Protein Synthesis Inhibitors:

Protein synthesis inhibitors work by targeting bacterial ribosomes and inhibiting bacterial protein synthesis. Bacterial ribosomes differ structurally from mammalian cytoplasmic ribosomes and are composed of 30S and 50S subunits. Mammalian ribosomes have 40S and 60S subunits. Selectivity for bacterial ribosomes minimizes potential adverse consequences encountered with the disruption of protein synthesis in mammalian host cells.
High concentrations of drugs such as chloramphenicol or the tetracyclines may cause toxic effects as a result of interaction with mitochondrial mammalian ribosomes.

I. Aminoglycosides (*Streptomycin*, *Gentamicin*, *Tobramycin*, *Neomycin* & *Amikacin*)

Aminoglycosides are used for the treatment of serious infections due to aerobic gram-negative bacilli; however, their clinical utility is limited due to serious toxicities.
Aminoglycosides have concentration-dependent bactericidal activity. They also exhibit a post-antibiotic effect which is continued bacterial suppression after drug concentrations fall below the minimum inhibitory concentration. Aminoglycosides are derived from either Streptomyces sp. (have -mycin suffixes) or Micromonosporaend (end in -micin).
Once-daily dosing regimen—total daily dose is given as a single injection. It is preferred because it is as effective as multiple-dose regimen, safer than multiple-dose regimen & convenient.

Mechanism of action:
Aminoglycosides diffuse through porin channels in the outer membrane of susceptible organisms. These organisms also have an oxygen-dependent system that transports the drug across the cytoplasmic membrane. Inside the cell, they bind the 30S ribosomal subunit, where they interfere with assembly of the functional ribosomal apparatus and/or cause the 30S subunit of the completed ribosome to misread the genetic code.

Pharmacokinetics:
*The highly polar, polycationic structure of the aminoglycosides prevents adequate absorption after oral administration; therefore, all aminoglycosides) must be given parenterally to achieve adequate serum concentrations. [Note: Neomycin is not given parenterally due to severe nephrotoxicity. It is administered topically for skin infections or orally to decontaminate the gastrointestinal tract prior to colorectal surgery and in hepatic encephalopathy].
*Concentrations achieved in CSF are inadequate, even in the presence of inflamed meninges. For central nervous system infections, the intrathecal or intraventricular routes may be utilized. All aminoglycosides cross the placental barrier and may accumulate in fetal plasma and amniotic fluid.
*More than 90% of the parenteral aminoglycosides are excreted unchanged in the urine. Accumulation occurs in patients with renal dysfunction; thus, dose adjustments are required. Neomycin is primarily excreted unchanged in the feces.

Adverse effects:

1. Ototoxicity: Ototoxicity (vestibular and auditory) is directly related to high peak plasma concentrations and the duration of treatment. Aminoglycosides accumulate in the endolymph and perilymph of the inner ear. Deafness may be irreversible and has been known to affect developing fetuses. Vertigo (especially in patients receiving streptomycin) may also occur. The important risk factors for ototoxicity are:
   a. Elderly patients.
   b. Repeated courses of aminoglycosides.
   c. Patients with pre-existing auditory impairment.
   d. Concurrent use of other ototoxic drugs such as cisplatin, vancomycin, minocycline, loop diuretics, etc.
2. Nephrotoxicity: Retention of the aminoglycosides by the proximal tubular cells disrupts calcium-mediated transport processes. This results in kidney damage ranging from mild, reversible renal impairment to severe, potentially irreversible acute tubular necrosis.
3. Neuromuscular paralysis: This adverse effect is associated with a rapid increase in concentration (for example, high doses infused over a short period) or concurrent administration with neuromuscular blockers. Patients with myasthenia gravis are particularly at risk. Prompt administration of calcium gluconate or neostigmine can reverse the block that causes neuromuscular paralysis.
4. Allergic reactions: Contact dermatitis is a common reaction to topically applied neomycin.

Notes:

Streptomycin: streptomycin is one of the first-line drugs for tuberculosis and is used in combination with other antitubercular drugs.

Gentamicin: It is available for parenteral and topical administration. It is the most commonly used aminoglycoside antibiotic for severe aerobic gram-negative bacillary infections (Urinary tract infection with pyelonephritis, pneumonia, meningitis, osteomyelitis, septicaemia and infected burns.

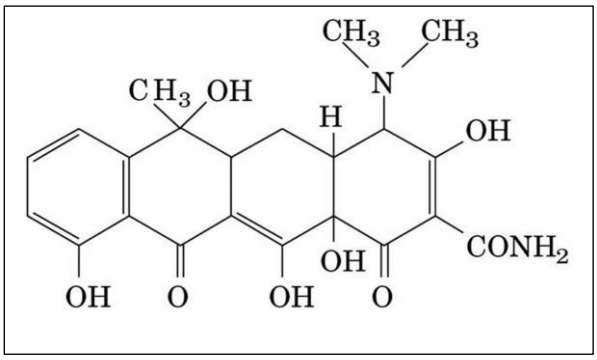
In dentistry gentamicin can be used in combination with amoxicillin/vancomycin for the prophylaxis of bacterial endocarditis in high-risk patients before dental or other surgical procedures. Combination broadens the spectrum of activity, produces synergistic effect and decreases emergence of resistance.

Gentamicin is used topically for gram-negative skin, eye and ear infections.

Amikacin: It has the broadest spectrum of activity among the aminoglycosides.

Tobramycin: is probably somewhat less nephrotoxic than gentamicin. It is superior to gentamicin against P. aeruginosa. Topical tobramycin eye drops are used to treat eye infections.

II. Tetracyclines: (*Demeclocycline*, *Doxycycline*, *Minocycline*,& *Tetracycline)*



Tetracyclines consist of four fused rings with a system of conjugated double bonds. Substitutions on these rings alter the individual pharmacokinetics and spectrum of antimicrobial activity. Tetracyclines are toxic to mitochondrial ribosomes in high concentrations.

The tetracyclines are bacteriostatic antibiotics.

Mechanism of action:

The drugs bind reversibly to the 30S subunit of the bacterial ribosome. This action prevents binding of tRNA to the mRNA–ribosome complex, thereby inhibiting bacterial protein synthesis.

Antibacterial spectrum:

The tetracyclines are bacteriostatic antibiotics effective against a wide variety of organisms, including gram-positive and gram-negative bacteria, protozoa, spirochetes, mycobacteria, and atypical species. They are commonly used in the treatment of acne and Chlamydia infections.

Uses:

1. Tetracycline is used in combination therapy with other drugs for treatment of peptic ulcer.
2. doxycycline is used in the treatment of Lyme disease, rocky mountain spotted fever, Mycoplasma pneumonia infections, chlamydial infections, anthrax, cholera, malaria in combination with other antimalarial agents, & in the treaement of brucellosis in combination with rifampin or gentamicin or streptomycin.
3. In dentistry: Tetracyclines are used as an adjuvant in chronic periodontitis refractory to other antibiotics. Doxycycline is useful for subgingival plaque as it:
   a. gets concentrated in gingival fluid.
   b. inhibits collagenase enzyme and prevents destruction of connective tissue in the gum.

Tetracyclines may be effective in the treatment of acute necrotizing gingivitis or periodontitis, either alone or in combination with metronidazole.

Pharmacokinetics:

*Tetracyclines are adequately absorbed after oral ingestion.

Administration with dairy products or other substances that contain divalent and trivalent cations (for example, magnesium, calcium and aluminum antacids, or iron supplements) decreases absorption, particularly for tetracycline due to the formation of nonabsorbable chelates . Both doxycycline and minocycline are available as oral and intravenous (IV) preparations.

*The tetracyclines concentrate well in the bile, liver, kidney, gingival fluid, and skin.

They bind to tissues undergoing calcification (for example, teeth and bones) or to tumors that have high calcium content. Penetration into most body fluids is adequate.

Only minocycline and doxycycline achieve therapeutic levels in the cerebrospinal fluid (CSF).

Minocycline also achieves high concentrations in saliva and tears, rendering it useful in eradicating the meningococcal carrier state.

All tetracyclines cross the placental barrier and concentrate in fetal bones and dentition.

* Tetracycline is primarily eliminated unchanged in the urine, whereas minocycline undergoes hepatic metabolism and is eliminated to a lesser extent via the kidney.
Doxycycline is preferred in patients with renal dysfunction, as it is primarily eliminated via the bile into the feces.

Adverse effects:
1. Gastric discomfort: Epigastric distress commonly results from irritation of the gastric mucosa and is often responsible for noncompliance with tetracyclines. Esophagitis may be minimized through coadministration with food (other than dairy products) or fluids and the use of capsules rather than tablets. [Note: Tetracycline should be taken on an empty stomach.]
2. Effects on calcified tissues: Deposition in the bone and primary dentition occurs during the calcification process in growing children. This may cause discoloration and hypoplasia of teeth and a temporary stunting of growth. For this reason, the use of tetracyclines is limited in pediatrics.
3. Hepatotoxicity: Rarely hepatotoxicity may occur with high doses, particularly in pregnant women and those with preexisting hepatic dysfunction or renal impairment.
4. Phototoxicity: Severe sunburn may occur in patients receiving a tetracycline who are exposed to sun or ultraviolet rays. This toxicity is encountered with any tetracycline, but more frequently with tetracycline and demeclocycline. Patients should be advised to wear adequate sun protection.
5. Vestibular dysfunction: Dizziness, vertigo, and tinnitus may occur particularly with minocycline, which concentrates in the endolymph of the ear and affects function.
6. Pseudotumor cerebri: Benign, intracranial hypertension characterized by headache and blurred vision may occur rarely in adults. Although discontinuation of the drug reverses this condition, it is not clear whether permanent sequelae may occur.

Contraindications:
The tetracyclines should not be used in pregnant or breast-feeding women or in children less than 8 years of age.
#Note: Use of outdated tetracyclines can cause renal damage.

III. Glycylcyclines: (*Tigecycline)*

Tigecycline exhibits bacteriostatic action by reversibly binding to the 30S ribosomal subunit and inhibiting bacterial protein synthesis.
Following IV infusion, tigecycline exhibits a large volume of distribution. It penetrates tissues well but achieves low plasma concentrations. Consequently, tigecycline is a poor option for bloodstream infections.
The primary route of elimination is biliary/fecal. No dosage adjustments are necessary for patients with renal impairment; however, a dose reduction is recommended in severe hepatic dysfunction.
It is indicated for the treatment of complicated skin and soft tissue infections, complicated intra-abdominal infections, and community-acquired pneumonia.

Adverse effects:
Tigecycline is associated with significant nausea and vomiting. Acute pancreatitis, including fatality, has been reported with therapy. Elevations in liver enzymes and serum creatinine may also occur. All-cause mortality in patients treated with tigecycline is higher than with other agents.
A boxed warning states that tigecycline should be reserved for use in situations when alternative treatments are not suitable.
Other adverse effects are similar to those of the tetracyclines and include photosensitivity, pseudotumor cerebri, discoloration of permanent teeth when used during tooth development, and fetal harm when administered in pregnancy.
Tigecycline may decrease the clearance of warfarin. Therefore, the international normalized ratio should be monitored closely when tigecycline is coadministered with warfarin.

IV. Macrolides and Ketolides: (Erythromycin, Clarithromycin, Azithromycin & Telithromycin)

Macrolides have a many-membered lactone ring with attached sugars.
Erythromycin was obtained from Streptomyces erythreus. Erythromycin was the first of these drugs to have clinical application, both as a drug of first choice and as an alternative to penicillin in individuals with an allergy to β-lactam antibiotics.
Clarithromycin (a methylated form of erythromycin) and azithromycin (having a larger lactone ring) have some features in common with, and others that improve upon, erythromycin.
Telithromycin, a semisynthetic derivative of erythromycin, is a "ketolide" antimicrobial agent.

Mechanism of action:
Erythromycin and other macrolides bind to bacterial 50S ribosomal subunit and inhibit protein synthesis. They are bacteriostatic but at high concentrations, they can act as bactericidal agents.
They are more active in alkaline pH.

Antibacterial spectrum:
1. Erythromycin: This drug is effective against many of the same organisms as penicillin G therefore, it may be considered as an alternative in patients with penicillin allergy.
2. Clarithromycin: Clarithromycin has activity similar to erythromycin, but it is also effective against Haemophilus influenzae and has greater activity against intracellular pathogens such as Chlamydia, Legionella, Moraxella, Ureaplasma species, and Helicobacter pylori.
3. Azithromycin: Although less active than erythromycin against streptococci and staphylococci, azithromycin is far more active against respiratory pathogens such as H. influenzae and Moraxella catarrhalis. Extensive use of azithromycin has resulted in growing Streptococcus pneumoniae resistance.
4. Telithromycin: Telithromycin has an antimicrobial spectrum similar to that of azithromycin. Moreover, the structural modification within ketolides neutralizes the most common resistance mechanisms that render macrolides ineffective.

Pharmacokinetics:

Erythromycin is destroyed by gastric acid (acid labile), hence, must be administered as Enteric-coated tablets to protect it from gastric acid. Clarithromycin, azithromycin, and telithromycin are stable in stomach acid and are readily absorbed. Food interferes with the absorption of erythromycin and azithromycin but can increase that of clarithromycin. Telithromycin is administered orally without regard to meals. Erythromycin and azithromycin are available in IV formulations.

Erythromycin and telithromycin undergo hepatic metabolism. They inhibit the oxidation of a number of drugs through their interaction with the cytochrome P450 system. Interference with the metabolism of drugs such as theophylline, statins, and numerous antiepileptics has been reported for clarithromycin.

Azithromycin is primarily concentrated and excreted in the bile as active drug. Erythromycin and its metabolites are also excreted in the bile. Partial reabsorption occurs through the enterohepatic circulation. In contrast, clarithromycin is hepatically metabolized, and the active drug and its metabolites are mainly excreted in the urine. The dosage of this drug should be adjusted in patients with renal impairment.

Adverse effects:

1. Gastric distress and motility: Gastrointestinal upset is the most common adverse effect of the macrolides and may lead to poor patient compliance (especially with erythromycin). The other macrolides seem to be better tolerated. Higher doses of erythromycin lead to smooth muscle contractions that result in the movement of gastric contents to the duodenum, an adverse effect sometimes employed for the treatment of gastroparesis or postoperative ileus.
2. Cholestatic jaundice.
3. Ototoxicity: Transient deafness has been associated with erythromycin, especially at high dosages. Azithromycin has also been associated with irreversible sensorineural hearing loss.
4. QTc prolongation: Macrolides and ketolides may prolong the QTc interval and should be used with caution in those patients with proarrhythmic conditions or concomitant use of proarrhythmic agents.
5. Contraindications

Patients with hepatic dysfunction should be treated cautiously with erythromycin, telithromycin, or azithromycin, because these drugs accumulate in the liver. Severe hepatotoxicity with telithromycin has limited its use, given the availability of alternative therapies.

6. Drug Interactions

Erythromycin, telithromycin, and clarithromycin inhibit the hepatic metabolism of a number of drugs, which can lead to toxic accumulation of these compounds. An interaction with digoxin may occur. One theory to explain this interaction is that the antibiotic eliminates a species of intestinal flora that ordinarily inactivates digoxin, leading to greater reabsorption of digoxin from the enterohepatic circulation.