Protein Synthesis Inhibitors

Pharmacology and Toxicology
General Pharmacology
Second Year Medical Students
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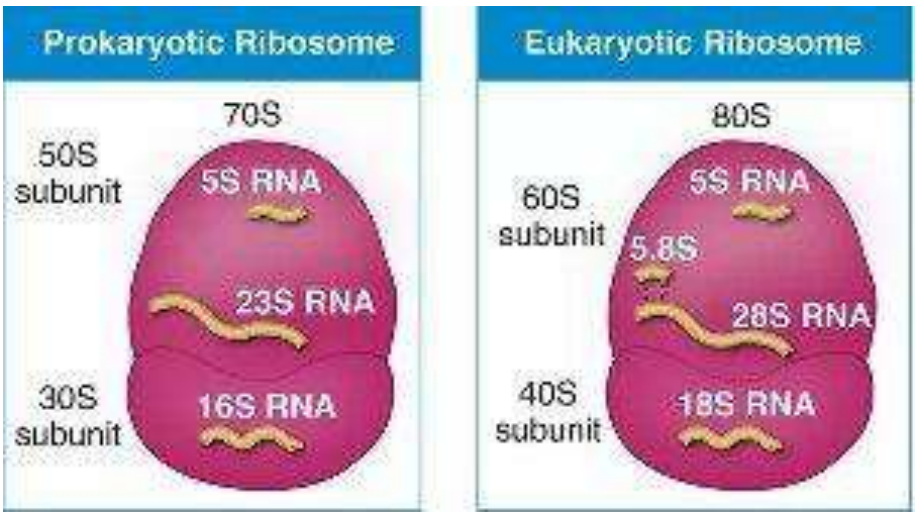
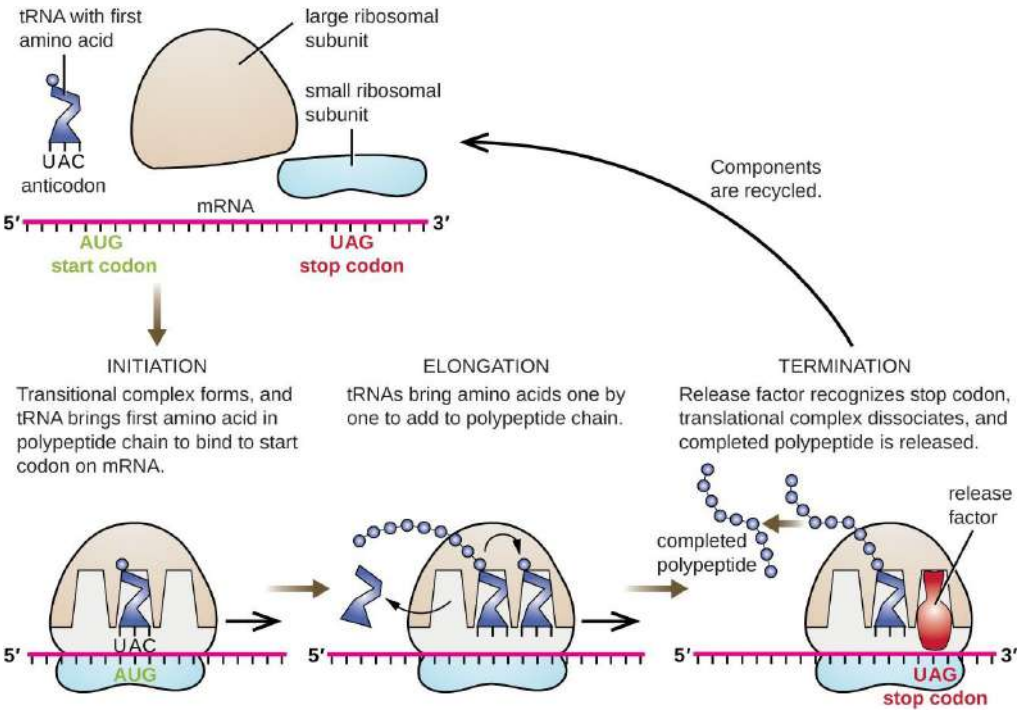
Textbook: Chapter 30 pp: 384-399

* We can benefit from this structure differance by target prokaryotic ribosomes rather than eukaryotic ribosomes.

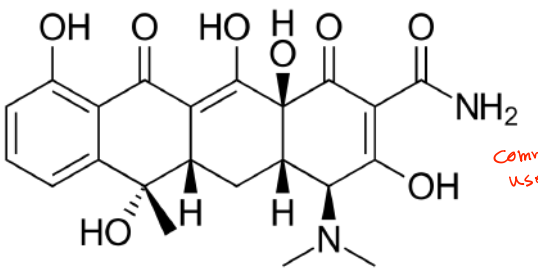
Bacterial Protein Synthesis





Tetracyclines

Tetracyclines



Tetracycline

common used

TETRACYCLINES

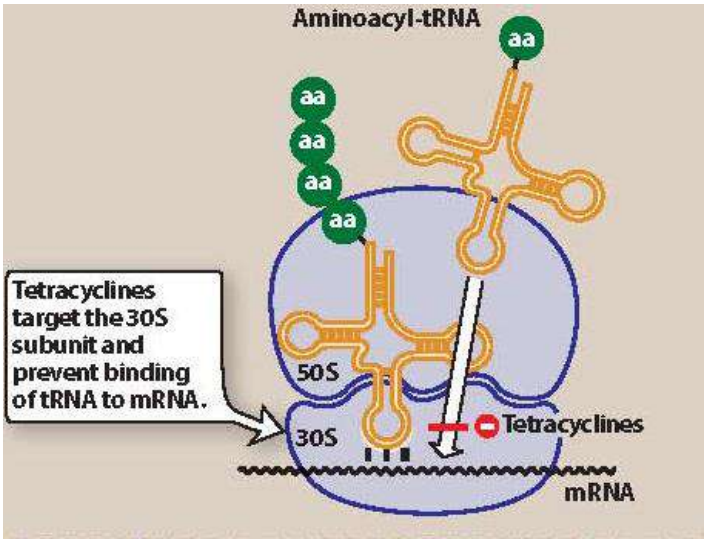
Demeclocycline DECLOMYCIN
Doxycycline VIBRAMYCIN
Minocycline MINOCIN
Tetracycline

Tetracyclines

Mechanism of action

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

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



Tetracyclines

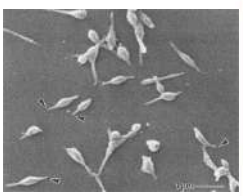
Antibacterial spectrum

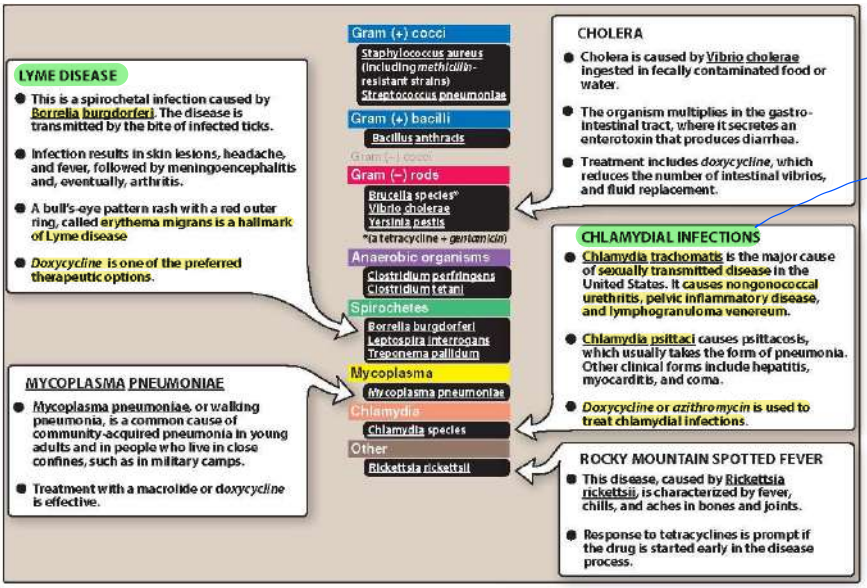
- Bacteriostatic
- Effective against gram-positive, gram-negative, protozoa, spirochetes, atypical, etc

Commonly used for the treatment of:

1. Acne (doxycycline) orally Cutibacterium acnes, bacteria that causes it
2. Chlamydia (doxycycline)
3. Peptic ulcer disease (tetracycline)
4. Lyme Disease (doxycycline)
5. Mycoplasma Pneumonia (doxycycline)

Therapeutic Spectrum of Doxycycline



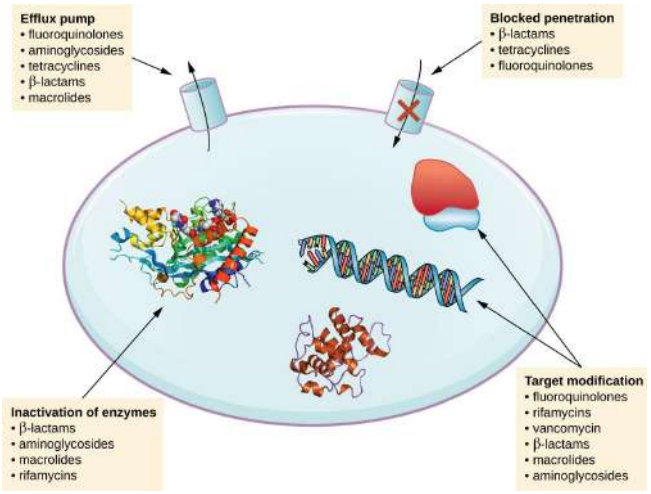


Cancer cells use efflux pump as resistance pathway

Tetracyclines

Mechanisms of resistance

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



Have high affinity to divalent & trivalent cations

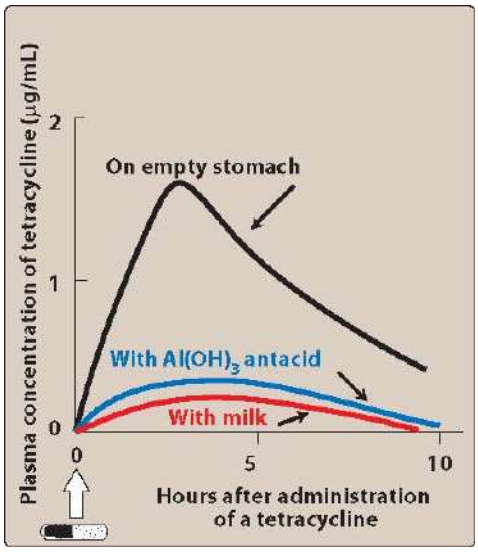
Tetracyclines

Pharmacokinetics

Absorption

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

Antacids → Have cations



Tetracyclines

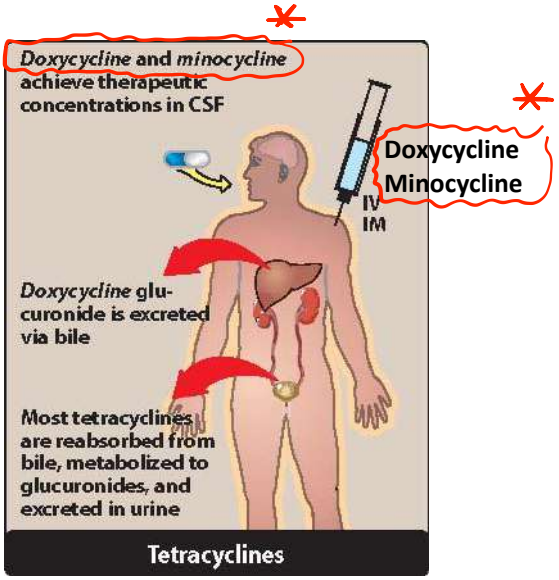
Pharmacokinetics

Distribution

- Distribute well in body fluids, including CSF Didn't used for meningitis.
- 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



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 abnormal or incomplete development of an organ or tissue

-growth problems

-pediatric use is limited


GI disturbance

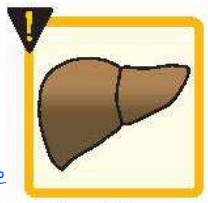

Deposition of drug in bones and teeth

Tetracyclines

Adverse effects

- **Hepatotoxicity**
- **Phototoxicity:** Frequent in ⇒ Tetracycline & Demeclocycline

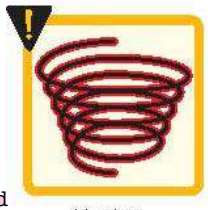
-severe sunburns (recommended to wear sun protection)


Liver failure


Phototoxicity

- **Vestibular dysfunction:**

-dizziness, vertigo, tinnitus


Vertigo


Avoid in pregnancy

- **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

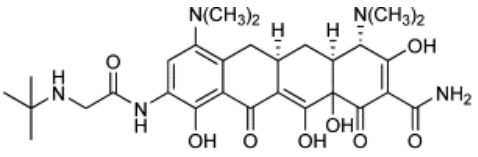
Contraindications

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

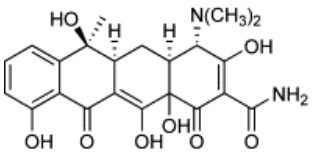
Glycylcyclines

Tigecycline

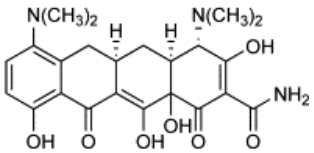
- Derivative of minocycline
- Same mechanism of action as tetracyclines
- Similar mechanisms of resistance



Tigecycline (**58**)



Tetracycline (**59**)



Minocycline (**60**)

Tigecycline

Not used as First line

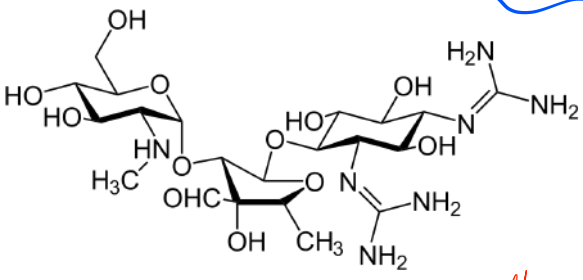
Antibacterial spectrum

- 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

Target G-ve



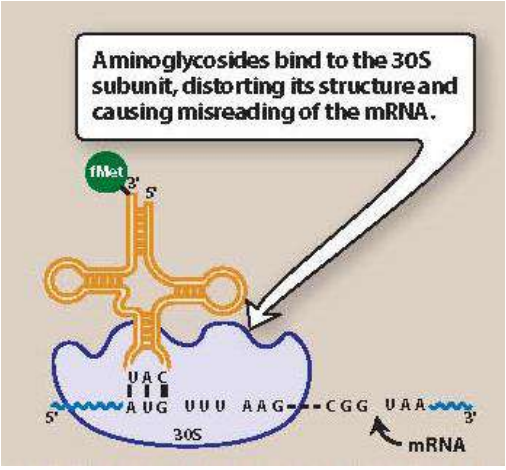
AMINOGLYCOSIDES

- *Amikacin*
- *Gentamicin* GARAMYCIN
- *Neomycin* NEO-FRADIN
- *Streptomycin* ← Anti TB
- *Tobramycin* TOBREX ← Cystic fibrosis in childrens

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

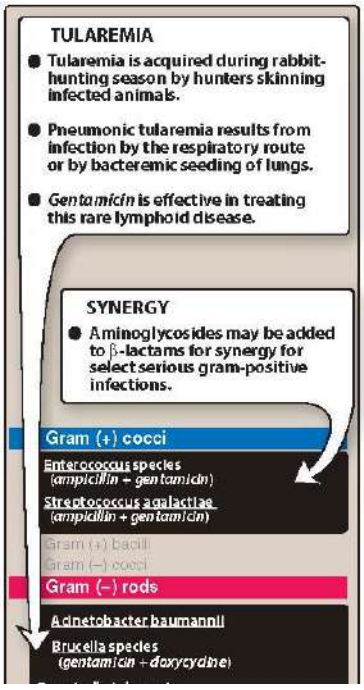


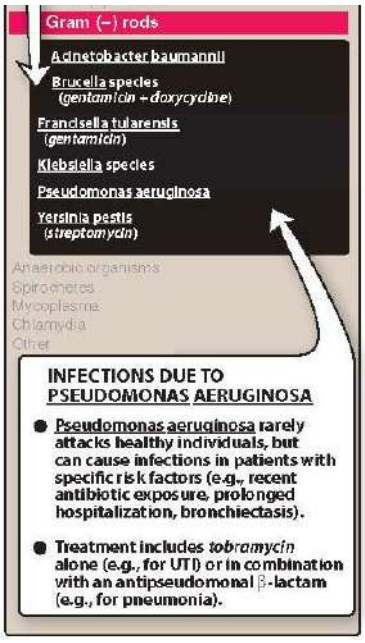
Aminoglycosides

Antibacterial spectrum

- Bactericidal
- Concentration-dependent Cmax ⇒ 8- 10 times of MIC
- Exhibit PAE
- Effective against gram-negative bacilli (INCLUDING multi-DRUG resistant *P. aeruginosa*)
- Used in combination with β-lactams

Synergic effect ⇐ Gentamycin + Ampicillin ⇒ Neonatal meningitis





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

tabomycine ⇒ inhalation

Pharmacokinetics

Absorption

-all are given IV (except neomycin) ← Just topical, no systemic

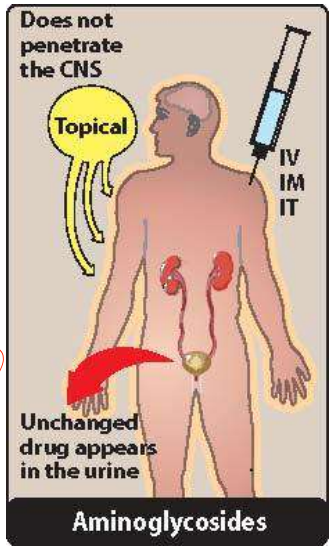
Distribution

-variable distribution in body fluids

-inadequate distribution in CSF

-cross the placenta

May be teratogenic



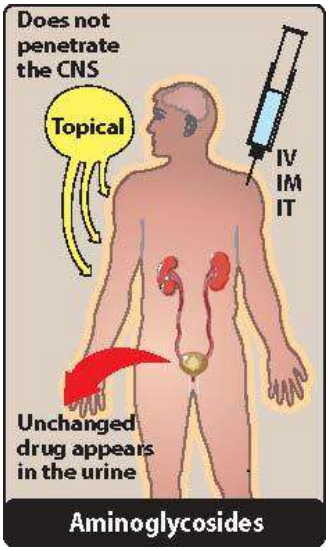
Aminoglycosides

Pharmacokinetics

Elimination

-90% are excreted unchanged in the urine

-accumulation occurs in cases of renal dysfunction



Aminoglycosides

Adverse effects

- **Ototoxicity (vestibular and auditory)**

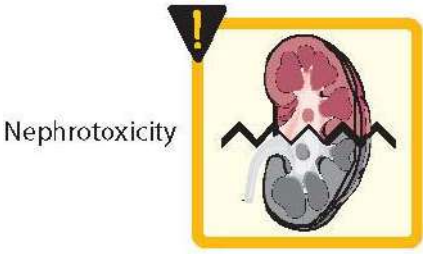
-might cause irreversible deafness

-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

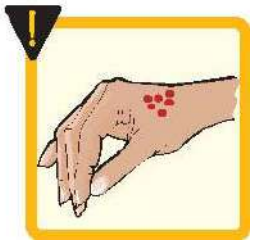
-patient with myasthenia gravis are at risk

- Allergic reaction

- Mostly contact dermatitis with topical neomycin

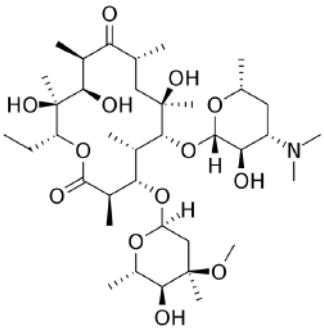
Paralysis

Skin rash

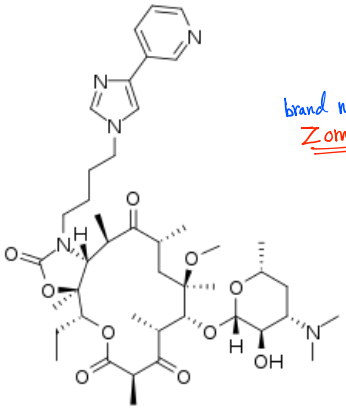


Macrolides and Ketolides

Macrolides and Ketolides



Erythromycin



Telithromycin

brand name
Zomax

MACROLIDES/KETOLIDES

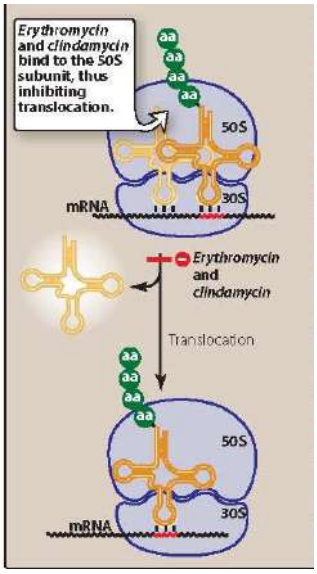
Azithromycin ZITHROMAX
Clarithromycin BIAXIN
Erythromycin VARIOUS
Telithromycin KETEK

interfers of Assembly two subunits of ribosomes

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 Had been used as alternative to penicillin G

-used in cases of penicillin allergy

- **Clarithromycin**

-similar to erythromycin

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

Cause pneumonia

infect gastric epithelium

Macrolides and Ketolides

Antibacterial spectrum

- **Azithromycin**

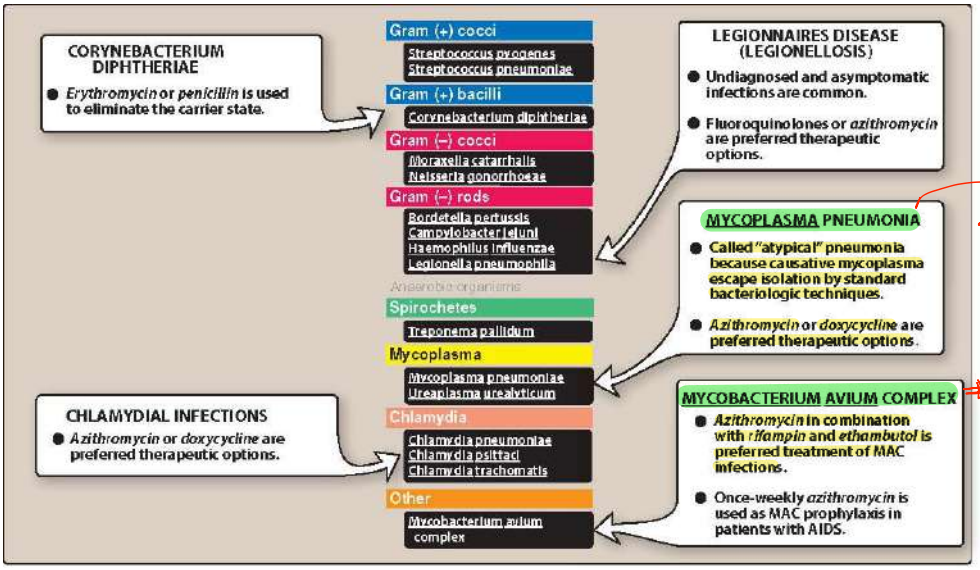
-less active against staph and strep species

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

-increasing S. pneumonia resistance

Concentration dependant

Clinical Spectrum of Macrolides



intracellular bacteria

opportunistic disease → in T-cell mediated diseases, HIV

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

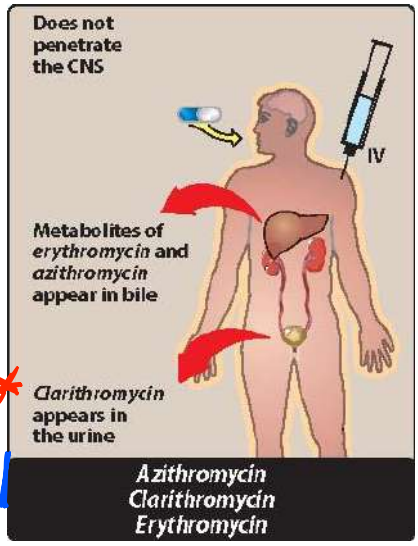
- **Distribution**

-distribute well in body fluids except CSF

- **Elimination**

-hepatic metabolism

-Inhibit CYP450 system (drug-drug interactions)



Macrolides and Ketolides

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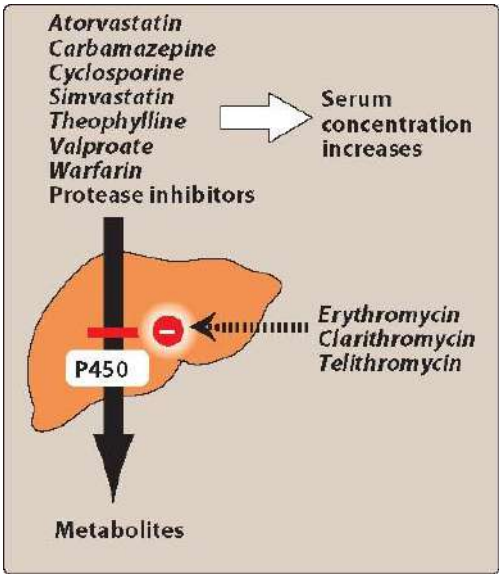
	Erythro-mycin	*Clarithro-mycin*	*Azithro-mycin*	*Telithro-mycin*
Oral absorption	Yes	Yes	Yes	Yes
Half-life (hours)	2	3.5	>40	10
Conversion to an active metabolite	No	Yes	No	Yes
Percent excretion in urine	15	50	12	13

Macrolides and Ketolides

Drug-drug interactions

- Inhibit hepatic metabolism of a number of drugs



Macrolides and Ketolides

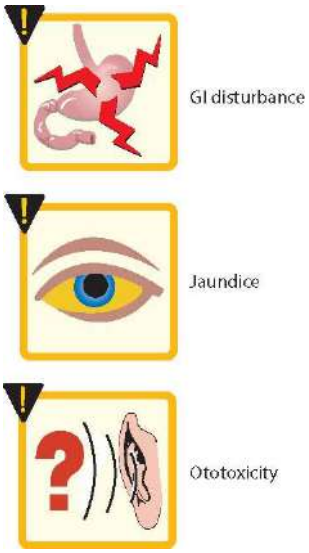
Adverse effects

- **Gastric distress and motility**

-high doses of erythromycin cause smooth muscle contraction and bowel movement.
Could this be helpful? Help in diabetic, because diabetic reduce gastric motility.

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

-contraindicated in patients with hepatic dysfunction



Fidaxomicin

Fidaxomicin

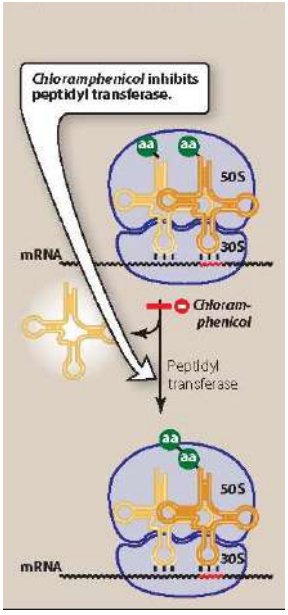
- **Structure:** macrocyclic, similar to macrolides
- **MOA**: acts on the σ subunit of RNA polymerase → disruption of bacterial transcription →  protein synthesis
- Very narrow-spectrum: gram-positive aerobes/anaerobes
- Poorly absorbed (remains in GI tract), primarily used for C. difficile infections
- 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



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

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

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.]

Critical Thinking Question

Becaus mitochondria ribosomes have 50S & 30S, like prokaryotic cells

?

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

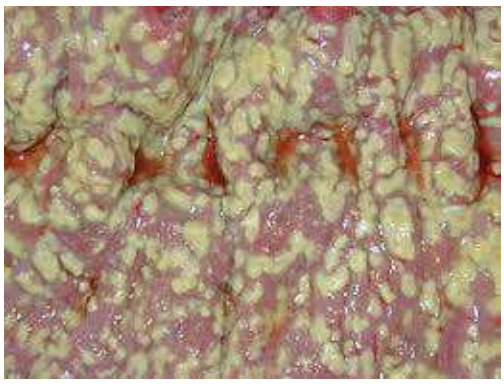
*Some one has sever infection with MRSA and prescribed clindamycin for 3 days then they return to clinic with bloody diarrhea, Here you should prescribe vancomycin

Not used in life-threatining MRSA like pneumonia & meningitis

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

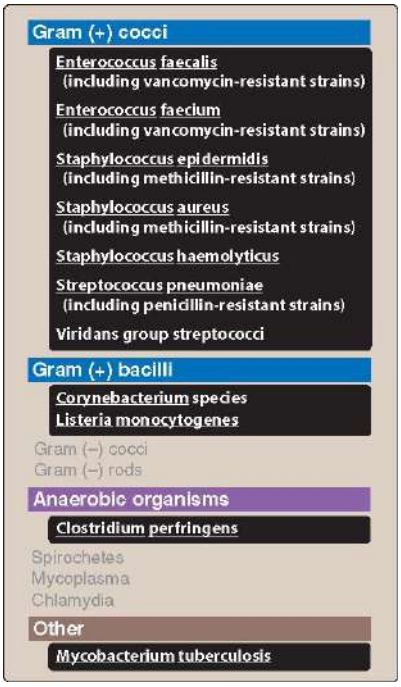


Oxazolidinones

Didn't used first-line in MRSA, it's used alternative for vancomycin or if MRSA resists vancomycin.

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)