Lecture 22:

Ahtibiotics

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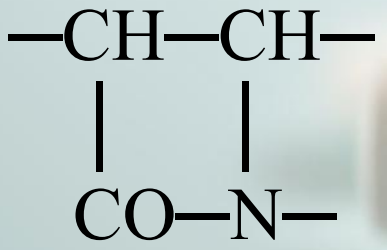
Antibiotics can be classified according to their chemical structure and mechanism of their action:

- **Inhibitors of cell wall synthesis**

- Unique to bacteria, this structure is not found in mammalian cells.
- It is a polymer of glycan units joined to each other by peptide cross-links, hence, the designation of peptidoglycan cell wall.

β-lactam antibiotics

They are the most important members of this group named after the β-lactam ring, which is essential to their activity:



- ***Penicillins***
- ***Cephalosporins***
- ***Carbapenems***

Penicillins

- They are the most widely effective antibiotics and are among the least toxic drugs known, the major adverse reaction to *Penicillins* is hypersensitivity.

Mechanism of action:

- *Penicillins* interfere with the last step of bacterial cell wall synthesis (transpeptidation), thus exposing the osmotically less stable membrane.
- Cell lysis can then occur, and these drugs are therefore bactericidal.
- *Penicillins* are, of course, only effective against rapidly growing organisms that synthesize a peptidoglycan cell wall.

- **Antibacterial spectrum:**
- Consequently, they are inactive against organisms devoid of this structure, such as mycobacteria, protozoa, fungi and viruses.
- Antibacterial spectrum of the various *Penicillins* is determined.

- In general, gram-positive microorganisms have cell walls that are easily traversed by *Penicillins*.
- Gram-negative microorganisms have an outer lipopolysaccharide membrane surrounding the cell wall that presents a barrier to the water-soluble *Penicillins*. For this reason, *Penicillins* have little use in the treatment of intracellular pathogens.

We have now 4 groups of Penicillins.

I. Natural.

Penicillin G(Benzylpenicillin)

Antimicrobal spectr of Penicillin G include gram-positive and gram-negative cocci, gram-positive bacilli and spirochetes.

Penicillin G is susceptible to inactivation by β-lactamases (penicillinases).

II. **Antistaphylococcal penicillins**

- Methicillin
- Oxacillin

They are penicillinase-resistant penicillines.

They may be used to the treatment of infections caused by penicillinase-producing staphylococci.

III. Extended – spectrum penicillins

- Ampicillin
- Amoxicillin

They have antibacterial spectrum similar to that of penicillin G, but are more effective against gram- negative bacilli.

Amoxicillin may cause eradication of H. pylori and very effective in the treatment of peptic ulcer.

Formation with a β-lactamase inhibitor, such as clavulanic acid or sulbactam, protects amoxicillin or ampicillin, respectively, from enzymatic hydrolysis and extends their antimicrobial spectrum.

IV. Antipseudomonal penicillins

- Piperacillin

It is the most potent of P. aeruginosa

Cephalosporins

- They have the same mode of action as *Penicillins*, but they tend to be more resistant than *Penicillins* to β-lactamases (this family of enzymes hydrolyzes the cyclic amide bond of the β-lactam ring, which results in loss of bactericidal activity).

- We have now

➢ *1st (Cefazolin)*

➢ *2nd (Cefuzoxime)*

➢ *3rd (Cefotaxime, Ceftriaxone, Cefoperazone)*

➢ *4th (Cefepime)*

➢ *5th (Ceftaroline)*

generation of *Cephalosporins.*

- ***Cefepime*** is the most clinically useful and has a wide antibacterial spectrum, which include P.aeruginosa.
- ***Ceftazoline*** is very effective in the treatment of nosocomial (hospital acquired) infection and MRSA.

- ***Cefoperazone*** may cause a disulfiram- like effect (when cefoperazone is ingested with alcohol)

This happens bevause these cephalosporins block the second step in alcohol oxidation, which results in the accumulation of acetaldehyde(very toxic agent).

- ***Carbapenems***
- This grup uncludes only one drug ***Imipenem***. It is active against penicillinase-producing gram-positive and gram-negative organisms, anaerobes.

Other agents affecting the cell wall

- ***Vancomycin***

  It is tricyclic glycopeptide that has become increasingly important because of its effectiveness against multiple drug resistant organisms such as methicillin-resistant staphylococci (MRSA) and enterococci.

- **Mechanism of action:**
- *Vancomycin* inhibits synthesis of bacterial cell wall phospholipids as well as peptidoglycan polymerization at a site earlier than that inhibited by β-lactam antibiotics.

All antibiotics affecting the cell wall have very specific antibacterial effect and have not any adverse effects without allergy and superinfections (overgrowth of Candida)-***adverse effects of all antibiotics.***

❑ Protein synthesis inhibitors

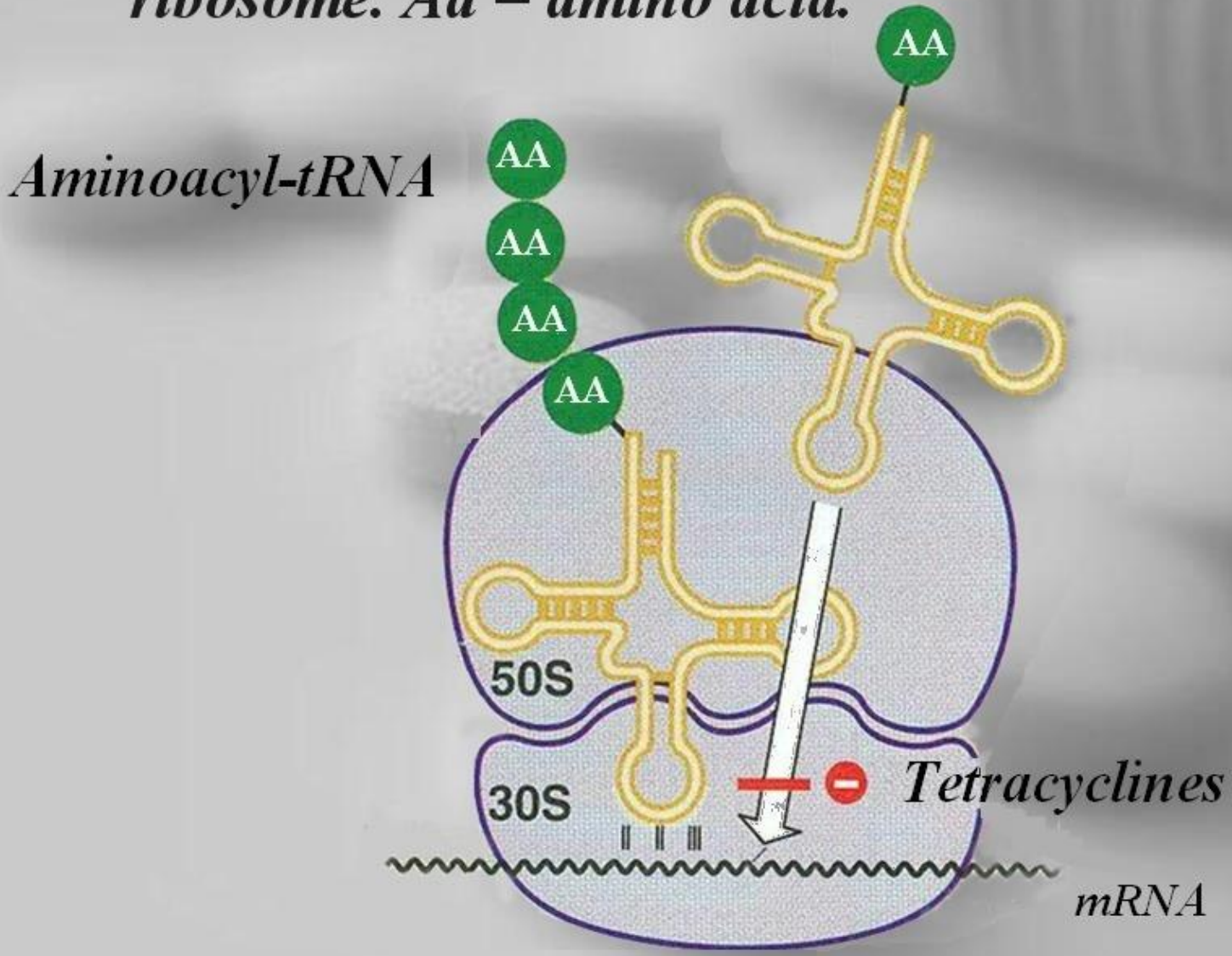
- **Tetracyclines:** *Doxycycline*
- **Aminoglycosides:** *Streptomycin*, *Gentamycin*
- **Macrolides:** *Erythromycin*, *Roxithromycin*, *Azithromycin*
- **Chloramphenicol** *(one drug)*

- ***Tetracyclines***
- They have 4 fused rings in structure.

Mechanism of action:

- They inhibit bacterial protein synthesis, (binding of the drug to 30S subunit of the bacterial ribosome is believed to block access of the amino acyl-tRNA to the mRNA-ribosome complex at the acceptor site).

Tetracyclines binds to the 30S ribosomal subunit, thus preventing the binding of aminoacyl – tRNA to the ribosome. Aa = amino acid.



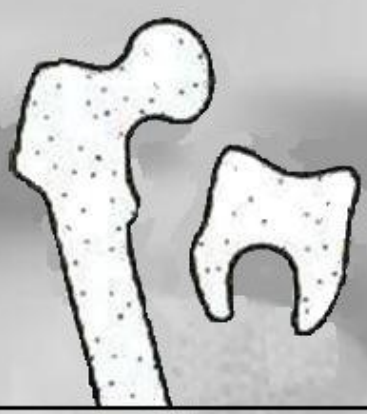
- **Antibacterial spectrum** of the *Tetracyclins* are very wide they are also effective against organisms other than bacteria (for example, entamoeba histolytica).
- *Tetracyclines* are generally bacteriostatic.

- **Adverse effects:**
- gastric discomfort;
- effects on calcified tissues (discoloration and hypoplasia of the teeth);
- fatal hepatotoxicity;
- phototoxicity;
- vestibular problems (vertigo);
- superinfections (overgrowths of Candida).

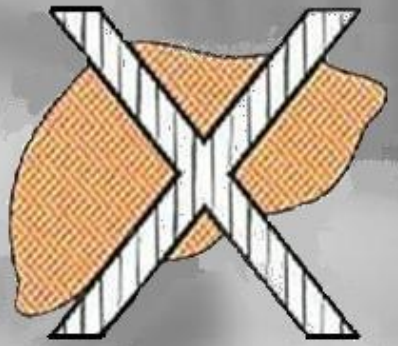
!!!Attention avoid pregnancy!!!

Some adverse effects of tetracycline

GI DISTURBANCES



DEPOSITION OF DRUG IN BONES AND TEETH



LIVER FAILURE

AVOID IN PREGNANCY

VERTIGO

PHOTOTOXICITY

- ***Aminoglycosides***

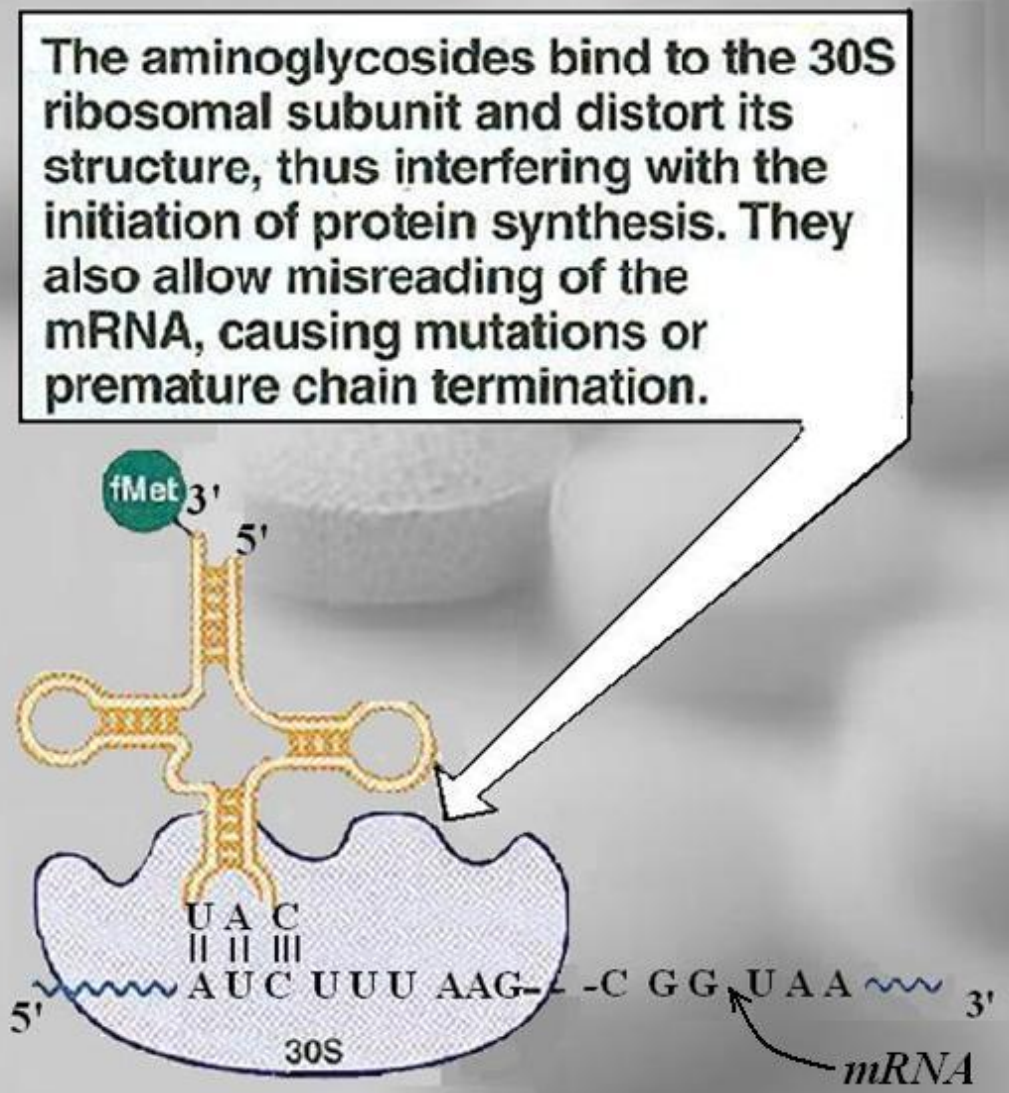
  They have two amino sugars structure.

  Mechanism of action:

- They inhibit bacterial protein synthesis by binding to the 30S ribosomal subunit, interfering with assembly of the functional ribosomal apparatus, or causing the 30S subunit of the complete ribosome to misread the genetic code. Polysomes became depleted because the *Aminoglycosides* interrupt the process of polysome disaggregation and assembly.

- *Aminoglycosides* synergize with β-lactam antibiotics because of the latters'action on cell wall synthesis, which enhances diffusion of *Aminoglycosides* into the bacterium.

Mechanism of action of the aminoglycosides



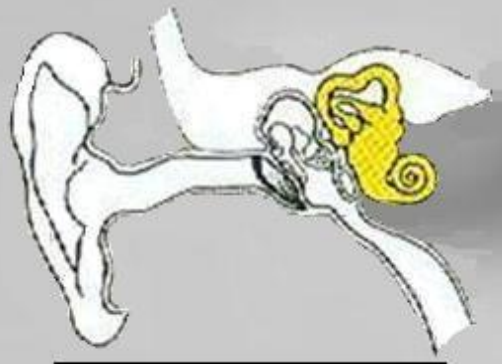
Antibacterial spectrum

- All *Aminoglycosides* are bactericidal.
- They are effective only against aerobic organisms, since anaerobes lack the oxygen-requiring transport system.
- ***Streptomycin*** is used to treat tuberculosis, plaque, tularemia.

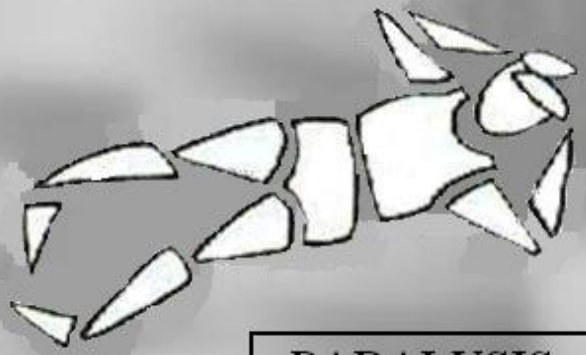
Adverse effects:

- ototoxicity (is directly related to high peak plasma levels and duratiion of treatment);
- nephrotoxicity;
- neuromuscular paralysis;
- allergic reactions;
- superinfections (overgrowths of Candida).

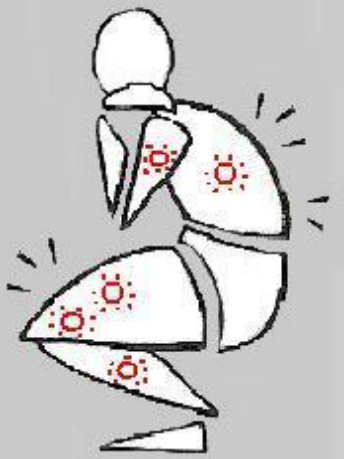
Some adverse effects of aminoglycosides



OTOTOXICITY



PARALYSIS



SKIN RASH
(Neomycin)

NEPHROTOXICITY

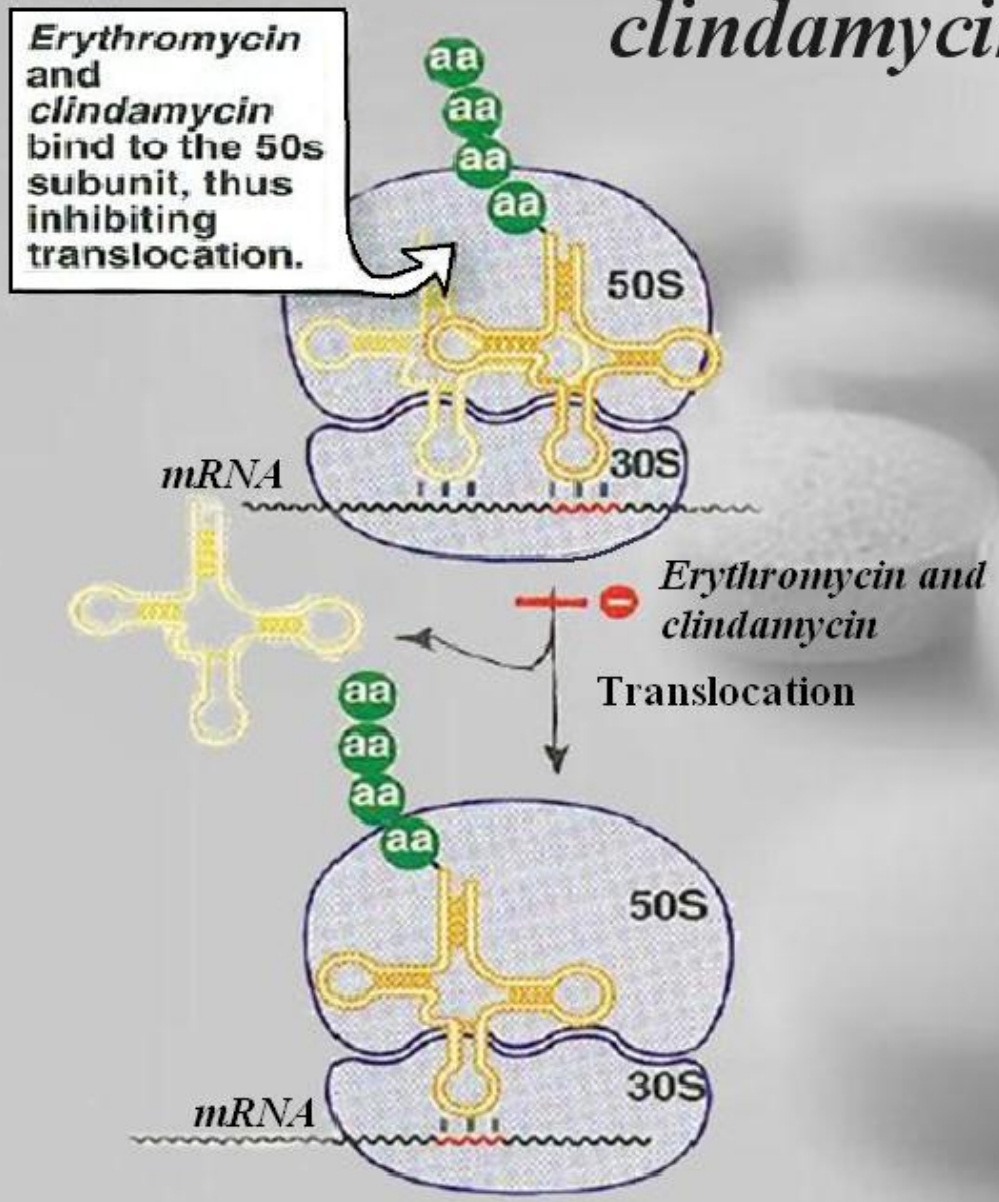
Macrolides

- They have a macrocyclic lactone structure.

Mechanism of action:

- They bind irreversibly to a site on the 50S subunit of the bacterial ribosome, thus inhibiting the translocation steps of protein synthesis.
- They are bacteriostatic, but may be cidal at higher doses.

Mechanism of action on erythromycin and clindamycin



Antibacterial spectrum

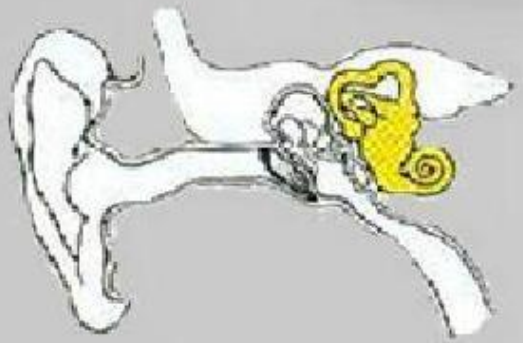
- They are effective against the same organisms as *Penicillines* plus chlamydia and mycoplasma.

Adverse effects:

- epigastric distress;
- cholestatic jaundice;
- ototoxicity;
- allergic reactions and superinfections are little.

Some adverse effects of macrolide antibiotics

JAUNDICE



OTOTOXICITY

GI DISTURBANCES

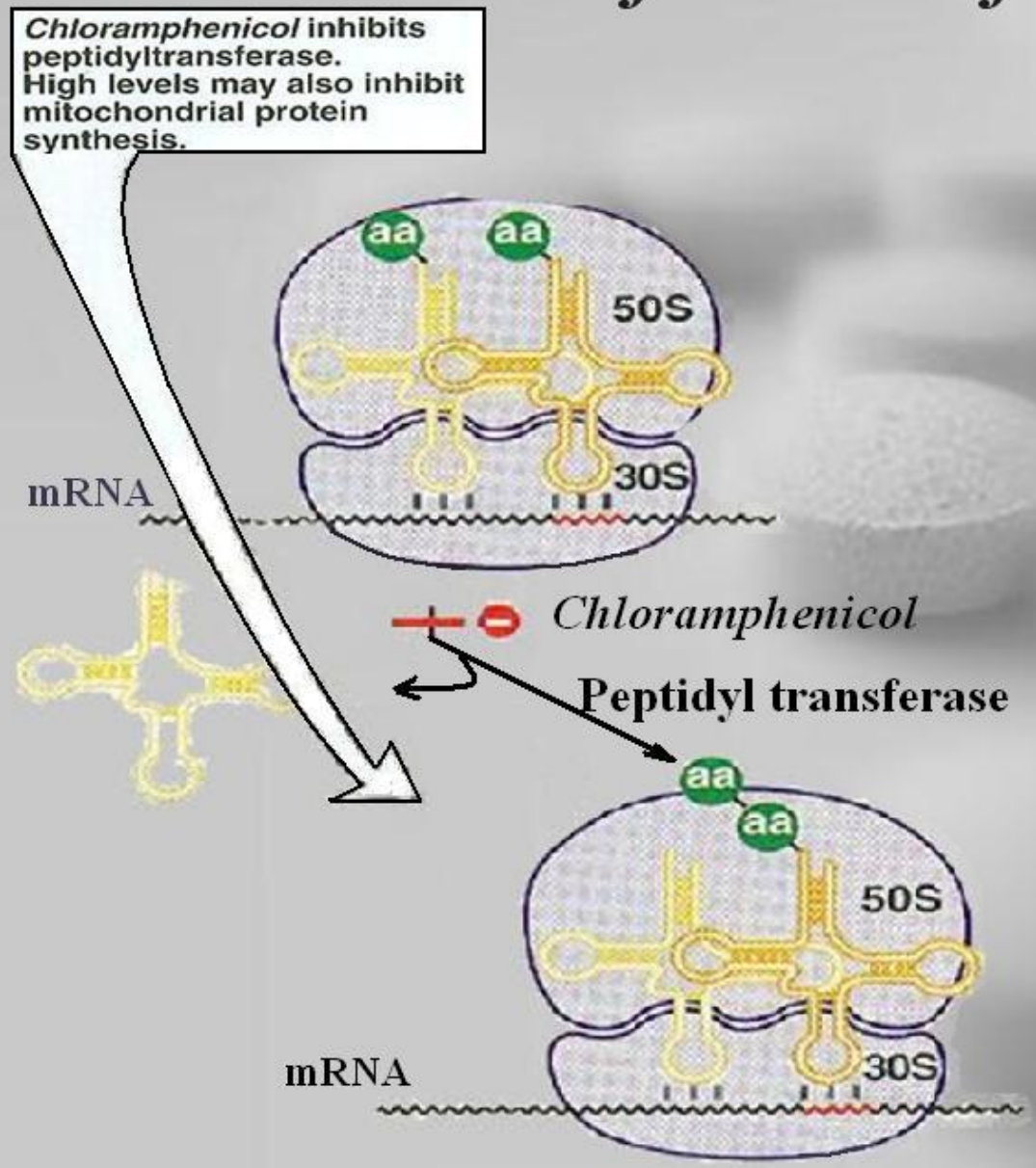
Chloramphenicol

- It is active against a wide range of gram-positive and gram-negative organisms, but because of its toxicity, its use is restricted to life-threatening infections in which there are no alternatives.

Mechanism of action:

- The drug binds to the bacterial 50S ribosomal subunit and inhibits protein synthesis at the peptidyl transferase reaction. Because of the similarity of mammalian mitochondrial ribosomes to those of bacteria, protein synthesis in these organelles may be inhibited at high doses of *Chloramphenicol*, producing bone marrow toxicity.

Mechanism of action of chloramphenicol



Adverse effects:

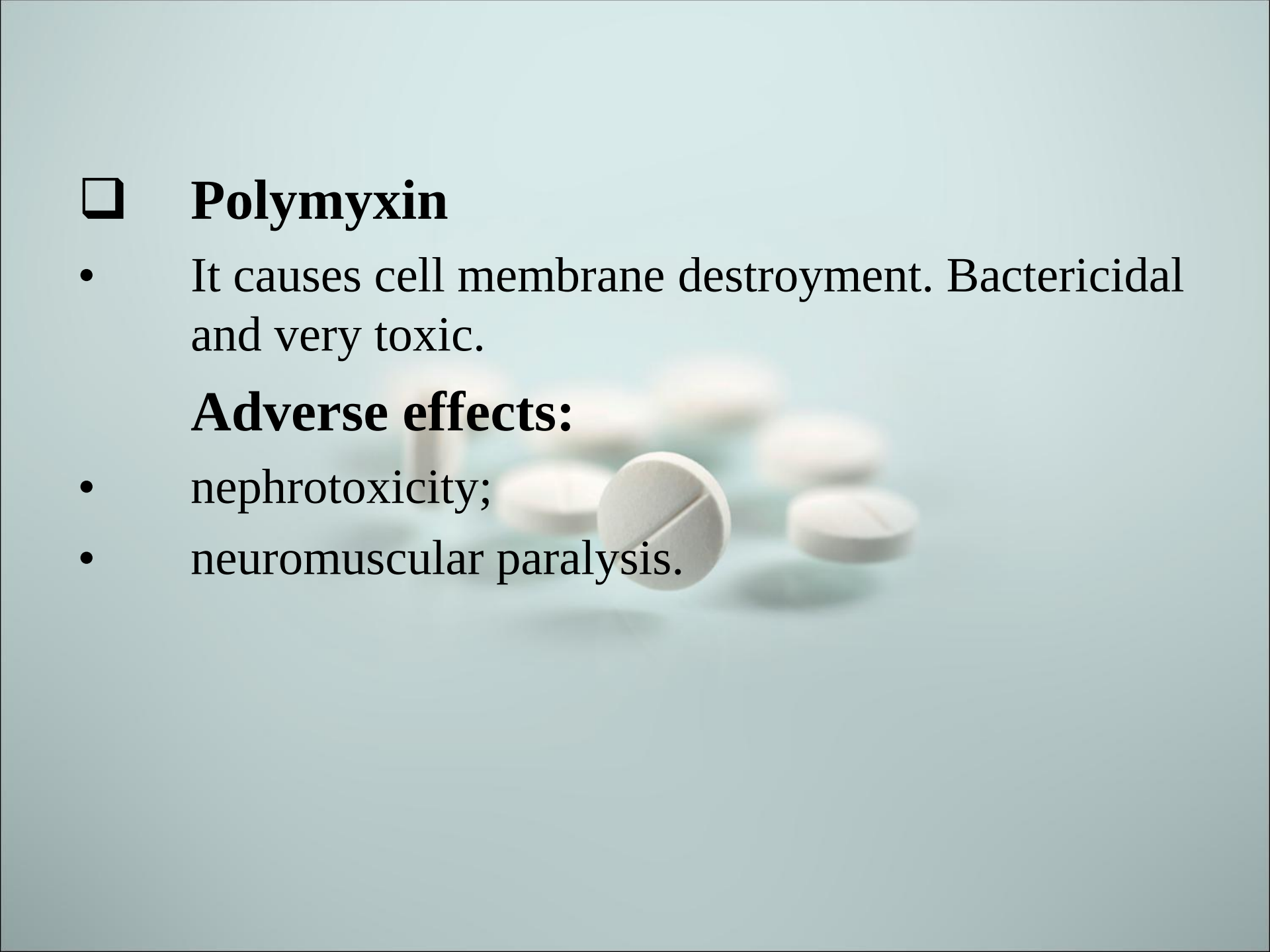
- anemias;
- gray baby syndrome (cardiovascular collapse, cyanosis – hence the term “gray baby” – and death);
- dermatitis;
- psychosis (may be);
- allergic reactions;
- superinfections (overgrowths of Candida).

❑ Polymyxin

- It causes cell membrane destroyment. Bactericidal and very toxic.

Adverse effects:

- nephrotoxicity;
- neuromuscular paralysis.



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END


Sandra Battaglia 2002