Protein Synthesis Inhibitors

Pharmacology and Toxicology

General Pharmacology

Second Year Medical Students

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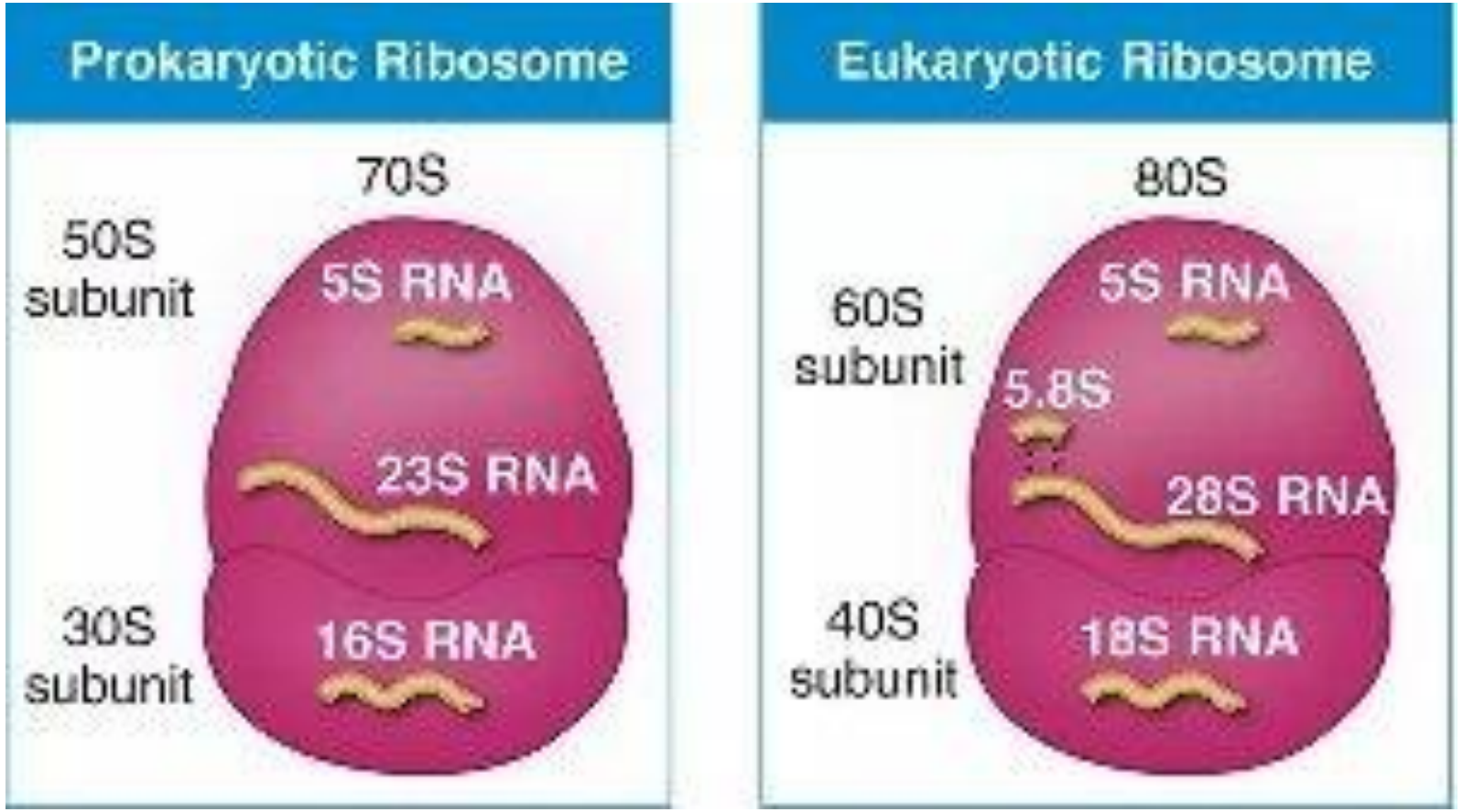
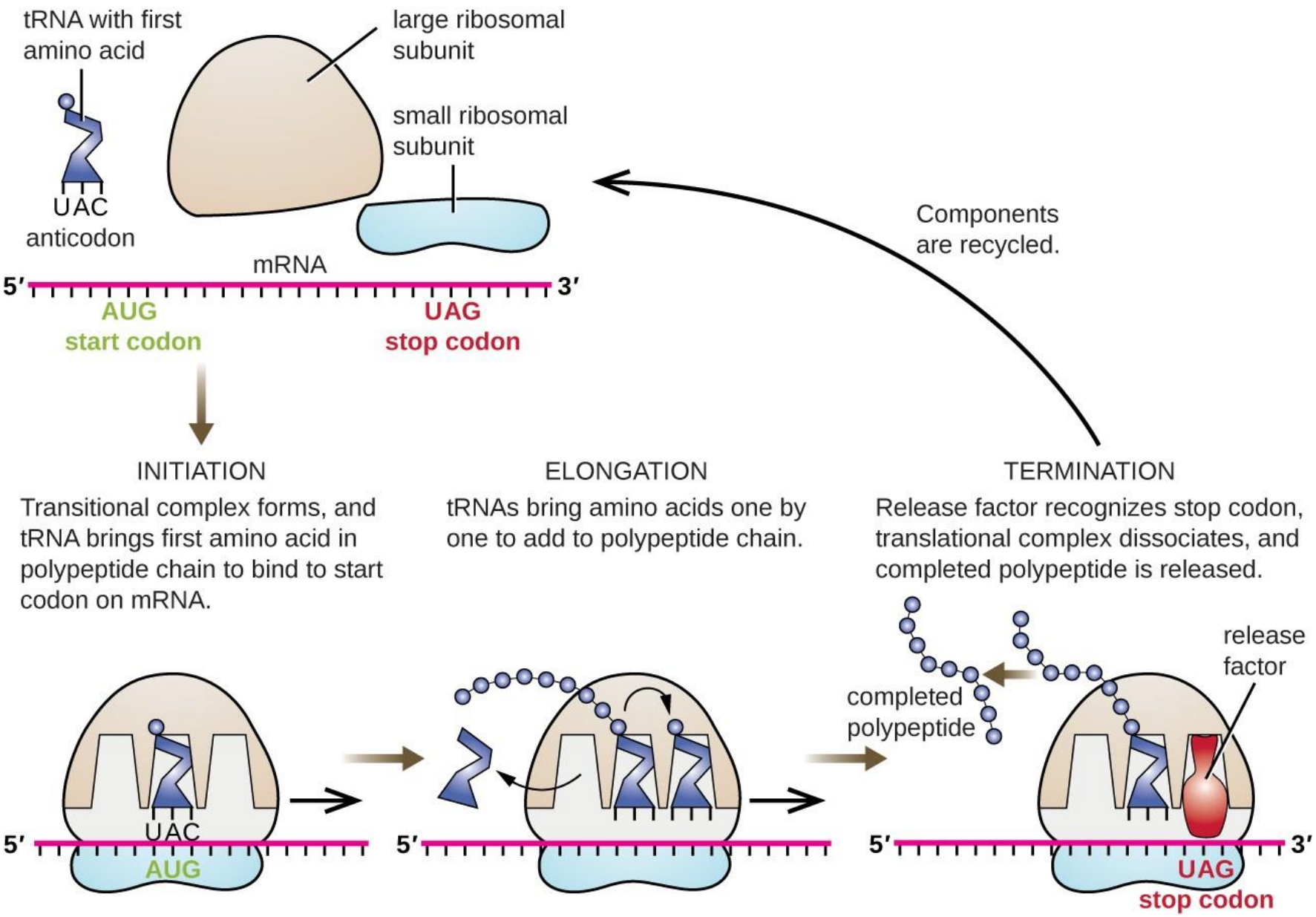
Faculty of Medicine

The Hashemite University

Textbook: Chapter 30 pp: 384-399

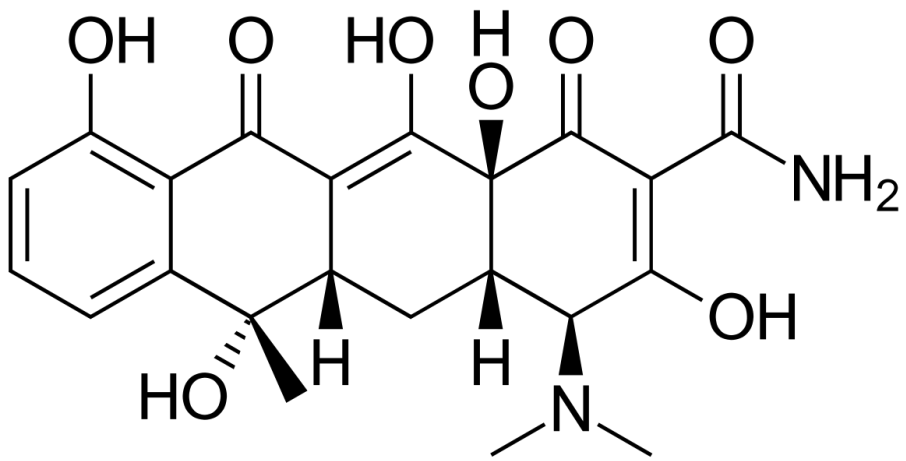
Bacterial Protein Synthesis





Tetracyclines

Tetracyclines



Tetracycline

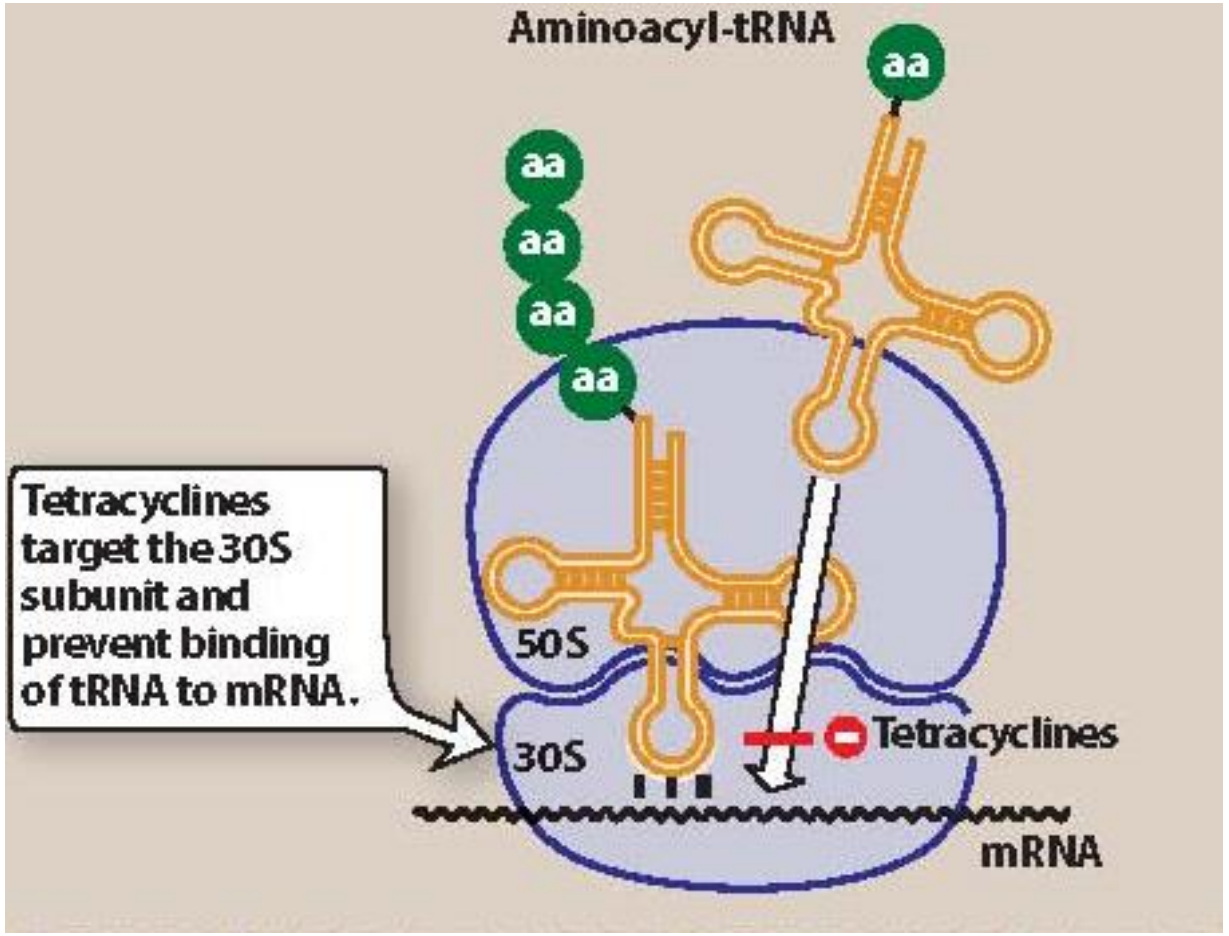
TETRACYCLINES	
Demeclocycline	DECLOMYCIN
Doxycycline	VIBRAMYCIN
Minocycline	MINOCIN
Tetracycline	

Tetracyclines

Mechanism of action

-bind ***reversibly*** to the **30S** subunit of bacterial ribosomes

-prevent the binding of tRNA to the mRNA-ribosome complex



Tetracyclines

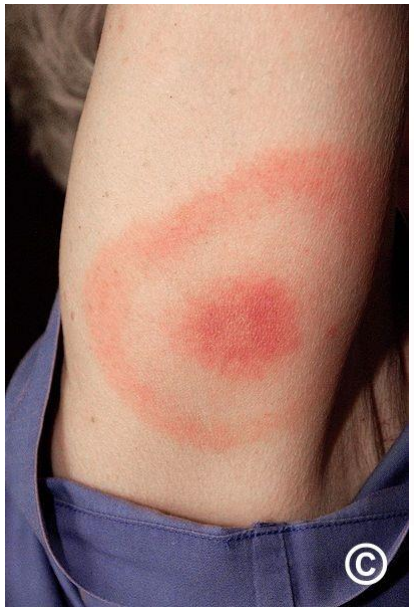
Antibacterial spectrum

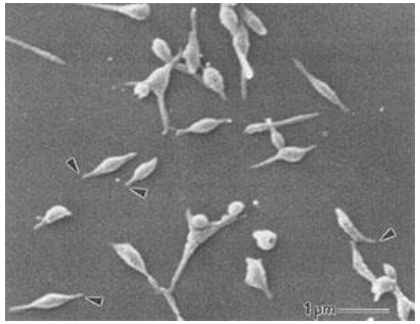
- Bacteriostatic
- Effective against gram-positive, gram-negative, protozoa, spirochetes, atypical, etc

Commonly used for the treatment of:

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

Therapeutic Spectrum of Doxycycline





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*
- Vibrio cholerae
- Yersinia pestis

*(a tetracycline + *gentamicin*)

Anaerobic organisms
- Clostridium perfringens
- Clostridium tetani

Spirochetes
- Borrelia burgdorferi
- Leptospira interrogans
- Treponema pallidum

Mycoplasma
- Mycoplasma pneumoniae

Chlamydia
- Chlamydia species

Other
- Rickettsia rickettsii

CHOLERA

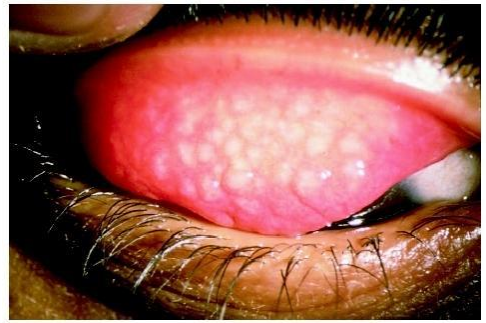
- Cholera is caused by Vibrio cholerae ingested in fecally contaminated food or water.
- The organism multiplies in the gastrointestinal tract, where it secretes an enterotoxin that produces diarrhea.
- Treatment includes *doxycycline*, which reduces the number of intestinal vibrios, and fluid replacement.

CHLAMYDIAL INFECTIONS

- Chlamydia trachomatis is the 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

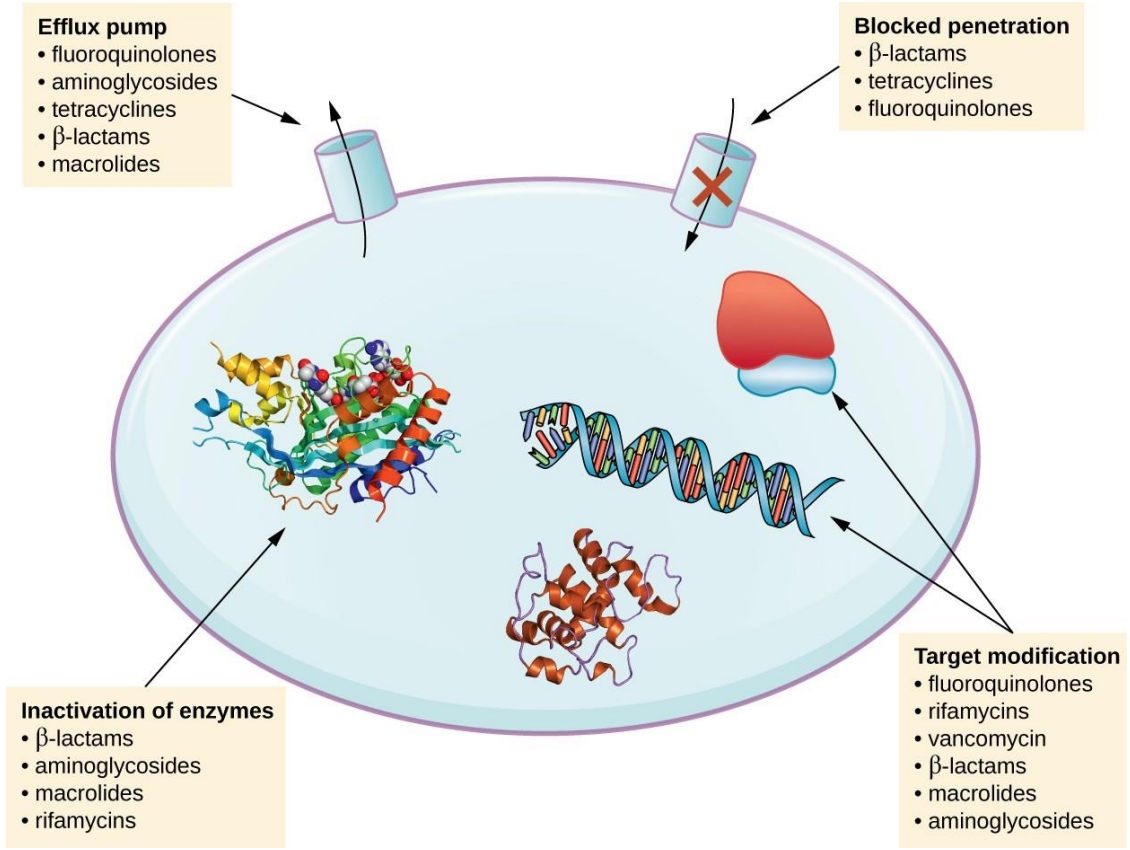
- This disease, caused by Rickettsia rickettsii, is characterized by fever, chills, and aches in bones and joints.
- Response to tetracyclines is prompt if the drug is started early in the disease process.



Tetracyclines

Mechanisms of resistance

- Efflux pump (most common)
- Enzymatic inactivation of the drug
- Interfering with binding to ribosomes
- Cross-resistance is *not* common

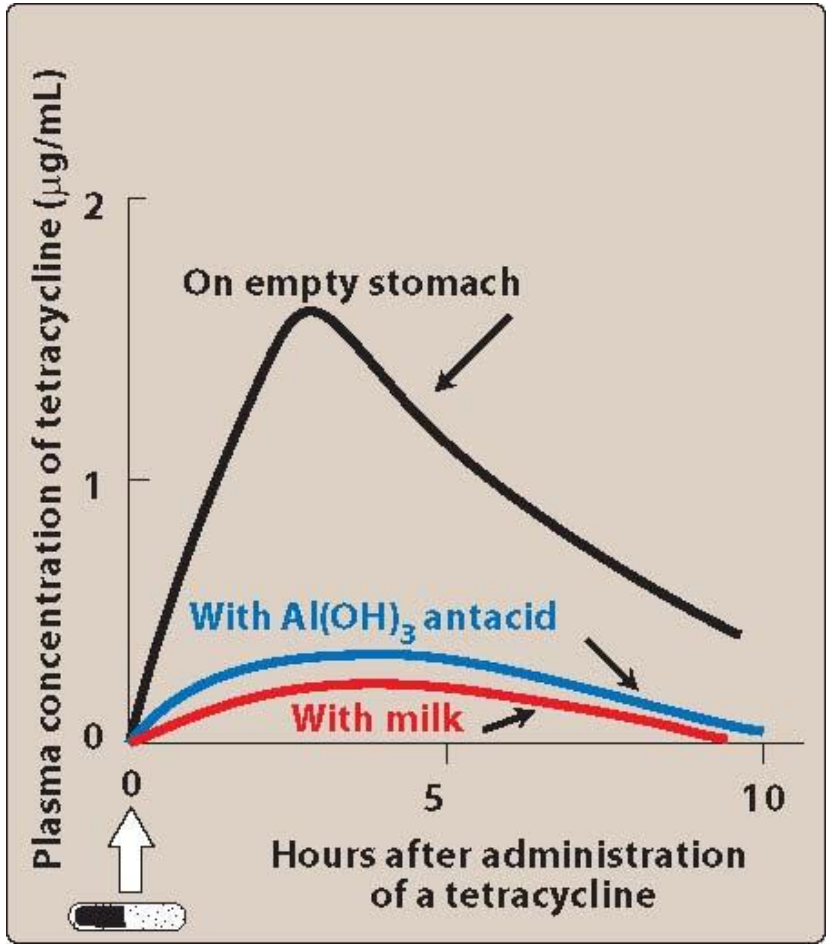


Tetracyclines

Pharmacokinetics

Absorption

- Oral
- Adequately absorbed
- ↓ absorption when administered with dairy (high cations) → formation of nonabsorbable chelates



Tetracyclines

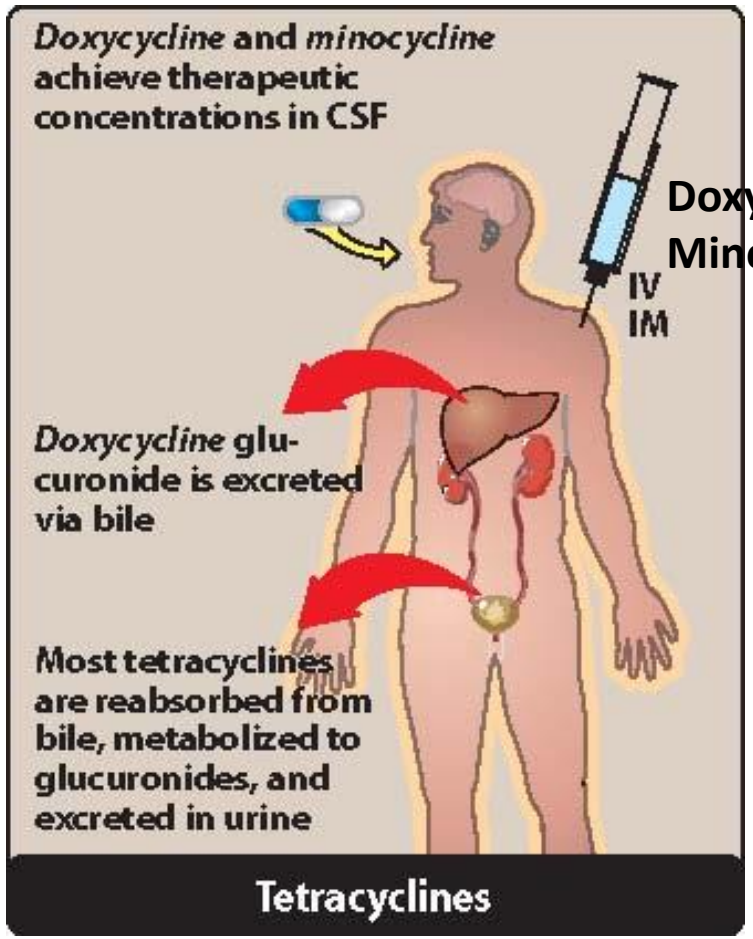
Pharmacokinetics

Distribution

- Distribute well in body fluids, including CSF
- Bind to tissues undergoing calcification e.g., bones, teeth.
- Cross placenta and deposit in fetal bones

Elimination

- Tetracycline eliminated unchanged in urine
- Doxycycline eliminated in bile/feces



Doxycycline
Minocycline

Tetracyclines

Adverse effects

- **Gastric discomfort:**

-irritation of gastric mucosa

-esophagitis

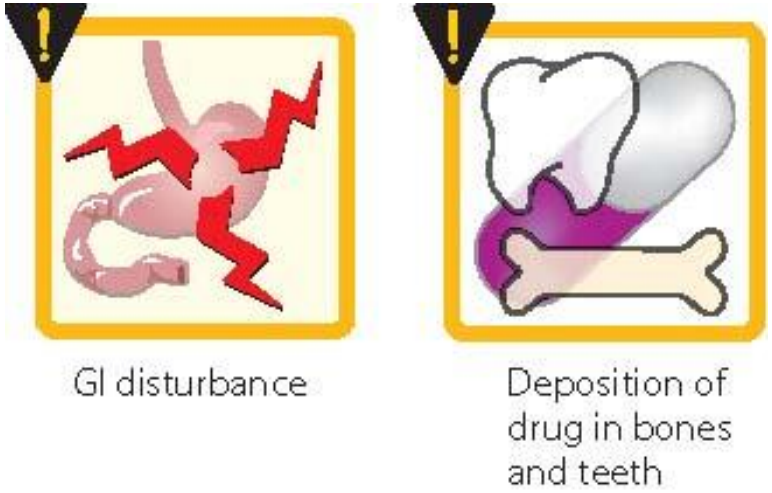
- **Effects on calcified tissues**

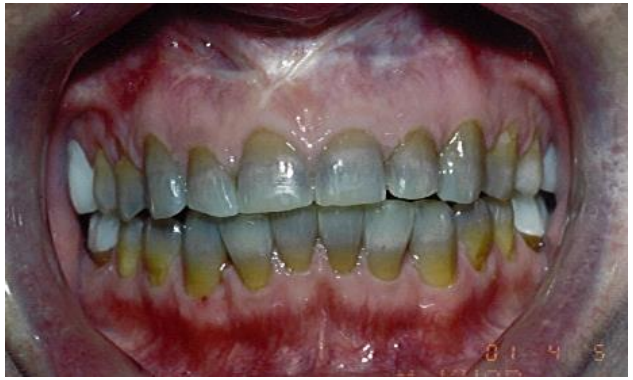
-deposited in tissues undergoing calcification, e.g., bones in children.

-dental hypoplasia

-growth problems

-pediatric use is limited





Tetracyclines

Adverse effects

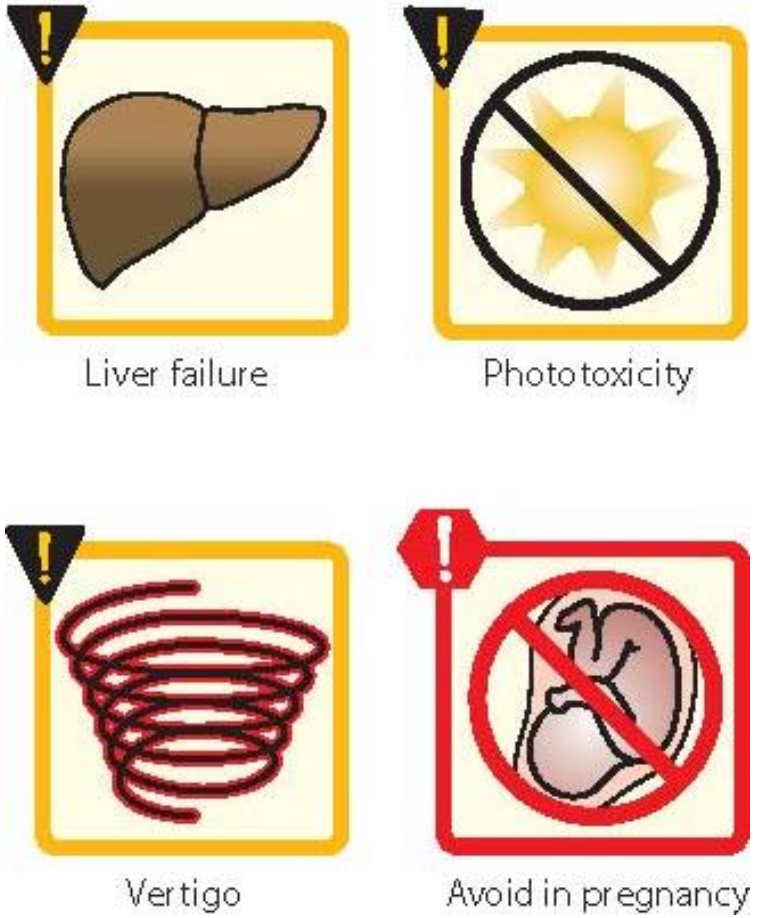
- **Hepatotoxicity**
- **Phototoxicity:**

-severe sunburns (recommended to wear sun protection)

- **Vestibular dysfunction:**

-dizziness, vertigo, tinnitus

- **Pseudotumor cerebri**



Tetracyclines

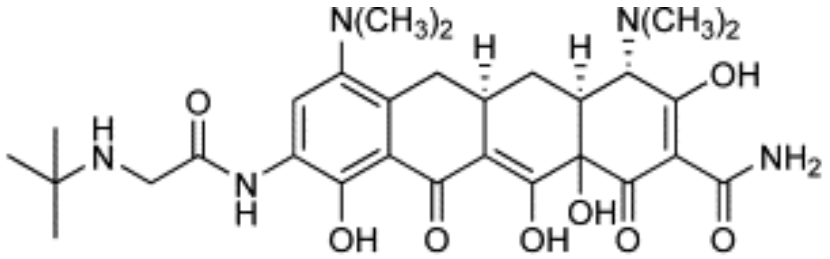
Contraindications

1. Pregnant women
2. Breast-feeding women
3. Pediatric age group <8 years

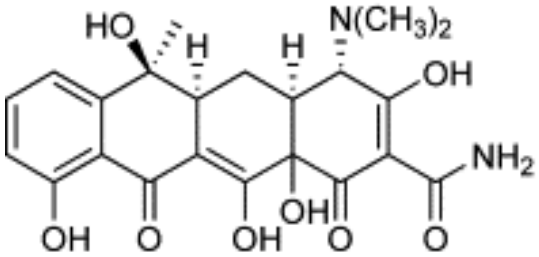
Glycylcyclines

Tigecycline

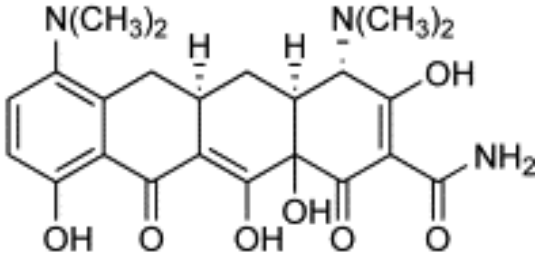
- Derivative of minocycline
- Same mechanism of action as tetracyclines
- Similar mechanisms of resistance



Tigecycline (**58**)



Tetracycline (**59**)



Minocycline (**60**)

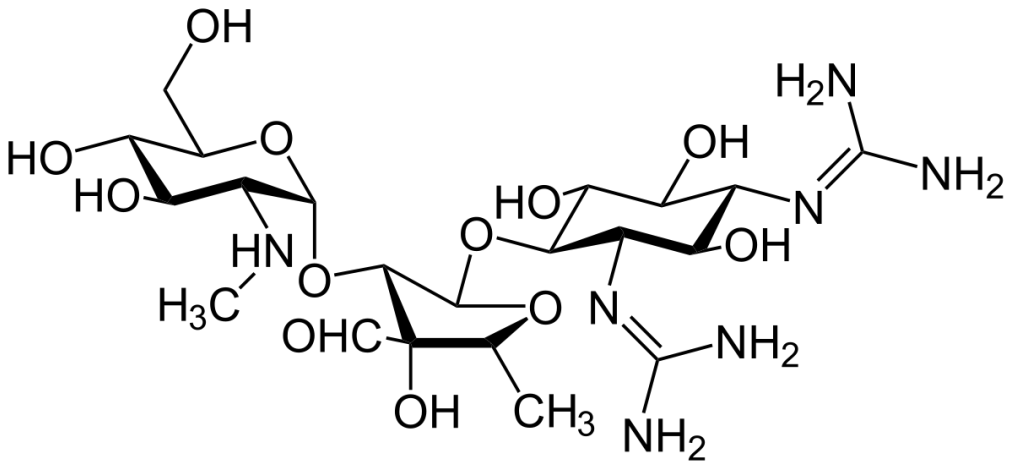
Tigecycline

Antibacterial spectrum

- Effective against MRSA
- Effective against multi-drug resistant streptococci
- Effective against vancomycin-resistant enterococci (VRE)
- Effective against ESBL gram-negative bacteria
- Effective against Acinetobacter spp
- NOT effective against Pseudomonas

Aminoglycosides

Aminoglycosides



AMINOGLYCOSIDES

Amikacin

Gentamicin GARAMYCIN

Neomycin NEO-FRADIN

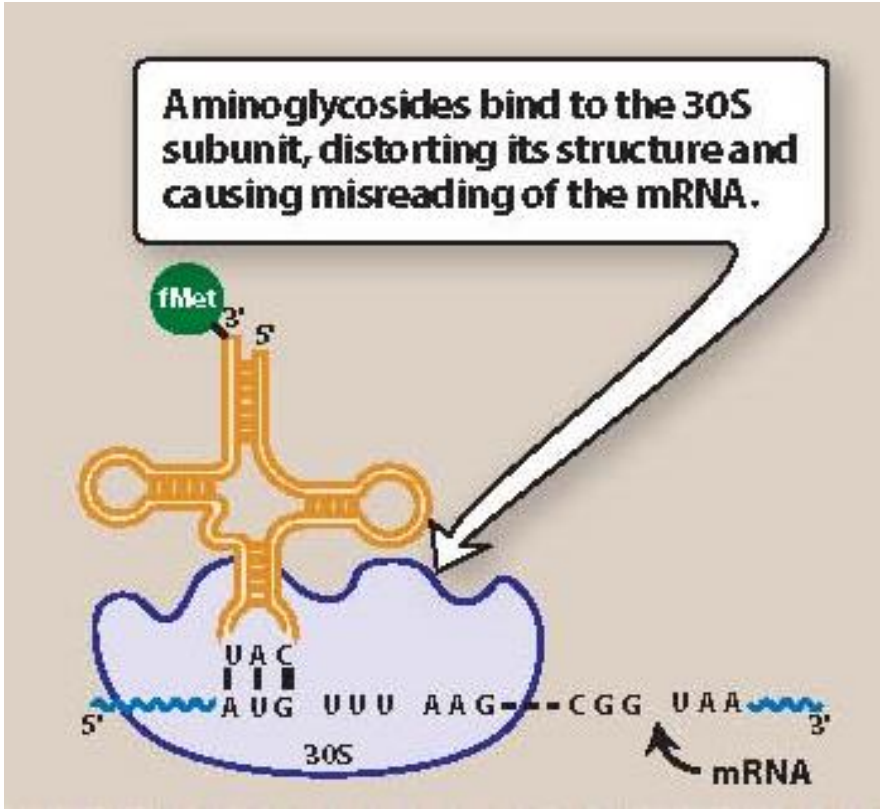
Streptomycin

Tobramycin TOBREX

Aminoglycosides

Mechanism of action

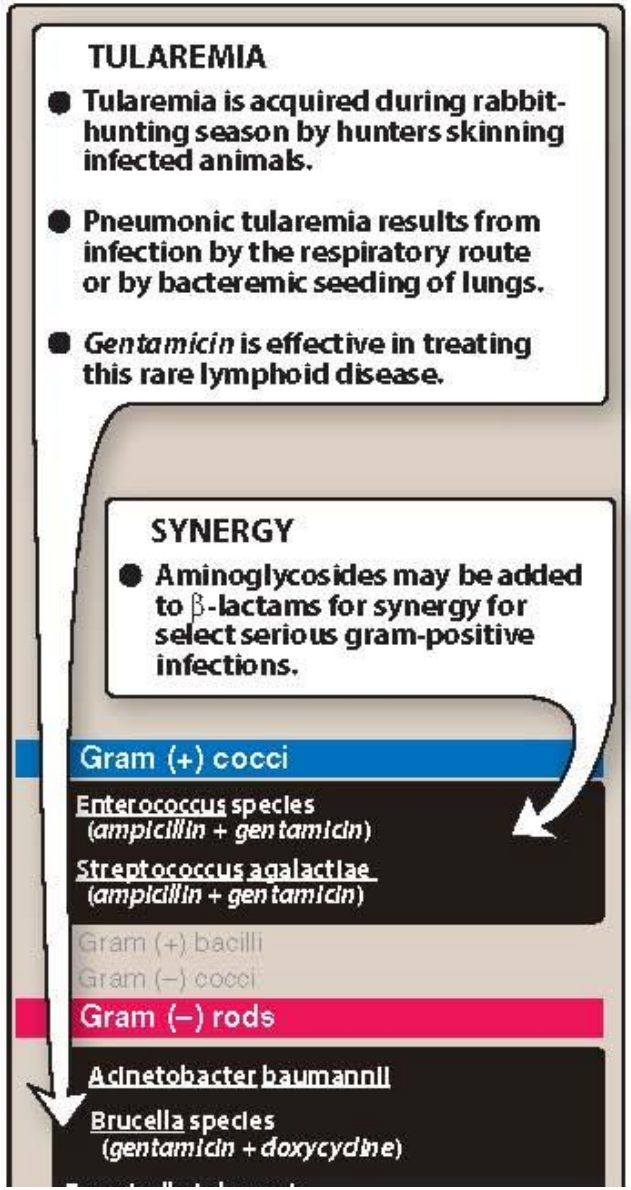
- Bind to 30S ribosomal subunit
- Interfere with assembly of the functional ribosomal apparatus
- Cause the 30S subunit of the completed ribosome to misread the genetic code

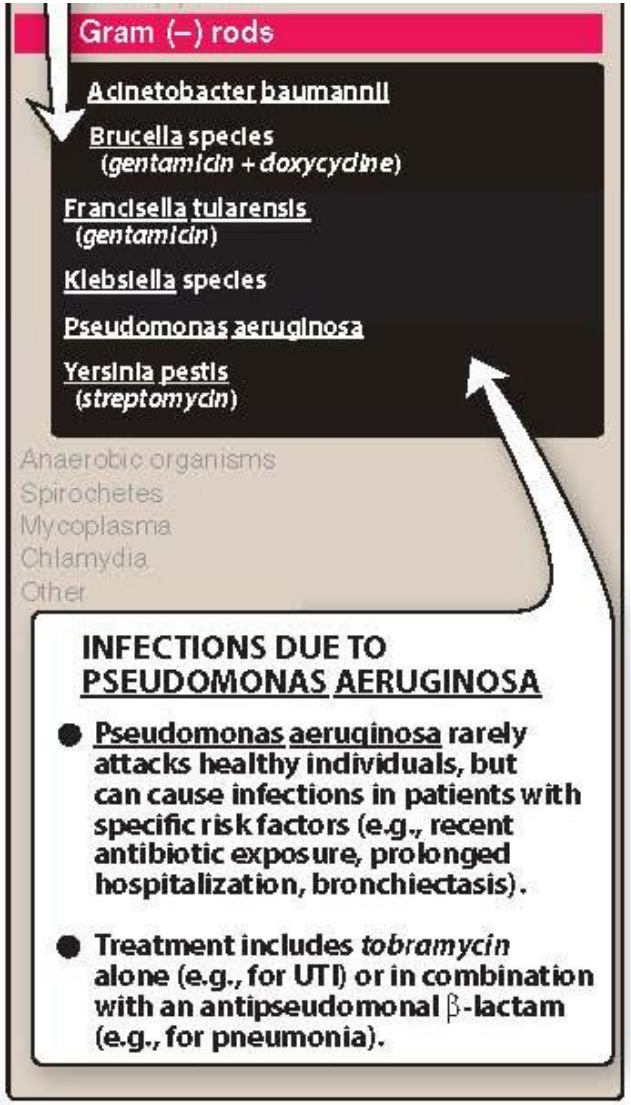


Aminoglycosides

Antibacterial spectrum

- Bactericidal
- Concentration-dependent
- Exhibit PAE
- Effective against gram-negative bacilli (INCLUDING multi-DRUG resistant *P. aeruginosa*)
- Used in combination with β-lactams





Some clinical uses of aminoglycosides

Aminoglycosides

Mechanisms of resistance

1) efflux pumps
2) decreased uptake
3) modification and inactivation by plasmid-associated synthesis of enzymes that hydrolyze aminoglycosides

   -Amikacin is less vulnerable to these enzymes

Aminoglycosides

Pharmacokinetics

Absorption

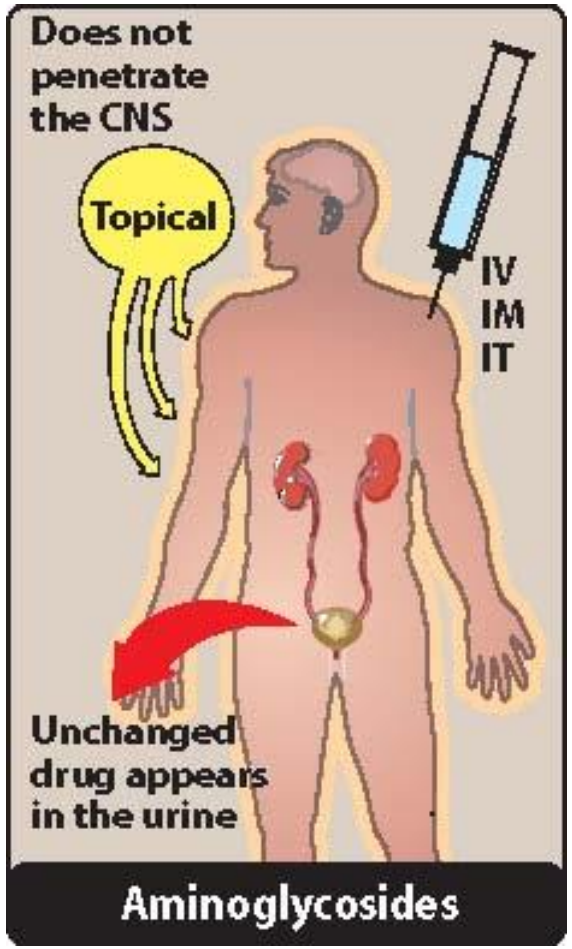
-all are given IV (except neomycin)

Distribution

-variable distribution in body fluids

-inadequate distribution in CSF

-cross the placenta



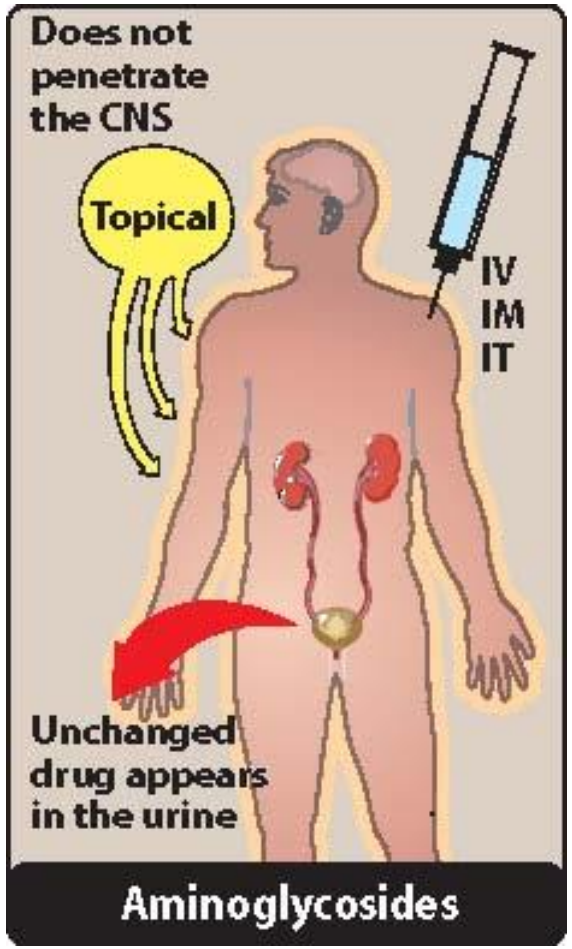
Aminoglycosides

Pharmacokinetics

Elimination

-90% are excreted unchanged in the urine

-accumulation occurs in cases of renal dysfunction



Aminoglycosides

Adverse effects

- **Ototoxicity (vestibular and auditory)**

-might cause irreversible deafness

-Vertigo (especially with streptomycin)

- **Nephrotoxicity**

-disrupt Ca^{++}-mediated transport processes

-from mild reversible renal impairment to irreversible acute tubular necrosis

Aminoglycosides

Adverse effects

- Neuromuscular paralysis

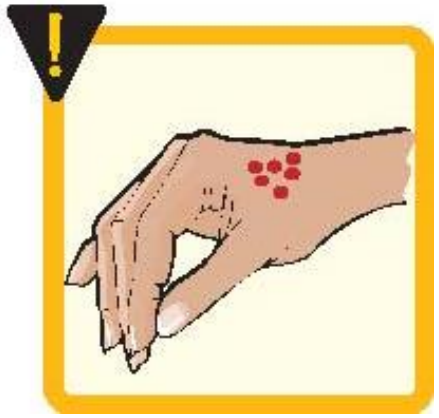
-patient with myasthenia gravis are at risk

- Allergic reaction

- Mostly contact dermatitis with topical neomycin

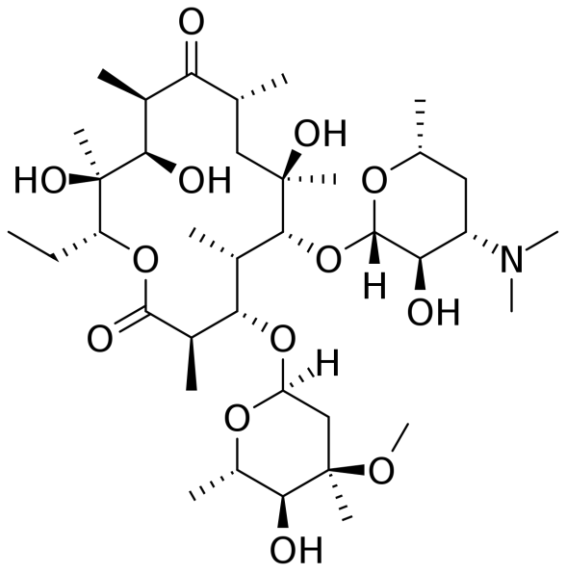
Paralysis

Skin rash

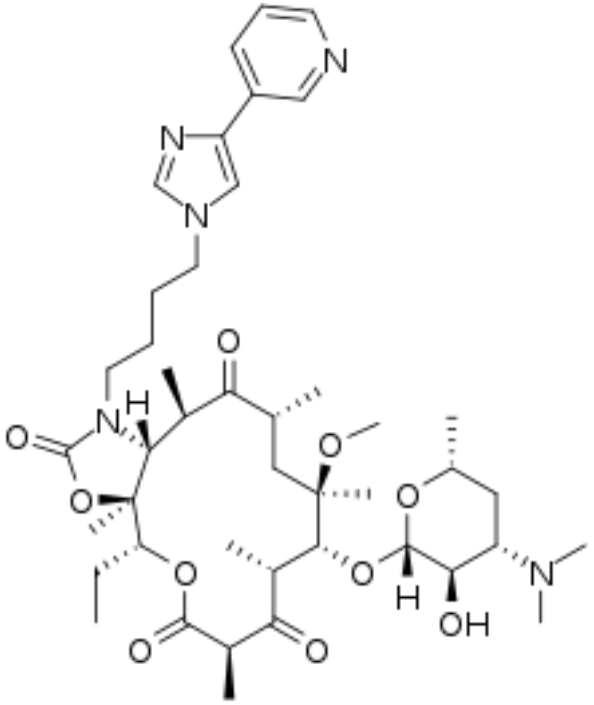


Macrolides and Ketolides

Macrolides and Ketolides



Erythromycin



Telithromycin

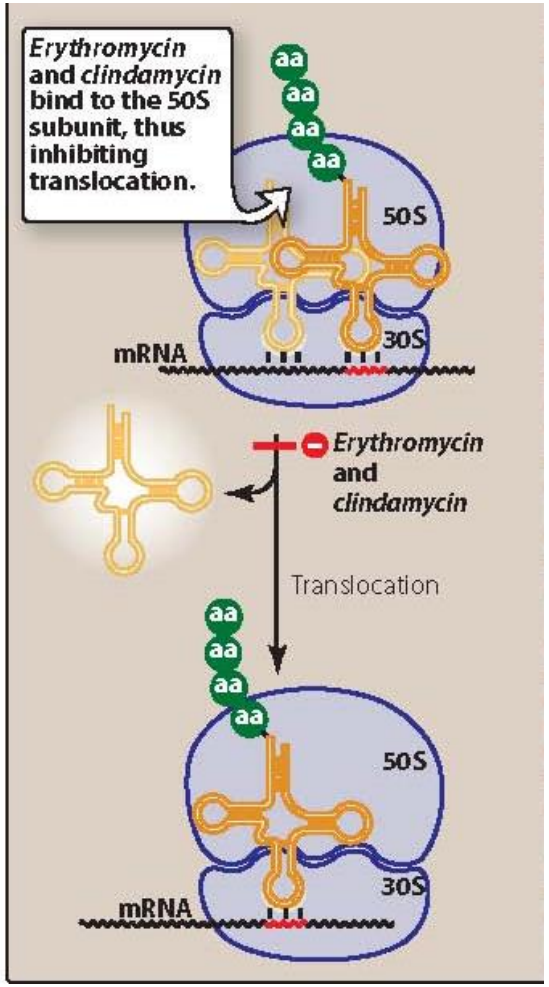
MACROLIDES/KETOLIDES

Azithromycin ZITHROMAX
Clarithromycin BIAXIN
Erythromycin VARIOUS
Telithromycin KETEK

Macrolides and Ketolides

Mechanism of action

- bind *irreversibly* to a site on the 50S subunit of the bacterial ribosome
- Inhibit translocation step
- Interfere with transpeptidation
- Binding site identical/near that of clindamycin or chloramphenicol



Macrolides and Ketolides

Antibacterial spectrum

-bacteriostatic (can be –cidal at high doses)

- **Erythromycin**

-similar spectrum to penicillin G

-used in cases of penicillin allergy

- **Clarithromycin**

-similar to erythromycin

-effective against intracellular pathogens, e.g. Chlamydia, Legionella, H. Pylori etc…

Macrolides and Ketolides

Antibacterial spectrum

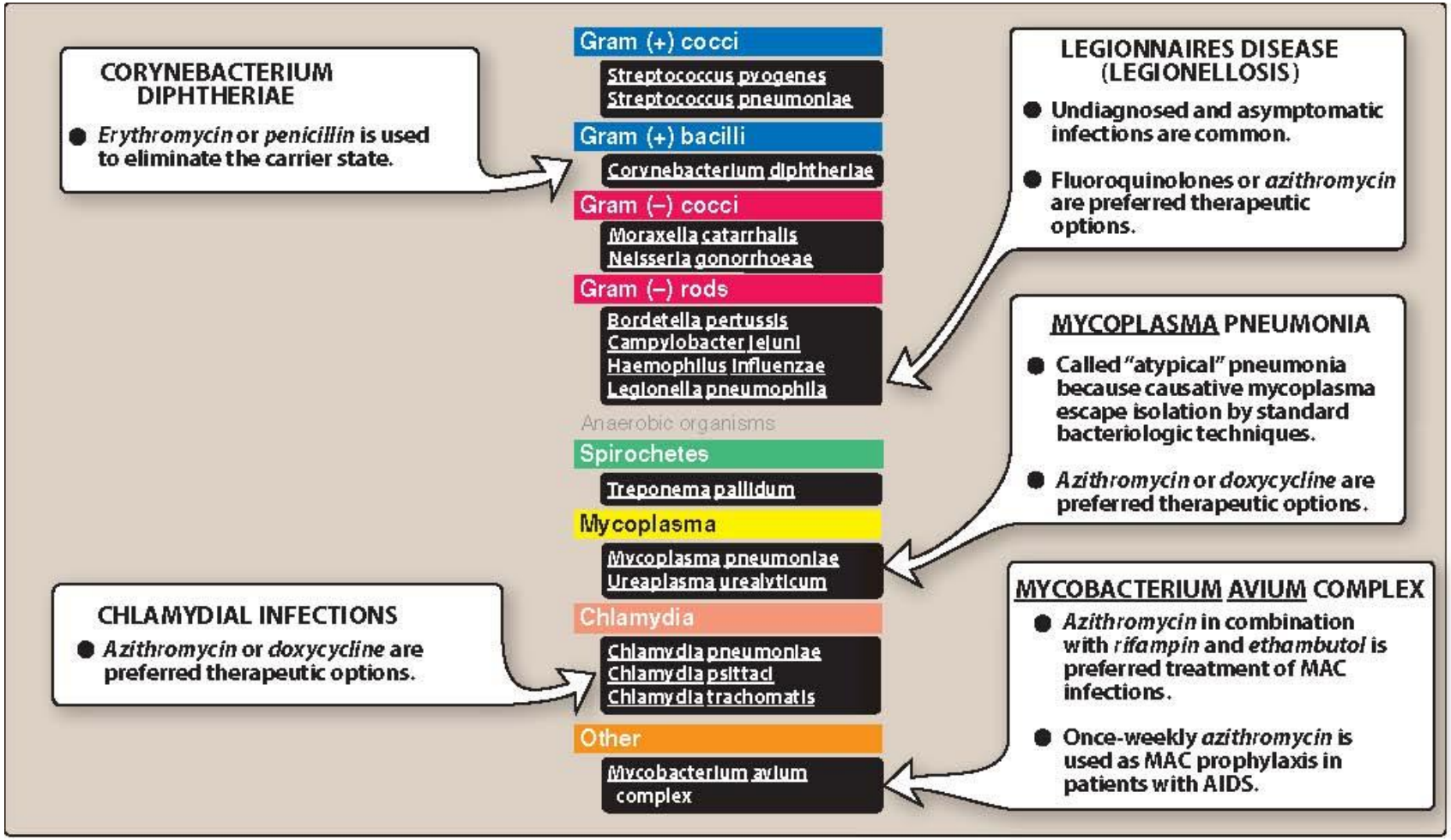
- **Azithromycin**

-less active against staph and strep species

-more active against RTI due to *H. influenzae* or *M.catarrhalis*

-increasing S. pneumonia resistance

Clinical Spectrum of Macrolides



Macrolides and Ketolides

Mechanisms of resistance

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
4) the presence of plasmid- associated erythromycin esterases in gram-negative organisms

Macrolides and Ketolides

Pharmacokinetics

- **Administration**

- oral (enteric-coated tablets for erythro)
- Erythro and azithro are available IV

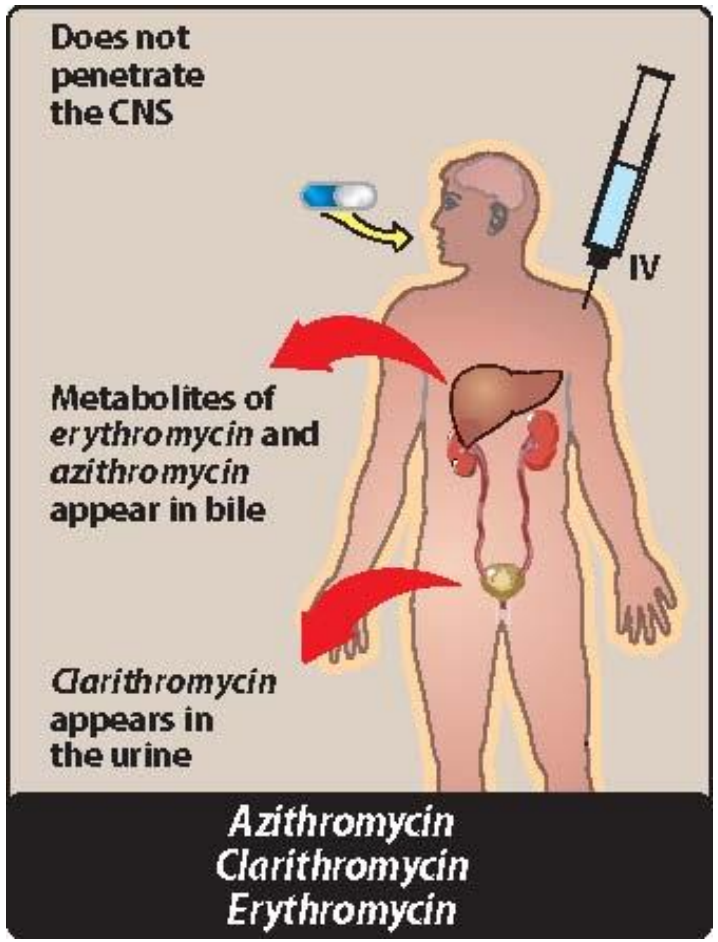
- **Distribution**

-distribute well in body fluids except CSF

- **Elimination**

-hepatic metabolism

-Inhibit CYP450 system (drug-drug interactions)



Macrolides and Ketolides

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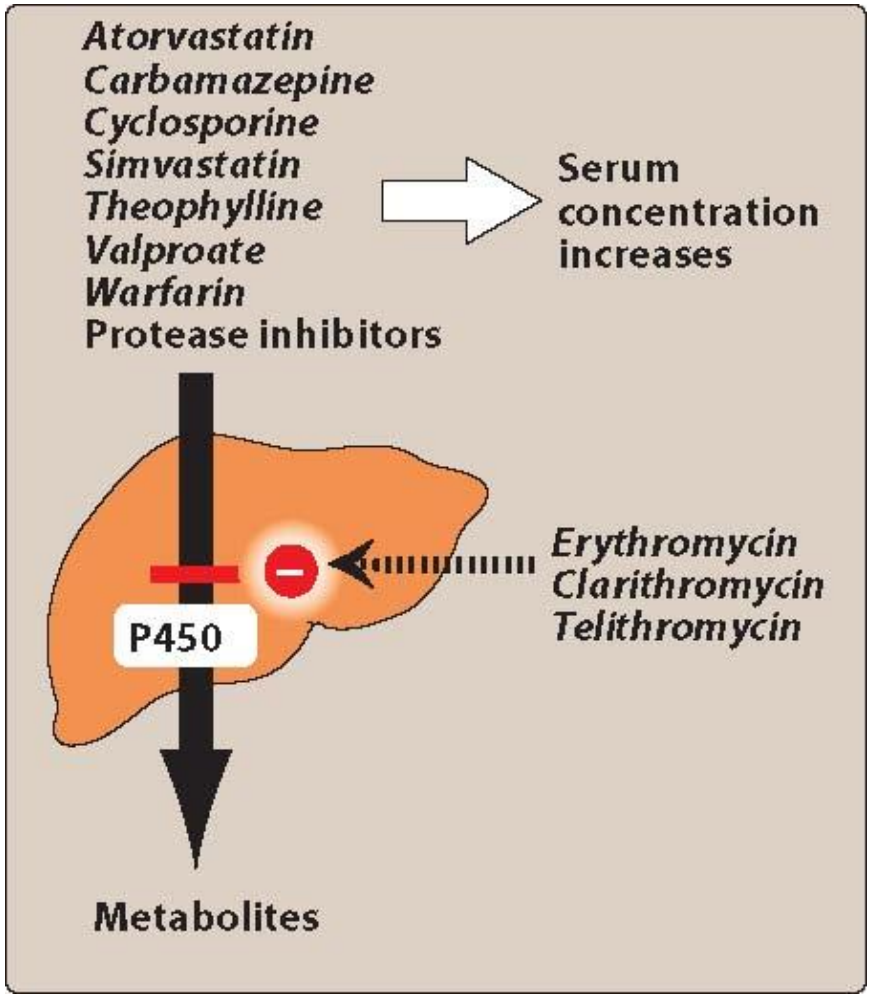
	Erythro-mycin	*Clarithro-mycin*	*Azithro-mycin*	*Telithro-mycin*
Oral absorption	Yes	Yes	Yes	Yes
Half-life (hours)	2	3.5	>40	10
Conversion to an active metabolite	No	Yes	No	Yes
Percent excretion in urine	15	50	12	13

Macrolides and Ketolides

Drug-drug interactions

- Inhibit hepatic metabolism of a number of drugs



Macrolides and Ketolides

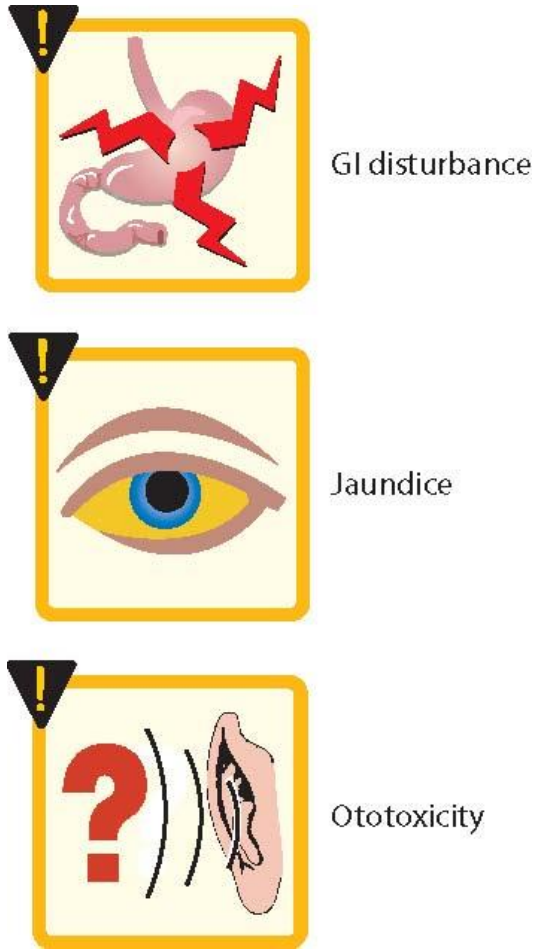
Adverse effects

- **Gastric distress and motility**

-high doses of erythromycin cause smooth muscle contraction and bowel movement. Could this be helpful?

- **Jaundice**
- **Ototoxicity**
- **Hepatotoxicity**

-contraindicated in patients with hepatic dysfunction



Fidaxomicin

Fidaxomicin

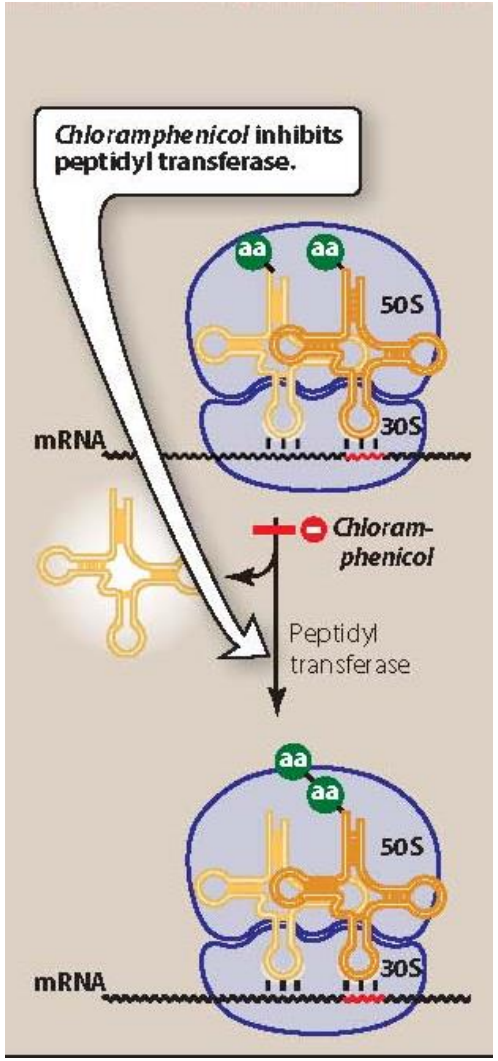
- **Structure:** macrocyclic, similar to macrolides
- **MOA**: acts on the σ subunit of RNA polymerase → disruption of bacterial transcription →  protein synthesis
- Very narrow-spectrum: gram-positive aerobes/anaerobes
- Poorly absorbed (remains in GI tract), primarily used for C. difficile infections
- Cross-resistance with other antibiotics is rare. Why?
- Cross-allergy with macrolides
- Adverse effects: nausea, vomiting, abdominal pain

Chloramphenicol

Chloramphenicol

- Broad-spectrum
- Mainly –static (but can be –cidal)
- Limited use due to high toxicity
- **MOA:** *reversibly* to the bacterial 50S ribosomal subunit and inhibits peptidyl transferase reaction
- Given IV: can be secreted in breast milk

Contraindicated in breastfeeding mothers



Chloramphenicol

Adverse effects

- **Aplastic anemia, hemolytic anemia** in case of G6PD deficiency
- **Gray baby syndrome**

-accumulation of the drug due to underdeveloped liver/kidney functions

-can cause death

- **Drug-drug interactions**

-inhibits liver enzymes

Critical Thinking Question

?

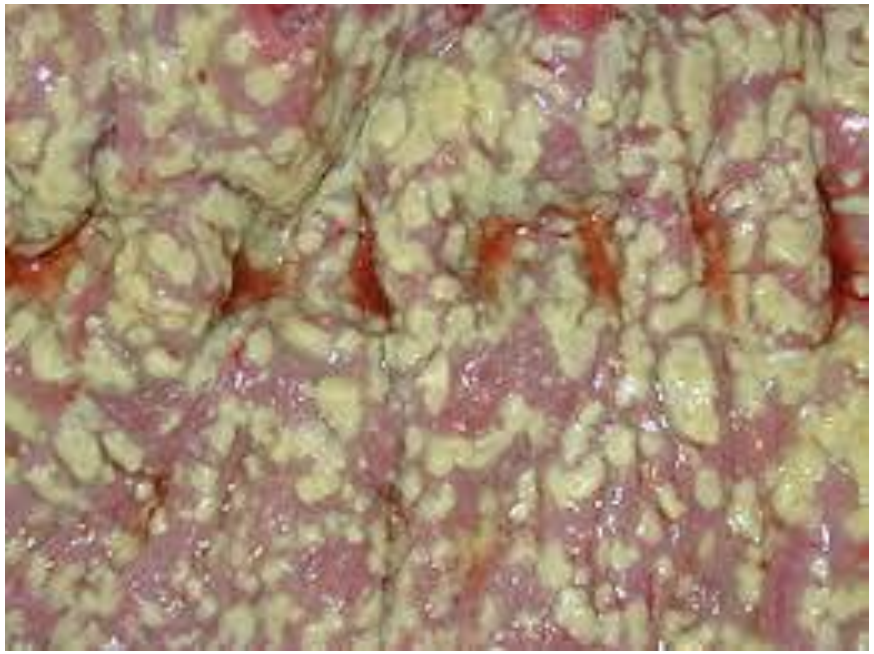
Since chloramphenicol is toxic due to its targeting of the mammalian protein synthesis … which type of ribosomes in mammalian cells will be most susceptible to inhibition by chloramphenicol? And why?

Clindamycin

Clindamycin

- **MOA**: same as erythromycin
- Effective against gram-positive bacteria: staph INCLUDING MRSA
- Oral and IV
- **Adverse effects**: skin rash, diarrhea : associated with pseudomembranous colitis caused by overgrowth of *C. diffcile*

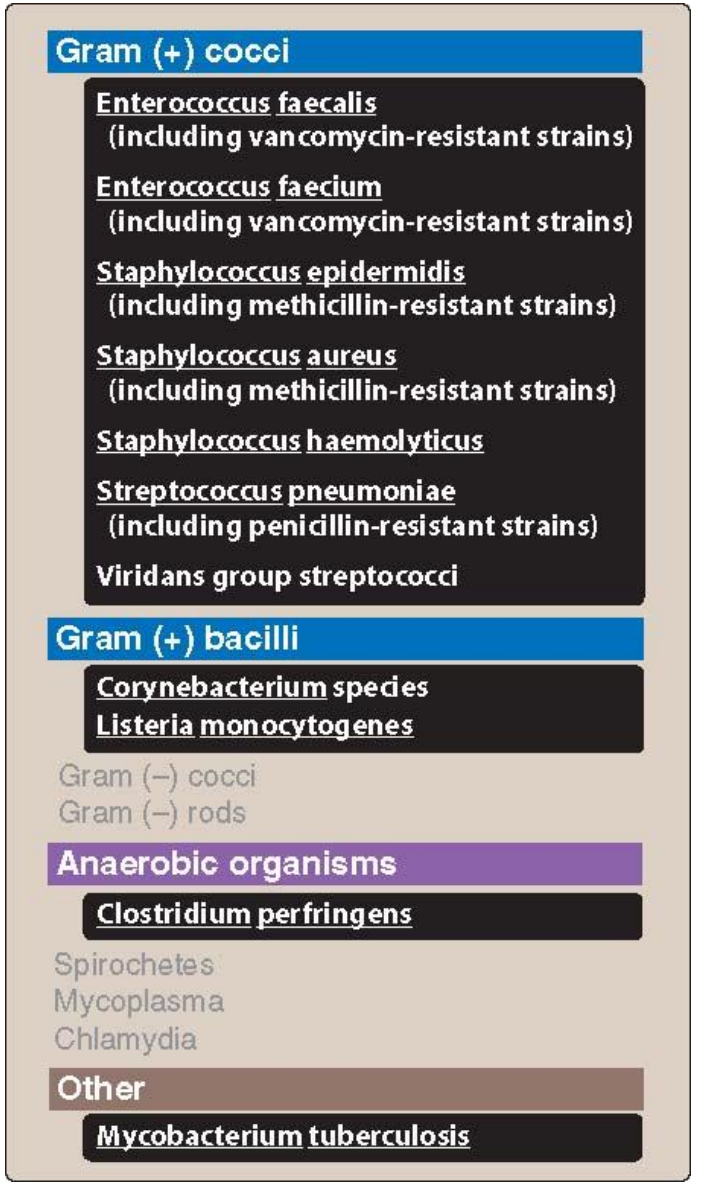
- Treated with vancomycin or metronidazole



Oxazolidinones

Linezolid

- Developed to treat resistant gram-positive organisms, such as MRSA (**not bacteremia.** Why?), VRE, resistant mycobacterium and penicillin-resistant streptococci
- **MOA**: binds to the bacterial 23S ribosomal RNA of the 50S sub-unit, thereby inhibiting the formation of the 70S initiation complex
- Bacteriostatic (-cidal against strep)



Linezolid

- **Main clinical uses:** Treatment of drug-resistant gram-positive organisms

  e.g., alternative to daptomycin for VRE
- **Pharmacokinetics**: oxidized in the liver into two inactive metabolites → excreted in urine
- **Adverse effects**: GI upset, thrombocytopenia, serotonin syndrome, peripheral neuropathy (with prolonged use)