Protein Synthesis Inhibitors

39

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I. 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. Figure 39.1 summarizes the protein synthesis inhibitors discussed in this chapter.

TETRACYCLINES
- ***Demeclocycline*** DECLOMYCIN
- ***Doxycycline*** VIBRAMYCIN
- ***Minocycline*** MINOCIN
- ***Tetracycline***

GLYCYLCYCLINES
- ***Tigecycline*** TYGACIL

AMINOGLYCOSIDES
- ***Amikacin***
- ***Gentamicin*** GARAMYCIN
- ***Neomycin*** NEO-FRADIN
- ***Streptomycin***
- ***Tobramycin*** TOBREX

MACROLIDES/KETOLIDES
- ***Azithromycin*** ZITHROMAX
- ***Clarithromycin*** BIAXIN
- ***Erythromycin*** VARIOUS
- ***Telithromycin*** KETEK

MACROCYCLIC
- ***Fidaxomicin*** DIFICID

LINCOSAMIDES
- ***Clindamycin*** CLEOCIN

OXAZOLIDINONES
- ***Linezolid*** ZYVOX

OTHERS
- ***Chloramphenicol*** CHLOROMYCETIN
- ***Quinupristin/Dalfopristin*** SYNERCID

Figure 39.1
Summary of protein synthesis inhibitors.

II. 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 (Figure 39.2).

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 (Figure 39.3). They are commonly used in the treatment of acne and Chlamydia infections (*doxycycline*).

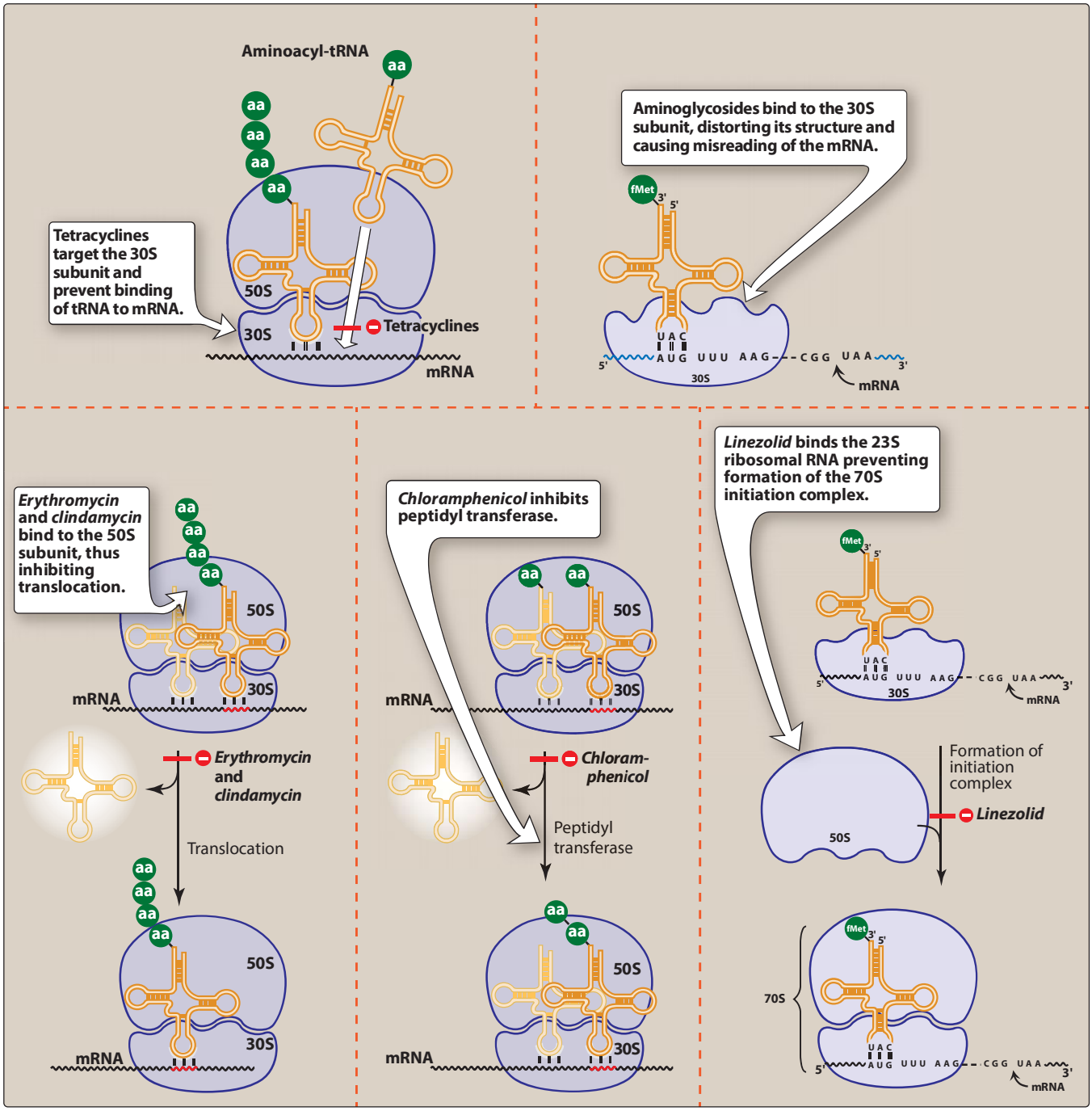

Figure 39.2
Mechanisms of action of the various protein synthesis inhibitors. aa = amino acid.

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

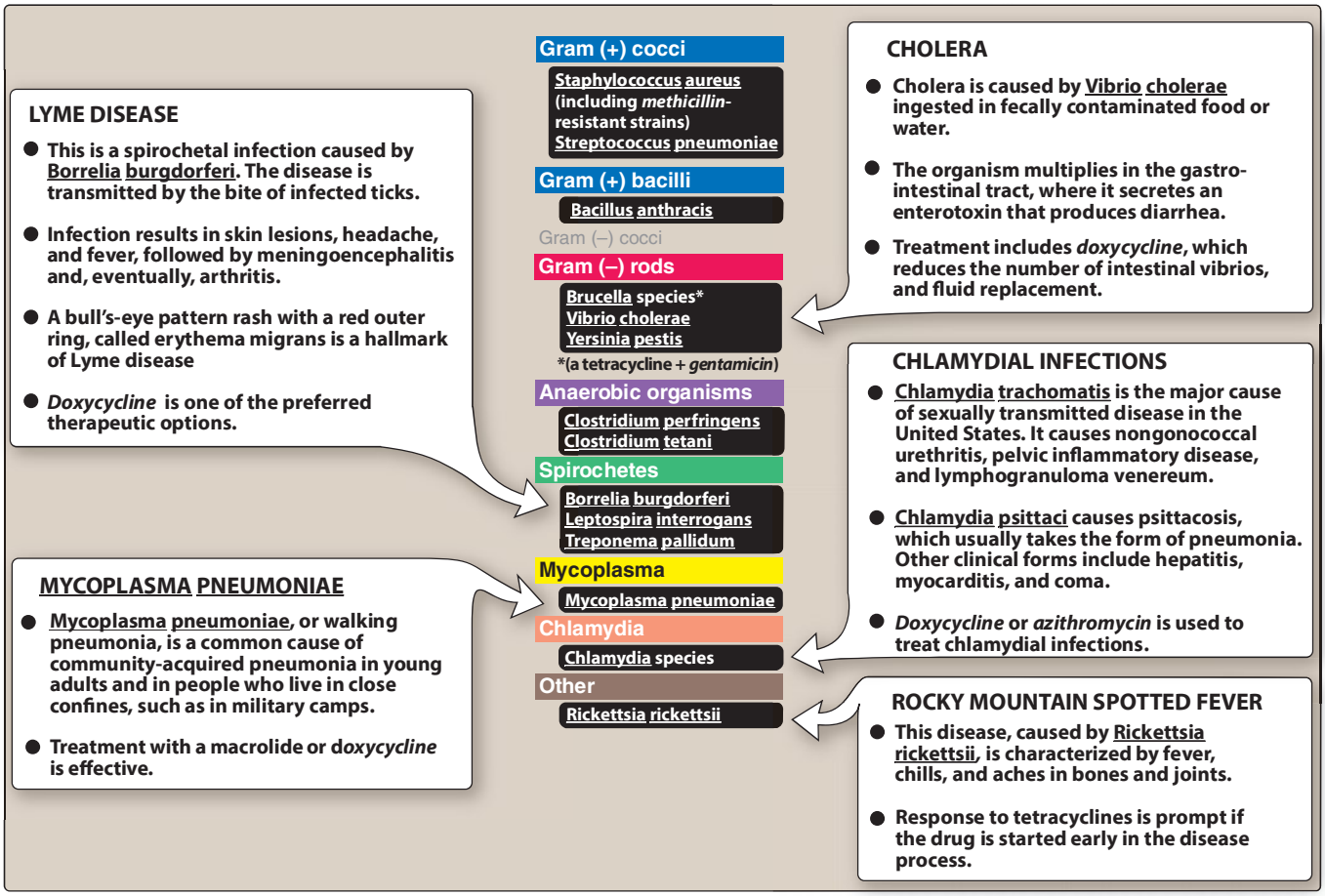

Figure 39.3
Typical therapeutic applications of tetracyclines.

binding to the ribosome. Resistance to one tetracycline does not confer universal resistance to all tetracyclines.

D. Pharmacokinetics

1. **Absorption:** Tetracyclines are adequately absorbed after oral ingestion (Figure 39.4). 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* [tet-rah-SYE-kleen], due to the formation of nonabsorbable chelates (Figure 39.5). Both *doxycycline* [dox-i-SYE-kleen] and *minocycline* [min-oh-SYE-kleen] are available as oral and intravenous (IV) preparations.

2. **Distribution:** The tetracyclines concentrate well in the bile, liver, kidney, gingival fluid, and skin. Moreover, they bind to tissues undergoing calcification (for example, teeth and bones) or to tumors that have a high calcium content. Penetration into most body fluids is adequate. Only *minocycline* and *doxycycline* achieve therapeutic levels in the cerebrospinal fluid (CSF). *Minocycline* also achieves high levels in saliva and tears, rendering it useful in eradicating the meningococcal carrier state. All tetracyclines

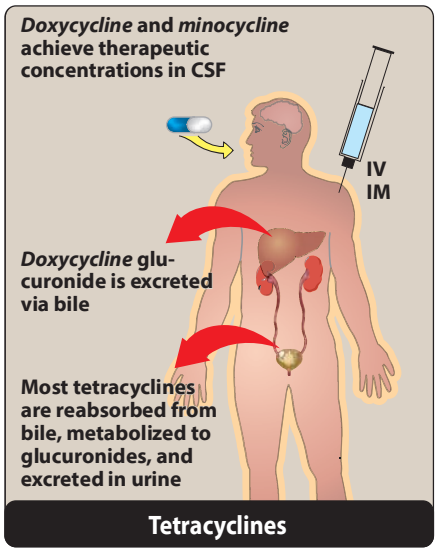

Figure 39.4
Administration and fate of tetracyclines. CSF = cerebrospinal fluid.

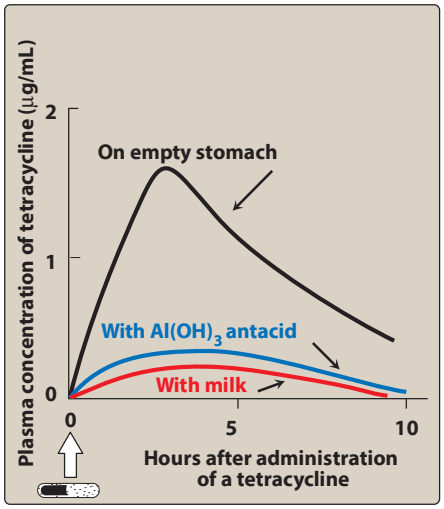

Figure 39.5
Effect of antacids and milk on the absorption of tetracyclines.

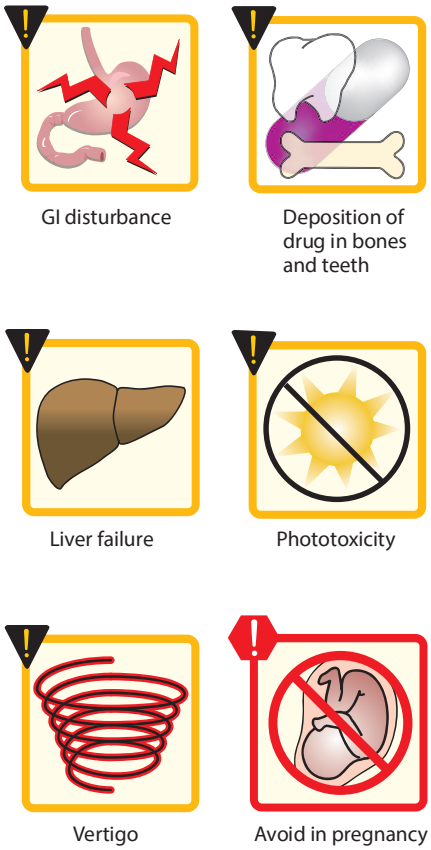

Figure 39.6
Some adverse effects of tetracyclines.

cross the placental barrier and concentrate in fetal bones and dentition.

3. **Elimination:** *Tetracycline* and *doxycycline* are not hepatically metabolized. *Tetracycline* is primarily eliminated unchanged in the urine, whereas *minocycline* undergoes hepatic metabolism and is eliminated to a lesser extent via the kidney. In renally compromised patients, *doxycycline* is preferred, as it is primarily eliminated via the bile into the feces.

E. Adverse effects

1. **Gastric discomfort:** Epigastric distress commonly results from irritation of the gastric mucosa (Figure 39.6) and is often responsible for noncompliance with tetracyclines. Esophagitis may be minimized through coadministration 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* and *demeclocycline* [dem-e-kloe-SYE-kleen]. 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.

III. GLYCYLCYCLINES

Tigecycline [tye-ge-SYE-kleen], a derivative of *minocycline*, is the first available member of the glycylcycline antimicrobial class. It is indicated for the treatment of complicated skin and soft tissue infections, as well as complicated intra-abdominal infections.

A. Mechanism of action

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

B. Antibacterial spectrum

Tigecycline exhibits broad-spectrum activity that includes *methicillin*-resistant staphylococci (MRSA), multidrug-resistant streptococci, vancomycin-resistant enterococci (VRE), extended-spectrum β-lactamase–producing gram-negative bacteria, Acinetobacter baumannii, and many anaerobic organisms. However, *tigecycline* is not active against Morganella, Proteus, Providencia, or Pseudomonas species.

C. Resistance

Tigecycline was developed to overcome the recent emergence of tetracycline class–resistant organisms that utilize efflux pumps and ribosomal protection to confer resistance. However, resistance is seen and is primarily attributed to overexpression of efflux pumps.

D. Pharmacokinetics

Following IV infusion, *tigecycline* exhibits a large volume of distribution. It penetrates tissues well but has low plasma concentrations. Consequently, *tigecycline* is a poor option for bloodstream infections. The primary route of elimination is biliary/fecal. No dosage adjustments are necessary for patients with renal impairment. However, a dose reduction is recommended in severe hepatic dysfunction.

E. Adverse effects

Tigecycline is associated with significant nausea and vomiting. Acute pancreatitis, including fatality, has been reported with therapy. Elevations in liver enzymes and serum creatinine may also occur. Other adverse effects are similar to those of the tetracyclines and include photosensitivity, pseudotumor cerebri, discoloration of permanent teeth when used during tooth development, and fetal harm when administered in pregnancy. *Tigecycline* may decrease the clearance of *warfarin* and increase prothrombin time. Therefore, the international normalized ratio should be monitored closely when *tigecycline* is coadministered with *warfarin.*

IV. 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

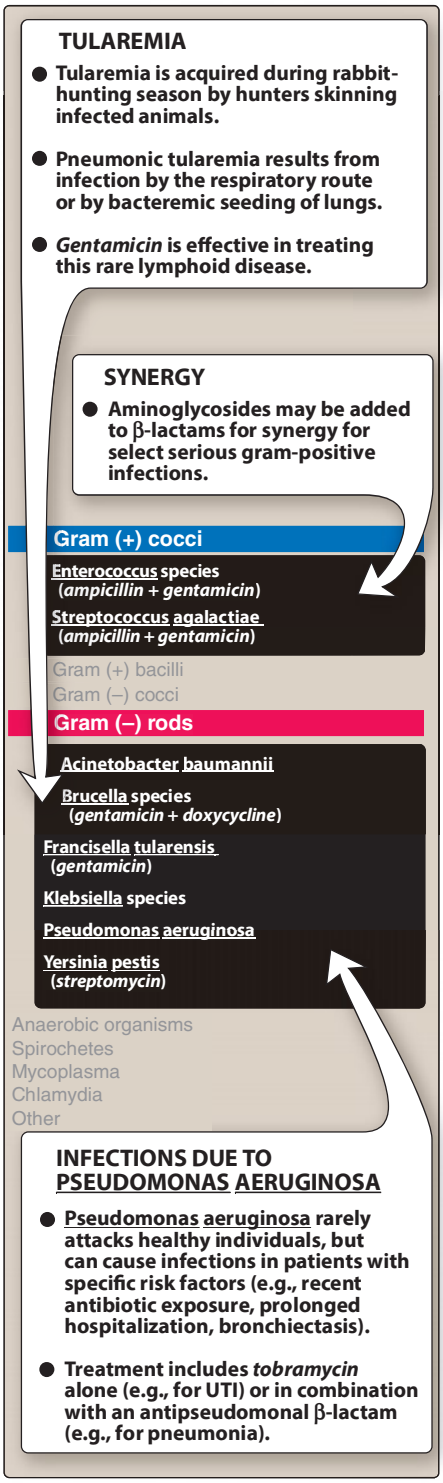

Figure 39.7
Typical therapeutic applications of aminoglycosides.

apparatus and/or cause the 30S subunit of the completed ribosome to misread the genetic code (Figure 39.2). 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 (C_{max}) of drug above the minimum inhibitory concentration (MIC) of the organism. For aminoglycosides, the target C_{max} 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, such as Pseudomonas aeruginosa, Klebsiella pneumoniae, and Enterobacter sp. Additionally, aminoglycosides are often combined with a β-lactam antibiotic to employ a synergistic effect, particularly in the treatment of Enterococcus faecalis and Enterococcus faecium infective endocarditis. Some therapeutic applications of four commonly used aminoglycosides—*amikacin* [am-i-KAY-sin], *gentamicin* [jen-ta-MYE-sin], *tobramycin* [toe-bra-MYE-sin], and *streptomycin* [strep-toe-MYE-sin]—are shown in Figure 39.7.

C. Resistance

Resistance to aminoglycosides occurs via: 1) efflux pumps, 2) decreased uptake, and/or 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.]

D. Pharmacokinetics

1. **Absorption:** The highly polar, polycationic structure of the aminoglycosides prevents adequate absorption after oral administration. Therefore, all aminoglycosides (except *neomycin* [nee-oh-MYE-sin]) must be given parenterally to achieve adequate serum levels (Figure 39.8). [Note: *Neomycin* is not given parenterally due to severe nephrotoxicity. It is administered topically for skin infections or orally for bowel preparation prior to colorectal surgery.]

2. **Distribution:** All the aminoglycosides have similar pharmacokinetic properties. Due to their hydrophilicity, tissue concentrations may be subtherapeutic, and penetration into most body fluids is variable. [Note: Due to low distribution into fatty tissue, the aminoglycosides are dosed based on lean body mass, not actual body weight.] Concentrations in CSF are inadequate, even in the presence of inflamed meninges. For central nervous system infections, the intrathecal (IT) route may be utilized. All aminoglycosides cross the placental barrier and may accumulate in fetal plasma and amniotic fluid.

3. **Elimination:** More than 90% of the parenteral aminoglycosides are excreted unchanged in the urine (Figure 39.8). Accumulation occurs in patients with renal dysfunction, and dose adjustments are required.

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 (Figure 39.9). 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.*

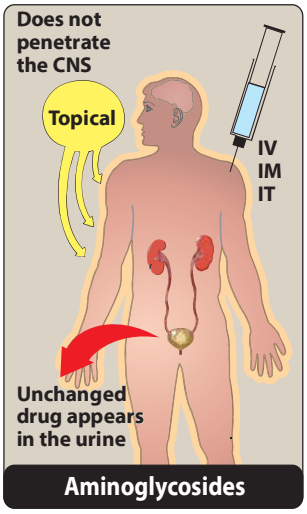

Figure 39.8
Administration and fate of aminoglycosides. CNS = central nervous system.

V. 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* [er-ith-roe-MYE-sin] was the first of these drugs to find clinical application, both as a drug of first choice and as an alternative to *penicillin* in individuals with an allergy to β-lactam antibiotics. *Clarithromycin* [kla-rith-roe-MYE-sin] (a methylated form of *erythromycin*) and *azithromycin* [a-zith-roe-MYE-sin] (having a larger lactone ring) have some features in common with, and others that improve upon, *erythromycin. Telithromycin* [tel-ith-roe-MYE-sin], a semisynthetic derivative of *erythromycin*, is the first "ketolide" antimicrobial agent. 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

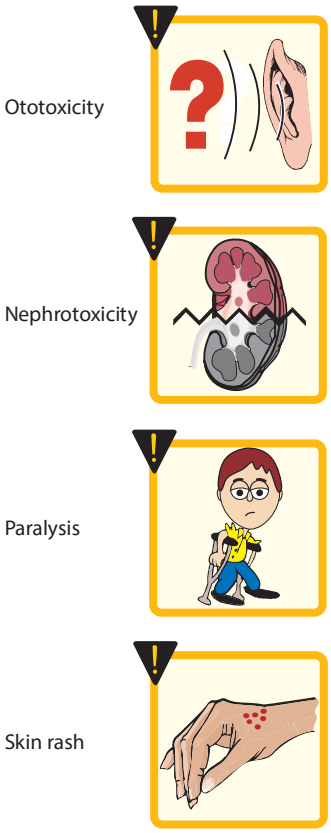

Figure 39.9
Some adverse effects of aminoglycosides.

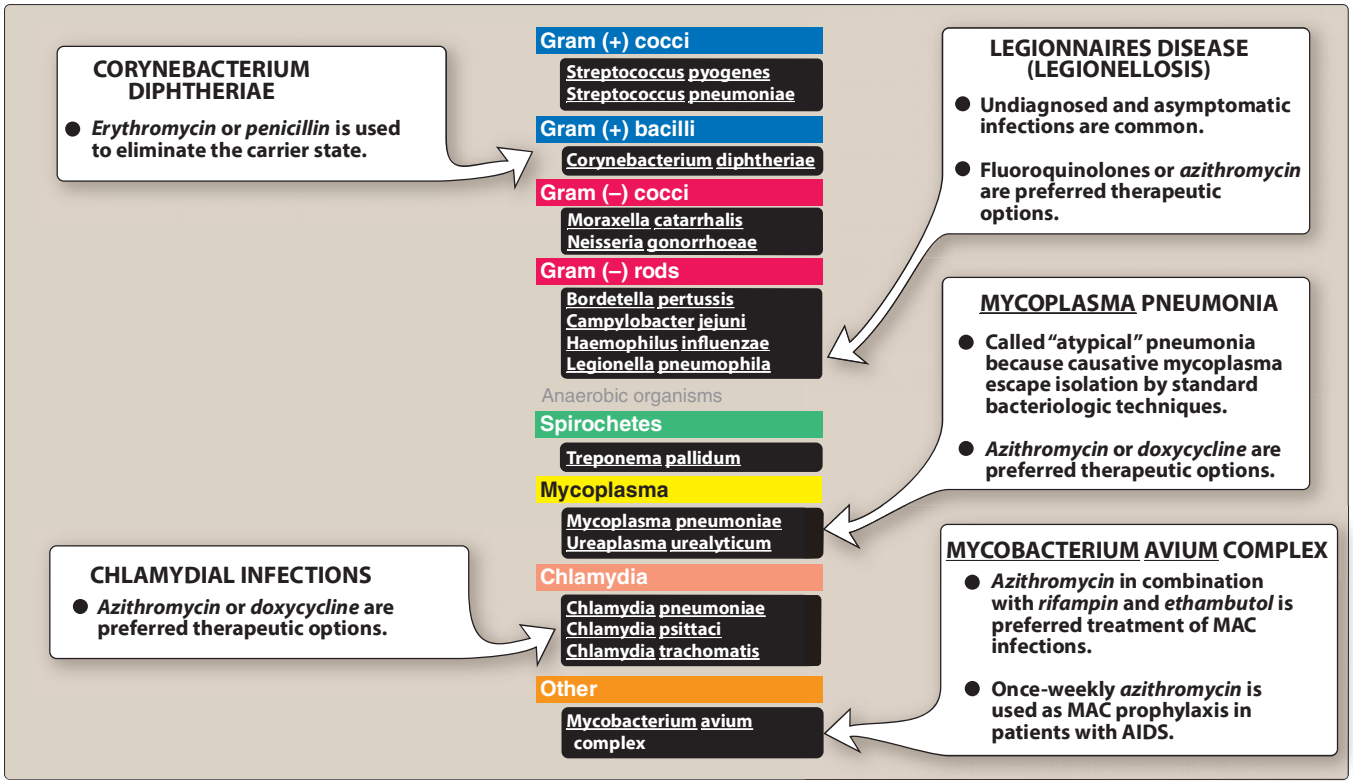

Figure 39.10
Typical therapeutic applications of macrolides.

synthesis (Figure 39.2). 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* (Figure 39.10). 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 Chlamydia, Legionella, Moraxella, Ureaplasma species and Helicobacter pylori, is higher than that of *erythromycin.*

3. **Azithromycin:** Although less active against streptococci and staphylococci than *erythromycin, azithromycin* is far more active against respiratory infections due to H. influenzae and Moraxella catarrhalis. Extensive use of *azithromycin* has resulted in growing Streptococcus pneumoniae resistance. *Azithromycin* is the preferred therapy for urethritis caused by Chlamydia trachomatis. Mycobacterium avium is preferentially treated with a macrolide-containing regimen, including *clarithromycin* or *azithromycin.*

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

C. Resistance

Resistance to macrolides is associated with: 1) the inability of the organism to take up the antibiotic, 2) the presence of efflux pumps, 3) a 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, and 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,* but *telithromycin* may be effective against macrolide-resistant organisms.

D. Pharmacokinetics

1. **Administration:** The *erythromycin* base is destroyed by gastric acid. Thus, either enteric-coated tablets or esterified forms of the antibiotic are administered. All are adequately absorbed upon oral administration (Figure 39.11). *Clarithromycin, azithromycin,* and *telithromycin* are stable in stomach acid and are readily absorbed. Food interferes with the absorption of *erythromycin* and *azithromycin* but can increase that of *clarithromycin. Erythromycin* and *azithromycin* are available in IV formulations.

2. **Distribution:** *Erythromycin* distributes well to all body fluids except the CSF. It is one of the few antibiotics that diffuses into prostatic fluid, and it also accumulates in macrophages. All four drugs concentrate in the liver. *Clarithromycin, azithromycin,* and *telithromycin* are widely distributed in the tissues. *Azithromycin* concentrates in neutrophils, macrophages, and fibroblasts, and serum levels are low. It has the longest half-life and the largest volume of distribution of the four drugs (Figure 39.12).

3. **Elimination:** *Erythromycin* and *telithromycin* are extensively metabolized hepatically. They inhibit the oxidation of a number of drugs through their interaction with the cytochrome P450 system. Interference with the metabolism of drugs, such as *theophylline*, statins, and numerous antiepileptics, has been reported for *clarithromycin*.

4. **Excretion:** *Erythromycin* and *azithromycin* are primarily concentrated and excreted in the bile as active drugs (Figure 39.11). Partial reabsorption occurs through the enterohepatic circulation. In contrast, *clarithromycin* and its metabolites are eliminated by the kidney as well as the liver. The dosage of this drug should be adjusted in patients with renal impairment.

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

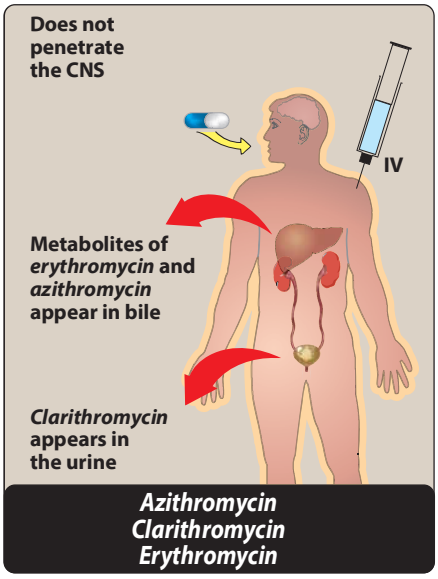

Figure 39.11
Administration and fate of the macrolide antibiotics. CNS = central nervous system.

	Erythromycin	Clarithromycin	Azithromycin	Telithromycin
Oral absorption	Yes	Yes	Yes	Yes
Half-life (hours)	2	3.5	>40	10
Conversion to an active metabolite	No	Yes	Yes	Yes
Percent excretion in urine	15	50	12	13

Figure 39.12
Some properties of the macrolide antibiotics.

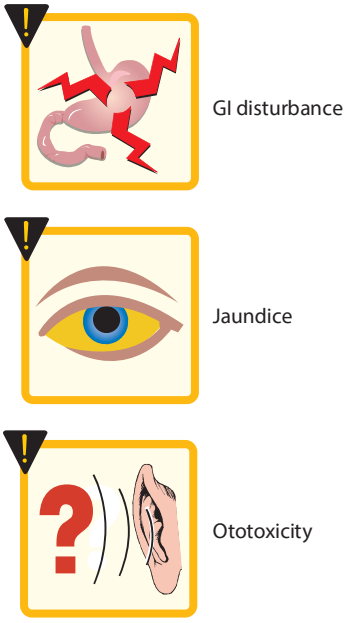

Figure 39.13
Some adverse effects of macrolide antibiotics.

compliance (especially with *erythromycin*). *Clarithromycin* and *azithromycin* seem to be better tolerated (Figure 39.13). 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, telithromycin,* or *azithromycin,* because these drugs accumulate in the liver. Severe hepatotoxicity with *telithromycin* has limited its use, given the availability of alternative therapies. Additionally, macrolides and ketolides may prolong the QT_c interval and should be used with caution in those patients with proarrhythmic conditions or concomitant use of proarrhythmic agents.

5. **Drug interactions:** *Erythromycin, telithromycin,* and *clarithromycin* inhibit the hepatic metabolism of a number of drugs, which can lead to toxic accumulation of these compounds (Figure 39.14). 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.

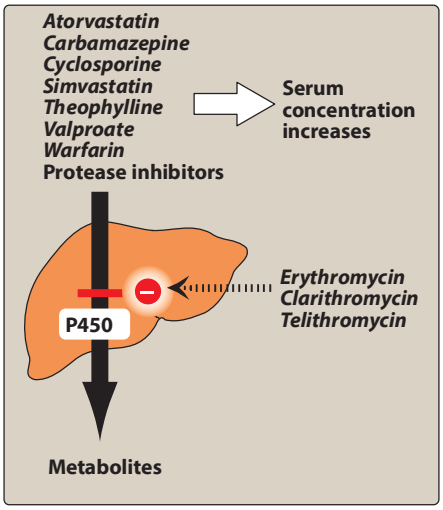

Figure 39.14
Inhibition of the cytochrome P450 system by *erythromycin, clarithromycin*, and *telithromycin.*

VI. FIDAXOMICIN

Fidaxomicin [fye-DAX-oh-MYE-sin] is a macrocyclic antibiotic with a structure similar to the macrolides; however, it has a unique mechanism of action. *Fidaxomicin* acts on the sigma subunit of RNA polymerase, thereby disrupting bacterial transcription, terminating protein synthesis, and resulting in cell death in susceptible organisms. *Fidaxomicin* has a very narrow spectrum of activity limited to gram-positive aerobes and anaerobes. While it possesses activity against staphylococci and enterococci, it is used primarily for its bactericidal activity against Clostridium difficile. Due to the unique target site, cross-resistance with other antibiotic classes has not been documented. Following oral administration, *fidaxomicin* has minimal systemic absorption and primarily remains within the gastrointestinal tract. This is ideal for the treatment of C. difficile infection, which occurs in the gut. This characteristic also likely contributes to the low rate of adverse effects. The most common adverse effects include nausea, vomiting, and abdominal pain. Hypersensitivity reactions including angioedema, dyspnea, and pruritus have occurred. *Fidaxomicin* should be used with caution in patients with a macrolide allergy, as they may be at increased risk for hypersensitivity. Anemia and neutropenia have been observed infrequently.

VII. CHLORAMPHENICOL

The use of *chloramphenicol* [klor-am-FEN-i-kole], 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 (Figure 39.2). 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, spirochetes, and anaerobes. 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.

D. Pharmacokinetics

Chloramphenicol is administered intravenously and is widely distributed throughout the body. It reaches therapeutic concentrations in the CSF. *Chloramphenicol* primarily undergoes hepatic metabolism to an inactive glucuronide, which is secreted by the renal tubule and eliminated in the urine. Dose reductions are necessary in patients with liver dysfunction or cirrhosis. It is also secreted into breast milk and should be avoided in breastfeeding mothers.

E. Adverse effects

1. **Anemias:** 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.

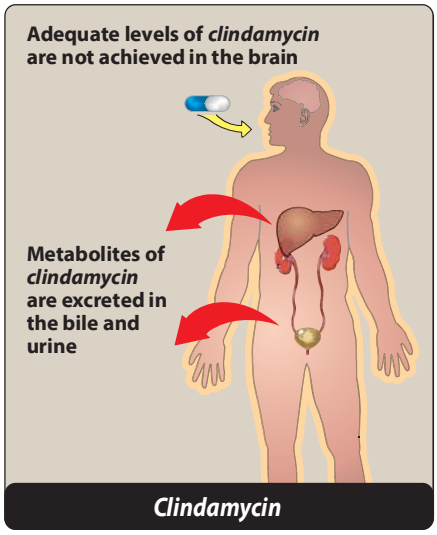

Figure 39.15
Administration and fate of *clindamycin.*

VIII. CLINDAMYCIN

Clindamycin [klin-da-MYE-sin] 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. C. difficile is always resistant to *clindamycin*, and the utility of *clindamycin* for gram-negative anaerobes (for example, Bacteroides *sp.*) is decreasing due to increasing resistance. *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 (Figure 39.15). 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.

IX. QUINUPRISTIN/DALFOPRISTIN

Quinupristin/dalfopristin [KWIN-yoo-pris-tin/DAL-foh-pris-tin] is a mixture of two streptogramins in a ratio of 30 to 70, respectively. Due to significant adverse effects, the drug is normally reserved for the treatment of severe *vancomycin*-resistant Enterococcus faecium (VRE) in the absence of other therapeutic options.

A. Mechanism of action

Each component of this combination drug binds to a separate site on the 50S bacterial ribosome. *Dalfopristin* disrupts elongation by interfering with the addition of new amino acids to the peptide chain. *Quinupristin* prevents elongation similar to the macrolides and causes release of incomplete peptide chains. Thus, they synergistically interrupt protein synthesis. The combination drug is bactericidal and has a long PAE.

B. Antibacterial spectrum

The combination drug is active primarily against gram-positive cocci, including those resistant to other antibiotics. Its primary use is in the treatment of E. faecium infections, including VRE strains, for which it is bacteriostatic. The drug is not effective against E. faecalis.

C. Resistance

Enzymatic processes commonly account for resistance to these agents. For example, the presence of a ribosomal enzyme that methylates the target bacterial 23S ribosomal RNA site can interfere in *quinupristin* binding. In some cases, the enzymatic modification can change the action from bactericidal to bacteriostatic. Plasmid-associated

acetyltransferase inactivates *dalfopristin.* An active efflux pump can also decrease levels of the antibiotics in bacteria.

D. Pharmacokinetics

Quinupristin/dalfopristin is injected intravenously (the drug is incompatible with a saline medium). The combination drug is particularly useful for intracellular organisms (for example, VRE) due to its excellent penetration of macrophages and neutrophils. Levels in the CSF are low. Both compounds undergo hepatic metabolism, with excretion mainly in the feces.

E. Adverse effects

Venous irritation commonly occurs when *quinupristin/dalfopristin* is administered through a peripheral rather than a central line. Hyperbilirubinemia occurs in about 25% of patients, resulting from a competition with the antibiotic for excretion. Arthralgia and myalgia have been reported when higher doses are used. *Quinupristin/dalfopristin* inhibits the cytochrome P450 (CYP3A4) isoenzyme, and concomitant administration with drugs that are metabolized by this pathway may lead to toxicities.

X. LINEZOLID

Linezolid [lih-NEH-zo-lid] is a synthetic oxazolidinone developed to combat resistant gram-positive organisms, such as *methicillin*-resistant Staphylococcus aureus, VRE, and *penicillin*-resistant streptococci.

A. Mechanism of action

Linezolid binds to the bacterial 23S ribosomal RNA of the 50S subunit, thereby inhibiting the formation of the 70S initiation complex (Figure 39.2).

B. Antibacterial spectrum

The antibacterial action of *linezolid* is directed primarily against gram-positive organisms, such as staphylococci, streptococci, and enterococci, as well as *Corynebacterium* species and Listeria monocytogenes (Figure 39.16). It is also moderately active against Mycobacterium tuberculosis and may be used against drug-resistant strains. However, its main clinical use is against drug-resistant gram-positive organisms. Like other agents that interfere with bacterial protein synthesis, *linezolid* is bacteriostatic. However, it is bactericidal against streptococci. *Linezolid* is an alternative to *daptomycin* for infections caused by VRE. Use of *linezolid* for the treatment of MRSA bacteremia is not recommended.

C. Resistance

Resistance primarily occurs via reduced binding at the target site. Reduced susceptibility and resistance have been reported in S. aureus and Enterococcus *sp.* Cross-resistance with other protein synthesis inhibitors does not occur.

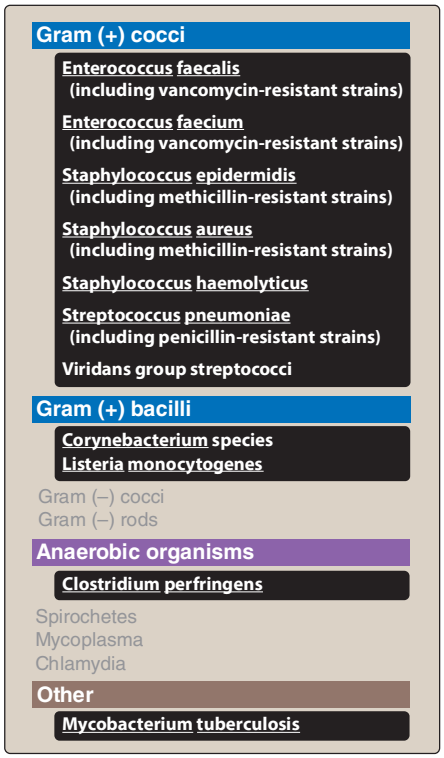

Figure 39.16
Antimicrobial spectrum of *linezolid.*

D. Pharmacokinetics

Linezolid is completely absorbed after oral administration. An IV preparation is also available. The drug is widely distributed throughout the body. Although the metabolic pathway of linezolid has not been fully determined, it is known that it is metabolized via oxidation to two inactive metabolites. The drug is excreted both by renal and nonrenal routes. No dose adjustments are required for renal or hepatic dysfunction.

E. Adverse effects

The most common adverse effects are gastrointestinal upset, nausea, diarrhea, headache, and rash. Thrombocytopenia has been reported, mainly in patients taking the drug for longer than 10 days. *Linezolid* possesses nonselective monoamine oxidase activity and may lead to serotonin syndrome if given concomitantly with large quantities of tyramine-containing foods, selective serotonin reuptake inhibitors, or monoamine oxidase inhibitors. The condition is reversible when the drug is discontinued. Irreversible peripheral neuropathies and optic neuritis (causing blindness) have been associated with greater than 28 days of use, limiting utility for extended-duration treatments.

Study Questions

Choose the ONE best answer.

39.1 Which of the following antibiotic combinations is inappropriate based on antagonism at the same site of action?

A. Clindamycin and erythromycin.
B. Doxycycline and amoxicillin.
C. Tigecycline and azithromycin.
D. Ciprofloxacin and amoxicillin.

Correct answer = A. Clindamycin and erythromycin share the same site of action on the 50S ribosomal subunit and may result in antagonism, rendering both drugs ineffective. They also share cross-resistance.

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

A. Cause rupture of tendons.
B. Deposit in tissues undergoing calcification.
C. Do not cross into the cerebrospinal fluid.
D. Can cause aplastic anemia.

Correct answer = B. Tetracyclines are contraindicated in this age group because they are deposited in tissues undergoing calcification, such as teeth and bone, and can stunt growth. Ciprofloxacin can interfere in cartilage formation and cause rupture of tendons and is also contraindicated in children, but it is a fluoroquinolone. Tetracyclines can cross into the cerebrospinal fluid. They do not cause aplastic anemia, a property usually associated with chloramphenicol.

39.3 A 30-year-old pregnant female has cellulitis caused by MRSA. Which of the following antibiotics would be the most appropriate option for outpatient therapy?

A. Doxycycline.
B. Clindamycin.
C. Quinupristin/dalfopristin.
D. Tigecycline.

Correct answer = B. Clindamycin is the safest option for the treatment of MRSA in a pregnant patient. Doxycycline and tigecycline can cross the placenta and can cause harm to the fetus. Moreover, quinupristin/dalfopristin and tigecycline are only available intravenously and would not be appropriate for home antibiotic therapy for the given indication.

39.4 A patient is being discharged from the hospital on a 3-week course of clindamycin. Which of the following potential adverse effects should be discussed with her?

A. Hyperbilirubinemia.
B. Nephrotoxicity.
C. Clostridium difficile diarrhea.
D. Pseudotumor cerebri.

Correct answer = C. Clindamycin, among other antibiotics, is associated with the development of C. difficile and pseudomembranous colitis due to disruption of normal gut flora, particularly with prolonged therapy. Hyperbilirubinemia is associated with quinupristin/dalfopristin, nephrotoxicity is associated with aminoglycosides, and pseudotumor cerebri can occur with tetracyclines.