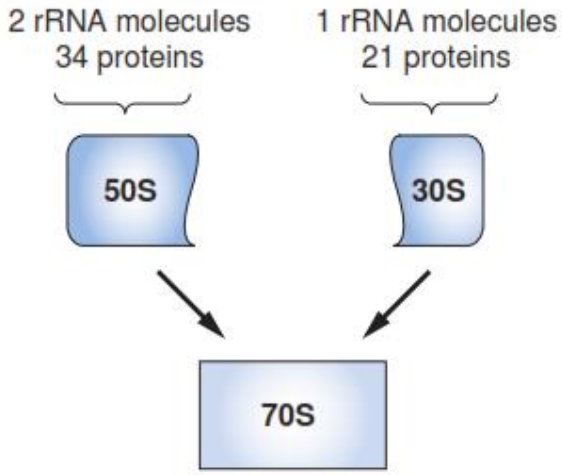
Protein Synthesis Inhibitors

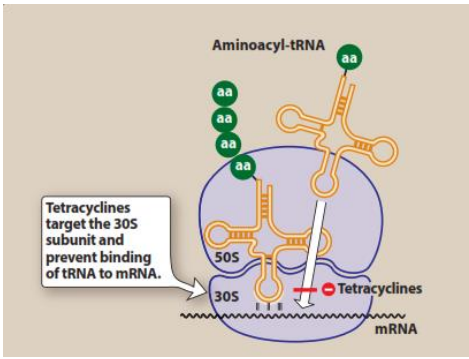
High concentrations of drugs such as chloramphenicol or the tetracyclines may cause toxic effects as a result of interaction with mitochondrial mammalian ribosomes, since the structure of mitochondrial ribosomes more closely resembles bacterial ribosomes.
Bacterial ribosomes differ structurally from mammalian cytoplasmic ribosomes and are composed of 30S and 50S subunits (mammalian ribosomes have 40S and 60S subunits).



TETRACYCLINES

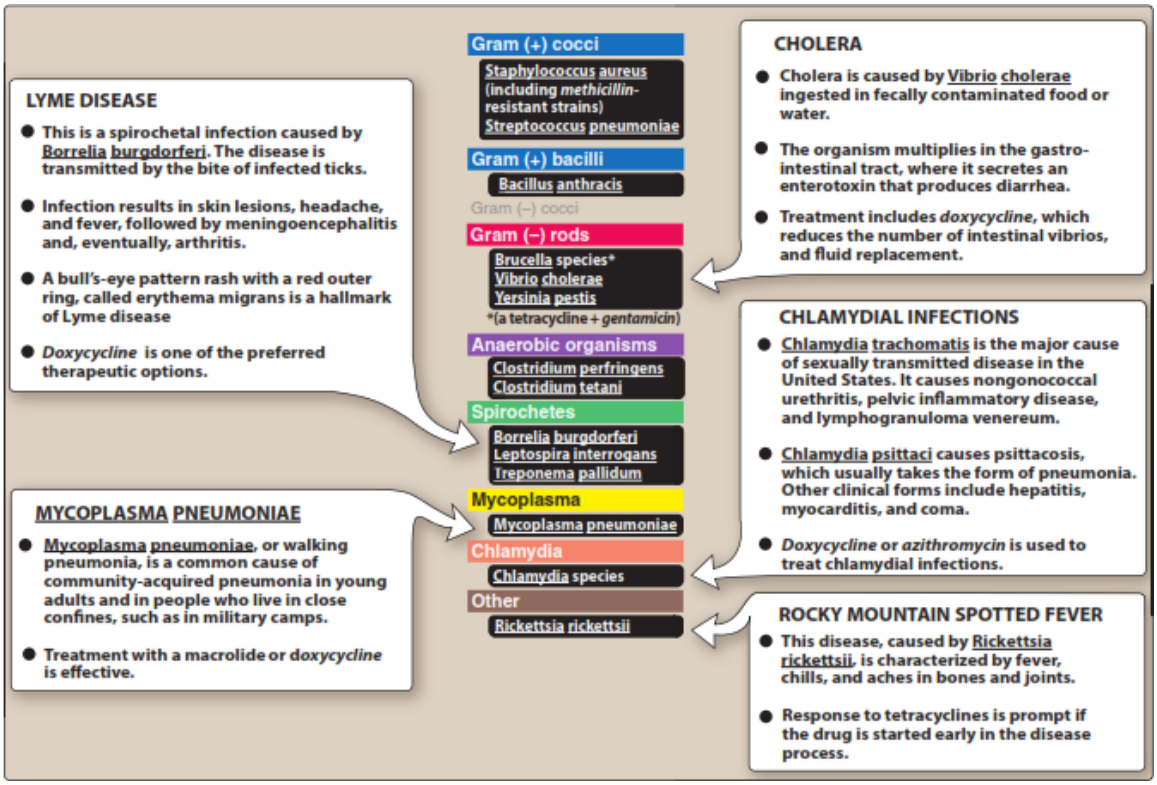
Mechanism of action

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 (doxycycline).



Indications

1. ***Clamydiae*** (e.g. psittacosis, trachoma, pelvic inflammatory diseases lymphogranuloma venereum)
2. ***Mycoplasma*** (pneumonia)
3. ***Rickettsia*** (Q fever, typhus)
4. ***Vibrio cholerae*** (cholera)
5. ***Haemophilus influenzae*** (e.g. bronchitis)
6. ***Brucella*** (brucellosis)

Resistance to Tetracycline

1. **Decreased intracellular accumulation** due to either impaired influx or increased efflux by an active transport protein pump

2. **Ribosome protection** due to production of proteins that interfere with tetracycline binding to the ribosome

3. **Enzyme inactivation of tetracycline**

Resistance to one tetracycline **does not confer universal resistance** to all tetracyclines.

Pharmacokinetics

Absorption

- Tetracyclines are adequately absorbed after oral ingestion.
- 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.
- Both **doxycycline** and **minocycline** are available as **oral** and intravenous (**IV**) preparations.

Distribution

- The tetracyclines concentrate well in the **bile**, **liver**, **kidney**, **gingival fluid**, and **skin**.
- Moreover, they bind to tissues undergoing calcification (for example, **teeth** and **bones**) or to **tumors** that have a **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 levels in **saliva** and tears, rendering it useful in eradicating the meningococcal carrier state.
- **<u>All tetracyclines cross the placental barrier and concentrate in fetal bones and dentition</u>**.

Elimination

- Tetracycline and doxycycline are not hepatically metabolized.
- **Tetracycline** is primarily eliminated unchanged in the **urine**, whereas **minocycline** undergoes **hepatic metabolism** and is eliminated to a lesser extent via the kidney.

Adverse effects

1. Gastric discomfort (Epigastric distress, Esophagitis) [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.)
3. Hepatotoxicity (occur with high doses, pregnant women preexisting hepatic dysfunction or renal impairment.)
4. Phototoxicity (exposure to sunlight results in darkening of skin)
5. Vestibular dysfunction. (Dizziness, vertigo, and tinnitus may occur particularly with minocycline and Doxycycline)
6. Pseudotumor cerebri (Benign, intracranial hypertension characterized by headache and blurred vision)
7. Contraindications (The tetracyclines **should not be used** in **pregnan**t or **breast-feeding** women or in **children less than 8 years** of age.)

Group	Agent	Lipid solubility	% of oral Dose absrption	Interaction with food on absorption	Major route of elimination	t½	
						Normal (hr)	Anuric (hr)
Short-acting	**Tetracycline** Oxytetracycline	**Low** Low	**75** 60	**↓** ↓	**Renal** Renal	**8** 9	**50-100** 50-65
Intermediate-acting	Demeclocycline	Moderate	65	↓	Renal	15	40-60
Long-acting	Doxycycline **Minocycline**	High **High**	90-100 **90-100**	(No change) **(No change)**	Hepatic **Hepatic**	12-22 **12-22**	12-22 **12-22**

Note: Tetracycline may achieve toxic levels in renal dysfunction, therefore, it is not suitable in such condition. Doxycycline does not accumulate in renal dysfunction, does not interact with food, and is given once or twice daily, while tetracycline should be given four times daily. These make doxycycline superior to tetracycline.

Caution: (When passing the date of expiry, particularly tetracycline, becomes nephrotoxic therefore should not be used).

GLYCYLCYCLINES

Tigecycline, a derivative of minocycline, is the first available member of the glycylcycline antimicrobial class. It is indicated for the treatment of complicated **skin** and **soft tissue infections**, as well as complicated **intra-abdominal infections**.

Mechanism of action

Tigecycline exhibits **bacteriostatic** action by reversibly binding to the **30S ribosomal** subunit and inhibiting protein synthesis.

Antibacterial spectrum

Tigecycline exhibits broad-spectrum activity that includes methicillin-resistant staphylococci (MRSA), multidrug-resistant streptococci, vancomycin-resistant enterococci (VRE), extended-spectrum β-lactamase–producing gram-negative bacteria, Acinetobacter baumannii, and many anaerobic organisms. However, tigecycline is not active against Morganella, Proteus, Providencia, or Pseudomonas species.

Resistance

Tigecycline was developed to overcome the recent emergence of tetracycline class–resistant organisms that utilize efflux pumps and ribosomal protection to confer resistance. However, resistance is seen and is primarily attributed to overexpression of efflux pumps.

Pharmacokinetics

- It penetrates tissues well but has **low plasma concentrations**. Consequently, tigecycline is a poor option for bloodstream infections.
- The primary route of elimination is **biliary/fecal**.

Adverse effects

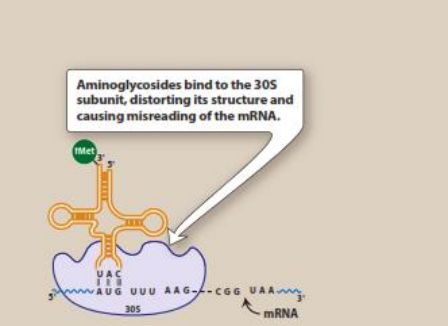
- ❖ nausea and vomiting.
- ❖ Acute pancreatitis.
- ❖ Elevations in liver enzymes and serum creatinine.
- ❖ Other adverse effects are similar to those of the tetracyclines
- ❖ Tigecycline may decrease the clearance of warfarin and increase prothrombin time.

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. Aminoglycosides are derived from either Streptomyces sp. (have-mycin suffixes) or Micromonospora sp. (end in -micin).

Mechanism of action

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**. Aminoglycosides are **unique** in that they are **bactericidal**. The bactericidal effect of aminoglycosides is concentration dependent. For aminoglycosides, the target C_{max} is **eight to ten** times the MIC.



postantibiotic effect (PAE)

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.

Antibacterial spectrum

The aminoglycosides are effective for the majority of aerobic gram-negative bacilli, including those that may be multidrug resistant, such as Pseudomonas aeruginosa, Klebsiella pneumoniae, and Enterobacter sp. Additionally, aminoglycosides are often combined with a β-lactam antibiotic to employ a synergistic effect, particularly in the treatment of Enterococcus faecalis and Enterococcus faecium infective endocarditis.

Resistance

1) efflux pumps,
2) decreased uptake, and/or
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**.

Amikacin is less vulnerable to these enzymes than other antibiotics in this group.

Pharmacokinetics

Absorption

Due to polarity, all aminoglycosides (except neomycin) must be given parenterally to achieve adequate serum levels. Neomycin is not given parenterally due to severe nephrotoxicity. It is administered topically for skin infections or orally for bowel preparation prior to colorectal surgery.

Distribution

Due to their hydrophilicity, tissue concentrations may be subtherapeutic, and penetration into most body fluids is variable. Concentrations in CSF are inadequate, even in the presence of inflamed meninges. For central nervous system infections, the intrathecal (IT) route may be utilized. All aminoglycosides cross the placental barrier and may accumulate in fetal plasma and amniotic fluid.

Elimination

More than 90% of the parenteral aminoglycosides are excreted unchanged in the urine. Accumulation occurs in patients with renal dysfunction, and dose adjustments are required.

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.

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.

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.

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.

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.

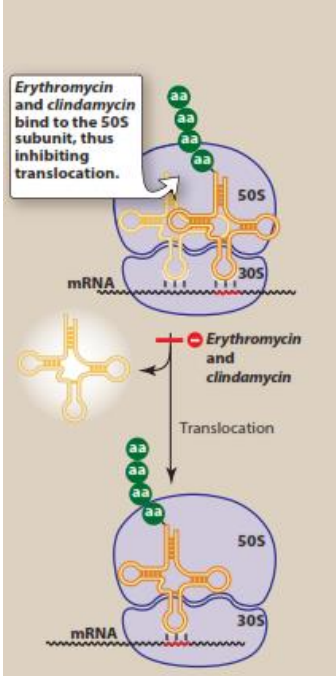
Clarithromycin (a methylated form of erythromycin) and **azithromycin** (having a larger lactone ring) have some features in common with, and others that improve upon, erythromycin.

Telithromycin, a semisynthetic derivative of erythromycin, is the first "**ketolide**" antimicrobial agent. Ketolides and macrolides have similar

antimicrobial coverage. However, the **ketolides** are **active against many macrolide-resistant gram-positive** strains.

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.



Antibacterial spectrum

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

Clarithromycin

- Clarithromycin has activity similar to erythromycin,
- it is also effective against Haemophilus influenzae.

- Its activity against intracellular pathogens, such as Chlamydia, Legionella, Moraxella, Ureaplasma species and Helicobacter pylori, is higher than that of erythromycin.

Azithromycin:

- less active against streptococci and staphylococci and more active against respiratory infections due to H. influenzae and Moraxella catarrhalis.
- Extensive use of azithromycin has resulted in growing Streptococcus pneumoniae resistance.
- preferred therapy for urethritis caused by Chlamydia trachomatis.
- Mycobacterium avium (clarithromycin or azithromycin).

Telithromycin:

- antimicrobial spectrum similar to that of azithromycin.
- Moreover, the structural modification within ketolides neutralizes the most common resistance mechanisms (methylase-mediated and efflux-mediated) that make macrolides ineffective.

Resistance

1) the inability of the organism to take up the antibiotic,
2) the presence of efflux pumps,
3) a 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, and
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 azithromycinn

share some cross resistance with erythromycin, but telithromycin may be effective against macrolide-resistant organisms.

Pharmacokinetics

Administration

The erythromycin base is destroyed by gastric acid. Thus, either enteric-coated tablets or esterified forms of the antibiotic are administered. All are adequately absorbed upon oral administration. 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.

Distribution

Erythromycin distributes well to all body fluids except the CSF. It is one of the few antibiotics that diffuses into prostatic fluid, and it also accumulates in macrophages. All four drugs concentrate in the liver. Clarithromycin, azithromycin, and telithromycin are widely distributed in the tissues. Azithromycin concentrates in neutrophils, macrophages, and fibroblasts, and serum levels are low. It has the longest half-life and the largest volume of distribution of the four drugs.

	Erythro-mycin	*Clarithro-mycin*	*Azithro-mycin*	*Telithro-mycin*
Oral absorption	**Yes**	**Yes**	**Yes**	**Yes**
Half-life (hours)	**2**	**3.5**	**>40**	**10**
Conversion to an active metabolite	**No**	**Yes**	**Yes**	**Yes**
Percent excretion in urine	**15**	**50**	**12**	**13**

Elimination

Erythromycin and telithromycin are extensively metabolized hepatically. 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.

Excretion

Erythromycin and azithromycin are primarily concentrated and excreted in the bile as active drugs. Partial reabsorption occurs through the enterohepatic circulation. In contrast, clarithromycin and its metabolites are eliminated by the kidney as well as the liver. The dosage of this drug should be adjusted in patients with renal impairment.

Adverse effects

1. Gastric distress and motility (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
2. Cholestatic jaundice (estolate form of erythromycin)
3. Ototoxicity (erythromycin, especially at high dosages. and Azithromycin)

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.
- Macrolides and ketolides may prolong the QT interval and should be used with caution in those patients with proarrhythmic conditions or concomitant use of proarrhythmic agents.

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. 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.

FIDAXOMICIN

- ✓ It has a unique mechanism of action by acting on the sigma subunit of RNA polymerase, terminating protein synthesis, and resulting in cell death.
- ✓ has a very narrow spectrum of activity limited to gram-positive aerobes and anaerobes.
- ✓ it is used primarily for its bactericidal activity against Clostridium difficile.
- ✓ has minimal systemic absorption and primarily remains within the gastrointestinal tract.

Adverse effects

- nausea, vomiting, and
- Abdominal pain.
- Hypersensitivity reactions (cross allergy with Macrolides)
- Anemia and neutropenia.

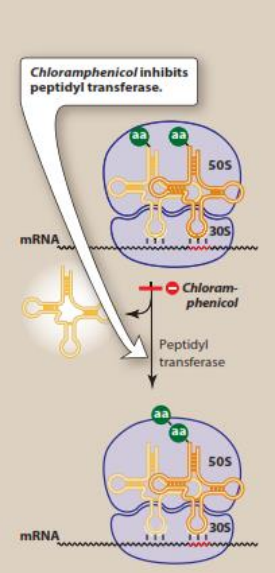
CHLORAMPHENICOL

The use of chloramphenicol, a broad-spectrum antibiotic, is restricted to life-threatening infections for which no alternatives exist.

Mechanism of action

Chloramphenicol binds reversibly to the bacterial 50S ribosomal sub-unit 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.



Antibacterial spectrum

- chlamydiae,
- rickettsiae,
- spirochetes, and
- anaerobes.

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

Resistance

1. presence of enzymes that inactivate chloramphenicol.
2. decreased ability to penetrate the organism

3. ribosomal binding site alterations.

Pharmacokinetics

- 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.
- It is also secreted into breast milk and should be avoided in breastfeeding mothers.

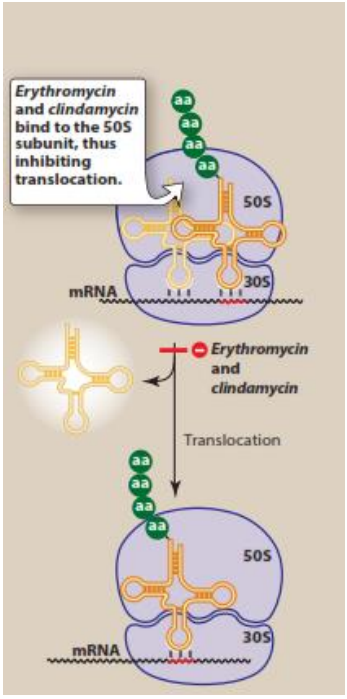
Adverse Effects

1. **Reversible bone marrow depression** (dose-related)
2. **Aplastic anaemia** (pancytopaenia and bone marrow aplasia, occurs with an incidence of 1 in 35,000 and is not related to dose; it occurs with oral, i.v., or even ophthalmic use of the drug. This reaction develops weeks or months after termination of the treatment.)
3. **Grey baby syndrome** (circulatory collapse, vomiting and fall in body temperature; this depends on the lower capacity to conjugate chloramphenicol in the liver in infants.)
4. **Acute haemolytic anaemia in G6PD deficient patients**

Note: The onset of action of chloramphenicol when given orally is more rapid than when given intravenously. This is because the i.v formulation of chloramphenicol (usually with succinate) has to be broken down in the liver to release chloramphenicol before it acts, while the capsule (usually with palmitate) form acts directly.

CLINDAMYCIN

Clindamycin has a mechanism of action that is the same as that of erythromycin.



Antibacterial spectrum

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

Resistance

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

1) the inability of the organism to take up the antibiotic,
2) the presence of efflux pumps,
3) a 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, and
4) the presence of plasmid-associated erythromycin esterases in gram-negative organisms such as Enterobacteriaceae.

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.

Pharmacokinetics

Administration

Clindamycin is available in both IV and oral formulations, but use of the oral form is limited by gastrointestinal intolerance.

Distribution

It distributes well into all body fluids including bone, but exhibits poor entry into the CSF.

Elimination

Clindamycin undergoes extensive oxidative metabolism to inactive products and is primarily excreted into the bile. 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.

Adverse effects

1. Diarrhea (serious pseudomembranous colitis) (most common).
2. Skin rashes.

QUINUPRISTIN/DALFOPRISTIN

Quinupristin/dalfopristin is a mixture of two streptogramins in a ratio of 30 to 70, respectively.

Mechanism of action

Each component of this combination drug binds to a separate site on the 50S bacterial ribosome. They synergistically interrupt protein synthesis. The combination drug is bactericidal and has a long PAE.

Antibacterial spectrum

- Active primarily against G +ve cocci, including those resistant to other antibiotics.
- Treatment of E. faecium infections, including VRE (bacteriostatic).
- Not effective against E. faecalis.

Resistance

1. Enzymatic processes commonly account for resistance to these agents.

- a ribosomal enzyme ----- methylates 23S ribosomal RNA site ------ interfere in quinupristin binding.
- the enzymatic modification --------- change the action from bactericidal to bacteriostatic.
- acetyltransferase inactivates dalfopristin.
- 2. An active efflux pump can also decrease levels of the antibiotics in bacteria.

Pharmacokinetics

Administration

Quinupristin/dalfopristin is injected intravenously (the drug is incompatible with a saline medium).

Distribution

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.

Elimination

Both compounds undergo hepatic metabolism, with excretion mainly in the feces.

Adverse effects

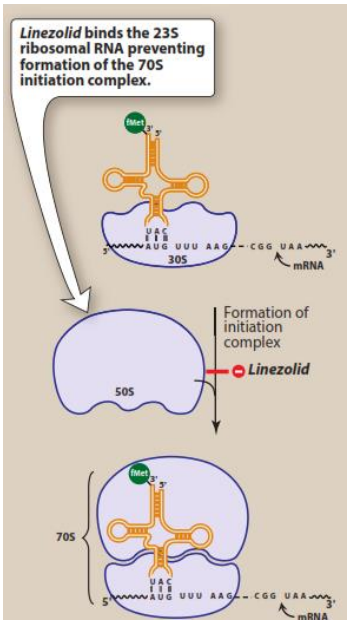
- Venous irritation (peripheral rather than a central line).
- Hyperbilirubinemia (25%) .
- Arthralgia and myalgia (higher doses).
- Quinupristin/dalfopristin inhibits the cytochrome P450 (CYP3A4).

LINEZOLID

Linezolid is a synthetic oxazolidinone developed to combat resistant gram-positive organisms, such as methicillin-resistant Staphylococcus aureus, VRE, and penicillin-resistant streptococci.

Mechanism of action

Linezolid binds to the bacterial 23S ribosomal RNA of the 50S sub-unit, thereby inhibiting the formation of the 70S initiation complex.



Antibacterial spectrum

1. Primarily against gram- positive organisms, such as

- staphylococci, streptococci, and enterococci, Corynebacterium species and Listeria monocytogenes.

2. moderately active against Mycobacterium tuberculosis.
3. its main clinical use is against drug-resistant gram positive organisms.

- ❖ Bacteriostatic (except streptococci)
- ❖ Linezolid is an alternative to daptomycin for infections caused by VRE.
- ❖ Use of linezolid for the treatment of MRSA bacteremia is not recommended.

Resistance

- ❑ 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.

Pharmacokinetics

- ✓ Linezolid is completely absorbed after oral administration.
- ✓ The drug is widely distributed throughout the body.
- ✓ It is metabolized via oxidation to two inactive metabolites.
- ✓ The drug is excreted both by renal and nonrenal routes.
- ✓ No dose adjustments are required for renal or hepatic dysfunction.

Adverse effects

- gastrointestinal upset,
- nausea,
- diarrhea,
- headache,
- rash.
- Thrombocytopenia (longer than 10 days).
- nonselective monoamine oxidase activity (serotonin syndrome) (reversible when the drug is discontinued).
- Irreversible peripheral neuropathies and optic neuritis (causing blindness) (greater than 28 days of use)