susceptible to inactivation by β-lactamases (penicillinases) that are produced by the resistant bacteria.
- Despite widespread use and increase in resistance to many types of bacteria, *penicillin* remains the *drug of choice* for the treatment of gas gangrene and syphilis .

- *Penicillin V* has a similar spectrum to that of *penicillin G*, but it is not used for treatment of bacteremia because of its poor oral absorption. *Penicillin V* is more acid stable than *penicillin G* and is often employed orally in the treatment of infections.

2. Anti-staphylococcal penicillin:

- *Methicillin* , *nafcillin* , *oxacillin* , and *dicloxacillin* are β-lactamase (penicillinase)-resistant penicillins.
- Their use is restricted to the treatment of infections caused by penicillinase-producing staphylococci, including *methicillin* sensitive Staphylococcus aureus (MSSA).
- Because of its toxicity (interstitial nephritis), *methicillin* is not used clinically in the United States except in laboratory tests to identify resistant strains of S. aureus.

3. Extended-spectrum penicillin:

Ampicillin and *amoxicillin* have an antibacterial spectrum similar to that of *penicillin G* but are more effective against gram negative bacilli.

- These extended-spectrum agents are also widely used in the treatment of respiratory infections, and *amoxicillin* is employed prophylactically by dentists in high-risk patients for the prevention of bacterial endocarditis.

- Resistance to these antibiotics is now a major clinical problem because of inactivation by plasmid-mediated penicillinases.
- Formulation with a β-lactamase inhibitor, such as *clavulanic acid* or *sulbactam,* protects *amoxicillin* or *ampicillin,* respectively, from enzymatic hydrolysis and extends their antimicrobial spectra. For example, without the β-lactamase inhibitor, MSSA is resistant to *ampicillin* and *amoxicillin.*

4. Antipseudomonal penicillins:

- *Piperacillin* and *ticarcillin* are called antipseudomonal penicillins because of their activity against Pseudomonas aeruginosa .
- These agents are available in <u>parenteral formulations only</u>.
- *Piperacillin* is the most potent of these antibiotics.
- Formulation of *ticarcillin* or *piperacillin* with *clavulanic acid* or *tazobactam*, respectively, extends the antimicrobial spectrum of these antibiotics to include penicillinase-producing organisms

C. Resistance

- **<u>Natural resistance to</u>** the penicillins occurs in organisms that either
    1. lack a peptidoglycan cell wall (for example, Mycoplasma pneumoniae)
    2. Have cell walls that are impermeable to the drugs.

- **<u>Acquired resistance</u>** to the penicillin by plasmid-mediated β-lactamases has become a significant clinical problem.

1. **B-Lactamase activity:** This family of enzymes hydrolyzes the cyclic amide bond of the β-lactam ring, which results in loss of bactericidal activity . They are the major cause of resistance to the penicillins and are an increasing problem.

- B-Lactamases either are **<u>constitutive</u>**, mostly produced by the bacterial chromosome or, are **<u>acquired</u>** by the transfer of plasmids.
- Some of the β-lactam antibiotics are poor substrates for β-lactamases and resist hydrolysis, thus retaining their activity against β-lactamase–producing organisms.

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

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

Adverse reactions

Penicillin are among the safest drugs, and blood levels are not monitored. However, adverse reactions may occur.

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

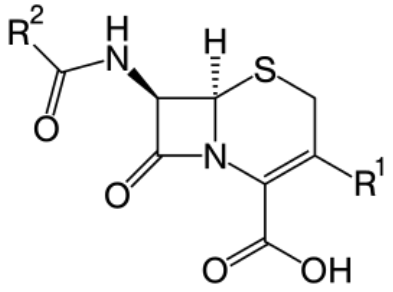
2. Diarrhea: Diarrhea is a common problem that is caused by a disruption of the normal balance of intestinal microorganisms. It occurs to a greater extent with those agents that are incompletely absorbed and have an extended antibacterial spectrum.

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

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

5. Hematologic toxicities: Decreased coagulation may be observed with high doses of *piperacillin*, *ticarcillin*, and *nafcillin* (and, to some extent, with *penicillin G*).

CEPHALOSPORINS



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

A. Antibacterial spectrum

Cephalosporin have been classified as first, second, third, fourth, and advanced generation, based largely on their bacterial susceptibility patterns and resistance to β-lactamases.

1. First generation: The first-generation cephalosporin act as *penicillin G* substitutes. They are resistant to the staphylococcal penicillinase (that is, they cover MSSA).

2. Second generation: The second-generation cephalosporin display greater activity against gram-negative organisms, whereas activity against gram-positive organisms is weaker. Ex.(*cefotetan* and *cefoxitin*)

3. Third generation: These cephalosporins have assumed an important role in the treatment of infectious diseases. Although they are less potent than first-generation cephalosporins against MSSA, the third-generation cephalosporins have enhanced activity against gram-negative bacilli, as well as most other enteric organisms.

- *Ceftriaxone* and *cefotaxime* have become agents of choice in the treatment of meningitis.
- *Ceftazidime* has activity against P. aeruginosa; however, resistance is increasing and use should be evaluated on a case-by-case basis.
- Third-generation cephalosporins must be used with caution, as they are associated with significant **"collateral damage,"** essentially meaning the induction and spread of antimicrobial resistance.

4-Fourth generation: *Cefepime* is classified as a fourth-generation cephalosporin and must be administered parenterally.

- *Cefepime* has a wide antibacterial spectrum, with activity against streptococci and staphylococci (but only those that are *methicillin* susceptible).

5. **Advanced generation:** *Ceftaroline* is a broad spectrum, advanced-generation cephalosporin that is administered IV as a prodrug, *ceftaroline fosamil*.

- It is the only commercially available β-lactam in the United States with activity against MRSA and is indicated for the treatment of complicated skin and skin structure infections and community-acquired pneumonia.
- In addition to its broad gram-positive activity, it also has similar gram negative activity to the third-generation cephalosporin *ceftriaxone*.

CEPHALOSPORIN			
1st GEN	2nd GEN	3rd GEN	4TH GEN
Cephalothin, Cephapirin, Cefazolin, Cephalexin, Cephradine	Cefamandol, Cefuroxime, Cefonicid, Ceforanide, Cefoxitin	Cefotaxime, Ceftriaxone, Cefoperazone, Ceftazidime, Cefixime	Cefepime, Cefpirome
Good against G +, moderate against G-	Good against G-, moderate against G+	More potent against G-, weak against G+	More potent against G-, extended activity against G+

OTHER β-LACTAM ANTIBIOTICS

A. Carbapenems

Carbapenems are synthetic β-lactam antibiotics that differ in structure from the penicillins in that the sulfur atom of the thiazolidine ring has been externalized and replaced by a carbon atom.

- *Imipenem* , *meropenem* , *doripenem* , and *ertapenem* are the drugs of this group currently available.

B. Monobactams

- The monobactams, which also disrupt bacterial cell wall synthesis, are unique because the β-lactam ring is not fused to another ring.
- *Aztreonam*, which is the only commercially available monobactam, has antimicrobial activity directed primarily against gram-negative pathogens. It lacks activity against gram positive organisms and anaerobes.
- *Aztreonam* is resistant to the action of most β-lactamases.
- *Aztreonam* is relatively *nontoxic*, but it may cause phlebitis, skin rash and, occasionally, abnormal liver function tests. This drug has a low immunogenic potential, and it shows little cross-reactivity with antibodies induced by other β-lactams. Thus, this drug may offer a safe alternative for treating patients who are allergic to other penicillins, cephalosporins, or carbapenems.

V. β-Lactamase inhibitors

- Hydrolysis of the β-lactam ring, either by enzymatic cleavage with a β-lactamase or by acid, destroys the antimicrobial activity of a β-lactam antibiotic.
- B-Lactamase inhibitors, such as *clavulanic* acid, *sulbactam* , and *tazobactam* , contain a β-lactam ring but, by themselves, do not have significant antibacterial activity or cause any significant adverse effects.

- Instead, they bind to and inactivate β-lactamases, thereby protecting the antibiotics that are normally substrates for these enzymes.
- The β-lactamase inhibitors are therefore formulated in combination with β-lactamase–sensitive antibiotics.

- **VANCOMYCIN**
- *Vancomycin* is a tricyclic glycopeptide that has become increasingly important in the treatment of life-threatening MRSA and *methicillin*-resistant Staphylococcus epidermidis (MRSE) infections, as well as enterococcal infections.
- The use of *vancomycin* to the treatment of serious infections caused by β-lactam resistant, gram-positive microorganisms or gram-positive infections in patients who have a serious allergy to the β-lactams.

- **POLYMYXINS**
- The polymyxins are cation polypeptides that bind to phospholipids on the bacterial cell membrane of gram-negative bacteria.
- They have a detergent-like effect that disrupts cell membrane integrity, leading to leakage of cellular components and ultimately cell death.
- Polymyxins are concentration-dependent bactericidal agents with activity against most clinically important gram-negative bacteria.
- Only two forms of polymyxin are in clinical use today, *polymyxin B* and *colistin* (*polymyxin E*).
- *Polymyxin B* is available in parenteral, ophthalmic, otic, and topical preparations.
- *Colistin* is only available as a prodrug, *colistimethate sodium*, which is administered IV or inhaled via a nebulizer.

- The use of these drugs has been limited for a long time, due to the increased risk of **nephrotoxicity and neurotoxicity** (for example, slurred speech, muscle weakness) when used systemically.

Protein Synthesis Inhibitors

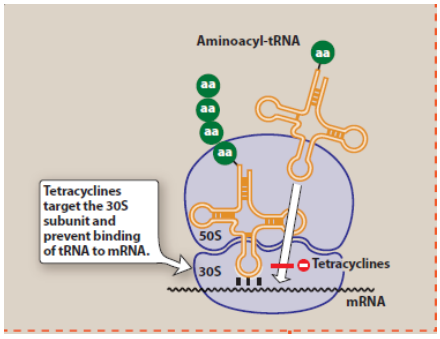
Overview

- A number of antibiotics exert their antimicrobial effects by targeting bacterial
  ribosomes and inhibiting bacterial protein synthesis.
- Bacterial ribosomes differ structurally from mammalian cytoplasmic ribosomes and are composed of 30S and 50S subunits (mammalian ribosomes have 40S and 60S subunits).
- In general, selectivity for bacterial ribosomes minimizes potential adverse consequences encountered with the disruption of protein synthesis in mammalian host cells.
- However, high concentrations of drugs such as chloramphenicol or the tetracyclines may cause toxic effects as a result of interaction with mitochondrial mammalian ribosomes, since the structure of mitochondrial ribosomes more closely resembles bacterial ribosomes.

Tetracyclines

Tetracyclines consist of four fused rings with a system of conjugated double bonds. Substitutions on these rings alter the individual pharmacokinetics and spectrum of antimicrobial activity.

A. Mechanism of action



- Tetracyclines enter susceptible organisms via **passive diffusion** and also by an **energy-dependent transport protein mechanism** unique to the bacterial inner cytoplasmic membrane.
- Tetracyclines concentrate intracellularly in susceptible organisms. The drugs bind **reversibly to the 30S** subunit of the bacterial ribosome.
- This action prevents binding of tRNA to the mRNA–ribosome complex, thereby inhibiting bacterial protein synthesis.

B. Antibacterial spectrum

The tetracyclines **are bacteriostatic antibiotics** effective against a wide variety of organisms, including gram-positive and gram-negative bacteria, protozoa, spirochetes, mycobacteria, and atypical species.

C. Resistance

- The most commonly encountered naturally occurring resistance to tetracyclines is an efflux pump that expels drug out of the cell, thus preventing intracellular accumulation.
- Other mechanisms of bacterial resistance to tetracyclines include enzymatic inactivation of the drug and production of bacterial proteins that prevent tetracyclines from binding to the ribosome. Resistance to one tetracycline does not confer universal resistance to all tetracyclines.

D. Pharmacokinetics

Absorption: Administration with dairy products or other substances that contain divalent and trivalent cations (for example, magnesium and aluminum antacids or iron supplements) decreases absorption, particularly for *tetracycline,* due to the formation of nonabsorbable chelates.

E. Adverse effects

1. Gastric discomfort: Epigastric distress commonly results from irritation of the gastric mucosa and is often responsible for noncompliance with tetracyclines. Esophagitis may be minimized through co-administration with food (other than dairy products) or fluids and the use of capsules rather than tablets. [Note: *Tetracycline* should be taken on an empty stomach.]

2. Effects on calcified tissues: Deposition in the bone and primary dentition occurs during the calcification process in growing children. This may cause discoloration and hypoplasia of teeth and a temporary stunting of growth. The use of tetracyclines is limited in pediatrics.

3. Hepatotoxicity: Rarely hepatotoxicity may occur with high doses, particularly in pregnant women and those with preexisting hepatic dysfunction or renal impairment.

4. Phototoxicity: Severe sunburn may occur in patients receiving a tetracycline who are exposed to sun or ultraviolet rays. This toxicity is encountered with any tetracycline, but more frequently with *tetracycline.* Patients should be advised to wear adequate sun protection.

5. Vestibular dysfunction: Dizziness, vertigo, and tinnitus may occur particularly with minocycline, which concentrates in the endolymph of the ear and affects function. Doxycycline may also cause vestibular dysfunction.

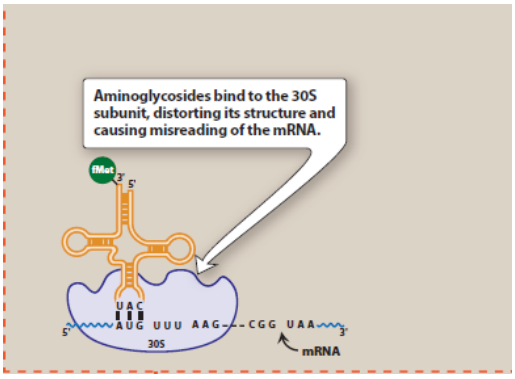
6. Pseudotumor cerebri: Benign, intracranial hypertension characterized by headache and blurred vision may occur rarely in adults. Although discontinuation of the drug reverses this condition, it is not clear whether permanent sequelae may occur.

7. Contraindications: The tetracyclines should not be used in pregnant or breast-feeding women or in children less than 8 years of age.

Aminoglycosides

- Aminoglycosides are used for the treatment of serious infections due to aerobic gram-negative bacilli. However, their clinical utility is limited by serious toxicities. The term "aminoglycoside" stems from their structure two amino sugars joined by a glycosidic linkage to a central hexose nucleus.
- Aminoglycosides are derived from either Streptomyces sp. (have *–mycin* suffixes) or Micromonospora sp. (end in *-micin*).

A. Mechanism of action



- Aminoglycosides diffuse through porin channels in the outer membrane of susceptible organisms.
- These organisms also have an oxygen-dependent system that transports the drug across the cytoplasmic membrane.
- Inside the cell, they *bind the 30S ribosomal* subunit, where they interfere with assembly of the functional ribosomal apparatus and/or cause the 30S subunit of the completed ribosome to misread the genetic code.
- **Antibiotics that disrupt protein synthesis are generally bacteriostatic; however, aminoglycosides are unique in that they are bactericidal**.
- The bactericidal effect of aminoglycosides is *concentration dependent*; that is, efficacy is dependent on the maximum concentration (Cmax) of drug above the minimum inhibitory concentration (MIC) of the organism.
- For aminoglycosides, the target Cmax is eight to ten times the MIC.
- They also exhibit a *postantibiotic effect (PAE),* which is continued bacterial suppression after drug levels fall below the MIC.
- The larger the dose, the longer the PAE. Because of these properties, extended interval dosing (a single large dose given once daily) is now more

commonly utilized than divided daily doses. This reduces the risk of nephrotoxicity and increases convenience.

B. Antibacterial spectrum

The aminoglycosides are effective for the majority of aerobic gram negative bacilli, including those that may be multidrug resistant, Additionally, aminoglycosides are often combined with a β-lactam antibiotic to employ a synergistic effect,

C. Resistance

Resistance to aminoglycosides occurs via:

1) Efflux pumps,

2) Decreased uptake,

3) Modification and inactivation by plasmid-associated synthesis of enzymes.

- Each of these enzymes has its own aminoglycoside specificity; therefore, cross-resistance cannot be presumed. [Note: *Amikacin* is less vulnerable to these enzymes than other antibiotics in this group.

E. Adverse effects

Therapeutic drug monitoring of *gentamicin*, *tobramycin*, and *amikacin* plasma levels is imperative to ensure adequacy of dosing and to minimize dose-related toxicities. The elderly are particularly susceptible to nephrotoxicity and ototoxicity.

1. Ototoxicity: Ototoxicity (vestibular and auditory) is directly related to high peak plasma levels and the duration of treatment. The antibiotic accumulates in the endolymph and perilymph of the inner ear. Deafness may be irreversible and has been known to affect developing fetuses. Patients simultaneously receiving concomitant ototoxic drugs, such as *cisplatin* or loop diuretics, are particularly at risk. Vertigo (especially in patients receiving *streptomycin*) may also occur.

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

3. Neuromuscular paralysis: This adverse effect is associated with a rapid increase in concentrations (for example, high doses infused over a short period.) or concurrent administration with neuromuscular blockers. Patients

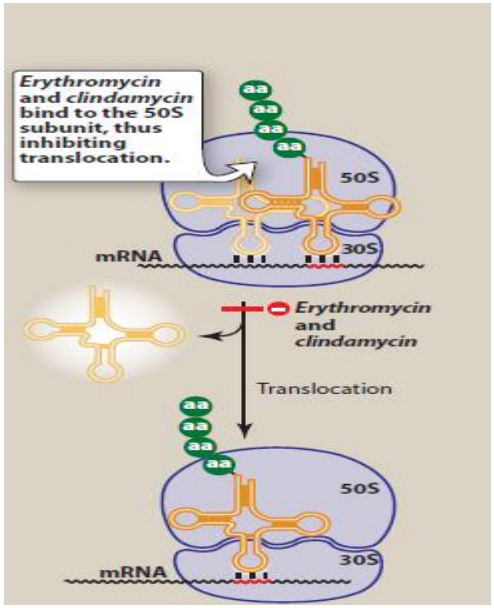
with myasthenia gravis are particularly at risk. Prompt administration of *calcium gluconate* or *neostigmine* can reverse the block that causes neuromuscular paralysis.

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

Macrolides and Ketolides

- The macrolides are a group of antibiotics with a macrocyclic lactone structure to which one or more deoxy sugars are attached.
- Erythromycin was the first of these drugs to find clinical application, both as a drug of first choice and as an alternative to penicillin in individuals with an allergy to β-lactam antibiotics.
- Clarithromycin (a methylated form of erythromycin) and azithromycin (having a larger lactone ring) have some features in common with, and others that improve upon, erythromycin.
- Ketolides and macrolides have similar antimicrobial coverage. However, the ketolides are active against many macrolide-resistant gram-positive strains.

A. Mechanism of action



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

B. Antibacterial spectrum

1. Erythromycin: This drug is effective against many of the same organisms as *penicillin G* . Therefore, it may be used in patients with *penicillin* allergy.

2. Clarithromycin: *Clarithromycin* has activity similar to *erythromycin*, but it is also effective against Haemophilus influenzae. Its activity against

intracellular pathogens, such as Helicobacter pylori, is higher than that of *erythromycin.*

3. Azithromycin: Although less active against streptococci and staphylococci than *erythromycin, azithromycin* is far more active against respiratory infections.

C. Resistance

Resistance to macrolides is associated with:

1) The inability of the organism to take up the antibiotic,

2) The presence of efflux pumps,

3) decreased affinity of the 50S ribosomal subunit for the antibiotic, resulting from the methylation of an adenine in the 23S bacterial ribosomal RNA in gram-positive organisms,

4) The presence of plasmid associated *erythromycin* esterases in gram-negative organisms such as Enterobacteriaceae.

- Resistance to *erythromycin* has been increasing, thereby limiting its clinical use (particularly for S. pneumoniae). Both *clarithromycin* and *azithromycin* share some cross-resistance with *erythromycin,*

E. Adverse effects

1. Gastric distress and motility: Gastric upset is the most common adverse effect of the macrolides and may lead to poor patient compliance (especially with *erythromycin*). *Clarithromycin* and *azithromycin* seem to be better tolerated. Higher doses of *erythromycin* lead to smooth muscle contractions that result in the movement of gastric contents to the duodenum, an adverse effect sometimes *used therapeutically for the treatment of gastroparesis or postoperative ileus*.

2. Cholestatic jaundice: This side effect occurs especially with the estolate form (not used in the United States) of *erythromycin*; however, it has been reported with other formulations.

3. Ototoxicity: Transient deafness has been associated with *erythromycin*, especially at high dosages. *Azithromycin* has also been associated with irreversible sensorineural hearing loss.

4. Contraindications: Patients with hepatic dysfunction should be treated cautiously with *erythromycin,* or *azithromycin,* because these drugs accumulate in the liver. Additionally, macrolides and ketolides may prolong

the QTc interval and should be used with caution in those patients with proarrhythmic conditions or concomitant use of proarrhythmic agents.

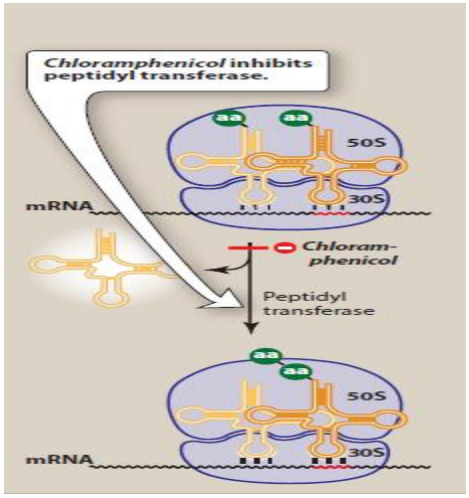
5. Drug interactions: *Erythromycin*, and *clarithromycin* inhibit the hepatic metabolism of a number of drugs, which can lead to toxic accumulation of these compounds. An interaction with *digoxin* may occur. In this case, the antibiotic eliminates a species of intestinal flora that ordinarily inactivates *digoxin*, thus leading to greater reabsorption of the drug from the enterohepatic circulation.

Chloramphenicol

The use of *chloramphenicol* , a broad-spectrum antibiotic, is restricted to life-threatening infections for which no alternatives exist.

A. Mechanism of action

Chloramphenicol binds reversibly to the bacterial 50S ribosomal subunit and inhibits protein synthesis at the peptidyl transferase reaction.



- Due to some similarity of mammalian mitochondrial ribosomes to those of bacteria, protein and ATP synthesis in these organelles may be inhibited at high circulating *chloramphenicol* levels, producing bone marrow toxicity.
- [Note: The oral formulation of *chloramphenicol* was removed from the US market due to this toxicity.]

B. Antibacterial spectrum

Chloramphenicol is active against many types of microorganisms including chlamydiae, rickettsiae. The drug is primarily bacteriostatic, but depending on the dose and organism, it may be bactericidal.

C. Resistance

Resistance is conferred by the presence of enzymes that inactivate *chloramphenicol.* Other mechanisms include decreased ability to penetrate the organism and ribosomal binding site alterations.

E. Adverse effects

1. Anemia: Patients may experience dose-related anemia, hemolytic anemia (seen in patients with glucose-6-phosphate dehydrogenase deficiency), and aplastic anemia. [Note: Aplastic anemia is independent of dose and may occur after therapy has ceased.]

2. Gray baby syndrome: Neonates have a low capacity to glucuronidate the antibiotic, and they have underdeveloped renal function. Therefore, neonates have a decreased ability to excrete the drug, which accumulates to levels that interfere with the function of mitochondrial ribosomes. This leads to poor feeding, depressed breathing, cardiovascular collapse, cyanosis (hence the term "gray baby"), and death. Adults who have received very high doses of the drug can also exhibit this toxicity.

3. Drug interactions: *Chloramphenicol* inhibits some of the hepatic mixed-function oxidases and, thus, blocks the metabolism of drugs such as *warfarin* and *phenytoin*, thereby elevating their concentrations and potentiating their effects.

CLINDAMYCIN

- *Clindamycin* has a mechanism of action that is the same as that of *erythromycin.*
- *Clindamycin* is used primarily in the treatment of infections caused by gram-positive organisms, including MRSA and streptococcus, and anaerobic bacteria.
- Resistance mechanisms are the same as those for *erythromycin*, and cross-resistance has been described.
- *Clindamycin* is available in both IV and oral formulations, but use of the oral form is limited by gastrointestinal intolerance.
- It distributes well into all body fluids including bone, but exhibits poor entry into the CSF.
- *Clindamycin* undergoes extensive oxidative metabolism to inactive products and is primarily excreted into the bile. Low urinary elimination limits its clinical utility for urinary tract infections. Accumulation has been reported in patients with either severe renal impairment or hepatic failure.
- In addition to skin rashes, the most common adverse effect is diarrhea, which may represent a serious pseudomembranous colitis caused by overgrowth of C. difficile.

- Oral administration of either *metronidazole* or *vancomycin* is usually effective in the treatment of C. difficile.

Quinolones and Urinary Tract Antiseptics

Fluoroquinolones

- ***Nalidixic acid*** is the predecessor to all fluoroquinolones, a class of man-made antibiotics. Over 10,000 fluoroquinolone analogs have been synthesized, including several with wide clinical applications.
- Fluoroquinolones in use today typically offer greater efficacy, a broader spectrum of antimicrobial activity, and a better safety profile than their predecessors.
- Unfortunately, fluoroquinolone use has been closely tied to Clostridium difficile infection and the spread of antimicrobial resistance in many organisms (for example, *methicillin* resistance in staphylococci).
- The unfavorable effects of fluoroquinolones on the induction and spread of antimicrobial resistance are sometimes referred to as "**collateral damage**," a term which is also associated with third-generation cephalosporins (for example, *ceftazidime*).

A. Mechanism of action

- Fluoroquinolones enter bacteria through porin channels and exhibit antimicrobial effects on **DNA gyrase (bacterial topoisomerase II) and bacterial topoisomerase IV.**

- Inhibition of DNA gyrase results in relaxation of supercoiled DNA, promoting DNA strand breakage.
- Inhibition of topoisomerase IV impacts chromosomal stabilization during cell division, thus interfering with the separation of newly replicated DNA.
- In gram-negative organisms, the inhibition of DNA gyrase is more significant than that of topoisomerase IV, whereas in gram-positive organisms, the opposite is true.
- Agents with higher affinity for topoisomerase IV (for example, *ciprofloxacin*) should not be used for S. pneumoniae infections, while those with more topoisomerase II activity (for example, *moxifloxacin*) should not be used for P. aeruginosa infections.

B. Antimicrobial spectrum

- Fluoroquinolones are bactericidal and exhibit area under the curve/minimum inhibitory concentration (AUC/MIC)–dependent killing.
- Bactericidal activity is more pronounced as serum drug concentrations increase to approximately 30-fold the MIC of the bacteria.
- In general, fluoroquinolones are effective against gram-negative organisms, gram-positive organisms, and some mycobacteria (Mycobacterium tuberculosis).

- Fluoroquinolones are typically not used for the treatment of Staphylococcus aureus or enterococcal infections. They are not effective against syphilis and have limited utility against Neisseria gonorrhoeae due to disseminated resistance worldwide
- ***Levofloxacin*** **and** ***moxifloxacin*** are sometimes referred to as "respiratory fluoroquinolones," because they have excellent activity against S. pneumoniae, which is a common cause of community-acquired pneumonia (CAP).
- Fluoroquinolones are commonly considered alternatives for patients with a documented severe β-lactam allergy.
- Fluoroquinolones may be classified into "generations" based on their antimicrobial targets.

1. The nonfluorinated quinolone *nalidixic acid* is considered to be first generation, with a narrow spectrum of susceptible organisms.
2. *Ciprofloxacin* and *norfloxacin* are second generation because of their activity against aerobic gram-negative and atypical bacteria.In addition, these fluoroquinolones exhibit significant intracellular penetration, allowing therapy for infections in which a bacterium spends part or all of its life cycle inside a host cell (for example, chlamydia, mycoplasma, and mycobacteria).

3. *Levofloxacin* is classified as third generation because of its increased activity against gram-positive bacteria
4. Lastly, the fourth generation includes only *moxifloxacin* because of its activity against anaerobic and gram- positive organisms.

C. Examples of clinically useful fluoroquinolones

1. Norfloxacin: is infrequently prescribed due to poor oral bioavailability and a short half-life. It is effective in treating nonsystemic infections, such as urinary tract infections (UTIs), prostatitis, and infectious diarrhea (unlabeled use).

2. Ciprofloxacin: is effective in the treatment of many systemic infections caused by gram- negative bacilli. Of the fluoroquinolones, it has the best activity against P. aeruginosa and is commonly used in cystic fibrosis patients for this indication. With 80% bioavailability, the intravenous and oral formulations are frequently interchanged. Traveler's diarrhea caused by E. coli as well as typhoid fever caused by Salmonella typhi can be effectively treated with *ciprofloxacin*. *Ciprofloxacin* is also used as a second-line agent in the treatment of tuberculosis. Although typically dosed twice daily, an extended-release formulation is available for once-daily dosing, which may improve patient adherence to treatment.

3. Levofloxacin: is the L-isomer of *ofloxacin* and has largely replaced it clinically. Due to its broad spectrum of activity, *levofloxacin* is utilized in a wide range of infections, including prostatitis, skin infections, CAP, and nosocomial pneumonia. Unlike *ciprofloxacin*, *levofloxacin* has excellent activity against S. pneumoniae respiratory infections. *Levofloxacin* has 100% bioavailability and is dosed once daily.

4. Moxifloxacin: not only has enhanced activity against gram-positive organisms (for example, S. pneumoniae) but also has excellent activity against many anaerobes, although resistance to Bacteroides fragilis has been reported. It has poor activity against P. aeruginosa. *Moxifloxacin* does not concentrate in urine and is not indicated for the treatment of UTIs.

D. Resistance

Although plasmid-mediated resistance or resistance via enzymatic degradation is not of great concern, high levels of fluoroquinolone resistance have emerged in gram-positive and gram-negative bacteria, primarily due to chromosomal mutations. Cross-resistance exists among the quinolones. The mechanisms responsible for this resistance include the following:

1. Altered target: Chromosomal mutations in bacterial genes have been associated with a decreased affinity for fluoroquinolones at their site of action. Both topoisomerase IV and DNA gyrase may undergo mutations.

2. Decreased accumulation: Reduced intracellular concentration is linked to 1) porin channels

2) Efflux pumps.

The former involves a decreased number of porin proteins in the outer membrane of the resistant cell, thereby impairing access of the drugs to the intracellular topoisomerases. The latter mechanism pumps drug out of the cell.

Adverse reactions

- In general, these agents are well tolerated. Like most antibiotics, the most common adverse effects of fluoroquinolones

1. Nausea, vomiting, and diarrhea.
2. Headache and dizziness or lightheadedness may occur. Thus, patients with central nervous system (CNS) disorders, such as epilepsy, should be treated cautiously with these drugs.
3. Peripheral neuropathy and glucose dysregulation (hypoglycemia and hypoglycemia) have also been noted.
4. Fluoroquinolones can cause phototoxicity, and patients taking these agents should be advised to use sunscreen and avoid excess exposure to sunlight. If phototoxicity occurs, discontinuation of the drug is advisable.

5. Articular cartilage erosion (arthropathy) has been observed in immature animals exposed to fluoroquinolones. Therefore, these agents should be avoided in pregnancy and lactation and in children under 18 years of age. [Note: Careful monitoring is indicated in children with cystic fibrosis who receive fluoroquinolones for acute pulmonary exacerbations.]
6. An increased risk of tendinitis or tendon rupture may also occur with systemic fluoroquinolone use.
7. *Moxifloxacin* and other fluoroquinolones may prolong the QTc interval and, thus, should not be used in patients who are predisposed to arrhythmias or those who are taking other medications that cause QT prolongation.
8. *Ciprofloxacin* can increase serum levels of *theophylline* by inhibiting its metabolism.
9. Quinolones may also raise the serum levels of *warfarin*, *caffeine*, and *cyclosporine*.

VI. URINARY TRACT ANTISEPTICS/ANTIMICROBIALS

- UTIs are prevalent in women of child-bearing age and in the elderly population. E. coli is the most common pathogen, causing about 80% of uncomplicated upper and lower UTIs.

- Staphylococcus saprophyticus is the second most common bacterial pathogen causing UTIs.
- In addition to *cotrimoxazole* and the quinolones previously mentioned, UTIs may be treated with any one of a group of agents called urinary tract antiseptics, including *methenamine*, *nitrofurantoin*, and the quinolone *nalidixic acid* (not available in the United States).
- 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

Mechanism of action: *Methenamine* decomposes at an acidic pH of 5.5 or less in the urine, thus producing formaldehyde, which acts locally and is toxic to most bacteria. Bacteria do not develop resistance to formaldehyde, which is an advantage of this drug. [Note: *Methenamine* is frequently formulated with a weak acid (for example, mandelic acid or hippuric acid) to keep the urine acidic. The urinary pH should be maintained below 6. Antacids, such as *sodium bicarbonate*, should be avoided.]

Antibacterial spectrum: *Methenamine* is primarily used for chronic suppressive therapy to reduce the frequency of UTIs. Routine use in patients with chronic urinary catheterization to reduce catheter associated bacteriuria

or catheter-associated UTI is not generally recommended. *Methenamine* should not be used to treat upper UTIs (for example, pyelonephritis). Urea-splitting bacteria that alkalinize the urine, such as Proteus species, are usually resistant to the action of *methenamine*.

Adverse effects: The major side effect of *methenamine* is

1. gastrointestinal distress
2. albuminuria,
3. hematuria,
4. Rashes may develop.

Methenamine mandelate is contraindicated in patients with renal insufficiency, because mandelic acid may precipitate. [Note: Sulfonamides, such as *cotrimoxazole*, react with formaldehyde and must not be used concomitantly with *methenamine*. The combination increases the risk of crystalluria and mutual antagonism.]

B. Nitrofurantoin

- *Nitrofurantoin* sensitive bacteria reduce the drug to a highly active intermediate that inhibits various enzymes and damages bacterial DNA.
- It is useful against E. coli, but other common urinary tract gram-negative bacteria may be resistant. Gram positive cocci (for example, S. saprophyticus) are typically susceptible.
- Hemolytic anemia may occur with *nitrofurantoin* use in patients with G6PD deficiency.
- Other adverse effects include gastrointestinal disturbances, acute pneumonitis, and neurologic problems.

- Interstitial pulmonary fibrosis has occurred in patients who take *nitrofurantoin* chronically.
- The drug should not be used in patients with significant renal impairment or women who are 38 weeks or more pregnant

Folic Acid Antagonists

Overview of the Folate Antagonists

- Enzymes requiring folate-derived cofactors are essential for the synthesis of purines and pyrimidines (precursors of RNA and DNA) and other compounds necessary for cellular growth and replication. Therefore, in the absence of folate, cells cannot grow or divide.
- To synthesize the critical folate derivative, tetrahydrofolic acid, humans must first obtain preformed folate in the form of folic acid from the diet.
- In contrast, many bacteria are impermeable to folic acid and other folates and, therefore, must rely on their ability to synthesize folate de novo.
- The sulfonamides (sulfa drugs) are a family of antibiotics that inhibit de novo synthesis of folate.
- A second type of folate antagonist *trimethoprim* prevents microorganisms from converting dihydrofolic acid to tetrahydrofolic acid, with minimal effect on the ability of human cells to make this conversion.
- Thus, both sulfonamides and *trimethoprim* interfere with the ability of an infecting bacterium

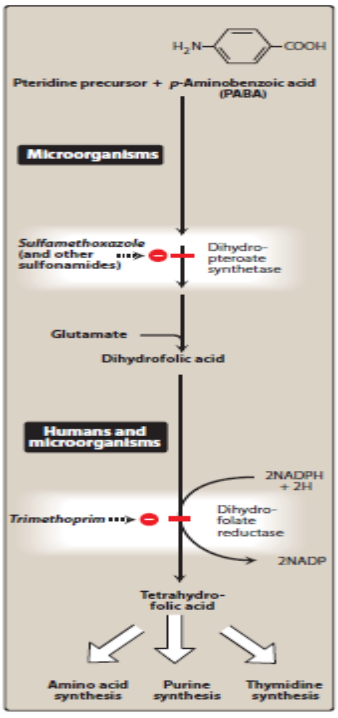


Figure 40.7
Inhibition of tetrahydrofolate synthesis by sulfonamides and *trimethoprim*.

to perform DNA synthesis. Combining the sulfonamide *sulfamethoxazole* with *trimethoprim* (the generic name for the combination is *cotrimoxazole*) provides a synergistic combination.

Sulfonamides

The sulfa drugs are seldom prescribed alone except in developing countries, where they are still employed because of their low cost and efficacy.

A. Mechanism of action

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

B. Antibacterial spectrum

Sulfa drugs are active against select Enterobacteriaceae in the urinary tract and Nocardia infections. In addition, ***sulfadiazine*** in combination with the

dihydrofolate reductase inhibitor ***pyrimethamine*** is the preferred treatment for toxoplasmosis.

C. Resistance

1. Naturally resistant, Bacteria that can obtain folate from their environment are to these drugs.
2. Acquired bacterial resistance to the sulfa drugs can arise from plasmid transfers or random mutations.

- Note: Organisms resistant to one member of this drug family are resistant to all.] Resistance is generally irreversible and may be due to

1) An altered dihydropteroate synthetase,

2) Decreased cellular permeability to sulfa drugs,

3) enhanced production of the natural substrate, PABA

Adverse effects

1. Crystalluria: Nephrotoxicity may develop as a result of crystalluria. Adequate hydration and alkalization of urine can prevent the problem by reducing the concentration of drug and promoting its ionization.

2. Hypersensitivity: Hypersensitivity reactions, such as rashes, **angioedema** or **Stevens-Johnson syndrome**, may occur. When patients report previous sulfa allergies, it is paramount to acquire a description of the reaction to direct appropriate therapy.

3. Hematopoietic disturbances: Hemolytic anemia is encountered in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Granulocytopenia and thrombocytopenia can also occur. Fatal reactions have been reported from associated agranulocytosis, aplastic anemia, and other blood dyscrasias.

4. Kernicterus: This disorder may occur in newborns, because sulfa drugs displace bilirubin from binding sites on serum albumin. The bilirubin is then free to pass into the CNS, because the blood–brain barrier is not fully developed.

5. Drug potentiation: Transient potentiation of the anticoagulant effect of *warfarin* results from the displacement from binding sites on serum albumin. Serum *methotrexate* levels may also rise through its displacement.

6. Contraindications: Due to the danger of kernicterus, sulfa drugs should be avoided in newborns and infants less than 2 months of age, as well as in pregnant women at term. Sulfonamides should not be given to patients receiving *methenamine*, since they can crystallize in the presence of formaldehyde produced by this agent.

Trimethoprim

Trimethoprim , a potent inhibitor of bacterial dihydrofolate reductase, exhibits an antibacterial spectrum similar to that of the sulfonamides.

Trimethoprim is most often compounded with *sulfamethoxazole* , producing the combination called *cotrimoxazole*.

A. Mechanism of action

The active form of folate is the tetrahydro derivative that is formed through reduction of dihydrofolic acid by dihydrofolate reductase. This enzymatic reaction is inhibited by *trimethoprim*, leading to a decreased availability of the tetrahydrofolate cofactors required for purine, pyrimidine, and amino acid synthesis. The bacterial reductase has a much stronger affinity for *trimethoprim* than does the mammalian enzyme, which accounts for the selective toxicity of the drug.

B. Antibacterial spectrum

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

C. Resistance

Resistance in gram-negative bacteria is due to the presence of an altered dihydrofolate reductase that has a lower affinity for *trimethoprim*. Efflux pumps and decreased permeability to the drug may play a role.

E. Adverse effects

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

Cotrimoxazole

The combination of *trimethoprim* with *sulfamethoxazole*, called *cotrimoxazole* , shows greater antimicrobial activity than equivalent quantities of either drug used alone . The combination was selected because of the synergistic activity and the similarity in the half-lives of the two drugs.

A. Mechanism of action

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

B. Antibacterial spectrum

- *Cotrimoxazole* has a broader spectrum of antibacterial action than the sulfa drugs alone. It is effective in treating UTIs and respiratory tract infections, toxoplasmosis, and *ampicillin*- or *chloramphenicol*-resistant salmonella infections.
- It has activity against **MRSA** and can be particularly useful for community-acquired skin and soft tissue infections caused by this organism.

C. Resistance

Resistance to the *trimethoprim–sulfamethoxazole* combination is less frequently encountered than resistance to either of the drugs alone, because it requires that the bacterium have simultaneous resistance to both drugs. Significant resistance has been documented in a number of clinically relevant organisms, including E. coli and MRSA.

E. Adverse effects

1. Reactions involving the skin are very common and may be severe in the elderly .
2. Nausea and vomiting are the most common gastrointestinal adverse effects.
3. Glossitis and stomatitis have been observed.
4. Hyperkalemia may occur, especially with higher doses.
5. Megaloblastic anemia,
6. leukopenia,

7. thrombocytopenia may occur and have been fatal.
8. The hematologic effects may be reversed by the concurrent administration of *folinic acid*, which protects the patient and does not enter the microorganism.
9. Hemolytic anemia may occur in patients with G6PD deficiency due to the *sulfamethoxazole* component.
10. Immunocompromised patients with PCP frequently show drug-induced fever, rashes, diarrhea, and/or pancytopenia.
11. Prolonged prothrombin times (increased INR) in patients receiving both *sulfamethoxazole* and *warfarin* have been reported, and increased monitoring is recommended when the drugs are used concurrently.
12. The plasma half-life of *phenytoin* may be increased due to inhibition of its metabolism.
13. *Methotrexate* levels may rise due to displacement from albumin-binding sites by *sulfamethoxazole*.

Anti-Protozoa Drugs

Protozoa 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 are no longer confined to specific geographic locales.

Because they are unicellular eukaryotes, the protozoal cells have metabolic processes **closer to** those of the human host than to prokaryotic bacterial pathogens. Therefore, protozoal diseases are less easily treated than bacterial infections, and many of the antiprotozoal drugs because serious toxic effects in the host, particularly on cells showing high metabolic activity.

Most antiprotozoal agents ***have not proven to be safe*** for pregnant patients.

II. Chemotherapy for 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 varying degrees of illness, from no symptoms to mild diarrhea to fulminating dysentery. The diagnosis is established by isolating E. histolytica from feces. Therapy is indicated for acutely ill patients and

asymptomatic carriers, since dormant E. histolytica may cause future infections in the carrier and be a potential source of infection for others.

Therapeutic agents for amebiasis are classified as **luminal**, **systemic**, or **mixed amebicides** according to the site of action . For example, luminal amebicides act on the parasite in the lumen of the bowel, whereas systemic amebicides are effective against amebas in the intestinal wall and liver. Mixed amebicides are effective against both the luminal and systemic forms of the disease, although luminal concentrations are too low for single-drug treatment.

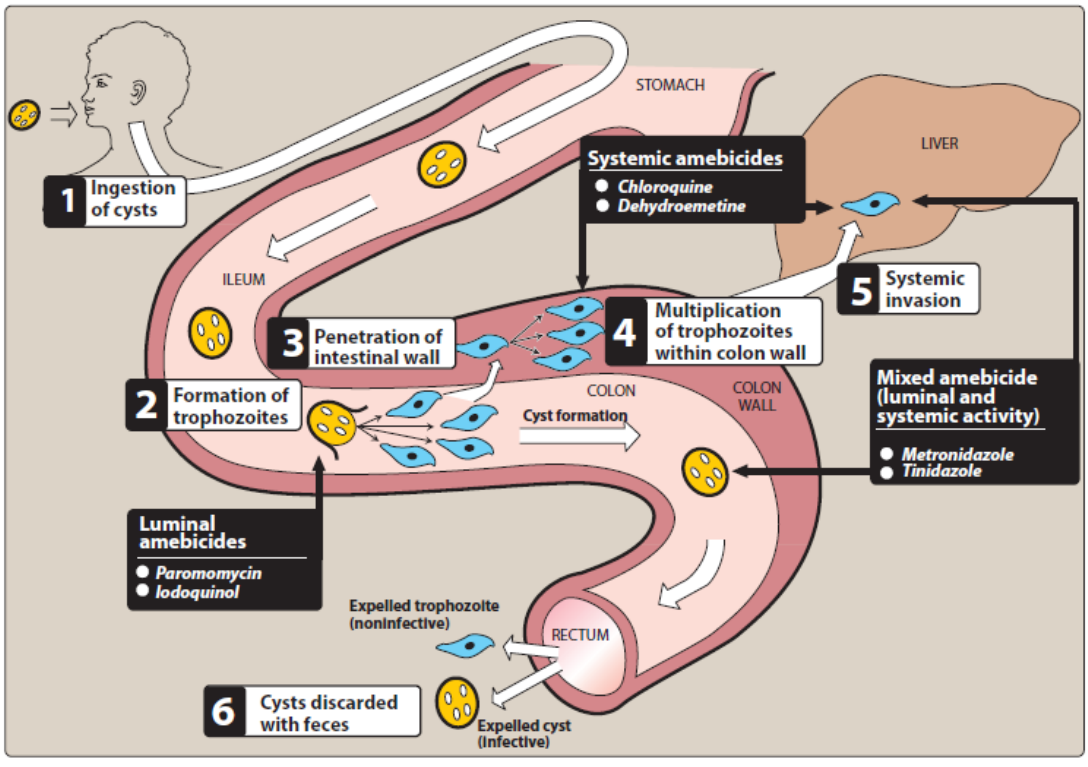


Figure 43.2
Life cycle of Entamoeba histolytica, showing the sites of action of amebicidal drugs.

A. Mixed amebicides

1. Metronidazole: a nitroimidazole, is the mixed amebicide of choice for treating amebic infections.

a. Mechanism of action: Amebas possess ferredoxin-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, resulting in death of the E. histolytica trophozoites.

Adverse effects: The most common adverse effects are nausea, vomiting, epigastric distress, and abdominal cramps. An unpleasant, metallic taste is commonly experienced.

Other effects include oral moniliasis (yeast infection of the mouth) and, rarely, neurotoxicity (dizziness, vertigo, and numbness or paresthesia), which may necessitate discontinuation of the drug. If taken with alcohol, a *disulfiram*-like reaction may occur .

d. Resistance: Resistance to *metronidazole* **is not a therapeutic problem** for amebiasis, although strains of trichomonads resistant to the drug have been reported.

2. Tinidazole: is a second-generation nitroimidazole that is similar to metronidazole in spectrum of activity, absorption, adverse effects, and drug interactions. *Tinidazole* is as effective as *metronidazole*, with a shorter

course of treatment, but it is **more expensive**. Alcohol consumption should be avoided during therapy.

B. Luminal amebicides

After treatment of invasive intestinal or extraintestinal amebic disease is complete, a luminal agent, such as *iodoquinol*, *diloxanide furoate*, or *paromomycin*, should be administered for treatment of the asymptomatic colonization state.

1. Iodoquinol: a halogenated 8-hydroxyquinolone, is amebicidal against E. histolytica and is effective against the luminal **trophozoite and cyst** forms. Adverse effects of *iodoquinol* include rash, diarrhea, and dose-related peripheral neuropathy, including a rare optic neuritis. Long-term use of this drug should be avoided.

C. Systemic amebicides

These drugs are useful for treating liver abscesses and intestinal wall infections caused by amebas.

1. Chloroquine: is used in combination with metronidazole to treat amebic liver abscesses. It eliminates trophozoites in liver abscesses, but it is not useful in treating luminal amebiasis. Therapy should be followed with a luminal amebicide. *Chloroquine* is also effective in the treatment of malaria.

III. Chemotherapy for Malaria

Malaria is an acute infectious disease caused by four species of the protozoal genus Plasmodium. It is transmitted to humans through the bite of a female Anopheles mosquito. **Plasmodium falciparum** is the most dangerous species, causing an acute, rapidly fulminating disease that is characterized by persistent high fever, orthostatic hypotension, and massive erythrocytosis (an abnormal elevation in the number of red blood cells accompanied by swollen, reddish limbs). P. falciparum infection can lead to capillary obstruction and death without prompt treatment. **Plasmodium vivax** causes a milder form of the disease. **Plasmodium 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.

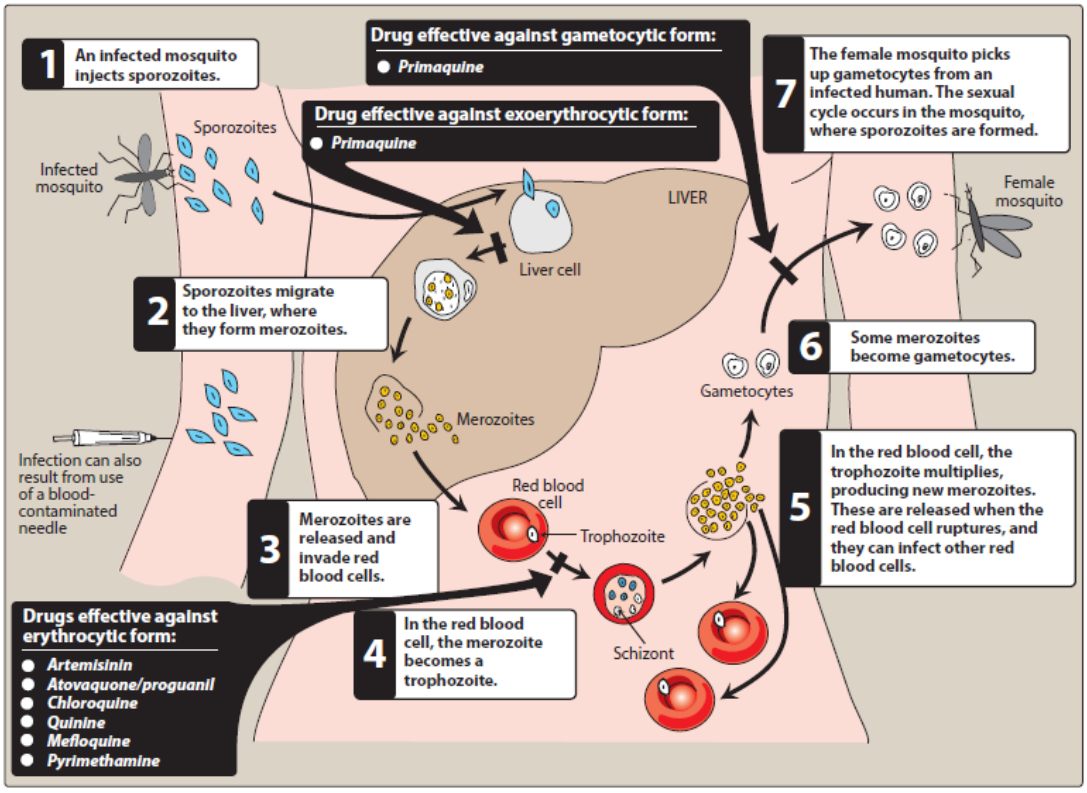


Figure 43.5
Life cycle of the malarial parasite, Plasmodium falciparum, showing the sites of action of antimalarial drugs.

A. Primaquine

8-aminoquinoline, is an oral antimalarial drug that eradicates primary exoerythrocytic (tissue) forms of plasmodia and the secondary exoerythrocytic forms of recurring malarias (P. vivax and P. ovale).

The sexual (gametocytes) forms of all four plasmodia are destroyed in the plasma or are prevented from maturing later in the mosquito, thereby interrupting transmission of the disease. [Note: *Primaquine* is not effective against the erythrocytic stage of malaria and, therefore, is used in

conjunction with agents to treat the erythrocytic form (for example, *chloroquine* and *mefloquine*).]

1. Mechanism of action: metabolites of *primaquine* are believed to act as oxidants that are responsible for the cidal action as well as for the hemolysis and methemoglobinemia encountered as toxicities.

3. Adverse effects: *Primaquine* is associated with drug-induced hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency. Large doses of the drug may cause abdominal discomfort (especially when administered in combination with *chloroquine*) and occasional methemoglobinemia.

Primaquine should not be used during pregnancy. All Plasmodium species may develop resistance to *primaquine*

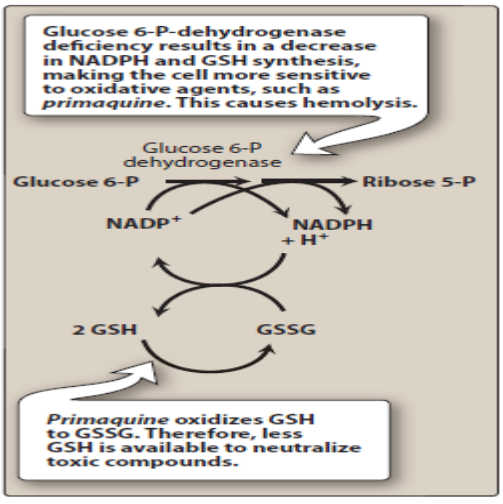


Figure 43.6
Mechanism of *primaquine-induced* hemolytic anemia. GSH = reduced glutathione; GSSG = oxidized glutathione; $NADP^+$ = nicotinamide adenine dinucleotide phosphate; NADPH = reduced nicotinamide adenine dinucleotide phosphate.

B. Chloroquine

Chloroquine is a synthetic 4-aminoquinoline that has been the mainstay of antimalarial therapy, and it is the drug of choice in the treatment of erythrocytic P. falciparum malaria, except in resistant strains.

Chloroquine is used in the prophylaxis of malaria for travel to areas with known *chloroquine*- sensitive malaria. [Note: *Hydroxychloroquine* is an alternative to *chloroquine* for the prophylaxis and treatment of *chloroquine*-sensitive malaria.] It is also effective in the treatment of extraintestinal amebiasis.

1. Mechanism of action: After traversing the erythrocytic and plasmodial membranes, *chloroquine* is concentrated in the acidic food vacuole of the malarial parasite, primarily by ion trapping. In the food vacuole, the parasite digests the host cell's hemoglobin to obtain essential amino acids. However, this process also releases large amounts of soluble heme, which is toxic to the parasite. To protect itself, the parasite polymerizes the heme to hemozoin (a pigment), which is sequestered in the food vacuole. *Chloroquine* specifically binds to heme, preventing its polymerization to hemozoin. The increased pH and the accumulation of heme result in oxidative damage to the phospholipid membranes, leading to lysis of both the parasite and the red blood cell.

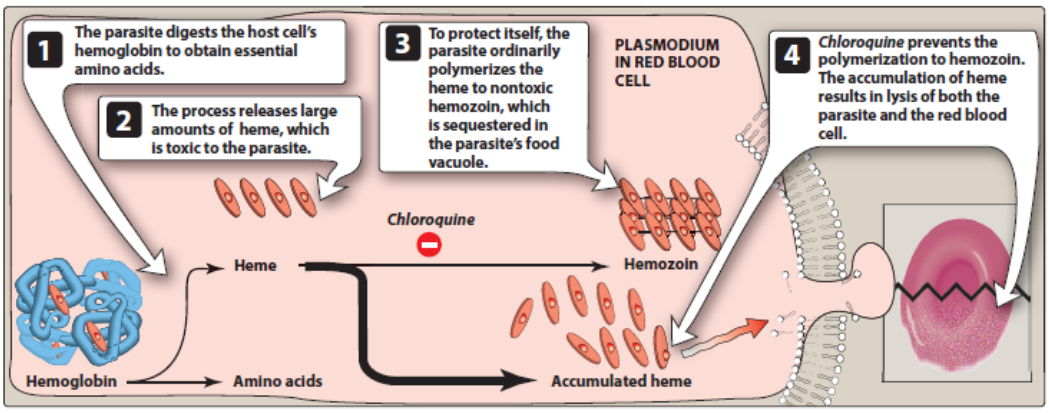


Figure 43.7
Action of *chloroquine* on the formation of hemozoin by Plasmodium species.

Adverse effects: Side effects are minimal at low prophylactic doses. At higher doses, gastrointestinal upset, pruritus, headaches, and blurred vision may occur . [Note: An ophthalmologic 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, severe gastrointestinal problems, or neurologic disorders.

Patients with psoriasis or porphyria should not be treated with *chloroquine*, because an acute attack may be provoked.

Chloroquine can prolong the QT interval, and use of other drugs that also cause QT prolongation should be avoided if possible.

4. Resistance: Resistance has become a serious medical problem throughout Africa, Asia, and most areas of Central and South America. *Chloroquine*-

resistant P. falciparum exhibits multigenic alterations that confer a high level of resistance.

IV. Chemotherapy for Trypanosomiasis

African trypanosomiasis (sleeping sickness) and American trypanosomiasis (also known as Chagas disease) are two chronic and, eventually, fatal diseases caused by species of Trypanosoma . In African sleeping sickness, it initially live and grow in the blood. The parasite later invades the CNS, causing inflammation of the brain and spinal cord that produces the characteristic lethargy and, eventually, continuous sleep.

A. Pentamidine

Pentamidine is active against a variety of protozoal infections, including African trypanosomiasis, for which it is used to treat the first stage (hemolymphatic stage without CNS involvement).

1. Mechanism of action: the paracyte concentrates *pentamidine* by an energy-dependent, high-affinity uptake system. [Note: Resistance is associated with inability to concentrate the drug.] Although its mechanism of action has not been defined, evidence exists that the drug interferes with parasite synthesis of RNA, DNA, phospholipids, and proteins.

3. Adverse effects: Serious renal dysfunction may occur, which is reversible on discontinuation. Other adverse reactions include hyperkalemia, hypotension, pancreatitis, hypoglycemia, hyperglycemia, and diabetes.

V. Chemotherapy for Leishmaniasis

There are three types of leishmaniasis: cutaneous, mucocutaneous, 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 animals to humans (and between humans) by the bite of infected sandflies. The diagnosis is established by demonstrating the parasite in biopsy material and skin lesions. For visceral leishmaniasis, parenteral treatments may include *amphotericin B* and pentavalent antimonials, such as *sodium stibogluconate*, with *pentamidine* and *paromomycin* as alternative agents. *Miltefosine* is an orally active agent for visceral leishmaniasis. The choice of agent depends on the species of Leishmania, host factors, and resistance patterns noted in area of the world where the infection is acquired.

A. Sodium stibogluconate

The pentavalent antimonial *sodium stibogluconate* is not effective in vitro. Therefore, it has been proposed that reduction to the trivalent antimonial compound is essential for activity. The exact mechanism of action has not been determined. Because it is not absorbed after oral administration,

sodium stibogluconate must be administered parenterally, and it is distributed in the extravascular compartment. Metabolism is minimal, and the drug is excreted in urine. Adverse effects include injection site pain, pancreatitis, elevated liver enzymes, arthralgias, myalgias, gastrointestinal upset, and cardiac arrhythmias. Renal and hepatic function should be monitored periodically.

VII. Chemotherapy for giardiasis

Giardia lamblia is the most commonly diagnosed intestinal parasite in the United States. It has two life cycle stages:

- binucleate trophozoite with four flagella and the drug-resistant,
- Four-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 stools. Although some infections are asymptomatic, severe diarrhea can occur, which can be very serious in immunocompromised patients. The treatment of choice is oral *metronidazole* for 5 days. An alternative is *tinidazole*, which is as effective as *metronidazole* in the treatment of giardiasis. This agent is administered orally as a single dose.

Nitazoxanide , a nitrothiazole derivative, is also approved for the treatment of giardiasis. For giardiasis, *nitazoxanide* is administered as a 3-day course

of oral therapy. The anthelmintic drug *albendazole* may also be efficacious for giardiasis.

Antiviral Drugs

- Viruses are obligate intracellular microorganism.
- They lack both a cell wall and a cell membrane, and they do not carry out metabolic processes.
- Viruses use much of the host's metabolic machinery, and few drugs are selective enough to prevent viral replication without injury to the infected host cells.
- Therapy for viral diseases is further complicated by the fact that the clinical symptoms appear late in the course of the disease, at a time when most of the virus particles have replicated.
- At this stage of viral infection, administration of drugs that ***block viral replication has limited effectiveness***.
- However, some antiviral agents are useful as ***prophylactic agents***.

Treatment of Respiratory Viral Infections

Viral respiratory tract infections for which treatments exist include influenza A and B and respiratory syncytial virus (RSV).

A. Neuraminidase inhibitors

- The neuraminidase inhibitors *oseltamivir* and *zanamivir* are effective against both type A and type B influenza viruses.

- Administered prior to exposure, neuraminidase inhibitors prevent infection and, when administered within 24 to 48 hours after the onset of symptoms, they modestly decrease the intensity and duration of symptoms.

1. Mechanism of action: Influenza viruses employ a specific neuraminidase that is inserted into the host cell membrane for the purpose of releasing newly formed virions. This enzyme is essential for the virus life cycle. ***Oseltamivir* and *zanamivir* selectively inhibit neuraminidase, thereby preventing the release of new virions and their spread from cell to cell.** .

B. Adamantane antivirals

The therapeutic spectrum of the adamantane derivatives, *amantadine* and *rimantadine* , is limited to **influenza A infections**.

Mechanism of action: *Amantadine* and *rimantadine* interfere with the function of the **viral M2 protein**, possibly blocking un-coating of the virus particle and preventing viral release within infected cells.

C. Ribavirin

Ribavirin , a synthetic guanosine analog, is effective against a broad spectrum of RNA and DNA viruses. For example, *ribavirin* is used in treating immunosuppressed infants and young children with severe

infections. *Ribavirin* is also effective in **chronic hepatitis C infections** when used in combination with *interferon-α.*

Mechanism of action: *Ribavirin* inhibits replication of **RNA and DNA** viruses. The drug is *first phosphorylated to the 5′-phosphate derivatives*, the major product being the compound ribavirin triphosphate, which exerts its antiviral action by **inhibiting guanosine triphosphate formation**, **preventing viral messenger RNA (mRNA) capping**, and **blocking RNA-dependent RNA polymerase**.

Treatment of hepatic viral infections

- The hepatitis viruses thus far identified (A, B, C, D, and E) each have a pathogenesis specifically involving replication in and destruction of hepatocytes.
- Of this group, hepatitis B (a DNA virus) and hepatitis C (an RNA virus) are the most common causes of **chronic hepatitis**, **cirrhosis**, and **hepatocellular carcinoma** and are the only hepatic viral infections for which therapy is currently available.
- Hepatitis A is a commonly encountered infection caused by oral ingestion of the virus, but it is not a chronic disease.
- Chronic hepatitis B may be treated with

    1. *Peg-interferon-α-2a*, which is injected subcutaneously once weekly.

2. *Interferon-α-2b* injected intramuscularly or subcutaneously three times weekly is also useful in the treatment of hepatitis B, but *peg-interferon-α-2a* has similar or slightly better efficacy with improved tolerability.

- Oral therapy for chronic hepatitis B includes *lamivudine, adefovir, entecavir*, *tenofovir*, or *telbivudine*. The preferred treatment for chronic hepatitis C is the combination of *peg-interferon-α-2a* or *peg-interferon-α-2b* plus *ribavirin*, which is more effective than the combination of standard interferon and *ribavirin*.

A. Interferon

- Interferon are a family of naturally occurring, that interfere with the ability of viruses to infect cells.
- In "pegylated" formulations polyethylene glycol has been covalently attached to either *interferon-α-2a* or *-α-2b* to increase the size of the molecule. The larger molecular size delays absorption from the injection site, lengthens the duration of action of the drug, and also decreases its clearance.

Mechanism of action: The antiviral mechanism is incompletely understood. It appears to involve the induction of host cell enzymes that inhibit viral

RNA translation, ultimately leading to the degradation of viral mRNA and tRNA.

B. Lamivudine

- This cytosine analog is an inhibitor of both hepatitis B virus (HBV) and human immunodeficiency virus (HIV) reverse transcriptases (RTs).
- *Lamivudine* must be phosphorylated by host cellular enzymes to the triphosphate (active) form. This compound competitively inhibits HBV RNA-dependent DNA polymerase.

C. Entecavir

- *Entecavir* is a guanosine nucleoside analog for the treatment of HBV infections. Following intracellular phosphorylation to the triphosphate, it competes with the natural substrate, deoxyguanosine triphosphate, for viral RT.
- *Entecavir* is effective against *lamivudine*-resistant strains of HBV and is dosed once daily.

D. Telbivudine

- *Telbivudine* is a thymidine analog that can be used in the treatment of HBV. *Telbivudine* is phosphorylated intracellular to the triphosphate, which can

either compete with endogenous thymidine triphosphate for incorporation into DNA or be incorporated into viral DNA, where it serves to terminate further elongation of the DNA chain.

Treatment of Herpes Virus infections

Herpes viruses are associated with a broad spectrum of diseases, for example, cold sores, viral encephalitis, and genital infections. The drugs that are effective against these viruses exert their actions during the acute phase of viral infections and are without effect during the latent phase.

A. Acyclovir

Acyclovir is the prototypic anti-herpetic therapeutic agent. The most common use of *acyclovir* is in therapy for genital herpes infections. It is also given prophylactically to seropositive patients before bone marrow transplant and post–heart transplant to protect such individuals from herpetic infections.

1. **Mechanism of action:** *Acyclovir*, a guanosine analog, is mono-phosphorylated in the cell by the herpes virus-encoded enzyme **thymidine kinase**. Therefore, virus-infected cells are most susceptible.

   The monophosphate analog is converted to the di- and triphosphate forms by the **host cell kinases**. Acyclovir triphosphate competes with

deoxyguanosine triphosphate as a substrate for viral DNA polymerase and is itself incorporated into the viral DNA, causing premature DNA chain termination.

B. Foscarnet

- Unlike most antiviral agents, *foscarnet* is not a purine or pyrimidine analog.
- Instead, it is a phosphonoformate (a pyrophosphate derivative) and does not require activation by viral (or cellular) kinases.
- *Foscarnet* is approved for CMV retinitis in immunocompromised hosts and for *acyclovir*-resistant HSV infections.
- *Foscarnet* works by **reversibly inhibiting** viral DNA and RNA polymerases, thereby interfering with viral DNA and RNA synthesis. Mutation of the polymerase structure is responsible for resistant viruses.

D. Ganciclovir

Ganciclovir is an analog of *acyclovir* that has greater activity against CMV. It is used for the treatment of CMV retinitis in immunocompromised patients and for CMV prophylaxis in transplant patients.

Mechanism of action: Like *acyclovir*, *ganciclovir* is activated through conversion to the nucleoside triphosphate by viral and cellular enzymes. The

nucleotide inhibits viral DNA polymerase and can be incorporated into the DNA resulting in chain termination.

Overview of the treatment for HIV infection

Viral life cycle is understood, and a combination of drugs is used to suppress replication of HIV and restore the number of $\mathbf{CD_4^+}$ cells and immune-competence to the host.

-This multidrug regimen is commonly referred to as "highly active antiretroviral therapy," or HAART .

-There are **five classes of antiretroviral drugs**, each of which targets one of the four viral processes.

1. Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs).
2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs).
3. Protease inhibitors (PIs).
4. Entry inhibitors.
5. The integrase inhibitors.

The preferred initial therapy is a combination of two NRTIs with a PI, an NNRTI, or an integrase inhibitor.

Selection of the appropriate combination is based on

1) Avoiding the use of two agents of the same nucleoside analog.

2)Avoiding overlapping toxicities and genotypic and phenotypic characteristics of the virus.

3) Patient factors, such as disease symptoms and concurrent illnesses.

4) Impact of drug interactions.

5) Ease of adherence to the regimen. The goals of therapy are to maximally and durably suppress HIV RNA replication, to restore and preserve immunologic function, to reduce HIV-related morbidity and mortality, and to improve quality of life.

VI. NRTIS used to treat HIV infection

1. Mechanism of action: NRTIs are analogs of native ribosides (nucleosides or nucleotides containing ribose), which all lack a 3′-hydroxyl group. Once they enter cells, they are phosphorylated by cellular enzymes to the corresponding triphosphate analog, which is preferentially incorporated into the viral DNA by RT. Because the 3′-hydroxyl group is not present, a 3′,5′-phosphodiester bond between an incoming nucleoside triphosphate and the growing DNA chain cannot be formed, and DNA chain elongation is terminated..

1- Zidovudine (AZT)

2. Stavudine (d4T)

3. Didanosine (ddI)

4. Tenofovir (TDF)

5. Lamivudine (3TC)

6. Emtricitabine (FTC)

7. Abacavir (ABC).

VII. NNRTIS used to treat HIV infection

- NNRTIs are highly selective, non-competitive inhibitors of HIV-1 RT. They bind to HIV RT at an allosteric hydrophobic site adjacent to the active site, inducing a conformational change that results in enzyme inhibition.
- They **do not require activation** by cellular enzymes. These drugs have common characteristics that include cross-resistance with other NNRTIs, drug interactions, and a high incidence of hypersensitivity reactions, including rash.

1. Nevirapine (NVP)

2. Delavirdine (DLV)

3. Efavirenz (EFV)

4. Etravirine (ETR)

5. Rilpivirine (RPV**)**.

VIII. Protease inhibitors used to treat HIV infection

Mechanism of action: All of the drugs in this group **are reversible inhibitors** of the HIV aspartyl protease (retropepsin), which is the viral enzyme responsible for cleavage of the viral poly-protein into a number of essential enzymes (RT, protease, and integrase) and several structural proteins. The inhibition prevents maturation of the viral particles and results in the production of noninfectious virions.

1. Ritonavir (RTV)
2. Saquinavir (SQV)
3. Indinavir (IDV)
4. Nelfinavir (NFV)
5. Fosamprenavir (FPV)
6. Lopinavir (LPV/r)
7. Atazanavir (ATV)
8. Tipranavir (TPV)
9. Darunavir (DRV)

IX. Entry inhibitors used to treat HIV infection

A. Enfuvirtide

Enfuvirtide is a fusion inhibitor. For HIV to gain entry into the host cell, it must fuse its membrane with that of the host cell. This is accomplished by

changes in the conformation of the viral transmembrane glycoprotein gp41, which occurs when HIV binds to the host cell surface. *Enfuvirtide* is a polypeptide that binds to gp41, preventing the conformational change.

B. Maraviroc

Maraviroc blocks the CCR5 co-receptor that works together with gp41 to facilitate HIV entry through the membrane into the cell. Prior to use of *maraviroc*, a test to determine viral tropism is required to distinguish whether the strain of HIV virus uses the CCR5 co-receptor, the CXCR4 co-receptor, or is dual-tropic.

X. Integrase inhibitors used to treat HIV infection

- The integrase strand transfer inhibitors (INSTIs), often called integrase inhibitors, work by inhibiting the insertion of proviral DNA into the host cell genome. The active site of the integrase enzyme binds to the host cell DNA and includes two divalent metal cations that serve as chelation targets for the INSTIs. As a result, when an INSTI is present, the active site of the enzyme is occupied and the integration process is halted.

A. Raltegravir, **B.** Elvitegravir, **C.** Dolutegravir