PHARMACOLOGY - 2

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PROTEIN SYNTHESIS-INHIBITING ANTIBIOTICS

PHARMACOLOGY-2

Protein Synthesis-Inhibiting Antibiotics/

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LEARNING OUTCOMES

After competing studying this chapter, the student should be able to:

- **Classify** the drugs into subgroups such as macrolides, oxazolidinediones, tetracyclines, aminoglycosides, etc.
- Recognize the **bacterial spectrum** of all these antibiotic groups.
- Summarize the most remarkable **pharmacokinetic features** of these drugs.
- Numerate the most important **side effects** associated with these agents.
- Select the **antibiotic of choice** to be used in certain infections, as associated with the patient status including comorbidity, the species of bacteria causing the infection and concurrently prescribed drugs.
- Reason some remarkable **clinical considerations** related to the use or contraindication or precaution of a certain drug.

PROTEIN SYNTHESIS INHIBITORS

- A number of antibiotics exert their antimicrobial effects by targeting bacterial **ribosomes** and inhibiting bacterial protein synthesis.
- Most of them are bacteriostatic.
- Bacterial ribosomes differ structurally from mammalian cytoplasmic ribosomes and are composed of 30S and 50S subunits (mammalian ribosomes have 40S and 60S subunits).
- This guarantees a reasonable level of **selectivity**; and **avoidance** of **serious side effects** due to protein synthesis inhibition.
- However, high concentrations of drugs such as **chloramphenicol** or the **tetracyclines** may cause toxic effects as a result of interaction with mitochondrial mammalian ribosomes, ***because the structure of mitochondrial ribosomes more closely resembles bacterial ribosomes.***

Antibiotics: Protein Synthesis Inhibitors

Summary of protein synthesis inhibitors

TETRACYCLINES
Demeclocycline DECLOMYCIN
Doxycycline DORYX, VIBRAMYCIN
Minocycline MINOCIN
Tetracycline GENERIC ONLY
GLYCYLCYCLINES
Tigecycline TYGACIL
AMINOGLYCOSIDES
Amikacin GENERIC ONLY
Gentamicin GENERIC ONLY
Neomycin GENERIC ONLY
Streptomycin GENERIC ONLY
Tobramycin TOBI, TOBREX
MACROLIDES/KETOLIDES
Azithromycin ZITHROMAX
Clarithromycin BIAXIN
Erythromycin E.E.S., ERY-TAB
Telithromycin GENERIC ONLY
MACROCYCLIC
Fidaxomicin DIFICID
LINCOSAMIDES
Clindamycin CLEOCIN
OXAZOLIDINONES
Linezolid ZYVOX
Tedizolid SIVEXTRO
OTHERS
Chloramphenicol GENERIC ONLY
Quinupristin/Dalfopristin SYNERCID

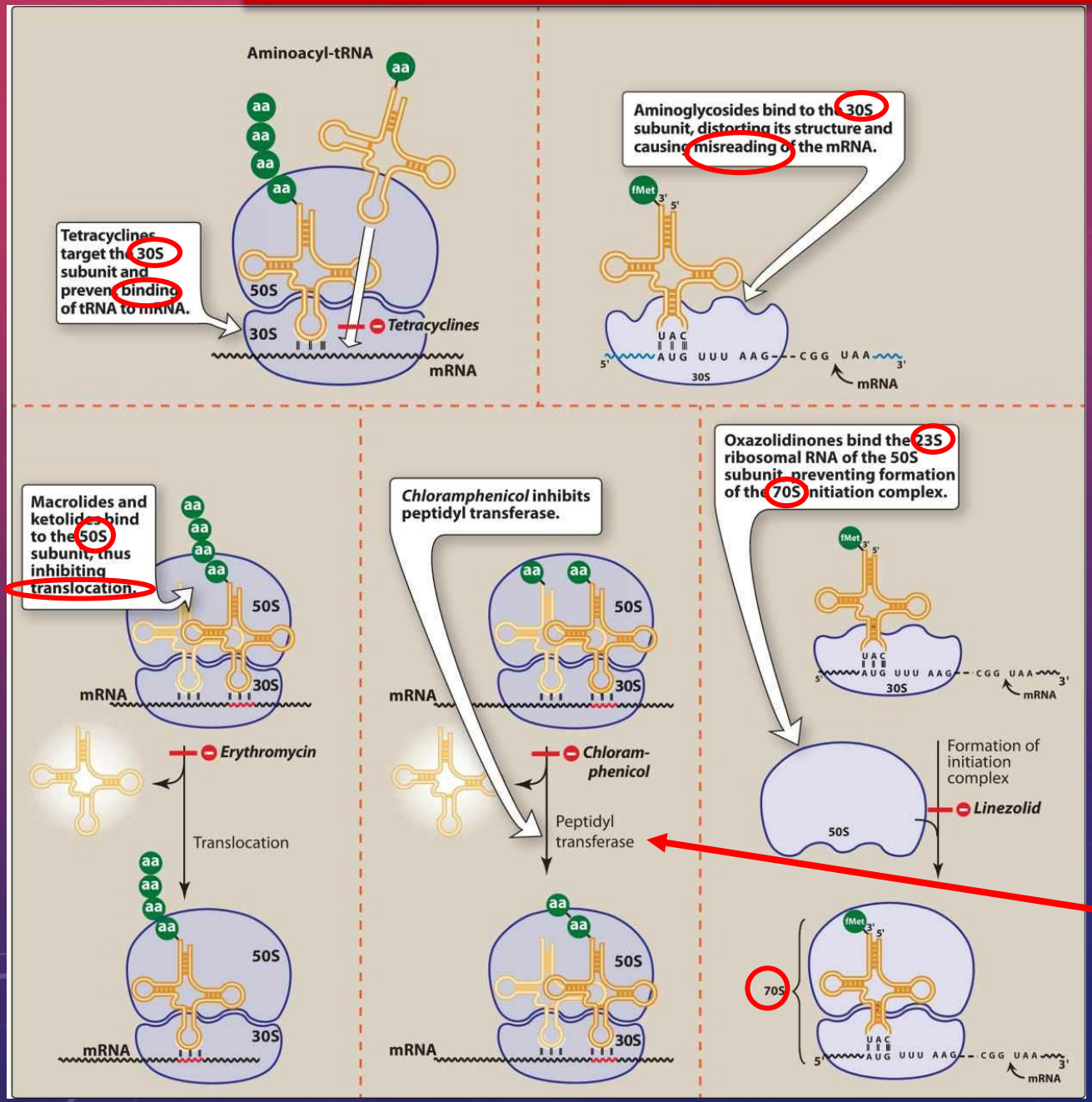
TETRACYCLINES:

- 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.

Mechanism of action:

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

PROTEIN SYNTHESIS INHIBITORS



Mechanisms of action of the various protein synthesis inhibitors.
aa = amino acid.

Catalyzes the addition of amino acid residue in order to grow polypeptide chain in protein synthesis.

PROTEIN SYNTHESIS INHIBITORS

ANTIBACTERIAL SPECTRUM:

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

RESISTANCE:

- The most commonly encountered naturally occurring resistance to tetracyclines is an **efflux pump** that prevents drug accumulation in the cell.
- 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.

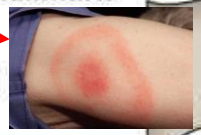
PROTEIN SYNTHESIS INHIBITORS

PEPTIC ULCER DISEASE

- Helicobacter pylori is a common cause of peptic ulcer disease.
- Treatment with a combination of *bismuth*, *metronidazole*, *tetracycline*, and a proton pump inhibitor is a highly effective regimen for eradication of H. pylori

LYME DISEASE

- This is a spirochetal infection caused by Borrelia burgdorferi. The disease is transmitted by the bite of infected ticks.
- Infection results in skin lesions, headache, and fever, followed by meningoencephalitis and, eventually, arthritis.
- A bull's-eye pattern rash with a red outer ring, called erythema migrans is a hallmark of Lyme disease



- *Doxycycline* is one of the preferred therapeutic options.

MYCOPLASMA PNEUMONIAE

- Mycoplasma pneumoniae, or walking pneumonia, is a common cause of community-acquired pneumonia in young adults and in people who live in close confines, such as in military camps.
- Treatment with a macrolide or *doxycycline* is effective.

Gram (+) cocci
- Staphylococcus aureus (including *methicillin*-resistant strains)
- Streptococcus pneumoniae

Gram (+) bacilli
- Bacillus anthracis

Gram (–) cocci

Gram (–) rods
- Brucella species*
- Helicobacter pylori
- Vibrio cholerae
- Yersinia pestis

Anaerobic organisms
- Clostridium perfringens
- Clostridium tetani

Spirochetes
- Borrelia burgdorferi
- Leptospira interrogans
- Treponema pallidum

Mycoplasma
- Mycoplasma pneumoniae

Chlamydia
- Chlamydia species

Other
- Rickettsia rickettsii

CHOLERA

- Cholera is caused by Vibrio cholerae ingested in fecally contaminated food or water.
- The organism multiplies in the gastro-intestinal tract, where it secretes an enterotoxin that produces diarrhea.
- Treatment includes *doxycycline*, which reduces the number of intestinal vibrios, and fluid replacement.

CHLAMYDIAL INFECTIONS

- Chlamydia trachomatis is a major cause of sexually transmitted disease in the United States. It causes nongonococcal urethritis, pelvic inflammatory disease, and lymphogranuloma venereum.
- Chlamydia psittaci causes psittacosis, which usually takes the form of pneumonia. Other clinical forms include hepatitis, myocarditis, and coma.
- *Doxycycline* or *azithromycin* is used to treat chlamydial infections.

ROCKY MOUNTAIN SPOTTED FEVER

- This disease, caused by Rickettsia rickettsii, is characterized by fever, chills, and aches in bones and joints.
- Response to tetracyclines is prompt if the drug is started early in the disease process.

PROTEIN SYNTHESIS INHIBITORS

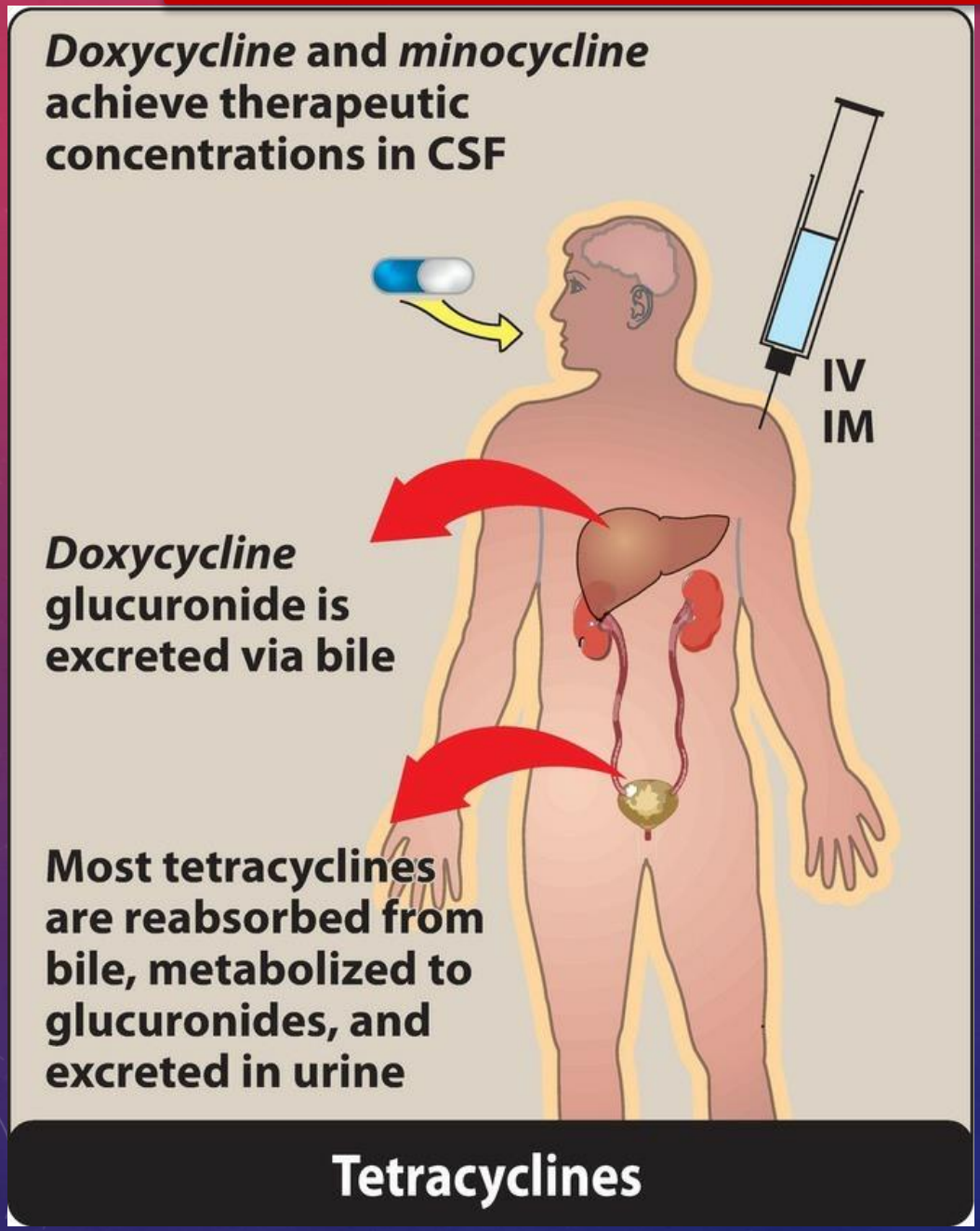
- Resistance to one tetracycline ***does not*** confer universal resistance to all tetracyclines.
- The development of ***cross-resistance*** may be dependent on the mechanism of resistance.

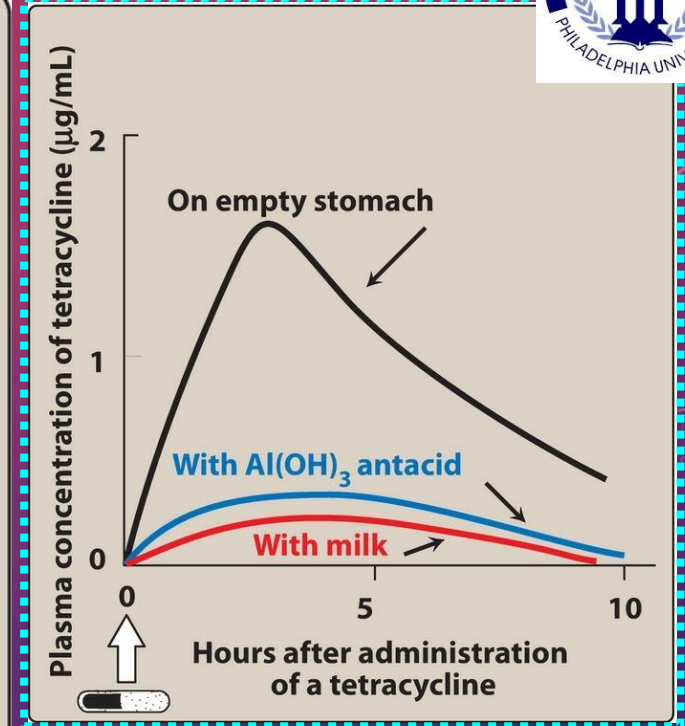
PHARMACOKINETICS:

Absorption:

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

PROTEIN SYNTHESIS INHIBITORS





Administration and fate of tetracyclines.
CSF = cerebrospinal fluid.

PROTEIN SYNTHESIS INHIBITORS

Distribution:

- 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.

PROTEIN SYNTHESIS INHIBITORS

ELIMINATION:

- Tetracycline is primarily eliminated unchanged in the urine,
- However, **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:

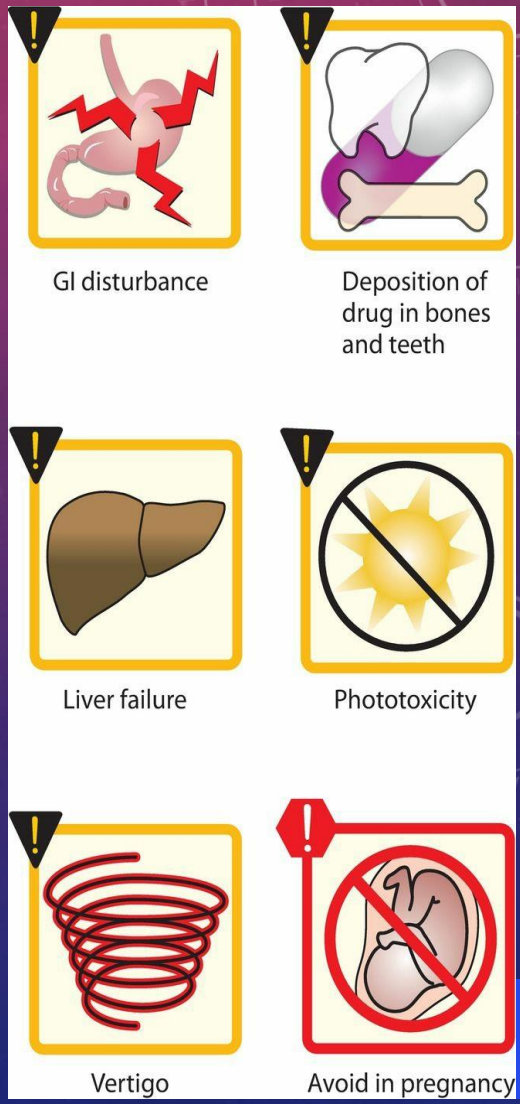
1. Gastric discomfort:

- 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.
- Tetracycline should be taken on an empty stomach.

TETRACYCLINE SIDE EFFECTS

2. Effects on calcified tissues:

- Deposition in the bone and primary dentition occurs during the calcification process in growing children {below 8}.
- This may cause discoloration, deformity and hypoplasia of teeth and a temporary stunting (impeding) of growth.
- For this reason, the use of tetracyclines is limited in pediatrics.



PROTEIN SYNTHESIS INHIBITORS

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;
- ✓ Staying out of direct sunlight, especially between the hours of 10:00 a.m. and 3:00 p.m., if possible.
- ✓ Wear protective clothing, including a hat and sunglasses.

5. Vestibular dysfunction:

- Dizziness, vertigo, and tinnitus may occur particularly with **minocycline**, which concentrates in the endolymph of the ear and affects function.
- These symptoms may also occur with **doxycycline**.

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 (complications)may occur.

CONTRAINDICATIONS:

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

PROTEIN SYNTHESIS INHIBITORS

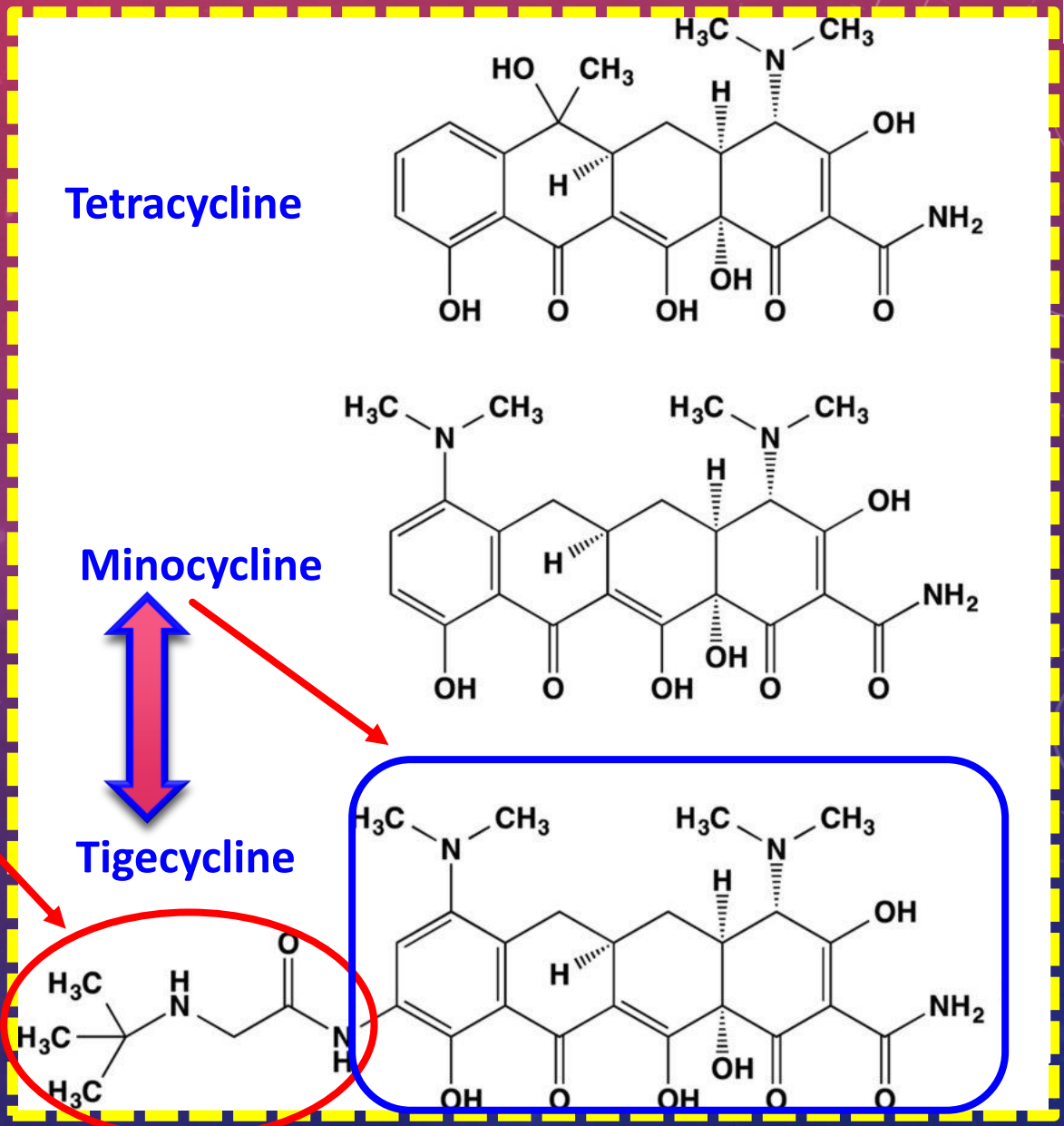
GLYCYLCYCLINES:

- They are a new generation of antibiotics derived from tetracyclines (received approval in 2005).
- They were developed to overcome issues with bacterial **resistance** to tetracyclines.
- **Tigecycline**, a derivative of **minocycline**, is the first member of the glycylcycline antimicrobial class.
- It is indicated for the treatment of complicated skin and soft tissue infections, complicated intra-abdominal infections, and community-acquired pneumonia.

Mechanism of action:

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

PROTEIN SYNTHESIS INHIBITORS



Antibacterial spectrum: (of tigecycline)

- Methicillin-resistant staphylococci (MRSA).
- Multidrug-resistant streptococci.
- Vancomycin-resistant enterococci (VRE).
- Extended-spectrum β-lactamase–producing gram negative bacteria.
- *Acinetobacter baumannii*.
- Many anaerobic organisms.

Tigecycline is **not active** against *Morganella*, *Proteus*, *Providencia*, or *Pseudomonas* species.

PROTEIN SYNTHESIS INHIBITORS

Resistance:

- Tigecycline was developed to overcome the emergence of tetracycline class–resistant organisms that utilize **efflux pumps** and **ribosomal protection** to confer resistance.
- Resistance is primarily attributed to **overexpression of efflux pumps.**

Pharmacokinetics:

- 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**.

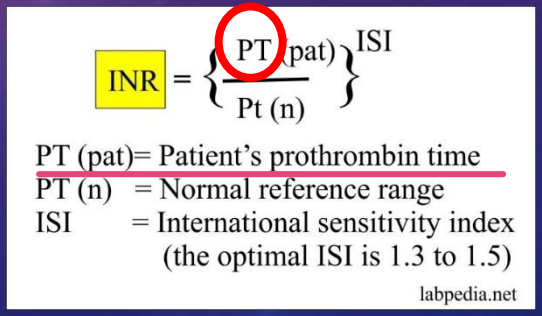
Adverse effects:

- Tigecycline is associated with significant **nausea** and **vomiting**.
- Acute **pancreatitis** that may be **fatal**.
- **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:** 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**, and **fetal harm** when administered in **pregnancy**.

DRUG-DRUG INTERACTION:

- Tigecycline may **decrease** the clearance of warfarin.
- Therefore, the international normalized ratio should be monitored closely when tigecycline is coadministered with warfarin.
- This ratio allows for easier comparisons of test results from different laboratories.
- It is used when blood-thinning medications are taken.
- When the INR is **higher** than the recommended range, it means that the **blood clots more slowly** than desired, and a lower INR means the blood clots more quickly than desired.

Then, as INR increases, prothrombin time increases (slow clotting; more blood-thinning).



AMINOGLYCOSIDES:

- 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**.

Mechanism of action:

- Aminoglycosides diffuse through **{1}** porin channels [**proteins that cross a cellular membrane and act as a pore**] in the outer membrane of susceptible organisms.
- These organisms also have an **{2}** 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.
- They Have concertation-dependent bactericidal activity.

PROTEIN SYNTHESIS INHIBITORS

- They also exhibit a **post-antibiotic** effect [continued bacterial suppression after drug concentrations fall below the MIC].

Antibacterial spectrum:

- They are effective against aerobic gram-negative bacteria including those that may be multidrug resistant, such as:
  - ✓ *Pseudomonas aeruginosa*.
  - ✓ *Klebsiella pneumoniae*.
  - ✓ *Enterobacter* sp.
- They 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.

PROTEIN SYNTHESIS INHIBITORS

Aminoglycosides include: TANGS:

Tobramycin

Amikacin

Neomycin

Gentamicin

Streptomycin

Plazomicin: new drug (2017).

AMINO:

Against Aerobic gram negatives

Mainly bactericidal

Inhibit protein synthesis at 30s subunit

Nephrotoxic

Ototoxic

Side effects of Aminoglycosides include: remember of NANO:

Neurotoxicity

Allergic reactions

Nephrotoxicity

Ototoxicity

REFERENCE: http://pharmwarthegame.blogspot.com/2018/09/aminoglycosides-mnemonics.html

RESISTANCE:

- Resistance to aminoglycosides occurs via:

1. Efflux pumps,
2. Decreased uptake, and/or
3. Modification and inactivation by plasmid-associated synthesis of enzymes.

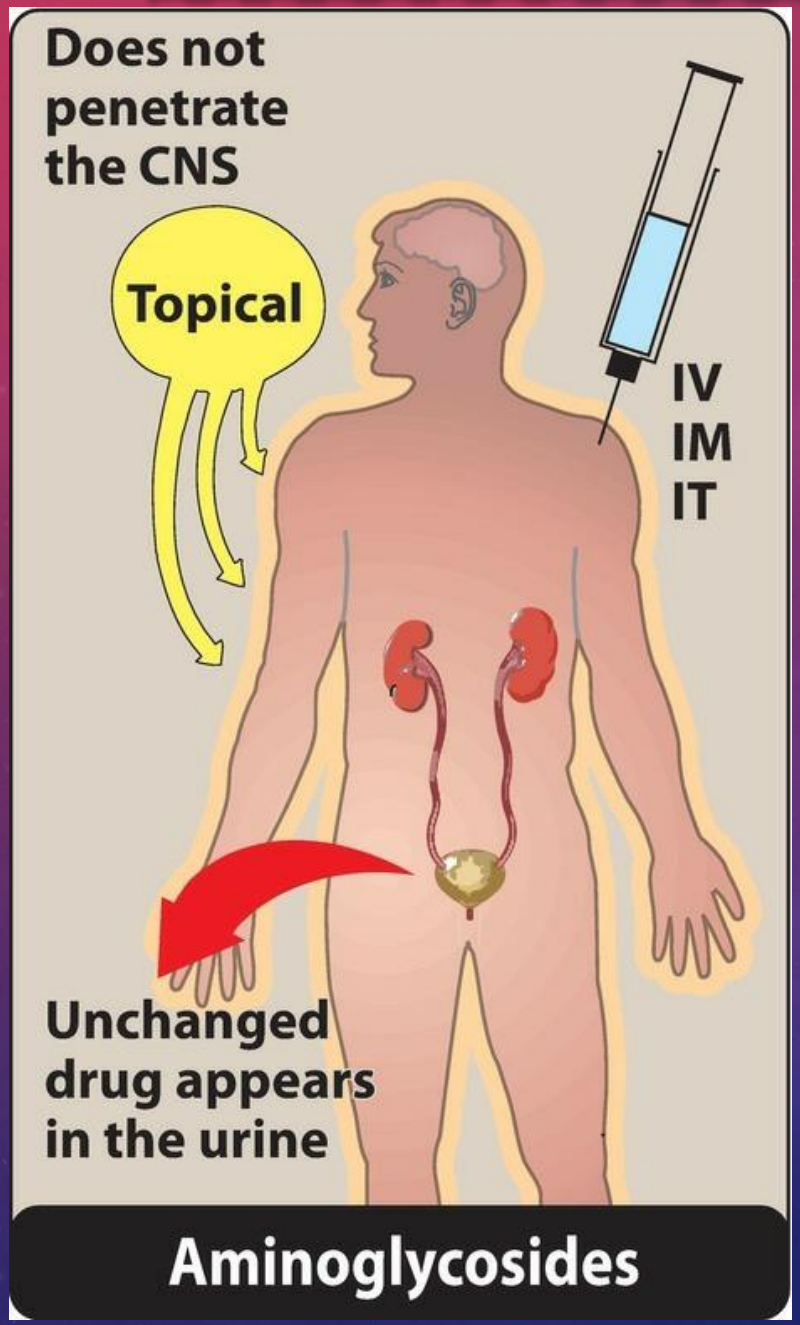
- Each of these enzymes has its own aminoglycoside specificity; therefore, cross-resistance cannot be presumed.
- **Amikacin** is less vulnerable (susceptible) to these enzymes than other antibiotics in this group.

PHARMACOKINETICS:

Absorption:

- The highly polar, polycationic structure of the aminoglycosides prevents adequate absorption after oral administration; thus,
- All aminoglycosides (except **neomycin** must be given parenterally to achieve adequate serum concentrations.
- **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.

PROTEIN SYNTHESIS INHIBITORS



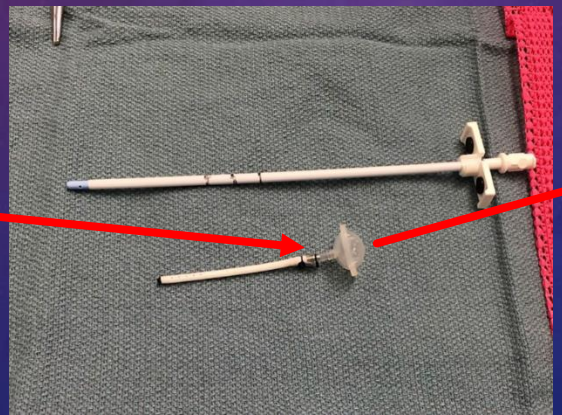
Administration and fate of aminoglycosides.

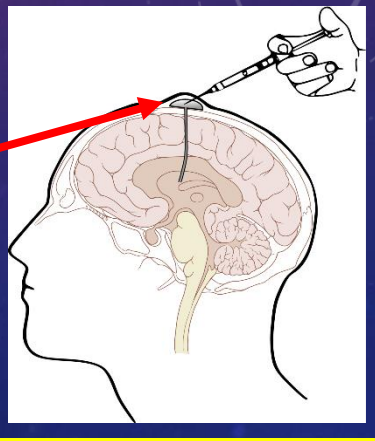
PROTEIN SYNTHESIS INHIBITORS

Distribution:

- Because of their **hydrophilicity**, aminoglycoside tissue concentrations may be subtherapeutic, and penetration into most body fluids is variable.
- 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.

Ommaya reservoir:
An intraventricular catheter for drug administration





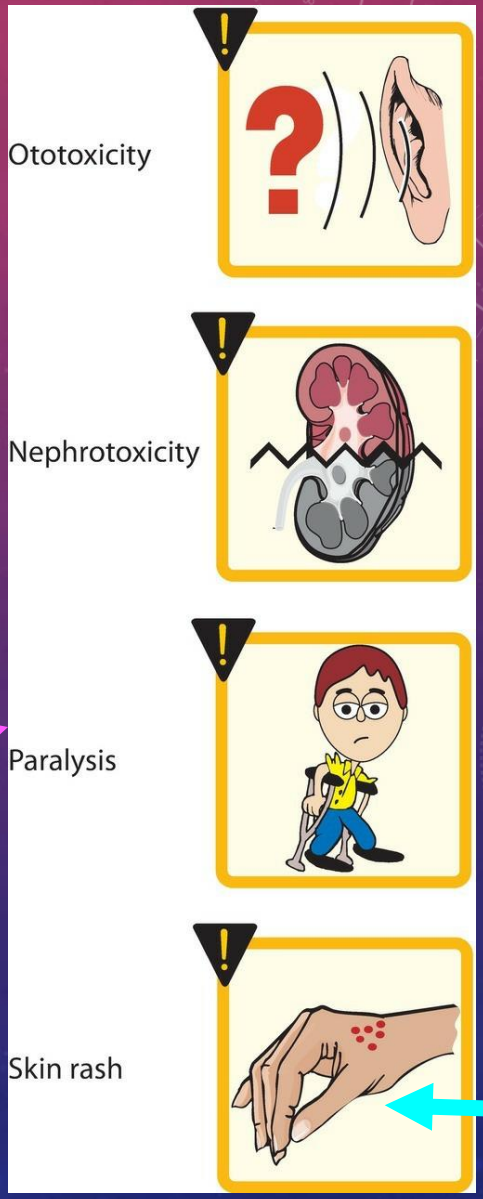
PROTEIN SYNTHESIS INHIBITORS

Elimination:

- 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:

- The elderly are particularly susceptible to nephrotoxicity and ototoxicity.

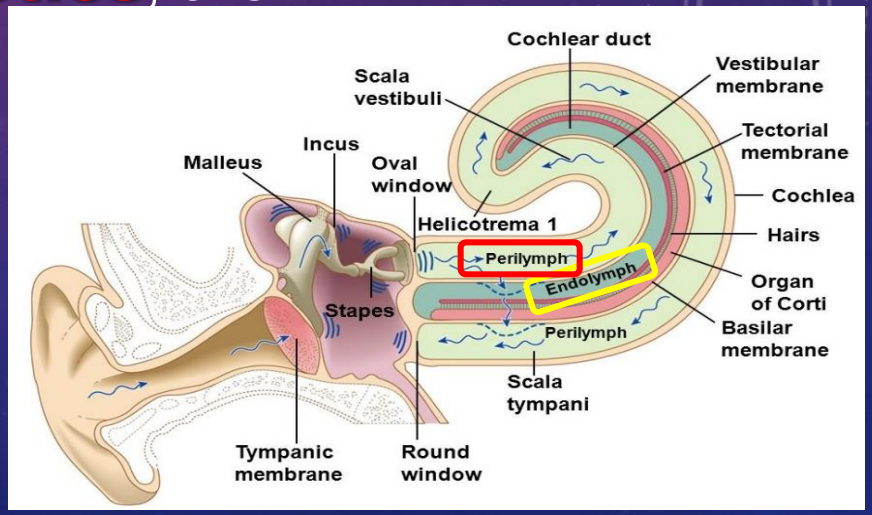


Contact dermatitis is a common reaction to topically applied ***neomycin***.

PROTEIN SYNTHESIS INHIBITORS

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 {free radicle formation}.
- 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.



PROTEIN SYNTHESIS INHIBITORS

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 {1} rapid increase in concentration (due to high doses infused over a short period) or {2} 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.

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 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 erythromycin and others.
- **Telithromycin,** a semisynthetic derivative of erythromycin, is a "ketolide" antimicrobial agent (no longer used in the United States).

PROTEIN SYNTHESIS INHIBITORS

MECHANISM OF ACTION:

- The macrolides and ketolides 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 considered as an ***alternative*** in patients with penicillin allergy.

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*.

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*.
- *H. influenzae* (6 strains have been identified), **strain B** is the most deadly to infants infected with this bacterium.
- Extensive use of azithromycin has resulted in growing *Streptococcus pneumoniae* resistance.

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.**

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. A decreased affinity of the 50S ribosomal subunit for the antibiotic due to ***methylation*** of an adenine in the 23S bacterial ribosomal RNA in gram-positive organisms.

PROTEIN SYNTHESIS INHIBITORS

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

- **Erythromycin** has limited clinical use due to increasing resistance.
- Both **clarithromycin** and **azithromycin** share SOME cross-resistance with erythromycin.
- It is COMPLETE cross-resistance (Katzung).
- Constitutive **methylase** production also confers resistance to structurally unrelated but mechanistically similar compounds such as **clindamycin** and **streptogramin B** [peptide antibiotics], that share the same protein binding site.
- **Telithromycin** {a third generation macrolide} may be effective against macrolide-resistant organisms.

PROTEIN SYNTHESIS INHIBITORS

- Telithromycin strongly binds simultaneously to two domains of 23S RNA of the 50S ribosomal subunit, while *older* macrolides bind strongly only to one domain and weakly to the second domain.

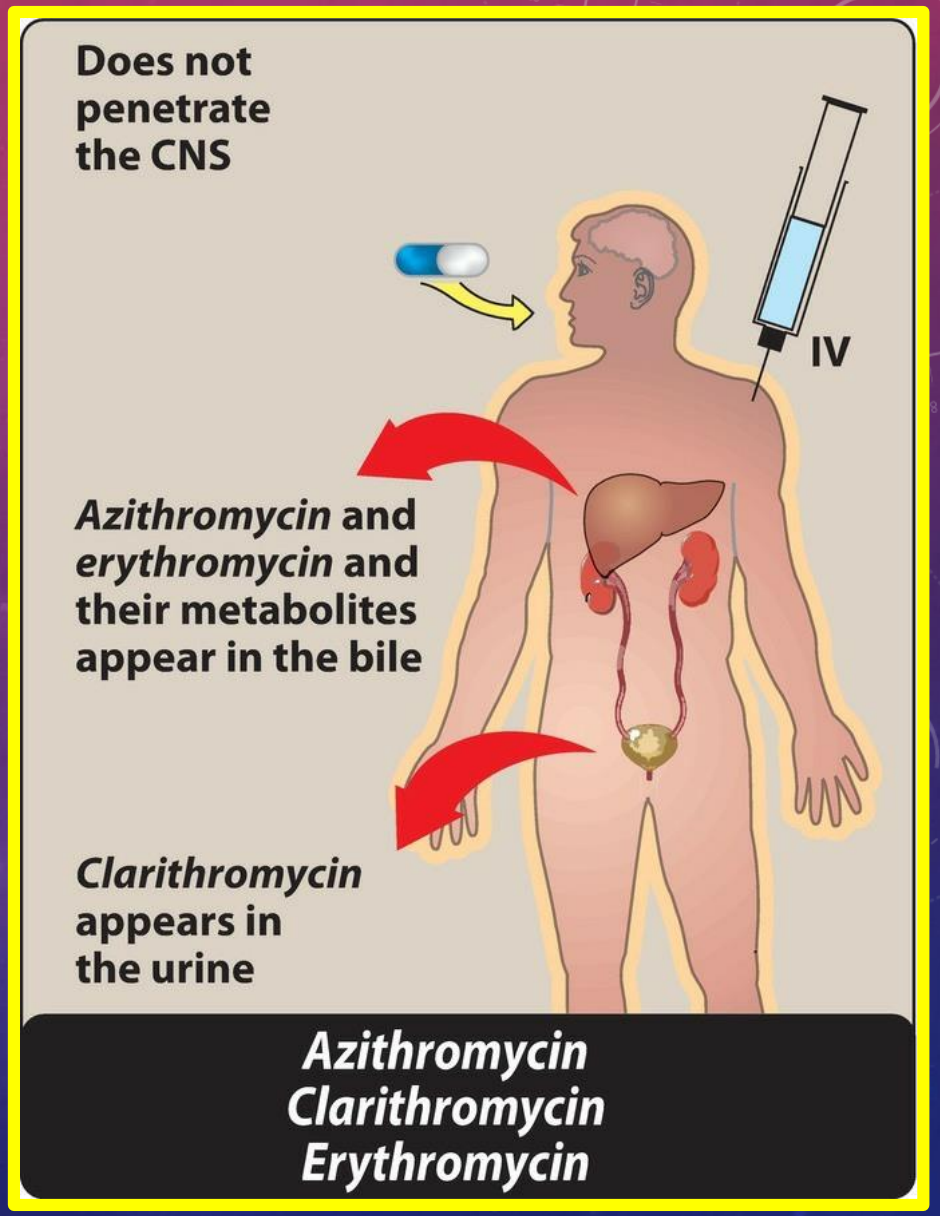
PHARMACOKINETICS:

ABSORPTION:

- The **erythromycin** base is destroyed by gastric acid; thus, either **enteric-coated** tablets or **esterified** forms of the antibiotic are administered and all have adequate oral absorption.
- **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.

PROTEIN SYNTHESIS INHIBITORS

- **Telithromycin** is administered **orally** without regard to meals.
- **Erythromycin** and **azithromycin** are available in **IV** formulations.



DISTRIBUTION:

- **Erythromycin** distributes well to all body fluids except the CSF.
- It is one of the few antibiotics that diffuse 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 concentrations are low.
- **Azithromycin** has the **largest volume of distribution** of the four drugs.

PROTEIN SYNTHESIS INHIBITORS

ELIMINATION:

- **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**.

Excretion:

- **Azithromycin** is primarily concentrated and excreted in the **bile** as active drug.
- **Erythromycin** and its metabolites are also excreted in the **bile**.

PROTEIN SYNTHESIS INHIBITORS

- **Clarithromycin** is hepatically metabolized, and the active drug and its metabolites are mainly excreted in the urine.
- Thus, the dosage of this drug should be adjusted in patients with renal impairment.

	Erythro-mycin	*Clarithro-mycin*	*Azithro-mycin*	*Telithro-mycin*
Oral absorption	Yes	Yes	Yes	Yes
Half-life (hours)	2	3.5	68	10
Conversion to an active metabolite	No	Yes	No	Yes
Percent excretion in urine	< 15	30–50	< 10	13

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.
- This adverse effect sometimes employed for the treatment of **gastroparesis** or **postoperative ileus**.

- **Gastroparesis**: stomach motility is slowed down.
- **Ileus**: lack of movement somewhere in the intestines.

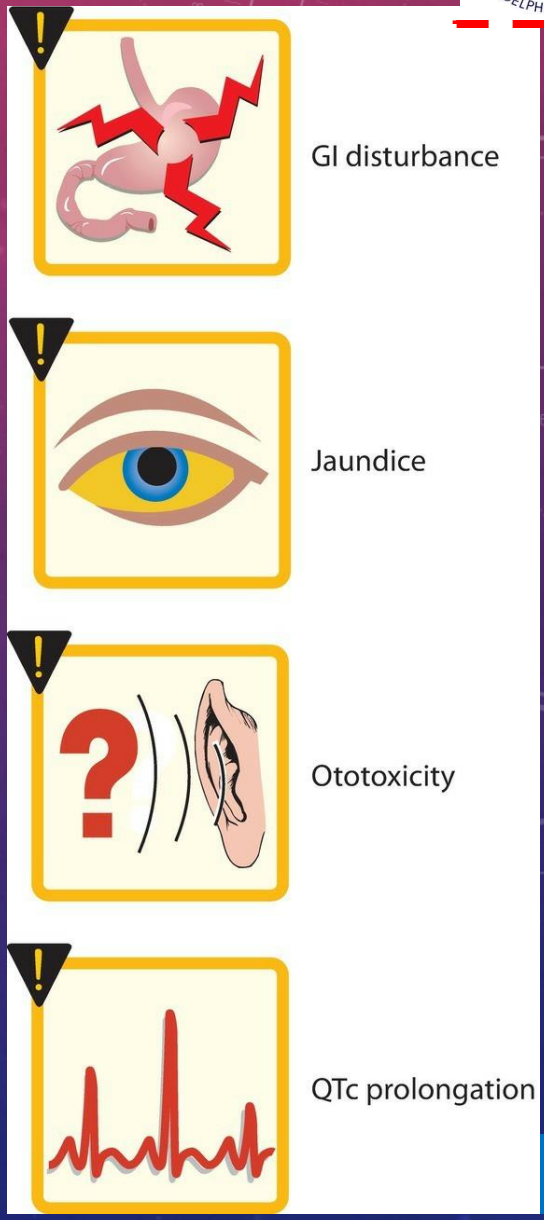
PROTEIN SYNTHESIS INHIBITORS

2. Cholestatic jaundice:

- This adverse effect occurs most commonly with the **estolate** form of erythromycin (not used in the United States).
- However, it has been reported with other formulations and other agents in this class.

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.

CONTRAINDICATIONS:

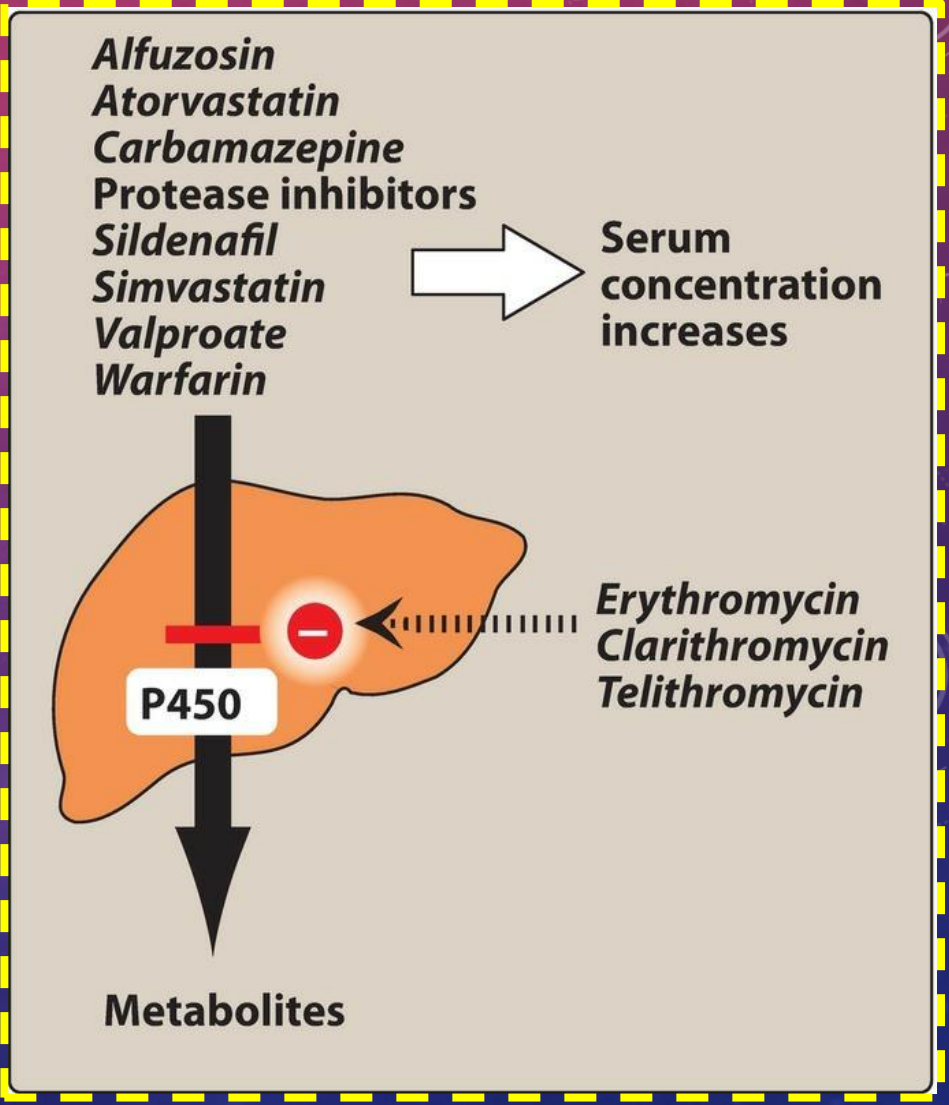
- Patients with hepatic dysfunction should be treated **cautiously** with **erythromycin**, **telithromycin**, or **azithromycin**, because these drugs accumulate in the liver.
- Severe **hepatotoxicity with telithromycin** has limited its use, given the availability of alternative therapies.

DRUG INTERACTIONS:

- **Erythromycin**, **telithromycin**, and **clarithromycin** inhibit the hepatic metabolism of a number of drugs, which can lead to *toxic accumulation* of these compounds.

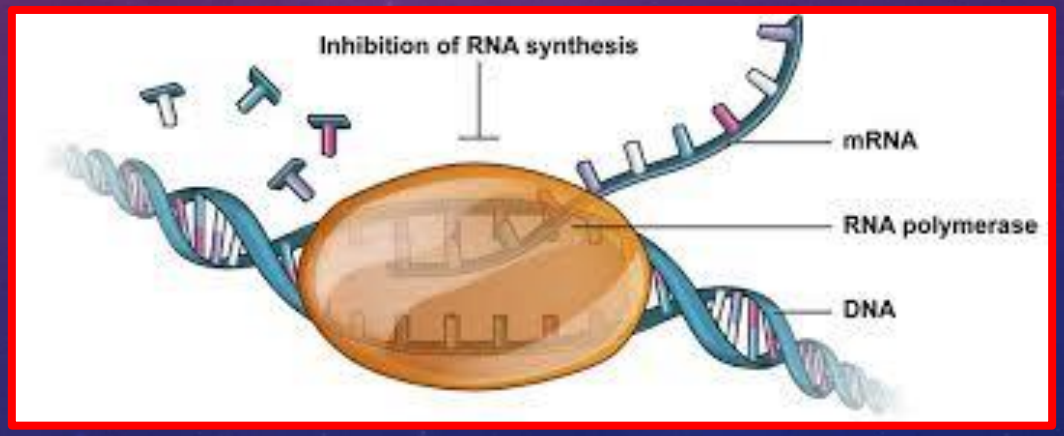
MACROLIDES INTERACTION WITH OTHER DRUGS

- 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.



FIDAXOMICIN:

- Fidaxomicin is a macrocyclic antibiotic with a structure similar to the macrolides.
- 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.



PROTEIN SYNTHESIS INHIBITORS

- enterococci, it is used primarily for its bactericidal activity against ***Clostridium difficile***. [FDA approvement]
- Because of 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, which renders it ideal for the treatment of ***C. difficile*** infection, which occurs in the gut.

ADVERSE EFFECTS:

- GIT-related: nausea – vomiting – and - abdominal pain.
- hypersensitivity.

- Fidaxomicin should be used with caution in patients with a macrolide allergy, as they may be at increased risk for hypersensitivity.

PROTEIN SYNTHESIS INHIBITORS

- 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 subunit and **inhibits protein synthesis** at the **peptidyl transferase** reaction.
- Because of some **similarity** of mammalian mitochondrial ribosomes to those of bacteria, protein and ATP synthesis in these organelles may be inhibited at high circulating chloramphenicol concentrations, **producing bone marrow toxicity.**
- The **oral** formulation of chloramphenicol was removed from the US market due to this toxicity

ANTIBACTERIAL SPECTRUM:

- Chloramphenicol is active against many types of microorganisms including **chlamydiae**, **rickettsiae**, **spirochetes**, and **anaerobes**.
- The drug is primarily bacteriostatic, but it may exert bactericidal activity depending on the dose and organism.

RESISTANCE:

- Resistance is conferred by the presence of [1] **enzymes** (**chloramphenicol acetyltransferase**, a plasmid-encoded enzyme) that inactivate chloramphenicol.
- Other mechanisms include [2] **decreased ability to penetrate the organism and ribosomal binding site alterations**.

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

PROTEIN SYNTHESIS INHIBITORS

ADVERSE EFFECTS:

1. Anemias:

- Patients may experience dose-related anemia, **hemolytic** anemia (observed in patients with glucose-6-phosphate dehydrogenase deficiency), and **aplastic** anemia.
- 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, which decreases their ability to excrete the drug.

- This leads to drug accumulation to concentrations that interfere with the function of mitochondrial ribosomes, causing poor feeding, depressed breathing, cardiovascular collapse, cyanosis (hence the term "gray baby"), and death.

- Adults who have received very high doses of chloramphenicol may also exhibit this toxicity.

DRUG INTERACTIONS:

- Chloramphenicol **inhibits** some of the hepatic mixed-function oxidases, preventing the metabolism of drugs such as **warfarin** and **phenytoin**, which may potentiate their effects.

CLINDAMYCIN:

- Clindamycin has a mechanism of action that is similar to that of the **macrolides**.
- 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.

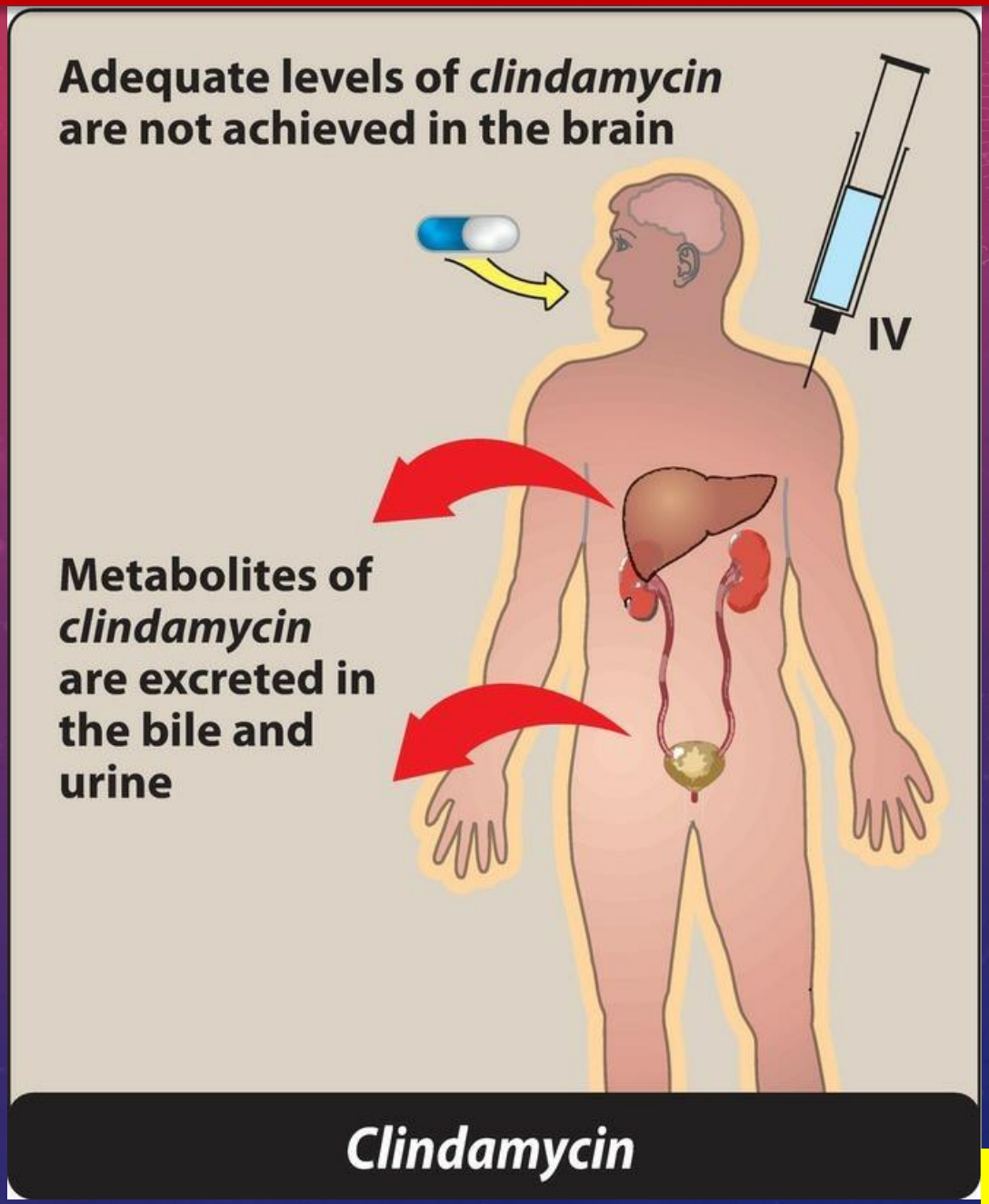
PROTEIN SYNTHESIS INHIBITORS

- *C. difficile* is resistant to clindamycin, and the utility of clindamycin for gram negative *anaerobes* (for example, *Bacteroides* sp.) is decreasing due to increasing resistance.
- Oral and parenteral administration.
- Distributes well to the body fluids, but poorly into the CSF.
- Metabolized to active and inactive metabolites.
- **Low** urinary excretion of active drug limits its clinical utility for urinary tract infections.

SIDE EFFECTS:

- Rash and **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* infection.

PROTEIN SYNTHESIS INHIBITORS



QUINUPRISTIN/DALFOPRISTIN:

- Quinupristin/dalfopristin is a mixture of two streptogramins in a ratio of 30 to 70, respectively.
- STREPTOGRAMINS: are a group of cyclic peptide antibiotics that inhibit, like macrolides, the synthesis of bacterial proteins.
- Due to significant adverse effects, this combination drug is normally reserved for the treatment of severe infections caused by vancomycin-resistant *Enterococcus faecium* (VRE) in the absence of other therapeutic options.

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.

PROTEIN SYNTHESIS INHIBITORS

- Quinupristin prevents elongation similar to the macrolides and causes release of incomplete peptide chains.
- Thus, they **synergistically** interrupt protein synthesis.
- The combination drug has *bactericidal* activity against most susceptible organisms and has a long **post antibacterial effect** [PAE].

Antibacterial spectrum:

- Quinupristin/dalfopristin is active primarily against **gram-positive cocci**, including those resistant to other antibiotics.
- Its **primary use** is for the treatment of ***E. faecium*** infections, including **VRE** strains, against which it is bacteriostatic.
- The drug is **not** effective against ***E. faecalis.***

PROTEIN SYNTHESIS INHIBITORS

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.

Pharmacokinetics:

Quinupristin/dalfopristin is available intravenously.

It does not achieve therapeutic concentrations in CSF.

PROTEIN SYNTHESIS INHIBITORS

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

Adverse effects:

- Venous irritation.
- 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 administered.
- Quinupristin/dalfopristin **inhibits** the cytochrome P450 CYP3A4 isoenzyme, and concomitant administration with drugs that are metabolized by this pathway may lead to toxicities.

PROTEIN SYNTHESIS INHIBITORS

❖ **Linezolid** and **tedizolid** are synthetic oxazolidinones developed to combat **gram-positive** organisms, including resistant isolates such as **methicillin-resistant Staphylococcus aureus**, **VRE**, and **penicillin-resistant streptococci**.

Mechanism of action:

❑ Linezolid and tedizolid bind to the bacterial **23S** ribosomal RNA of the **50S** subunit, thereby **inhibiting the formation of the 70S initiation complex and translation of bacterial proteins**.

Antibacterial spectrum:

➢ **Gram-positive** organisms such as staphylococci, streptococci, and enterococci, *Corynebacterium* species , *Mycobacterium tuberculosis* [moderate activity] and *Listeria monocytogenes.*

PROTEIN SYNTHESIS INHIBITORS

- The main clinical use of linezolid and tedizolid is to treat infections caused by **drug-resistant gram-positive** organisms.
- **Linezolid** is an alternative to **daptomycin** for infections caused by **VRE**.
- Because they are bacteriostatic, the oxazolidinones are **not** recommended as **first-line** treatment for **MRSA** bacteremia.

RESISTANCE:

- Resistance primarily occurs via **reduced binding** at the target site.
- **Cross-resistance** with other protein synthesis inhibitors does **not** occur.

PHARMACOKINETICS:

- Linezolid and tedizolid are well absorbed after **oral** administration.
- **IV** formulations are also available.
- These drugs distribute widely throughout the body.
- **Linezolid** is excreted both by renal and nonrenal routes.
- **Tedizolid** is mainly excreted in the feces.
- **No dose adjustments are required for either agent for renal or hepatic dysfunction.**

PROTEIN SYNTHESIS INHIBITORS

ADVERSE EFFECTS:

- Most common: **Gastrointestinal** upset, nausea, diarrhea, headache, and rash.
- Hematologic: **Thrombocytopenia** has been reported, usually in patients taking the drug for longer than 10 days.
- Linezolid and tedizolid possess nonselective monoamine oxidase-inhibiting activity and may lead to **serotonin syndrome** if given concomitantly with:
  1. Large quantities of **tyramine**-containing foods.
  2. Selective **serotonin reuptake inhibitors**, or
  3. **Monoamine oxidase inhibitors**.
- The condition is reversible when the drug is discontinued.

PROTEIN SYNTHESIS INHIBITORS

- The FDA has issued a warning regarding the use of the drug with **serotonergic** agents.

CONT. ADVERSE EFFECTS:

❖ Irreversible peripheral **neuropathies** and **optic neuritis** causing **blindness** have been associated with greater than **28** days of use, limiting utility for extended-duration treatments.

Serotonin syndrome (SS):

- A group of symptoms that may occur with the use of certain serotonergic medications or drugs.
- The degree of symptoms can range from mild to severe.
- Symptoms include high body temperature, agitation, increased reflexes, tremor, sweating, dilated pupils, and diarrhea.→ **lactic acidosis**

THE END

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