Pharmacology

Subject : protein synthesis inhibitors

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وَقُل رَّبِّ زِدْنِي عِلْمًا

Protein Synthesis Inhibitors

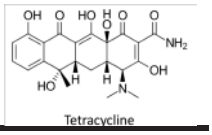
30

Jacqueline Jourjy

these drugs will have more adverse effects

I. OVERVIEW

A number of antibiotics exert their antimicrobial effects by targeting bacterial ribosomes and inhibiting bacterial protein synthesis. Most of these agents exhibit bacteriostatic activity. 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, because the structure of mitochondrial ribosomes more closely resembles bacterial ribosomes. Figure 30.1 summarizes the antimicrobial protein synthesis inhibitors discussed in this chapter.


Tetracycline

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 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 30.2).

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. They are commonly used in the treatment of acne and Chlamydia infections (Figure 30.3).

TETRACYCLINES
Demeclocycline DECLOMYCIN
Doxycycline DORYX, VIBRAMYCIN
Minocycline MINOCIN
Tetracycline GENERIC ONLY
GLYCYLCYCLINES
Tigecycline TYGACIL
AMINOGLYCOSIDES
Amikacin GENERIC ONLY
Gentamicin GENERIC ONLY
Neomycin GENERIC ONLY
Streptomycin GENERIC ONLY
Tobramycin TOBI, TOBREX
MACROLIDES/KETOLIDES
Azithromycin ZITHROMAX
Clarithromycin BIAXIN
Erythromycin E.E.S., ERY-TAB
Telithromycin GENERIC ONLY
MACROCYCLIC
Fidaxomicin DIFICID
LINCOSAMIDES
Clindamycin CLEOCIN
OXAZOLIDINONES
Linezolid ZYVOX
Tedizolid SIVEXTRO
OTHERS
Chloramphenicol GENERIC ONLY
Quinupristin/Dalfopristin SYNERCID

Figure 30.1
Summary of protein synthesis inhibitors.

Commonly used for the treatment of:

1. Acne (doxycycline)
2. Chlamydia (doxycycline)
3. Peptic ulcer disease (tetracycline)
4. Lyme Disease (doxycycline)
5. Mycoplasma Pneumonia (doxycycline)

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mycoplasma ← lack a cell wall ∴ cause atypical infection

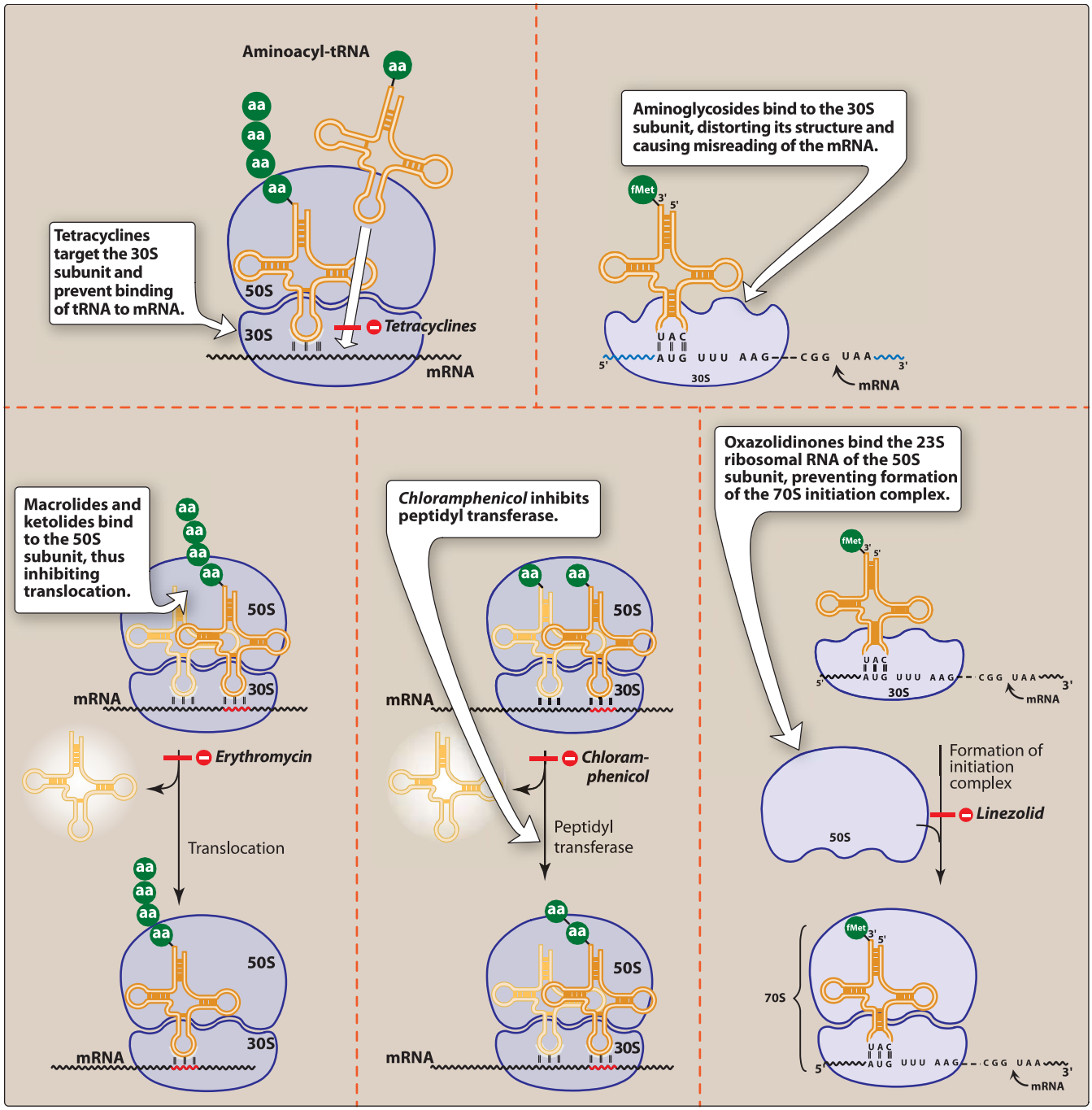
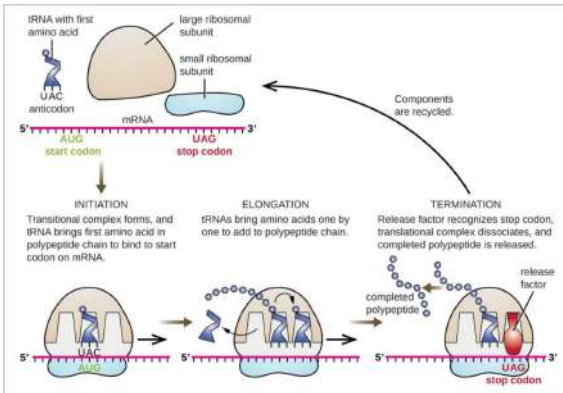
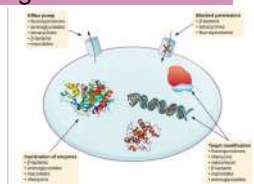


Figure 30.2
Mechanisms of action of the various protein synthesis inhibitors. aa = amino acid.



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 binding to the ribosome. Resistance to one tetracycline does



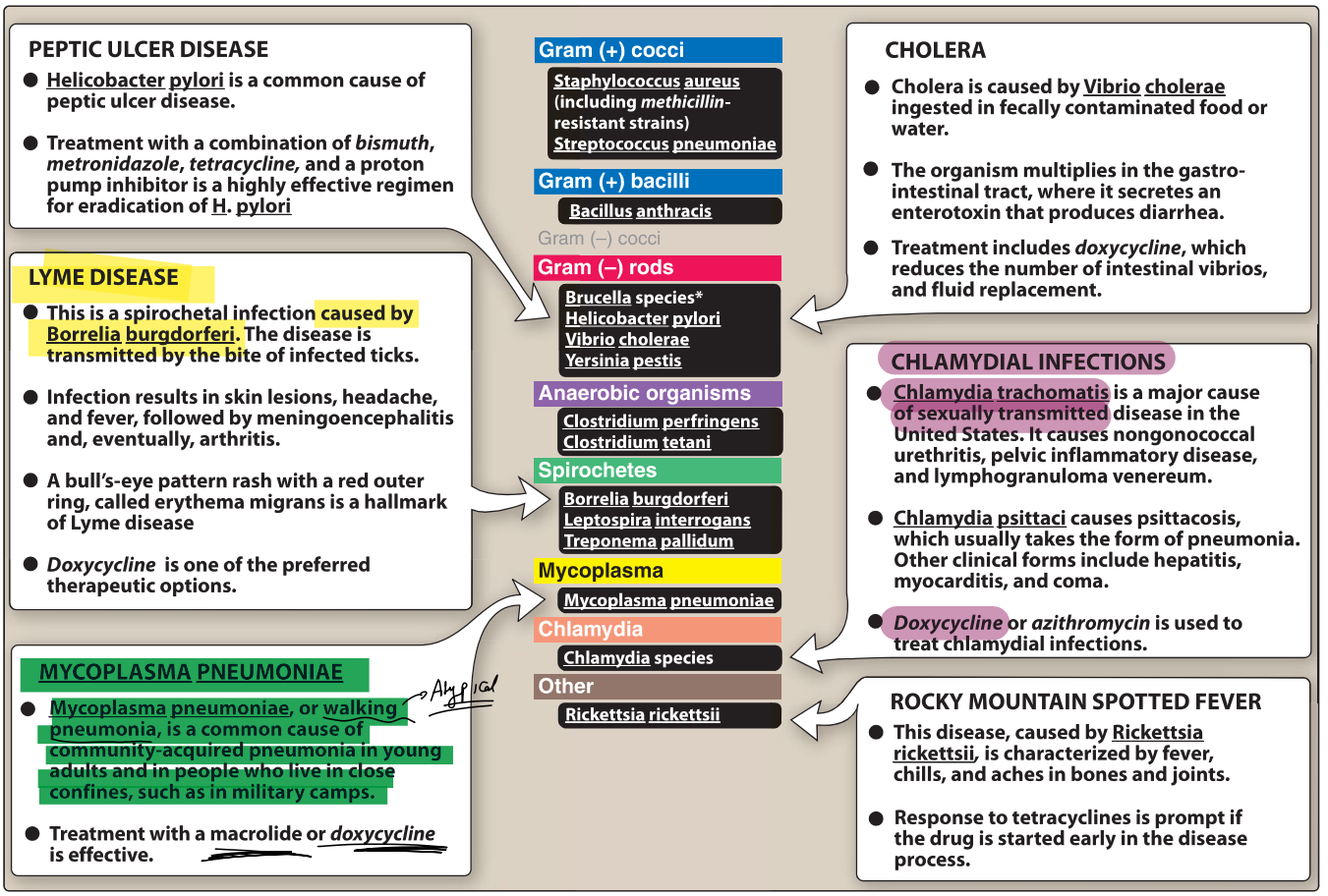


Figure 30.3
Typical therapeutic applications of tetracyclines. *A *tetracycline* + *gentamicin*.

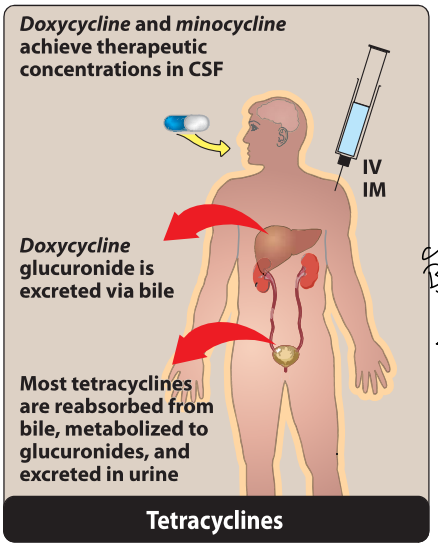


Figure 30.4
Administration and fate of tetracyclines. CSF = cerebrospinal fluid.

not confer universal resistance to all tetracyclines, and the development of cross-resistance may be dependent on the mechanism of resistance.

D. Pharmacokinetics

1. **Absorption:** Tetracyclines are adequately absorbed after oral ingestion (Figure 30.4). Administration with dairy products or other substances that contain divalent and trivalent cations (for example, magnesium, calcium and aluminum antacids, or iron supplements) decreases absorption, particularly for *tetracycline* [tet-rah-SYE-kleen], due to the formation of nonabsorbable chelates (Figure 30.5). 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 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 concentrations in saliva and tears, rendering it useful in eradicating the meningococcal carrier state. All *tetracyclines* cross the placental barrier and concentrate in fetal bones and dentition.

3. **Elimination:** *Tetracycline* is primarily eliminated unchanged in the urine, whereas *minocycline* undergoes hepatic metabolism and is eliminated to a lesser extent via the kidney. *Doxycycline* is preferred in patients with renal dysfunction, 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 30.6) 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. For this reason, 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.

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.

GLYCYLCYCLINES

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

A. Mechanism of action

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

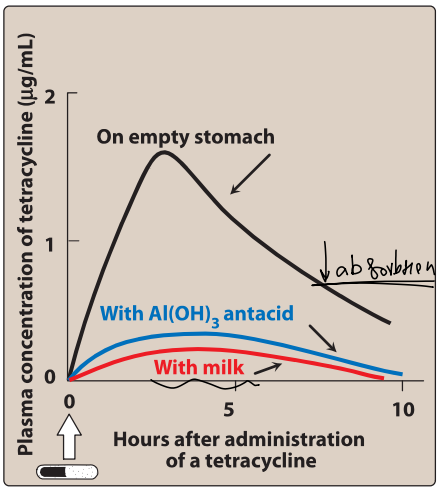


Figure 30.5
Effect of antacids and milk on the absorption of tetracyclines.

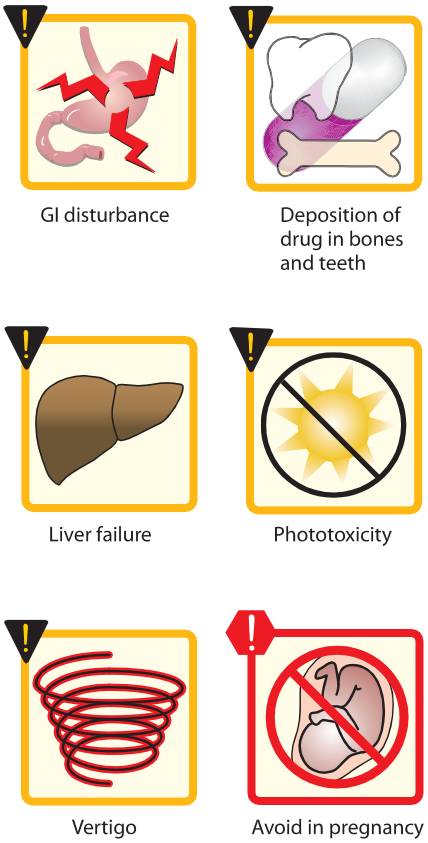


Figure 30.6
Some adverse effects of tetracyclines. GI = gastrointestinal.

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. *Tigecycline* is not active against Morganella, Proteus, Providencia, or Pseudomonas species.

C. Resistance

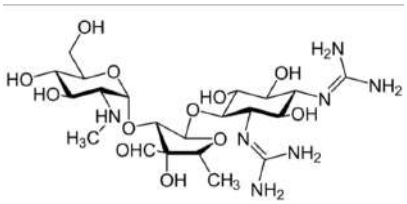
Tigecycline was developed to overcome the emergence of tetracycline class–resistant organisms that utilize efflux pumps and ribosomal protection to confer resistance. Resistance to *tigecycline* has been observed and is primarily attributed to overexpression of efflux pumps.

D. Pharmacokinetics

Following IV infusion, *tigecycline* exhibits a large volume of distribution. It penetrates tissues well but achieves 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. All-cause mortality in patients treated with *tigecycline* is higher than with other agents. A boxed warning states that *tigecycline* should be reserved for use in situations when alternative treatments are not suitable. 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*. Therefore, the international normalized ratio should be monitored closely when *tigecycline* is coadministered with *warfarin*.



IV. AMINOGLYCOSIDES

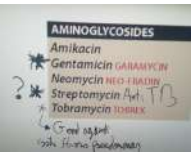
Aminoglycosides are used for the treatment of serious infections due to aerobic gram-negative bacilli; however, their clinical utility is limited due to serious toxicities.

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 (Figure 30.2). Aminoglycosides have concentration-dependent bactericidal activity; that is, their 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 concentrations fall below the MIC. The larger the dose, the longer the PAE. Because of these properties, high-dose extended-interval dosing is commonly utilized. This dosing strategy also 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 30.7.

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 concentrations (Figure 30.8). [Note: *Neomycin* is not given parenterally due to severe nephrotoxicity. It is administered topically for skin infections or orally to decontaminate the gastrointestinal tract prior to colorectal surgery.]

2. **Distribution:** Because of their hydrophilicity, aminoglycoside tissue concentrations may be subtherapeutic, and penetration into most body fluids is variable. Concentrations achieved in CSF are inadequate, even in the presence of inflamed meninges. For central nervous system infections, the intrathecal or intraventricular routes may be utilized. All aminoglycosides cross the placental barrier and may accumulate in fetal plasma and amniotic fluid.

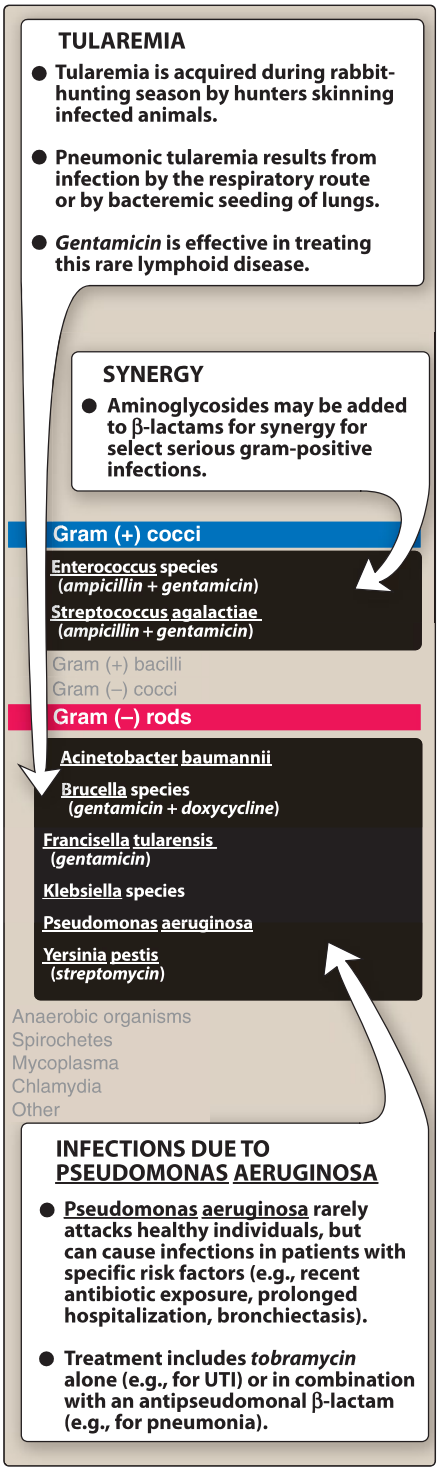


Figure 30.7
Typical therapeutic applications of aminoglycosides. UTI = urinary tract infection.

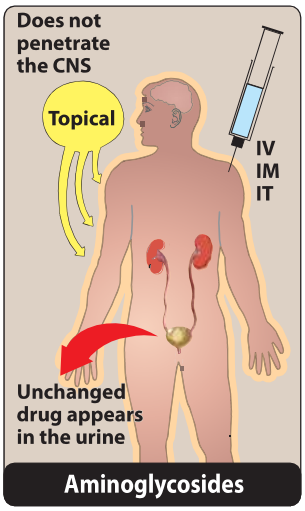


Figure 30.8
Administration and fate of aminoglycosides. CNS = central nervous system.

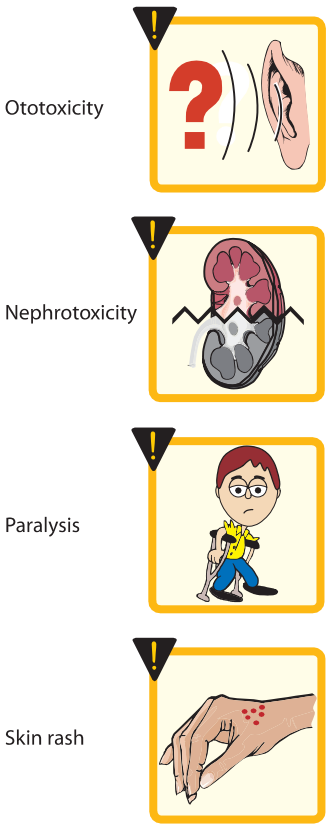


Figure 30.9
Some adverse effects of aminoglycosides.

3. **Elimination:** More than 90% of the parenteral aminoglycosides are excreted unchanged in the urine (Figure 30.8). Accumulation occurs in patients with renal dysfunction; thus, dose adjustments are required. *Neomycin* is primarily excreted unchanged in the feces.

E. Adverse effects

Therapeutic drug monitoring of *gentamicin*, *tobramycin*, and *amikacin* plasma concentrations is imperative to ensure appropriateness of dosing and to minimize dose-related toxicities (Figure 30.9). The elderly are particularly susceptible to nephrotoxicity and ototoxicity.

1. **Ototoxicity:** Ototoxicity (vestibular and auditory) is directly related to high peak plasma concentrations and the duration of treatment. Aminoglycosides accumulate 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 concentration (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.*

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 have 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 a "ketolide" antimicrobial agent (no longer used in the United States).

A. Mechanism of action

The macrolides and ketolides bind irreversibly to a site on the 50S subunit of the bacterial ribosome, thus inhibiting translocation steps