Pharmacology I

Protein Synthesis Inhibitors

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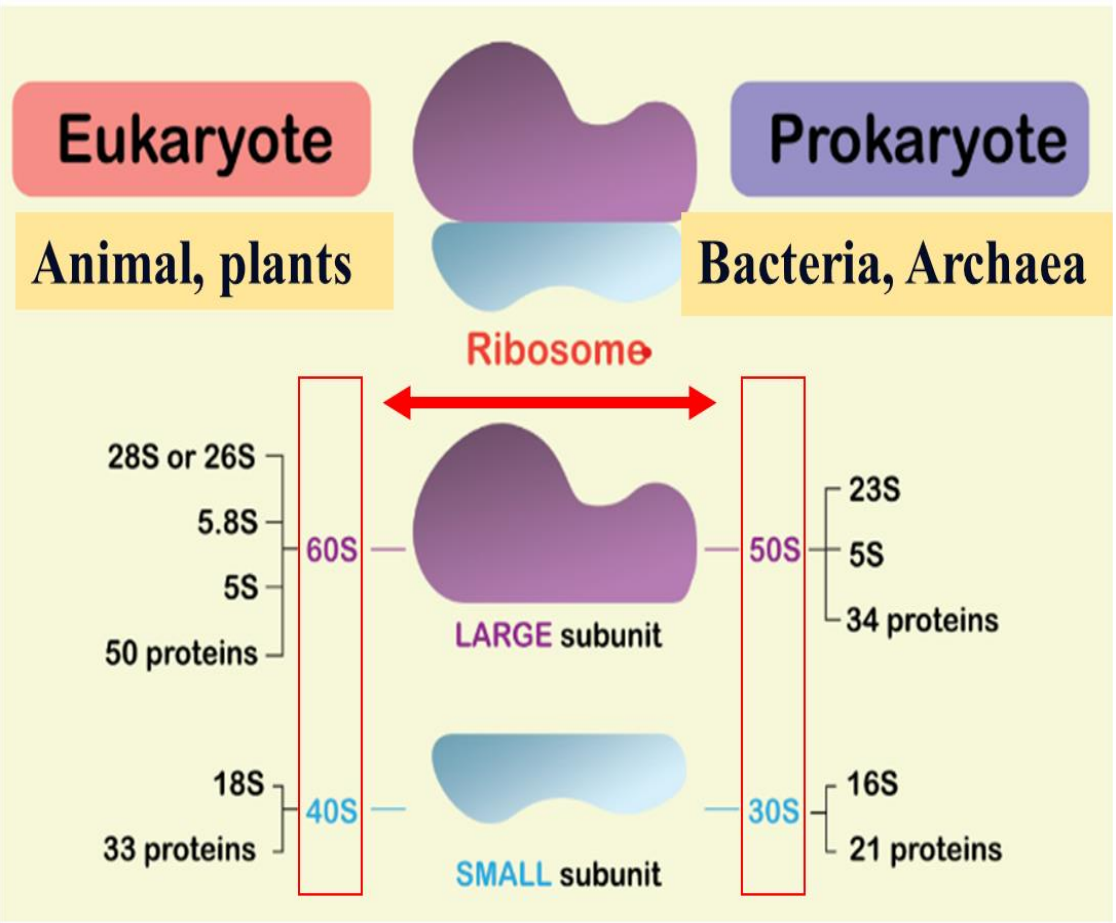
Lecture No. : 9

Protein Synthesis Inhibitors

- 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** are composed of **30S and 50S subunits** which differ structurally from **mammalian cytoplasmic ribosomes** which have **40S and 60S subunits**.



Protein Synthesis Inhibitors

- 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*.

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

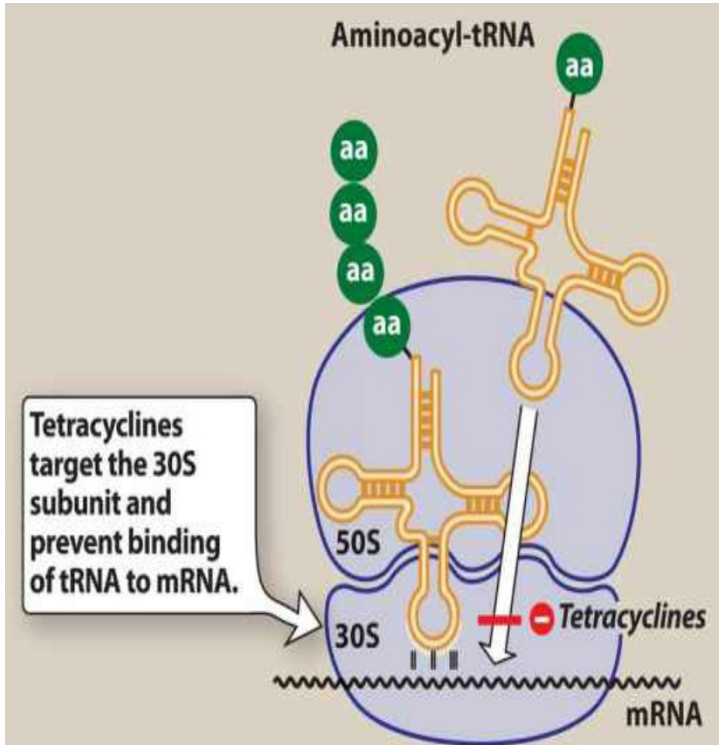
OTHERS

Chloramphenicol GENERIC ONLY
Quinupristin/Dalfopristin SYNE

Tetracyclines

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**.



TETRACYCLINES

B. Antibacterial spectrum

- The tetracyclines are **bacteriostatic antibiotics** effective against a wide variety of organisms, including

1. **Gram-positive**
2. **Gram-negative bacteria,**
3. **Protozoa,**
4. **Spirochetes,**
5. **Mycobacteria,**
6. **Atypical species.**

- They are commonly used in the **treatment of acne and Chlamydia infections**.

PEPTIC ULCER DISEASE

- Helicobacter pylori is a common cause of peptic ulcer disease.
- Treatment with a combination of *bismuth*, *metronidazole*, *tetracycline*, and a proton pump inhibitor is a highly effective regimen for eradication of H. pylori

LYME DISEASE

- This is a spirochetal infection caused by Borrelia burgdorferi. The disease is transmitted by the bite of infected ticks.
- Infection results in skin lesions, headache, and fever, followed by meningoencephalitis and, eventually, arthritis.
- A bull's-eye pattern rash with a red outer ring, called erythema migrans is a hallmark of Lyme disease
- *Doxycycline* is one of the preferred therapeutic options.

MYCOPLASMA PNEUMONIAE

- Mycoplasma pneumoniae, or walking pneumonia, is a common cause of community-acquired pneumonia in young adults and in people who live in close confines, such as in military camps.
- Treatment with a macrolide or *doxycycline* is effective.

Gram (+) cocci
- Staphylococcus aureus (including *methicillin*-resistant strains)
- Streptococcus pneumoniae

Gram (+) bacilli
- Bacillus anthracis

Gram (–) cocci

Gram (–) rods
- Brucella species*
- Helicobacter pylori
- Vibrio cholerae
- Yersinia pestis

Anaerobic organisms
- Clostridium perfringens
- Clostridium tetani

Spirochetes
- Borrelia burgdorferi
- Leptospira interrogans
- Treponema pallidum

Mycoplasma
- Mycoplasma pneumoniae

Chlamydia
- Chlamydia species

Other
- Rickettsia rickettsii

CHOLERA

- Cholera is caused by Vibrio cholerae ingested in fecally contaminated food or water.
- The organism multiplies in the gastrointestinal tract, where it secretes an enterotoxin that produces diarrhea.
- Treatment includes *doxycycline*, which reduces the number of intestinal vibrios, and fluid replacement.

CHLAMYDIAL INFECTIONS

- Chlamydia trachomatis is a major cause of sexually transmitted disease in the United States. It causes nongonococcal urethritis, pelvic inflammatory disease, and lymphogranuloma venereum.
- Chlamydia psittaci causes psittacosis, which usually takes the form of pneumonia. Other clinical forms include hepatitis, myocarditis, and coma.
- *Doxycycline* or *azithromycin* is used to treat chlamydial infections.

ROCKY MOUNTAIN SPOTTED FEVER

- This disease, caused by Rickettsia rickettsii, is characterized by fever, chills, and aches in bones and joints.
- Response to tetracyclines is prompt if the drug is started early in the disease process.

TETRACYCLINES

C. Resistance

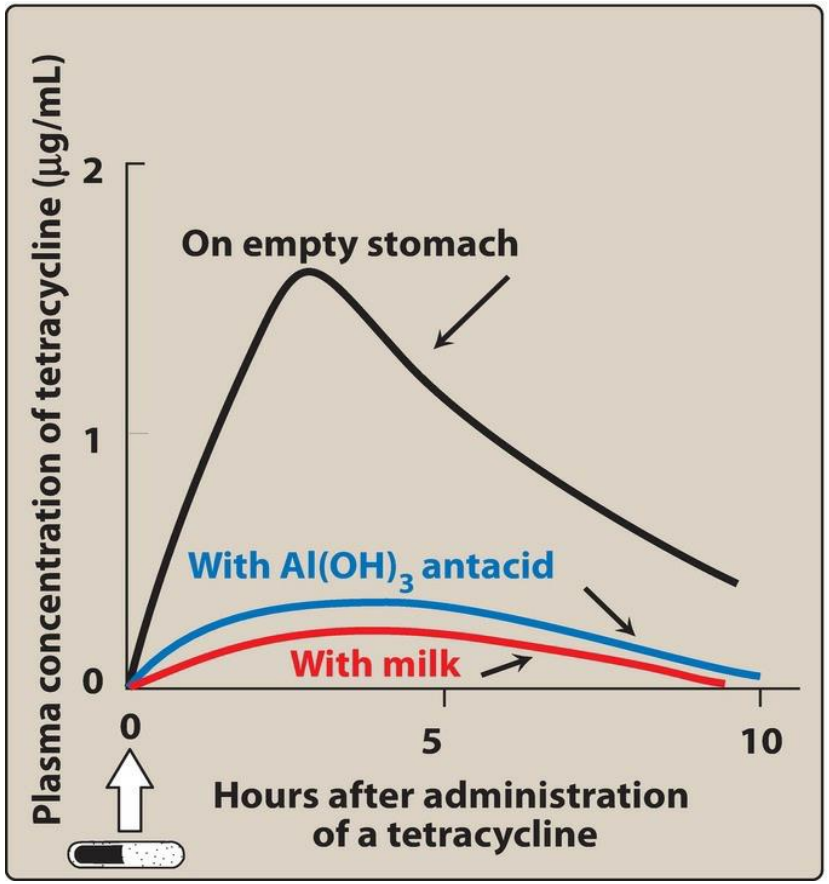
- The **most commonly** encountered naturally occurring resistance to tetracyclines is **an efflux pump that expels drug out of the cell**, thus preventing intracellular accumulation.
- **Other mechanisms** of bacterial resistance to tetracyclines include **enzymatic inactivation of the drug** and **production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

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, calcium and aluminum antacids, or iron supplements} decreases absorption, particularly for *tetracycline*, due to the formation of non-absorbable chelates.
- Both ***doxycycline* and *minocycline*** are available **as oral and intravenous** {IV} preparations.



TETRACYCLINES

D. Pharmacokinetics

2. Distribution:

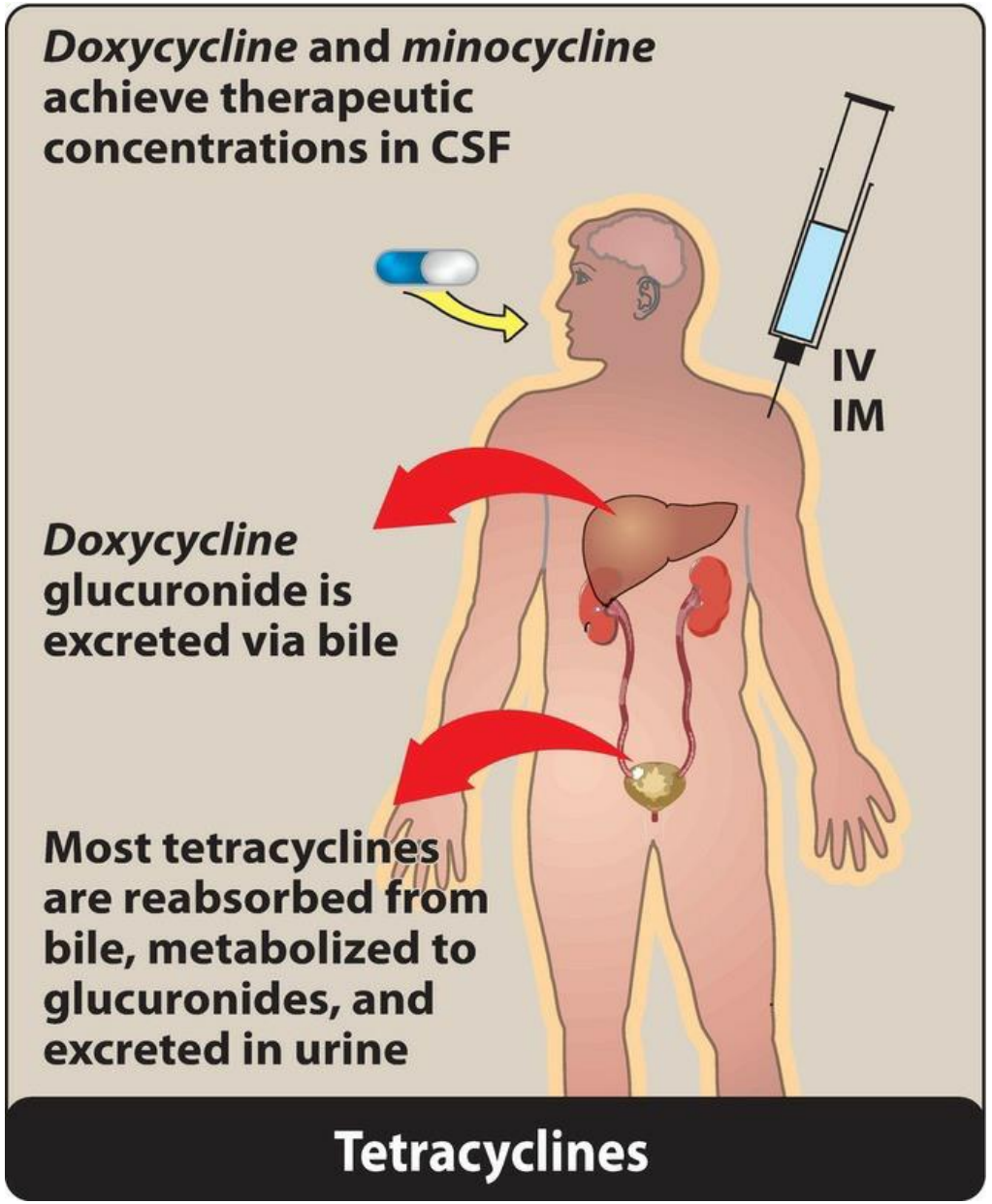
- The tetracyclines **concentrate** well in the **bile, liver, kidney, gingival fluid, and skin.** Moreover, they bind to **tissues undergoing calcification** {for example, teeth and bones} or to tumors that have high calcium content. Penetration into most body fluids is adequate.
- **Only** *minocycline* and *doxycycline* achieve therapeutic levels in **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.

TETRACYCLINES

- **D. Pharmacokinetics**

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***.



TETRACYCLINES

E. Adverse effects

1. **Gastric discomfort: Epigastric distress** commonly results from irritation of the gastric mucosa and is often responsible for noncompliance with tetracyclines.
2. **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***.]

TETRACYCLINES

E. Adverse effects

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 inhibiting of growth.
- ***For this reason, the use of tetracyclines is limited in pediatrics***.

TETRACYCLINES

E. Adverse effects

3. Hepatotoxicity: Rarely hepatotoxicity may occur with **high doses**, particularly in pregnant women and those with pre-existing 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***.

- Patients should be advised to wear adequate sun protection.

TETRACYCLINES

E. Adverse effects

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.

TETRACYCLINES

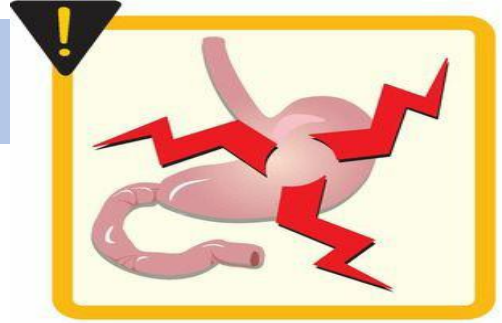
7. Contraindications:

The tetracyclines should not be used in

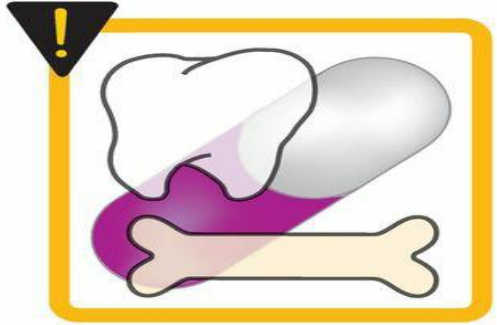
1. **Pregnant or**
2. **Breast-feeding women or**
3. **In children less than 8 years of age**.

TETRACYCLINES

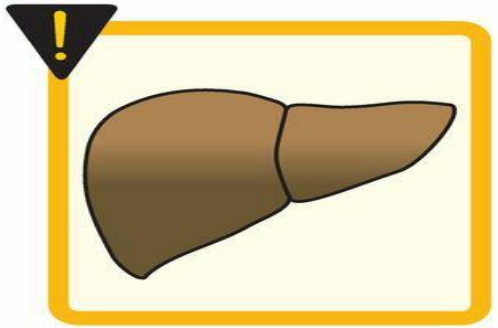
E. Adverse effects



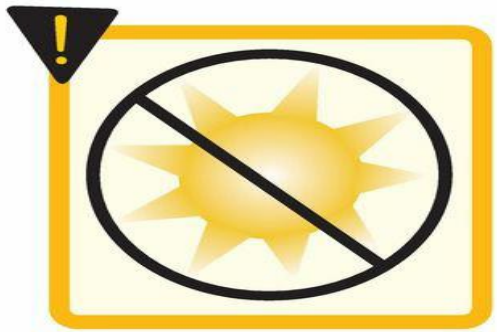
GI disturbance



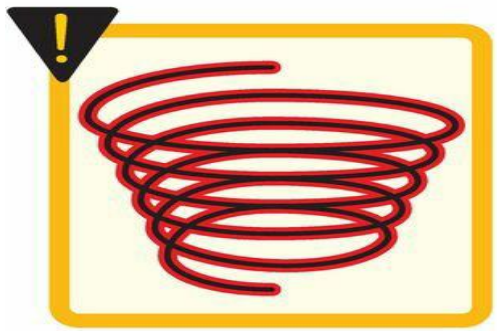
Deposition of drug in bones and teeth



Liver failure



Phototoxicity

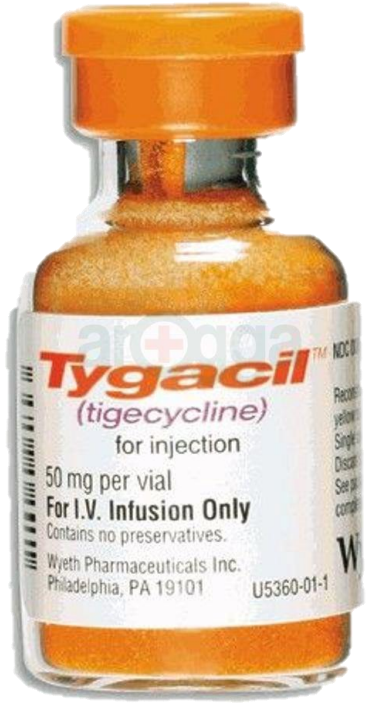


Vertigo

Avoid in pregnancy

GLYCYLCYCLINES

- **Tigecycline**, a derivative of *minocycline*, **is the first member of the glycylcycline antimicrobial class**. It is **indicated** (uses) for the treatment of



1. **Complicated skin and soft tissue infections**,
2. **Complicated intra-abdominal infections**, and
3. **Community-acquired pneumonia**.

A. Mechanism of action

- *Tigecycline* exhibits bacteriostatic action by **reversibly** binding to the 305 ribosomal subunit and inhibiting bacterial protein synthesis.

GLYCYLCYCLINES

B. Antibacterial spectrum

- *Tigecycline* exhibits **broad-spectrum activity** that **includes**

1. **Methicillin- resistant staphylococci (MRSA),**
2. **Multidrug-resistant streptococci,**
3. **Vancomycin-resistant enterococci (VRE),**
4. extended-spectrum β-lactamase--producing **gram-negative bacteria,**
5. **Acinetobacter baumannii**,
6. Many **anaerobic organisms**.

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

GLYCYLCYCLINES

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***.

GLYCYLCYCLINES

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**.

GLYCYLCYCLINES

E. Adverse effects

- ***Tigecycline*** is associated with significant

1. Nausea and vomiting.
2. Acute pancreatitis, including fatality, has been reported with therapy.
3. Elevations in liver enzymes and serum creatinine may also occur.
4. All-cause mortality in patients treated with *tigecycline* is higher than with other agents.

GLYCYLCYCLINES

E. Adverse effects

- ***Tigecycline***
- A boxed warning states that *tigecycline* **should be reserved** for use in situations when alternative treatments are not suitable.

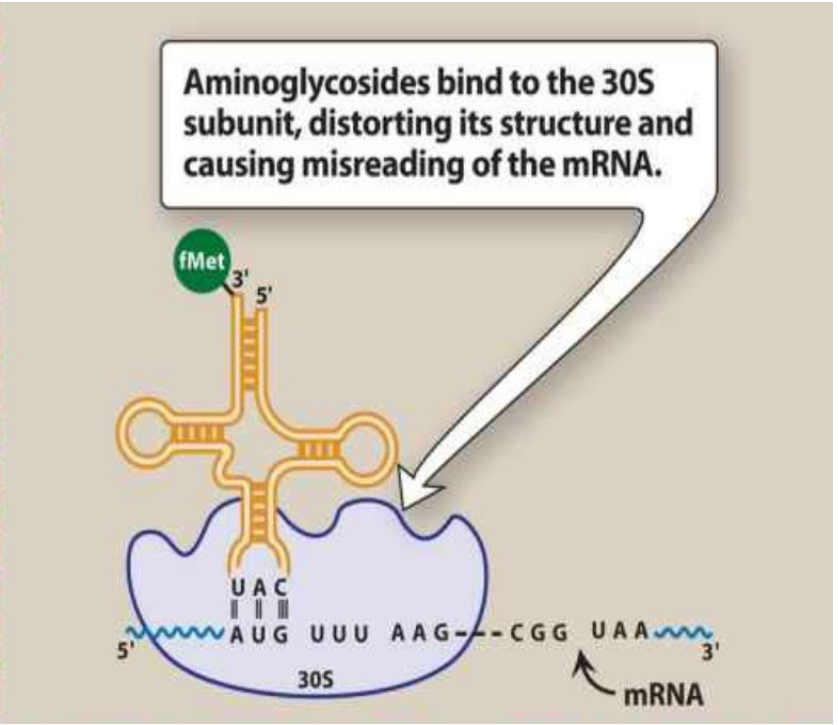
5. Other adverse effects are similar to those of the tetracyclines and include **photosensitivity**, **pseudotumor cerebri**, **discoloration** of permanent **teeth** when used during tooth development, and fetal harm when administered in pregnancy.

6. *Tigecycline* may **decrease** the clearance of *warfarin*. Therefore, the **international normalized ratio should be monitored** closely when *tigecycline* is coadministered with *warfarin*.

AMINOGLYCOSIDES:

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.



AMINOGLYCOSIDES:

A. Mechanism of action

- Aminoglycosides have **concentration-dependent bactericidal activity**;
- They also exhibit a postantibiotic effect (PAE), which is continued bacterial suppression after drug concentrations fall below the MIC.
- Because of these properties, **high-dose extended-interval dosing* is commonly utilized**.
- This dosing strategy also reduces the risk of nephrotoxicity and increases convenience.

***administration of the total daily amount of aminoglycoside as one dose**

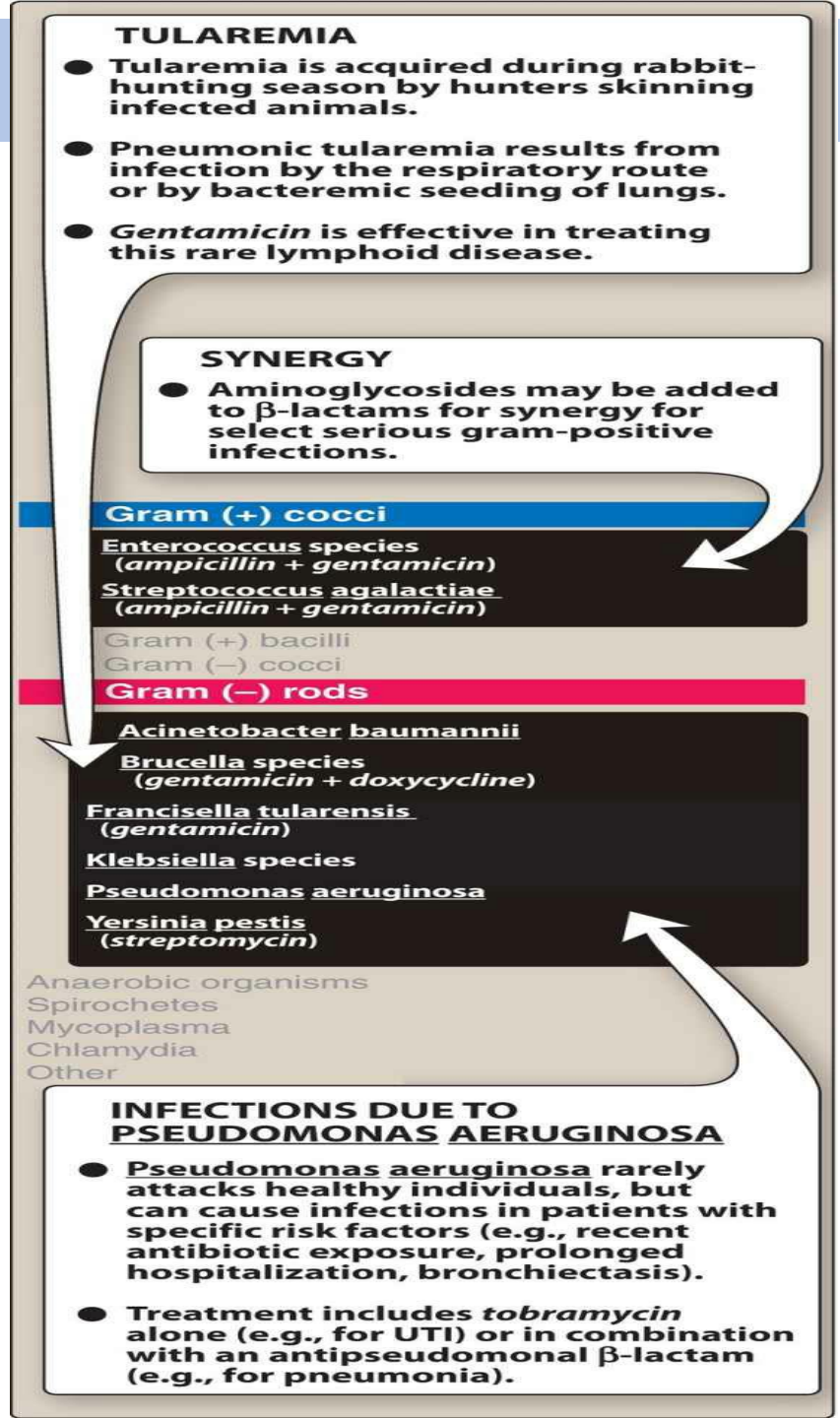
Aminoglycosides

B. Antibacterial spectrum

- The aminoglycosides are effective for the majority of **aerobic gram-negative bacilli**, including those that may be multidrug resistant, such as

1. ***Pseudomonas aeruginosa*,**
2. ***Klebsiella pneumoniae*, and**
3. ***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**.



Aminoglycosides

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.]

Aminoglycosides

D. Pharmacokinetics

highly polar, polycationic

1. Absorption:

- The ***highly polar, polycationic*** structure of the aminoglycosides prevents adequate absorption after oral administration; therefore,
- All aminoglycosides (except *neomycin* must be given parenterally to achieve adequate serum concentrations
- [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.]

Aminoglycosides

D. Pharmacokinetics

2. **Distribution**:

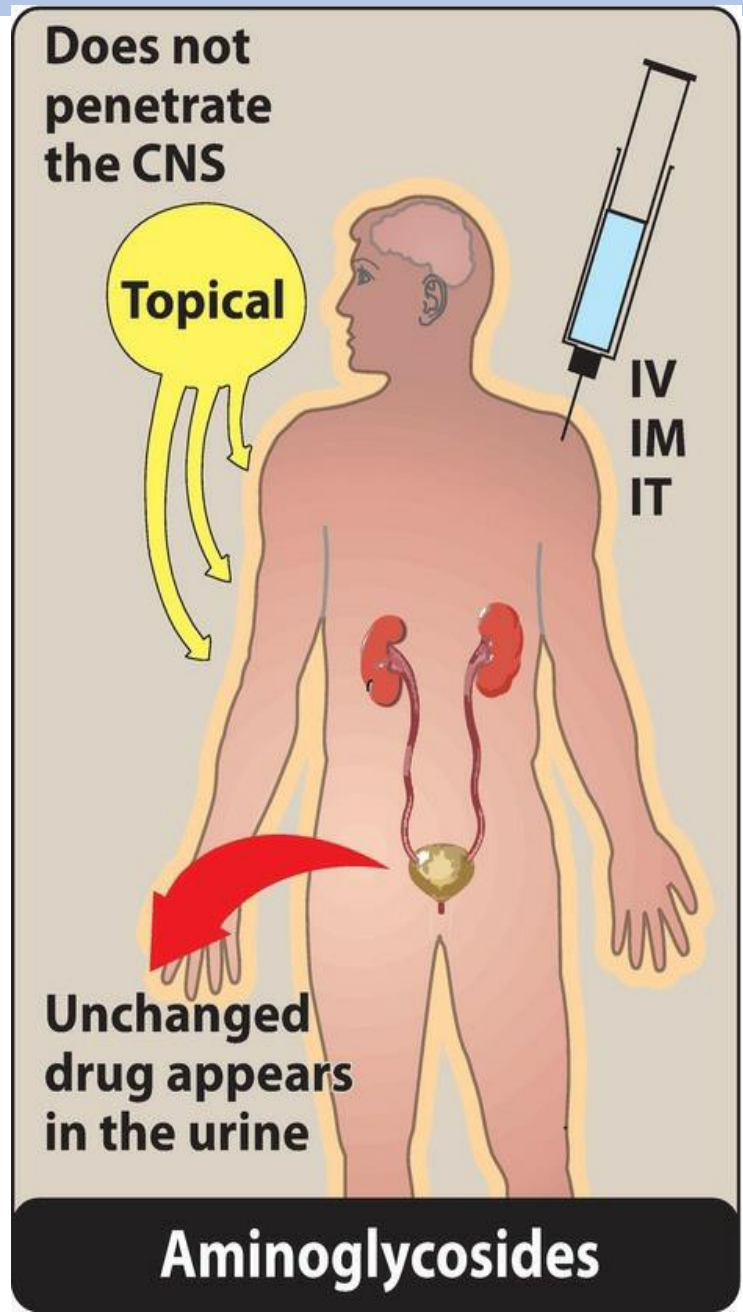
- Because of their **hydrophilicity**, aminoglycoside tissue concentrations may be subtherapeutic, and penetration into most body fluids is variable.
- Concentrations achieved in CSF are **inadequate**, even in the presence of inflamed meninges.
- For central nervous system infections, the intrathecal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

Aminoglycosides

D. Pharmacokinetics

3. Elimination:

- More than 90% of the parenteral aminoglycosides are excreted **unchanged in the urine** .
- Accumulation occurs in patients with **renal dysfunction**; thus, dose adjustments are required.
- *Neomycin* is primarily excreted unchanged in the **feces**.



Aminoglycosides

E. Adverse effects

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.
- **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.

Aminoglycosides

E. Adverse effects

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.

Ototoxicity

Nephrotoxicity

Paralysis

Skin rash

Aminoglycosides

E. Adverse effects

3. Neuromuscular paralysis:

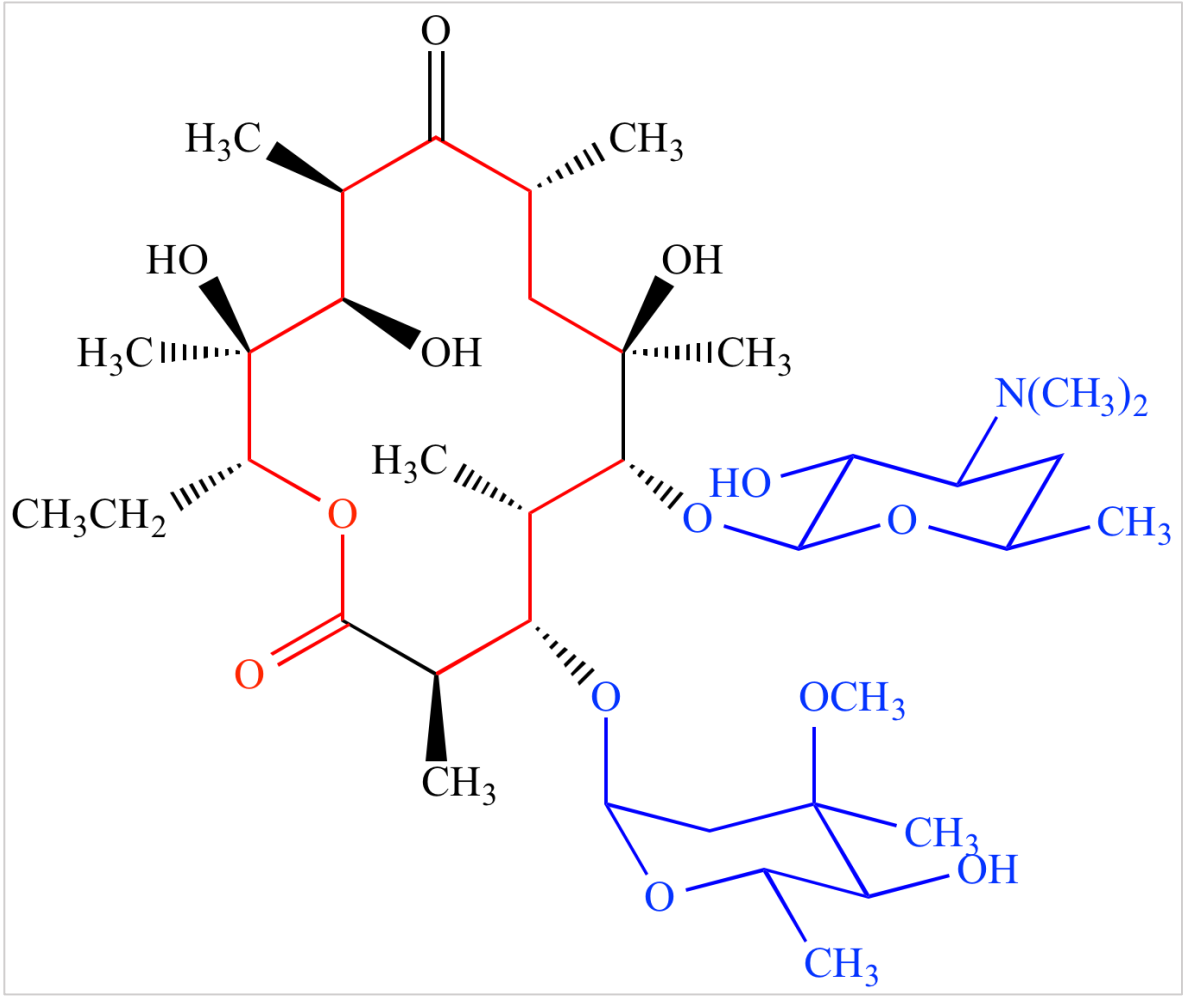
- high doses infused over a short period or concurrent administration with **neuromuscular blockers**.
- Patients with **myasthenia gravis** are particularly at risk.
- Prompt administration of *calcium gluconate* or *neostigmine* can reverse the block that causes neuromuscular paralysis.

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.



Molecular structure of erythromycin, a widely used macrolide antibiotic. Atoms of the large-ring lactone is shown in red, and the deoxysugars in blue.

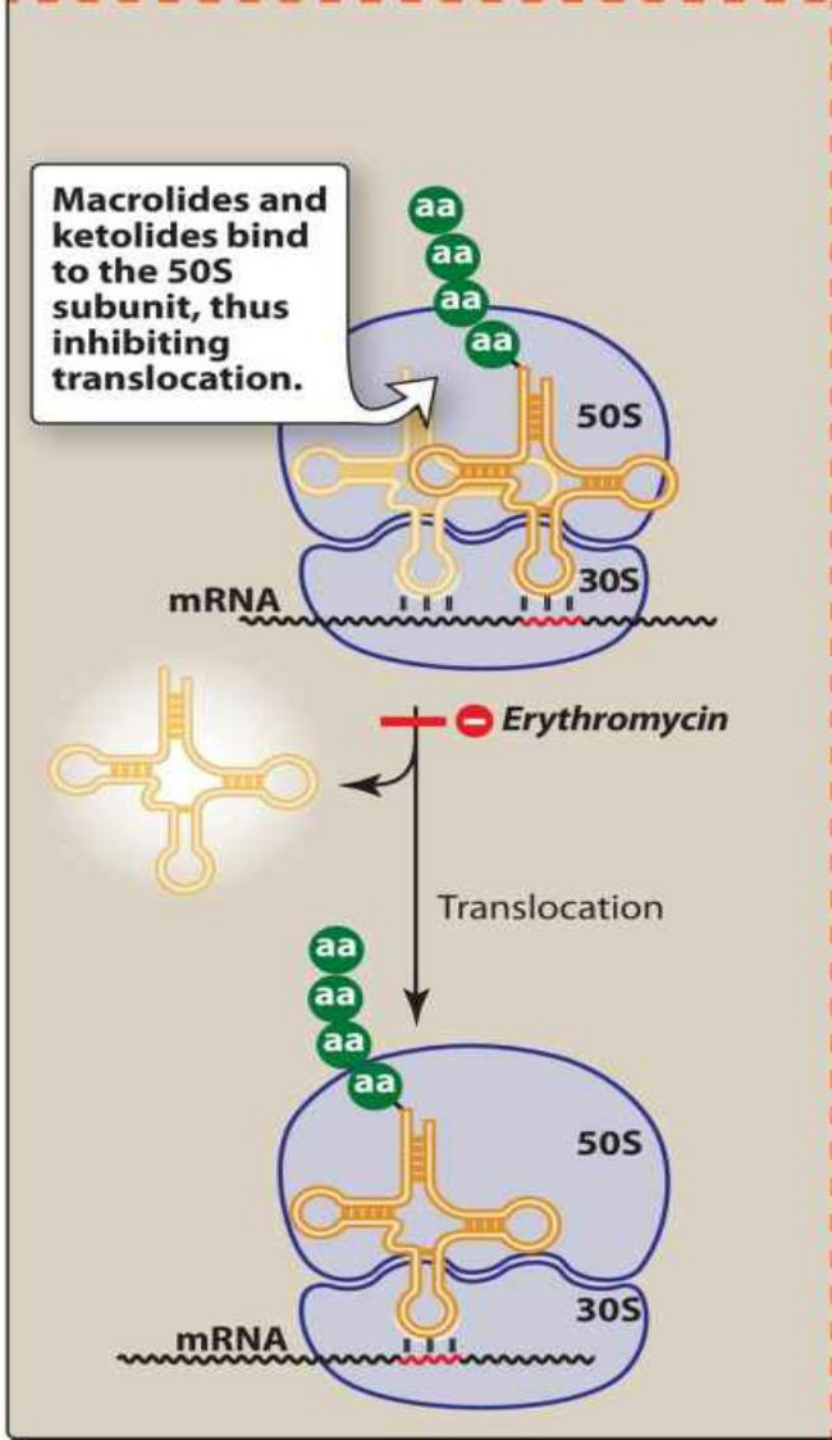
Macrolides and Ketolides

- ***Erythromycin*** 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*** (a methylated form of *erythromycin)* and
- ***azithromycin*** (having a larger lactone ring) have some features in common with, and others that improve upon, *erythromycin*.
- ***Telithromycin*** a semisynthetic derivative of *erythromycin*, is a "**ketolide**" antimicrobial agent.

Macrolides and Ketolides

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 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***.



Macrolides and Ketolides

B. Antibacterial spectrum

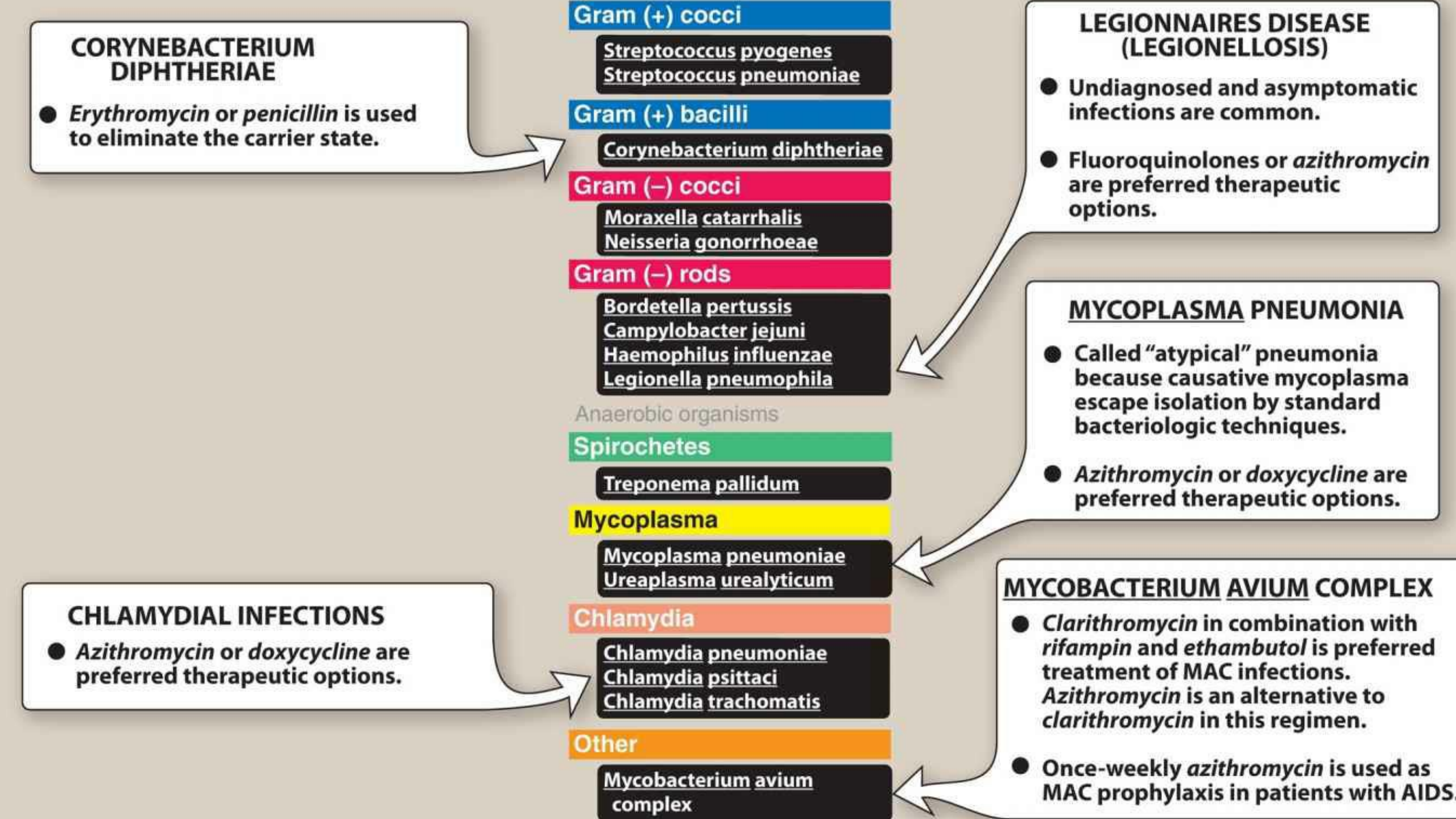
1. **Erythromycin:** This drug is effective against many of the **same** organisms as *penicillin G* ; therefore, it may be considered as an alternative in patients with *penicillin* allergy.

2. **Clarithromycin:** *Clarithromycin* has activity similar to *erythromycin*, but it is also effective against *Haemophilus influenzae* and has greater activity against intracellular pathogens such as *Chlamydia, Legionella, Moraxella, Ureaplasma species,* and *Helicobacter pylori*

Macrolides and Ketolides

B. Antibacterial spectrum

3. **Azithromycin:** Although less active than *erythromycin* against streptococci and staphylococci, *azithromycin* is **far more active** against respiratory pathogens such as *H. influenzae* and *Moraxella catarrhalis.*
4. **Telithromycin:** Telithromycin has an antimicrobial spectrum similar to that of azithromycin.
5. Moreover, the structural modification within **ketolides** **neutralizes** the most common resistance mechanisms that render macrlides ineffective.


CORYNEBACTERIUM DIPHTHERIAE
Erythromycin or penicillin is used to eliminate the carrier state.
Gram (+) cocci
Streptococcus pyogenes
Streptococcus pneumoniae
Gram (+) bacilli
Corynebacterium diphtheriae
Gram (–) cocci
Moraxella catarrhalis
Neisseria gonorrhoeae
Gram (–) rods
Bordetella pertussis
Campylobacter jejuni
Haemophilus influenzae
Legionella pneumophila
Anaerobic organisms
Spirochetes
Treponema pallidum
Mycoplasma
Mycoplasma pneumoniae
Ureaplasma urealyticum
Chlamydia
Chlamydia pneumoniae
Chlamydia psittaci
Chlamydia trachomatis
Other
Mycobacterium avium complex
LEGIONNAIRES DISEASE (LEGIONELLOSIS)
Undiagnosed and asymptomatic infections are common.
Fluoroquinolones or azithromycin are preferred therapeutic options.
MYCOPLASMA PNEUMONIA
Called "atypical" pneumonia because causative mycoplasma escape isolation by standard bacteriologic techniques.
Azithromycin or doxycycline are preferred therapeutic options.
CHLAMYDIAL INFECTIONS
Azithromycin or doxycycline are preferred therapeutic options.
MYCOBACTERIUM AVIUM COMPLEX
Clarithromycin in combination with rifampin and ethambutol is preferred treatment of MAC infections. Azithromycin is an alternative to clarithromycin in this regimen.
Once-weekly azithromycin is used as MAC prophylaxis in patients with AIDS.

Macrolides and Ketolides

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 due to 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 the Enterobacteriaceae.

- ***Erythromycin*** has limited clinical use due to increasing resistance.
- Both *clarithromycin* and *azithromycin* share some cross-resistance with *erythromycin.*
- *Telithromycin* may be effective against macrolide-resistant organisms.

Macrolides and Ketolides

D. Pharmacokinetics

1. Absorption:

- The *erythromycin* base is destroyed by gastric acid; thus, either enteric coated tablets or esterified forms of the antibiotic are administered and all have adequate oral absorption .
- *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*.
- *Telithromycin* is administered orally without regard to meals.
- *Erythromycin* and *azithromycin* are available in IV formulations.

Macrolides and Ketolides

D. Pharmacokinetics

2. Distribution:

- *Erythromycin* distributes **well** to all body fluids **except** the CSF.
- It is one of the few antibiotics that diffuse 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* has the largest volume of distribution of the four drugs.

Macrolides and Ketolides

D. Pharmacokinetics

3. Elimination:

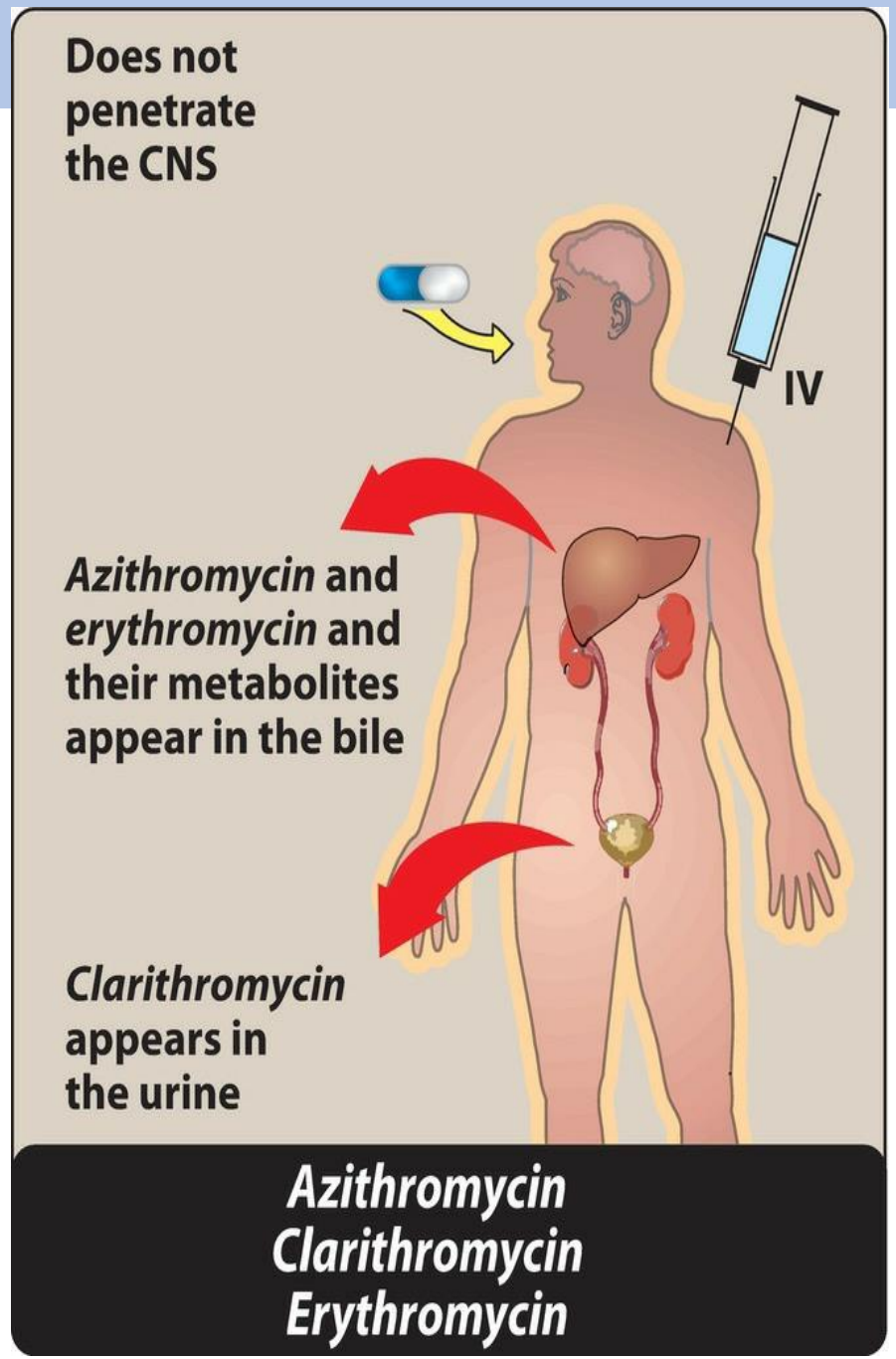
- *Erythromycin* and *telithromycin* undergo hepatic metabolism.
- They inhibit the oxidation of a number of drugs through their interaction with the cytochrome P450 system.
- **Interference** with the metabolism of drugs such as *theophylline*, statins, and numerous antiepileptics has been reported for ***clarithromycin***.

Macrolides and Ketolides

D. Pharmacokinetics

4. Excretion:

- ***Azithromycin*** is primarily concentrated and excreted in the **bile** as active drug.
- ***Erythromycin*** and its metabolites are also excreted in the **bile**.
- In contrast, ***clarithromycin*** is hepatically metabolized, and the active drug and its metabolites are mainly excreted in the **urine**.
- The dosage of this drug should be adjusted in patients with renal impairment.



Macrolides and Ketolides

- **E. Adverse effects**

1. Gastric distress and motility:

- Gastrointestinal upset is the most common adverse effect of the macrolides and may lead to poor patient compliance (especially with *erythromycin).* Higher doses of *erythromycin* lead to smooth muscle contractions that result in the movement of gastric contents to the duodenum, an adverse effect sometimes employed **for the treatment of gastroparesis or postoperative ileus**.

2. **Cholestatic jaundice**:

- This adverse effect occurs most commonly with the **estolate form** of *erythromycin* (not used in the United States); however, it has been reported with other formulations and other agents in this class.

Macrolides and Ketolides

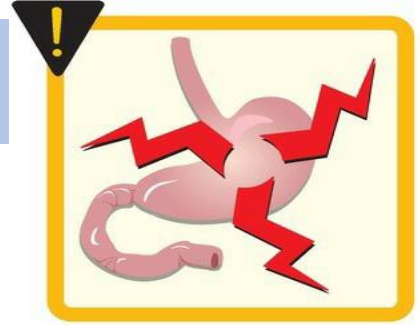
E. Adverse effects

3. **Ototoxicity**:

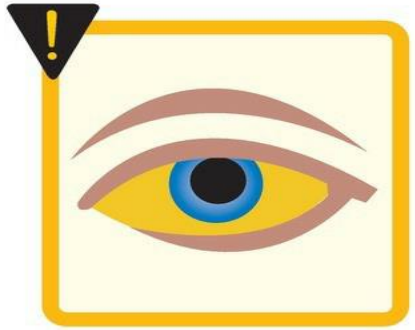
- Transient deafness has been associated with *erythromycin*, especially at high dosages. *Azithromycin* has also been associated with irreversible sensorineural hearing loss.

4. **QTc prolongation**:

- 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.



GI disturbance



Jaundice

Ototoxicity

QTc prolongation

Macrolides and Ketolides

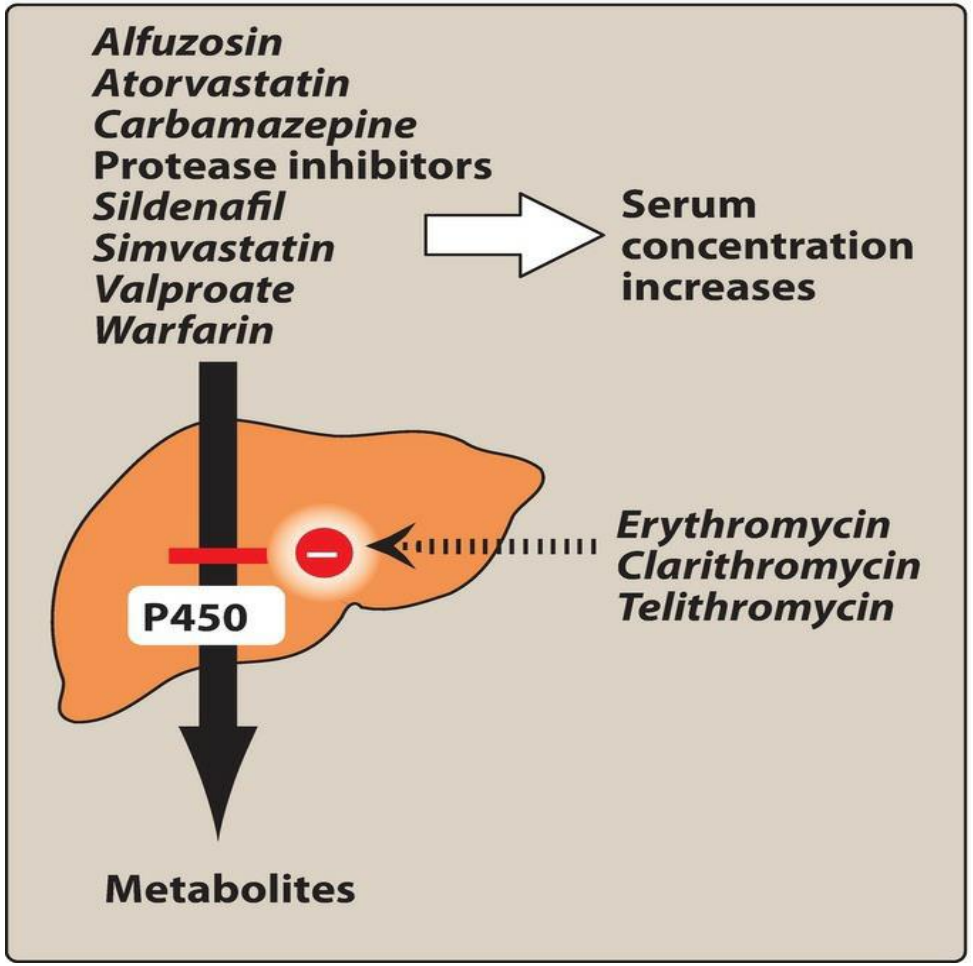
Contraindication:

- 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.

Macrolides and Ketolides

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.
- One theory to explain this interaction is that the antibiotic eliminates a species of intestinal flora that ordinarily inactivates *digoxin*, leading to greater reabsorption of *digoxin* from the enterohepatic circulation.



Fidaxomicin

- *Fidaxomicin* 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

- *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*.

Fidaxomicin

- Because of 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.

Fidaxomicin

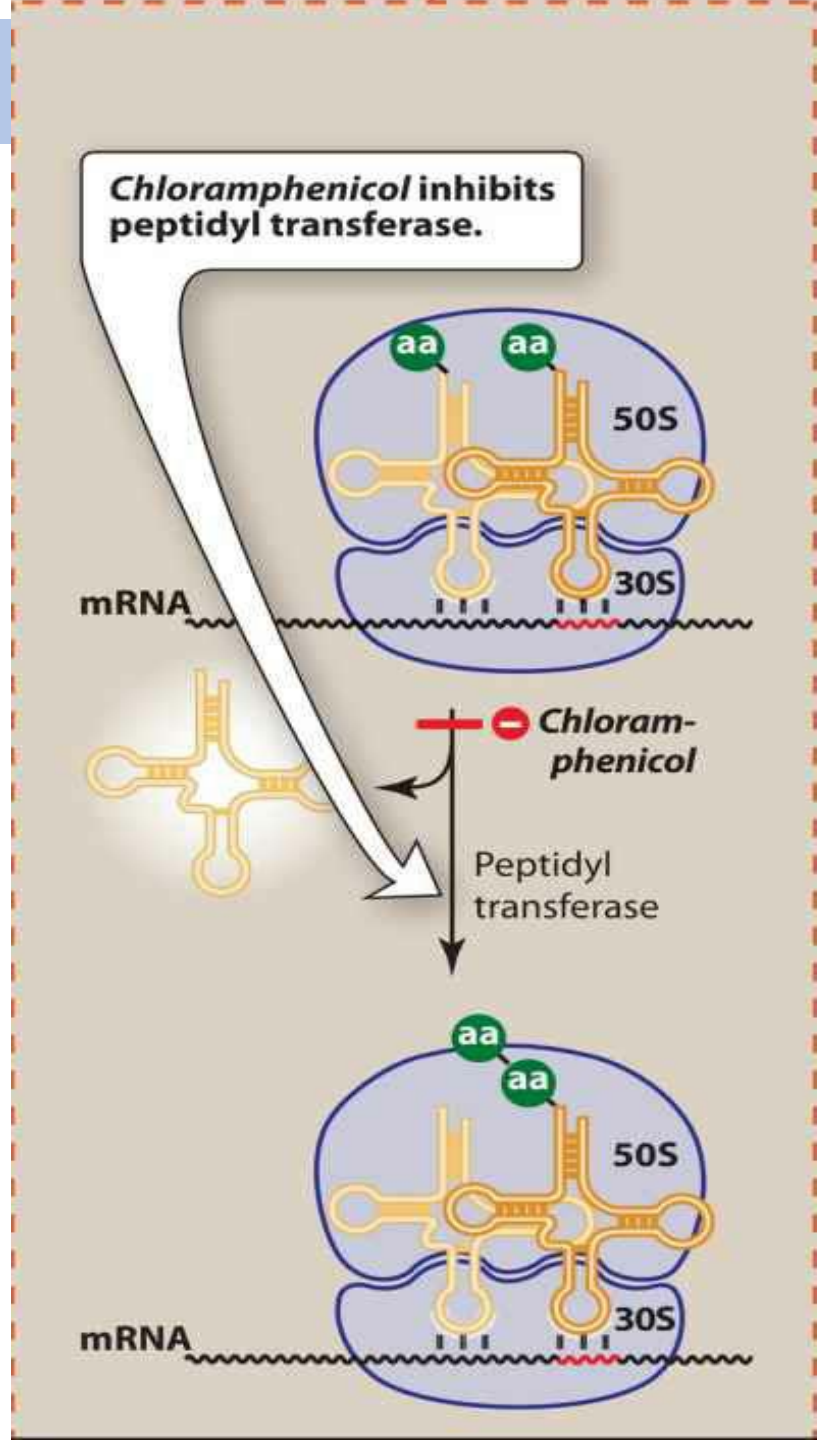
- The most common **adverse effects** include

1. Nausea, vomiting, and abdominal pain.
2. Anemia and neutropenia have been observed infrequently.
3. 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.

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



Chloramphenicol

- **B. Antibacterial spectrum**
- *Chloramphenicol* is active against many types of microorganisms including chlamydiae, rickettsiae, spirochetes, and anaerobes.
- The drug is primarily bacteriostatic, but it may exert bactericidal activity depending on the dose and organism.

Chloramphenicol

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**.

Chloramphenicol

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**.
- *Chloramphenicol* is also secreted into breast milk and should be avoided in breastfeeding mothers.

Chloramphenicol

E. Adverse effects

1. Anemias:

- Patients may experience dose-related anemia, **hemolytic anemia** (observed 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, which decreases their ability to excrete the drug.
- This leads to drug accumulation to concentrations that interfere with the **function of mitochondrial ribosomes**, causing poor feeding, depressed breathing, cardiovascular collapse, cyanosis (hence the term "gray baby"), and death. *Adults who have received very high doses of chloramphenicol may also exhibit this toxicity*.

Chloramphenicol

3. Drug Interactions:

- *Chloramphenicol* inhibits some of the hepatic mixed-function oxidases, preventing the metabolism of drugs such as *warfarin* and *phenytoin*, which may potentiate their effects.

Clindamycin

- *Clindamycin* has a mechanism of action that is similar to that of the macrolides.
- *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 resistant to clindamycin***, and the utility of *clindamycin* for gram-negative anaerobes (for example, Bacteroides sp.) is decreasing due to increasing resistance.

Clindamycin

- *Clindamycin* is available in both IV and oral formulations, but use of oral *clindamycin* **is limited by gastrointestinal intolerance**.
- It distributes well into all body fluids but **exhibits poor entry into the CSF**.
- *Clindamycin* undergoes **extensive oxidative metabolism** to active and inactive products and is excreted **into bile and urine**.
- Low urinary excretion of active drug 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 rash**, 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 infection.

Clindamycin

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Quinupristin/Dalfopristin

- *Quinupristin/dalfopristin* is a mixture of two streptogramins in a ratio of 30 to 70, respectively.
- Due to significant adverse effects, this combination drug is **normally reserved for the treatment of severe infections** caused by *vancomycin-resistant Enterococcus faecium (VRE)* in the absence of other therapeutic options.

Quinupristin/Dalfopristin

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 has bactericidal activity against most susceptible organisms and has a long PAE.

Quinupristin/Dalfopristin

B. Antibacterial spectrum

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

Quinupristin/Dalfopristin

C. Resistance

Enzymatic processes commonly account for resistance to these agents. For example, the presence of a ribosomal enzyme that methylates the target bacterial 238 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.

Quinupristin/Dalfopristin

D. Pharmacokinetics

- *Quinupristin l dalfopristin* is available intravenously. It does not achieve therapeutic concentrations in CSF. Both compounds undergo hepatic metabolism, with excretion mainly in the feces.

Quinupristin/Dalfopristin

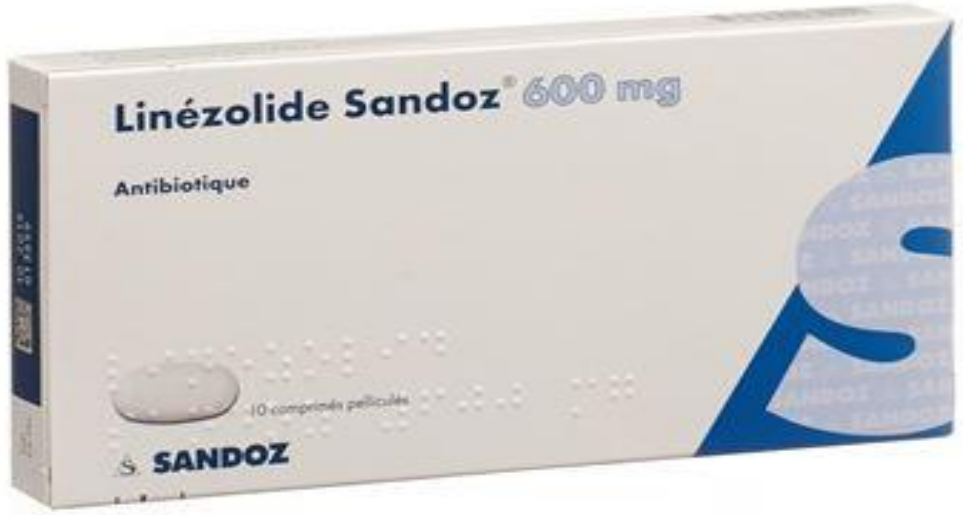
E. Adverse effects

- 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 administered.
- *Quinupristin/dalfopristin* inhibits the cytochrome P450 CYP3A4 isoenzyme, and concomitant administration with drugs that are metabolized by this pathway may lead to toxicities.

Oxazolidinones

- ***Linezolid*** **and** ***tedizolid*** are synthetic oxazolidinones developed to combat **gram positive organisms**, including resistant isolates such as

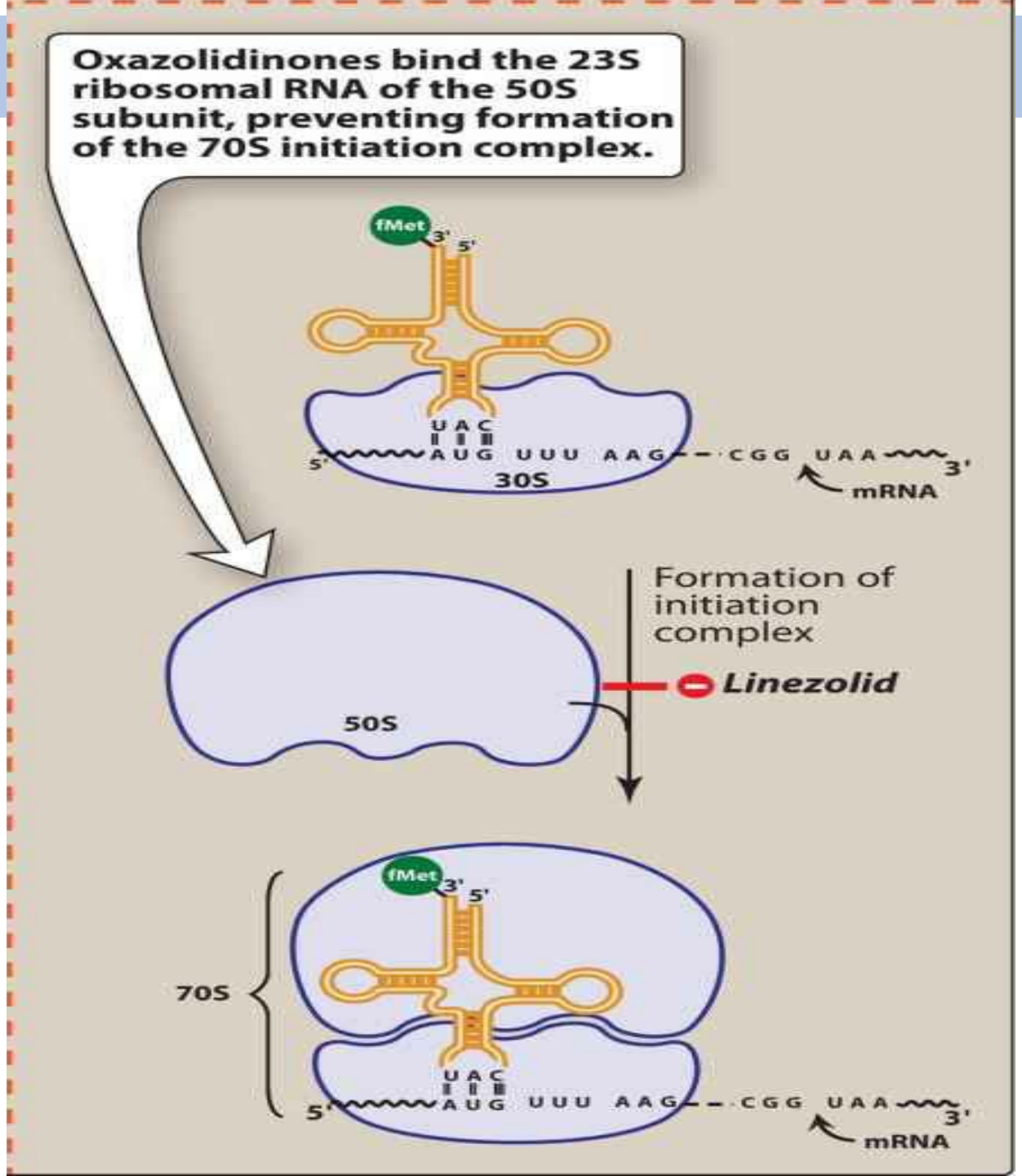
1. *methicillin-resistant* Staphylococcus aureus,
2. VRE, and
3. *penicillin-resistant* streptococci.



Oxazolidinones

- **A. Mechanism of action**

- *Linezolid* and *tedizolid* bind to the *bacterial 23S ribosomal RNA of the 50S subunit*, thereby inhibiting the formation of the 70S initiation complex and translation of bacterial proteins.



Oxazolidinones

B. Antibacterial spectrum

- The antibacterial action of the oxazolidinones is directed primarily against

1. **gram-positive organisms** such as staphylococci, streptococci, and enterococci, Corynebacterium species and Listeria monocytegenes.
2. It is also moderately active against **Mycobacterium tuberculosis**.
3. The main clinical use of *linezolid* and *tedizolid* is to **treat infections caused by drug-resistant gram-positive organisms**. Like other agents that interfere with bacterial protein synthesis, ***linezolid* and *tedizolid* are bacteriostatic**; however, ***linezolid* has bactericidal activity against streptococci**.
4. *Linezolid* is an alternative to *daptomycin* for infections caused by VRE. Because they are bacteriostatic, the oxazolidinones are not recommended as first-line treatment for MRSA bacteremia.

Oxazolidinones

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***.

Oxazolidinones

D. Pharmacokinetics

- *Linezolid* and *tedizolid* are well absorbed after **oral administration**.
- IV formulations are also available.
- These drugs distribute widely 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 non-renal routes. Tedizolid is metabolized by sulfation, and the majority of elimination occurs via the liver, and drug is mainly excreted in the feces.
- No dose adjustments are required for either agent for renal or hepatic dysfunction.

Oxazolidinones

E. Adverse effects

- The most common adverse effects are **gastrointestinal upset**, **nausea, diarrhea, headache, and rash**.
- **Thrombocytopenia** has been reported, usually in patients taking the drug for longer than 10 days.
- *Linezolid* and *tedizolid* possess 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.

Quinolones, Folic Acid Antagonists, and Urinary Tract Antiseptics

FLUOROQUINOLONES

Ciprofloxacin CIPRO
Delafloxacin BAXDELA
Gemifloxacin FACTIVE
Levofloxacin LEVAQUIN
Moxifloxacin AVELOX, MOXEZA, VIGAMOX
Ofloxacin GENERIC ONLY

INHIBITORS OF FOLATE SYNTHESIS

Mafenide SULFAMYLON
Silver sulfadiazine SILVADENE, SSD, THERMAZENE
Sulfadiazine GENERIC ONLY
Sulfasalazine AZULFIDINE

INHIBITORS OF FOLATE REDUCTION

Pyrimethamine DARAPRIM
Trimethoprim PRIMSOL, TRIMPEX

COMBINATION OF INHIBITORS OF FOLATE SYNTHESIS AND REDUCTION

Cotrimoxazole (trimethoprim + sulfamethoxazole) BACTRIM, SEPTRA

URINARY TRACT ANTISEPTICS

Methenamine HIPREX, UREX
Nitrofurantoin MACROBID, MACRODANTIN

Quinolones, Folic Acid Antagonists, and Urinary Tract Antiseptics

I- Fluoroquinolone

- The discovery of quinolone antimicrobials led to the development of numerous compounds utilized in clinical practice.
- Following the synthesis of **nalidixic acid** in the early 1960s, continued modification of the quinolone nucleus expanded the spectrum of activity, improved pharmacokinetics, and stabilized compounds against common mechanisms of resistance. Due to these enhancements, quinolone antimicrobials were rapidly integrated into human and agricultural medicine.
- Unfortunately, overuse resulted in rising rates of resistance in **gram-negative and gram positive organisms,** increased frequency of ***Clostridium difficile infections***, and identification of numerous untoward adverse effects.
- Consequently, these agents have been **relegated to second-line options for various indications**

I- Fluoroquinolone

- **Mechanism of action**
- Most bacterial species maintain two distinct **type II topoisomerases** that assist with deoxyribonucleic acid (DNA) replication, (DNA gyrase), and topoisomerase IV.
- DNA gyrase is responsible for reducing torsional stress ahead of replicating forks by breaking double-strand DNA and introducing negative supercoils.
- Topoisomerase IV assists in separating daughter chromosomes once replication is completed. fluoroquinolones bind to these enzymes and interfere with DNA ligation.
- This interference increases the number of permanent chromosomal breaks, triggering cell lysis. In general, fluoroquinolones have different targets for gram-negative (DNA gyrase) and gram-positive organisms (topoisomerase IV), resulting in rapid cell death.

I- Fluoroquinolone

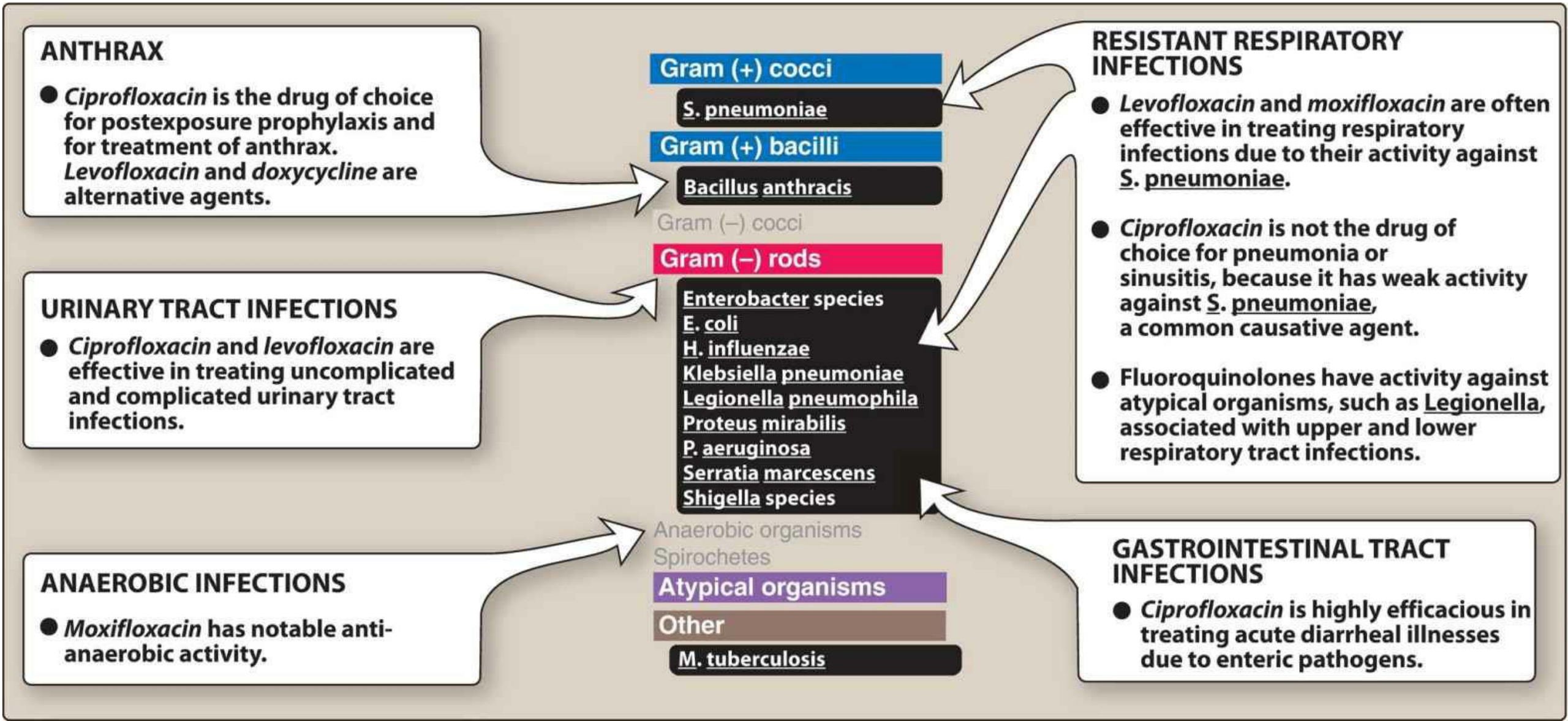
- **Antimicrobial spectrum**
- Fluoroquinolones are bactericidal and exhibit area-under-the-curve/minimum inhibitory concentration (AUC/MIC)-dependent killing. A major facet of their development centered on improving microbiologic coverage. Modifications to the quinolone nucleus steadily improved topoisomerase inhibitory activity and facilitated bacterial cell wall penetration. These changes enhanced activity against a variety of pathogens including Aerobic gram-negative and gram-positive organisms, atypical organisms (for example, chlamydia, legionella, and mycoplasma spp.), and Anaerobes. Based on the impact of these structural changes, fluoroquinolones are often classified according to the spectrum of activity. First-generation compounds (for example, nalidixic acid) were narrowspectrum agents with activity against aerobic gram-negative bacilli, mostly Enterobacteriaceae. Second-generation compounds (for example, ciprofloxacin) exhibit improved intracellular penetration and broadened coverage, which includes Enterobacteriaceae, Pseudomonas aeruginosa, Haemophilus influenzae, Neisseria spp., Chlamydia spp., and Legionella spp.

I- Fluoroquinolone

- **Antimicrobial spectrum**
- Second-generation compounds (for example, ciprofloxacin) exhibit improved intracellular penetration and broadened coverage, which includes Enterobacteriaceae, Pseudomonas aeruginosa, Haemophilus influenzae, Neisseria spp., Chlamydia spp., and Legionella spp.
- Third-generation compounds (for example, levofloxacin) maintain the bacterial spectrum of second-generation agents, with improved activity against Streptococcus spp., including S. pneumoniae, methicillin-susceptible Staphylococcus aureus, Stenotrophomonas maltophilia, and Mycobacterium spp. Fourth-generation compounds (moxifloxacin, gemifloxacin, and delafloxacin) have enhanced gram-positive activity, including Staphylococcus and Streptococcus spp. Delafloxacin has activity against methicillin-resistant Staphylococcus aureus (MRSA) and Enterococcus faecalis. Further, delafloxacin and moxifloxacin have activity against Bacteroides fragilis and Prevotella spp., while maintaining activity against Enterobacteriaceae and Haemophilus influenzae. From this group, only delafloxacin has activity against Pseudomonas aeruginosa. Lastly, these agents maintain atypical coverage, with moxifloxacin and delafloxacin showing activity against Mycobacteria spp. Common therapeutic applications of fluoroquinolones are shown in Figure 31.2.

I- Fluoroquinolone

- **Antimicrobial spectrum**



I- Fluoroquinolone

- **Resistance**
- Numerous mechanisms of fluoroquinolone resistance exist in clinical pathogens. High-level fluoroquinolone resistance is primarily driven by chromosomal mutations within topoisomerases, decreased entry, efflux systems, and modifying enzymes play a role.

I- Fluoroquinolone

Mechanisms responsible for resistance include the following:

1. Altered target binding

- Mutations in bacterial genes encoding DNA gyrase or topoisomerase IV (for example, gyrA or parC) alter target site structure and reduce the binding efficiency of fluoroquinolones.

2. Decreased accumulation

- Reduced intracellular concentration is linked to 1) a reduction in membrane permeability or 2) efflux pumps. Alterations in membrane permeability are mediated through a reduction in outer membrane porin proteins, thus limiting drug access to topoisomerases. Efflux pumps actively remove fluoroquinolones from the cell.

3. Fluoroquinolone degradation

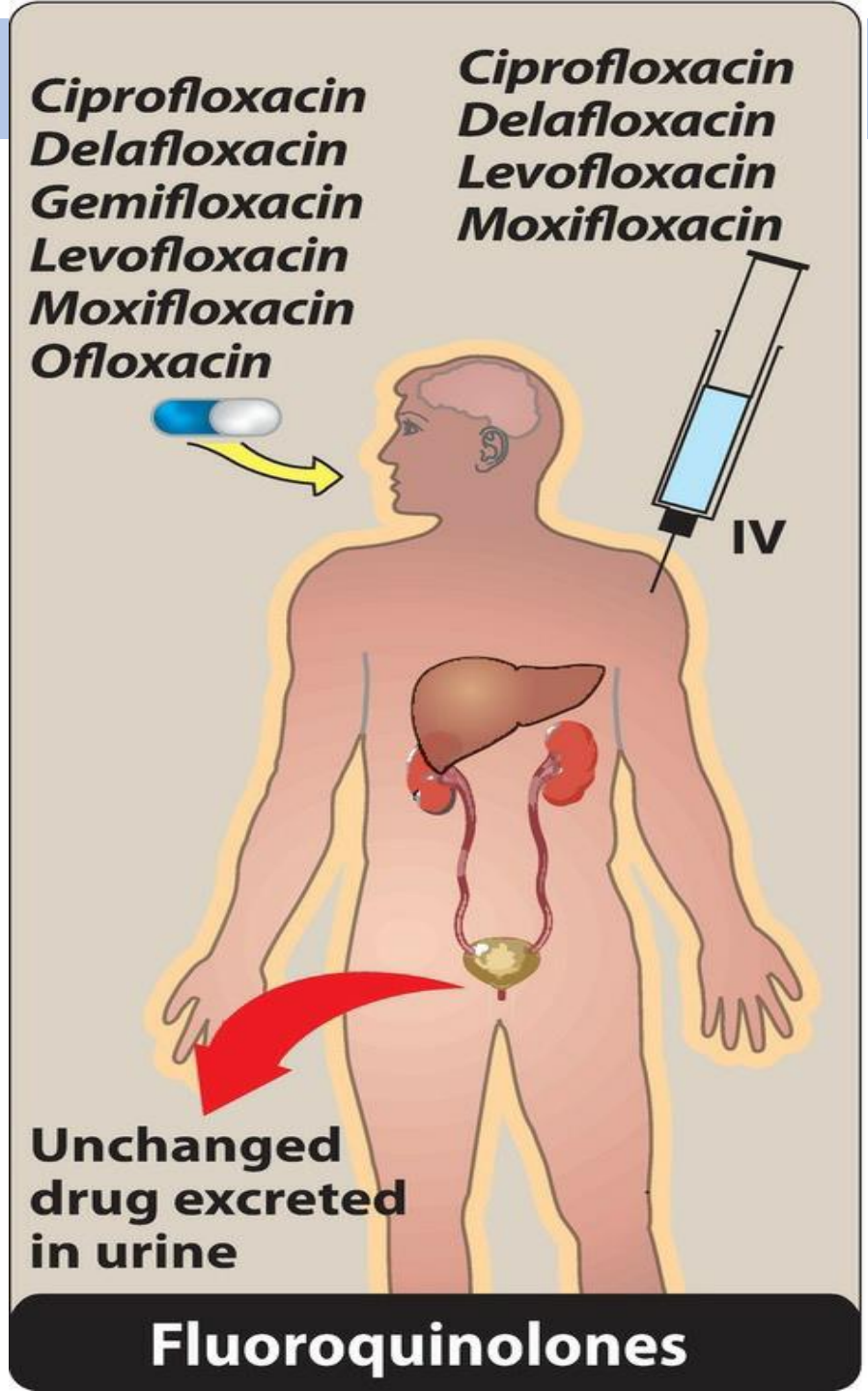
- An aminoglycoside acetyltransferase variant can acetylate fluoroquinolones, rendering them inactive.

I- Fluoroquinolone

- **Pharmacokinetics**

1. Absorption

- Fluoroquinolones are well absorbed after oral administration, with levofloxacin and moxifloxacin having a bioavailability that exceeds 90% . Ingestion of fluoroquinolones with sucralfate, aluminum- or magnesium-containing antacids, or dietary supplements containing iron or zinc can reduce the absorption. Calcium and other divalent cations also interfere with the absorption of these agents.

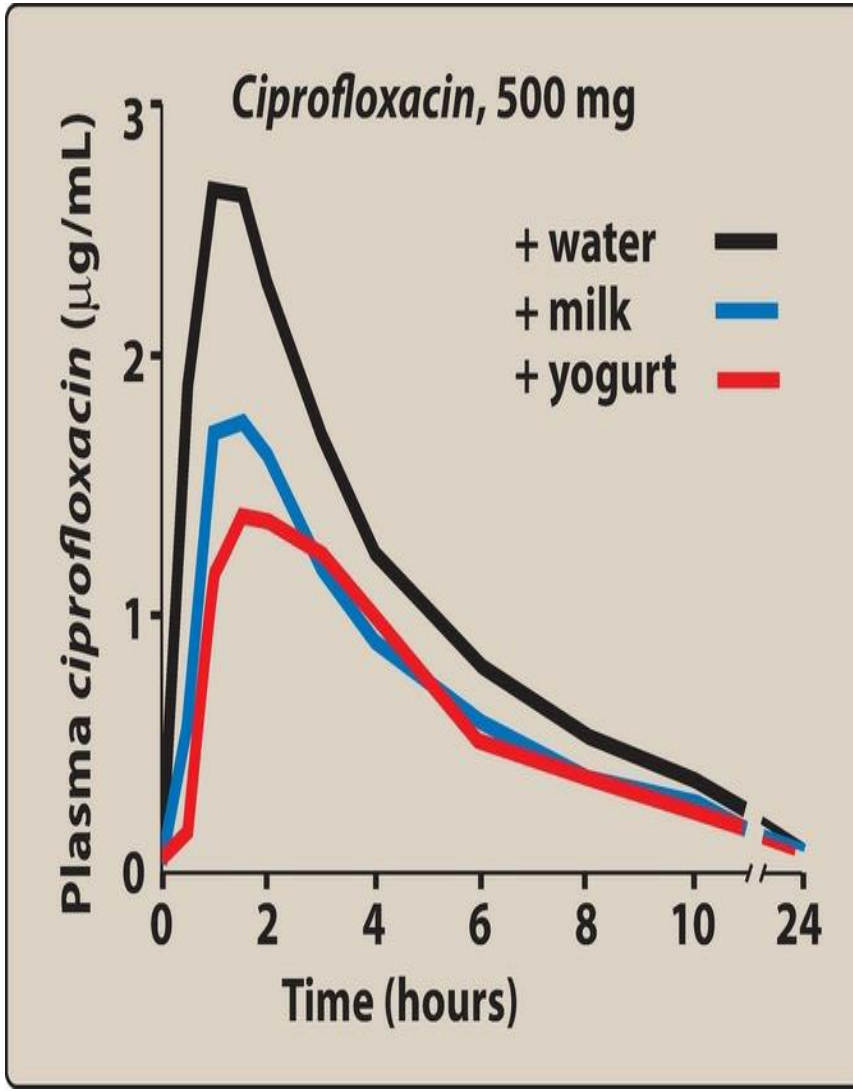


I- Fluoroquinolone

- **Pharmacokinetics**

2. Distribution

- Binding to plasma proteins ranges from 20% to 84%. Fluoroquinolones distribute well into all tissues and body fluids. Concentrations are high in bone, urine (except moxifloxacin), kidney, prostatic tissue (but not prostatic fluid), and lungs as compared to serum. Penetration into cerebrospinal fluid is good, and these agents may be considered in certain central nervous system (CNS) infections. Accumulation in macrophages and polymorphonuclear leukocytes results in activity against intracellular organisms such as Listeria, Chlamydia, and Mycobacterium.

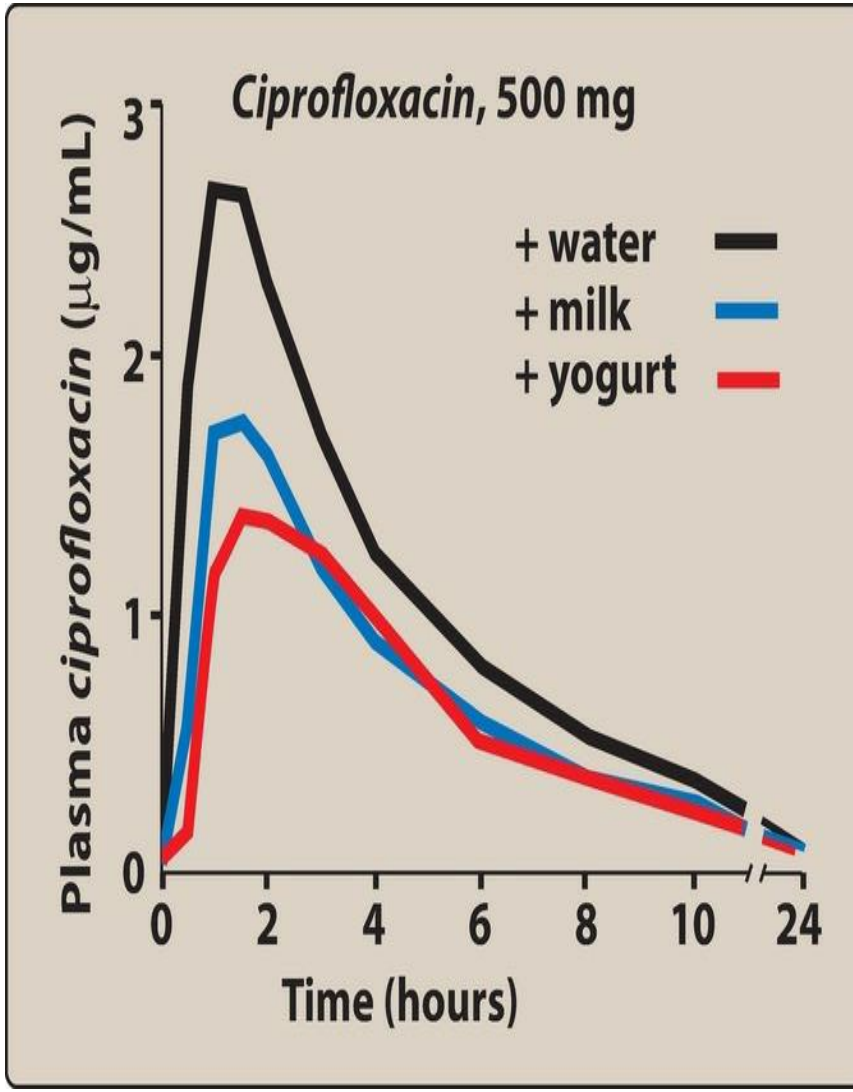


I- Fluoroquinolone

- **Pharmacokinetics**

3. Elimination

- Most fluoroquinolones are excreted renally. Therefore, dosage adjustments are needed in renal dysfunction. Moxifloxacin is metabolized primarily by the liver, and while there is some renal excretion, no dose adjustment is required for renal impairment (see Figure 31.3).



I- Fluoroquinolone

- **Adverse Reactions**
- In general, fluoroquinolones are well tolerated (Figure 31.5). Common adverse effects leading to discontinuation are nausea, vomiting, headache, and dizziness. These agents carry boxed warnings for tendinitis, tendon rupture, peripheral neuropathy, and CNS effects (hallucinations, anxiety, insomnia, confusion, and seizures). Patients taking fluoroquinolones are at risk for phototoxicity resulting in exaggerated sunburn reactions. Patients should use sunscreen and avoid excessive exposure to ultraviolet (UV) light. Arthropathy is uncommon, but arthralgia and arthritis are reported with fluoroquinolone use in pediatric patients.

I- Fluoroquinolone

- **Adverse Reactions**
- Use in the pediatric population should be limited to distinct clinical scenarios (for example, cystic fibrosis exacerbation). Hepatotoxicity or blood glucose disturbances (usually in diabetic patients receiving oral hypoglycemic agents or insulin) have been observed.Identification of any of these events should result in prompt removal of the agent.
- Fluoroquinolones may prolong the QTc interval, and these agents should be avoided in patients predisposed to arrhythmias or taking medication associated with QT prolongation. Ciprofloxacin inhibits P450 1A2- and 3A4-mediated metabolism. Serum concentrations of medications such as theophylline, tizanidine, warfarin, ropinirole, duloxetine, caffeine, sildenafil, and zolpidem may be increased (Figure 31.6).

I- Fluoroquinolone

- **Adverse Reactions**

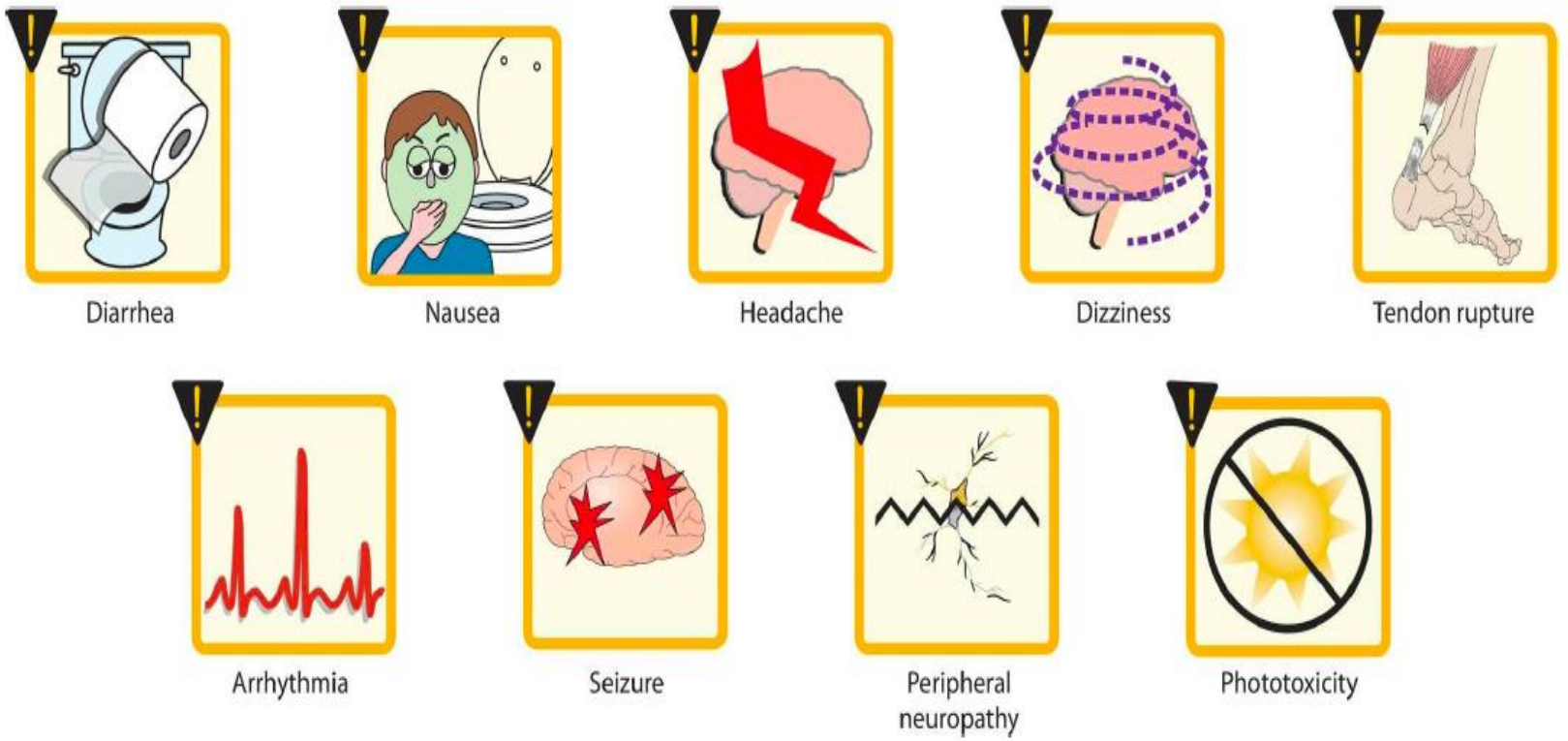


Figure 31.5 Some adverse reactions to fluoroquinolones.

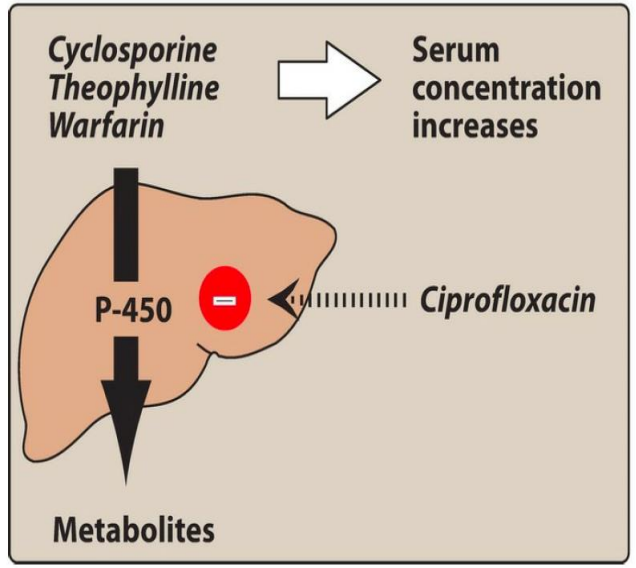


Figure 31.6 Drug interactions with *ciprofloxacin*.

I- Fluoroquinolone

- **Examples of clinically useful fluoroquinolones**
- Due to increasing resistance and boxed warnings, fluoroquinolones should be used with caution in select circumstances. They may be considered in patients who do not tolerate other agents (for example, severe beta-lactam allergies) or as definitive therapy once susceptibilities are available. Listed below are potential indications for these agents:

I- Fluoroquinolone

- **Examples of clinically useful fluoroquinolones**

1. Ciprofloxacin

- Ciprofloxacin has good activity against **gram-negative bacilli**, including *P. aeruginosa*. Ciprofloxacin is used in the treatment of ***traveler's diarrhea***, ***typhoid fever, and anthrax***. It is a ***second-line agent for infections arising from intra-abdominal, lung, skin, or urine sources***. Of note, ***high-dose therapy*** should be employed when treating ***Pseudomonas infections***.

I- Fluoroquinolone

- **Examples of clinically useful fluoroquinolones**

2. Levofloxacin

- Levofloxacin has similar activity to ciprofloxacin and they are often interchanged when managing gram-negative bacilli, including P. aeruginosa. Levofloxacin has enhanced activity against S. pneumonia and is first-line therapy for community-acquired pneumonia (CAP). It is a second-line agent for the treatment of S. maltophilia.

I- Fluoroquinolone

- **Examples of clinically useful fluoroquinolones**

3. Moxifloxacin

- Moxifloxacin has enhanced activity against gram-positive organisms (for example, S. pneumoniae), gram-negative anaerobes, and Mycobacterium spp. The drug may be used for CAP, but not hospital-acquired pneumonia due to poor coverage of P. aeruginosa. It may be considered for mild-to-moderate intra-abdominal infections but should be avoided if patients have fluoroquinolone exposure within the previous three months, due to increasing B. fragilis resistance. Moxifloxacin may be considered a second-line agent for the management of drug-susceptible tuberculosis.

I- Fluoroquinolone

- **Examples of clinically useful fluoroquinolones**

4. Gemifloxacin

- Gemifloxacin is indicated for the management of community-acquired respiratory infections. Unlike the other compounds, it is only available as an oral formulation.

I- Fluoroquinolone

- **Examples of clinically useful fluoroquinolones**

5. Delafloxacin

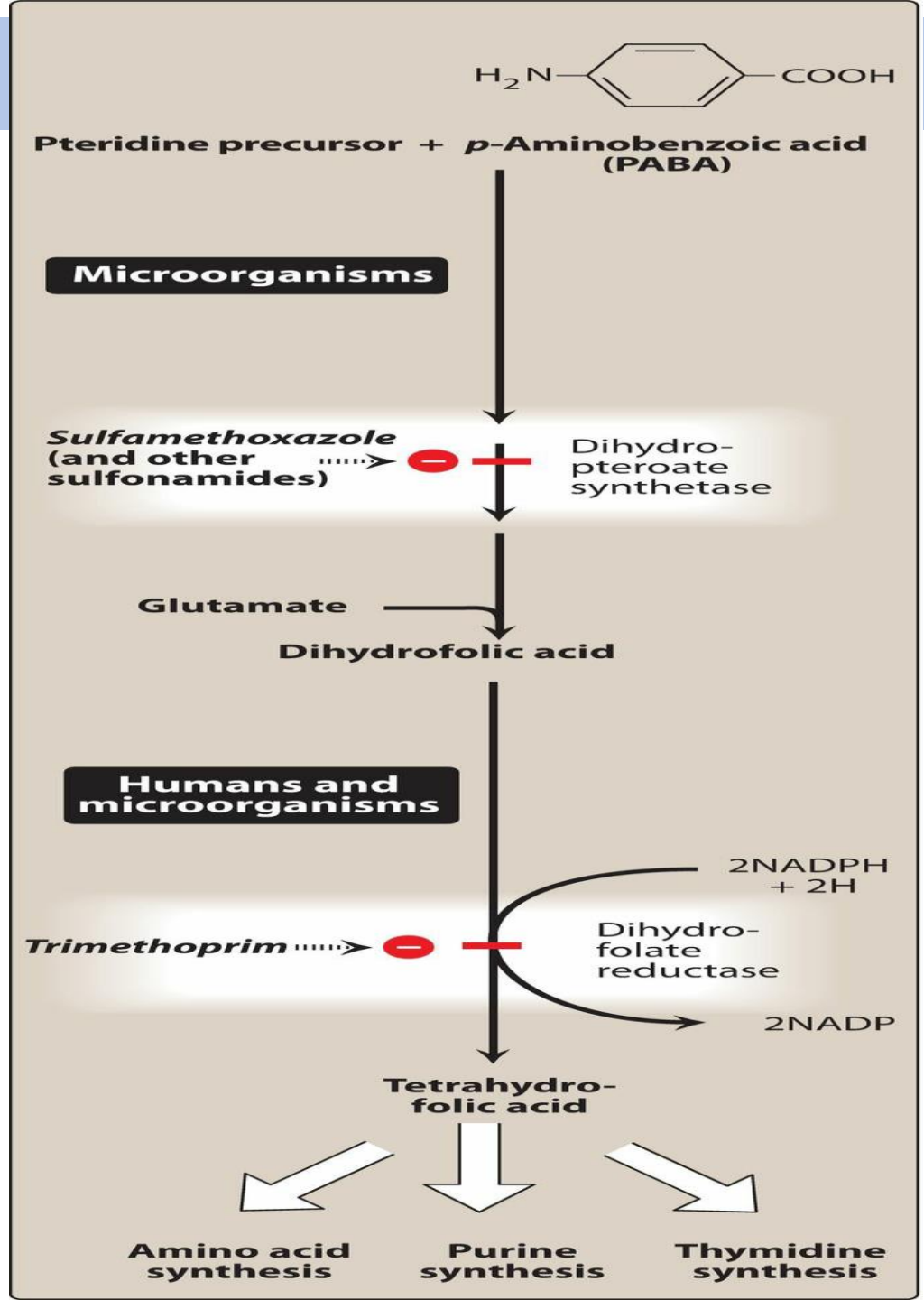
- Delafloxacin has improved activity against gram-positive cocci, including MRSA and Enterococcus spp. Due to its spectrum of activity, it is an option for managing acute bacterial skin and skin structure infections. It is available as an intravenous and oral formulation.

II- Folate Antagonists

- Folic acid is a coenzyme essential in the synthesis of ribonucleic acid (RNA), DNA, and certain amino acids.
- In the **absence of folate**, cells **cannot** grow or divide.
- Humans use dietary folate to synthesize the critical folate derivative, **tetrahydrofolic acid**.
- By contrast, many bacteria are impermeable to folate derivatives and rely on their ability to **synthesize folate *de novo*** (Figure).

II- Folate Antagonists

- **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**.



II- Folate Antagonists

- Thus, both **sulfonamides** and **trimethoprim** interfere with the ability of an infecting bacterium to **perform DNA synthesis** and other **essential cellular functions**.
- The combination of the **sulphonamide sulfamethoxazole** with **trimethoprim** (the generic name for the combination is **cotrimoxazole**) provides a **synergistic** effect.

III. Sulfonamides

- **Sulfa drugs** were among the first antibiotics used in clinical practice.
- Today, they are **seldom** prescribed alone except in developing countries, where they are employed **because of low cost and efficacy**.

III. Sulfonamides

- **Mechanism of action**

- Microorganisms use the enzyme **dihydropteroate synthetase** to create **dihydrofolic acid** from the precursor molecule **p-aminobenzoic acid (PABA).**

- **Sulfonamides** are synthetic **analogs of PABA**.

- Because of their structural similarity, sulfonamides **compete** with PABA to **inhibit dihydropteroate synthetase and the genesis of bacterial dihydrofolic acid**.

- These agents, including **cotrimoxazole**, are **bacteriostatic.**

III. Sulfonamides

- **Antibacterial spectrum**

- Sulfa drugs have in vitro activity against **gram negative** and **gram-positive organisms**. Common organisms include Enterobacteriaceae, Haemophilus influenzae, Streptococcus spp., Staphylococcus spp., and Nocardia.

- Additionally, **sulfadiazine** in combination with the dihydrofolate reductase inhibitor **pyrimethamine** is the preferred treatment for **toxoplasmosis**.

III. Sulfonamides

❑ Resistance

- Bacteria that **obtain folate from their environment** are **naturally resistant to sulfa drugs**. Acquired bacterial resistance to the sulfa drugs can arise from plasmid transfers or random mutations. Resistance may be due to

1. **Altered dihydropteroate synthetase**,
2. **Decreased cellular permeability to sulfa drugs**,
3. **Enhanced production of the natural substrate**, PABA.

- [Note: organisms resistant to one member of this drug family are resistant to all.]

III. Sulfonamides

❑ Pharmacokinetics

1. Absorption

- Most sulfa drugs are **well absorbed** following oral administration.
- An **exception** is **sulfasalazine**. It is **not absorbed** when administered orally or as a suppository and, therefore, is reserved for the treatment **of chronic inflammatory bowel diseases**.
- [Note: Intestinal flora **split sulfasalazine** into **sulfapyridine** and **5- aminosalicylate**, with the latter exerting the **anti-inflammatory effect**. Absorption of sulfapyridine can lead to toxicity in patients who are slow acetylators.]

III. Sulfonamides

❑ Pharmacokinetics

1. Absorption

- **Intravenous sulfonamides** are generally **reserved** for patients who are **unable to take oral preparations** or have **severe infections**.
- Because of **the risk of sensitization**, sulfa drugs are **not** usually applied **topically**.

III. Sulfonamides

❑ Pharmacokinetics

1. Absorption

- However, **in burn units**, silver sulfadiazine or mafenide acetate (α-amino-ptoluenesulfonamide) creams have been effective in reducing **burn-associated sepsis** **because they prevent colonization of bacteria**.
- [Note: Silver sulfadiazine is preferred because **mafenide** produces **pain on application** and its **absorption** may contribute to acid–base disturbances.]

III. Sulfonamides

❑ Pharmacokinetics

2. Distribution

- Sulfa drugs are **bound to serum albumin** in circulation and **widely distribute** throughout body tissues.
- Sulfa drugs penetrate well into **cerebrospinal fluid** (even in the absence of inflammation) and **cross the placental barrier** to enter fetal tissues.

III. Sulfonamides

❑ Pharmacokinetics

3. Metabolism

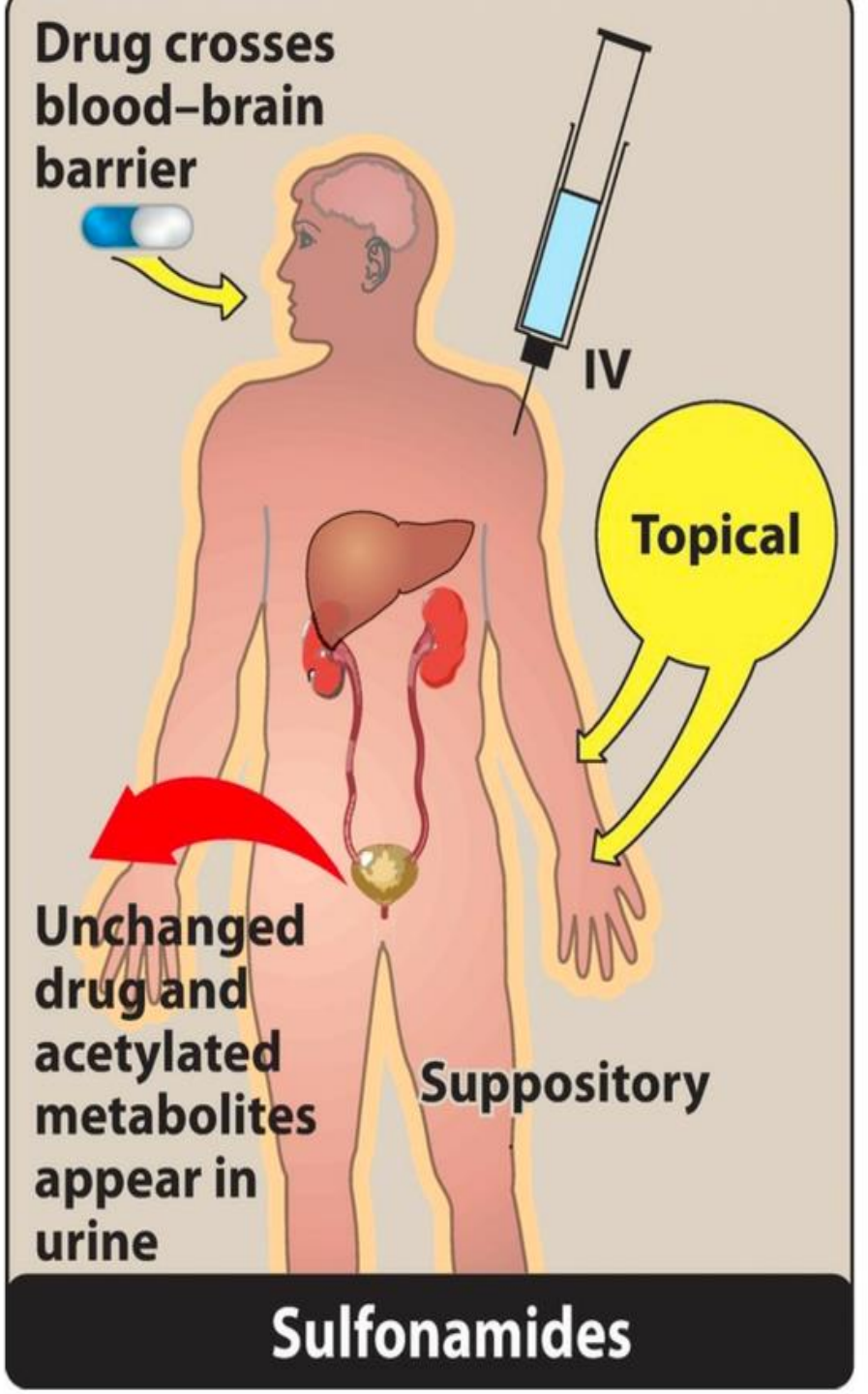
- Sulfa drugs are **acetylated** and **conjugated** primarily in the liver.
- The acetylated product is lacking of antimicrobial activity but retains the **toxic potential** to **precipitate** at **neutral or acidic pH**.
- This causes **crystalluria** (“stone formation”) and potential damage to the kidney.

III. Sulfonamides

❑ Pharmacokinetics

4. Excretion

- Unchanged sulfa drugs and metabolites are eliminated via **glomerular filtration and secretion**, requiring dose adjustments with **renal impairment**.
- Sulfonamides may be eliminated in **breast milk**.



III. Sulfonamides

❑Adverse effects

1. Crystalluria

- **Nephrotoxicity** may develop as a result of crystalluria.
- **Adequate hydration and alkalinization** of urine can prevent the problem by reducing the concentration of drug and promoting its ionization.

III. Sulfonamides

❑Adverse effects

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.

III. Sulfonamides

❑Adverse effects

3. Hematopoietic disturbances

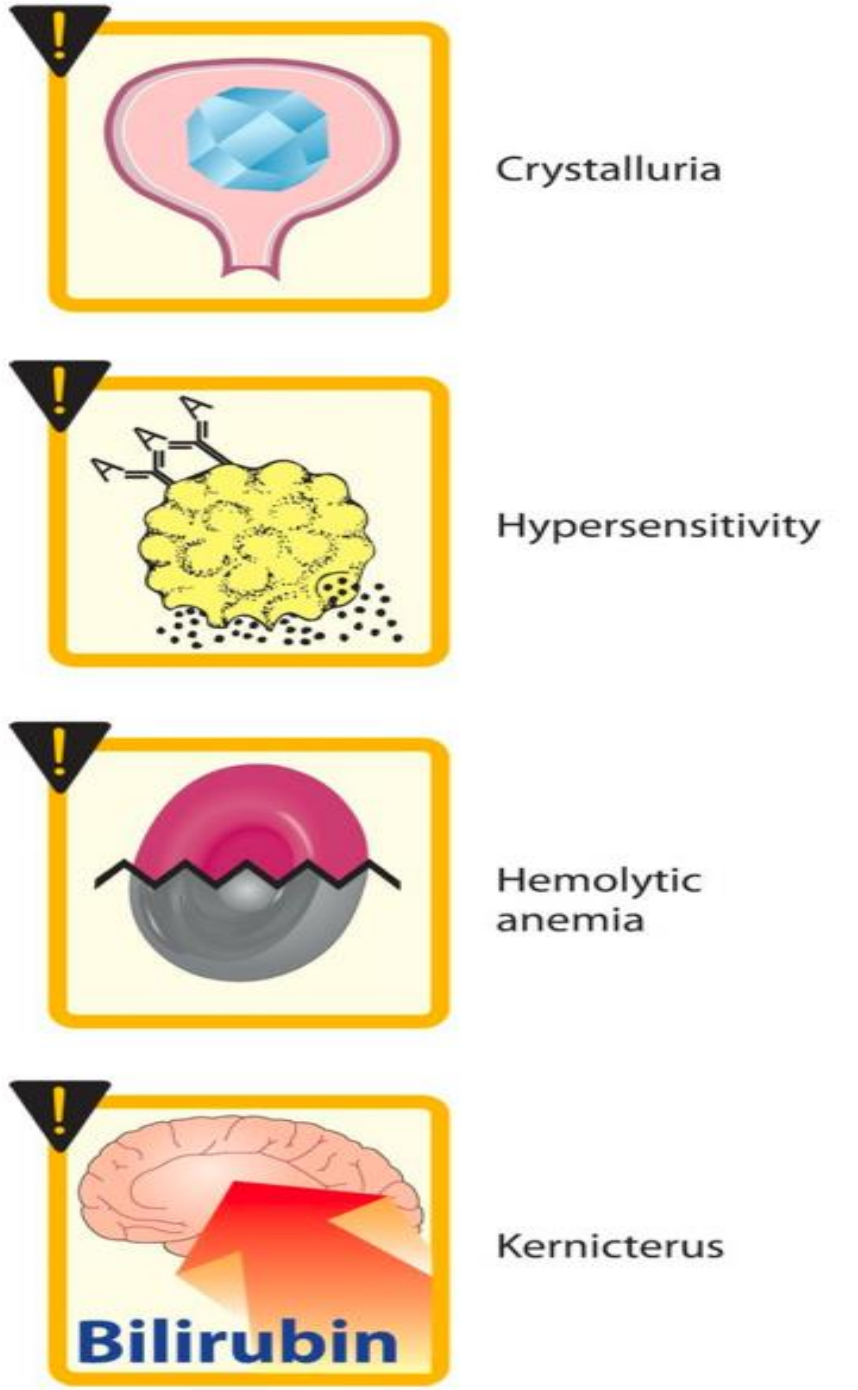
- **Hemolytic anemia** is encountered in patients with **glucose-6-phosphate dehydrogenase (G6PD)** deficiency.
- **Granulocytopenia** and **thrombocytopenia** can also occur.
- Fatal reactions have been reported from associated **agranulocytosis, aplastic anemia, and other blood dyscrasias**.

III. Sulfonamides

❑Adverse effects

4. Kernicterus

- **Bilirubin-associated brain damage** (kernicterus) 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.



ome adverse reactions to sulfonamides.

III. Sulfonamides

❑Adverse effects

5. Drug potentiation

- **Sulfamethoxazole potentiates** the anticoagulant effect of **warfarin** due to **inhibition** of CYP2C9, resulting in reduced clearance of warfarin.
- **Sulfonamides** may also **displace warfarin** from binding sites on serum albumin.
- Serum **methotrexate** levels may rise through **protein binding displacement**.
- Other **CYP2C9 substrates**, such as **phenytoin**, may have **increased** concentrations when given with sulfonamides.

III. Sulfonamides

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.

IV. Trimethoprim

- **Trimethoprim**, a potent **inhibitor** of bacterial **dihydrofolate reductase**, was initially available in combination with the sulfonamide sulfamethoxazole, and later approved for use as a single agent.
- Today, trimethoprim is most commonly used in combination with sulfamethoxazole.

IV. Trimethoprim

- **Mechanism of action**
- Trimethoprim is a potent **inhibitor** of bacterial **dihydrofolate reductase**.
- Inhibition of this enzyme prevents the **formation of the metabolically active form of folic acid**, **tetrahydrofolic acid**, and thus, **interferes** with **normal** bacterial cell functions.
- Trimethoprim **binds** to bacterial **dihydrofolate reductase** more readily than it does to human dihydrofolate reductase, which accounts for the selective toxicity of the drug.

IV. Trimethoprim

- **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 **urinary tract infections** (UTIs) and in the **treatment of bacterial prostatitis** (although fluoroquinolones and cotrimoxazole are preferred).

IV. Trimethoprim

- **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** drug may play and decreased permeability to the drug may play a role.

IV. Trimethoprim

- **Pharmacokinetics**
- It is **rapidly absorbed** following **oral administration**.
- Because the drug is a **weak base**, higher concentrations of trimethoprim are achieved in the relatively **acidic prostatic and vaginal fluids**.
- The drug is widely distributed into body tissues and fluids, including penetration into the **cerebrospinal fluid**.
- It undergoes some O-demethylation, but 60% to 80% is renally excreted unchanged.

IV. Trimethoprim

- **Adverse effects**
- It can produce the effects of **folic acid deficiency**.
- These effects include **megaloblastic anemia**, **leukopenia**, and **granulocytopenia**, especially in pregnant and those with nutrient-poor diets.
- These blood disorders may be reversed by **simultaneous** administration of **folinic acid** (also known as leucovorin), which does not enter bacteria.
- Trimethoprim has a potassium-sparing effect and may cause **hyperkalemia**, especially at higher doses and when administered with other medication that causes **hyperkalemia** (for example, **angiotensin-converting enzyme inhibitors**).

V. 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.

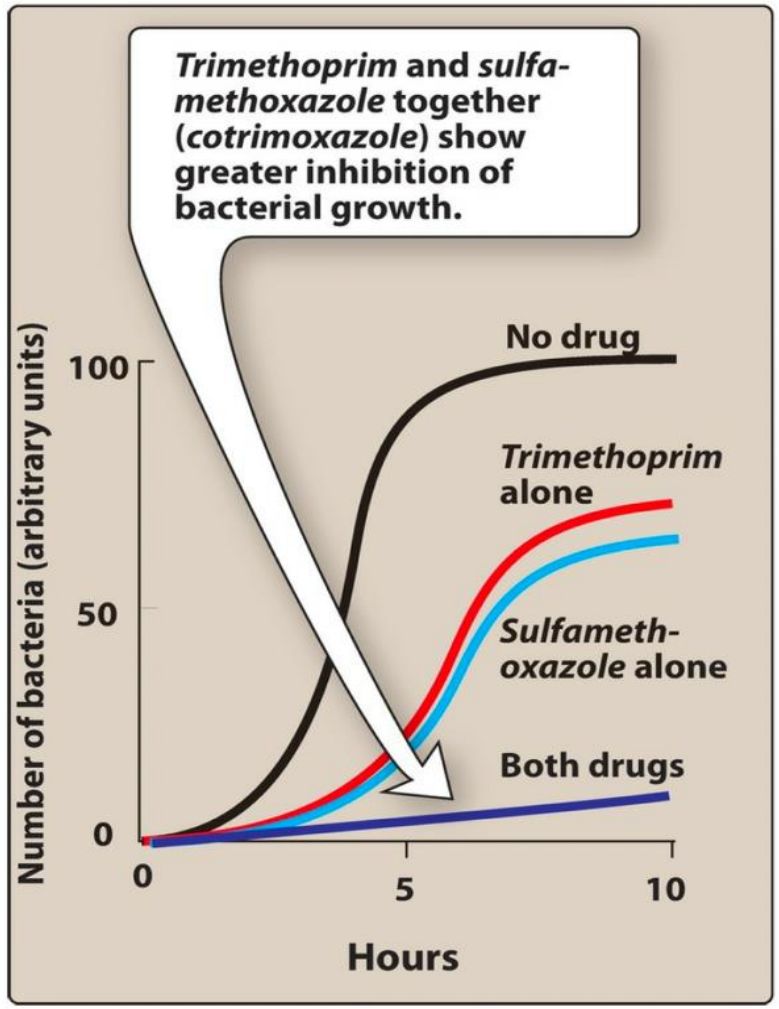


Figure 31.10 Synergism between *trimethoprim* and *sulfamethoxazole* inhibits growth of E. coli.

V. Cotrimoxazole

- **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 the **reduction of dihydrofolate to tetrahydrofolate** .

V. Cotrimoxazole

- **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**, as well as **Pneumocystis jirovecii**, **toxoplasmosis**, **Listeria monocytogenes**, and **Salmonella infections**.
- It has activity against **methicillin-resistant S. aureus** and can be particularly useful for **skin and soft tissue infections** caused by this organism.
- It is the drug of choice for infections caused by susceptible **Nocardia spp. And Stenotrophomonas maltophilia**.

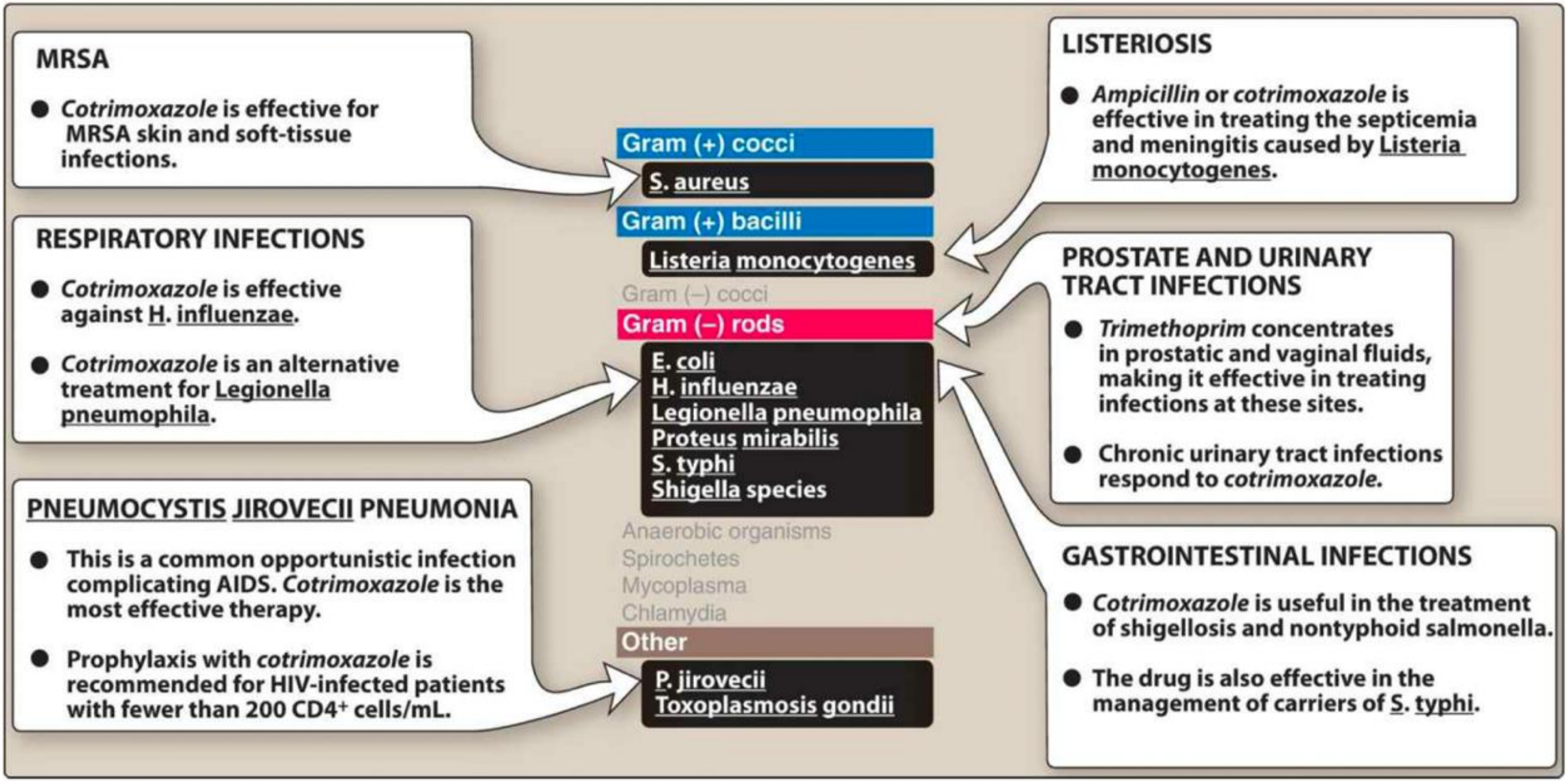


Figure 31.11 Typical therapeutic applications of *cotrimoxazole* (*sulfamethoxazole* plus *trimethoprim*).

V. Cotrimoxazole

- **Resistance**

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

V. Cotrimoxazole

- **Pharmacokinetics**
- **Cotrimoxazole** is generally administered orally (Figure 31.12).
- **Intravenous administration** may be utilized in patients with severe pneumonia caused by **Pneumocystis jirovecii**. Both agents are distributed throughout the body.
- Trimethoprim concentrates in the relatively acidic milieu of prostatic fluids, and this accounts for the use of trimethoprim–sulfamethoxazole in the treatment of prostatitis.
- Cotrimoxazole readily crosses the blood–brain barrier. Both parent drugs and their metabolites are excreted in the urine.

V. Cotrimoxazole

- **Adverse effects**
- Adverse reactions and drug interactions related to cotrimoxazole are similar to those expected with each of the individual components, sulfamethoxazole and trimethoprim (Figure 31.13).
- The most common adverse reactions are nausea and vomiting, skin rash, hematologic toxicity, and hyperkalemia.

V. Cotrimoxazole

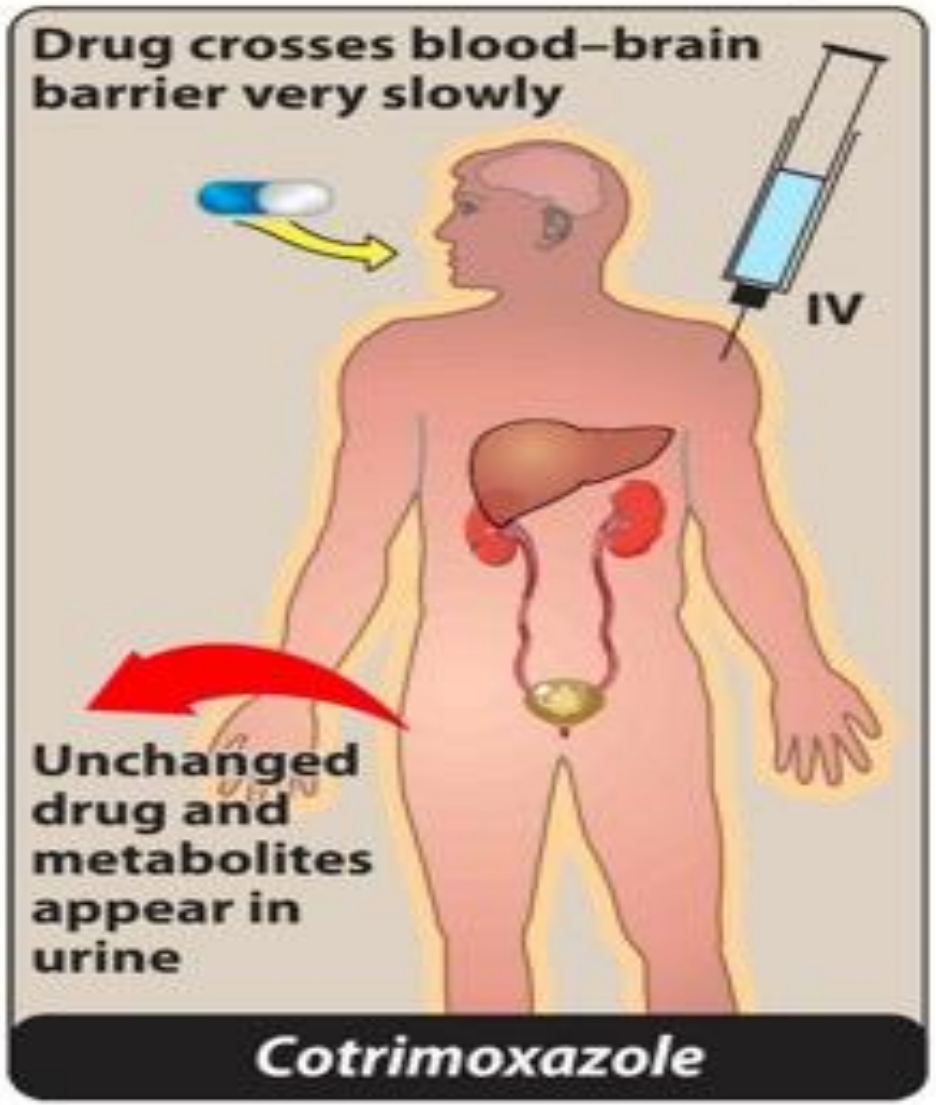


Figure 31.12 Administration and fate of cotrimoxazole

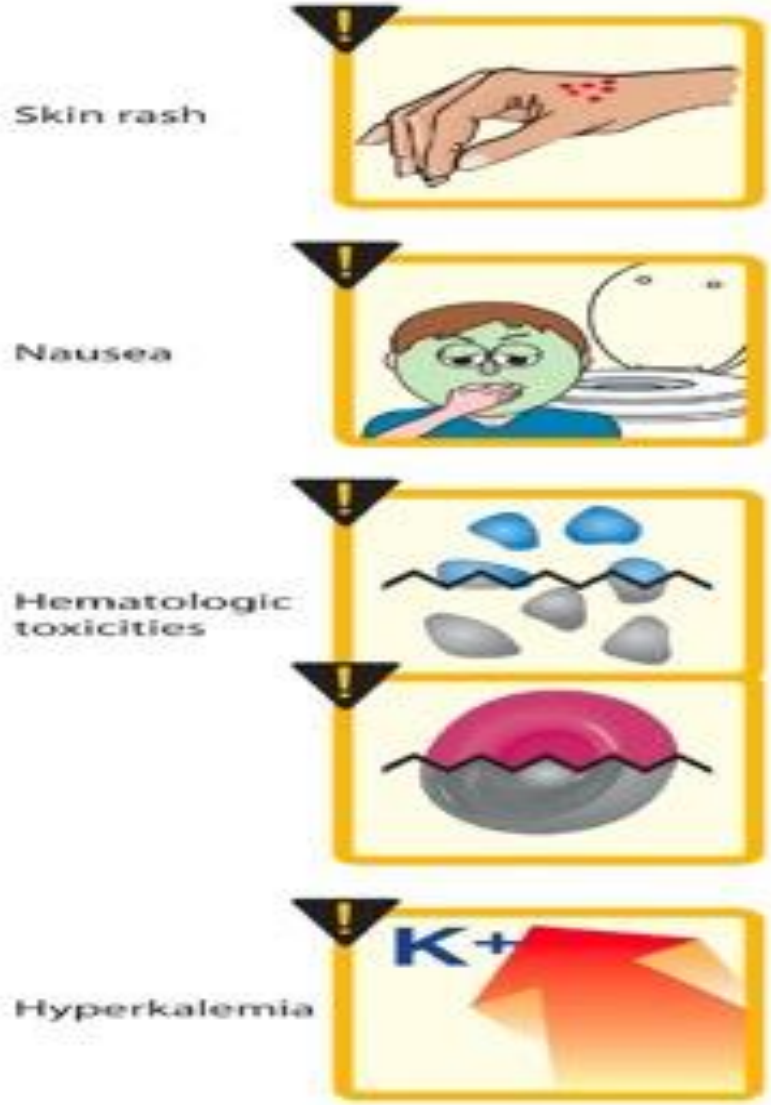


Figure 31.13 Some adverse reactions to cotrimoxazole

VI. Urinary Tract Antiseptics/Antimicrobials

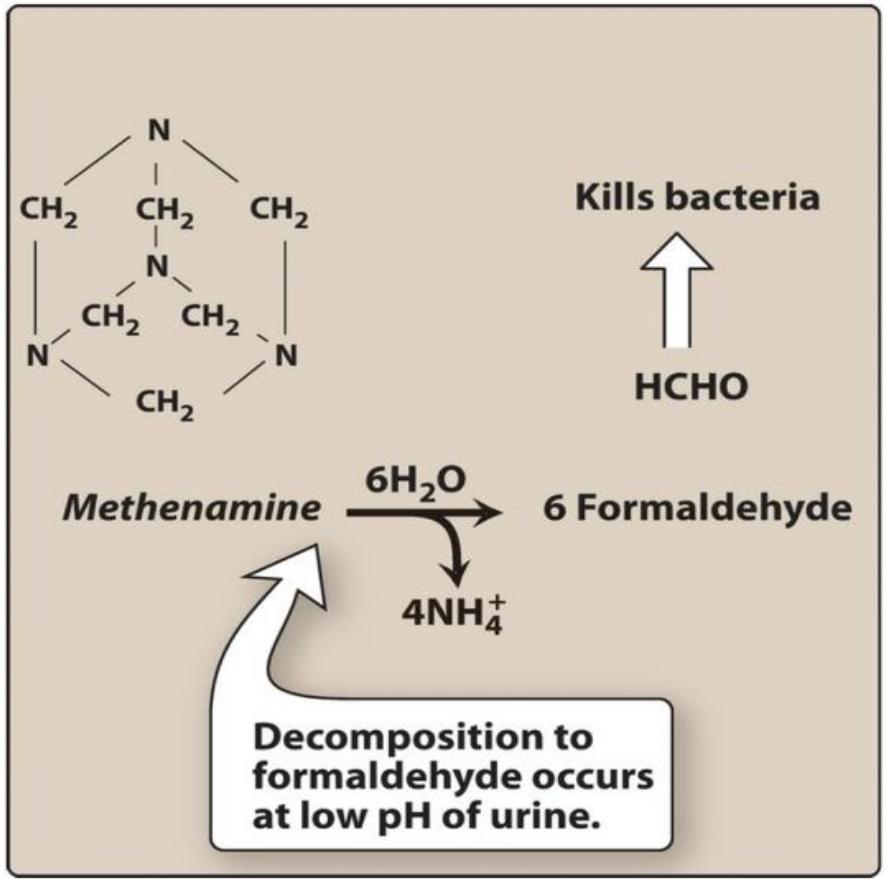
- UTIs are one of the most common bacterial infections in the world, primarily impacting women and the elderly.
- Historically, **fluoroquinolones** and **cotrimoxazole** have been the first-line therapy for the treatment of UTIs.
- Unfortunately, **resistance** has increased among common pathogens (for example, E. coli).
- As a result, **methenamine**, **nitrofurantoin**, and **fosfomycin** can be considered for **treatment** or **suppression of recurrence**, due to their efficacy against common pathogens and high concentrations in the urine.

VI. Urinary Tract Antiseptics/Antimicrobials

A. Methenamine

- **Mechanism of action**

- Methenamine salts are hydrolyzed to ammonia and formaldehyde in acidic urine (pH ≤ 5.5). Formaldehyde denatures proteins and nucleic acids, resulting in bacterial cell death. Methenamine is combined with a weak acid (for example, hippuric acid) to maintain urine acidity and promote the production of formaldehyde.



VI. Urinary Tract Antiseptics/Antimicrobials

A. Methenamine

- **Antibacterial spectrum**
- Methenamine is primarily used for chronic suppressive therapy to reduce the frequency of UTIs.
- Methenamine is active against **E. coli**, **Enterococcus spp., and Staphylococcus spp**.
- It has some activity against **Proteus spp. and Pseudomonas aeruginosa**, but urine pH must be kept **acidic to achieve bactericidal activity**.
- The main benefit of methenamine is the lack of selection for resistant organisms.

VI. Urinary Tract Antiseptics/Antimicrobials

A. Methenamine

- **Pharmacokinetics**
- Methenamine is **orally absorbed**, with up to **30% decomposing** in gastric juices, unless **protected** by **enteric coating**.
- It reaches the **urine** through **tubular secretion** and **glomerular filtration**.
- Concentrations are sufficient to treat susceptible organisms.
- Due to **ammonia formation**, use should be avoided in **hepatic insufficiency**.

VI. Urinary Tract Antiseptics/Antimicrobials

A. Methenamine

- **Adverse effects**
- The major adverse effect of methenamine is **gastrointestinal distress**, although at higher doses, **albuminuria, hematuria, and rashes** may develop.
- Methenamine mandelate is **contraindicated** in patients with **renal insufficiency**, because mandelic acid may precipitate.
- The methenamine hippurate formulation should be used instead.
- [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**.]

VI. Urinary Tract Antiseptics/Antimicrobials

B. Nitrofurantoin

- Nitrofurantoin was introduced into clinical practice for the management of cystitis in the early 1950s.
- For decades, it was rarely used, but was revived due to increasing antibiotic resistance among **Enterobacteriaceae** and is considered **first-line therapy for uncomplicated cystitis**.
- Nitrofurantoin works by **inhibiting DNA and RNA synthesis**.
- Susceptible organisms include **E. coli, Klebsiella spp.**, **Enterococcus spp.**, and **Staphylococcus spp**.
- Following oral administration, it is **rapidly absorbed**, with nearly **40% excreted unchanged in the urine**. Overall, nitrofurantoin is **well tolerated**.

VI. Urinary Tract Antiseptics/Antimicrobials

B. Nitrofurantoin

- **Common adverse events** include **nausea**, **vomiting**, and **diarrhea**.
- The use of the **microcrystalline formulation** decreases the incidence of gastrointestinal toxicity.
- Rare complications of therapy include **pulmonary fibrosis**, **neuropathy**, and **autoimmune hepatitis**.
- These events are observed with prolonged exposure greater than 1 month.
- Additionally, patients with impaired renal function should not receive nitrofurantoin due to an increased risk of adverse events.