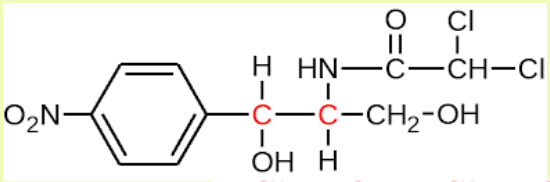
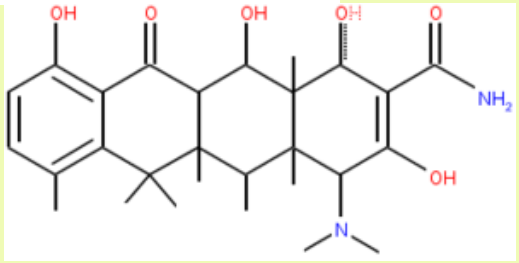
Poltava State Medical University
Department of Pharmacology, Clinical pharmacology and Pharmacy

PHARMACOLOGY OF ANTIBIOTICS OF DIFFERENT GROUPS. PRINCIPLES OF THE RATIONAL THERAPY BY ANTIBIOTICS

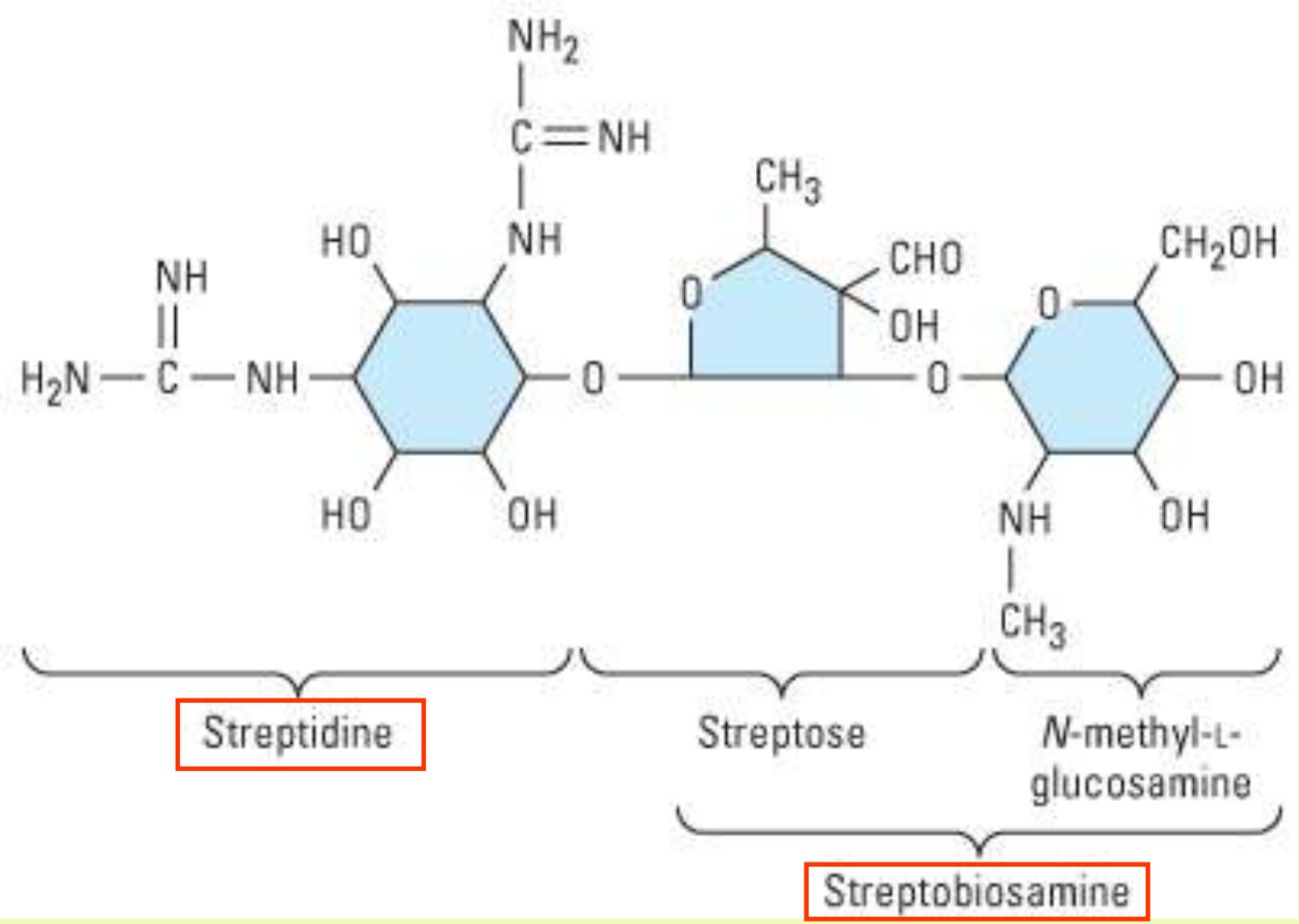




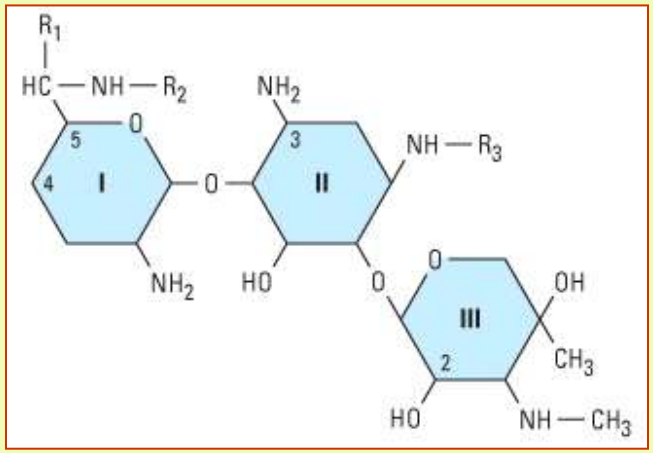
CONTENTS

I. AMINOGLYCOSIDES

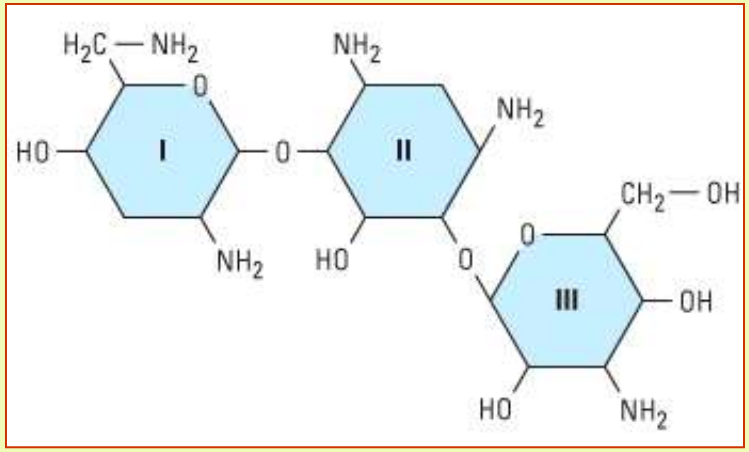
Aminoglycosides have a hexose ring,
to which various amino sugars are attached
by glycosidic linkages.
They are water-soluble, stable in solution, and more active at alkaline than at acid pH.
Aminoglycosides have polar groups in their molecules and do not absorb in GIT.



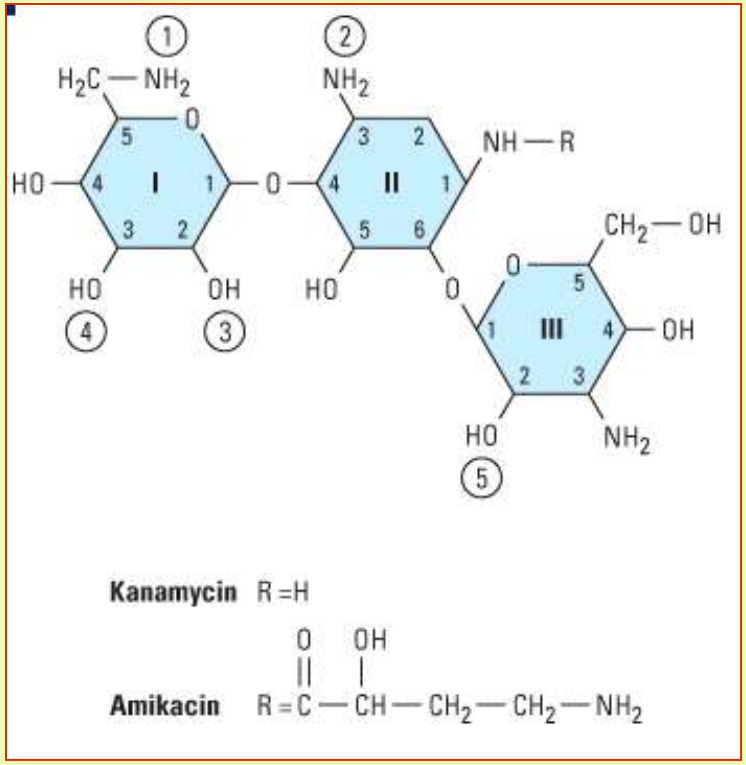
Streptomycin



Gentamicin



Tobramycin



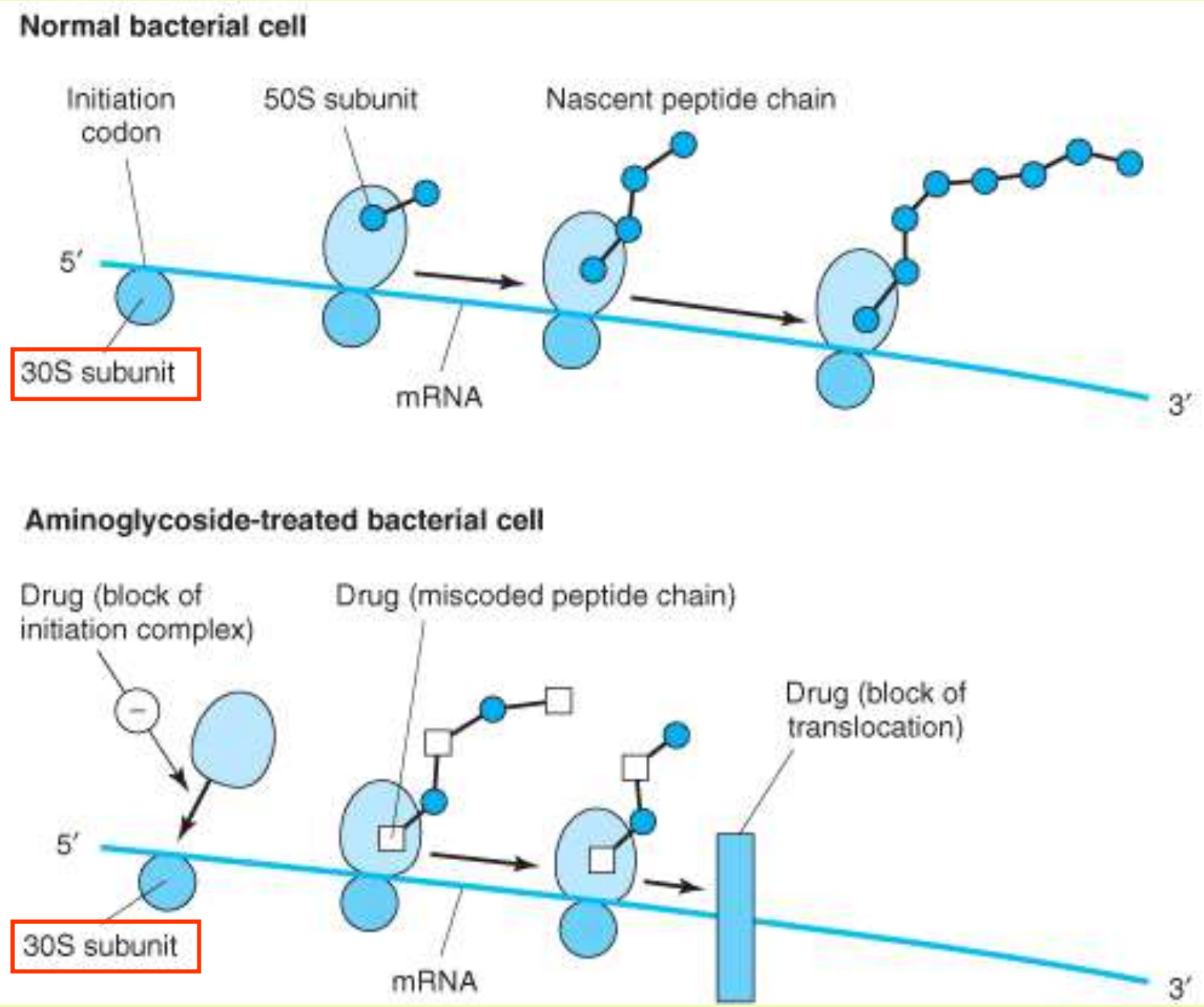
Mechanism of action

Inside the cell, aminoglycosides bind to specific 30S-subunit ribosomal proteins and inhibit protein synthesis in at least three ways:

(1) interference with the initiation complex of peptide formation;

(2) misreading of mRNA, which causes incorporation of incorrect amino acids into the peptide, resulting in a nonfunctional or toxic protein;

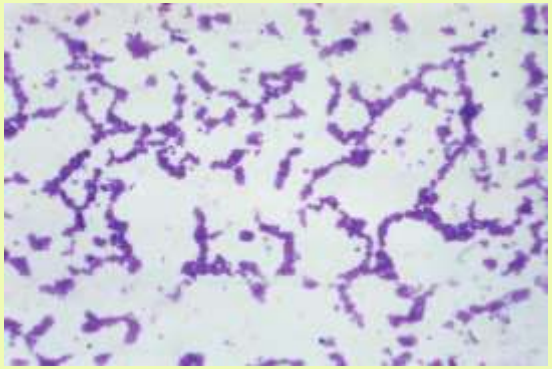
(3) breakup of polysomes into nonfunctional monosomes.


Normal bacterial cell
Initiation codon
50S subunit
Nascent peptide chain
5′
30S subunit
mRNA
3′
Aminoglycoside-treated bacterial cell
Drug (block of initiation complex)
Drug (miscoded peptide chain)
Drug (block of translocation)
5′
30S subunit
mRNA
3′

Type of action and spectrum

Aminoglycosides act as bactericidal
on dividing and non-dividing extracelular microorganisms.

They are active against staphylococci and aerobic Gram-negative organisms including P. aeruginosa and almost all the Enterobacteriaceae.



Clinical uses

Aminoglycosides are mostly used against Gram-negative enteric bacteria, especially when the isolate may be drug-resistant.

They are almost always used in combination with a β-lactam antibiotic to extend coverage to include potential Gram-positive pathogens and to take advantage of the synergism between these two classes of drugs.

Penicillin-aminoglycoside combinations also are used to achieve bactericidal activity in the treatment of enterococcal, viridans streptococcal and staphylococcal endocarditis.

Side effects

All aminoglycosides are ototoxic and nephrotoxic.

These adverse reactions are more likely to be encountered when therapy is continued for more than 5 days, at higher doses, in the elderly, and in the setting of renal insufficiency.

Ototoxicity can manifest as auditory damage, resulting in tinnitus and high-frequency hearing loss initially, or as vestibular damage, evident by vertigo, ataxia, and loss of balance.

Streptomycin and gentamicin are the most vestibulotoxic.

Neomycin, kanamycin, and amikacin are the most ototoxic agents.

Neomycin, tobramycin, and gentamicin are the most nephrotoxic.

In very high doses, aminoglycosides can produce a curare-like effect (neurotoxicity) with neuromuscular blockade that results in respiratory paralysis (is reversible by calcium gluconate or neostigmine).

Hypersensitivity occurs infrequently.

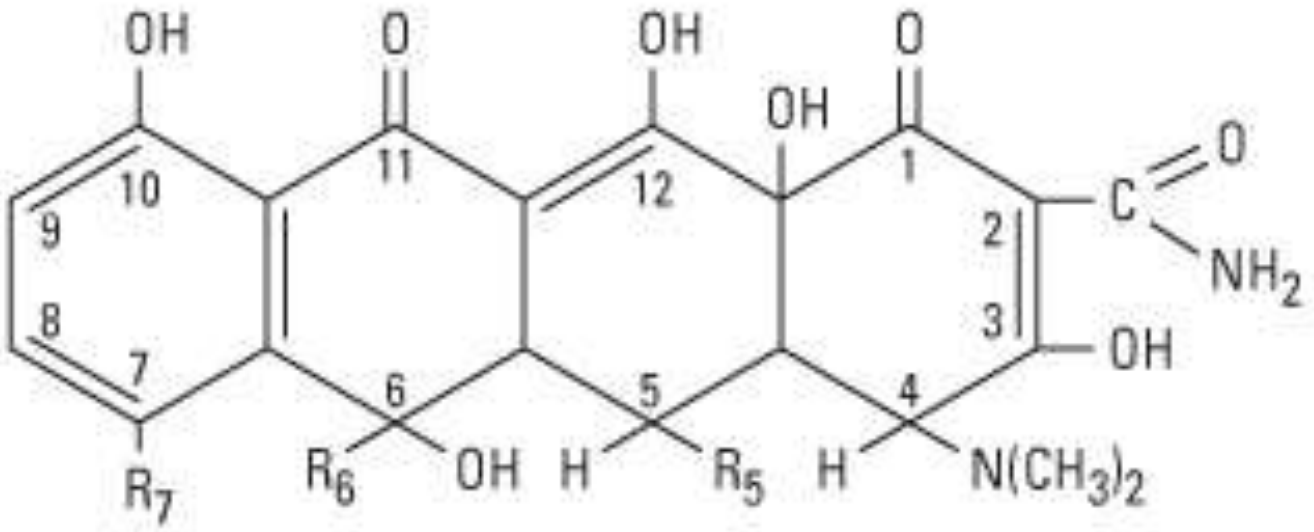
Mechanisms of resistance

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. Impaired entry of aminoglycoside into the cell. This may be genotypic, resulting from mutation or phenotypic, resulting from growth conditions.
3. The receptor protein on the 30S ribosomal subunit may be deleted or altered as a result of a mutation.

Streptomycin is an old well known aminoglycoside antibiotic. Its antibacterial activity is due to its binding to the 30S subunit of the bacterial ribosome and inhibiting of protein synthesis. It has a wide spectrum of antibacterial activity but is primarily used to treat mycobacterial infections (IM).

Side effects are eighth nerve toxicity (vestibulotoxicity more than deaf-ness), nephrotoxicity, allergic reactions.

II. TETRACYCLINES

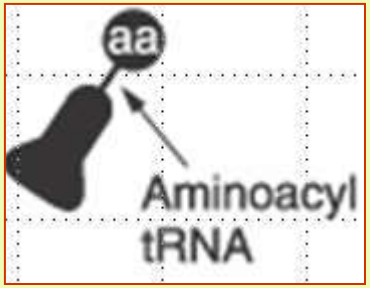


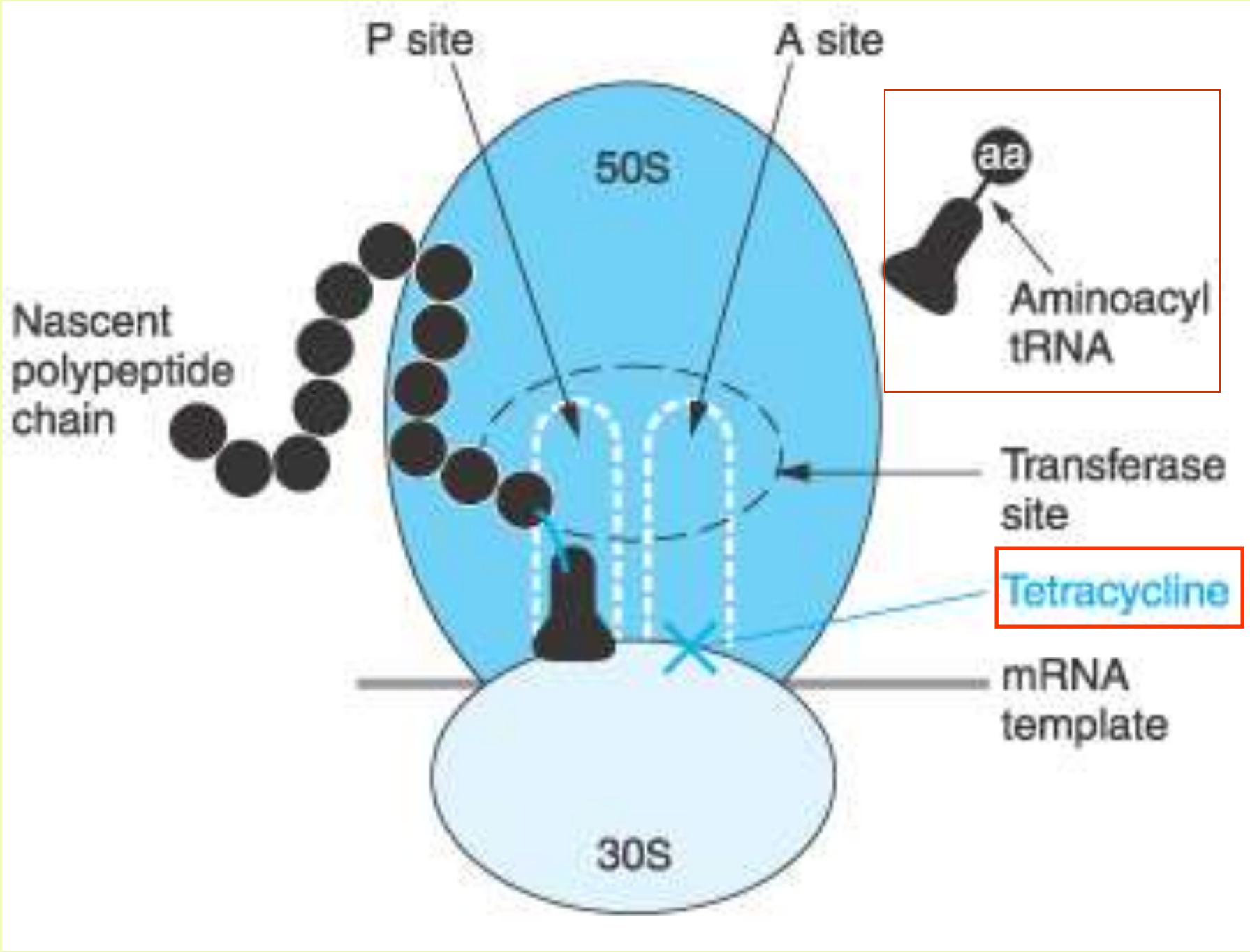
	R_7	R_6	R_5	Renal Clearance (mL/min)
Chlortetracycline	—Cl	—CH_3	—H	35
Oxytetracycline	—H	—CH_3	—OH	90
Tetracycline	—H	—CH3	—H	65
Demeclocycline	—Cl	—H	—H	35
Methacycline	—H	=CH_2*	—OH	31
Doxycycline	—H	—CH_3*	—OH	16
Minocycline	—$N(CH_3)_2$	—H	—H	10

Mechanism of action

Tetracyclines enter microorganisms in part by passive diffusion and in part by an energy-dependent process of active transport. Susceptible cells concentrate the drug intracellularly. Once inside the cell, tetracyclines bind reversibly to the 30S subunit of the bacterial ribosome, blocking the binding of aminoacyl-tRNA to the acceptor site on the mRNA-ribosome complex This prevents addition of amino acids to the growing peptide.

Tetracyclines are broad-spectrum bacteriostatic antibiotics that inhibit protein synthesis.




P site
A site
50S
aa
Aminoacyl tRNA
Nascent polypeptide chain
Transferase site
Tetracycline
mRNA template
30S

Antimicrobial activity

Tetracyclines are active against many Gram-positive and Gram-negative bacteria, including anaerobes, rickettsiae, chlamydiae, mycoplasmas, and L-forms; and against some protozoa, eg, amebas.

The antibacterial activities of most tetracyclines are similar except that tetracycline-resistant strains may be susceptible to doxycycline and minocycline, all of which are poor substrates for the *efflux pump* that mediates resistance.

Pharmacokinetics

Tetracyclines mainly differ in their absorption after oral administration and their elimination. Absorption after oral administration is approximately 60–70% for tetracycline, oxytetracycline, and methacycline; and 95–100% for doxycycline and minocycline.

A portion of an orally administered dose of tetracycline remains in the gut lumen, modifies 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 divalent cations (Ca^{2+}, Mg^{2+}, Fe^{2+}) or Al^{3+}; by dairy products and antacids, which contain multivalent cations; and by alkaline pH.

Tetracyclines are 40–80% bound by serum proteins.
Tetracyclines are distributed widely to tissues and body fluids except for CNS.
Minocycline reaches very high concentrations in tears and saliva, which makes it useful for eradication of the meningococcal carrier state.
Tetracyclines cross the placenta to reach the fetus and are also excreted in milk. As a result of chelation with calcium, tetracyclines are bound to and damage – growing bones and teeth.

Tetracyclines are excreted mainly in bile and urine. Concentrations in bile exceed those in serum tenfold. Some of the drug excreted in bile is reabsorbed from the intestine (enterohepatic circulation) and may contribute to maintenance of serum levels.
From 10 to 50% of various tetracyclines is excreted into the urine, mainly by glomerular filtration. 10-40% of the drug is excreted in feces.
Doxycycline, in contrast to other tetracyclines, is eliminated by nonrenal mechanisms.
Tetracyclines and macrolides have a good intracellular distribution.

Tetracyclines are classified as:

(1) **short-acting** (chlortetracycline, tetracycline, oxytetracycline) based on plasma $t_{1/2}$ of 6–8 h;
(2) **intermediate acting** (demeclocycline and methacycline) – $t_{1/2}$ 12 h;
(3) **long-acting** (doxycycline and minocycline) with plasma $t_{1/2}$ 16–18 h.

The almost complete absorption and slow excretion of doxycycline and minocycline allow for once-daily dosing.

Clinical uses

Tetracyclines are the drugs of choice in infections with *M. pneumoniae*, chlamydiae, rickettsiae, and some spirochetes.

They are used in combination regimens for gastric and duodenal ulcer disease caused by *H. pylori*.

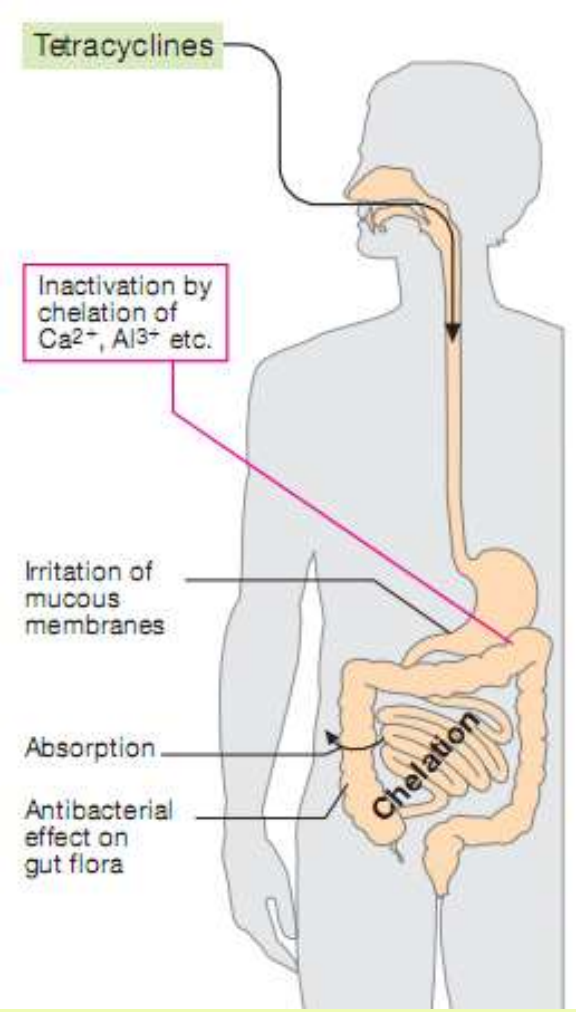
They may be used in various Gram-positive and Gram-negative bacterial infections, including *Vibrio* infections, but in cholera, tetracycline resistance has appeared during epidemics.

Tetracyclines remain effective in most chlamydial infections, including sexually transmitted diseases.
A tetracycline usually in combination with an aminoglycoside is indicated for plague, tularemia, and brucellosis.
Tetracyclines are sometimes used in the treatment of protozoal infections due to *E. histolytica* or *P. falciparum*.
Other uses include acne, exacerbations of bronchitis, community-acquired pneumonia, Lyme disease, relapsing fever, leptospirosis, and nontuberculous mycobacterial infections (due to *M. marinum*).

Side effects

Nausea, vomiting, and diarrhea are the most common reasons for tetracycline medication (direct local irritation of the GIT).

Nausea, anorexia, and diarrhea can be controlled by administering the drug with food or carboxymethylcellulose, reducing drug dosage, or discontinuing the drug.



Tetracyclines modify the normal flora, with suppression of susceptible coliform organisms and overgrowth of pseudomonas, proteus, staphylococci, resistant coliforms, clostridia, and candida. This can result in intestinal functional disturbances candidiasis, or enterocolitis.

Tetracyclines are bound to calcium deposited in newly formed bone or teeth in young children. When a tetracycline is given during pregnancy, it is deposited in the fetal teeth, leading to enamel dysplasia. ("tetracyclin teeth"). It is deposited in bone and causes deformity or growth Inhibition (in fetus or children under 8 years of age).

Tetracyclines can impair hepatic function, especially during pregnancy, in patients with preexisting hepatic insufficiency and when high doses are given IV.

Tetracyclines other than doxycycline may accumulate to toxic levels in patients with impaired kidney function.

Renal injury is a conraindication to the administration of tetrcyclins.

IV injection can lead to venous thrombosis.

IM injection produces painful local irritation and should be avoided.

Systemically administered tetracycline, especially demeclocycline, can induce sensitivity to sunlight or ultraviolet light, particularly in fair-skinned persons.

Dizziness, vertigo, nausea, and vomiting have been noted particularly with doxycycline and minocycline at high doses.

Mechanisms of resistance

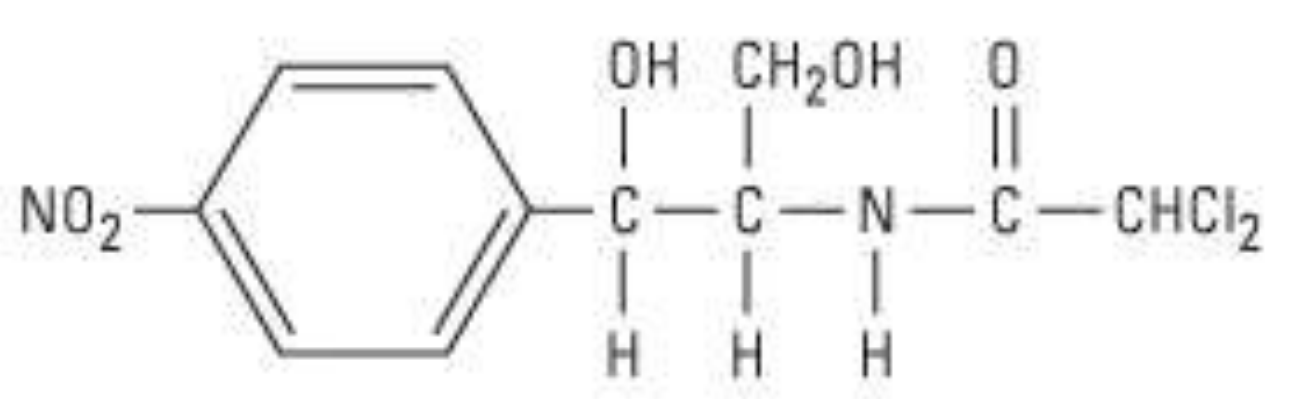
to tetracyclines and its analogues are:

(1) 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) enzymatic inactivation.

III. AMPHENICOLS

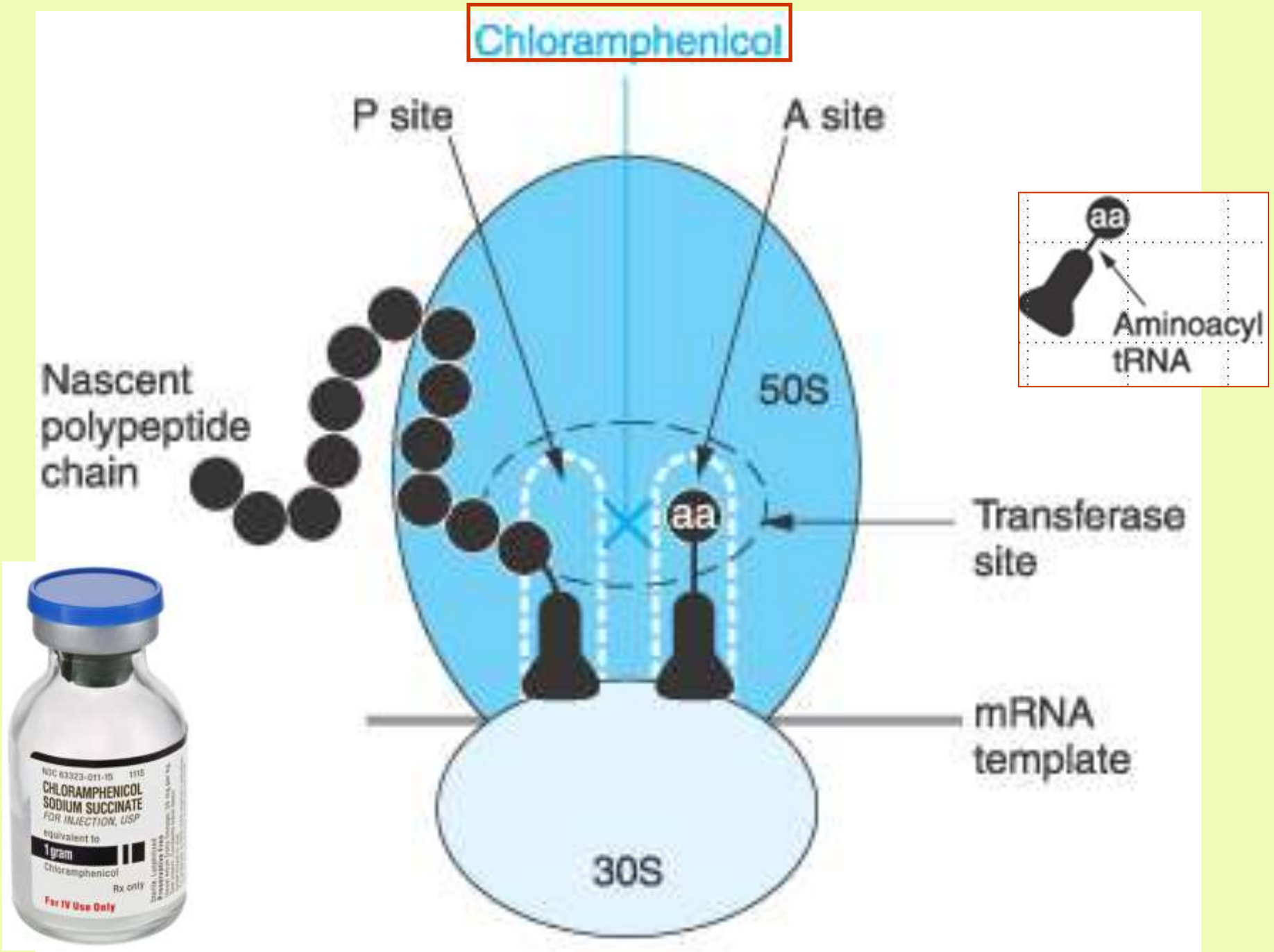


- **Chloramphenicol**
- **Thiamphenicol** (with SH– group instead of $N0_2$– group): less side effects but less antibacterial activity

Chloramphenicol isolated from *Streptomyces venezuelae* was the first broad-spectrum antibacterial developed (1947). It is now produced synthetically because has a very simple structure.

Mechanism of action

It is a nonionized, highly lipophilic compound that enters bacterial cells by passive diffusion and binds primarily to the 50S ribosomal subunit. Bacterial protein synthesis is inhibited.


Chloramphenicol
P site
A site
aa
Aminoacyl tRNA
Nascent polypeptide chain
50S
aa
Transferase site
mRNA template
30S
NDC 63323-011-15
CHLORAMPHENICOL SODIUM SUCCINATE
FOR INJECTION, USP
equivalent to
1 gram
Chloramphenicol
Rx only
For IV Use Only

Chloramphenicol can also bind to the mammalian ribosome (70S) that resembles bacterial ribosomes and interfere with mitochondrial protein synthesis. This is particularly relevant **in erythropoietic cells**.
It is bacteriostatic for most Gram-positive and many Gram-negative aerobic bacteria.
Resistance is commonly plasmid-mediated and occurs as a result of enzymatic inactivation by several types of chloramphenicol transacetylase.

Clinical uses

Because of potential toxicity and bacterial resistance chloramphenicol is rarely used.

It may be considered for treatment of serious rickettsial infections such as typhus and Rocky Mountain spotted fever.

It is an alternative to a beta-lactams for treatment of meningococcal meningitis in patients who have major hypersensitivity reactions to penicillin or bacterial meningitis caused by penicillin-resistant strains of pneumococci.

Side effects of chloramphenicol

Adults occasionally develop nausea, vomiting, and diarrhea. This is rare in children.

Oral or vaginal candidiasis may occur as a result of alteration of normal microbial flora.

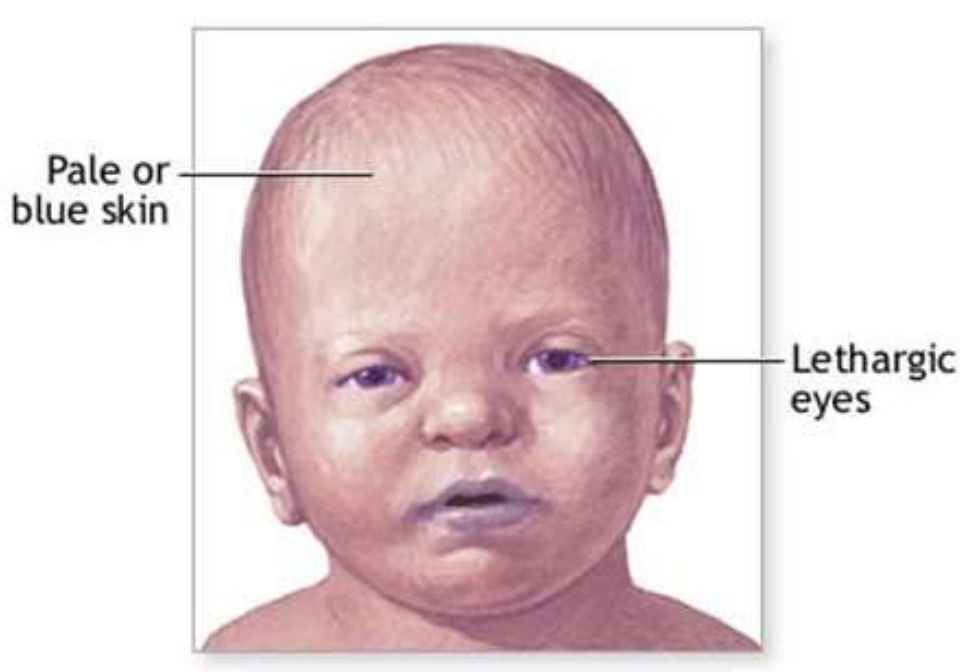
Chloramphenicol causes a dose-related reversible suppression of red cell production at dosages exceeding 50 mg/kg/d after 1–2 weeks.

Aplastic anemia, a rare consequence of chloramphenicol administration by any route. It tends to be irreversible and can be fatal.

Newborn infants lack an effective glucuronic acid conjugation mechanism for the degradation and detoxification of chloramphenicol.

When infants are given dosages above 50 mg/kg/d, the drug may accumulate, resulting in the grey baby syndrome with vomiting, flaccidity, hypothermia, gray color, shock, and collapse.

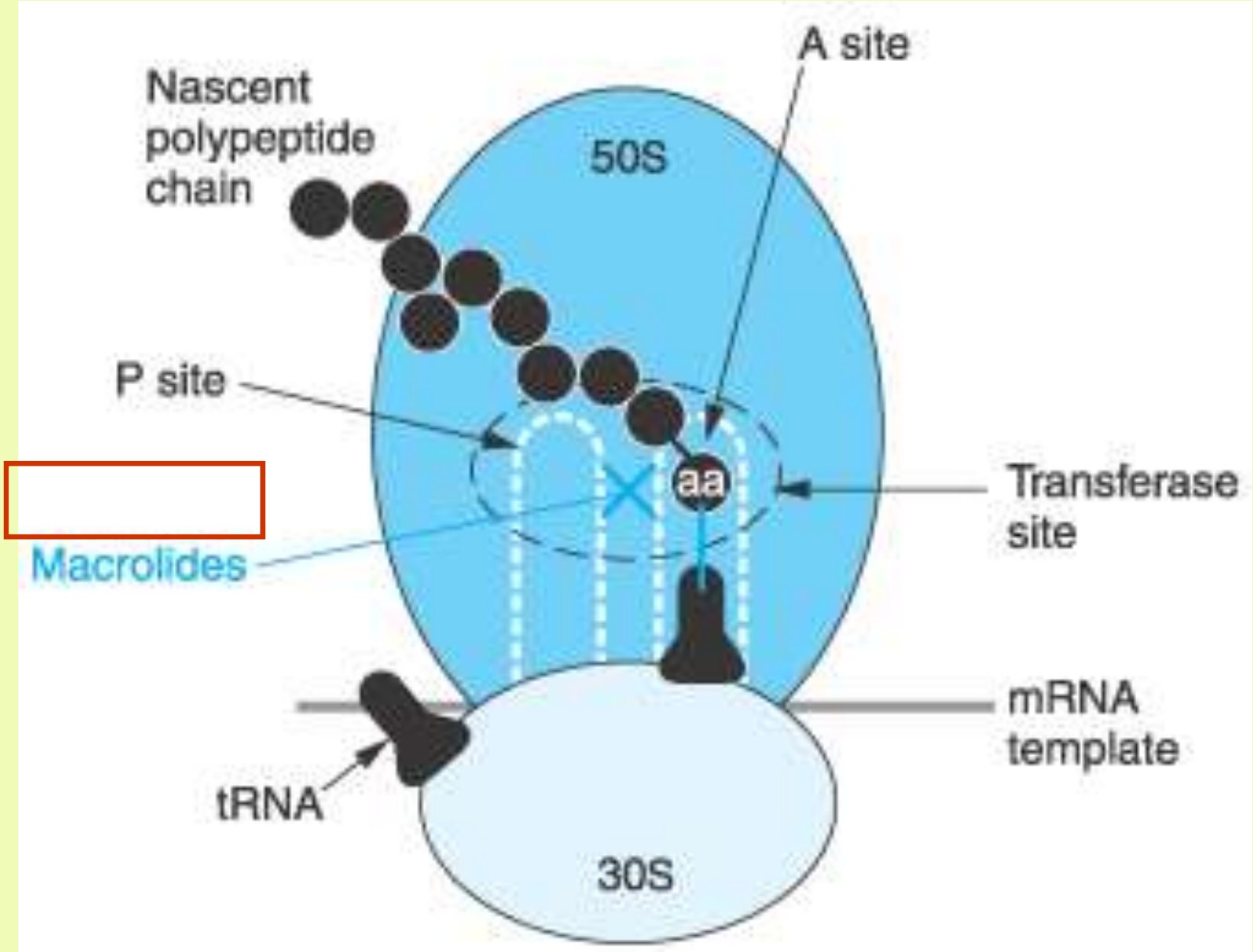
To avoid this toxic effect, chloramphenicol should be used with caution in infants and the dosage limited to 50 mg/kg/d or less (during the first week of life) in full-term infants.



IV. MACROLIDES and KETOLIDES

Azithromycin ($t_{1/2}$ 40–68 h)
Erythromycin
Clarithromycin (***antihelicobacter activity***)
Josamycin (*saliva excretion*)
Midecamycin
Oleandomycin (*saliva excretion*)
Roxithromycin
Spiramycin (*saliva excretion*)
Ketolides: Telithromycin

Inhibition of protein synthesis by macrolides



Antibacterial spectrum of macrolides

Active against Gram-positive aerobic bacteria, *Mycoplasma* and *Bartonella henselae* (cat scratch disease) with good intracellular distributions.

Erythromycin

Erythromycin is a drug of choice for treatment of *Campylobacter jejuni* infections.

It is one of the drugs of choice for treatment of *Mycoplasma* infections.

Erythromycin has greater activity against Staphylococcus than lincomycin but not clindamycin.

Resistance to erythromycin is usually plasmid encoded.

Side effects of erythromycin

Anorexia, nausea, vomiting, and diarrhea accompany oral administration. GI intolerance, which is due to a direct stimulation of gut motility, is the most common reason for discontinuing erythromycin and substituting another antibiotic.

Erythromycin can produce acute cholestatic hepatitis (fever, jaundice, impaired liver function). Most patients recover from this, but hepatitis recurs if the drug is readministered.

Erythromycin metabolites can inhibit cytochrome P450 enzymes and thus increase the serum concentrations of some other drugs.

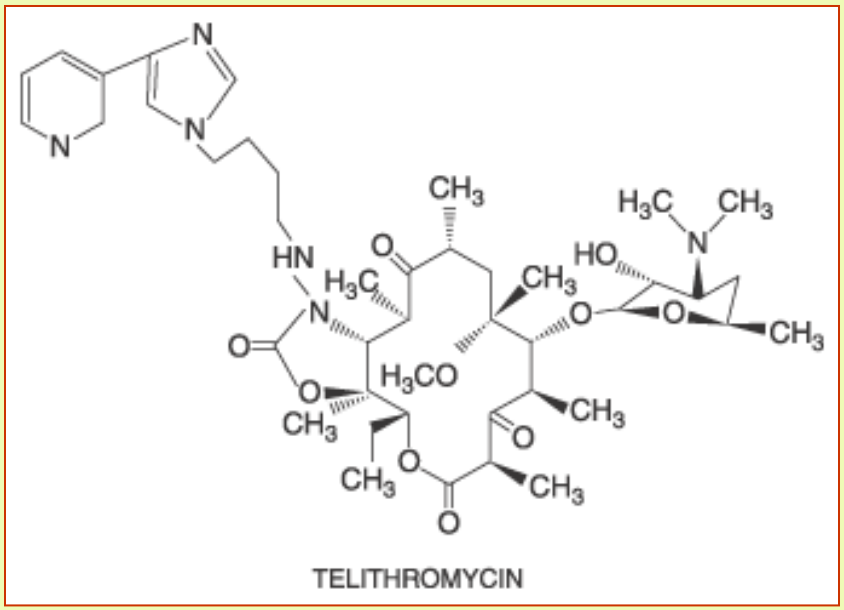
Resistance to erythromycin

is usually plasmid-encoded. Three mechanisms have been identified:

(1) reduced permeability of the cell membrane or active efflux;

(2) production (by Enterobacteriaceae) of esterases that hydrolyze macrolides;

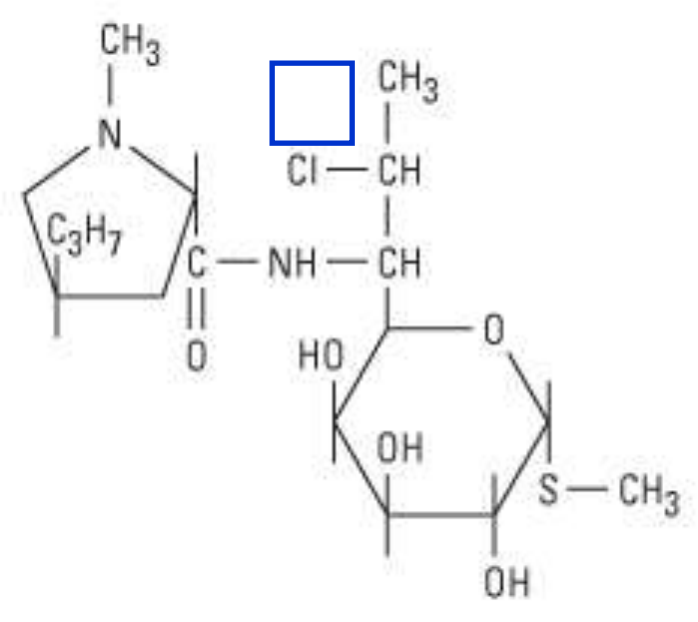
(3) modification of the ribosomal binding site (so-called ribosomal protection) by chromosomal mutation or by a macrolide-inducible or constitutive methylase. Cross-resistance is complete between erythromycin and the other macrolides.



Many macrolide-resistant strains are susceptible to ***ketolides***, for. e.g.:

Telithromycin is active in vitro against *S. pyogenes, S. pneumoniae, S. aureus, H. influenzae, Moraxella catarrhalis*, mycoplasmas, *Legionella*, C*hlamydia, H. pylori, N. gonorrhoeae, B. fragilis, and T. gondii*.

V. LINCOSAMIDES



Clindamycin
is a chlorine-substituted derivative of **lincomycin**, an antibiotic that is elaborated by *Streptomyces lincolnensis.*

Clindamycin is indicated for treatment of *anaerobic infection caused by bacteroides and other anaerobes* that often participate in mixed infections.
Clindamycin is used to treat penetrating wounds of the abdomen and the gut; infections of female genital tract, and aspiration pneumonia.
Clindamycin is now recommended rather than erythromycin for prophylaxis of endocarditis in patients with valvular heart disease who are undergoing certain dental procedures.
Common ***adverse effects*** are diarrhea and colitis due to *C. difficile;* nausea, skin rashes; impaired liver function and neutropenia.

VI. STREPTOGRAMINS

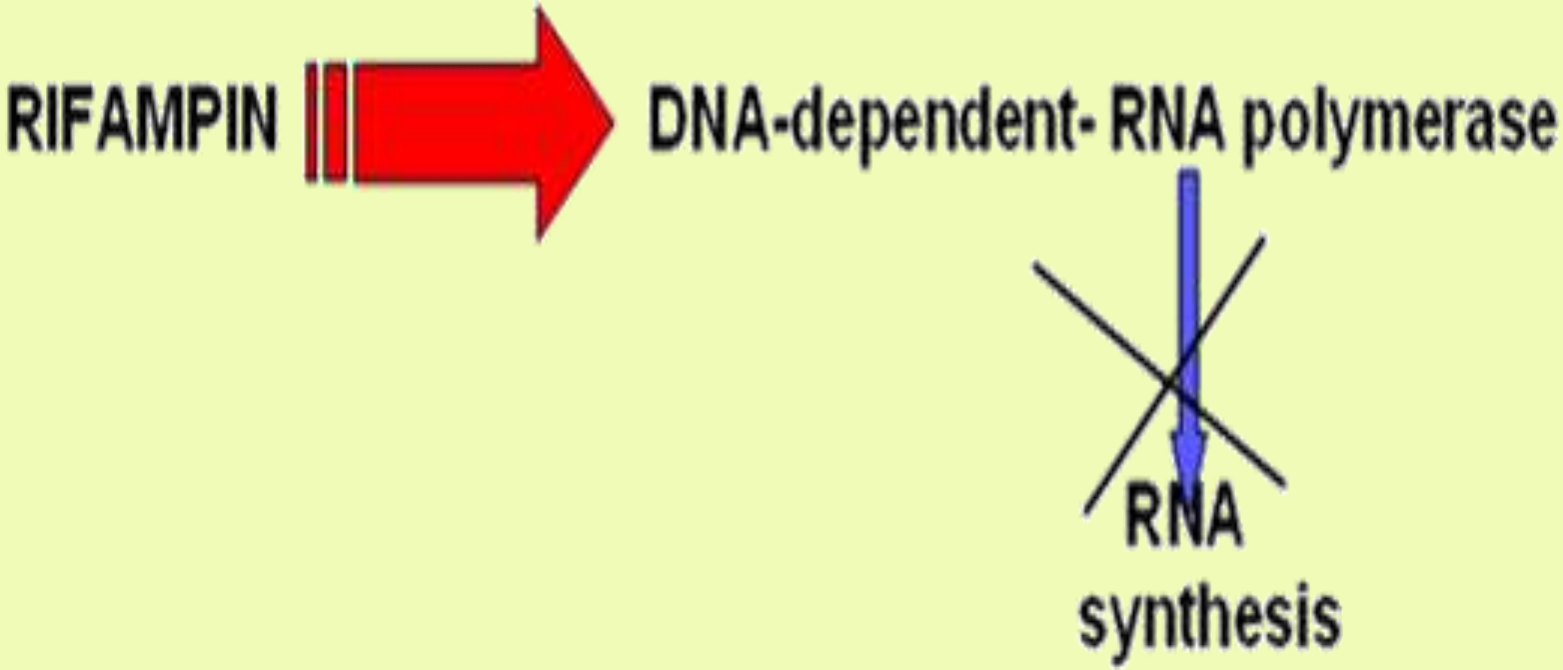
Quinupristin-dalfopristin is a combination of two streptogramins – quinupristin, a streptogramin B, and dalfopristin, a streptogramin A in a 30:70 ratio. It is a protein synthesis inhibitor rapidly bactericidal for most microorganisms.

It is approved for the treatment of infections caused by staphylococci or by vancomycin-resistant strains of *E. faecium*, but not *E. faecalis*.

The principal toxicities are infusion-related events, such as pain at the infusion site, and arthralgia-myalgia syndrome.

VII. RIFAMICINS

Rifamicins are antibiotics which disturb functions of nucleic acids. In such a way they inhibit mRNA synthesis and following protein synthesis



Spectrum of action includes most Gram-positive and many Gram-negative microorganisms, *Mycobacterium tuberculosis, Mycobacterium leprae*.

Clinical uses are tuberculosis (in combination with other agents), atypical mycobacterial infections, leprosy, bacterial infections caused by sensitive microbes: pneumonia, cholecystitis, osteomyelitis, etc (as alternative antibiotic because of rapid imaging of resistance).

Side effects are manifested as red discoloration of urine, sweat, tears, and contact lenses; proteinuria and impaired antibody response; changes in the half-life of a number of co-administered drugs metabolized by cytochrome P-450 system due to the induction of microsomal oxidation. rash, GI disturbances, renal damage jaundice and severe hepatic dysfunction also can occur.

VIII. GLYCOPEPTIDES

Teicoplanin, Bacitracin and Vancomycin work by blocking the construction of a cell wall. They interfere with the transport of peptdoglycans through the cytoplasmic membrane and are active against Gram-positive bacteria. Bacitracin is a polypeptide mixture, markedly nephrotoxic and used only topically with neomycin.

Vancomycin and Teicoplanin are the drugs of choice for the pseudomembranous enterocolitis caused by *C. difficile*. They are not absorbed.

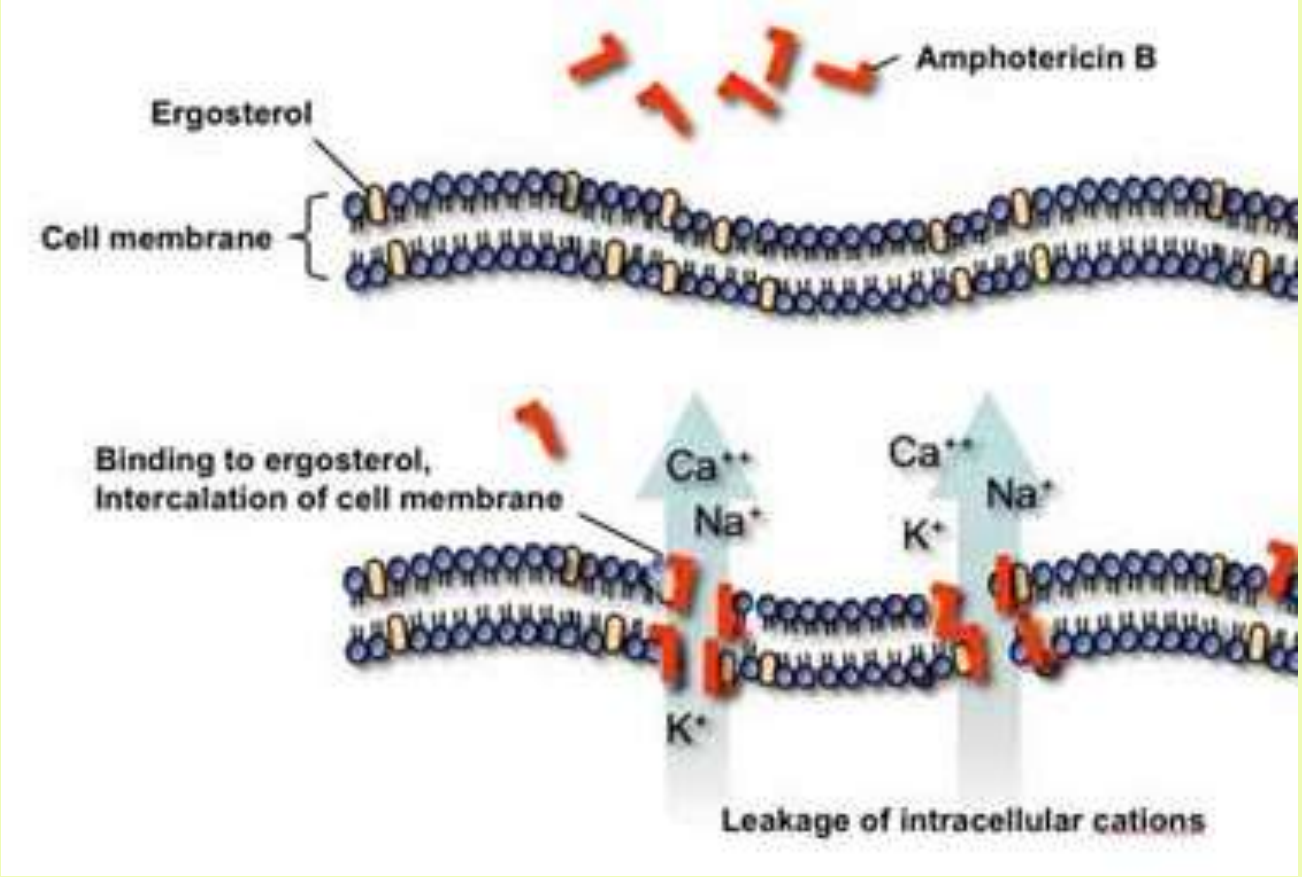
Vancomycin is used IV to treat complicated skin infections, bloodstream infections, endocarditis bone and joint infections, and meningitis caused by methicillin resistant *S.aureus*.

Common side effects include pain in the area of injection, allergic reactions, and occasionally hearing loss, low BP, or bone marrow suppression.

Vancomycin is on the WHO List of Essential Medicinesas critically important for human medicine

IX.POLYENES

Polyenes are the antifungal antibiotics influencing structure of cell membranes.



Nystatin is a polienic antibiotic with narrow spectrum of action influencing *C. albicans.* is used to treat Candida infections of skin, mucous membranes, and intestinal tract; is well tolerated.

Amphotericin B is a broad-spectrum antifungal agent effective against *Histoplasma capsulatum, Cryptococcus neoformans, Coccidioides immitis, Candida* species, *Blastomyces dermatitidis,* some strains of *Aspergillus* and *Sporotrichum.* It is the most effective drug available for systemic fungal infections which is approved for the treatment of life-threatening fungal infections in patient with impaired immunity; pulmonary, cutaneous, and disseminated forms of blastomycosis; acute pulmonary coccidiomycosis; pulmonary histoplasmosis; *C. neoformans* infections, candidiasis, including disseminated forms. The drug may cause many ***side effects*** hypersensitivity reactions, anaphylaxis, fever, chill, headache, gastrointestinal disturbances; decreased renal function.

X. POLYMYXINS

Ttere are **polymixins B, E, M.**They interact with a specific lipopolysaccharide component of the bacterial cell membrane. Membrane lipid structure is distorted with an increase in permeability to polar molecules resulting in marked changes in the cell metabolism. Polymixins have narrow spectrum of action including Gram-negative rods and *P. aeruginosa.*

Colistin (Polymyxin E) has a bactericidal action against Gram-negative bacilli.

Oral colistin is used to *sterilise* the bowel before surgery.

Inhaled colistin is used to treat chest Infections in patients with cystic fibrosis.

CONTROL TASKS

- A patient with prostatitis was prescribed with doxycycline. A doctor advised to avoid sun bathes during the treatment. Which probable adverse reaction is a reason for such instruction?

A. Phototoxicity B. Hepatotoxicity C. Nephrotoxiity D. Ototoxicity E. Dysbacteriasis. (A)

- Rickettsia infection was successfully treated with chloramphenicol, but the therapy was complicated by endotoxic reaction. What is the origin of this complication?

A. Bacteriolysis and release of endotoxins B. Direct toxicity for bone marrow C. Nephrotoxicity of antibiotic D. Hepatotoxicity of antibiotic E. Hypersensitivity and allergic reaction. (A)

- A patient came to a doctor with complaints of urine and lacrimal liquid painted red. It is known from the patient's anamnesis that he was treated for pulmonary tuberculosis. What anti-tubercular antibiotic became the cause of such complications?

A. Amikacinum B. Streptomycini sulfas C. Rifampicinum D. Tetracyclinum E. Erythromycinum. (C)

THE END

Thank you

for attention!