College of Dentist Medicine
3rd year stage, pharmacology lecture.

Protein Synthesis Inhibitors

- A number of antibiotics exert their antimicrobial effects by targeting the bacterial ribosome.
- In general, the bacterial ribosome is smaller (70S) than the mammalian ribosome (80S) and is composed of 50S and 30S subunits (as compared to 60S and 40S subunits).

Tetracyclines

- The tetracyclines are a group of closely related compounds .
- They consist of four fused rings with a system of conjugated double bonds.

Mechanism of action

- Entry of these agents into susceptible organisms is mediated both by 1- passive diffusion and by 2- an energy-dependent transport protein mechanism unique to the bacterial inner cytoplasmic membrane.
- Non-resistant strains concentrate the tetracyclines intracellularly.
- The drug binds reversibly to the 30S subunit of the bacterial ribosome.

Antibacterial spectrum

As broad-spectrum, bacteriostatic antibiotics, the tetracyclines are effective against gram-positive and gram-negative bacteria as well as against organisms other than bacteria.

Resistance

- Widespread resistance to the tetracyclines limits their clinical use. **1-** inability of the organism to accumulate the drug, thus producing resistance. **2-** Other less important mechanisms of bacterial resistance to tetracyclines include enzymatic inactivation of the drug.

Pharmacokinetics

- Absorption: All tetracyclines are adequately but incompletely absorbed after oral ingestion .
- However, taking these drugs concomitantly with dairy foods in the diet decreases absorption due to the formation of non-absorbable chelates of the tetracyclines with calcium ions.
- Non-absorbable chelates are also found in magnesium and aluminum antacids and in iron preparations).

- Distribution: The tetracyclines concentrate in the liver, kidney, spleen, and skin, and they bind to tissues undergoing calcification (for example, teeth and bones).
- Penetration into most body fluids is adequate.
- **All tetracyclines cross the placental barrier and concentrate in fetal bones and dentition.**

- Doxycycline can be employed for treating infections in renally failure patients, because it is preferentially excreted via the bile into the feces. **[Note: Tetracyclines are also excreted in breast milk.]**

Adverse effects

Gastric discomfort: gastric distress commonly results from irritation of the gastric mucosa and is often responsible for non-compliance in patients treated with these drugs.

Effects on calcified tissues: Deposition in the bone and primary dentition occurs during calcification in growing children. This causes discoloration and hypoplasia of the teeth and a temporary stunting of growth.

Fatal hepatotoxicity: This side effect has been known to occur in pregnant women who received high doses of tetracyclines.

Superinfections: 1- Overgrowths of Candida (for example, in the vagina) or of resistant staphylococci (in the intestine) may occur. 2- Pseudomembranous colitis due to an overgrowth of Clostridium difficile has also been reported.

Contraindications:1- Renally impaired patients should not be treated with any of the tetracyclines except doxycycline.2- The tetracyclines should not be employed in pregnant or breast-feeding women or in children less than 8 years of age.

Aminoglycosides

- Aminoglycoside antibiotics had been the mainstays for treatment of serious infections due to aerobic gram-negative bacilli.

- All members of this family are believed to inhibit bacterial protein synthesis.

Mechanism of action

- Susceptible gram-negative organisms allow aminoglycosides to diffuse through porin channels in their outer membranes.

- These organisms also have an oxygen-dependent system that transports the drug across the cytoplasmic membrane.
- The antibiotic then binds to the 30S ribosomal subunit .

Antibacterial spectrum

- The aminoglycosides are effective in the empirical treatment of infections suspected of being due to aerobic gram-negative bacilli, including Pseudomonas aeruginosa.
- To achieve an additive or synergistic effect, aminoglycosides are often combined with a β-lactam antibiotic.
- All aminoglycosides are bactericidal.

Resistance

Resistance can be caused by **1)** decreased uptake of drug when the oxygen-dependent transport system for aminoglycosides or porin channels are absent and **2)** plasmid-associated synthesis of enzymes.

Pharmacokinetics

Administration: 1- The highly polar, structure of the aminoglycosides prevents adequate absorption after oral administration . Therefore, all aminoglycosides (except neomycin must be given parenterally to achieve adequate serum levels.
2- [Note: The severe nephrotoxicity associated with neomycin precludes parenteral administration, and its current use is limited to topical application for skin infections or oral administration to prepare the bowel prior to surgery.]

Distribution: All aminoglycosides cross the placental barrier and may accumulate in fetal plasma.

Adverse effects

Ot**otoxicity**: Deafness may be irreversible and has been known to affect fetuses in utero.

Nephrotoxicity: Acute tubular necrosis, which can be irreversible.

Allergic reactions: Contact dermatitis is a common reaction to topically applied neomycin.

<u>Macrolides</u>

- The macrolides are a group of antibiotics .
- **Erythromycin** was the first of these drugs to find clinical application, both as a drug of first choice and as an alternative to penicillin in individuals who are allergic to β-lactam antibiotics.
- The newer members of this family, **clarithromycin** and **azithromycin** ,

Mechanism of action
The macrolides bind irreversibly to a site on the 50S subunit of the bacterial ribosome, thus inhibiting the steps of protein synthesis.

Antibacterial spectrum
Erythromycin: This drug is effective against many of the same organisms as penicillin G, therefore, it is used in patients who are allergic to the penicillins.

Clarithromycin: This antibiotic has a spectrum of antibacterial activity similar to that of erythromycin, but it is also effective against Haemophilus influenzae. Its activity against intracellular pathogens, such as Chlamydia, Legionella, Moraxella, and Helicobacter pylori, is higher than that of erythromycin.

Azithromycin: It is far more active against respiratory infections due to H. influenzae and Moraxella catarrhalis. Azithromycin is now the preferred therapy for urethritis caused by Chlamydia trachomatis.

Telithromycin: This drug has an antibacterial spectrum similar to that of azithromycin.

Resistance
1) the inability of the organism to take up the antibiotic or the presence of an efflux pump **2)** a decreased affinity of the 50S ribosomal subunit for the antibiotic.

Chloramphenicol

Chloramphenicol is active against a wide range of gram-positive and gram-negative organisms. However, because of its toxicity, its use is restricted to life-threatening infections for which no alternatives exist.

Mechanism of action
The drug binds to the bacterial 50S ribosomal subunit and inhibits protein synthesis.

Antimicrobial spectrum
- Chloramphenicol, a broad-spectrum antibiotic, is active not only against bacteria but also against other microorganisms, such as rickettsiae.
- Chloramphenicol has excellent activity against anaerobes.
- The drug is either bactericidal or (more commonly) bacteriostatic, depending on the organism.

Pharmacokinetics
- Chloramphenicol may be administered either intravenously or orally.
- It is completely absorbed via the oral route because of its lipophilic nature.

- It readily enters the normal CSF.
- Chloramphenicol is also secreted into breast milk.

Adverse effects

The clinical use of chloramphenicol is limited to life-threatening infections because of the serious adverse effects associated with its administration. In addition to gastrointestinal upsets, overgrowth of Candida albicans may appear on mucous membranes.

LINCOSAMIDES

Clindamycin and lincomycin

- Clindamycin has a mechanism of action that is the same as that of erythromycin.
- Clindamycin is employed primarily in the treatment of infections caused by anaerobic bacteria, such as Bacteroides fragilis, which often causes abdominal infections associated with trauma.
- It is also significantly active against, gram-positive cocci.
- Clindamycin is well absorbed by the oral route.
- It distributes well into all body fluids except the CSF.
- Penetration into bone occurs even in the absence of inflammation.
- The most serious adverse effect is potentially fatal pseudomembranous colitis caused by overgrowth of C. difficile, which elaborates necrotizing toxins.
- Oral administration of either metronidazole or vancomycin is usually effective in controlling this serious problem.

Oxazolidinones

- are mainly used as antimicrobials. The antibacterial effect of oxazolidinones is by working as protein synthesis inhibitors, targeting an early step involving the binding of N-formylmethionyl-tRNA to the ribosome.
- Some of the most important oxazolidinones are the last generation of antibiotics used against gram-positive pathogens.
- These antibiotics are considered as a choice of last resort where every other antibiotic therapy has failed.
- Examples of antibiotic oxazolidinones include:
- Linezolid , which is available for intravenous administration and also has the advantage of having excellent oralbioavailability.
- Posizolid, which appears to have excellent, targeted bactericidal activity against all common gram-positive bacteria, regardless of resistance to other classes of antibiotics.

- Tedizolid, which is approved for acute skin infections
- Cycloserine is a second line drug against tuberculosis

Streptogramins

- Are a class of antibiotics. Streptogramins are effective in the treatment of vancomycin-resistant Staphylococcus aureus (VRSA) and vancomycin-resistant Enterococcus (VRE), two of the most rapidly growing strains of multidrug-resistant bacteria.
- They fall into two groups: streptogramin A and streptogramin B.

Members include:

- Quinupristin/dalfopristin
- Pristinamycin
- Virginiamycin