Athar Batch

Pharmacology

Lecture: 31

Done By : Toleen Alkasaji

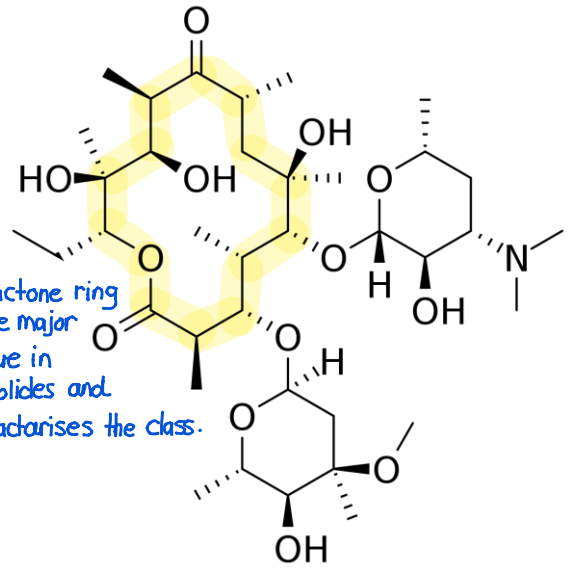
النادي الطبي

Macrolides and Ketolides

Both have very similar structure and mechanism of action.

the chemical structure of the drug is important in knowing the mechanism of action, mechanism of resistance, allergies and cross of allergies.

Macrolides and Ketolides



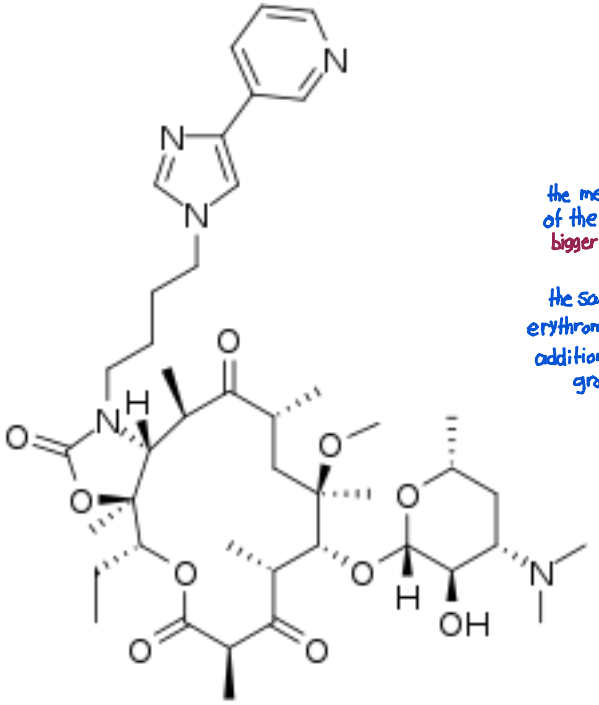
the lactone ring is the major feature in microlides and characterises the class.

Erythromycin

the first identified macrolide.

the use of the erythromycin has been largely replaced by the azithromycin and clarithromycin.

- Better antibacterial coverage.
- Better adverse effects profile.



Telithromycin

has a slightly difference in the structure

MACROLIDES/KETOLIDES	
Azithromycin	ZITHROMAX
Clarithromycin	BIAXIN
Erythromycin	VARIOUS
Telithromycin	KETEK

the methylated form of the erythromycin. bigger lactone ring

the same as the erythromycin in the addition to the methyl group.

The main mechanism of action like the other protein synthesis inhibitors.

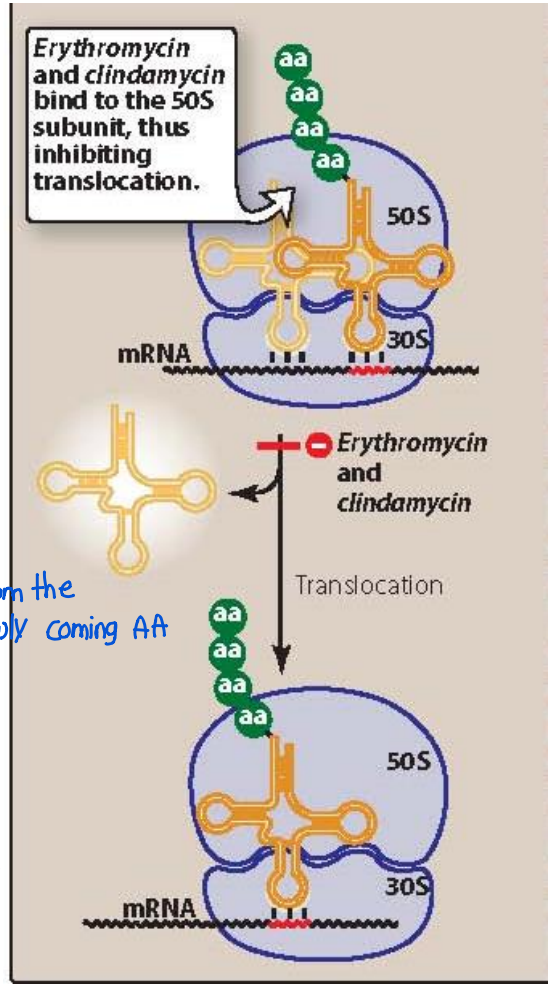
Macrolides and Ketolides

Mechanism of action

- bind *irreversibly* to a site on the 50S subunit of the bacterial ribosome
  the large subunit.
  - Inhibit translocation step
    the inhibition of the translocation of the growing amino acid tRNA from the A site to the P site.
  - Interfere with transpeptidation
    the inhibition of the growing peptide from the P site and the attachment of the newly coming AA in the A site.
- Binding site identical/near that of clindamycin or chloramphenicol
  other protein synthesis inhibitors have the exact site of binding as the macrolides or near each other.

the inhibition of the protein synthesis in the bacteria.

the breaking of the bond between the growing peptide and the tRNA and then the formation of a newly bond between the growing peptide and the newly coming amino acid.



Macrolides and Ketolides

Antibacterial spectrum

-bacteriostatic (can be –cidal at high doses) or against certain types of bacteria.

- **Erythromycin**

-similar spectrum to penicillin G

the main use :

-used in cases of penicillin allergy the best alternative to penicillin G is the erythromycin.

- **Clarithromycin** and Azithromycin.

-similar to erythromycin wider antibacterial coverage.

-effective against intracellular pathogens, e.g. Chlamydia, Legionella, H. Pylori etc... like certain types of bacteria that are called the intracellular pathogenes and infect the host cells intracellulary.

the microorganism that is involved in the pathogenesis of the peptic ulcer disease.

usually is treated in combination of antibiotics.

Macrolides and Ketolides

Antibacterial spectrum

- **Azithromycin** one of the prefered drugs for the treatment of lower/upper respiratory tract infections.

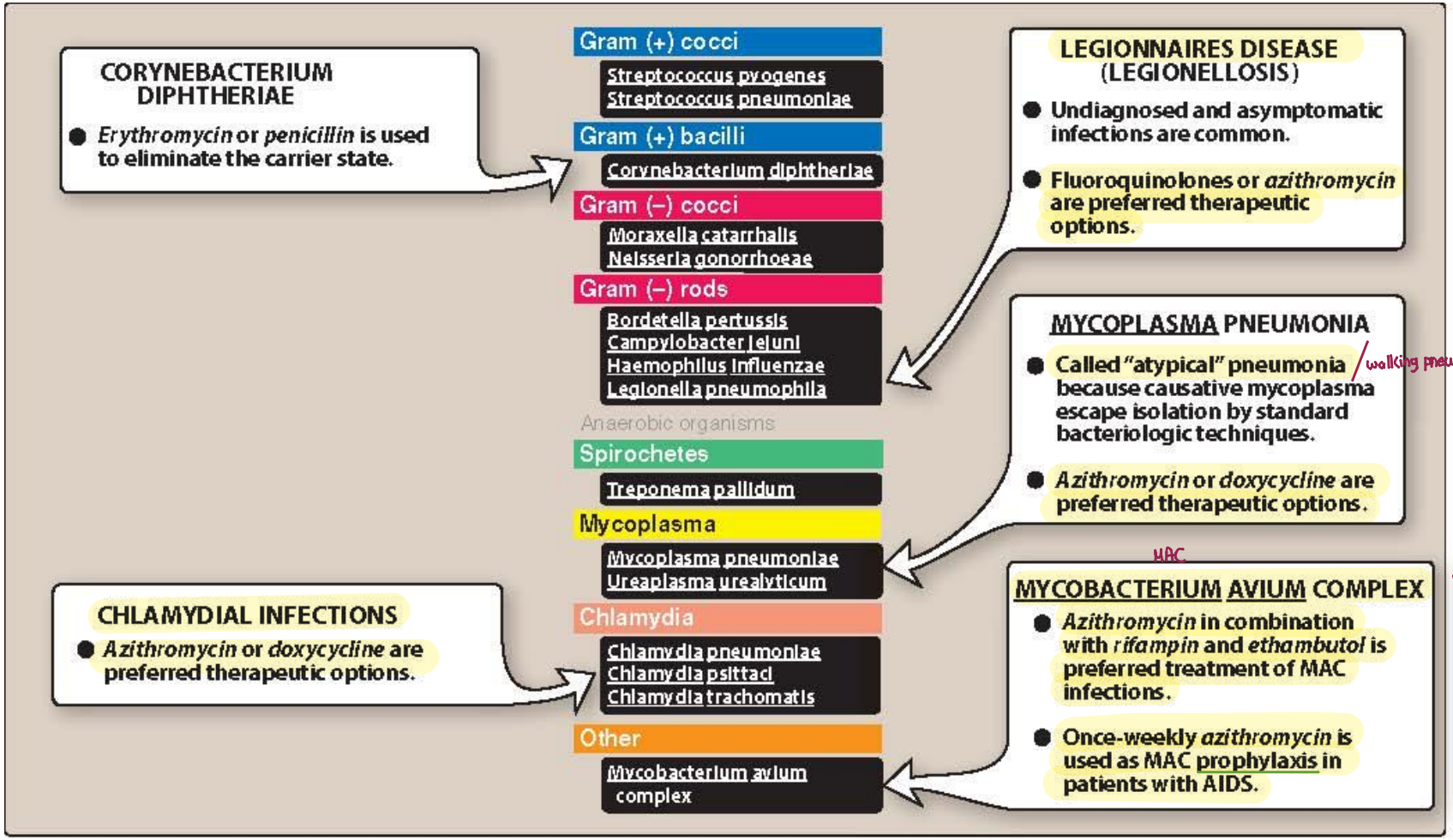
-less active against staph and strep species

-more active against RTI due to *H. influenzae* or *M.catarrhalis* especially the gram negative bacteria.

-increasing S. pneumonia resistance

the main cause community aquired pneumonia infection.

Clinical Spectrum of Macrolides



walking pneumonia.

common in young adults.

MAC

caused by an opportunistic microorganism.

it doesn't affect people with healthy and functional immune system.

* immunocompromised patients are more susciptible to get infected.

Macrolides and Ketolides

they need to cross the cell membrane and reach the ribosomal complex inside the cytoplasm.

Mechanisms of resistance

1) the inability of the organism to take up the antibiotic
2) the presence of efflux pumps — on the plasma membrane and responsible in pumping the antibiotic outside the cells.
3) a decreased affinity of the 50S ribosomal subunit for the antibiotic — in the gene encoding for certain components in the 50s subunit. by mutations at the specific binding site of the macrolides.
4) the presence of plasmid- associated erythromycin esterases in gram-negative organisms — they can cleave or hydrolyse the macrolides especially the erythromycin.

Macrolides and Ketolides

Pharmacokinetics

- **Administration** they are well absorbed from the gastrointestinal tract.

- oral (enteric-coated tablets for erythro)

not stable in the gastric environment, it loses activity and may get hydrolysised.

- Erythro and azithro are available IV but they are commonly given orally.

- **Distribution**

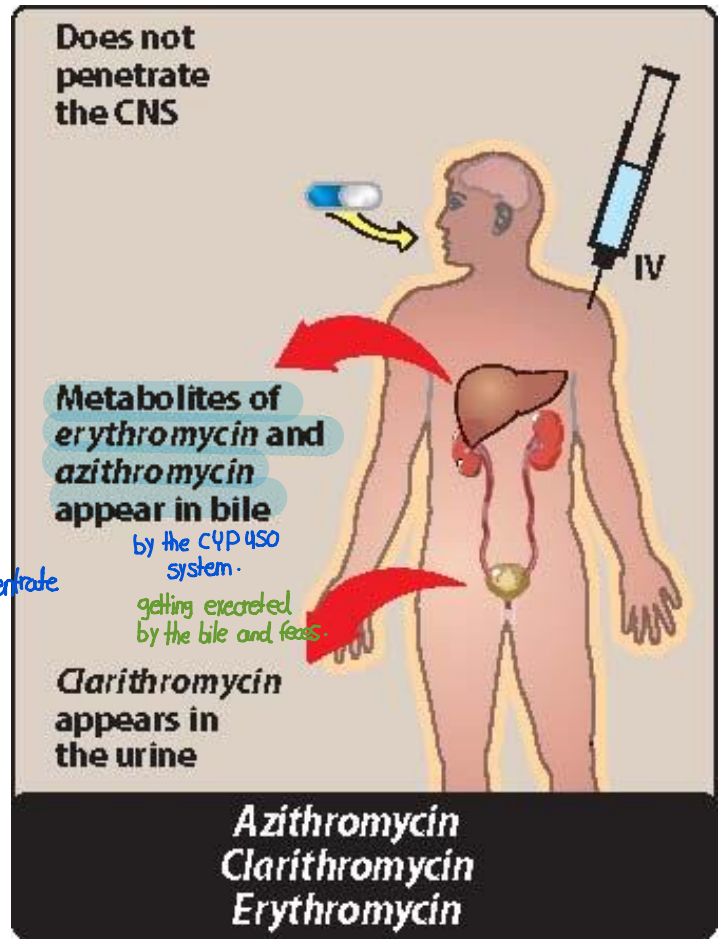
-distribute well in body fluids except CSF like the prostatic fluid which is hard for most drugs to reach to.

they have poor penteration to the BBB and don't concentrate in the CNS.

- **Elimination**

-hepatic metabolism

-Inhibit CYP450 system (drug-drug interactions)



Macrolides and Ketolides

Pharmacokinetics

- **Administration**

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

depending on the metabolic and elimination rate.

- **Distribution**

-distribute well in body fluids except CSF

- **Elimination**

-hepatic metabolism

-Inhibit CYP450 system (drug-drug interactions)

وبكونوا عادي لما عنهم نفس الوظيفة

certain drugs when they are metabolised by the liver they can be converted to active metabolites.

the major function of the hepatic metabolism is to convert the active form to an inactive form. able to get excreted by bile and urine.

it's available in 3-4 tablets in the course.

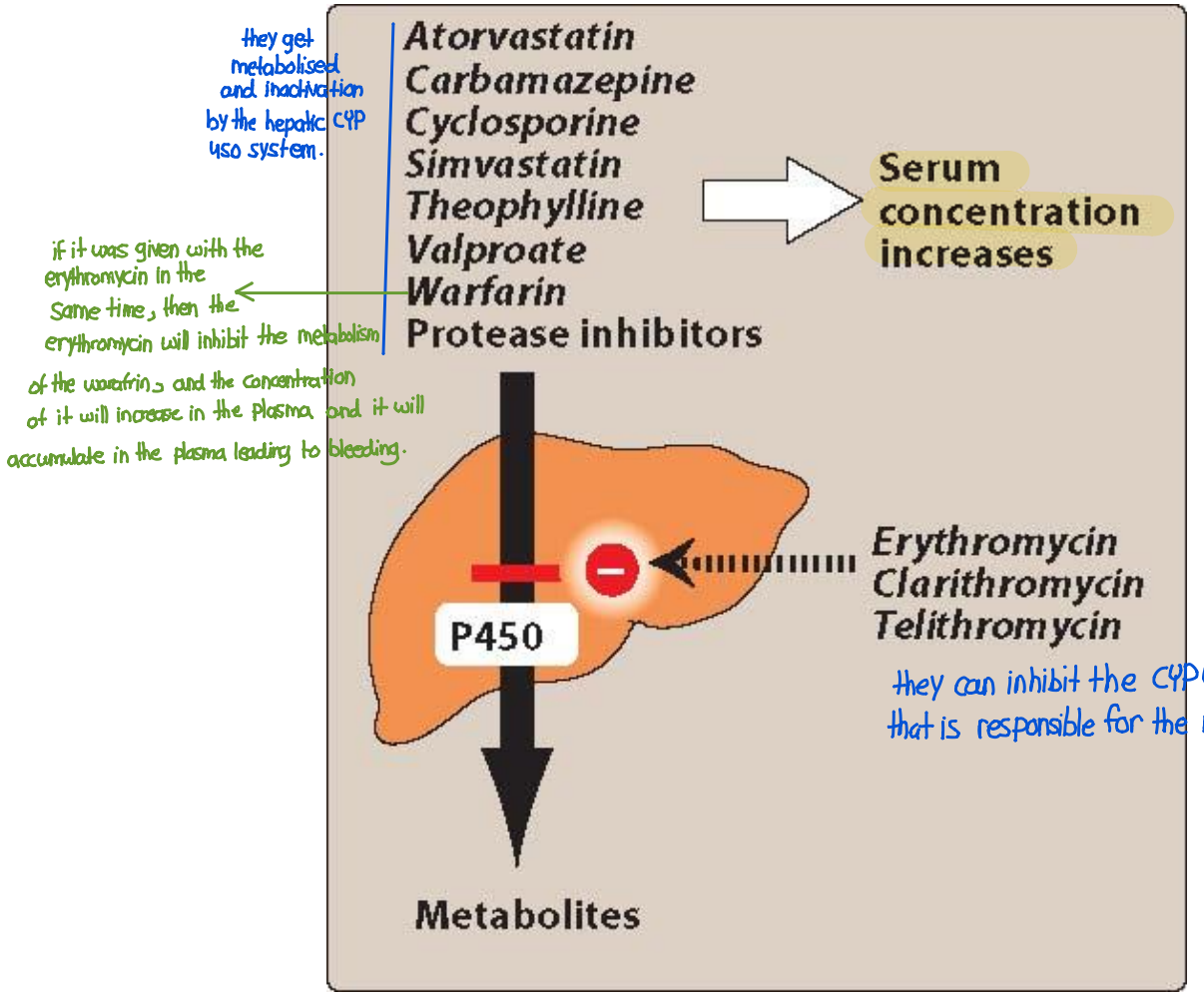
	Erythro-mycin	Clarithro-mycin	Azithro-mycin	Telithro-mycin
Oral absorption	Yes	Yes	Yes	Yes
Half-life (hours)	2 requires multiple dosing	3.5	>40 it requires very few doses to achieve the effect.	10
Conversion to an active metabolite	No	Yes	No	Yes
Percent excretion in urine	15	50 the major route of excretion in this antibiotic is more dependant in the kidney.	12	13

they are heavily metabolised in the liver and are excreted by bile and feces.

Macrolides and Ketolides

Drug-drug interactions

- Inhibit hepatic metabolism of a number of drugs



it's a problem because there are drugs that have a narrow therapeutic index.

they can inhibit the CYP450 system in the liver that is responsible for the metabolism of many drugs.

Macrolides and Ketolides

Adverse effects

- **Gastric distress and motility** — nausea, bloating, diarrhea... not severe but annoying.

may cause diarrhea in the patients

-high doses of erythromycin cause smooth muscle contraction and bowel movement.

Could this be helpful?

this adverse effect is used to treat a condition called the gastroparesis.

*Diabetic patients have systemic neuropathy, injury in many nerves including the nerves of the autonomic NS that innervate the smooth muscles lining the GIT, leading to the delayed gastric emptying.

- **Jaundice** — it's related to the hepatic metabolism, thus increasing the serum levels of billirubin which starts depositing in the body in sclera.

*cholestatic jaundice that occurs more with erythromycin.

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

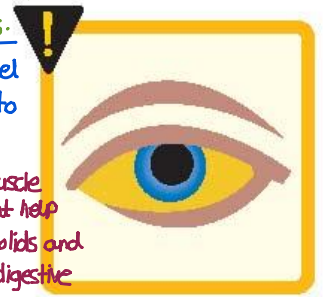
-contraindicated in patients with hepatic dysfunction

GI disturbance

the gastrointestinal tract including the stomach has multiple layers of smooth muscles.

they lead to bowel contraction and to peristalsis

the wave-like muscle contractions that help in moving the solids and liquids in the digestive system.



Jaundice

Ototoxicity

Fidaxomicin

Fidaxomicin

similar to the macrolides but isn't a macrolide.

- **Structure:** macrocyclic, similar to macrolides
- **MOA**: acts on the σ subunit of RNA polymerase (responsible for the transcription of DNA to mRNA.) → disruption of bacterial transcription →  protein synthesis (at an early step.)
- Very narrow-spectrum: gram-positive aerobes/anaerobes
- Poorly absorbed (remains in GI tract), primarily used for C. difficile infections (locally for pseudomembraneous colitis)
- Cross-resistance with other antibiotics is rare. Why? (because it has a unique mechanism of action.)
- Cross-allergy with macrolides (because they have a similar structure to microlides.)
- Adverse effects: nausea, vomiting, abdominal pain

Chloramphenicol

is a famous drug that isn't nowadays widely used.

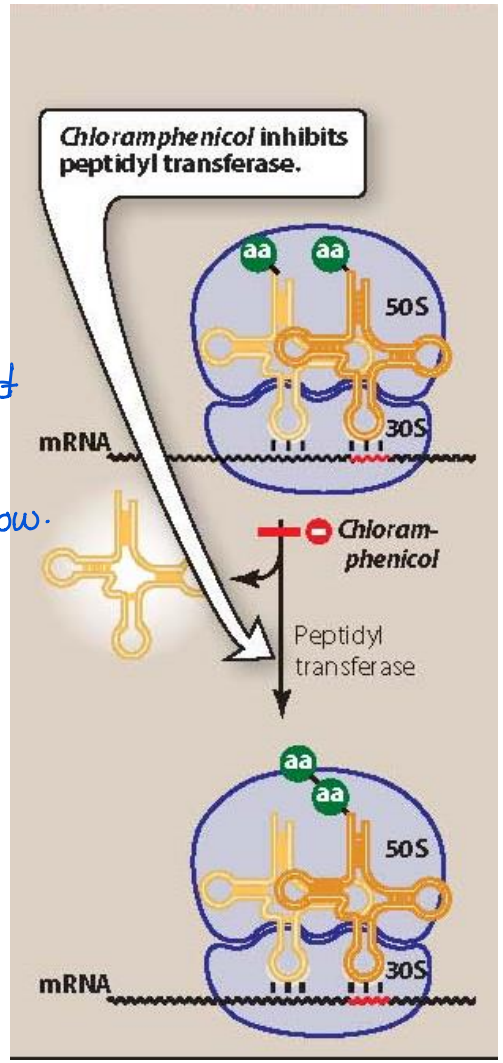
* it's an important example of a drug that inhibits the protein synthesis in bacteria and has low selective toxicity to bacteria.

Chloramphenicol

- Broad-spectrum
- Mainly –static (but can be –cidal) against certain types of bacteria.
- Limited use due to high toxicity when uses at high doses, it may affect the human (mammalian) proteins, especially in the cells of bone marrow.
- **MOA:** *reversibly* to the bacterial 50S ribosomal subunit and inhibits peptidyl transferase reaction inhibits the transpeptidation.
- Given IV: can be secreted in breast milk it has very good distribution.

Contraindicated in breastfeeding mothers + pregnant women.

it may inhibit the action of the transferase enzyme



Chloramphenicol

Adverse effects

due to damage in the function of the bone marrow and being unable to produce WBCs.

- **Aplastic anemia, hemolytic anemia** in case of G6PD deficiency

the breakdown of the RBCs in the bloodstream.

may occur in adults at high doses.

- **Gray baby syndrome**

<28 days old

especially in neonates.

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

leading to respiratory failure
cardiovascular failure
severe cynosis.

the hepatic metabolism isn't developed enough to be able to metabolise many drugs.

-can cause death

- **Drug-drug interactions**

-inhibits liver enzymes

Critical Thinking Question

?

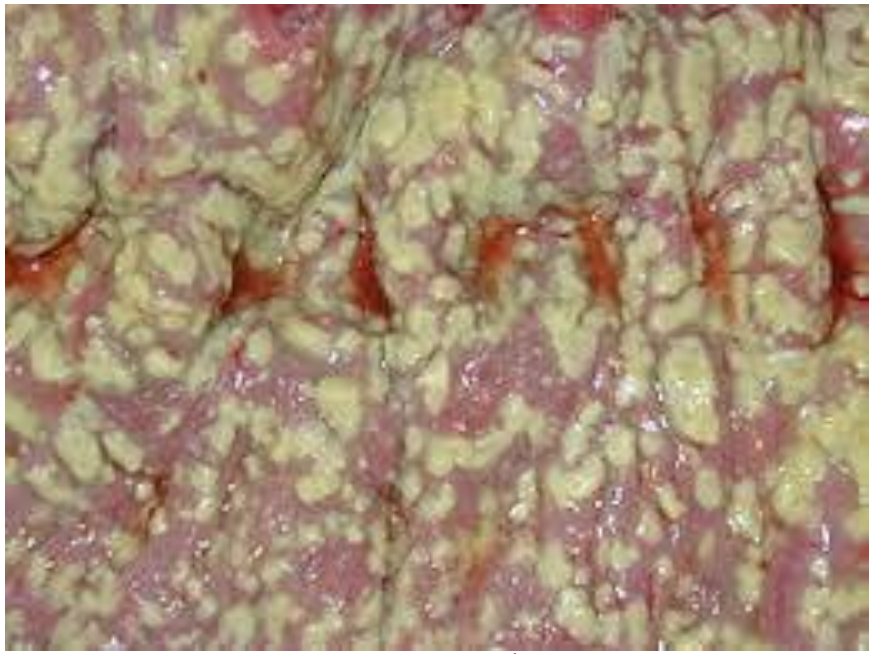
Since chloramphenicol is toxic due to its targeting of the mammalian protein synthesis … which type of ribosomes in mammalian cells will be most susceptible to inhibition by chloramphenicol? And why?

Clindamycin

Clindamycin

- **MOA**: same as erythromycin in the mechanism of action. mechanism of resistance. "the same binding site".
- Effective against gram-positive bacteria: staph INCLUDING MRSA
- Oral and IV and topically like creme.
- **Adverse effects**: skin rash, diarrhea (severe) : associated with pseudomembranous colitis caused by overgrowth of *C. diffcile*

- Treated with vancomycin or metronidazole



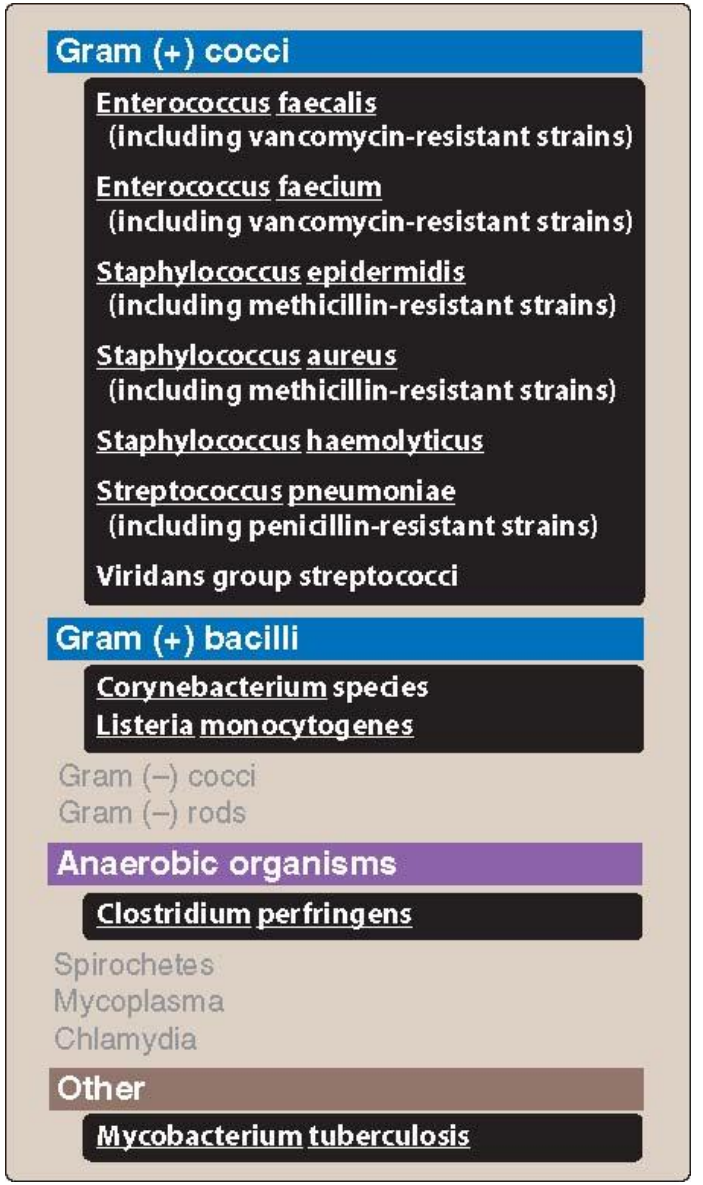
the colon in the case of pseudomembraneous colitis.

Oxazolidinones

Linezolid

similar to the spectrum of the vancomycin.

- Developed to treat resistant gram-positive organisms, such as MRSA (**not bacteremia.** Why?), VRE, resistant mycobacterium and penicillin-resistant streptococci because it's a bacteriostatic drug & and usually if the MRSA causes bacteremia then we prefer to use cidial drugs.
- **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) more than 28 days of use.