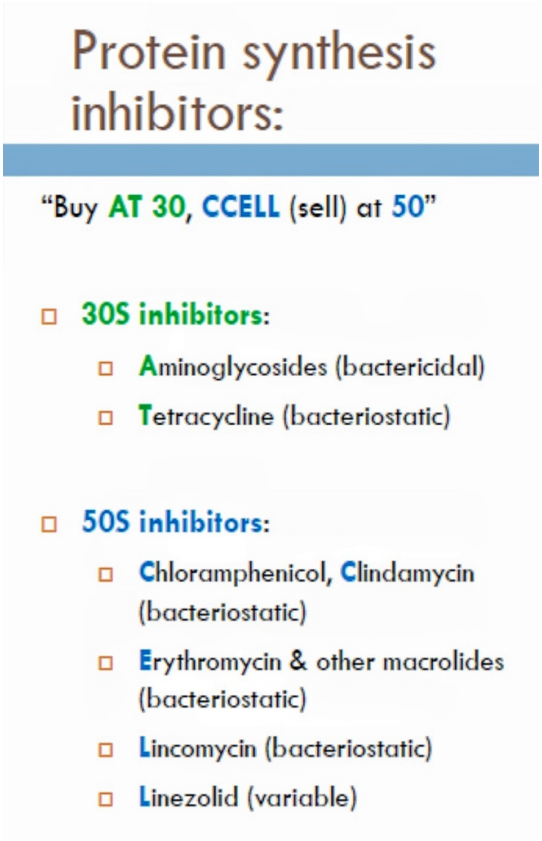
Protein Synthesis Inhibitors

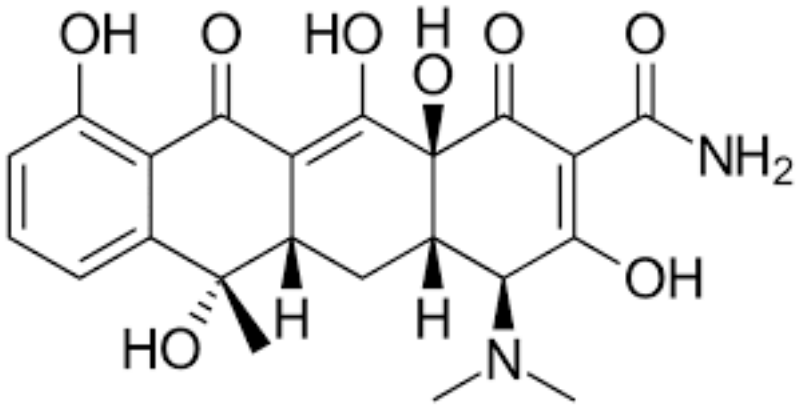
Overview

- A number of antibiotics exert their antimicrobial effects 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).
- In general, selectivity for bacterial ribosomes minimizes potential adverse consequences encountered with the disruption of protein synthesis in mammalian host cells.
- However, high concentrations of drugs such as chloramphenicol or the tetracyclines may cause toxic effects because of interaction with mitochondrial mammalian ribosomes, since the structure of mitochondrial ribosomes more closely resembles bacterial ribosomes.



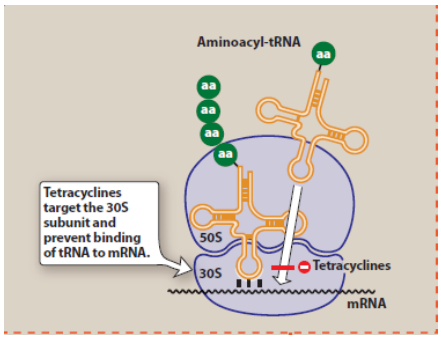
Tetracyclines

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.



Tetracycline structure

A. Mechanism of Action



- Tetracyclines enter susceptible organisms via **passive diffusion** and also by an **energy-dependent transport protein mechanism** unique to the bacterial inner cytoplasmic membrane.
- Tetracyclines concentrate intracellularly in susceptible organisms. 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.

B. Antibacterial spectrum

The tetracyclines **<u>are bacteriostatic antibiotics</u>** effective against a wide variety of organisms, including gram-positive and gram-negative bacteria, protozoa, spirochetes, mycobacteria, and atypical species.

C. Resistance

- The most commonly encountered naturally occurring resistance to tetracyclines is an efflux pump that expels drug out of the cell, thus preventing intracellular accumulation.
- Other mechanisms of bacterial resistance to tetracyclines include enzymatic inactivation of the drug and production of bacterial proteins that prevent tetracyclines from binding to the ribosome. **Resistance to one tetracycline does not confer universal resistance to all tetracyclines.**

D. Pharmacokinetics

Absorption: Administration with dairy products or other substances that contain divalent and trivalent cations (for example, magnesium and aluminum antacids or iron supplements) decreases absorption, particularly for *tetracycline*, due to the formation of nonabsorbable chelates.

E. 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 co-administration 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. 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.* 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. Doxycycline may also cause vestibular dysfunction.

6. Pseudotumor cerebri: Benign, intracranial hypertension characterized by headache and blurred vision may occur rarely in adults. Although

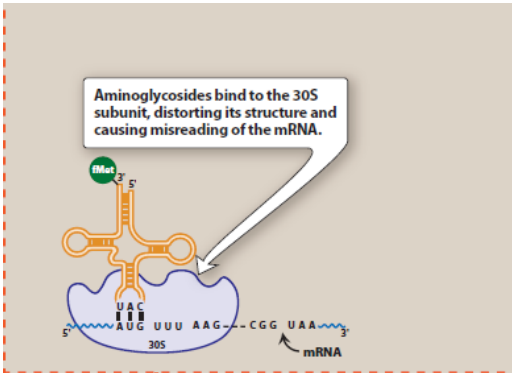
discontinuation of the drug reverses this condition, it is not clear whether permanent sequelae may occur.

7. Contraindications: The tetracyclines **should not be** used in pregnant or breast-feeding women or in children less than 8 years of age.

Aminoglycosides

- Aminoglycosides are used for the treatment of serious infections due to aerobic gram-negative bacilli. However, their clinical utility is limited by **serious toxicities**.
- The term "aminoglycoside" stems from their structure two amino sugars joined by a glycosidic linkage to a central hexose nucleus.
- Aminoglycosides are derived from either Streptomyces sp. (have *–mycin* suffixes) or Micromonospora sp. (end in *-micin*).

A. 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.
- **Antibiotics that disrupt protein synthesis are generally bacteriostatic; however, aminoglycosides are unique in that they are bactericidal**.
- The bactericidal effect of aminoglycosides is ***concentration dependent***; that is, efficacy is dependent on the maximum concentration (Cmax) of drug above the minimum inhibitory concentration (MIC) of the organism.
- For aminoglycosides, the target Cmax is *eight to ten* times the MIC.
- They also exhibit a *postantibiotic effect (PAE),* which is continued bacterial suppression after drug levels fall below the MIC.
- The larger the dose, the longer the PAE. Because of these properties, extended interval dosing (a single large dose given once daily) is now more commonly

utilized than divided daily doses. This reduces the risk of nephrotoxicity and increases convenience.

B. Antibacterial spectrum

The aminoglycosides are effective for the majority of aerobic gram negative bacilli, including those that may be multidrug resistant, Additionally, aminoglycosides are often combined with a β-lactam antibiotic to employ a synergistic effect,

C. Resistance

Resistance to aminoglycosides occurs via:

1) Efflux pumps.

2) Decreased uptake.

3) Modification and inactivation by plasmid-associated synthesis of enzymes.

- Each of these enzymes has its own aminoglycoside specificity; therefore, cross-resistance cannot be presumed. [Note: *Amikacin* is less vulnerable to these enzymes than other antibiotics in this group.

E. Adverse effects

Therapeutic drug monitoring of *gentamicin*, *tobramycin*, and *amikacin* plasma levels is imperative to ensure adequacy of dosing and to minimize dose-related toxicities. The elderly are particularly susceptible to nephrotoxicity and ototoxicity.

1. Ototoxicity: Ototoxicity (vestibular and auditory) is directly related to high peak plasma levels and the duration of treatment. The antibiotic accumulates in the endolymph and perilymph of the inner ear. Deafness may be irreversible and has been known to affect developing fetuses. Patients simultaneously receiving concomitant ototoxic drugs, such as *cisplatin* or loop diuretics, are particularly at risk. Vertigo (especially in patients receiving *streptomycin*) may also occur.

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 concentrations (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

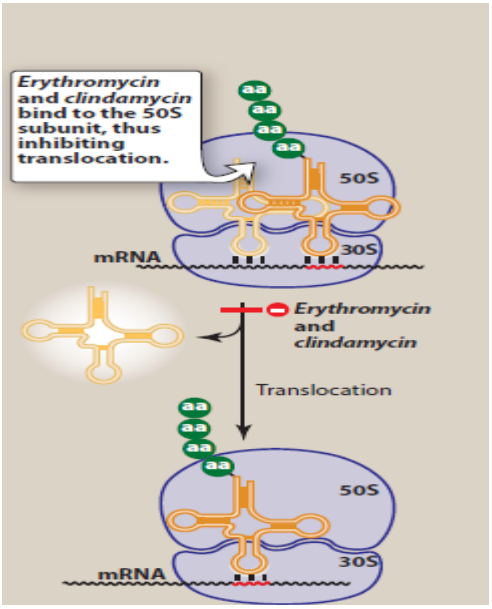
calcium gluconate or *neostigmine* can reverse the block that causes neuromuscular paralysis.

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

Macrolides and Ketolides

- The macrolides are a group of antibiotics with a macrocyclic lactone structure to which one or more deoxy sugars are attached.
- 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 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.
- Ketolides and macrolides have similar antimicrobial coverage. However, the ketolides are active against many macrolide-resistant gram-positive strains.

A. Mechanism of action



- The macrolides **bind irreversibly to a site on the 50S subunit of the bacterial ribosome**, thus inhibiting translocation steps of protein synthesis.
- They may also interfere with other steps, such as transpeptidation.
- Generally considered to be bacteriostatic, they may be bactericidal at higher doses.
- Their binding site is either identical to or in close proximity to that for *clindamycin* and *chloramphenicol.*

B. Antibacterial spectrum

1. Erythromycin: This drug is effective against many of the same organisms as *penicillin G* . Therefore, it may be used in patients with *penicillin* allergy.

2. Clarithromycin: *Clarithromycin* has activity similar to *erythromycin,* but it is also effective against Haemophilus influenzae. Its activity against intracellular pathogens, such as Helicobacter pylori, is higher than that of *erythromycin.*

3. Azithromycin: Although less active against streptococci and staphylococci than *erythromycin, azithromycin* is far more active against respiratory infections.

C. Resistance

Resistance to macrolides is associated with:

1) The inability of the organism to take up the antibiotic,

2) The presence of efflux pumps,

3) decreased affinity of the 50S ribosomal subunit for the antibiotic, resulting from the methylation of an adenine in the 23S bacterial ribosomal RNA in gram-positive organisms,

4) The presence of plasmid associated *erythromycin* esterases in gram-negative organisms such as Enterobacteriaceae.

- Resistance to *erythromycin* has been increasing, thereby limiting its clinical use (particularly for S. pneumoniae). Both *clarithromycin* and *azithromycin* share some cross-resistance with *erythromycin,*

E. Adverse effects

1. Gastric distress and motility: Gastric upset is the most common adverse effect of the macrolides and may lead to poor patient compliance (especially with *erythromycin*). *Clarithromycin* and *azithromycin* 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 *used therapeutically for the treatment of gastroparesis or postoperative ileus*.

2. Cholestatic jaundice: This side effect occurs especially with the estolate form (not used in the United States) of *erythromycin*; however, it has been reported with other formulations.

3. Ototoxicity: Transient deafness has been associated with *erythromycin,* especially at high dosages. *Azithromycin* has also been associated with irreversible sensorineural hearing loss.

4. Contraindications: Patients with hepatic dysfunction should be treated cautiously with *erythromycin,* or *azithromycin,* because these drugs accumulate in the liver. Additionally, 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.

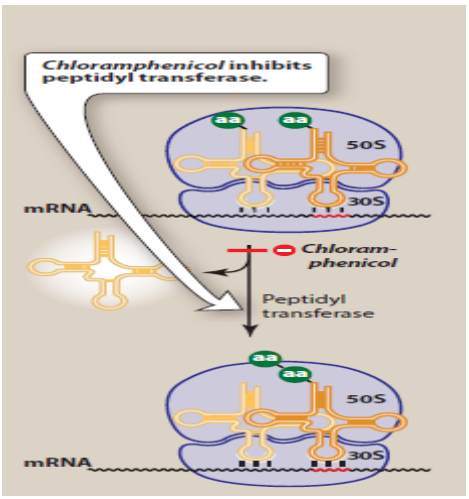
5. Drug interactions: *Erythromycin,* and *clarithromycin* inhibit the hepatic metabolism of a number of drugs, which can lead to toxic accumulation of these compounds. An interaction with *digoxin* may occur. In this case, the antibiotic eliminates a species of intestinal flora that ordinarily inactivates *digoxin*, thus leading to greater reabsorption of the drug from the enterohepatic circulation.

Chloramphenicol

The use of *chloramphenicol* , 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. 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.

E. Adverse effects

1. Anemia: 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.

CLINDAMYCIN

- *Clindamycin* 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.
- *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.