Protein synthesis inhibitors 2

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VI. FIDAXOMICIN

- *Fidaxomicin [fye-DAX-oh-MYE-sin] is a macrocyclic antibiotic with a* structure similar to the macrolides; however, it has a unique mechanism of action.

- *Fidaxomicin acts on the sigma subunit of RNA polymerase,* thereby disrupting bacterial transcription, terminating protein synthesis, and resulting in cell death in susceptible organisms.

- *Fidaxomicin* has a very narrow spectrum of activity limited to gram-positive aerobes and anaerobes.

- While it possesses activity against staphylococci and enterococci, it is used primarily for its bactericidal activity against Clostridium difficile.

- Due to the unique target site, cross-resistance with other antibiotic classes has not been documented.

- Following oral administration, *fidaxomicin has minimal systemic absorption and primarily* remains within the gastrointestinal tract.

- This is ideal for the treatment of C. difficile infection, which occurs in the gut.

- This characteristic also likely contributes to the low rate of adverse effects.

- The most common adverse effects include nausea, vomiting, and abdominal pain.
- Hypersensitivity reactions including angioedema, dyspnea, and pruritus have occurred.
- *Fidaxomicin should be used with caution* in patients with a macrolide allergy, as they may be at increased risk for hypersensitivity.
- Anemia and neutropenia have been observed infrequently.

VII. CHLORAMPHENICOL

- The use of *chloramphenicol [klor-am-FEN-i-kole], a broad-spectrum antibiotic,* is restricted to life-threatening infections for which no alternatives exist.

- **A. Mechanism of action**
- *Chloramphenicol binds reversibly to the bacterial 50S ribosomal subunit* and inhibits protein synthesis at the peptidyl transferase reaction.

- Due to some similarity of mammalian mitochondrial ribosomes to those of bacteria, protein and ATP synthesis in these organelles may be inhibited at high circulating *chloramphenicol levels,* producing bone marrow toxicity.

- [Note: The oral formulation of *chloramphenicol* was removed from the US market due to this toxicity.]

- **B. Antibacterial spectrum**
- *Chloramphenicol is active against many types of microorganisms* including
  - chlamydiae,
  - rickettsiae,
  - spirochetes, and
  - anaerobes.

- The drug is primarily bacteriostatic, but depending on the dose and organism, it may be bactericidal.

- **C. Resistance**
- 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.

D. Pharmacokinetics

- *Chloramphenicol is administered intravenously and is widely distributed* throughout the body.
- It reaches therapeutic concentrations in the CSF.
- *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.
- It is also secreted into breast milk and should be avoided in breastfeeding mothers.

E. Adverse effects

- **1. Anemias:**
- Patients may experience
  - dose-related anemia,
  - hemolytic anemia (seen 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.]

- **2. Gray baby syndrome:**
- Neonates have a low capacity to glucuronidate 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 (hence the term “gray baby”), and death.

- Adults who have received very high doses of the drug can also exhibit this toxicity.

- **3. Drug interactions:**
- *Chloramphenicol* inhibits some of the hepatic mixed-function oxidases and, thus, blocks the metabolism of drugs such as *warfarin* and *phenytoin,* thereby elevating their concentrations and potentiating their effects.

VIII. CLINDAMYCIN

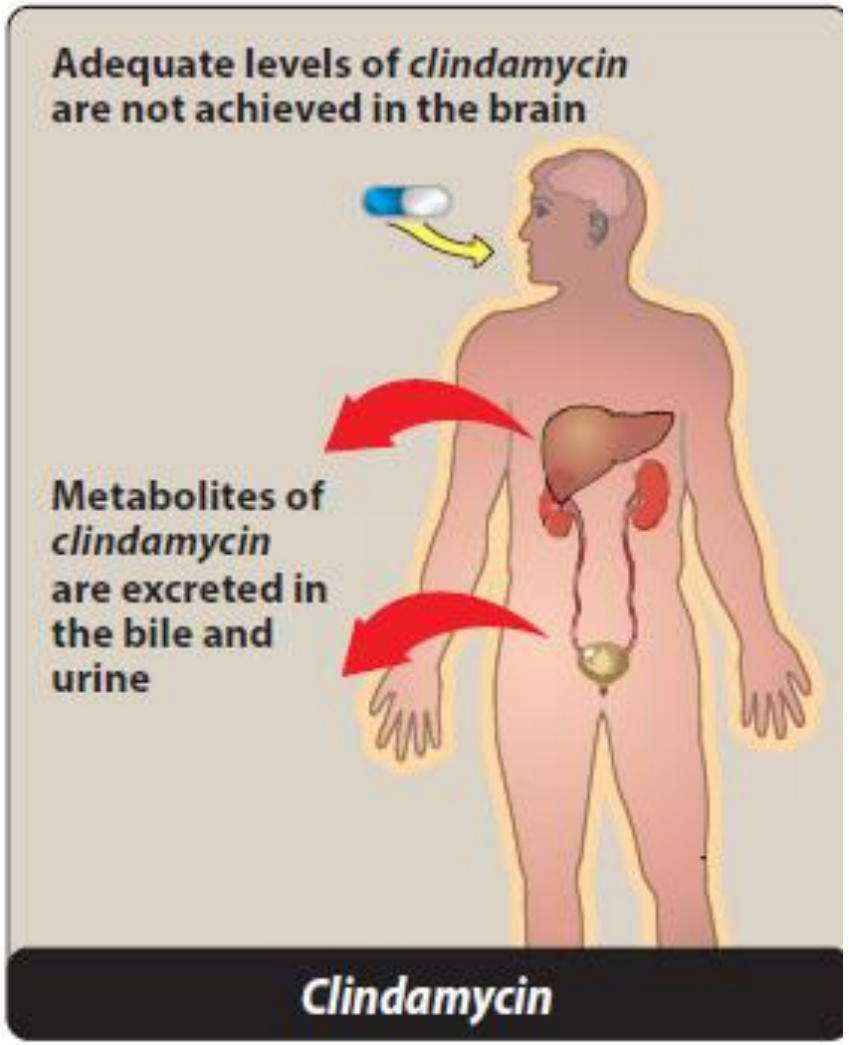
- *Clindamycin* [klin-da-MYE-sin] has a mechanism of action that is the same as that of *erythromycin.*

- *Clindamycin* is used primarily in the treatment of infections caused by gram-positive organisms, including MRSA and streptococcus, and anaerobic bacteria.

- Resistance mechanisms are the same as those for *erythromycin,* and cross-resistance has been described.

- C. difficile is always resistant to *clindamycin*, and the utility of *clindamycin* for gram-negative anaerobes (for example, Bacteroides *sp.*) is decreasing due to increasing resistance.

- *Clindamycin* is available in both IV and oral formulations, but use of the oral form is limited by gastrointestinal intolerance.
- It distributes well into all body fluids including bone, but exhibits poor entry into the CSF.
- *Clindamycin* undergoes extensive oxidative metabolism to inactive products and is primarily excreted into the bile.
- Low urinary elimination limits its clinical utility for urinary tract infections.
- Accumulation has been reported in patients with either severe renal impairment or hepatic failure.


Adequate levels of *clindamycin* are not achieved in the brain
Metabolites of *clindamycin* are excreted in the bile and urine
Clindamycin

- In addition to skin rashes, the most common adverse effect is diarrhea, which may represent a serious pseudomembranous colitis caused by overgrowth of C. difficile.

- Oral administration of either *metronidazole* or *vancomycin* is usually effective in the treatment of C. difficile.

IX. QUINUPRISTIN/DALFOPRISTIN

- *Quinupristin/dalfopristin* [KWIN-yoo-pris-tin/DAL-foh-pris-tin] is a mixture of two streptogramins in a ratio of 30 to 70, respectively.

- Due to significant adverse effects, the drug is normally reserved for the treatment of severe *vancomycin*-resistant Enterococcus faecium (VRE) in the absence of other therapeutic options.

A. Mechanism of action

- Each component of this combination drug binds to a separate site on the 50S bacterial ribosome.
- *Dalfopristin* disrupts elongation by interfering with the addition of new amino acids to the peptide chain.
- *Quinupristin* prevents elongation similar to the macrolides and causes release of incomplete peptide chains.
- Thus, they synergistically interrupt protein synthesis.
- The combination drug is bactericidal and has a long PAE.

B. Antibacterial spectrum

- The combination drug is active primarily against gram-positive cocci, including those resistant to other antibiotics.
- Its primary use is in the treatment of E. faecium infections, including VRE strains, for which it is bacteriostatic.
- The drug is not effective against E. faecalis.

C. Resistance

- Enzymatic processes commonly account for resistance to these agents.
- For example, the presence of a ribosomal enzyme that methylates the target bacterial 23S ribosomal RNA site can interfere in *quinupristin* binding.
- In some cases, the enzymatic modification can change the action from bactericidal to bacteriostatic.
- Plasmid-associated acetyltransferase inactivates *dalfopristin.*
- An active efflux pump can also decrease levels of the antibiotics in bacteria.

D. Pharmacokinetics

- *Quinupristin/dalfopristin* is injected intravenously (the drug is incompatible with a saline medium).
- The combination drug is particularly useful for intracellular organisms (for example, VRE) due to its excellent penetration of macrophages and neutrophils.
- Levels in the CSF are low.
- Both compounds undergo hepatic metabolism, with excretion mainly in the feces.

E. Adverse effects

- Venous irritation commonly occurs when *quinupristin/dalfopristin* is administered through a peripheral rather than a central line.
- Hyperbilirubinemia occurs in about 25% of patients, resulting from a competition with the antibiotic for excretion.
- Arthralgia and myalgia have been reported when higher doses are used.
- *Quinupristin/ dalfopristin* inhibits the cytochrome P450 (CYP3A4) isoenzyme, and concomitant administration with drugs that are metabolized by this pathway may lead to toxicities.

X. LINEZOLID

- *Linezolid* [lih-NEH-zo-lid] is a synthetic oxazolidinone developed to combat resistant gram-positive organisms, such as *methicillin*-resistant Staphylococcus aureus, VRE, and *penicillin*-resistant streptococci.

- **A. Mechanism of action**
- *Linezolid* binds to the bacterial 23S ribosomal RNA of the 50S subunit, thereby inhibiting the formation of the 70S initiation complex

B. Antibacterial spectrum

- The antibacterial action of *linezolid* is directed primarily against gram positive organisms, such as staphylococci, streptococci, and enterococci, as well as *Corynebacterium* species and Listeria monocytogenes.
- It is also moderately active against Mycobacterium tuberculosis and may be used against drug-resistant strains.
- However, its main clinical use is against drug-resistant gram-positive organisms.
- Like other agents that interfere with bacterial protein synthesis, *linezolid* is bacteriostatic. However, it is bactericidal against streptococci.
- *Linezolid* is an alternative to *daptomycin* for infections caused by VRE.
- Use of *linezolid* for the treatment of MRSA bacteremia is not recommended. (because it is bacteriostatic)

- **C. Resistance**
- 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.

- **D. Pharmacokinetics**
- *Linezolid* is completely absorbed after oral administration.
- An IV preparation is also available.
- The drug is widely distributed throughout the body.
- The drug is excreted both by renal and nonrenal routes.
- No dose adjustments are required for renal or hepatic dysfunction.

E. Adverse effects

- The most common adverse effects are gastrointestinal upset, nausea, diarrhea, headache, and rash.
- Thrombocytopenia has been reported, mainly in patients taking the drug for longer than 10 days.
- *Linezolid* possesses nonselective monoamine oxidase activity (??)and may lead to serotonin syndrome if given concomitantly with large quantities of
  - tyramine-containing foods,
  - selective serotonin reuptake inhibitors, or
  - monoamine oxidase inhibitors.
- The condition is reversible when the drug is discontinued.
- Irreversible peripheral neuropathies and optic neuritis (causing blindness) have been associated with greater than 28 days of use, limiting utility for extended-duration treatments.