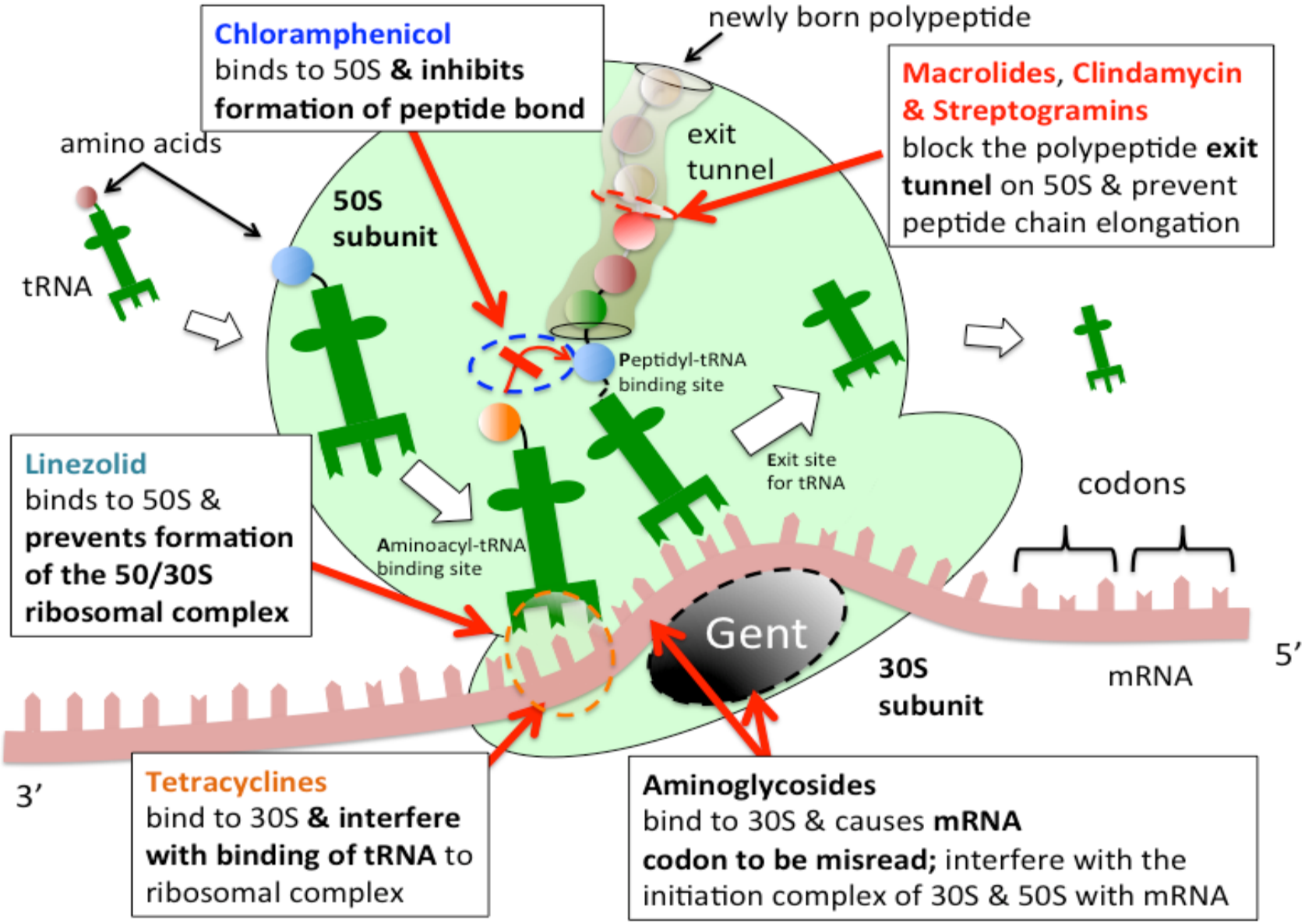
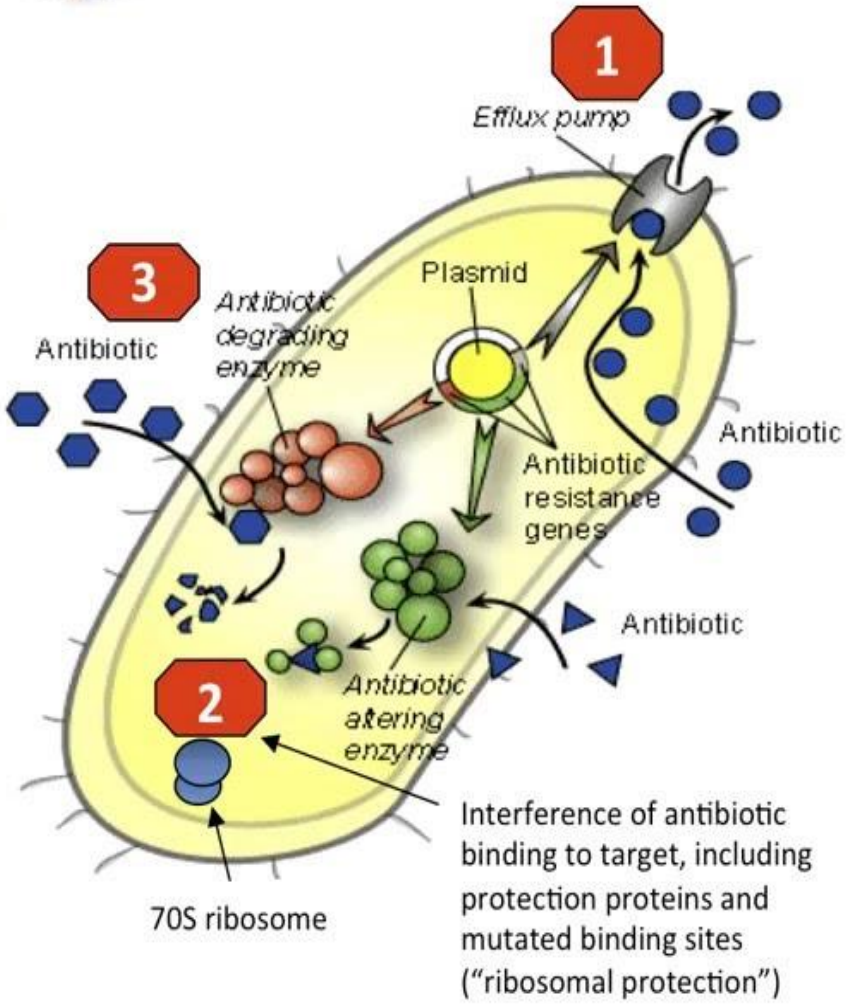
Aminoglycosides,
Tetracyclines,
Amphenicols,
Macrolides,
Lincozamides,
Streptogramins &
Oxazolidinones

Inhibition of bacterial protein synthesis



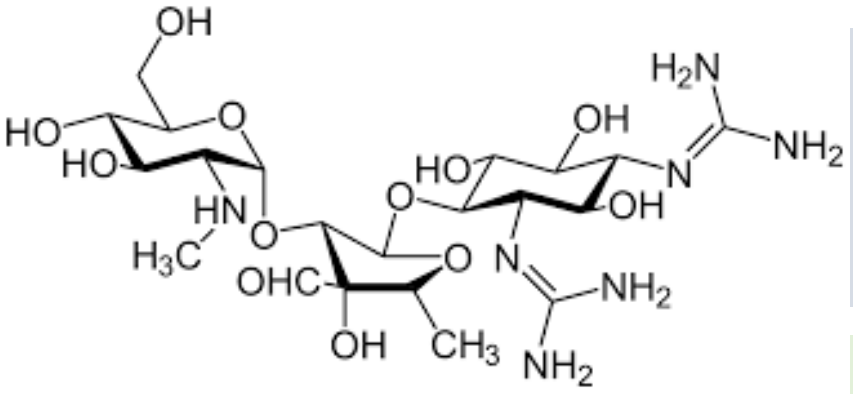
Major Bacterial Resistance Mechanisms to Protein Synthesis Inhibitors



3 Major Mechanisms:

1. **Impaired influx or increased efflux**
   - E.g., Tet(AE) and Tet(K) efflux pumps (tetracyclines)
   - E.g., altered active transporters (aminoglycosides)
2. **"Ribosomal protection"**
   - E.g., Tet(M) ribosomal protection protein (tetracyclines)
   - E.g., "MLS_B resistance" vs. macrolides, lincosamides, and streptogramin B
3. **Enzymatic inactivation (degradation, alteration)**
   - E.g., bacterial esterases (macrolides)
   - E.g., acetyl-, phospho-, and adenylyltransferases (aminoglycosides)

Aminoglycosides

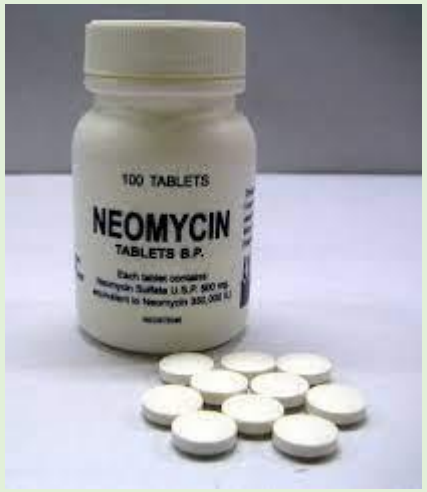


System

- ✓Streptomycin
- ✓Amikacin
- ✓Kanamycin
- ✓Tobramycin
- ✓Sizomycin

Topic

- ✓Neomycin
- ✓Framycetin



COMMON PROPERTIES

1. All are **used as sulfate salts**. (**Highly water soluble**; **solutions are stable** for months.)

2 . They **ionize in solution**

- Not absorbed orally
- **Distribute only extracellularly**
- Do not penetrate brain or CSF

3 . All are **excreted unchanged**

4. All are **bactericidal**

- **more active at alkaline pH**.

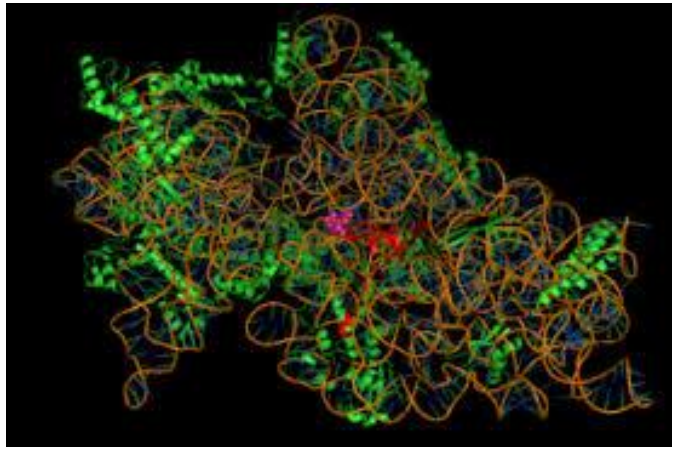
5 . Interferring with bacterial **protein synthesis**.

6 . All are active primarily **against aerobic gram negative bacilli** and do not inhibit anaerobes.

7 . Only **partial cross resistance** among them.

8 . Have relatively **narrow margin of safety.**

9. All exhibit **ototoxicity and nephrotoxicity.**



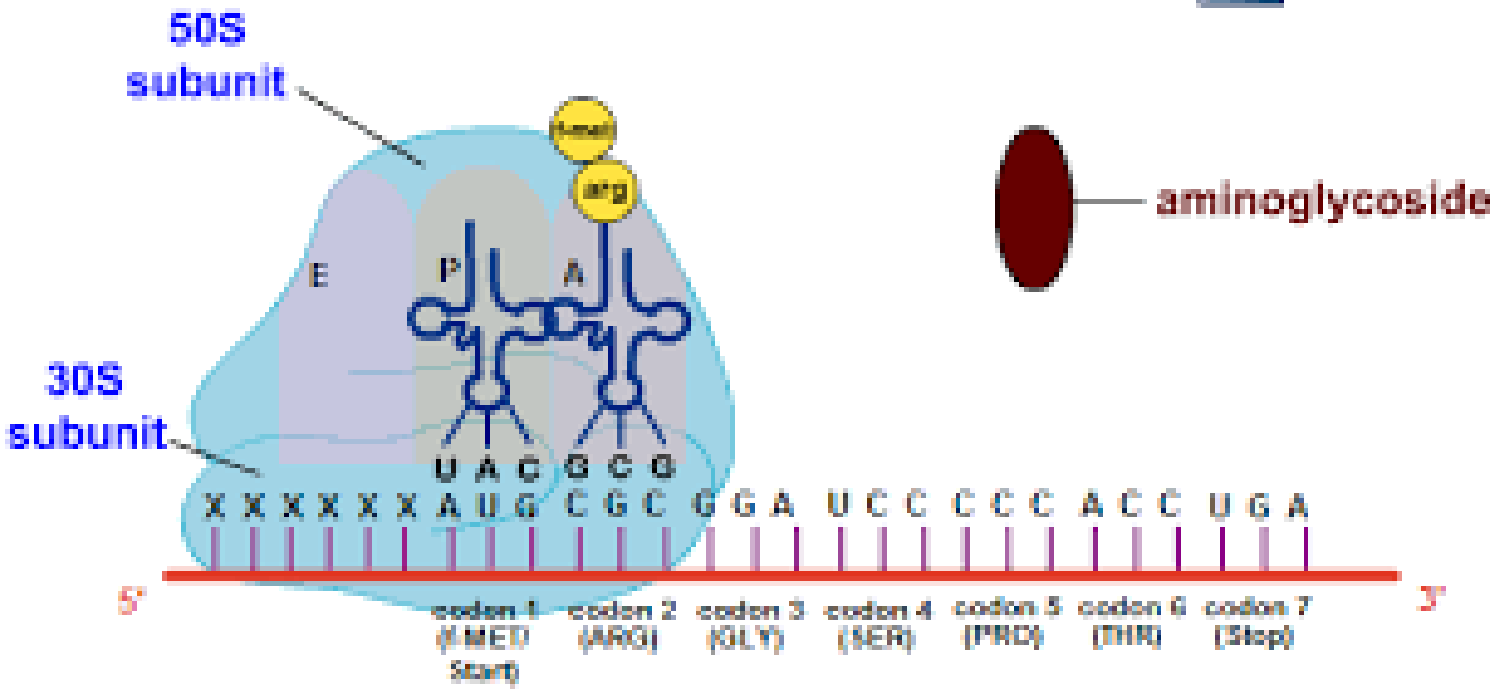
MECHANISM OF ACTION

- Bactericidal antibiotics
- **Described in two main steps:**
  (a) **Transport** through the bacterial cell wall and cytoplasmic membrane.
  (b) **Binding to ribosome** resulting in inhibition of protein synthesis.

TRANSPORT INTO BACTERIA

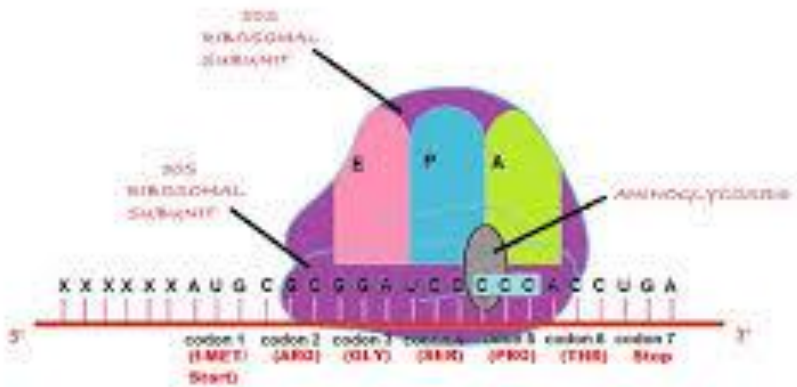
- A multistep process.
- They **diffuse across** through porin channels.
- Entry from the periplasmic space (**space between the inner cytoplasm membrane and the bacterial outer membrane**) across the cytoplasm membrane is carrier mediated.
- These processes are **inactivated under anaerobic conditions.**
- **Penetration** is also favoured by **high pH**.
- Inhibitors of bacterial cell wall (β-lactams, vancomycin) enhance entry aminoglycosides and **exhibit synergism**.

play



INHIBITION OF PROTEIN SYNTHESIS

- Once inside the bacterial cell
- **Streptomycin binds to 30s ribosomes**
- **Other aminoglycosides** bind to 50S subunit, as well as to 305-505 interface.
- They freeze initiation of protein synthesis
- Prevent polysome formation and promote their disaggregation to monosomes.
- Binding to 30s-50s juncture causes **distortion of mRNA codon recognition**
- Resulting in misreading of the code: one or more wrong amino acids are entered in the peptide chain and/ or **peptides of abnormal lengths** are produced.
- Different aminoglycosides cause misreading at different levels depending upon **their selective affinity for specific ribosomal proteins.**



As a result, until there will be no complete polypeptide chain will be produced until the 505 ribosomal subunit reach the stop codon.

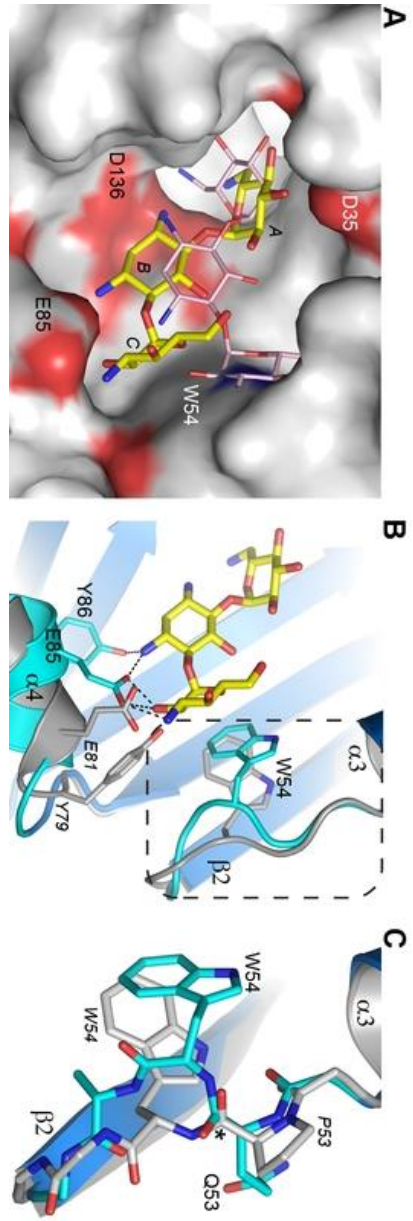
INHIBITION OF PROTEIN SYNTHESIS

- The **cidal action** based on **secondary changes in** the **integrity of** bacterial **cell membrane**.
- After exposure to aminoglycosides, sensitive **bacteria become more permeable**; ions, amino acids and even proteins **leak out followed by cell death**.
- This probably results from **incorporation of the defective proteins into the cell membrane.**
- One of the consequences of aminoglycoside induced alteration of cell membrane is **augmentation of the carrier-mediated entry of the antibiotic.**
- This **reinforces the lethal action**.
- The **cidal action is concentration dependent**
- **Exert** a long and concentration dependent **'postantibiotic effect'.**

Mechanisms of Resistance

Three principal mechanisms have been established:

- (1) production of a transferase enzyme or enzymes inactivates the aminoglycoside by **adenylylation, acetylation, or phosphorylation.** This is the principal type of resistance encountered clinically.
- (2) There is impaired entry of aminoglycoside into the cell. This may be genotypic, resulting from mutation or **deletion of a porin protein** or proteins involved in transport and maintenance of the electrochemical gradient; or phenotypic, eg, resulting from growth conditions under which the **oxygen-dependent transport** process described above is not functional.
- (3) The receptor protein on the **30S ribosomal subunit** may be deleted or altered as a result of a mutation.



Aminoglycoside Uses

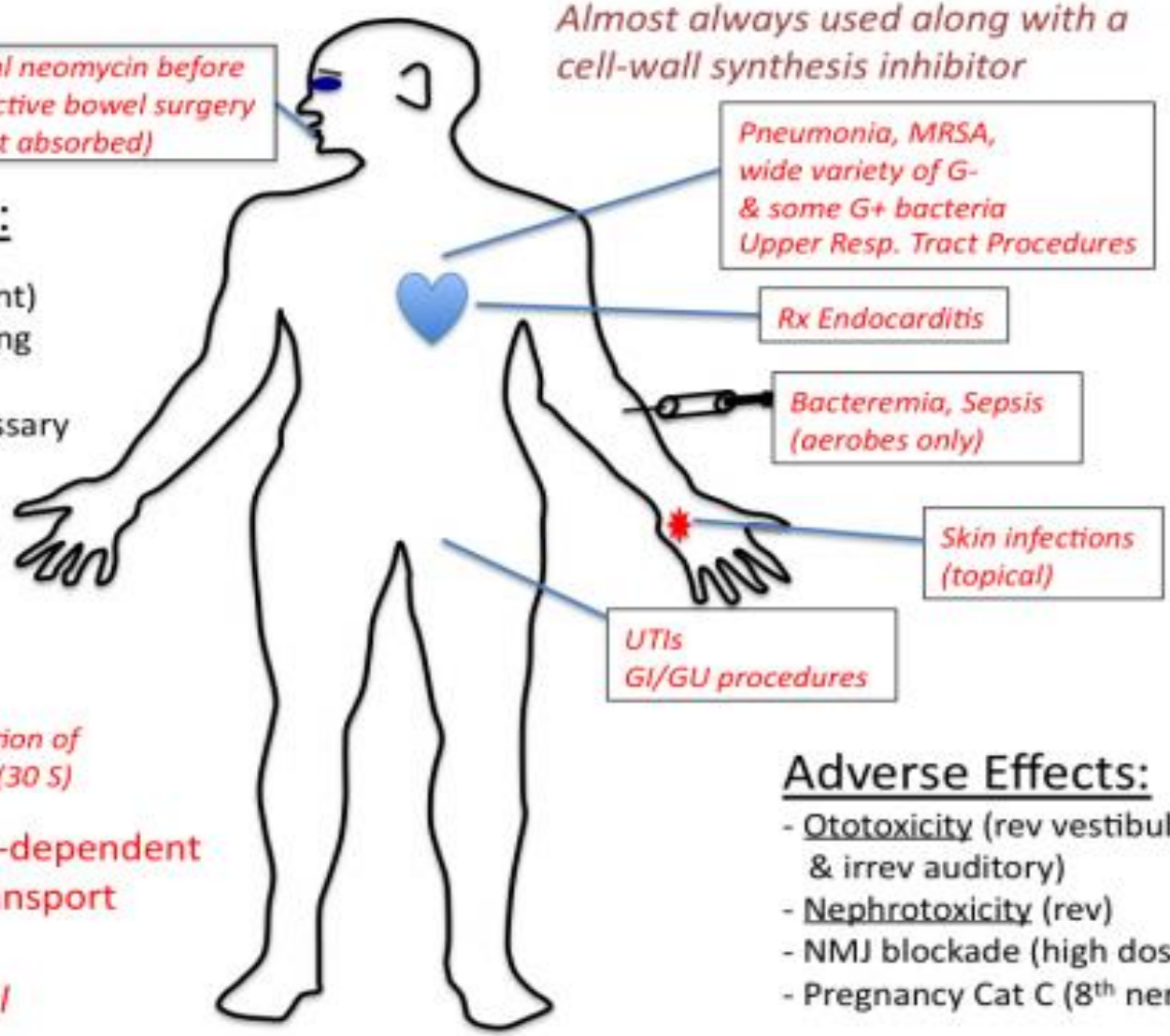
Routes:

im *or* iv,
topical

Pharmacokinetics:

-Vd = ECS (25% body weight)
- adjust maintenance dosing based upon [creatinine]
- plasma monitoring necessary

Almost always used along with a cell-wall synthesis inhibitor



Oral neomycin before elective bowel surgery (not absorbed)

Pneumonia, MRSA, wide variety of G- & some G+ bacteria Upper Resp. Tract Procedures

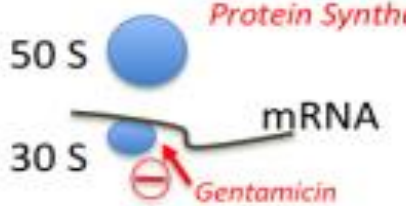
Rx Endocarditis

Bacteremia, Sepsis (aerobes only)

Skin infections (topical)

UTIs GI/GU procedures

Mechanism:



Irreversible inhibition of Protein Synthesis (30 S)

O_2-dependent transport

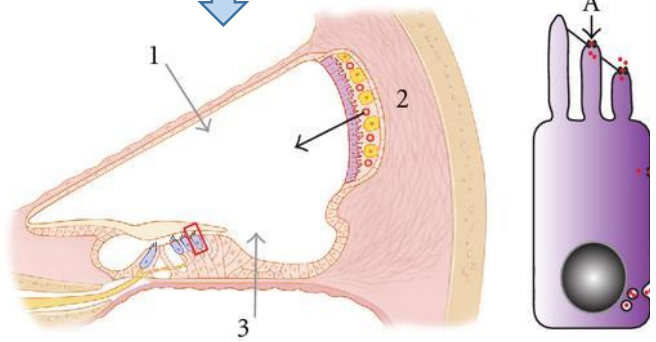
bactericidal

Adverse Effects:

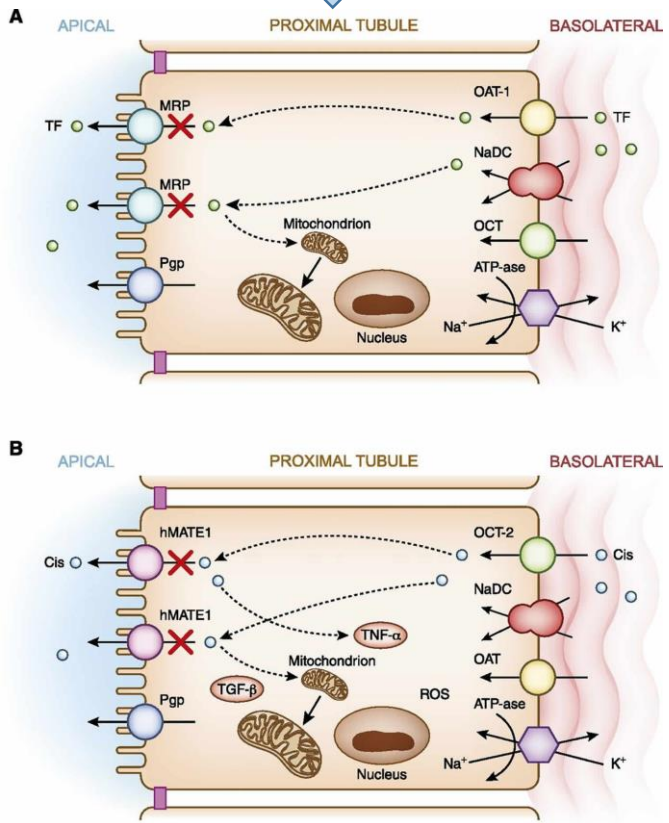
- Ototoxicity (rev vestibular & irrev auditory)
- Nephrotoxicity (rev)
- NMJ blockade (high dose)
- Pregnancy Cat C (8th nerve)

Aminoglycosides Side effects

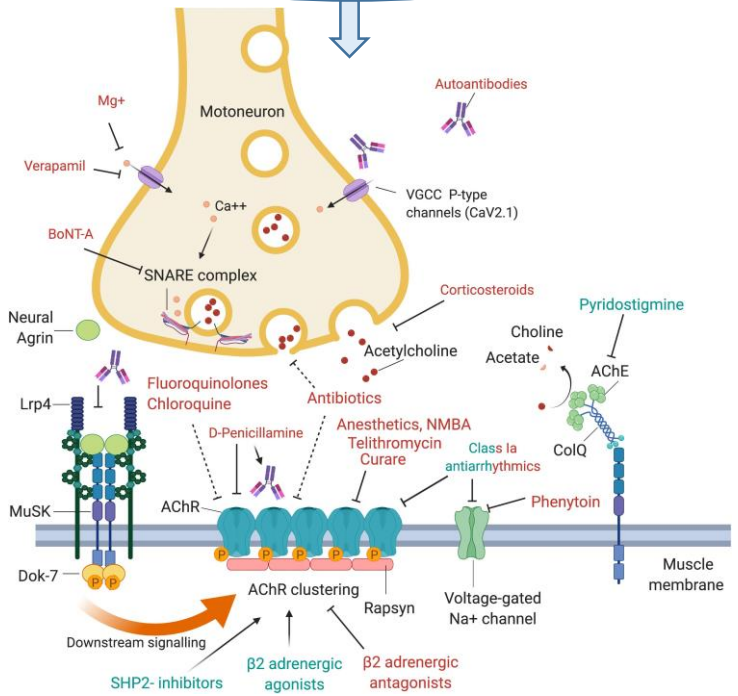
Ototoxicity



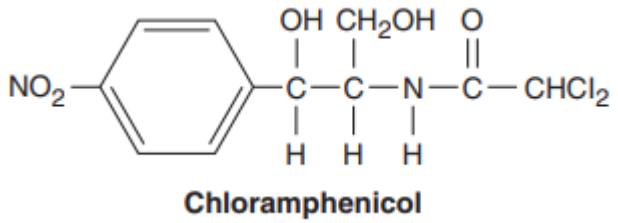
Nephrotoxicity



Neuromuscular blockade



Amphenicols : CHLORAMPHENICOL

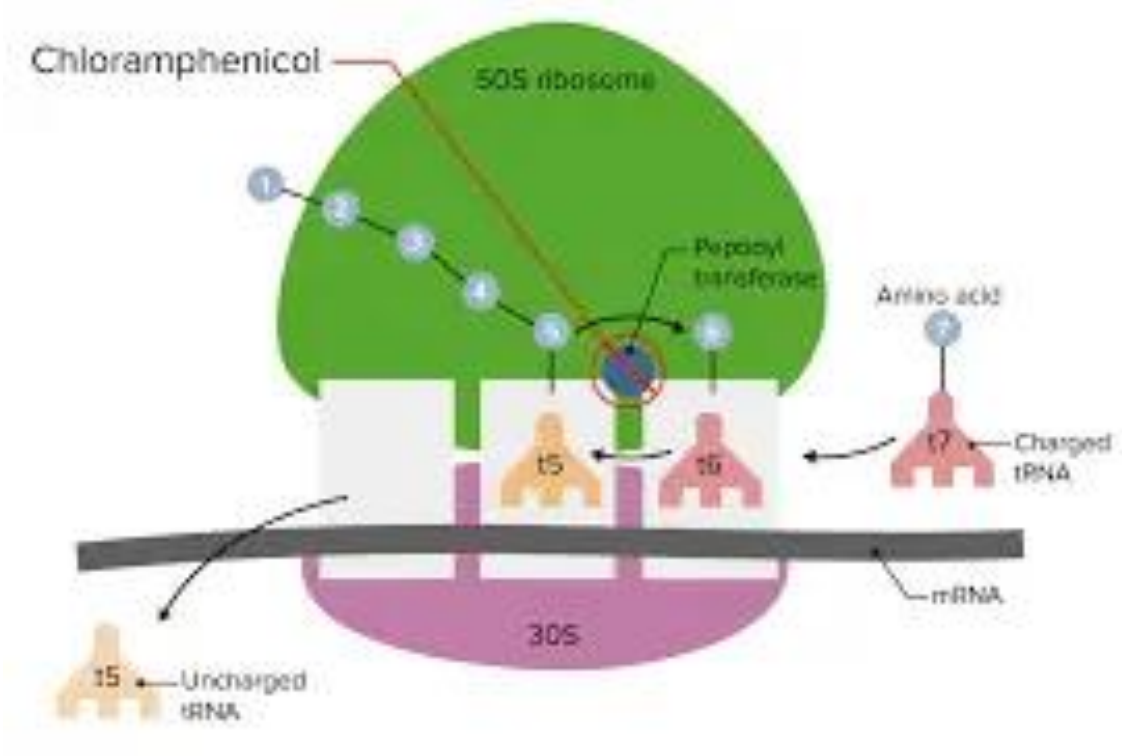


Chloramphenicol

Chloramphenicol has a wide spectrum of antimicrobial activity and is usually bacteriostatic (50S).

Chloramphenicol is a bacteriostatic broad-spectrum antibiotic that is active against both aerobic and anaerobic gram-positive and gram negative organisms. It is active also against Rickettsiae but not Chlamydiae. Most gram-positive bacteria are inhibited at concentrations of 1–10 mcg/mL, and many gram-negative bacteria are inhibited by concentrations of 0.2–5 mcg/mL.

H influenzae, Neisseria meningitidis , and some strains of bacteroides are highly susceptible, and for these organisms, chloramphenicol may be bactericidal.



CHLORAMPHENICOL

Toxicity

1. Gastrointestinal disturbances - superinfection, especially candidiasis.

2. Bone marrow - Inhibition of red cell maturation leads to a decrease in circulating erythrocytes.

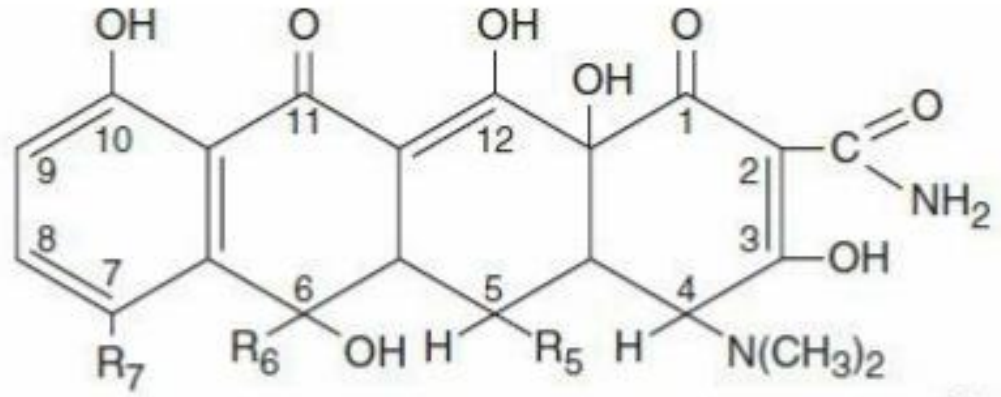
3. Gray baby syndrome - This syndrome occurs in infants characterized by decreased red blood cells, cyanosis, and cardiovascular collapse.

4. Drug interactions - Chloramphenicol inhibits hepatic drug metabolizing enzymes, thus increasing the elimination half-lives of drugs including phenytoin, tolbutamide and warfarin.

Gray baby syndrome

TETRACYCLINES

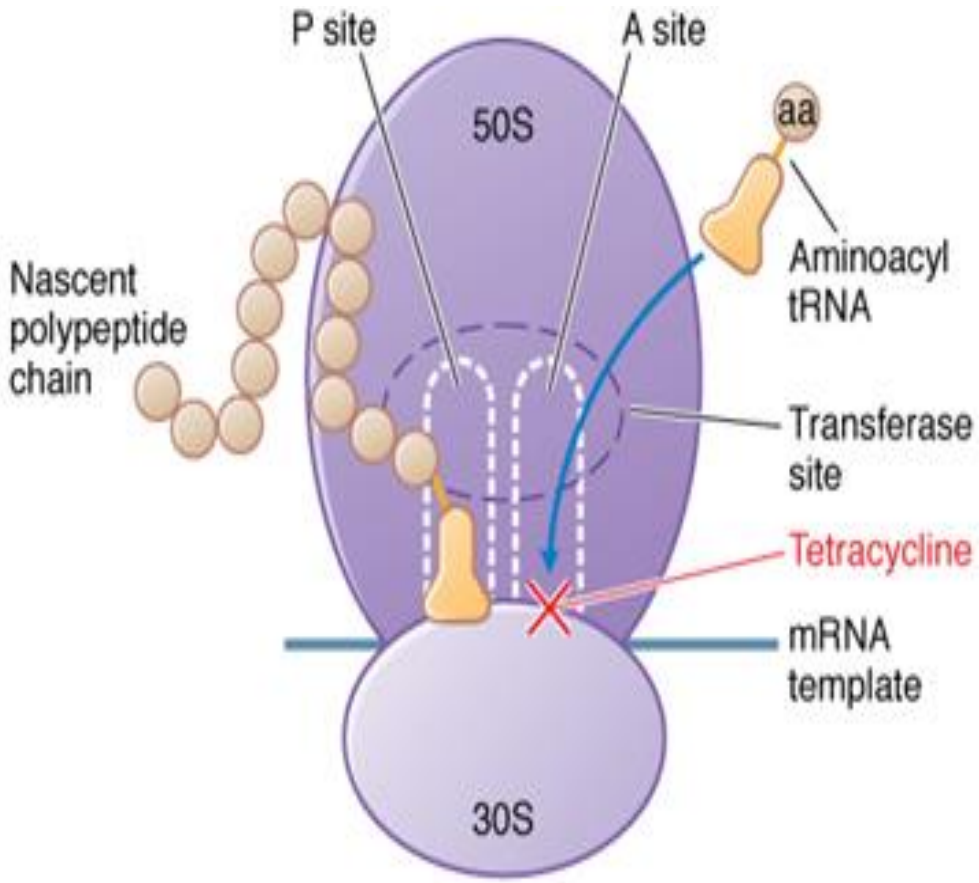
All of the tetracyclines have the basic structure shown at right:



	R_7	R_6	R_5	Renal Clearance (mL/min)
Chlortetracycline	—Cl	$-CH_3$	—H	35
Oxytetracycline	—H	$-CH_3$	—OH	90
Tetracycline	—H	—CH3	—H	65
Demeclocycline	—Cl	—H	—H	35
Methacycline	—H	$=CH_2$*	—OH	31
Doxycycline	—H	$-CH_3$*	—OH	16
Minocycline	$-N(CH_3)_2$	—H	—H	10

*There is no — OH at position 6 on methacycline and doxycycline.

Tetracyclines

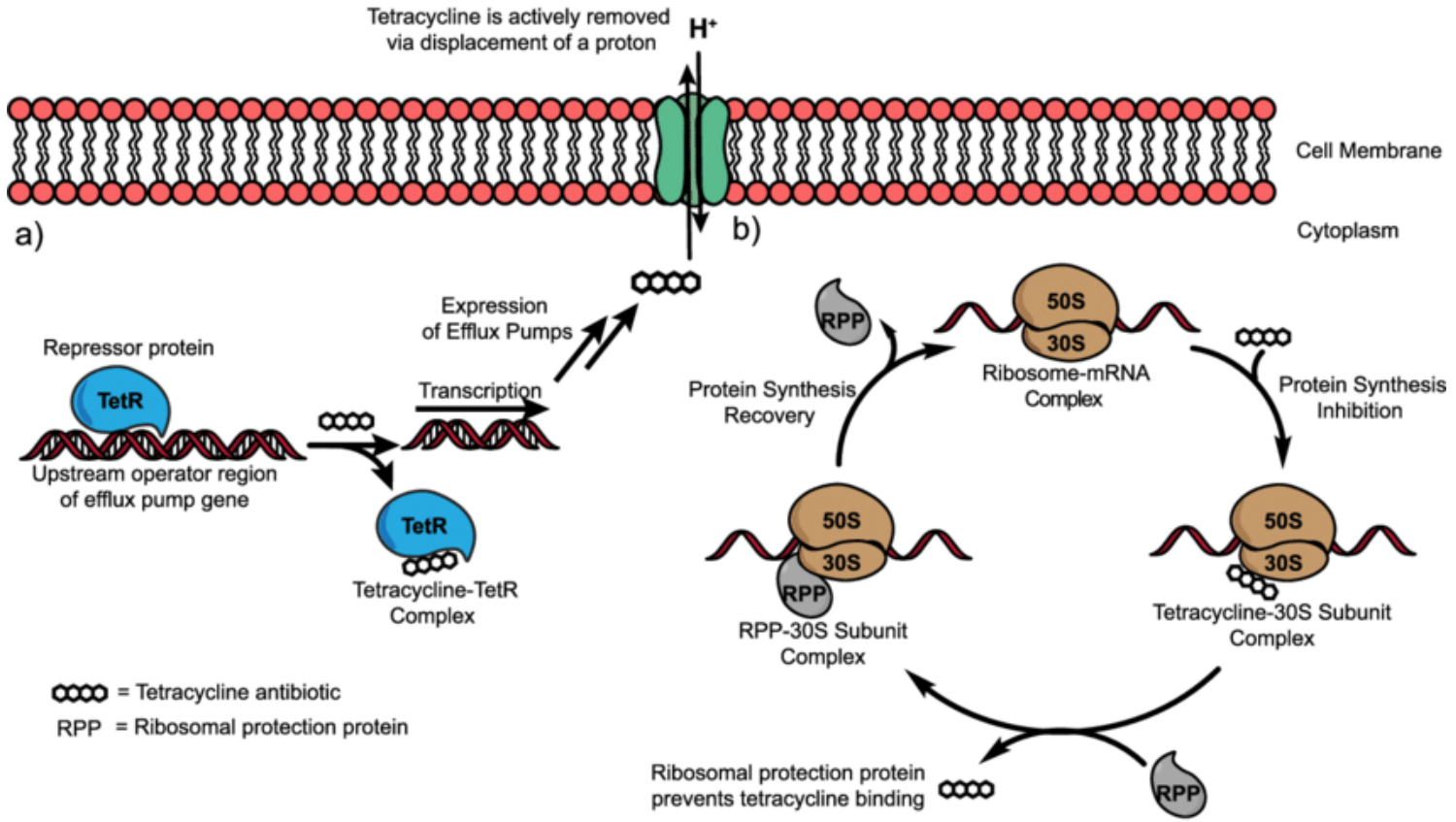


Tetracyclines are active against many gram-positive and gram negative bacteria, including certain anaerobes, rickettsiae, chlamydiae, and mycoplasmas.

Mechanism of action

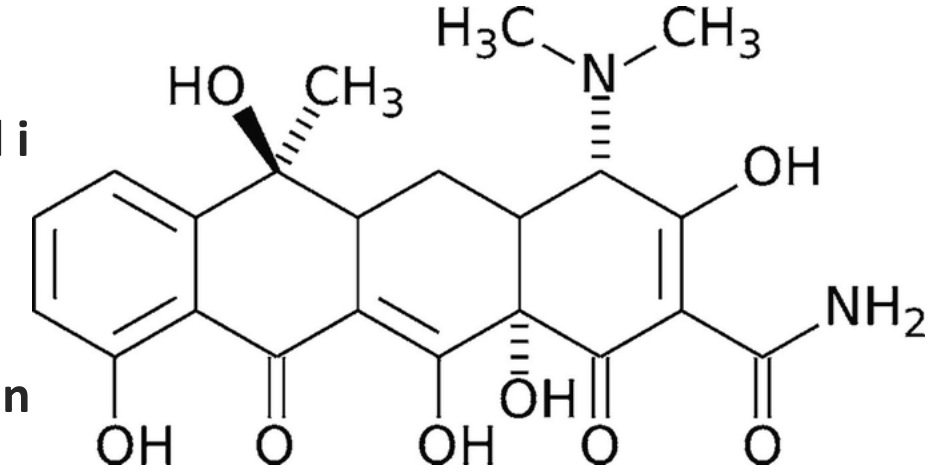
- ✓ Tetracyclines are broad-spectrum bacteriostatic antibiotics
- ✓ **Tetracycline** inhibits protein synthesis by blocking the attachment of charged aminoacyl-tRNA to the A site on the ribosome.
- ✓ **Tetracycline** binds to the 30S and 50S subunit of microbial ribosomes. Thus, it prevents introduction of new amino acids to the nascent peptide chain.

Three mechanisms of resistance to tetracycline analogs have been described:



- impaired influx or increased efflux by an active transport protein pump
- ribosome protection due to production of proteins that interfere with tetracycline binding to the ribosome
- enzymatic inactivation

Pharmacokinetics



Tetracyclines differ in their absorption after oral administration and i their elimination.

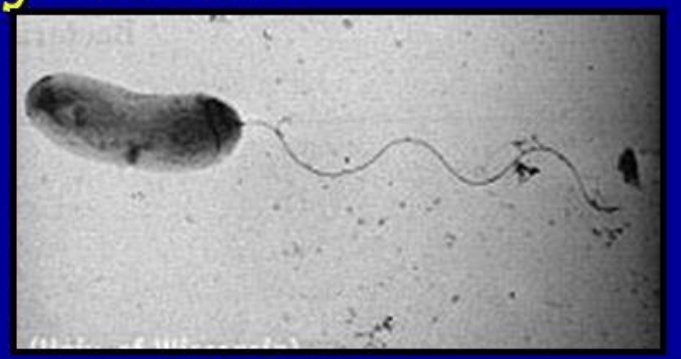
Absorption after oraladministration is approximately 30% for chlortetracycline; 60–70% for tetracycline, oxytetracycline, demeclocycline, and methacycline; and 95–100% for doxycycline an minocycline.

Tigecycline is poorly absorbed orally and must be administered intravenously. A portion of an orally administered dose of tetracycline remains in the gut lumen, alters intestinal flora, and is excreted in the feces. Absorption occurs mainly in the upper small intestine and is impaired by food (except doxycycline and minocycline); by multivalent cations (Ca^{2+} , Mg^{2+}, Fe^{2+}, Al^{3+}); by dairy products and antacids, which contain multivalent cations; and by alkaline pH. Specially buffered tetracycline solutions are formulated for intravenous administration.

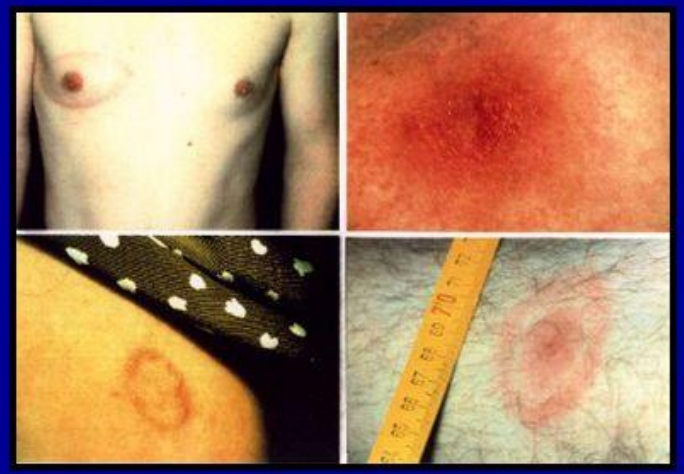
Tetracyclines are 40–80% bound by serum proteins.

Therapeutic Uses of Tetracyclines

- Syphilis
- Anthrax
- Bacillary infections
  - Brucellosis
  - Tularemia
  - Cholera
- Infections with spirochetes
  - Yaws
  - Lyme disease
  - Relapsing fever



Vibrio cholerae



Lyme Disease

Tetracyclines -Toxicity

- ✓ Gastrointestinal disturbances

  Nausea, vomiting, and diarrhea, Tetracyclines alter the normal gastrointestinal flora

- ✓ Bony structures and teeth

  (tooth enamel dysplasia and irregularities in bone growth)

- ✓ Hepatic toxicity

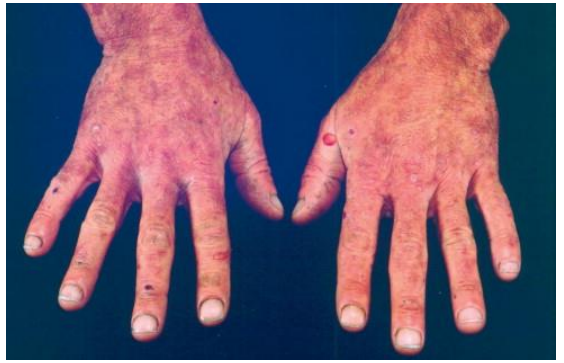
  (impair liver function and lead to hepatic necrosis)

- ✓ Renal toxicity

  (renal tubular acidosis, Fanconi's syndrome)

- ✓ Photosensitivity

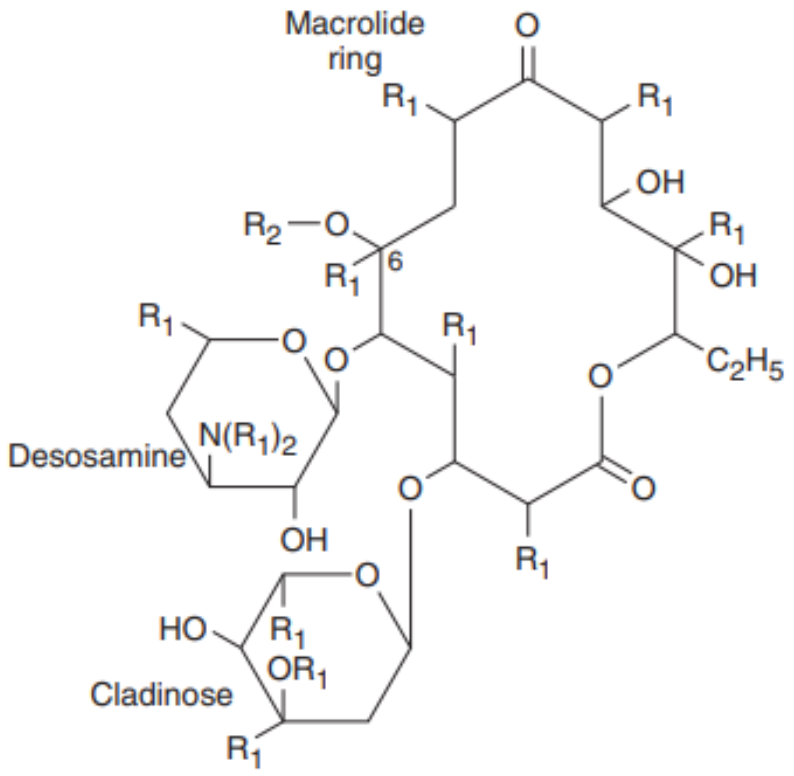
  (skin sensitivity to ultraviolet light)



- ✓ Vestibular toxicity
- ✓ Teratogenic

MACROLIDES

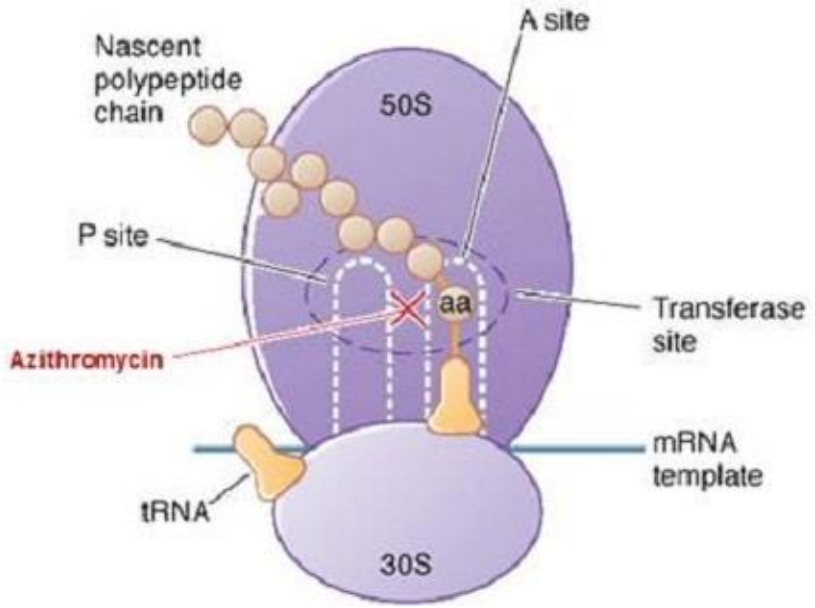
- The macrolides are a group of closely related compounds characterized by a macrocyclic lactone ring (usually containing 14 or 16 atoms) to which deoxy sugars are attached. The prototype drug, **erythromycin**, which consists of two sugar moieties attached to a 14-atom lactone ring, was obtained in 1952 from *Streptomyces erythreus*. Clarithromycin and azithromycin are semisynthetic derivatives of erythromycin.



Erythromycin (R_1 = CH_3, R_2 = H)

Clarithromycin (R_1, R_2 = CH_3)

Mechanism of Action & Antimicrobial Activity

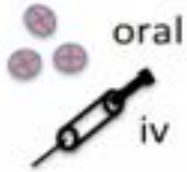


The antibacterial action of erythromycin and other macrolides may be inhibitory or bactericidal, particularly at higher concentrations, for susceptible organisms. Activity is enhanced at alkaline pH. Inhibition of protein synthesis occurs via binding to the 50S ribosomal RNA.

Erythromycin is active against susceptible strains of gram-positive organisms, especially pneumococci, streptococci, staphylococci, and corynebacteria. Mycoplasma pneumoniae , L pneumophila , Chlamydia trachomatis , Chlamydia psittaci, Chlamydia pneumoniae , H pylori, Listeria monocytogenes, and certain mycobacteria (Mycobacterium kansasii, Mycobacterium scrofulaceum) are also susceptible. Gramnegative organisms such as Neisseria sp, Bordetella pertussis, Bartonella henselae, and Bartonella quintana as well as some Rickettsia species, Treponema pallidum , and Campylobacter species are susceptible. Haemophilus influenzae is somewhat less susceptible.

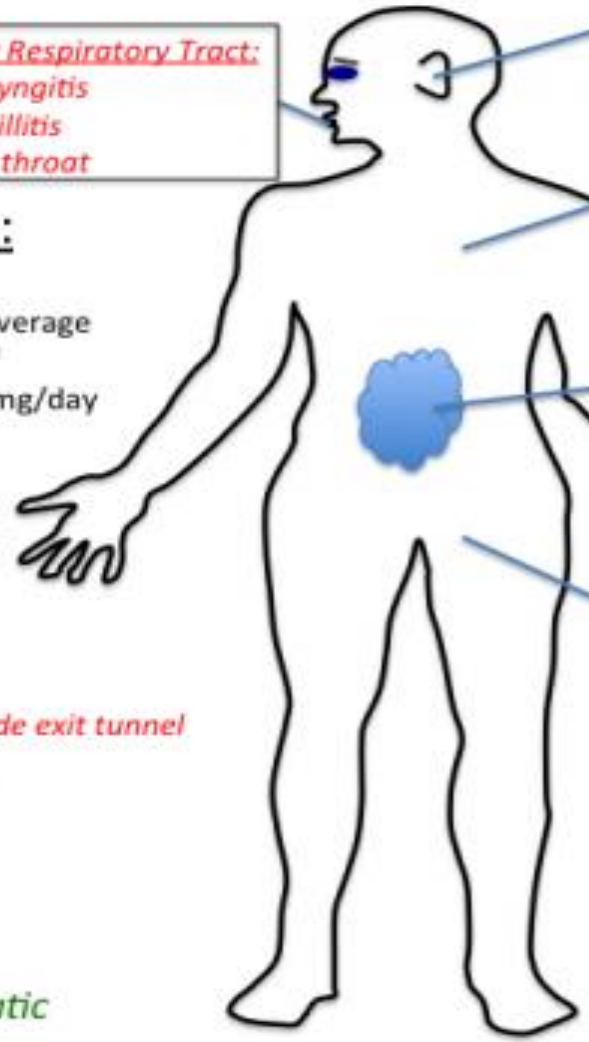
Macrolide Uses

Routes:



Pharmacokinetics:

- Azithromycin $t_{1/2}$ =3 days
- a 1 g dose provides 7 day coverage
- common therapy consists of 500 mg loading dose & 250 mg/day for 4 more days.



Upper Respiratory Tract:
- *Pharyngitis*
- *Tonsillitis*
- *Sore throat*

Otitis Media

Lower respiratory tract infections:
Pneumonia
MAC (Mycobacterium avis complex)
Legionnaire's
Anthrax

Ulcers (H. pylori)
drug combo including Clarithromycin

Uncompliated skin infections (staph)

STDs
Chancroid disease in men
Chlamydia
Gonorrhea

Mechanism:

Bind to 50S & block polypeptide exit tunnel to prevent chain elongation

bacteriostatic

Adverse Effects:

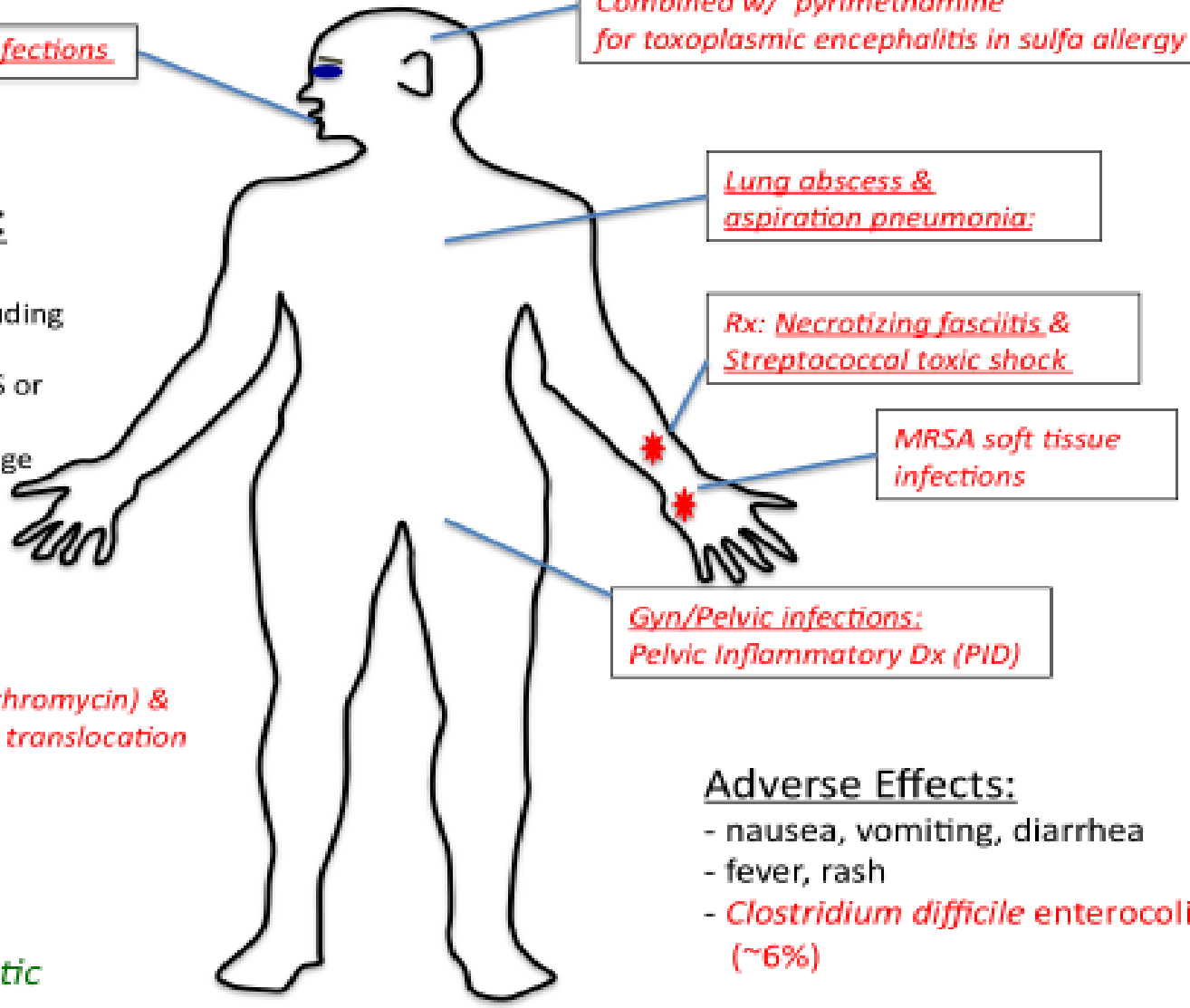
- nausea, vomiting, diarrhea
- abdominal pain
- liver toxicity (estolate related)
- **inhibit P-450** (drug interactions)
- ↑ QTc

Clindamycin Therapeutics

Routes:

Pharmacokinetics:

- $t_{1/2}$ = 2.5 hrs
- penetrates most tissues including abscesses
- does NOT penetrate into CNS or intracellular
- hepatic metabolism, no dosage adjustment with renal failure



Mechanism:

Binds to 50S (same site as erythromycin) & inhibits peptidyl transferase & translocation

bacteriostatic

Adverse Effects:

- nausea, vomiting, diarrhea
- fever, rash
- *Clostridium difficile* enterocolitis (~6%)

Thank You For Attention!

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