Anti Microbial Therapy
Protein Synthesis Inhibitors

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Protein Synthesis Inhibitors are:

1. Tetracyclines
2. Aminoglycosides
3. Macrolides
4. Chloramphenicol
5. Linezolid
6. Clindamycin

Tetracyclines

- Broad spectrum antibiotics
- Bacteriostatic antibiotics
- Against gram-positive and gram-negative bacteria as well as against organisms other than bacteria

Classification According to Duration of Action:

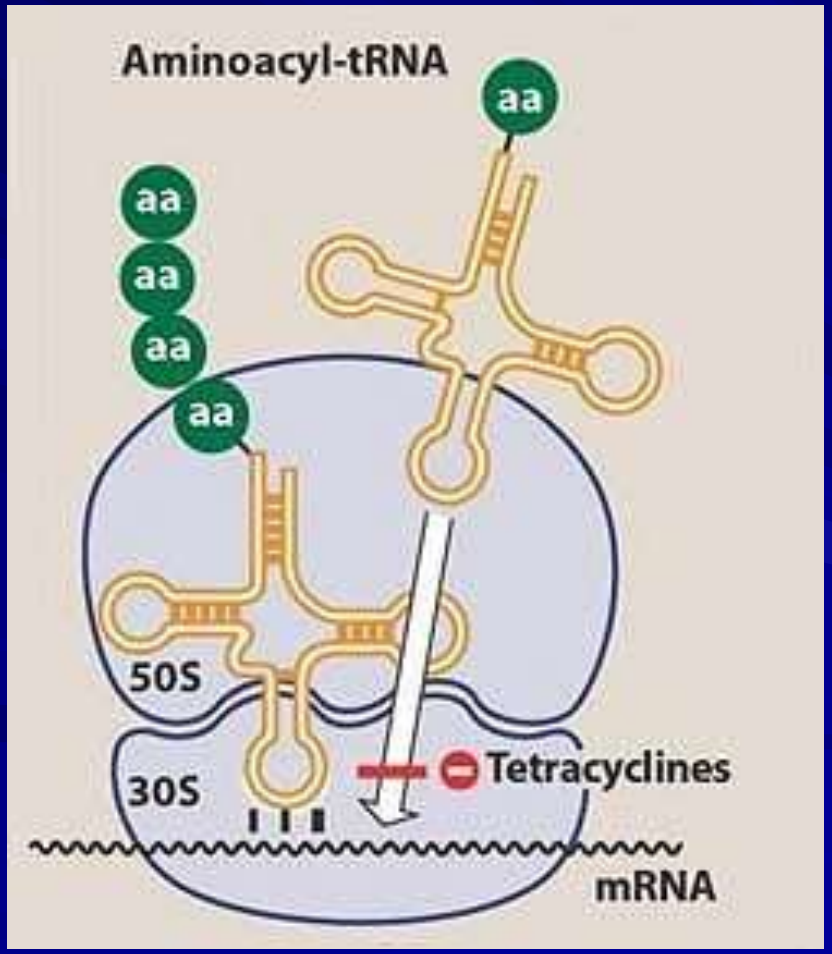
- **Short-acting (Half-life is 6-8 hrs)**
  - Tetracycline
  - Chlortetracycline
  - Oxytetracycline
- **Intermediate-acting (Half-life is ~12 hrs)**
  - Demeclocycline
  - Methacycline
- **Long-acting (Half-life is 16 hrs or more)**
  - Doxycycline
  - Minocycline
  - Tigecycline

Mechanism of Action of Tetracyclines

Inhibited bacterial protein synthesis by:

- The drug enter to organisms by passive diffusion and by an energy-dependent transport protein mechanism through bacterial inner cytoplasmic membrane.
- Tetracyclines concentrate intracellularly.
- Binds reversibly to the 30S subunit of the bacterial ribosomal subunit in the mRNA translation complex & inhibit binding of amino acyl-tRNA to the mRNA-ribosome complex at the acceptor site.

Tetracyclines binds to the 30S ribosomal subunit, thus preventing the binding of aminoacyl-tRNA to the ribosome. aa = amino acid



Pharmacokinetic of Tetracyclin

- Diet decreases absorption due to the formation of non absorbable chelates of the tetracyclines with calcium ions & with divalent and trivalent cations (found in magnesium and aluminum antacids and in iron preparations).
- Doxycycline &minocycline are almost totally absorbed on oral administration.
- Doxycycline is the preferred tetracycline for parenteral administration.

Side Effects of Tetracyclins

1. **Epigastric distress**: this can be controlled if the drug is taken with foods other than dairy products.
2. **Deposition in the bone and primary dentition:** occurs during calcification in growing children. & cause discoloration and hypoplasia of the teeth and a temporary stunting of growth.
3. **Hepatotoxicity:** in pregnant women who received high doses of tetracyclines, especially with pyelonephritis pregnant women

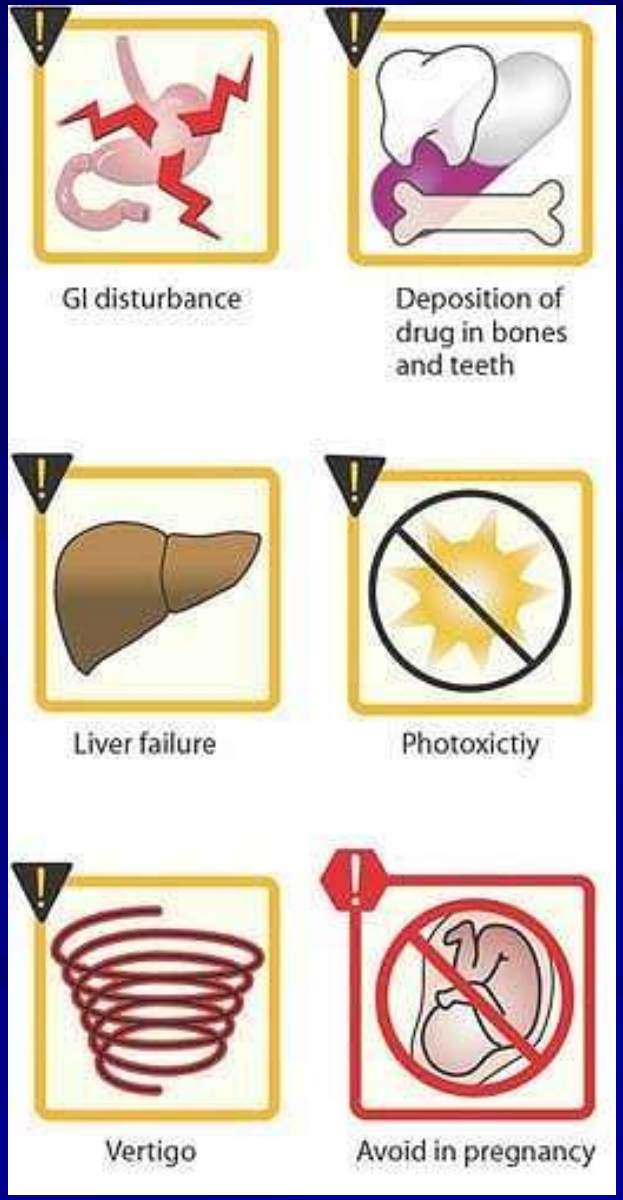
Other Side Effects of Tetracyclins

4. **Phototoxicity**: sunburn, occurs when a patient receiving a tetracycline is exposed to sun or ultraviolet rays (with tetracycline, doxycycline and demeclocycline) .
5. **Vestibular problems**: (dizziness, nausea, and vomiting) occur particularly with minocycline & Doxycycline

Other Side Effects of Tetracyclins

6. **Pseudotumor cerebri**: Benign, intracranial hypertension (reversible) characterized by headache and blurred vision may occur rarely in adults.
7. **Superinfections**: Overgrowths of Candida in the vagina or of resistant staphylococci in the intestine, Pseudomembranous colitis due to an overgrowth of Clostridium difficile

Some Adverse Effects of Tetracycline



Contraindications of Tetracyclins :

- Renally impaired patients should not be treated with any of the tetracyclines EXCEPT doxycycline. Accumulation of tetracyclines may cause a higher-than-normal level of urea or other nitrogen-containing compounds in the blood)by interfering with protein synthesis, thus promoting amino acid degradation.
- Pregnant or breast-feeding women
- Children less than 8 years of age.

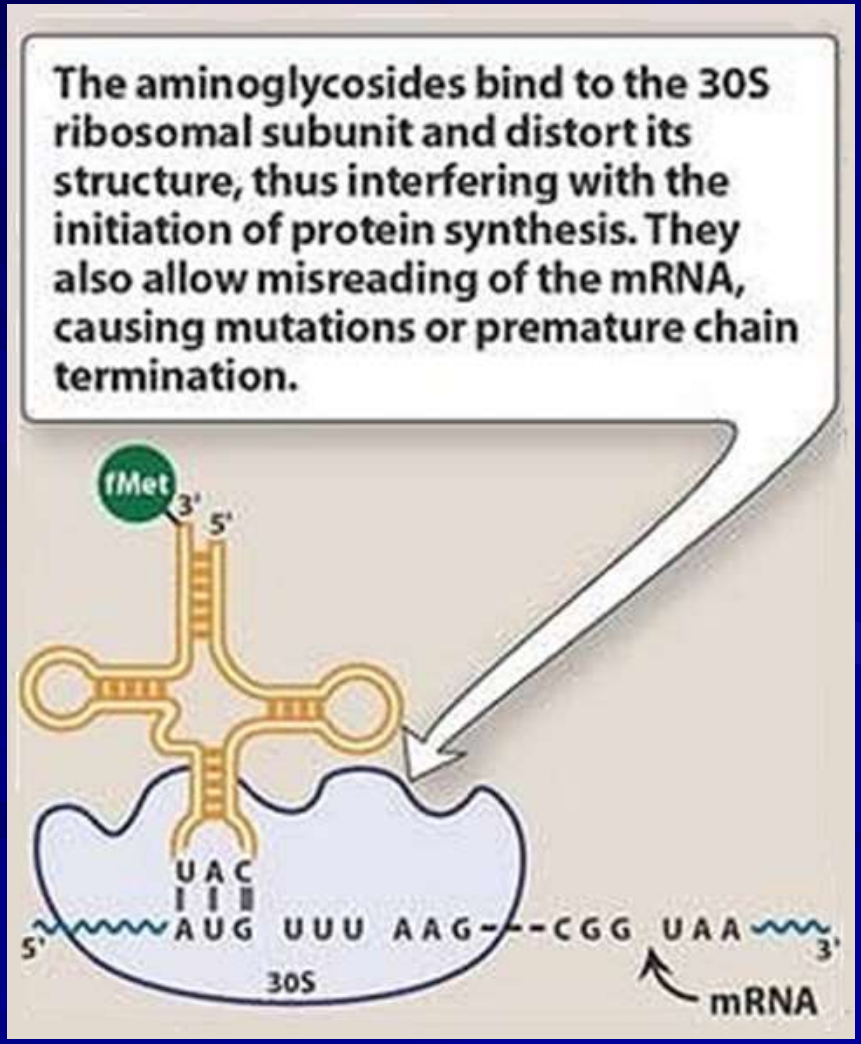
Aminoglycosides
Amikacin
Gentamicin
Tobramycin
Streptomycin

- Inhibit bacterial protein synthesis
- Bactericidal (other antibiotics that affect protein synthesis are generally bacteriostatic)
- Active against aerobic gram-negative bacilli, including Pseudomonas aeruginosa
- Replaced by safer antibiotics, such as the third- and fourth-generation cephalosporins, the fluoroquinolones and the carbapenems (due to toxicities)

Mechanism of Action of Aminoglycosides

- Effective only against aerobic organisms because anaerobes lack the oxygen-requiring drug transport system (through which the Aminoglycosides diffuse)
- The aminoglycoside bind to the 30 s ribosomal subunit
- Distort its structure, thus interfering with the initiation of protein synthesis
- They also allow misreading of the mRNA causing mutations or premature chain termination

Mechanism of Action of the Aminoglycosides



Pharmacokinetic of Aminoglycosides

All aminoglycosides must be given parenterally EXCEPT neomycin (because of nephrotoxicity) and current use is limited to topical application for skin infections or oral administration to prepare bowel prior to surgery.

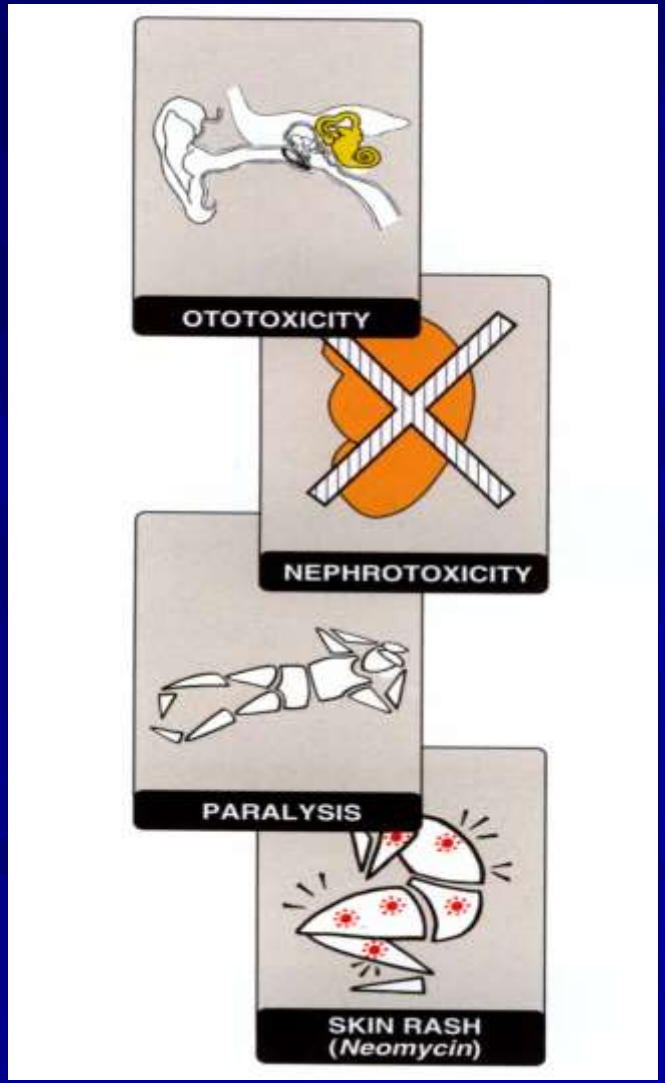
Side Effects of Aminoglycosides

Toxicities increase with old age, previous exposure to aminoglycosides and liver disease

1. **Ototoxicity:**
    - Vestibular and cochlear related to the dose &duration of treatment (accumulates in inner ear and destroyed hear cells)
    - Deafness may be irreversible and has been known to affect fetuses in utero.
    - Concomitent uses with other ototoxic drug (cisplatin, furosemide, bumetanide, or ethacrynic acid increase the risk.
    - Vertigo and loss of balance (with streptomycin) because these drugs affect the vestibular apparatus.

2. **Nephrotoxicity:** Mild, reversible renal impairment to severe, irreversible acute tubular necrosis
3. **Neuromuscular paralysis**
    - The drugs decrease the release of acetylcholine from prejunctional nerve endings and the sensitivity of the postsynaptic site.
    - Patients with myasthenia gravis are particularly at risk.
    - Prompt administration of calcium gluconate or neostigmine can reverse the block.
4. **Allergic reactions:** Contact dermatitis is a common reaction to topically applied neomycin

Some Adverse Effects of Aminoglycosides



Macrolides

- Erythromycin
- Clarithromycin
- Azithromycin
- Dirithromycin
- Roxithromycin
- Tulathromycin
- Ketolides
  - Telithromycin
  - Cethromycin

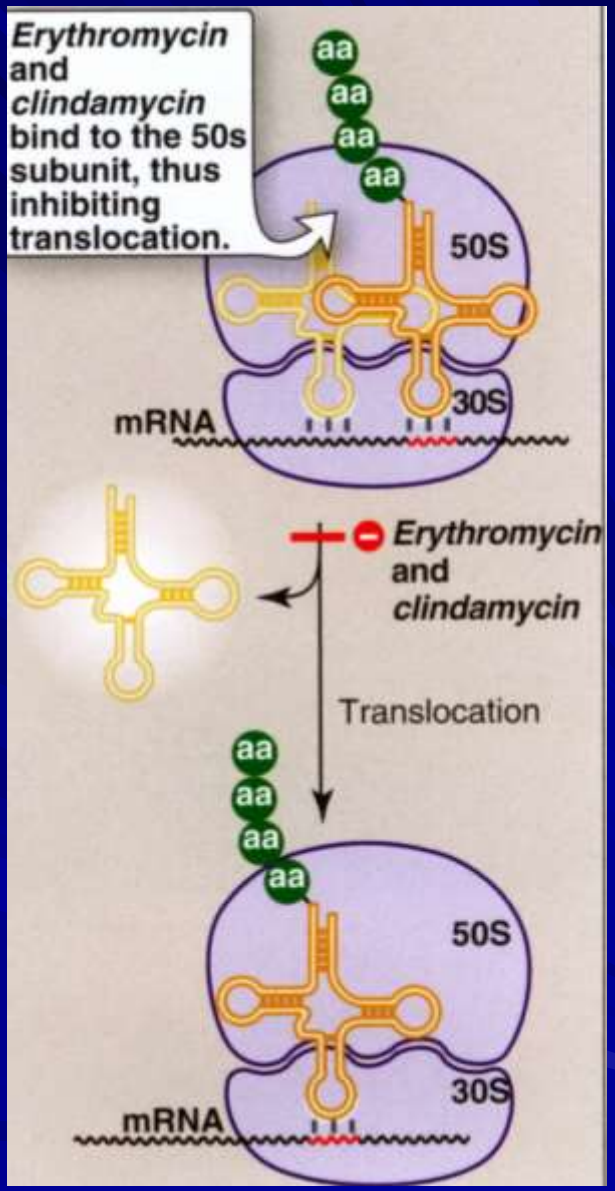
- Spiramycin (Treatment of Toxoplasmosis)
- Ansamycins: (Rifamycins) (treatment of tuberculosis, leprosy and AIDS-related mycobacterial infections

Note: Non-antibiotic macrolide.

The drugs Tacrolimus and Sirolimus are Non-antibiotic macrolide used as immunosuppressants.

Mechanism of Action of Macrolides

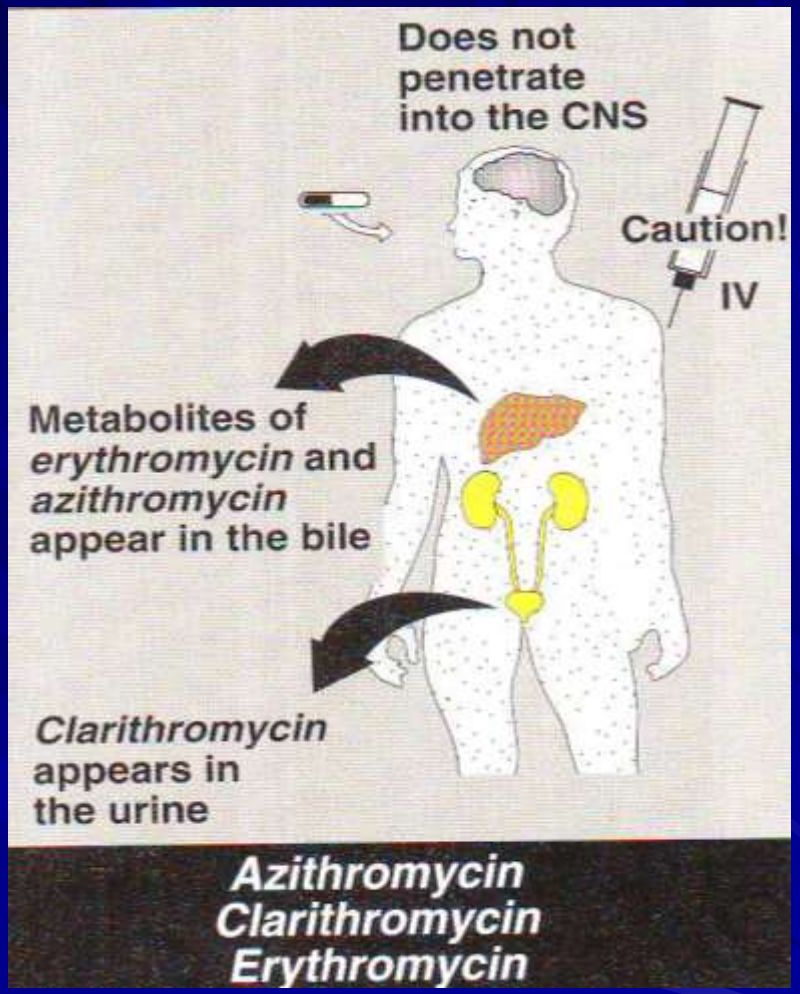
- They are bacteriostatic but bactericidal at higher doses
- Bind to a site on 50 S subunit of bacterial ribosome (irreversibly) and interfere with protein synthesis.



Mechanism of action of erythromycin and clindamycin

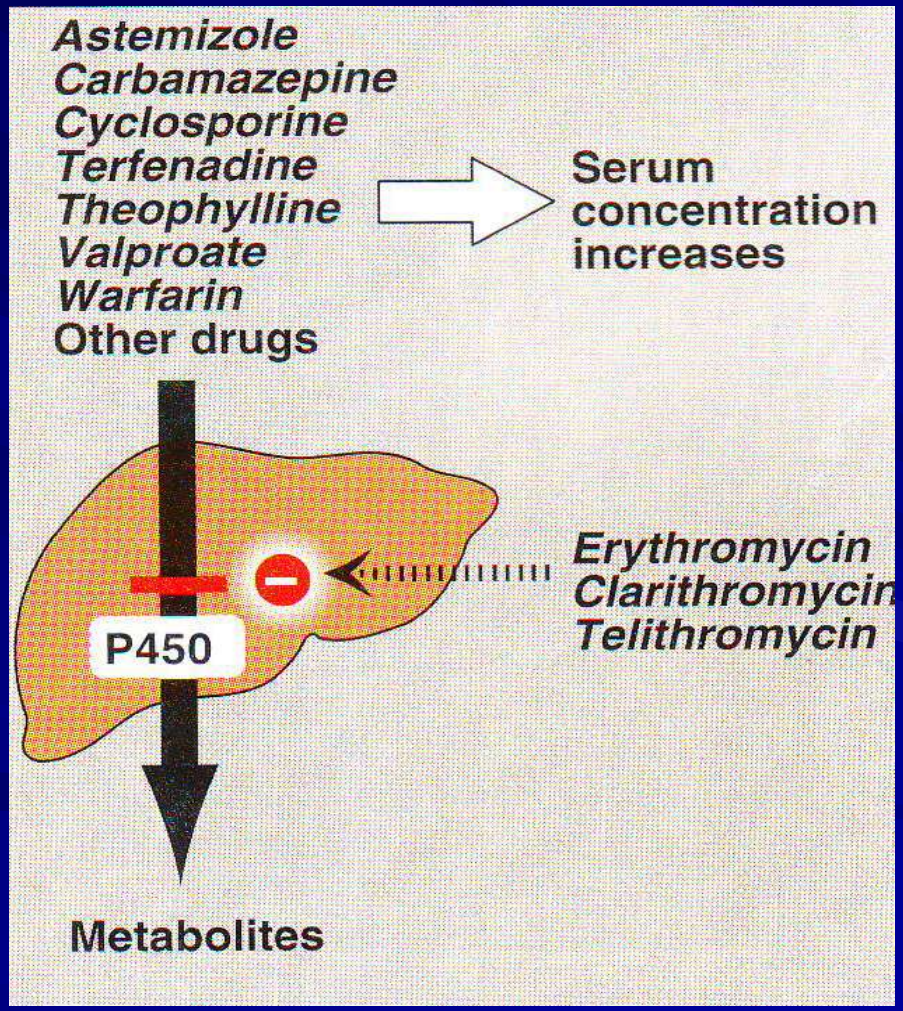
Pharmacokinetics of Macrolides

- Erythromycin is available as estolate, stearate, propionate & succinate salts.
- Absorption after oral administration is best with erythromycin estolate, even if there is food in the stomuch



Administration and Fate of the Macrolide Antibiotics

Inhibition Of The Cytochrome P450 System By Erythromycin, Clarithromycin and Telithromycin.



Erythromycin

- As alternative to penicillin in allergic patients.
- As prophylaxis against endocarditis during dental procedures in individuals with valvular heart disease

Clarithromycin

- Effective against Haemophilus influenzae, intracellular pathogens; Chlamydia, Legionella, Moraxella, and effective against Helicobacter pylori, leprosy, effective against protozoa including Toxoplasma gondii.

Azithromycin

- Less active against streptococci and staphylococci than erythromycin
- More active against respiratory infections due to H. influenzae and Moraxella catarrhalis than erythromycin.
- Azithromycin is now the preferred therapy for urethritis caused by Chlamydia trachomatis.
- Azithromycin, effective against protozoa including Toxoplasma gondii
- Has activity against Mycobacterium avium-intracellulare complex in patients with acquired immunodeficiency syndrome and disseminated infections patients.

Telithromycin

- This ketolide drug has an antibacterial spectrum similar to that of azithromycin.
- The structural modification within ketolides neutralizes the most common resistance mechanisms (methylase-mediated and efflux-mediated) that make macrolides ineffective

Adverse Effects of Macrolides

1. Epigastric distress (erythromycin) anorexia, nausea, vomiting, diarrhea
2. Cholestatic jaundice (with the estolate form of erythromycin) due to a hypersensitivity reaction to the estolate form.
3. Other allergic reaction fever, eosenophilia and rashes
4. Ototoxicity: Transient deafness (erythromycin) at high dosages.

Contraindications of Macrolides

- Patients with hepatic dysfunction should be treated cautiously with erythromycin, telithromycin, or azithromycin, these drugs accumulate in the liver&,sever hepatotoxicity with telithromycin
- Telithromycin prolong the QTc interval in some patients & should be avoided in patients with congenital prolongation of the QTc interval and in those patients with proarrhythmic conditions
- Telithromycin should be given with caution in renally compromised patients
- Telithromycin is contraindicated in patients with myasthenia gravis.

Drug Interactions of Macrolides

1. Erythromycin, telithromycin and clarithromycin are enzyme inhibitors (inhibit metabolism of a number of drugs)
2. This antibiotic eliminates a species of intestinal flora that ordinarily inactivates digoxin & lead to greater reabsorption of the drug from the enterohepatic circulation.

Note: No interactions have been reported for azithromycin.

Chloramphenicol

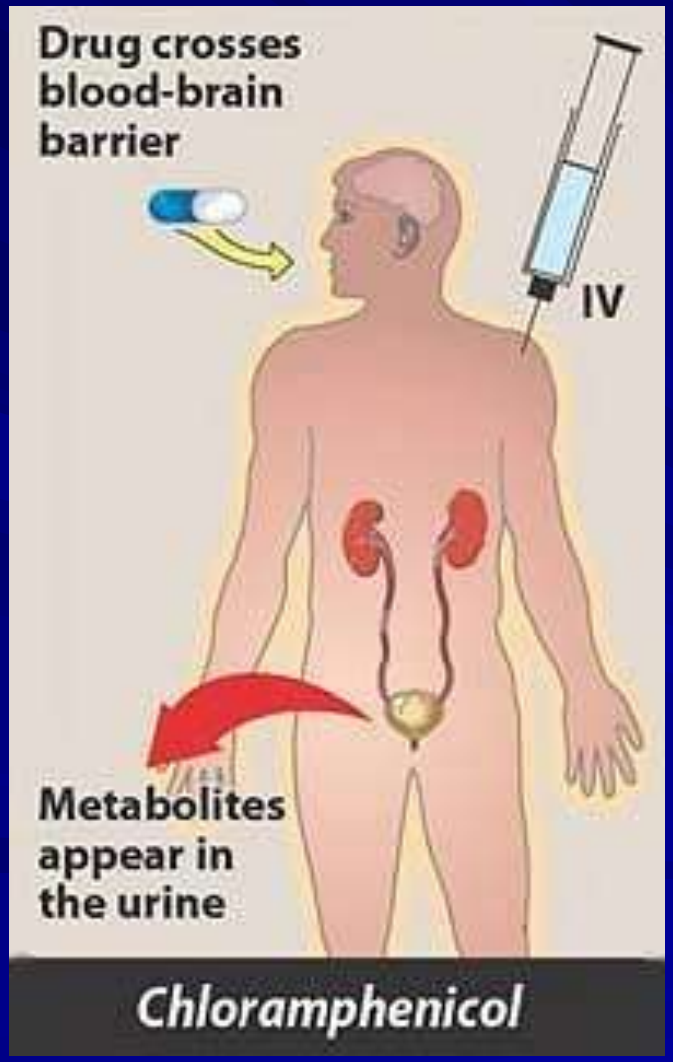
- Broad-spectrum antibiotic
- Active not only against bacteria but also against other microorganisms, such as rickettsiae.
- Pseudomonas aeruginosa is not affected, nor are the chlamydiae.
- Chloramphenicol has excellent activity against anaerobes.
- Its use is restricted to life-threatening infections (because of its toxicity)

Mechanism of Action of Chloramphenicol

- Binds to bacterial 50S ribosomal subunit and inhibits protein synthesis at peptidyl transferase reaction.

Note: Chloramphenicol, Because of similarity of mammalian mitochondrial ribosomes to those of bacteria, protein synthesis in these organelles may be inhibited at high circulating chloramphenicol levels, producing bone marrow toxicity.

Administration and Fate of Chloramphenicol

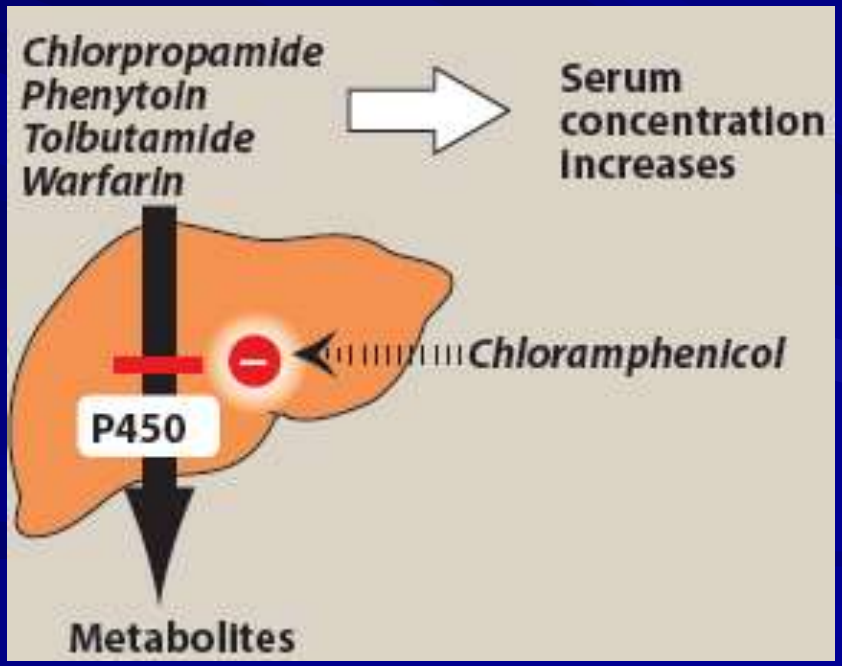


Side Effects of Chloramphenicol

1. **Anemias:**
   - Hemolytic anemia occurs in patients with low levels of glucose 6-phosphate dehydrogenase.
   - Reversible anemia
   - Aplastic anemia
2. **Gray Baby Syndrome:**
   - Neonates have a low capacity to glucuronylate the antibiotic, and they have underdeveloped renal function. Therefore, neonates have a decreased ability to excrete the drug, which accumulates to levels that interfere with the function of mitochondrial ribosomes. This leads to poor feeding, depressed breathing, cardiovascular collapse, cyanosis (gray baby) and death.
   - This toxicity occurs also in adults (high doses)

Drug Interactions of Chloramphenicol

- Inhibit the metabolism warfarin, phenytoin, tolbutamide, and chlorpropamide, thereby elevating their concentrations and potentiating their effects



Inhibition of the cytochrome P450 system by chloramphenicol

Quinupristin / Dalfopristin

- Is mixture bactericidal
- Active primarily against gram-positive cocci, including those resistant to other antibiotics (MRSA, vancomycin-resistant entero coccus faecium (VRE).

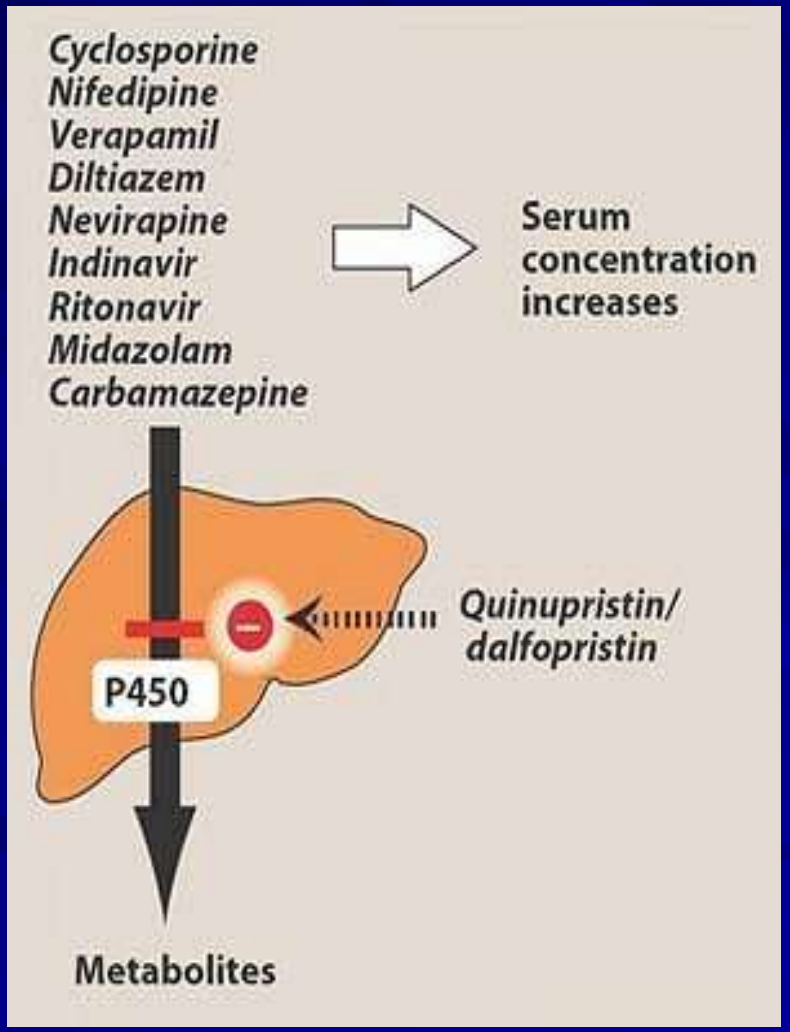
Mechanism of Action:

- Each component of this combination drug binds to a separate site on 50S bacterial ribosome. Thus, they synergistically interrupt protein synthesis.

Pharmacokinetics of Quinupristin/Dalfopristin

- Is injected intravenously
- Drug penetrates macrophages and polymorpho-nucleocytes, a property that is important, because VRE are intracellular.
- Low Levels of drugs in the CSF
- Parent drugs and metabolites are cleared through the liver and eliminated via the bile into the feces, Urinary excretion is secondary.

Inhibition of Cytochrome P450 System by Quinupristin/Dalfopristin



Adverse Effects Quinupristin/Dalfopristin

1. Venous irritation
2. Arthralgia and myalgia
3. Hyperbilirubinemia
4. Interactions: quinupristin/dalfopristin to inhibit the cytochrome P450 (CYP3A4) isozyme

Clindamycin

- Mechanism of action it is simillar to that of erythromycin.
- Used in the treatment of infections caused by anaerobic bacteria, such as Bacteroides fragilis, which causes abdominal infections associated with trauma

Adverse Effect of Clindamycin

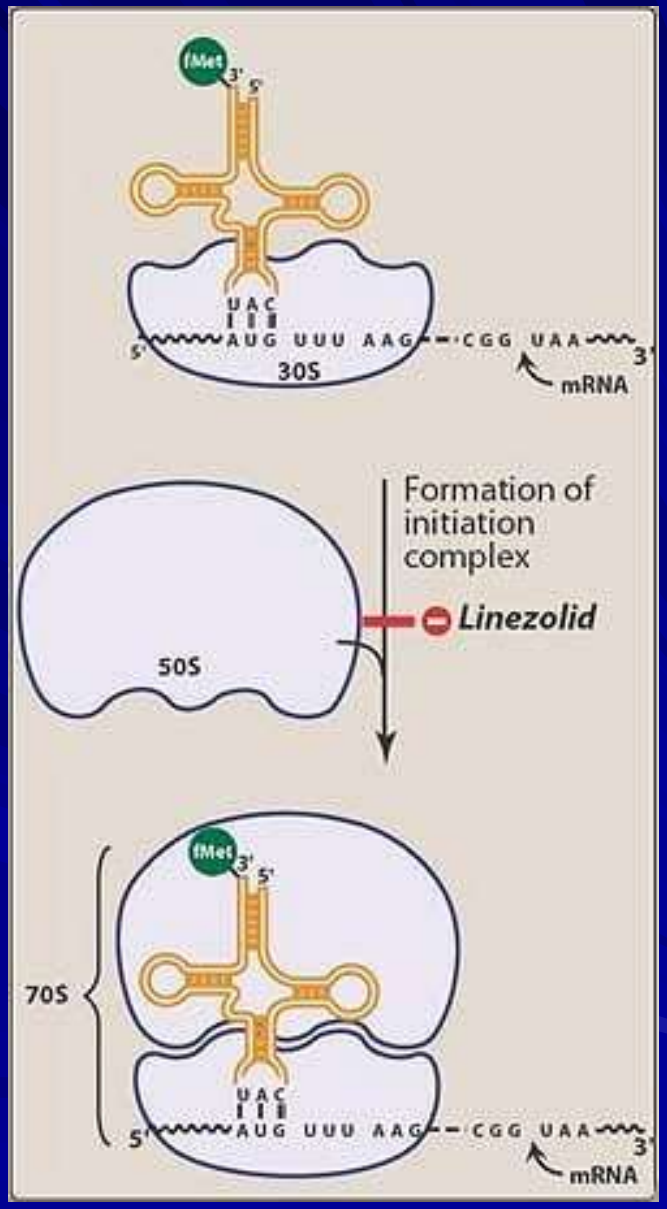
1. Pseudomembranous collites by C. difficile (potentially fatal), oral administration of Vancomycin should be reserved for a condition that does not respond to metronidazole.
2. Impaired liver function

Linezolid

- Bacteriostatic but it is cidal against the streptococci and Clostridium perfringens. Active primarily against gram-positive organisms (staphylococci, streptococci, and enterococci, as well as Corynebacterium species and Listeria monocytogenes
- Active against resistant gram-positive organisms (MRSA, VRSA, VRE and Listeria monocytogenes).
- Linezolid is completely absorbed on oral administration. An intravenous preparation is also available

Mechanism of Action of Linezolid

- Inhibits bacterial protein synthesis by inhibiting formation of 70S initiation complex.
- Binds to a site on the 50S subunit.



Mechanism of action of linezolid

Adverse Effects of Linezolid

1. Gastrointestinal upset, nausea and diarrhea,
2. Headaches and rash.
3. Thrombocytopenia 2 % of patients who were on the drug for longer than 2 weeks.
4. Linezolid inhibits monoamine oxidase activity, patients are cautioned not to consume large quantities of tyramine-containing foods.
5. Reversible enhancement of the pressor effects of pseudoephedrine