

# Protein synthesis inhibitors 2

Phar 538 Dr. Abdullah Rabba Ref. textbook: Lippincott's  
Illustrated Reviews: Pharmacology

# 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.



Source: Usatine RP, Smith MA, Mayeaux EJ, Chumley HJ. The Color Atlas of Family Medicine, Second Edition: www.accessmedicine.com  
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- 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.

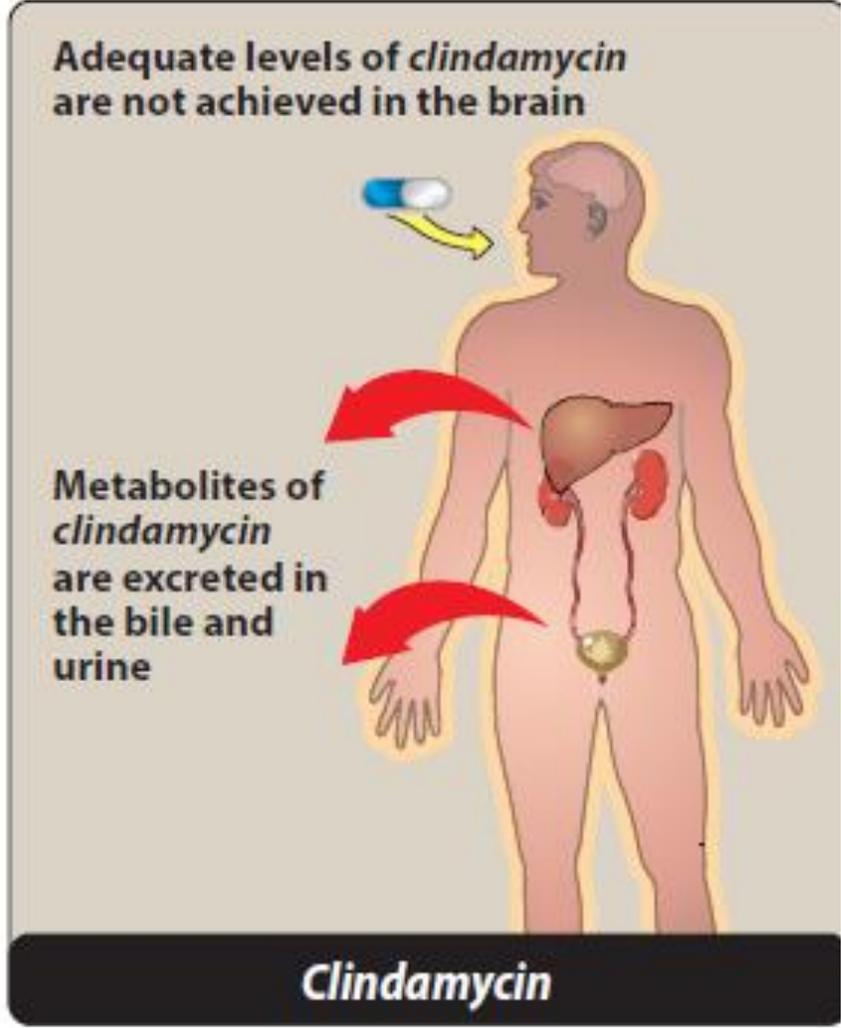
- **3. Drug interactions:**

- *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**.



- 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.