Protein Synthesis Inhibitors

- 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.

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.

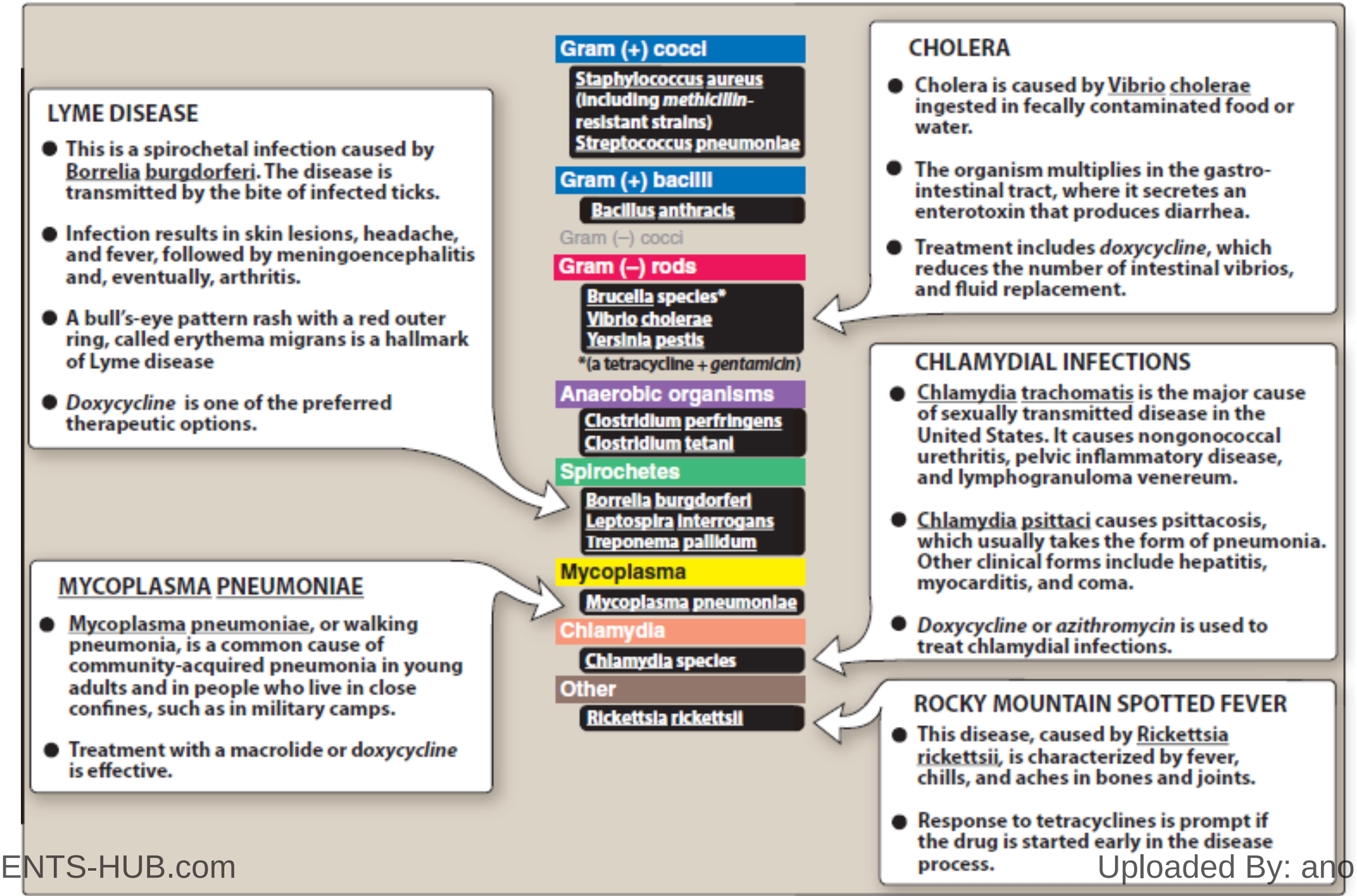
A. Mechanism of action

- 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

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 (*doxycycline*).



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

- **1. Absorption:**
- Tetracyclines are adequately absorbed after oral ingestion.

- 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

- Both *doxycycline* [dox-i-SYE-kleen] and *minocycline* [min-oh-SYE-kleen] are available as oral and intravenous (IV) preparations.

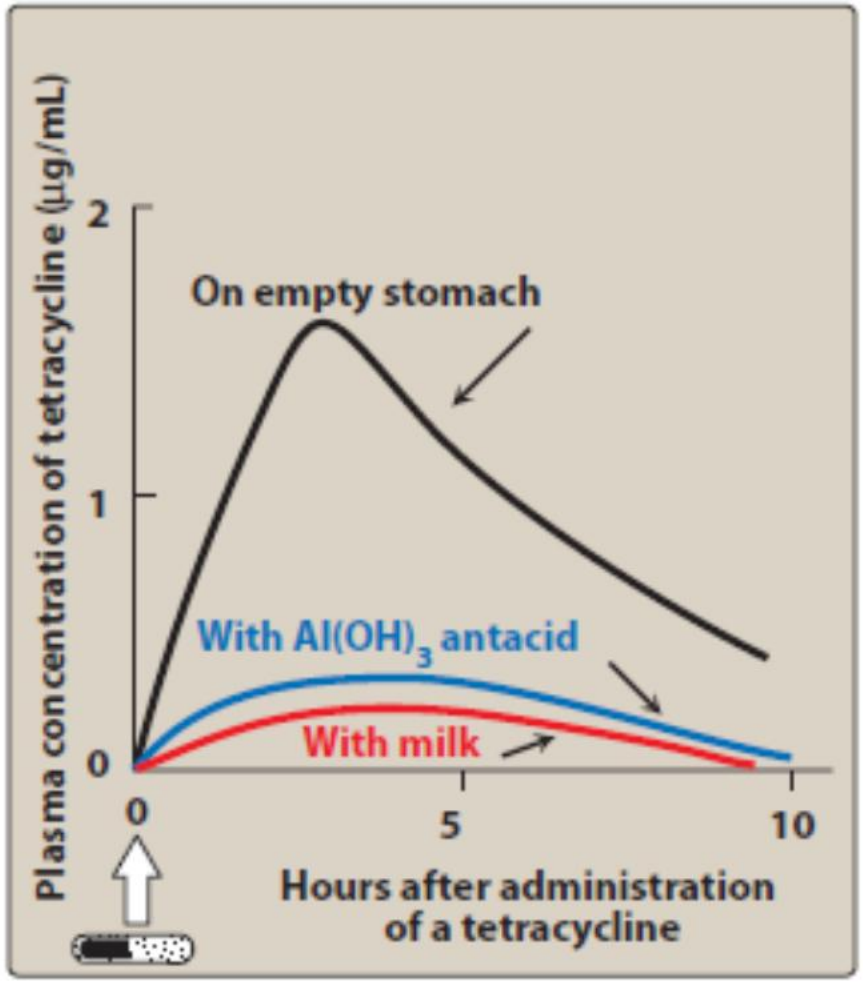
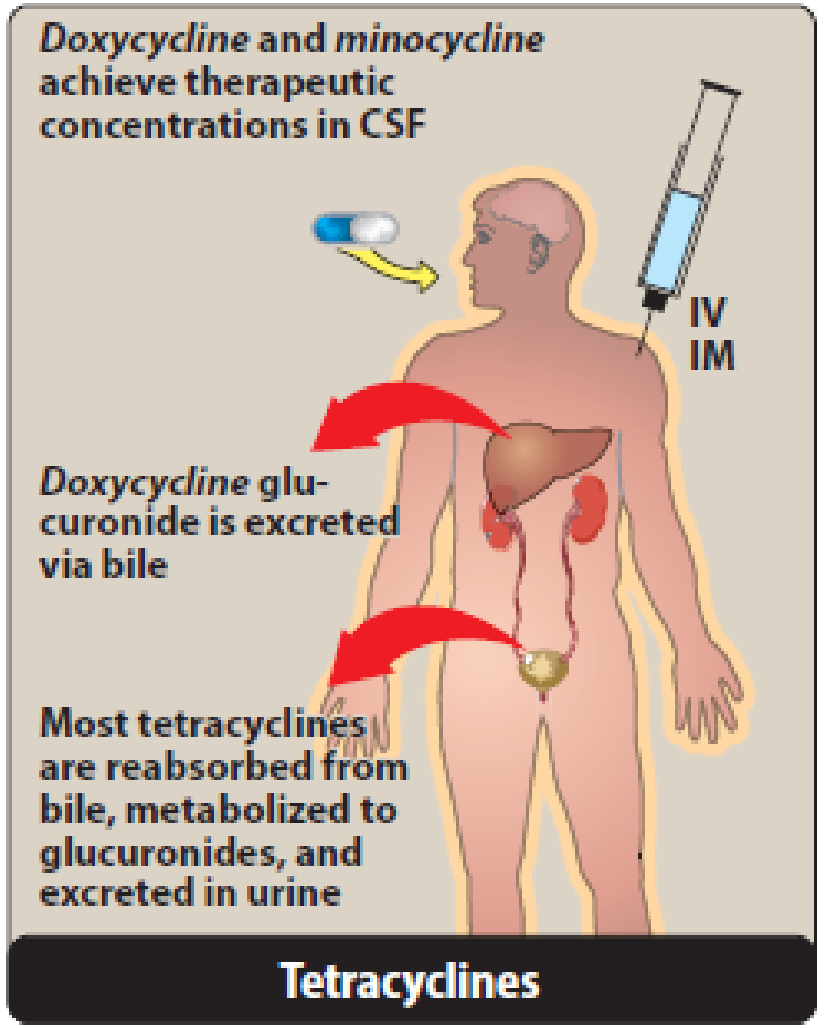


Figure 39.5

Effect of antacids and milk on the absorption of tetracyclines.

- **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 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.

- 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 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:**

- Pregnant or

- breast-feeding women or in

- children less than 8 years of age.

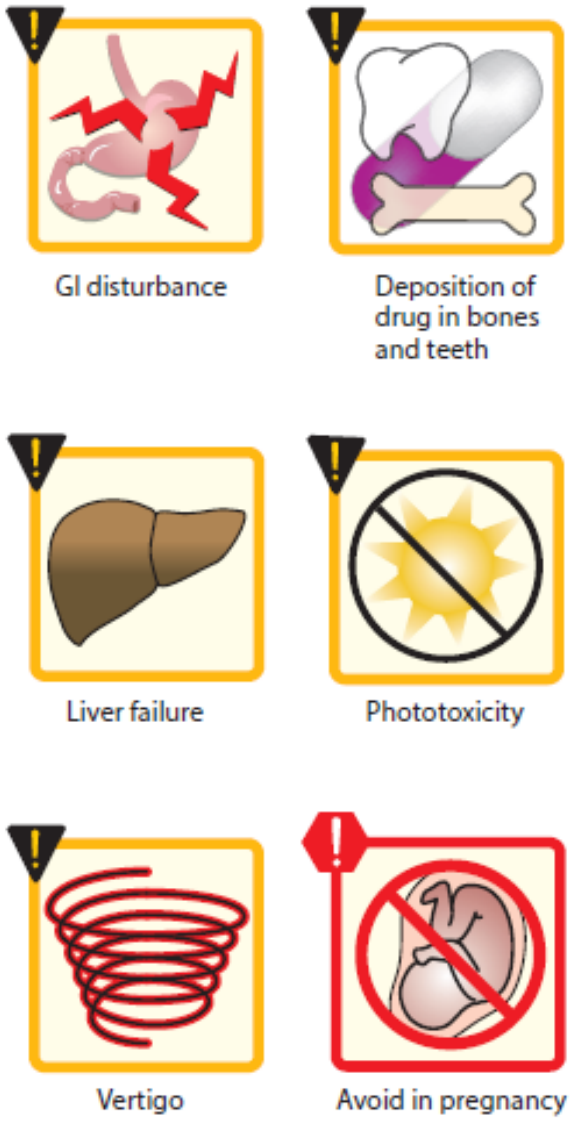


Figure 39.6
Some adverse effects of tetracyclines.

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.

- **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

- *amikacin* [am-i-KAY-sin],
- *gentamicin* [jen-ta-MYE-sin],
- *tobramycin* [toe-bra-MYE-sin], and
- *streptomycin* [strep-toe-MYE-sin
- neomycin [nee-oh-MYEsin

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 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.

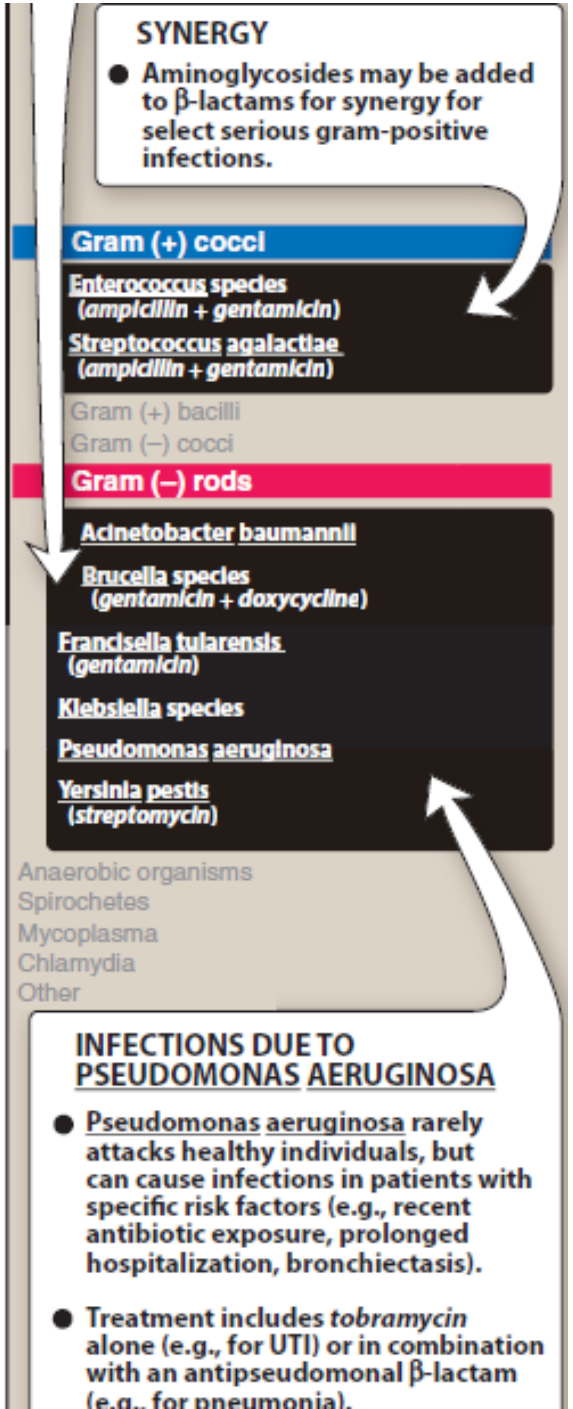
- The larger the dose, the longer the PAE. Because of these properties, extended interval dosing (a single large dose given once daily) is now more commonly utilized than divided daily doses. This reduces the risk of nephrotoxicity and increases convenience.

B. Antibacterial spectrum

- The aminoglycosides are effective for the majority of aerobic gram negative bacilli, including those that may be multidrug resistant, 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—
  -]—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-MYEsin]) 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:

- 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

- 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 .

- 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.

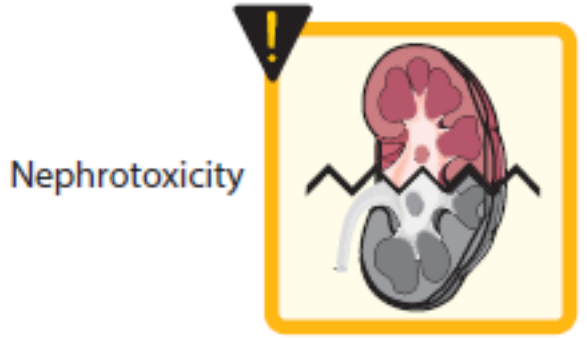
- This results in kidney damage ranging from
  - mild, reversible renal impairment to
  - severe, potentially irreversible, acute tubular necrosis.

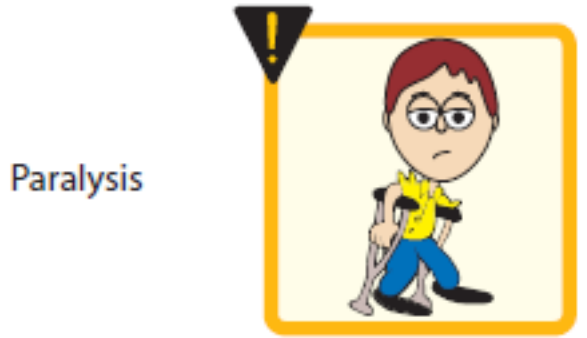
- **3. Neuromuscular paralysis:**
- This adverse effect is associated with a rapid increase in concentrations (for example, high doses infused over a short period.) or concurrent administration with neuromuscular blockers.

- 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.*





V. MACROLIDES AND KETOLIDES

- *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* [klarith- 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 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
  - 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.

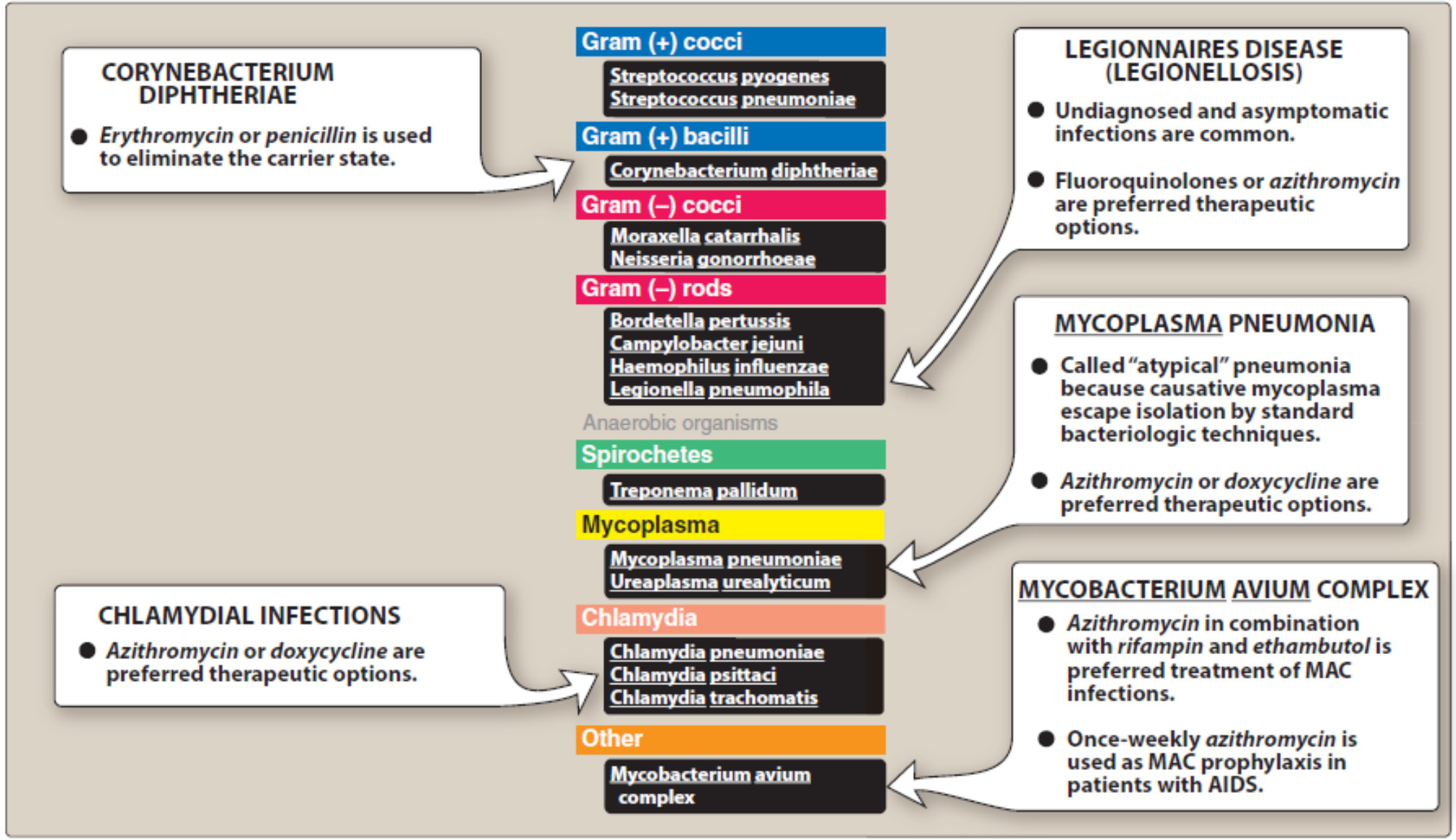
- Extensive use of *azithromycin* has resulted in growing Streptococcus pneumoniae resistance.

- *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 .

- *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.

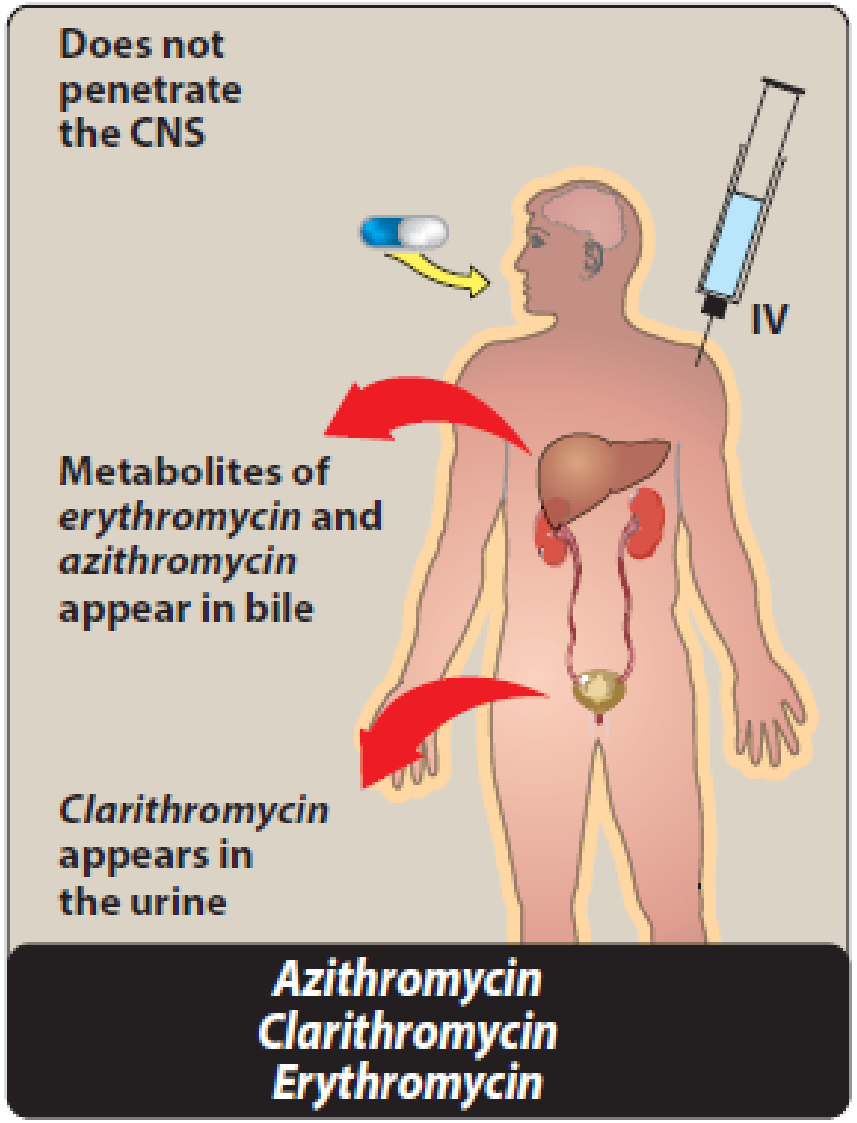
- **2. Distribution:**
- *Erythromycin* distributes well to all body fluids except the CSF.
- It is one of the few antibiotics that diffuses into prostatic fluid, and it also accumulates in macrophages.
- All four drugs concentrate in the liver.
- *Clarithromycin, azithromycin,* and *telithromycin* are 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

- **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.
- 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.



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

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, 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 QTc 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.

- 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.

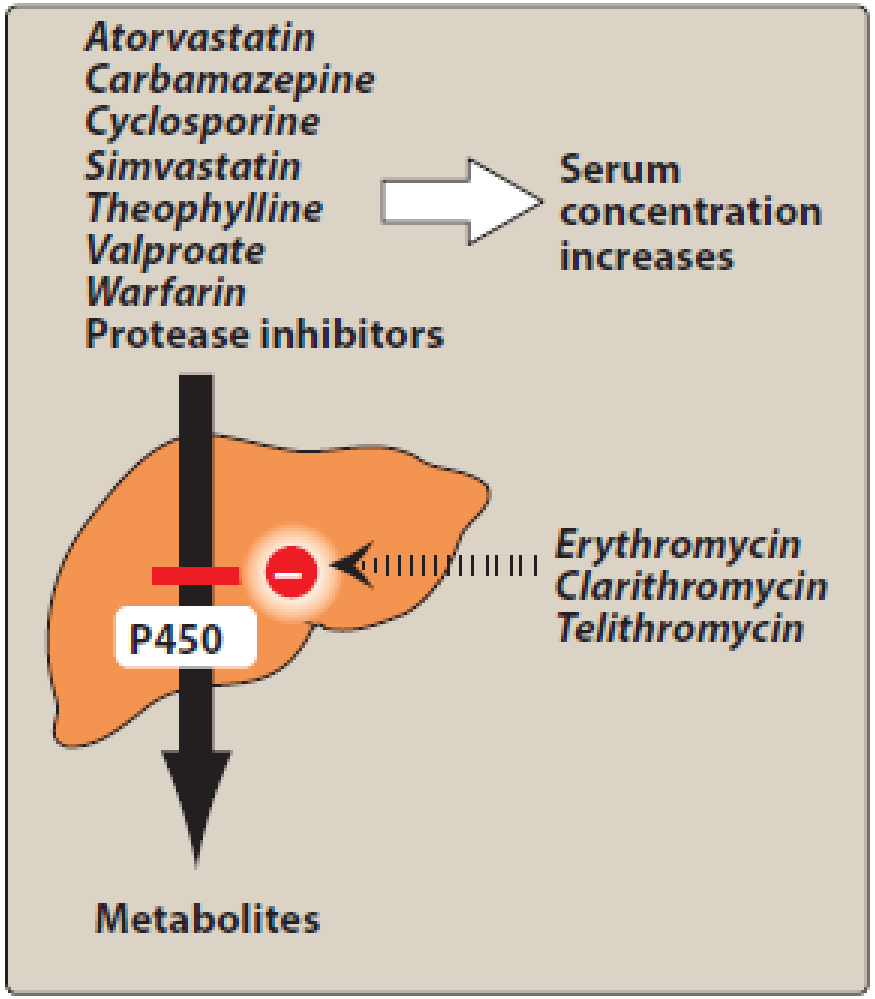


Figure 39.14
Inhibition of the cytochrome P450 system by *erythromycin*, *clarithromycin*, and *telithromycin*.

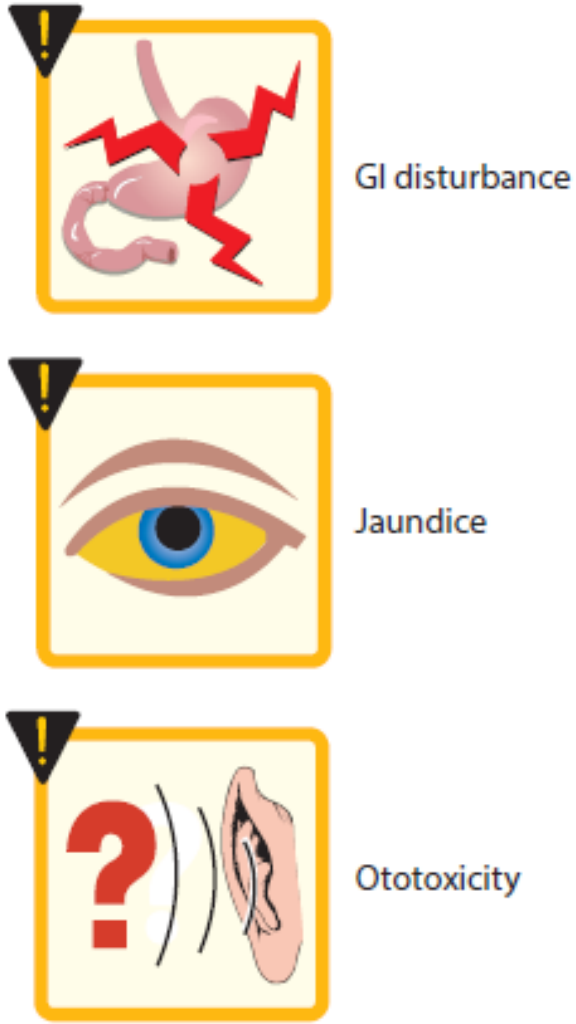


Figure 39.13
Some adverse effects of macrolide antibiotics.