Protein Synthesis Inhibitors

Pharmacology and Toxicology

General Pharmacology

Second Year Medical Students

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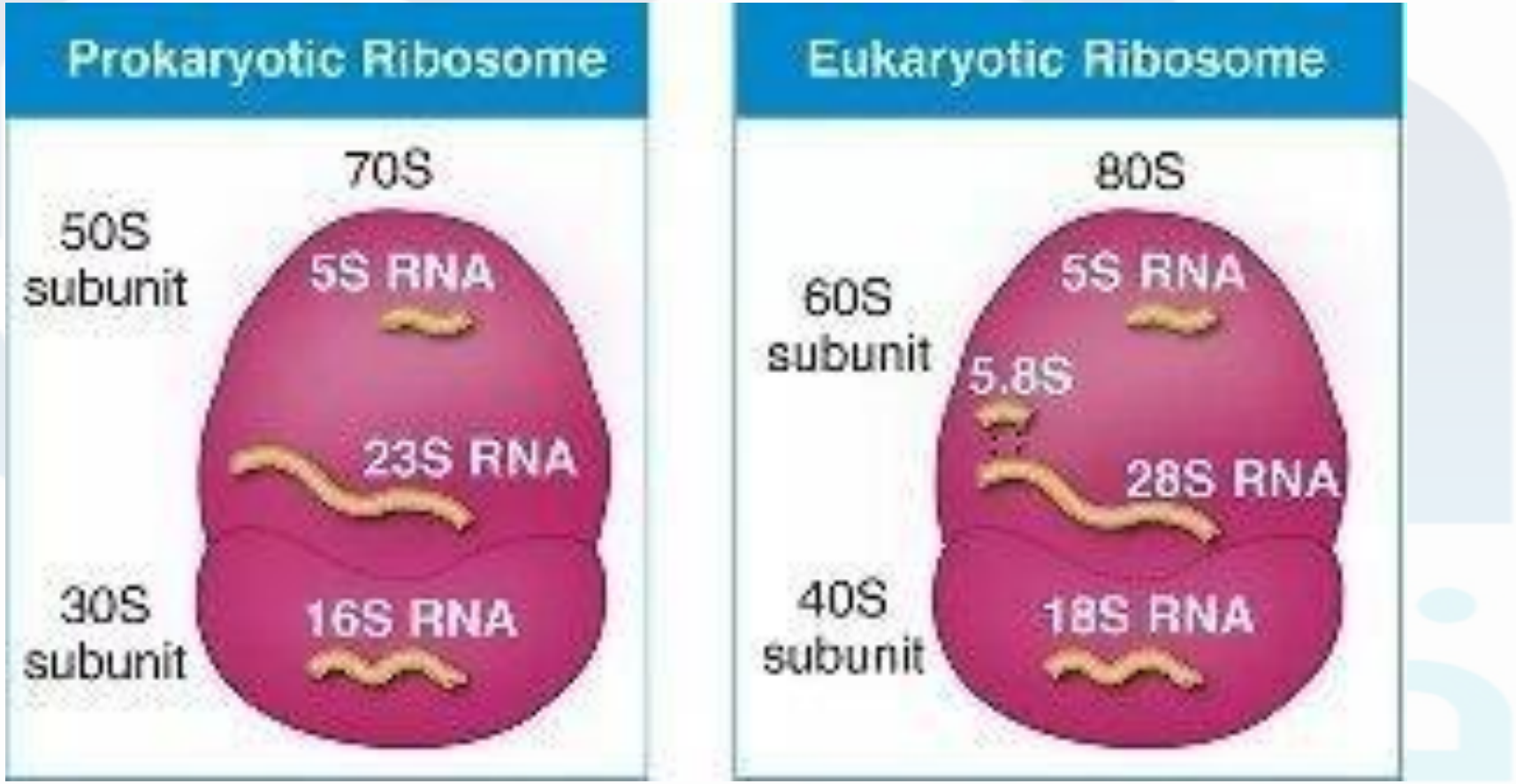
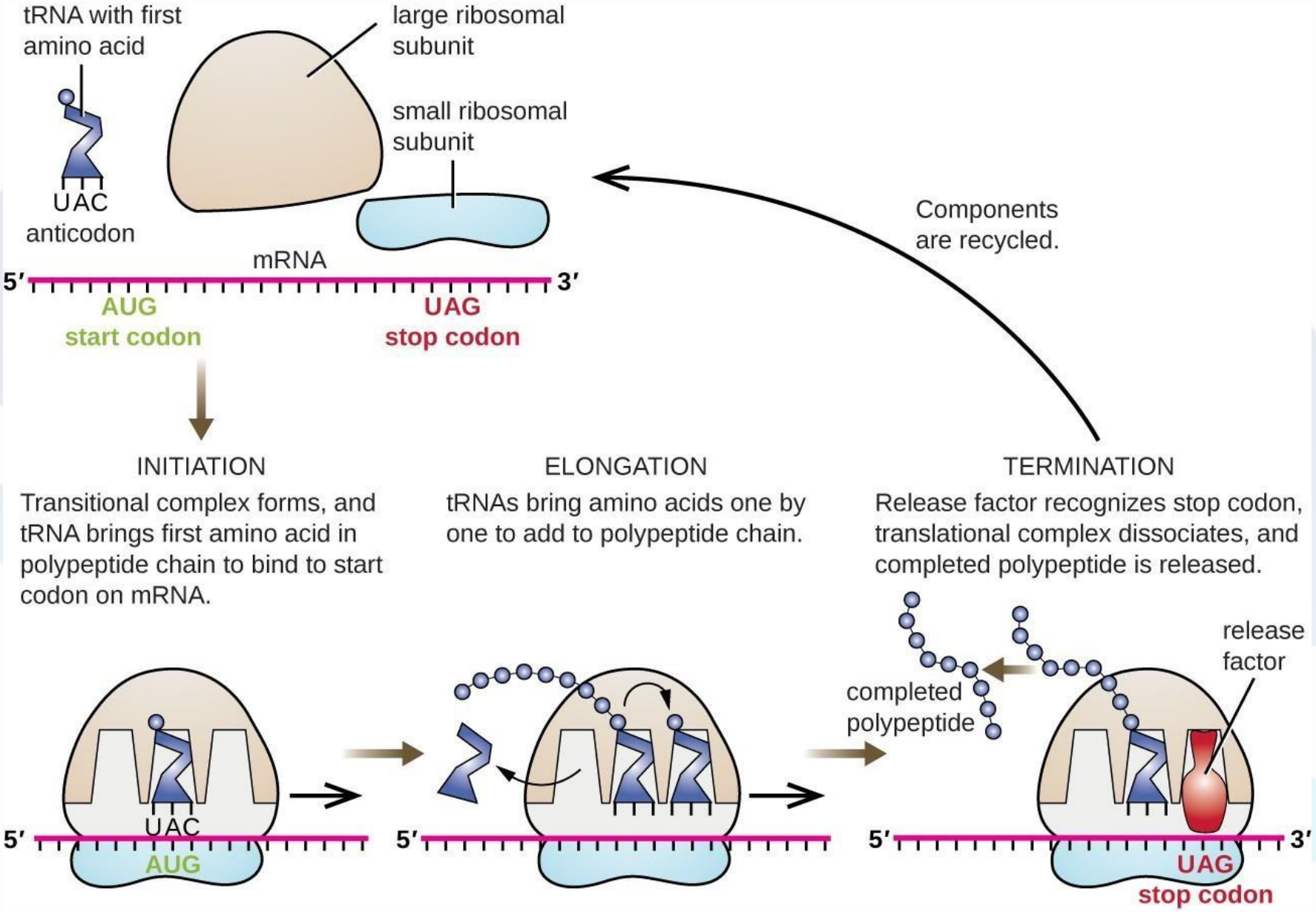
Faculty of Medicine

The Hashemite University

Textbook: Chapter 30 pp: 384-399

Bacterial Protein Synthesis



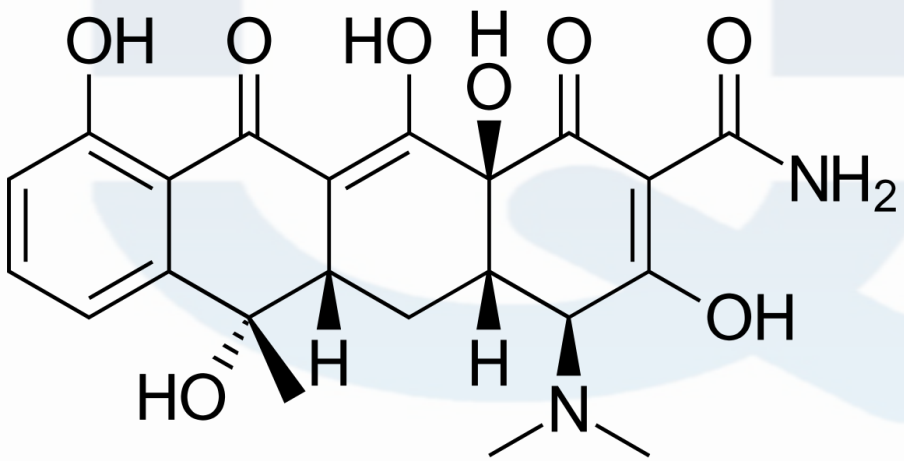


Tetracyclines

Sheet prepared by:-

Dr Ahmad Almohtaseb

Tetracyclines



Tetracycline

TETRACYCLINES	
Demeclocycline	DECLOMYCIN
Doxycycline	VIBRAMYCIN
Minocycline	MINOCIN
Tetracycline	

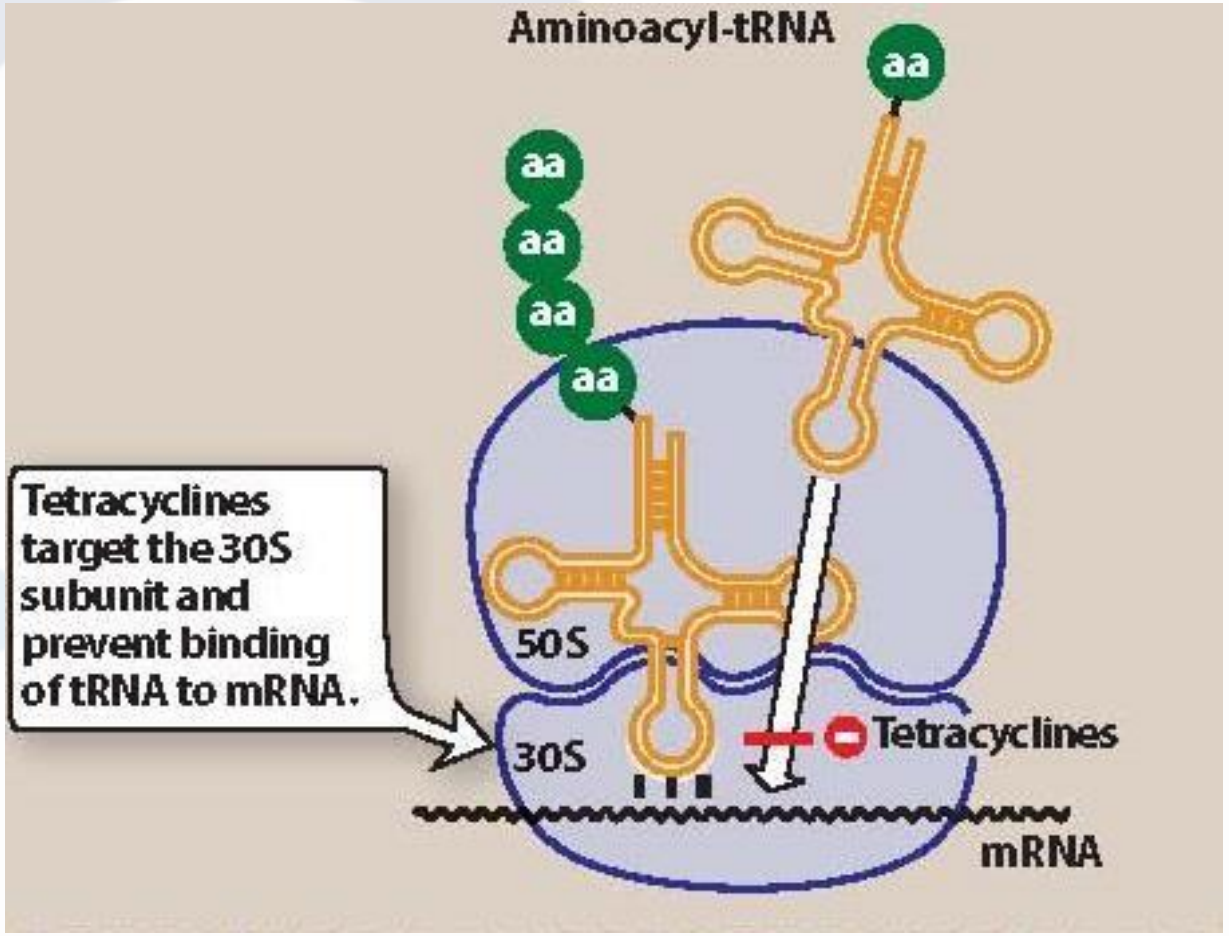
consist of **four aromatic fused rings**, substitutions on these rings alter the individual pharmacokinetics and spectrum of antimicrobial activity.

Tetracyclines

Mechanism of action

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

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



For Tetracyclines and other protein synthesis inhibitors to work , they have to cross bacterial plasma membrane and concentrate within the cytoplasm (site of protein synthesis in bacteria) ,it can cross plasma membrane via passive diffusion or shunted through special energy dependent transporter in susceptible organisms then it binds with its target (30s subunit) resulting in prevent binding of new tRNA with mRNA ribosome complex .

Tetracyclines

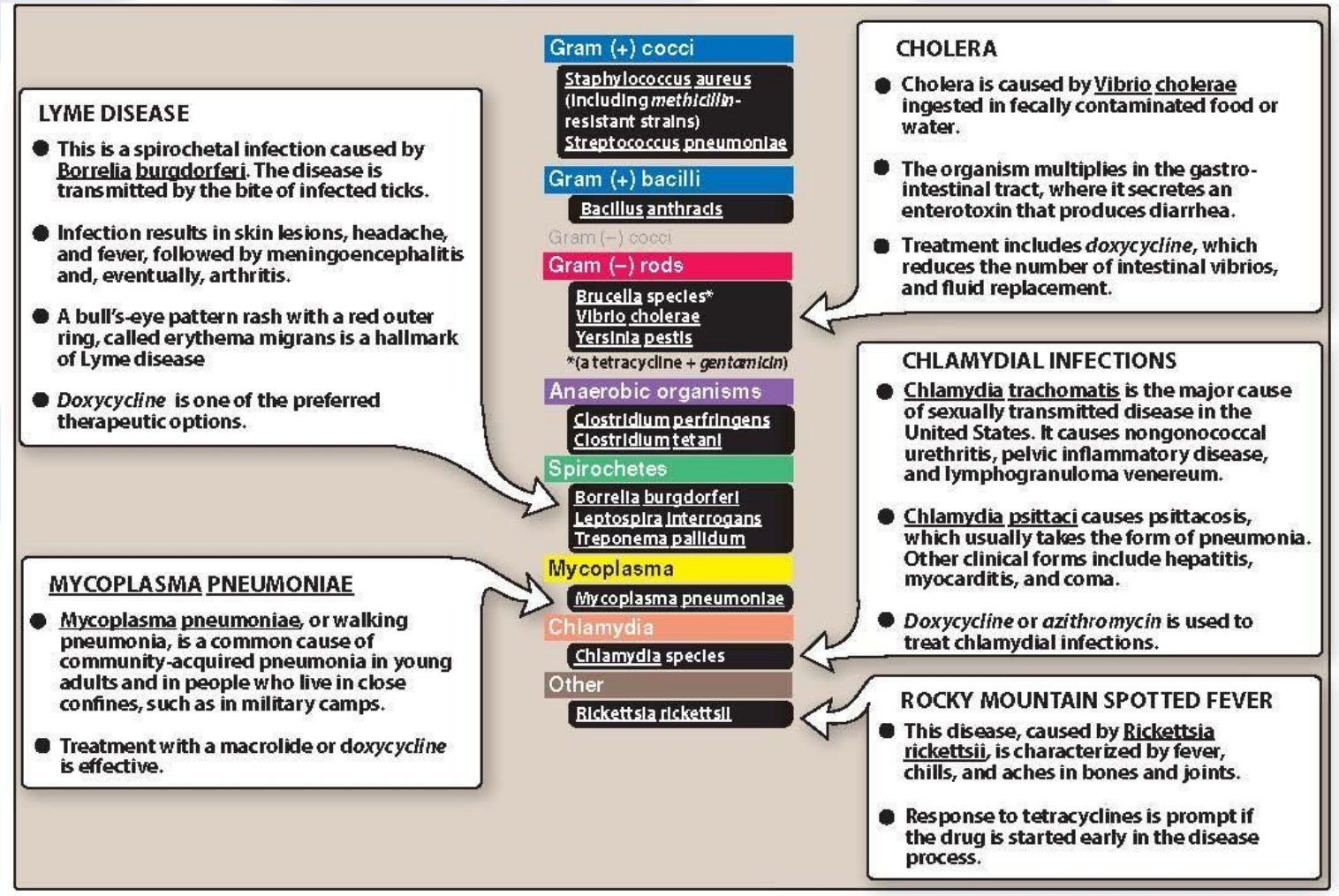
Antibacterial spectrum

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

Commonly used for the treatment of:

1. Acne (doxycycline)
2. Chlamydia: sexually transmitted,usually accompanied by gonnorhea. in certain cases can cause eye infection or mucus membrane infection (doxycycline)
3. Peptic ulcer disease (tetracycline)
4. Lyme Disease common in northern America (doxycycline)
5. Mycoplasma Pneumonia (doxycycline)

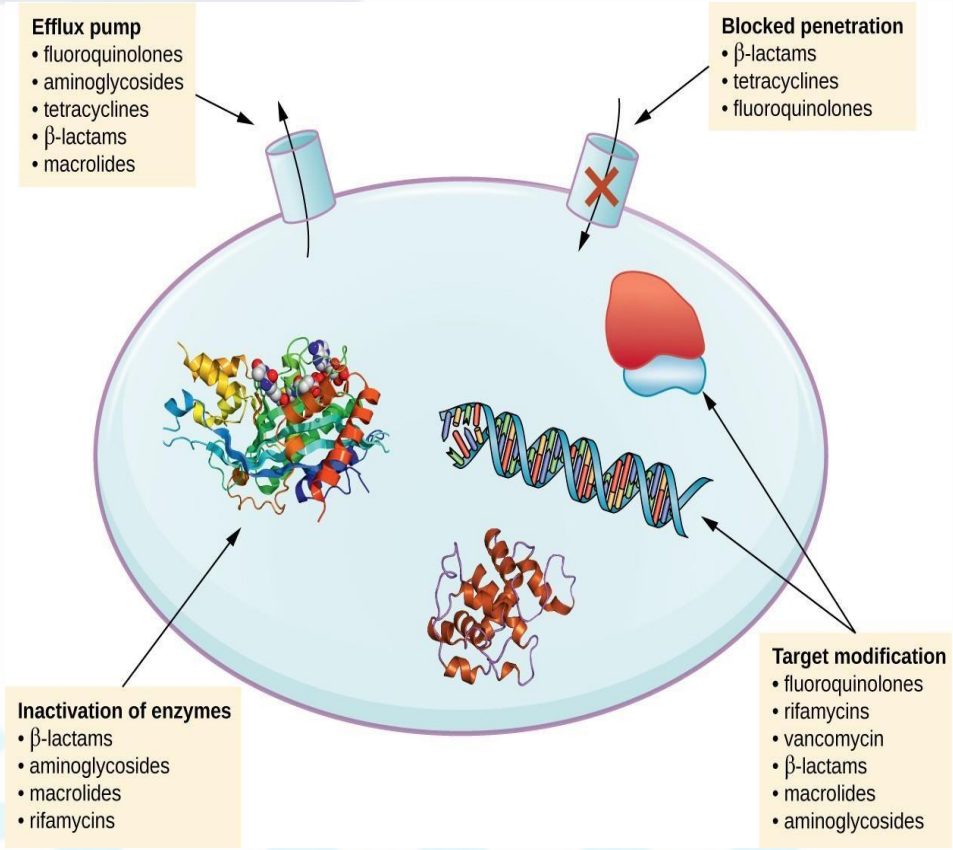
Therapeutic Spectrum of Doxycycline



Tetracyclines

Mechanisms of resistance

- Efflux pump (most common)
- Enzymatic inactivation of the drug
- Interfering with binding to ribosomes
- Cross-resistance is *not* Common(that means resistance to one tetracycline doesn't confer universal resistance to all tetracyclines, and development of cross resistance may be dependent on the mechanism of resistance.)

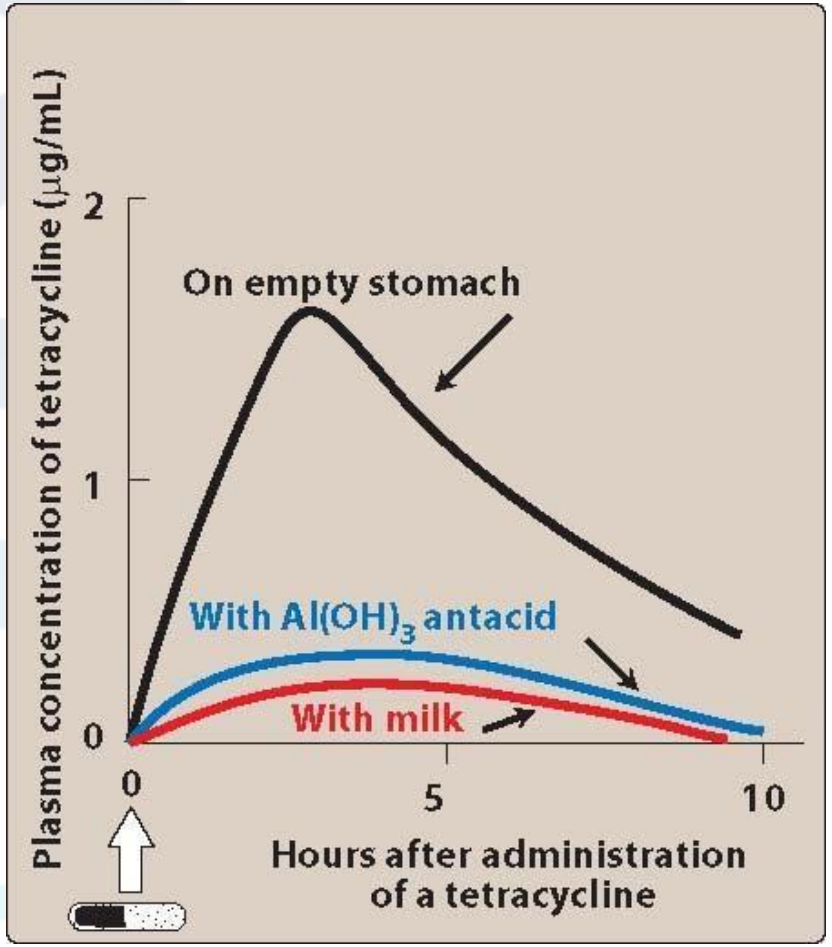


Tetracyclines

Pharmacokinetics

Absorption

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



Tetracyclines

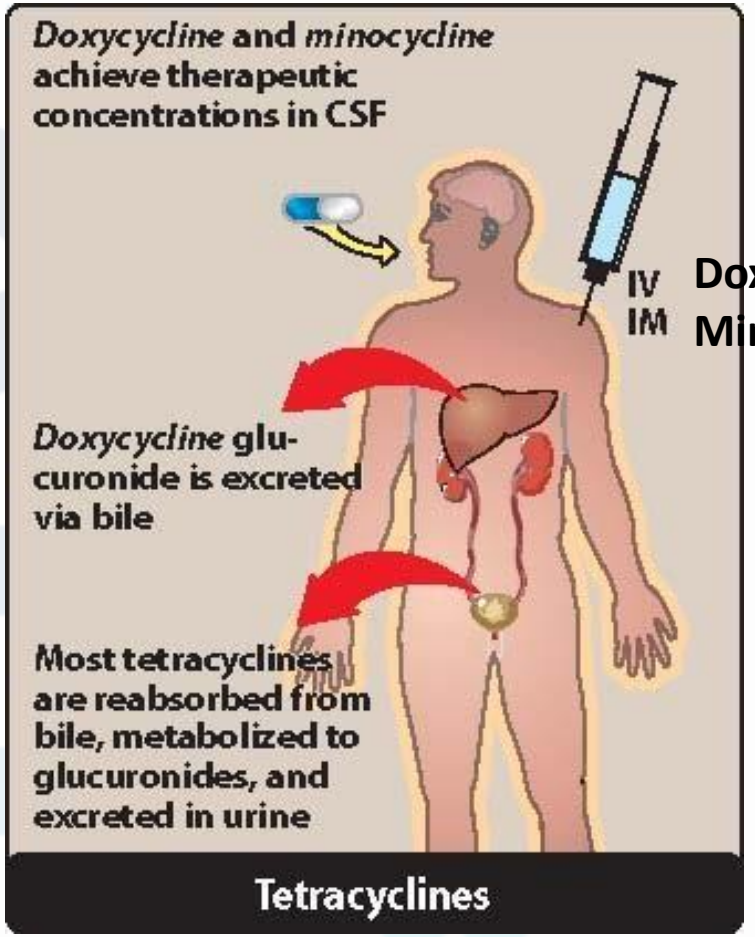
Pharmacokinetics

Distribution

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

Elimination

- Tetracycline eliminated unchanged in urine
- Doxycycline eliminated in bile/feces(no need to adjust dose in renal failure)



Minocycline also **achieves high concentrations in saliva and tears,** rendering it useful in **eradicating the meningococcal carrier**

Tetracyclines

Adverse effects

- **Gastric discomfort:**

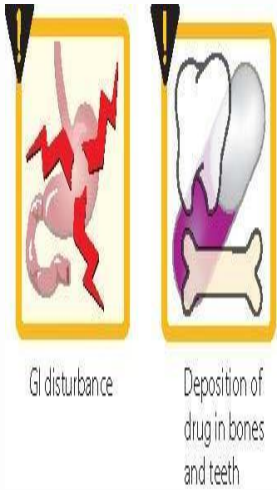
-irritation of gastric mucosa(epithelium)→ epigastric distress→non-compliance!

-esophagitis

(if irritation is severe) Irritation is minimized through coadminstration With food or with fluids (other than dairy products!!)

You can also use dosage forms of enteric coating or capsules instead of tablets .

Tetracycline should be taken on an empty stomach always.



- **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(**particularly in pregnant women and those with preexisting hepatic dysfunction)
- **Phototoxicity:**
  -severe sunburns (recommended to wear sun protection)→more commonly with tetra and demeclo
  - **Vestibular dysfunction:**

  -dizziness, vertigo, tinnitus→ more commonly with minocycline
  - **Pseudotumor cerebri(increased intracranial pressure→headache and blurred vision)**

Tetracyclines

Contraindications

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

Tetracycline mnemonic

Sports drink→ GI upset and hepatotoxicity

Pseudotumor cerebri, vertigo

Phototoxicity

Cycle can't get across colored mountains→ Not effective against pseudomonas

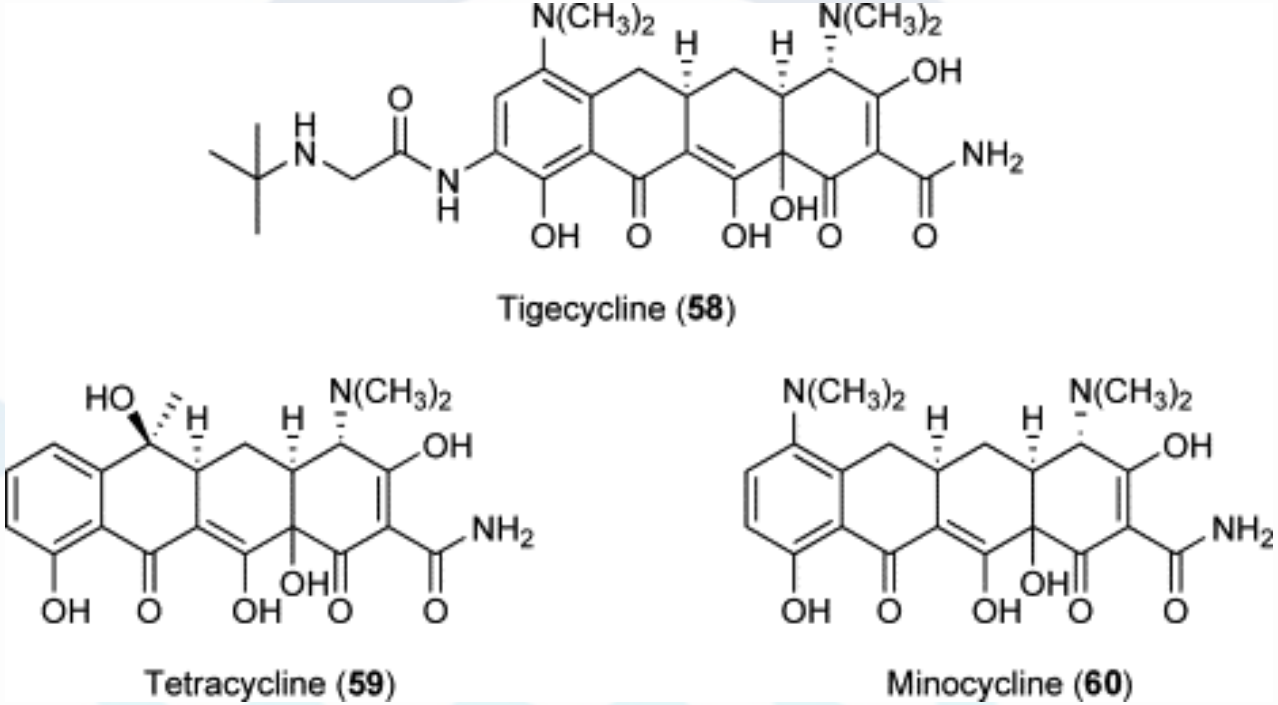
Bicycle: broad spectrum including MRSA

Pregnant lady can't ride bicycle

Glycylcyclines

Tigecycline

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



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

Tigecycline is indicated for the treatment of complicated skin and soft tissue infections, complicated intra-abdominal infections, and community-acquired pneumonia.

Resistance:-

Tigecycline was developed to overcome the emergence of tetracycline class-resistant organisms that utilize efflux pumps and ribosomal protection to confer resistance.

Resistance to tigecycline has been observed and is primarily attributed to overexpression of efflux pumps

D. Tigecycline Pharmacokinetics:-

Following IV infusion, tigecycline exhibits a **large volume of distribution**(due to its lipophilicity)→It penetrates tissues well but achieves low plasma concentrations. Consequently, tigecycline is a poor option for bloodstream infections(septicemia)

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

Adverse effects of Tigecycline:

Significant nausea and vomiting, Acute pancreatitis.

All-cause mortality in patients treated with tigecycline is higher than with other agents.

Due to its adverse effects it's not used as first line.

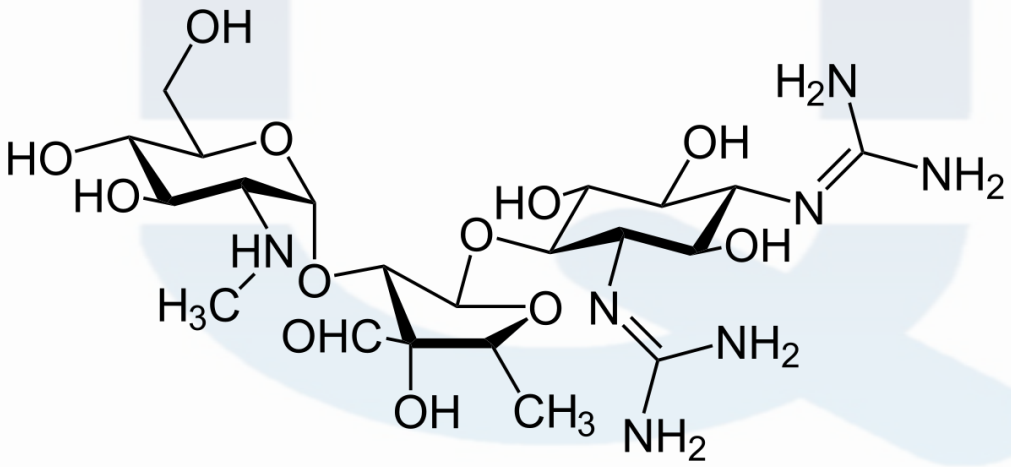
A boxed warning states that tigecycline should be reserved for use in situations when alternative treatments are not suitable

Other adverse effects are similar to those of the tetracyclines

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

Aminoglycosides

Aminoglycosides



AMINOGLYCOSIDES
Amikacin
Gentamicin GARAMYCIN
Neomycin NEO-FRADIN
Streptomycin
Tobramycin TOBREX

Clinical applications of aminoglycosides

Amikacin : IV

- Gentamicin
- Neomycin :is given topically in skin
- Tobramycin : in respiratory infection (cystic fibrosis, which favors pseudomonal infections)
- Streptomycin: antiTb drug قديما

قل استخدامه النه يوجد ادوية احسن منه وبسبب سميته

Vancomycin,daptomycin and Fosfomycin **are not aminoglycosides**

They are non-beta lactam cell wall inhibitors

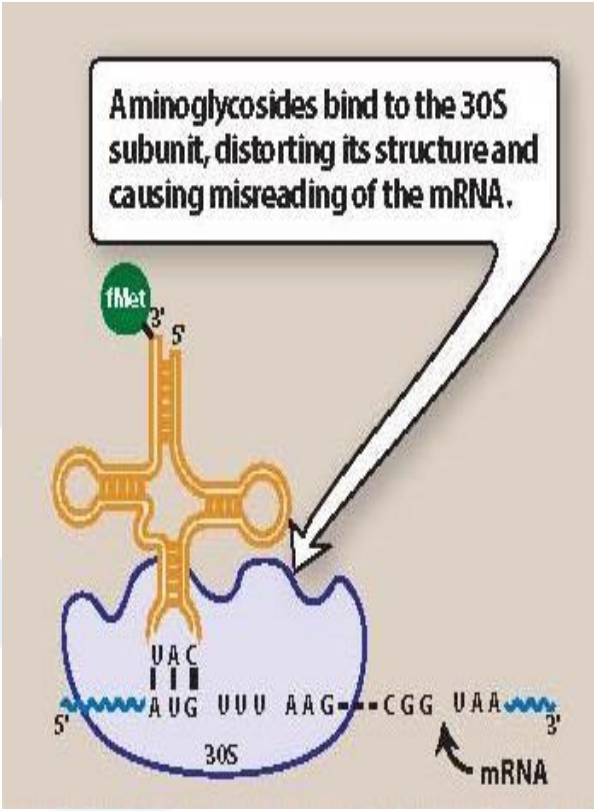
Aminoglycosides

Mechanism of action:-

Aminoglycosides diffuse through **porin channels** in the outer membrane of **susceptible gram(-ve) organisms.**

These organisms also have an **oxygen-dependent system** that transports the drug across the cytoplasmic membrane

- 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(my note:because of misread toxic protein production!!)
- Concentration-dependent(their efficacy is dependent on the maximum concentration (Cmax) of drug above the minimum inhibitory concentration (MIC) of the organism. For aminoglycosides, the target Cmax is eight to ten times the MIC)
- Exhibit PAE(. The larger the dose, the longer the PAE, so high-dose extended-interval dosing is commonly utilized. This strategy also reduces the risk of nephrotoxicity and increases convenience
- Effective against aerobic gram-negative bacilli (INCLUDING multi- DRUG resistant *P. aeruginosa, klebsiella etc…*)
- **Used in combination with β-lactams for synergism**

Some clinical uses of aminoglycosides

11. **An 18-day-old neonate has been brought to the pediatric unit by her parents. She has been crying inconsolably, irritable, and poorly breast-feeding. Her vitals show high temperature and elevated heart rate. You are worried that she might have meningitis and want to initiate empirical antimicrobial therapy. Knowing that L. monocytogenes is a common pathogen in this age group, your treatment regimen must include which of the following synergistic drug combinations?**

A. Piperacillin + tazobactam
B. Ticarcillin + amikacin
C. Nafcillin + ciprofloxacin
D. Ampicillin + gentamicin
E. trimethoprim + sulfamethoxazole

Answer: D

Aminoglycosides

Mechanisms of resistance

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

Cross-resistance is unlikely

-Amikacin is less vulnerable to these enzymes

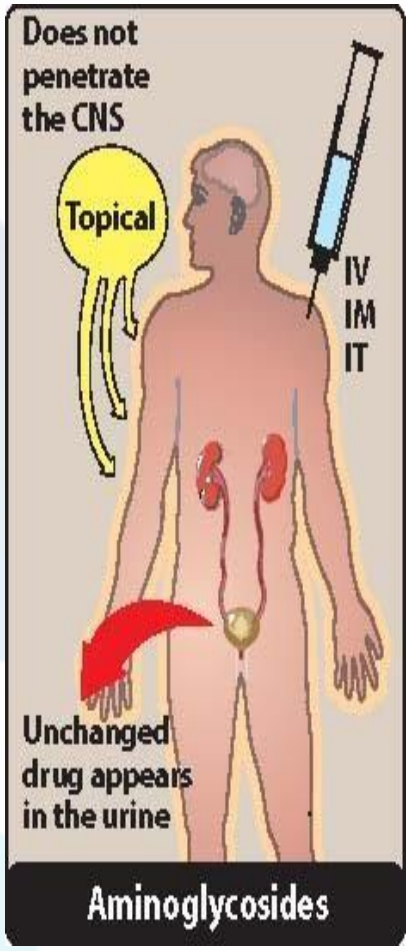
Aminoglycosides

Pharmacokinetics Absorption

-Aminoglycosides are very bulky and charged.

all are given IV (except neomycin)

. [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.]



Distribution

-variable distribution in body fluids

-inadequate distribution in CSF(For central nervous system infections, the intrathecal or intraventricular routes may be utilized.)

-cross the placenta and affects fetuses

Aminoglycosides

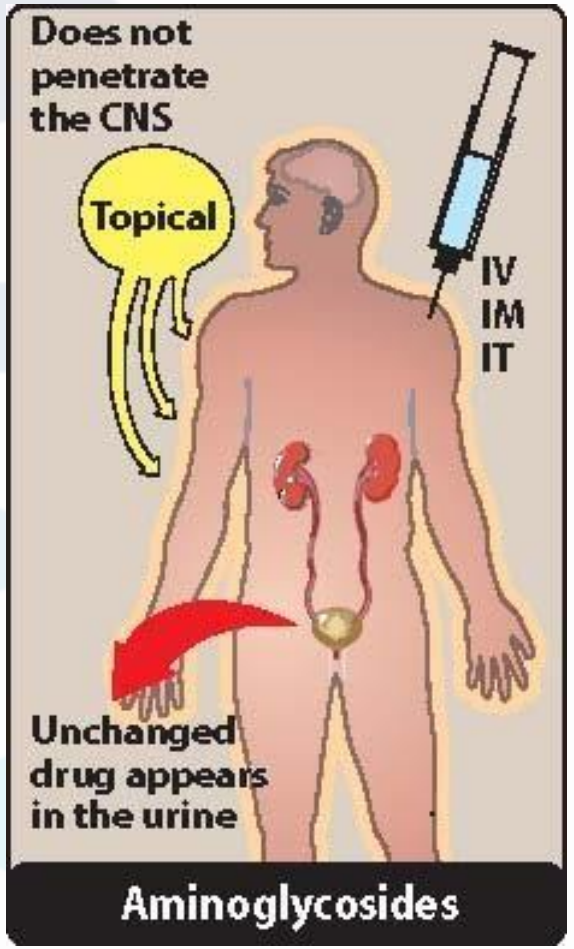
Pharmacokinetics

Elimination

-90% are excreted unchanged in the urine

-accumulation occurs in cases of renal dysfunction

-Neomycin is excreted unchanged in feces.



Therapeutic drug monitoring of gentamicin, tobramycin, and amikacin plasma concentrations is **imperative to ensure appropriateness of dosing and to minimize dose-related toxicities**

.

Aminoglycosides

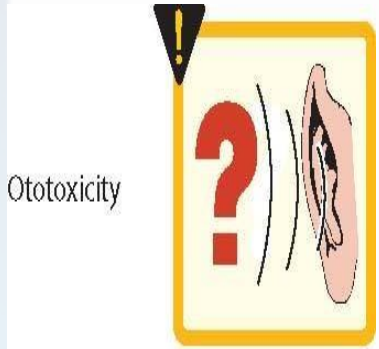
Adverse effects

- **Ototoxicity (both vestibular and auditory)**

directly related to **high peak plasma concentrations** and the **duration of treatment.**

-might cause **irreversible** **deafness, even to fetuses when it crosses placenta!!**

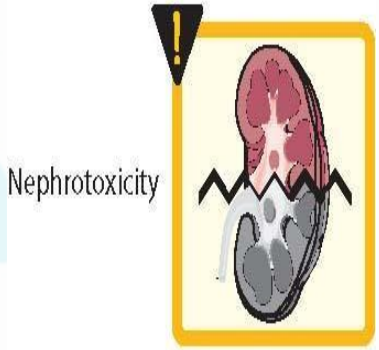
-**Vertigo** (especially with **streptomycin**)



- **Nephrotoxicity**

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

-from mild reversible renal impairment to irreversible acute tubular necrosis



The elderly are particularly susceptible to nephrotoxicity and ototoxicity

Aminoglycosides

Adverse effects

- Neuromuscular paralysis

-patient with myasthenia gravis are at risk

associated with a rapid increase in concentration (for example, high doses infused over a short period) or concurrent administration with neuromuscular blockers

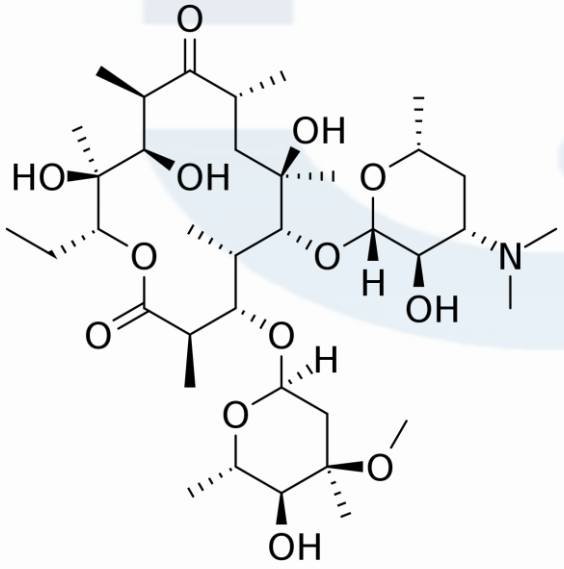
- Allergic reaction

- Mostly **contact dermatitis** with **topical neomycin**

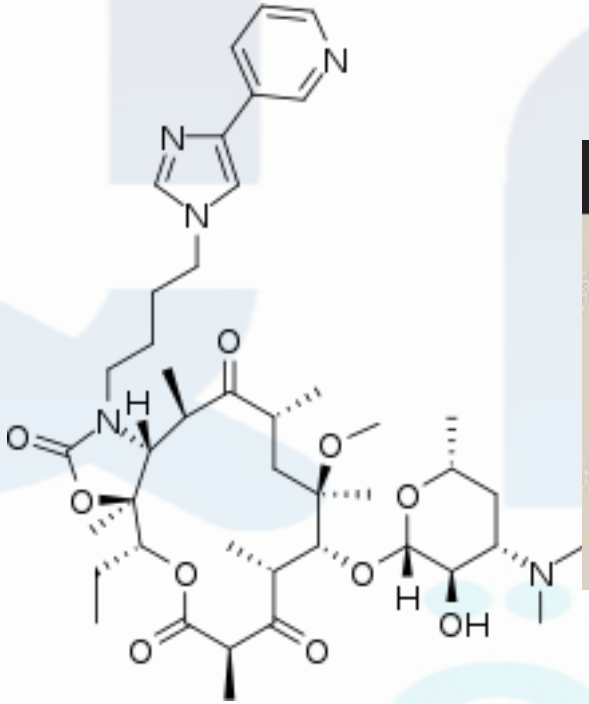
Macrolides and Ketolides

Macrolides and Ketolides

Macrolides have a macrocyclic polylacetonic lactone structure attached to one or moredeoxy sugars.
The lactone ring is the primary structure in macrolides ,
and they are bulky compounds .



Erythromycin



Telithromycin(a ketolide derived from erythromycin)

MACROLIDES/KETOLIDES

Azithromycin	ZITHROMAX
Clarithromycin	BIAXIN
Erythromycin	VARIOUS
Telithromycin	KETEK

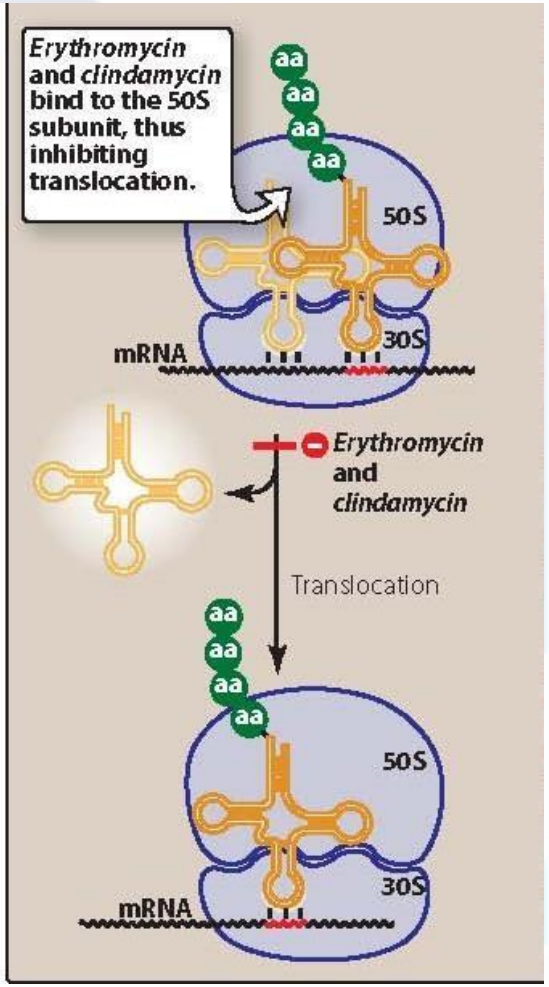
Clarithromycin has a methyl group

the used of erythromycin has been largely replaced by azithromycin & clarithromycin because they have slightly better antibacterial coverage & better adverse effect profile , Zomac"azithromycin" has a larger lactone ring

Macrolides and Ketolides

Mechanism of action

- bind *irreversibly* to a site on the 50S subunit of the bacterial ribosome(mnemonic: macrolides bind to the macro"big" lid"ribosome part)
- Inhibit translocation(leading) step
- Interfere with transpeptidation(the movement of polypeptide from the P-site to be linked with the amino acid on the A-site)
- 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 syphilis ,gas gangrene, and strep pyogenes prophylaxis)

-used in cases of penicillin allergy

- **Clarithromycin**

-similar to erythromycin but extended to include some gram negatives like H.influenze

-effective against intracellular pathogens, e.g. Chlamydia, Legionella, H. Pylori etc… (Mnemonic :Cells are cleared from pathogens by clarithromycin)

Macrolides and Ketolides

Antibacterial spectrum

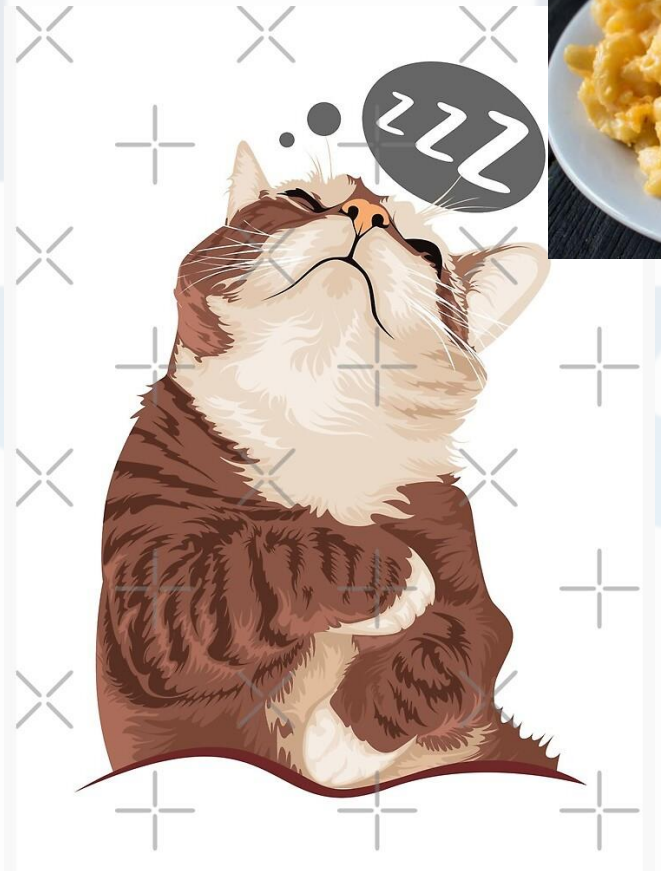
- **Azithromycin**

-less active against staph and strep species

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

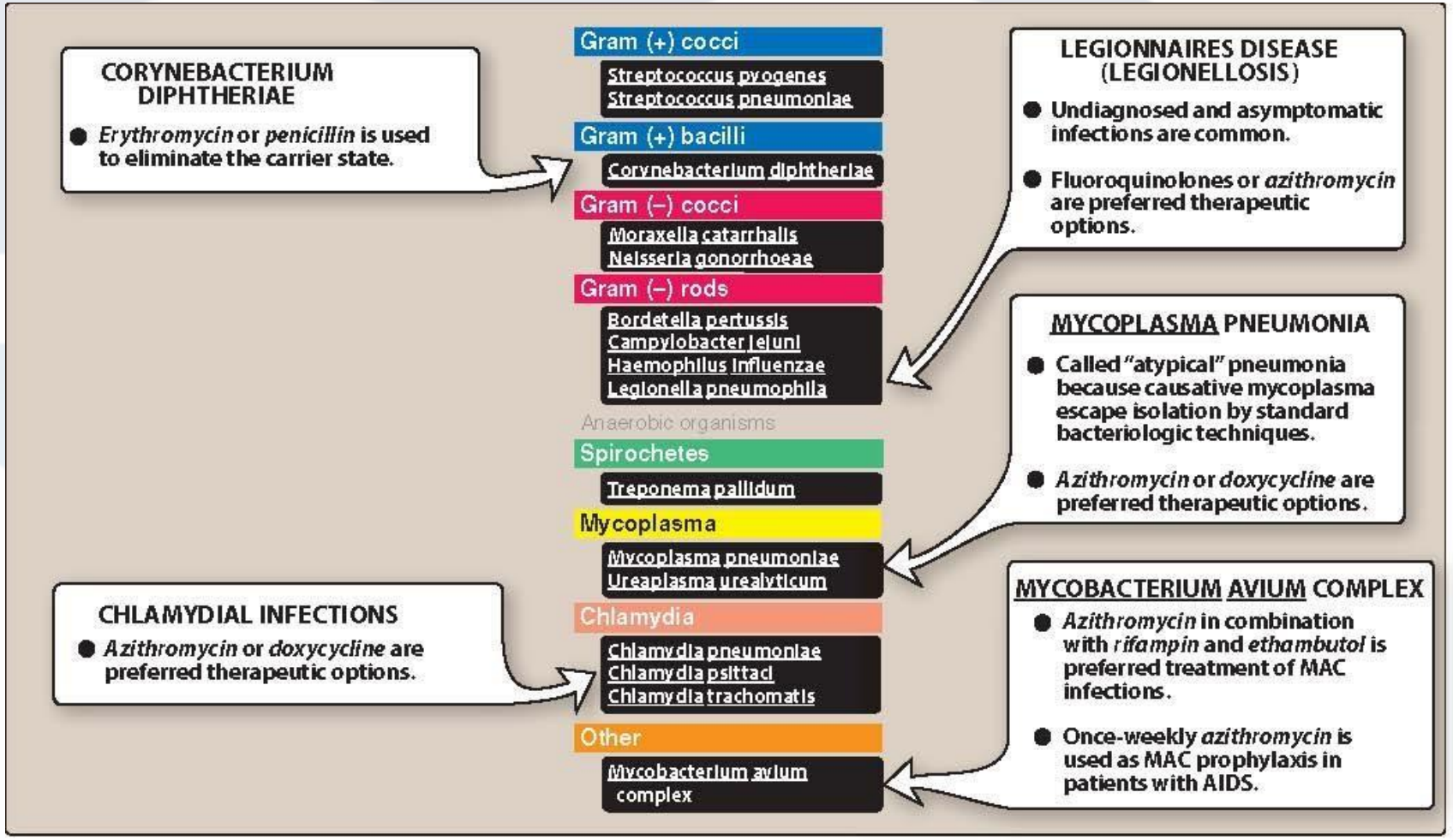
-increasing S. pneumonia resistance

Mnemonic



Cat(Moraxella catarrhalis dreaming about macaroni(macrolides)→zzzzz z(azithromycin)

Clinical Spectrum of Macrolides



Cat(Moraxella catarrhalis dreaming about macaroni(macrolides)→zzzzzz(azithromycin)

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(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**

Telithromycin may be effective against macrolide-resistant organisms

Erythromycin has **limited clinical use** due to increasing resistance.

Both **clarithromycin and azithromycin** **share some cross-resistance** with **erythromycin**

Macrolides and Ketolides

Pharmacokinetics

- **Administration**

- oral (enteric-coated tablets for erythron, The erythromycin base is destroyed by gastric acid;)
- Food interferes with the absorption of erythromycin and azithromycin but can increase that of clarithromycin. Telithromycin is administered orally without regard to meals.
- Erythro and azithro are available IV

- **Distribution**

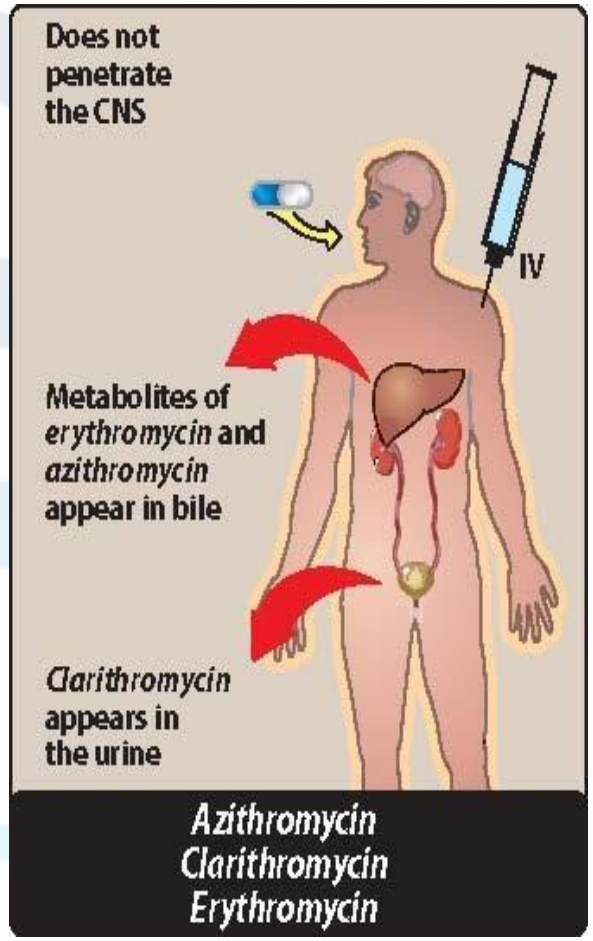
-distribute well in body fluids(including prostatic fluid) except CSF and can concentrate in neutrophils,macrophages, fiborblasts etc…

Azithromycin has the largest Vd

Elimination

-hepatic metabolism

-Inhibit CYP450 system (drug-drug interactions)



Dr sheriff slide reminder

Examples of Enzyme Inhibitors

Cimetidine- **c**hloramphenicol - **c**iprofloxacin- erythromycin - ketocenazol - ♀ **(F)** estrogen, progesterone, contraceptive pills.

2. Pathological factors which affect hepatic activity e.g. liver failure starvation, cancer → ↓ activity of HME → need to adjust dose.

3. Pharmacogenetic variations in metabolizing enzymes e.g. slow & fast acetylators (see pharmacogenetics).

4. Hepatic blood flow: drugs ↓ hepatic blood flow → ↓drug matabolism

5. Age: ↓ enzymatic activity in extremities of age

- Premature babies have ↓ conjugate of chloramphenicol → fatal gray baby syndrome.

6. Sex: female sex hormones are HME inhibitors → receive lower doses than male.

20

4. Excretion:

Azithromycin and erythromycin is primarily concentrated and excreted in the bile as active drug. Partial reabsorption occurs through the enterohepatic circulation.

In contrast, **clarithromycin is hepatically metabolized, and the active drug and its metabolites are mainly excreted in the urine(mnemonic: clarithro has renal clearance)**. The dosage of this drug should be adjusted in patients with renal impairment.

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

-InhibitCYP450 oxidation system(drug-drug interactions)

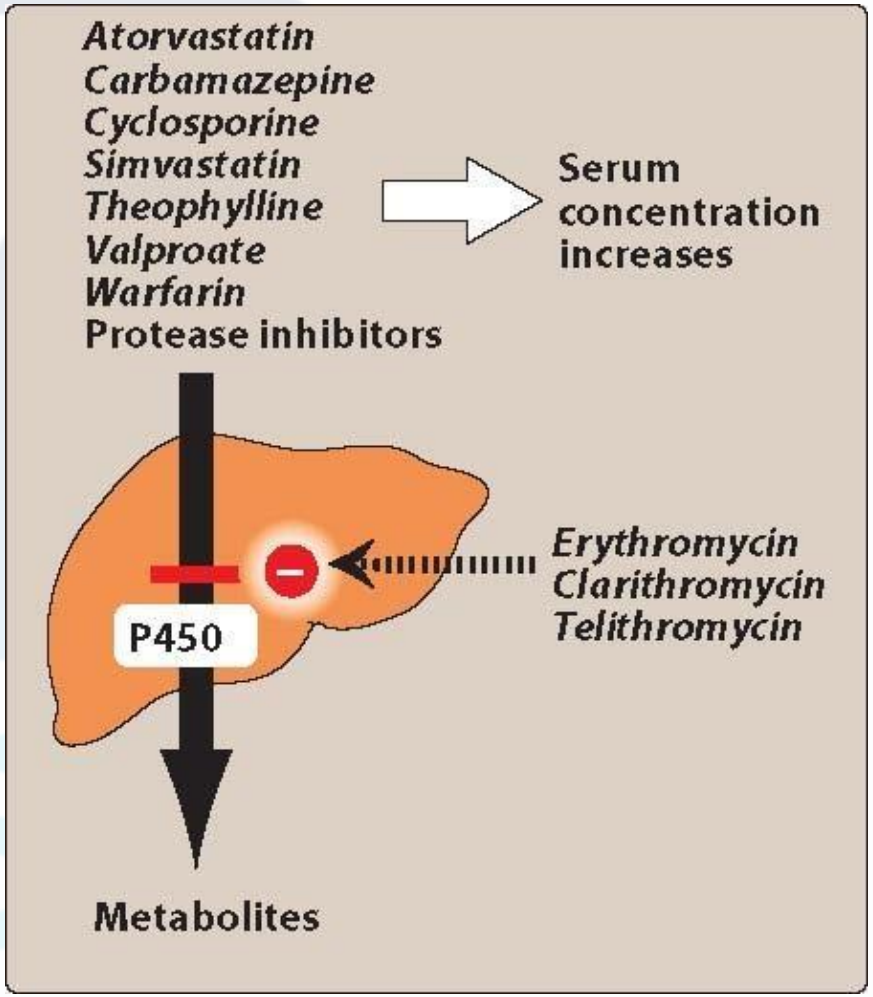
	Erythro-mycin	*Clarithro-mycin*	*Azithro-mycin*	*Telithro-mycin*
Oral absorption	Yes	Yes	Yes	Yes
Half-life (hours)	2	3.5	>40	10
Conversion to an active metabolite	No	Yes	No	Yes
Percent excretion in urine	15	50	12	13

Macrolides and Ketolides

Drug-drug interactions

- Inhibit hepatic metabolism of a number of drugs, increasing their serum levels→toxicity.

This is especially of concern with warfarin which might cause bleeding



Macrolides and Ketolides

Adverse effects

- **Gastric distress and motility**

-high doses of erythromycin cause smooth muscle contraction and bowel movement. Could this be helpful? yes , this adverse effect can be used for the treatment of gastroparesis or postoperative ileus. Gastroparesis paralysis in the nerve supply of the stomach , seen in patients with diabetes which result in delayed emptying

GI disturbance

Hepatotoxicity

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

Jaundice

-contraindicated in patients with hepatic dysfunction(especially telithromycin)

Ototoxicity

QTc prolongation: Macrolides and ketolides may prolong the OTc interval and should be used with caution in those patients with proarrhythmic conditions or concomitant use of proarrhythmic agent

Fidaxomicin

Fidaxomicin

- **Structure:** macrocyclic, similar to macrolides with a lactone ring
- **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(but not the first line drug, first line drug is vancomycin)
- Cross-resistance with other antibiotics is rare. Why? because of the unique target site
- Cross-allergy with macrolides
- Adverse effects: **nausea, vomiting, abdominal pain**, rarely anemia and neutropenia

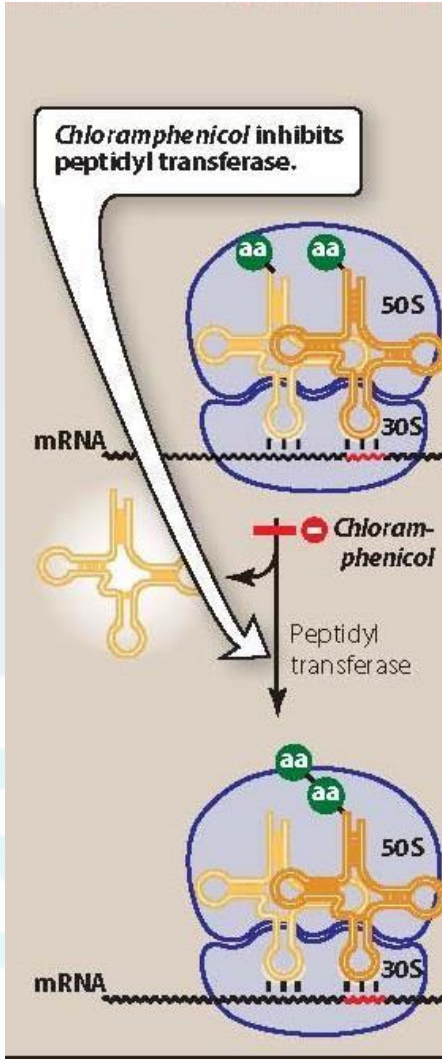
Chloramphenicol

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: widely distributed including CSF, can be secreted in breast milk Contraindicated in breastfeeding mothers

•* it can cross the placental barrier , so it's contraindicated in pregnant women



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..

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

Adverse effects

- **Aplastic anemia(dose-independent and may occur after stopping drug), hemolytic anemia(**in case of G6PD deficiency)
- **Gray baby syndrome**

-accumulation of the drug due to

underdeveloped liver and kidney functions

-can cause death by respiratory and cardiovascular failure

Gray body syndrome may occur in adults if given in high dose

- **Drug-drug interactions**

-inhibits liver enzymes

Critical Thinking Question

?

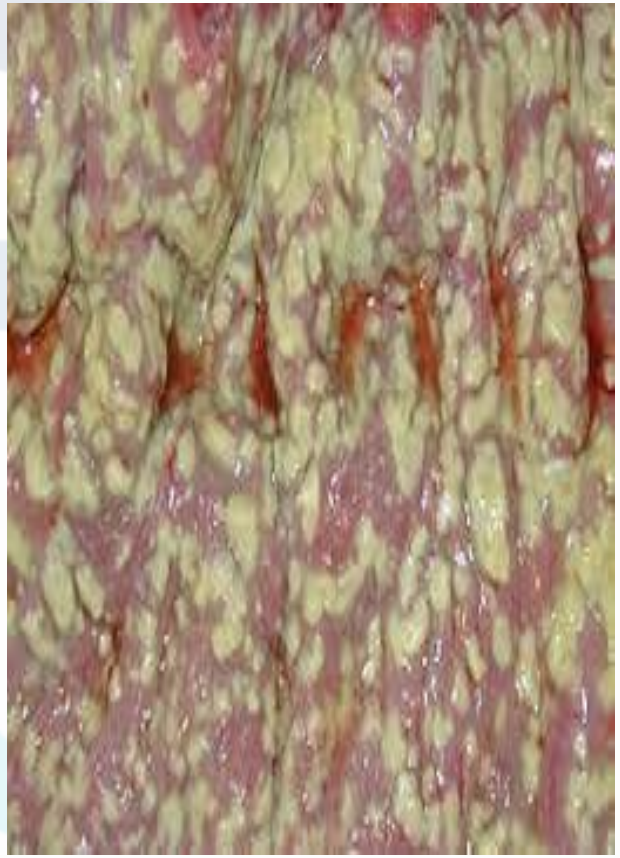
Since chloramphenicol is toxic due to its targeting of the mammalian protein synthesis … which type of ribosomes in mammalian cells will be most susceptible to inhibition by chloramphenicol? And why?

Mitochondrial mammalian ribosomes , because the structure of mitochondrial ribosomes more closely resembles bacterial ribosomes

Clindamycin

Clindamycin

- **MOA**: same as erythromycin
- Effective against gram-positive bacteria: staph INCLUDING MRSA(broad spectrum antibiotic)
- utility of clindamycin for gram-negative anaerobes (for example, Bacteroides sp.) is decreasing due to increasing resistance
- Oral(limited by GI upset) and IV, and topical(for acne)
- It distributes well into all body fluids but exhibits poor entry into the CSF.



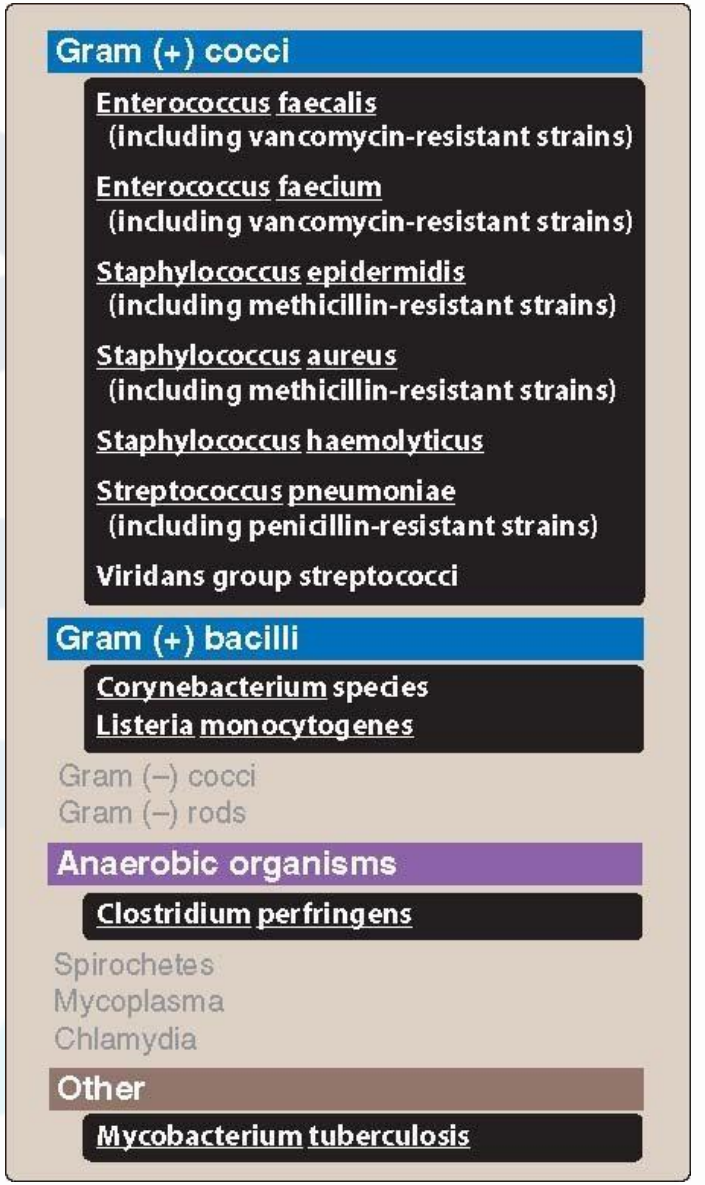
- Clindamycin undergoes extensive oxidative metabolism to active and inactive products and is excreted into bile and urine. Low urinary excretion of active drug limits its clinical utility for urinary tract infections
- Resistance mechanisms are the same as those for erythromycin, and cross-resistance has been described.
- **Adverse effects**: skin rash, diarrhea(most common) : associated with pseudomembranous colitis caused by overgrowth of *C. diffcile*

- Treated with oral vancomycin or metronidazole

Oxazolidinones

Linezolid

- Developed to treat resistant gram- positive organisms, such as MRSA (**not bacteremia. Why? Because linezolid is a bacteriostatic agent**), 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)

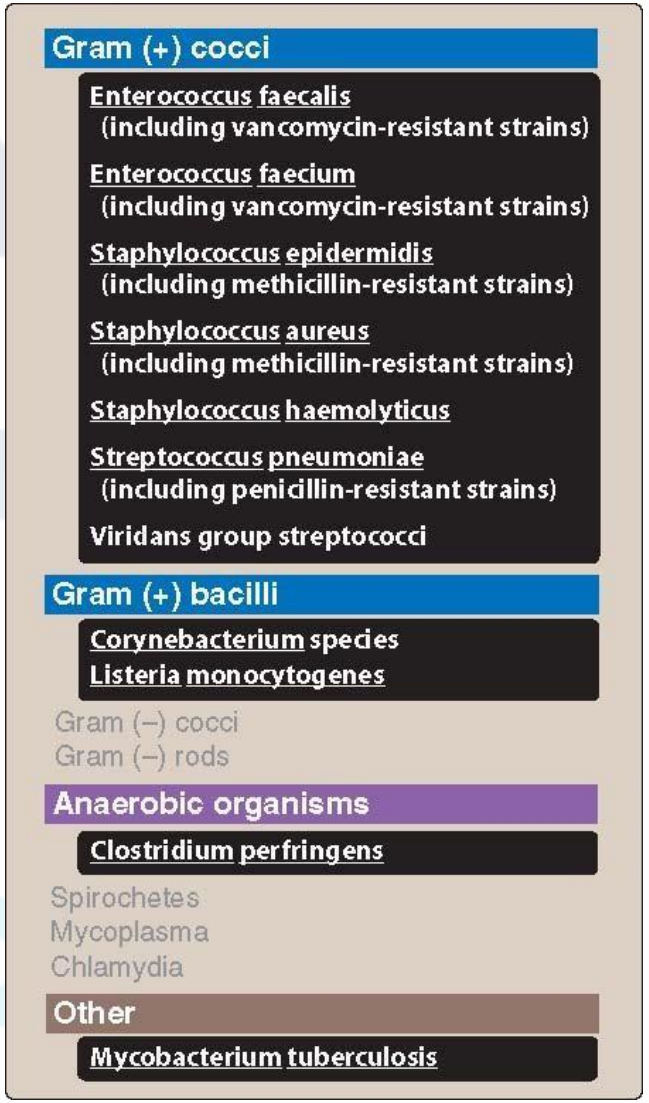


Linezolid

- **Main clinical uses:** Treatment of drug- resistant gram-positive organisms, corynebacteria, and listeria

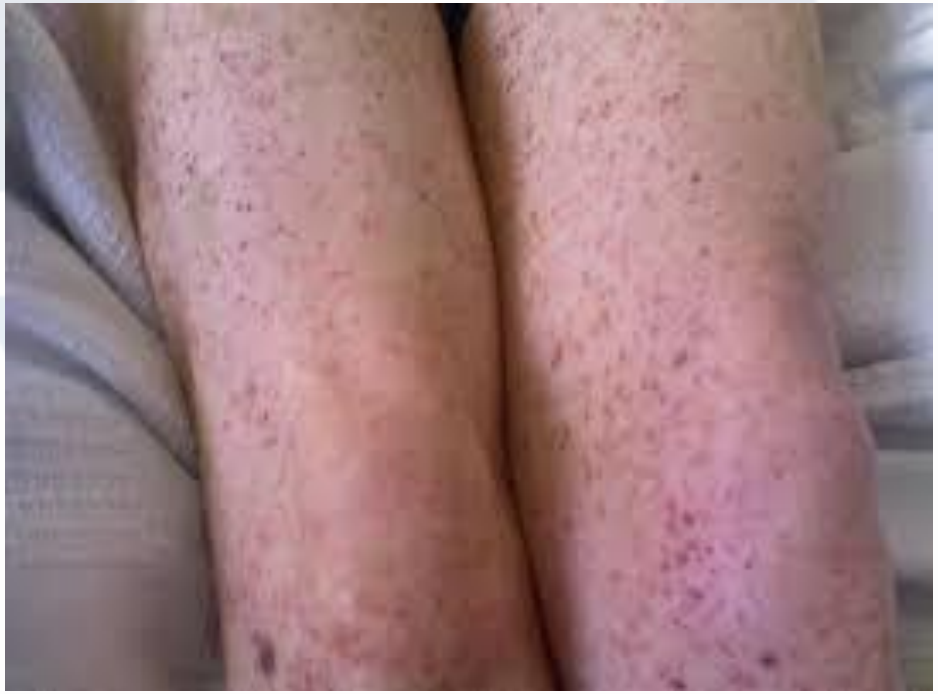
  e.g., alternative to daptomycin for VRE

- **Pharmacokinetics**: oxidized in the liver into two inactive metabolites → excreted in urine.
- The drug is excreted both by renal and nonrenal 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.

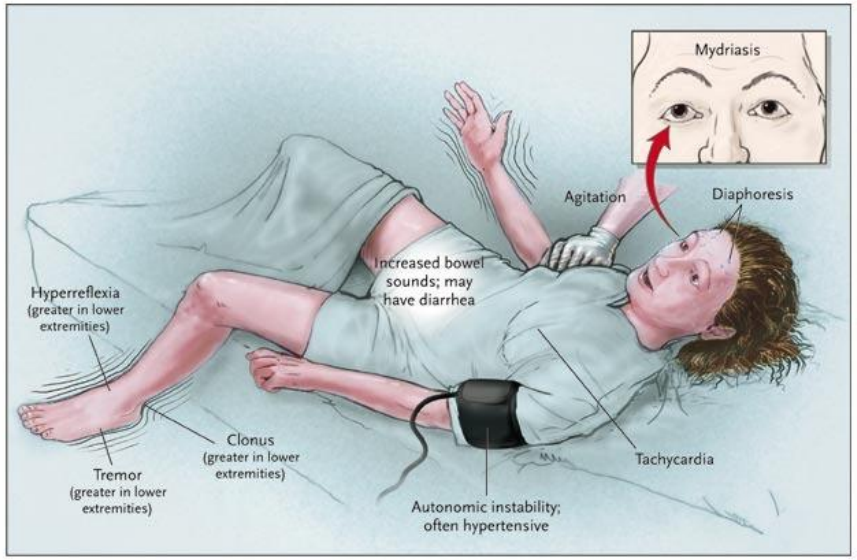


Adverse effects: GI upset, thrombocytopenia, serotonin syndrome(if given concomitantly with large quantities of tyramine-containing foods, selective serotonin reuptake inhibitors, or monoamine oxidase inhibitors), peripheral neuropathy (with prolonged use)

Thrmobocytopenia



Serotonin syndrome



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**.