ANTIBIOTIC GROUPS AND THEIR INDICATIONS – PART 2

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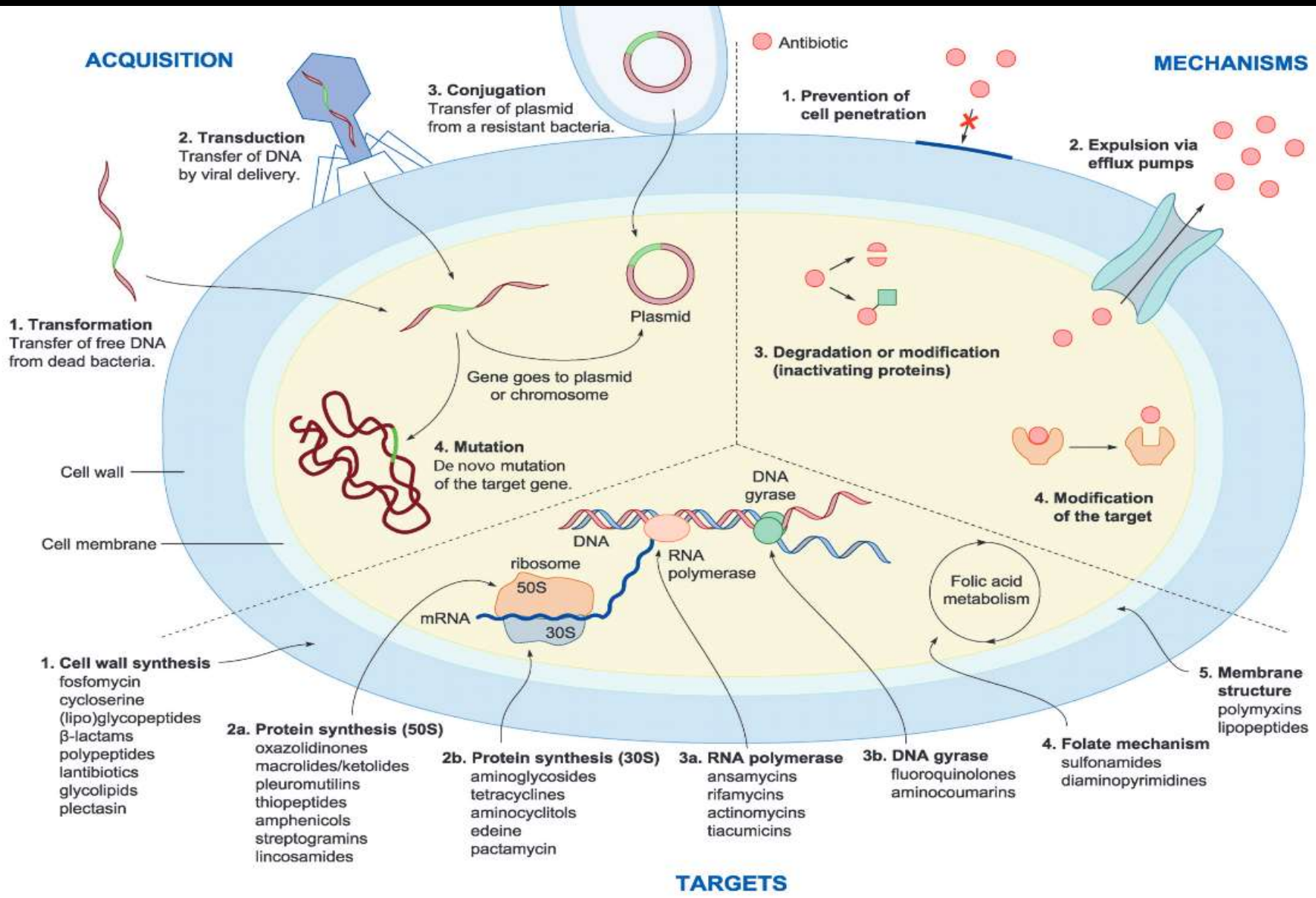
Review – antibiotic targets, acquisition and mechanism of resistance



Inhibitors of the 50S Ribosomal Subunit - Macrolides

- Macro – macrocyclic lactone 12, 14, 16 ring
- Products of genus *Streptomyces*
- Antibacterial activity agains most gram-positive bacteria + chlamydias, mycoplasmas…
- Erytromycin
- Semysynthetic derivatives : clarithromycin, azithromycin…

Macrolides

- Mechanism resistence :
- Target site modification by methylation of ribosome (23 rRNA) – MLS_B phenotype
- cross resistance – macrolides +lincosamides+ $streptogramin_B$
- active efflux
- enzymatic inactivation

Macrolides

- Clinical uses :
- Upper respiratory infection, alternatives of penicilins (hypesentivity) – streptococcal pharyngitis, maxillary sinusitis…
- Pneumonia
- *Mycobacteruim avium Complex infection*
- *Helicobacter pylori* infection…

Lincosamides

- Lincomycin, clindamycin
- Antibacterial spectrum : gram-positive cocci, anaerobes
- Resistance : $MLS_{B,}$ enzymatic inactivation
- Clinical uses : mixed aerobic and anaerobic infection (abdominal), pneumonia with abscesses; staphylococcal osteomyelitis…

Inhibitors of the 30S Ribosomal Subunit - Aminoglycosides

- Natural products of streptomyces
- 1943 – streptomycin…
- Spectrum of activity : broad range of gram-negative bacilli, staphylococci,mycobacteria
- Currently used antibiotics : gentamicin, amikacin..
- **Significant nefro and ototoxicity – in risk patients must be monitored serum concentration**

Aminoglycosides

- Resistance :
- decreased uptake and accumulation
- Aminoglycosides modifying enzymes (acetyltranseferases..)
- Change of bacterial ribosomes
- Resistance not cross linked
- Arising slowly

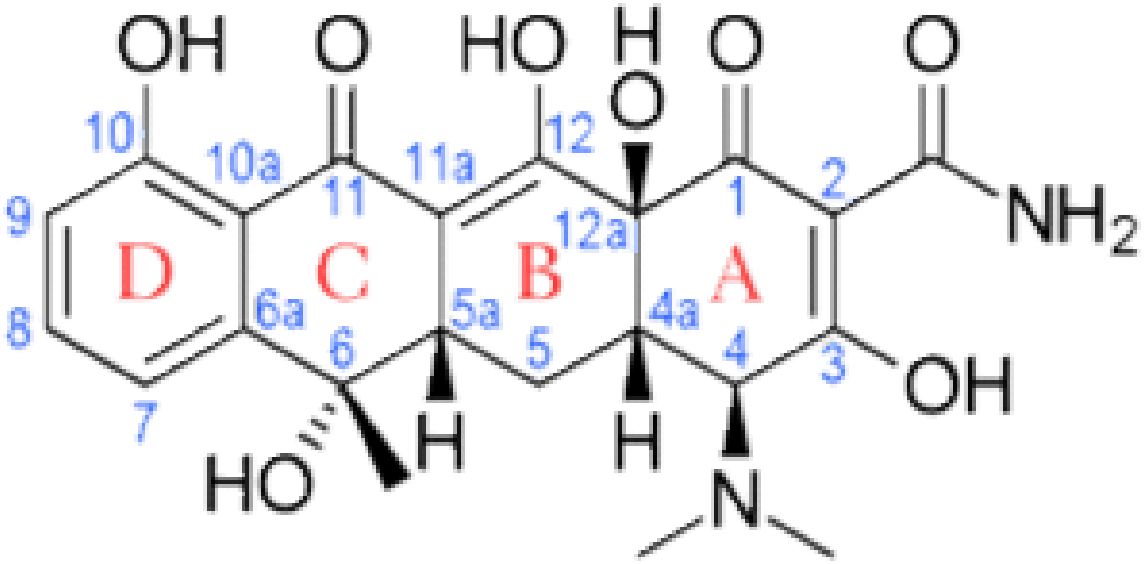
Aminoglycosides

- Clinical uses :
- Only parenteral forms
- Serious hospital infections
- Restricted for prolonged therapy and for patients with renal failure
- Optimal monitoring plasma concentrations
- Combinations with other groups – beta-lactams, fluoroquinolons…

TETRACYCLINES

- **Bacteriostatic drugs**
- **Natural products: tetracycline**
- **Semisynthetic derivatives: doxycycline, minocycline…**
- **Oral and parenteral forms**
- **Broad-spectrum activity: G + and G^- bacteria, mycoplasmas, chlamydia, rickettsiae, spirochetes, mycobacteria…**

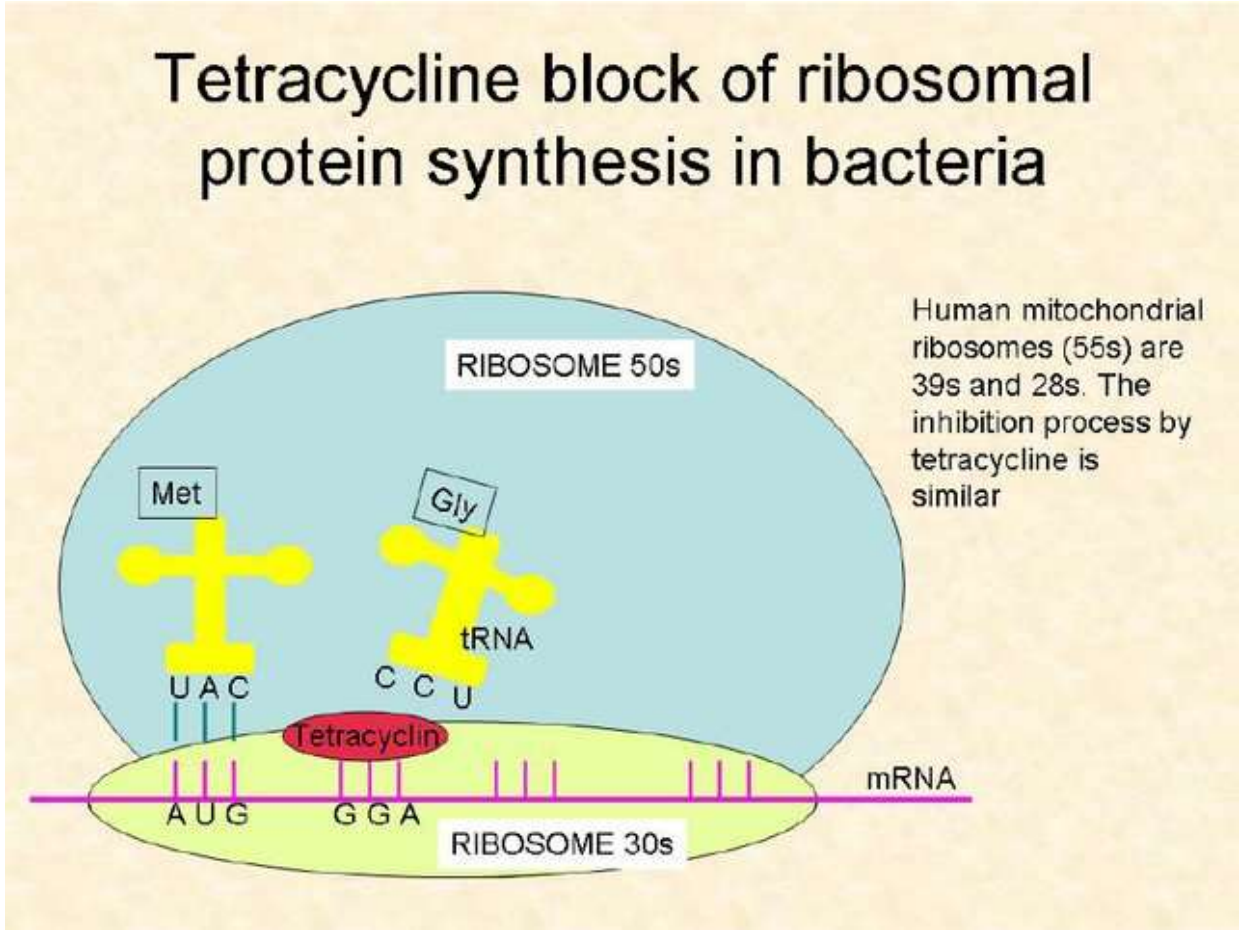
Structure



Tetracycline molecules comprise a linear fused tetracyclic nucleus (rings designated A, B, C and D) to which a variety of functional groups are attached.Tetracyclines are named for their four ("tetra-") hydrocarbon rings ("-cycl-") derivation ("-ine").

References: https://en.wikipedia.org/wiki/Tetracycline_antibiotics

Mechanism of action



References: https://www.researchgate.net/publication/285051696_TETRACYCLINES_AGAINST_CANCER_A_REVIEW/figures?lo=1

TETRACYCLINES - CLINICAL USE

- **Respiratory infections (mycoplasma, chlamydia)**
- **Urogenital infections (urethritis)**
- **Lyme borreliosis**
- **Leptospirosis**
- **Anthrax …**
- **Mycobacteriosis (marinum, cheilonei, fortuitum…)**

- **High degree of resistance - streptococci, staphylococci…**

SIDE EFFECTS, TOXICITY

- **Dysmicrobia - because of the broad spectrum of activity**
- **Indigestion, nausea, diarrhea**
- **Contraindications in pregnancy and childhood - storage in bones and teeth - chelation with Ca^{2+} - disorders of bone development and tooth decay - brown spots on the enamel…**

GLYCYLCYCLINES

- **Tigecycline**
- **Parenteral**
- **New class of antibiotics, connection to tetracyclines**
- **Broad-spectrum activity including highly resistant Gram negative bacteria (ESBL producers..) and MRSA, VRSA, VRE, … anaerobes, mycoplasmas, chlamydia**

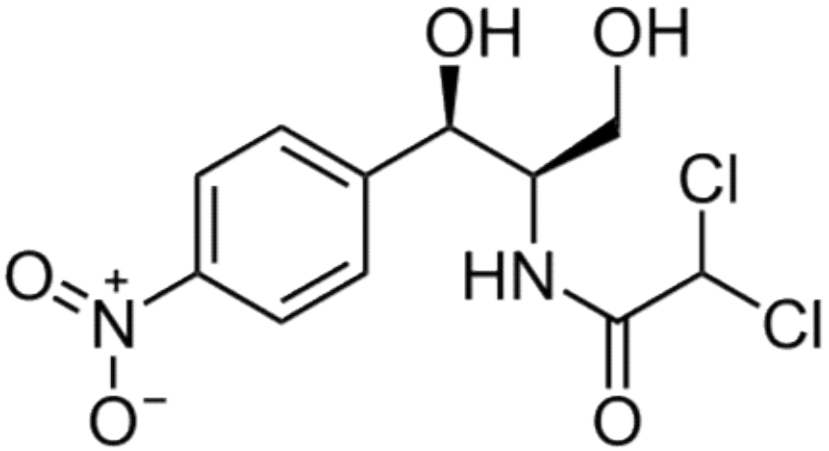
- **Clinical use : reserve antibiotic, serious intra-abdominal infections, skin and subcutaneous infections…**

CHLORAMPHENICOL

Proteosynthesis inhibitor

- **Semisyntetic antibiotic, derived from Streptomyces venequelae**
- **Bacteriostatic effect**
- **Broad spectrum of activity:**
- **G + and G- bacteria**
- **Bordetella pertussis**
- **Leptospira**
- **Anaerobes…**

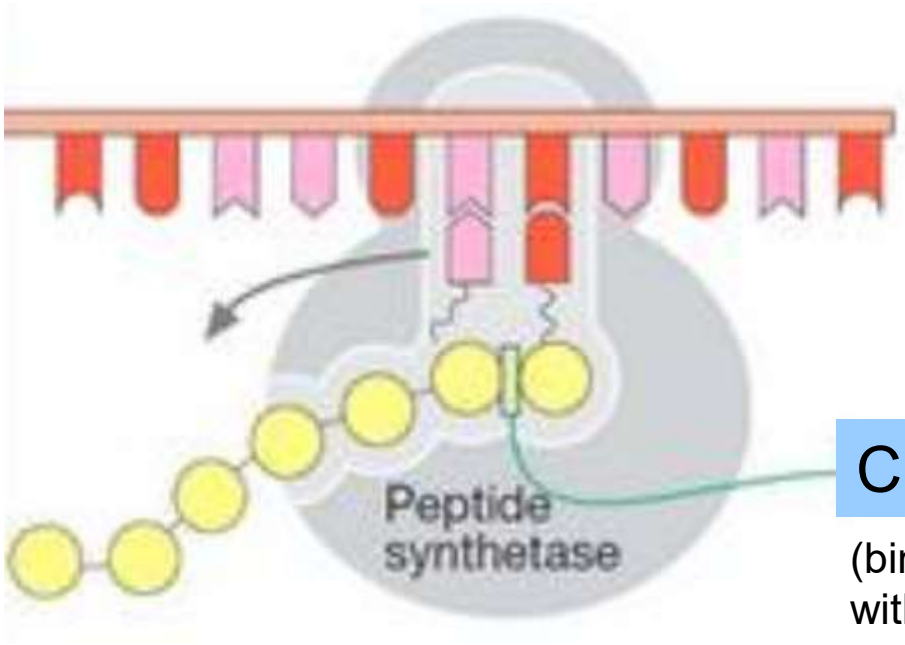
Structure



Chloramphenicol is an organochlorine compound that is dichloro-substituted acetamide containing a nitrobenzene ring, an amide bond and two alcohol functions.

References: https://pubchem.ncbi.nlm.nih.gov/compound/Chloramphenicol

Mechanism of action



Chloramphenicol

(binds and interfere
with peptidyl transferase)

- Site of action for chloramphenicol on the 50S ribosomal subunit:This prevents linkage of amino acids to the peptide chain, resulting in inhibition of protein synthesis.

References: https://www.researchgate.net/publication/285051696_TETRACYCLINES_AGAINST_CANCER_A_REVIEW/figures?lo=1

CHLORAMPHENICOL – CLINICAL USE

- **Anaerobic and mixed infections**
- **Typhoid fever**
- **Abscessive infections in abdominal surgery, gynecology, pneumology..**
- **Purulent meningitis, brain abscess**

-reliable penetration into the cerebrospinal fluid, crossing the blood-brain barrier

CHLORAMPHENICOL- SIDE EFFECTS, TOXICITY

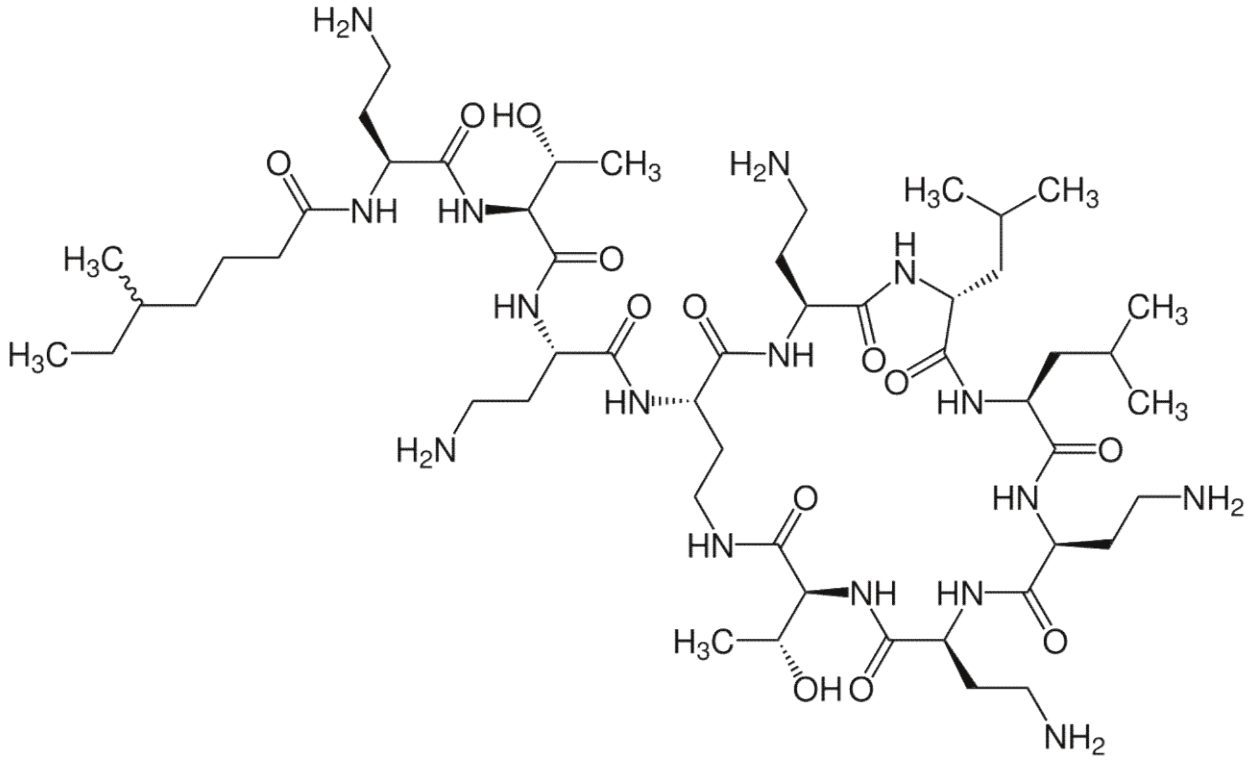
- **Reversible myelosupression**
- **Aplastic anemia - fatal course (exceptionally), possibility even after local application**
- **Do not repeat the application at intervals shorter than ½ year - reducing the risk of aplastic anemia**
- **"Gray baby syndrome" - high serum levels, immaturity of the liver enzymatic systems**

- Most doctors are concerned about side effects and try to avoid the use of chloramphenicol…

PEPTIDES

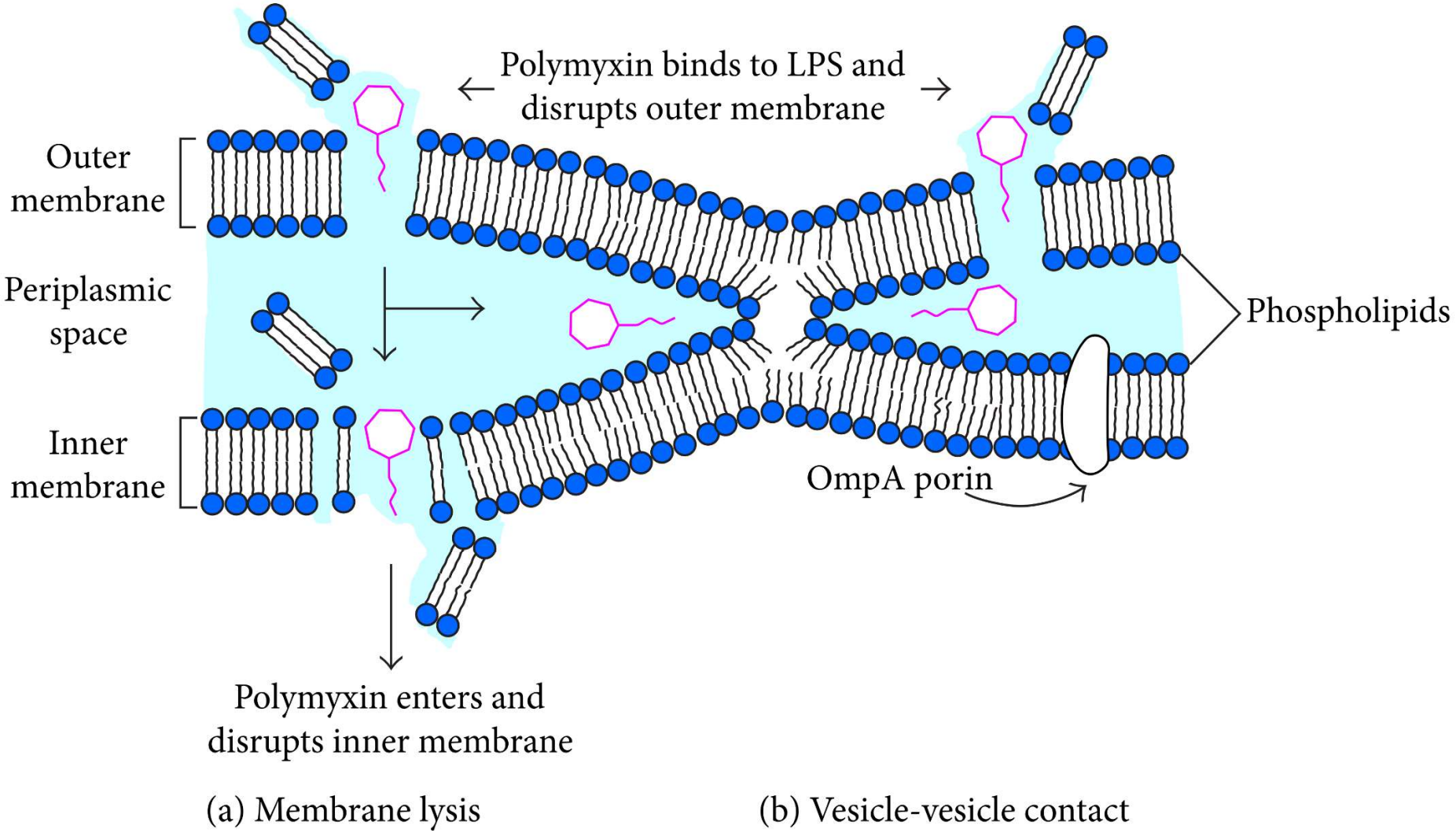
- **Disruption of cytoplasmic membrane -polymyxins or cell wall function - bacitracin**
- **Bactericidal effect**
- **Bacitracin - topical application (with aminoglycoside neomycin) – G+ spectrum of activity – staphylococci, streptococci**
- **Polymyxins A-E; colistin (polymyxin E) – parenteral forms**

Structure (polymyxin)



Polymyxins are a group of cyclic polypeptides which are biosynthesized by bacteria belonging to the genus Bacillus

Mechanism of action



POLYMIXINS - COLISTIN

- **Spectrum of activity : enterobacteria, *Pseudomonas aeruginosa*, *Acinetobacter* spp.**
- **no activity on a Gram of positive bacteria**
- **reserve antibiotic for the treatment of serious infections of multidrug resistant (MDR) gram negative etiology**
- **A 21st century remedy for the treatment of multidrug-resistant pseudomonas and acinobacter infections?**

…..but in recent years a new type of plasmid transmitted resistance has emerged. It is linked to *mcr* genes.

COLISTIN – CLINICAL USE

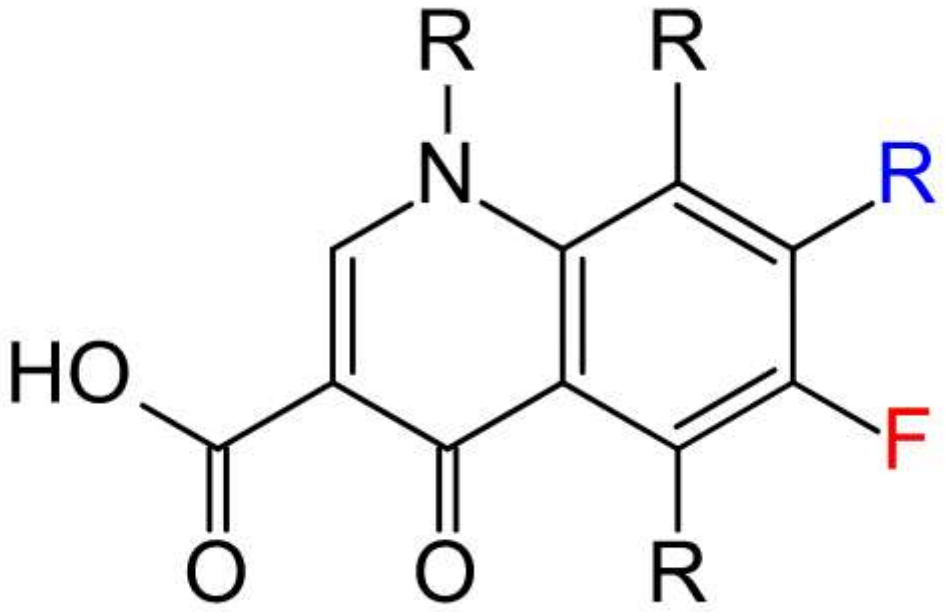
- **Reserve antibiotic - especially for situations where there is no other choice**
- **Different types of pseudomonas infections**
- **Different types of enterobacterial infections**
- **Nosocomial pneumonia**
- **Sepsis**
- **Complicated UTI…**

- **topical use - inhalation in case of nosocomial pneumonia**

COLISTIN – toxicity

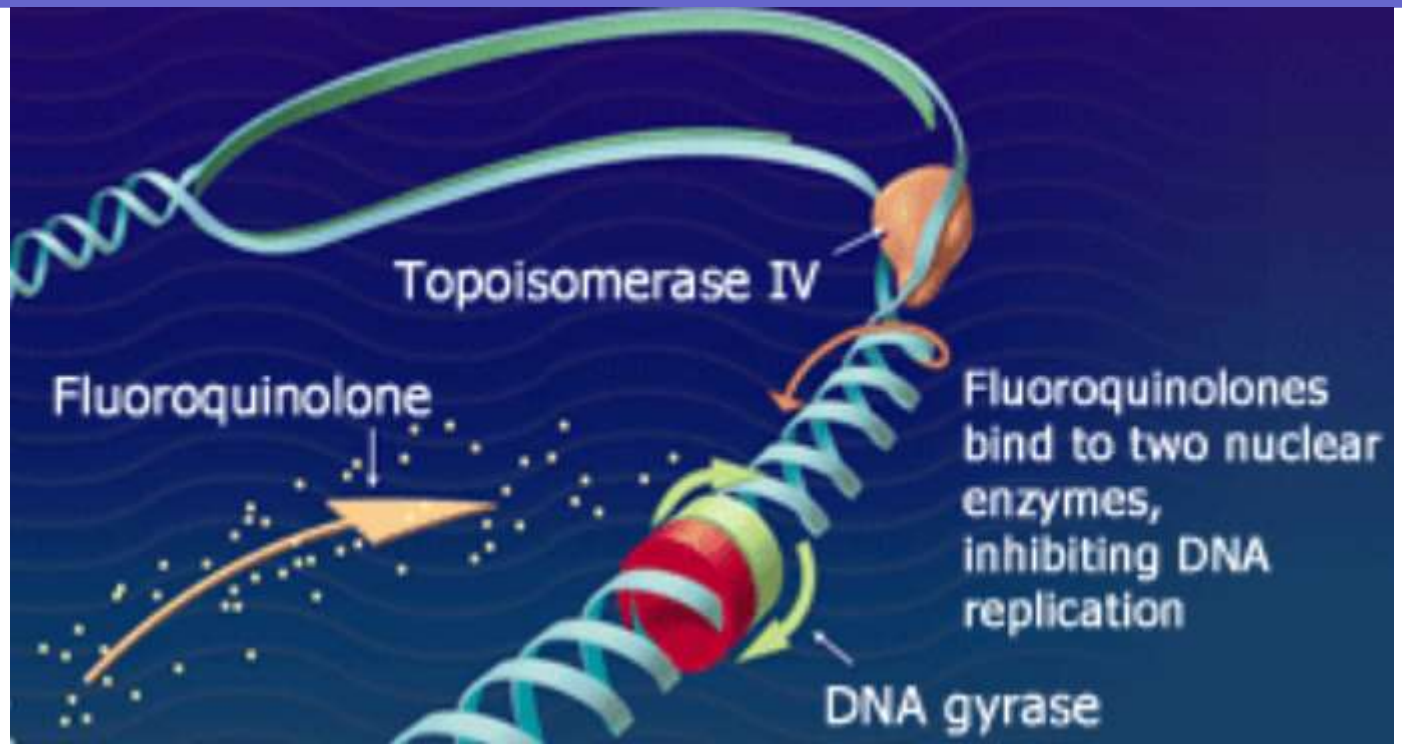
- **Nephrotoxicity - the risk increases when combined with other nephrotoxic preparations (aminoglycosides, vancomycin ..)**
- **Neurotoxicity**
- **Neuromuscular blockade**

Fluoroquinolone structure



* Bicyclic core structure (all)
* Ketone functional group (quinolones)
* Fluorine atom (fluoroquinolones)

Mechanism of action



Fluoroquinolones directly inhibit bacterial DNA synthesis by binding to:

* Topoisomerase II (DNA gyrase) in gram-negative organisms

* Topoisomerase IV in gram-positive organisms

FLUOROQUINOLONES

- Exhibit antimicrobial/bactericidal effects on DNA gyrase (bacterial topoisomerase II) and bacterial topoisomerase IV

- Fluoroquinolones may be classified into "generations" based on their antimicrobial targets.
- First generation: nonfluorinated quinolone nalidixic acid, with a narrow spectrum of susceptible organisms.
- Second generation ciprofloxacin and ofloxacin...
- Third generation levofloxacin is classified as because of its increased activity against gram-positive bacteria.
- Fourth generation includes only moxifloxacin

CIPROFLOXACIN, OFLOXACIN

- **Spectrum of antimicrobial activity: mainly Gram negative bacteria including *Pseudomonas aeruginosa*, activity on Gram of positive bacteria and anaerobes is limited**
- **Oral and parenteral forms**
- **Clinical use : urinary tract infections , prostatitis, also effective in the treatment of many systemic infections caused by gram negative bacilli, ciprofloxacin is also used as a second-line agent in the treatment of tuberculosis**

- In many countries popular antibiotics in the treatment of community and hospital infections

MOXIFLOXACIN

- **Extended antibacterial activity on Gram of positive bacteria, atypical agents (mycoplasma, chlamydia, legionela) and partly anaerobes**
- **Clinical use : mainly respiratory tract infections (pneumonia, sinusitis..)**
- **Sometimes referred to as "repiratory quinolone" due to the ideal spectrum for respiratory pathogens**
- **reserve antibiotic in Czech Republic, common antibiotic in countries where high levels of pneumococcal resistance to penicilline**

FLUOROQUINOLONES – RESISTANCE

- **Cross-resistance exists among the quinolones -** it arises relatively easily and quickly
- **High levels of fluoroquinolone resistance have emerged in Gram-positive and Gram-negative bacteria, primarily due to chromosomal mutations**

- Chromosomal mutations in bacterial genes. Both topoisomerase IV and DNA gyrase may undergo mutations

Decreased accumulation:

- decreased number of porin proteins in the outer membrane.

- efflux pumps

- **Most hospital bacteria are already resistant to fluoroquinolones**

FLUOROQUINOLONES – TOXICITY, SIDE EFFECTS

- **Inflammation or rupture of tendons**
- **joint and muscle problems**
- **severe skin reactions, phototoxicity**
- **damage to peripheral nerves, sensory disorders,**
- **psychiatric problems,**
- **impaired kidney or liver function,**
- **dysmicrobia**
- **common drug interactions…**

FLUOROQUINOLONES – CONCLUSION

- **Current recommendations :**

- **do not prescribe fluoroquinolones for non-serious infections or infections where other options are possible (especially in outpatient practice with empirical treatment),**
- **as they may rarely cause long-term / permanent disabling side effects…**

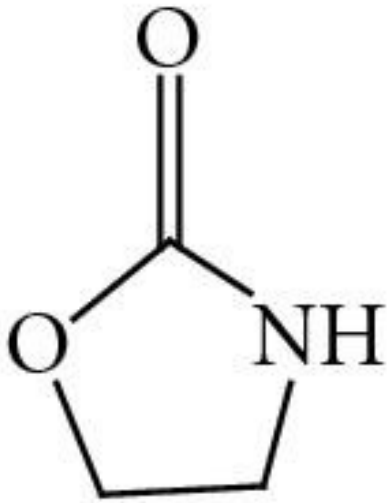
OXAZOLIDINONES

- **Inhibition of proteosynthesis**
- **Bacteriostatic effect**
- **First representative of the group : linezolid**

Oral and parenteral forms

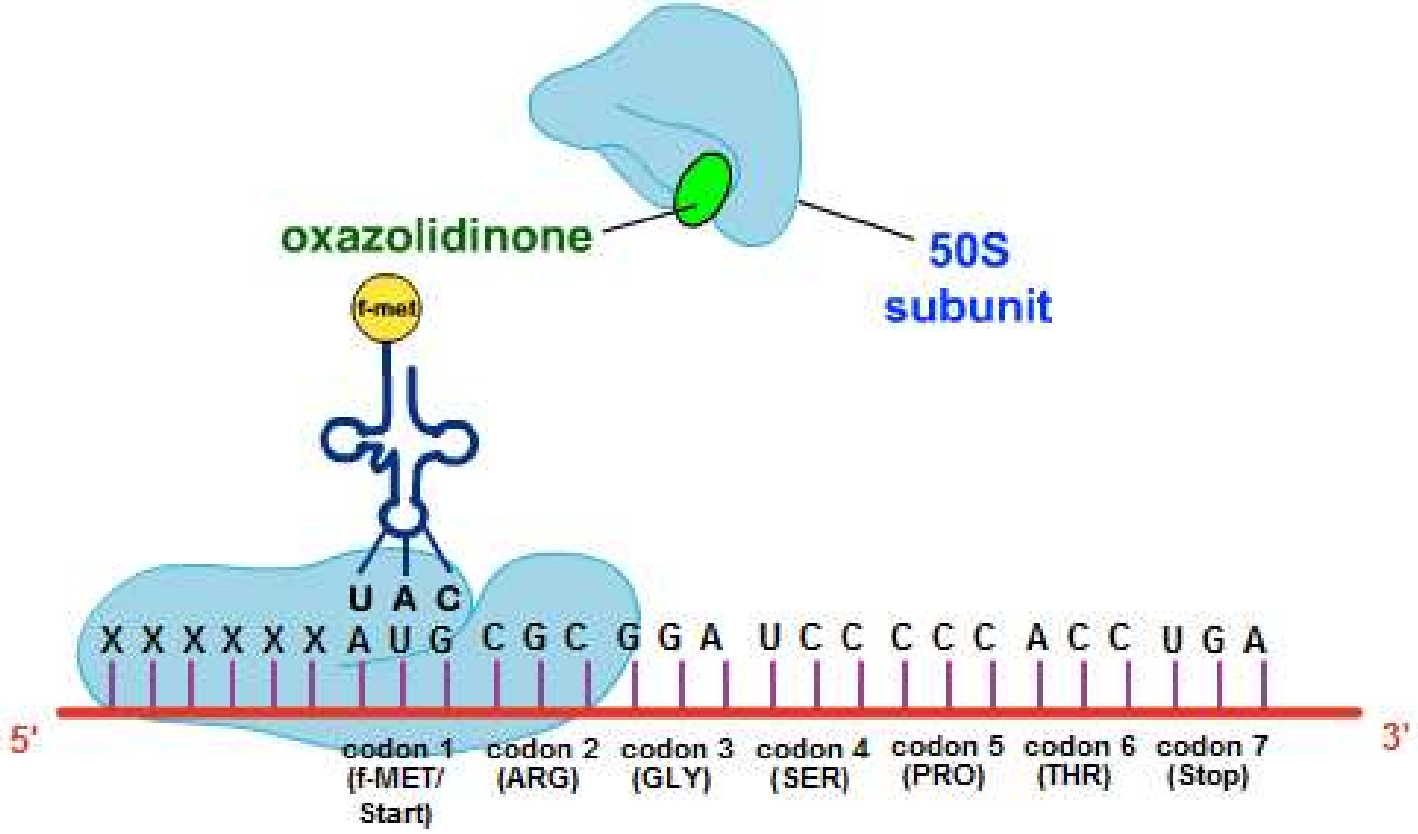
- **Spectrum: Gram positive bacteria including MRSA, VRE…**
  inactive on gram of negative bacteria
- **Clinical use : Reserve antibiotic for the treatment of infections caused by MDR bacteria (pneumonia, skin and soft tissue infections, orthopedic infections ..)**
  Excellent tolerability, low toxicity
- **Limit - possibility of hematopoietic attenuation - long-term administration, especially longer than 1 month**

Structure



Oxazolidinones are a class of azoles, oxazolidines with the carbon between the nitrogen and oxygen oxidized to a ketone, hence oxazolidinone

Mechanism of action

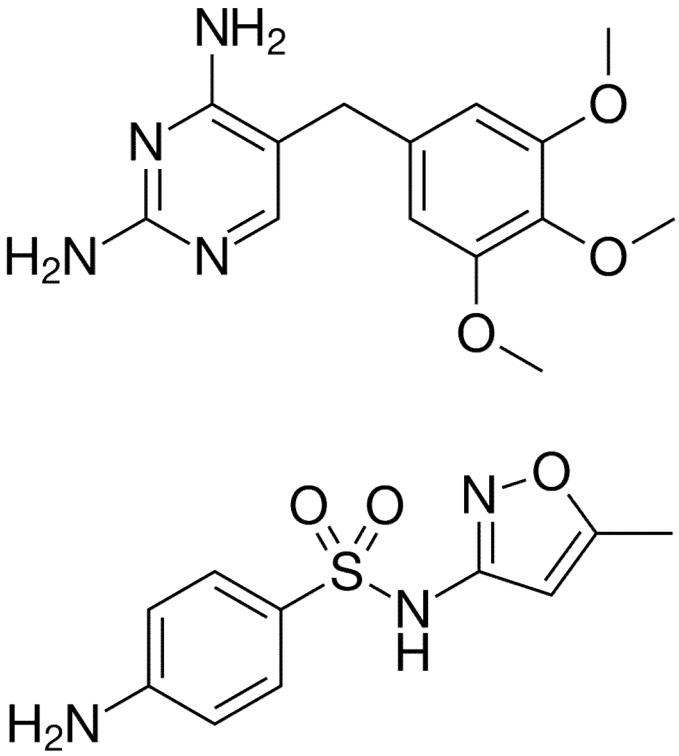


Oxazolidinones inhibit protein synthesis by binding at the P site at the ribosomal 50S subunit. Resistance to other protein synthesis inhibitors does not affect oxazolidinone activity; however rare development of oxazolidinone resistance cases, associated with 23S r-RNA alterations during treatment, has been reported

COTRIMOXAZOLE

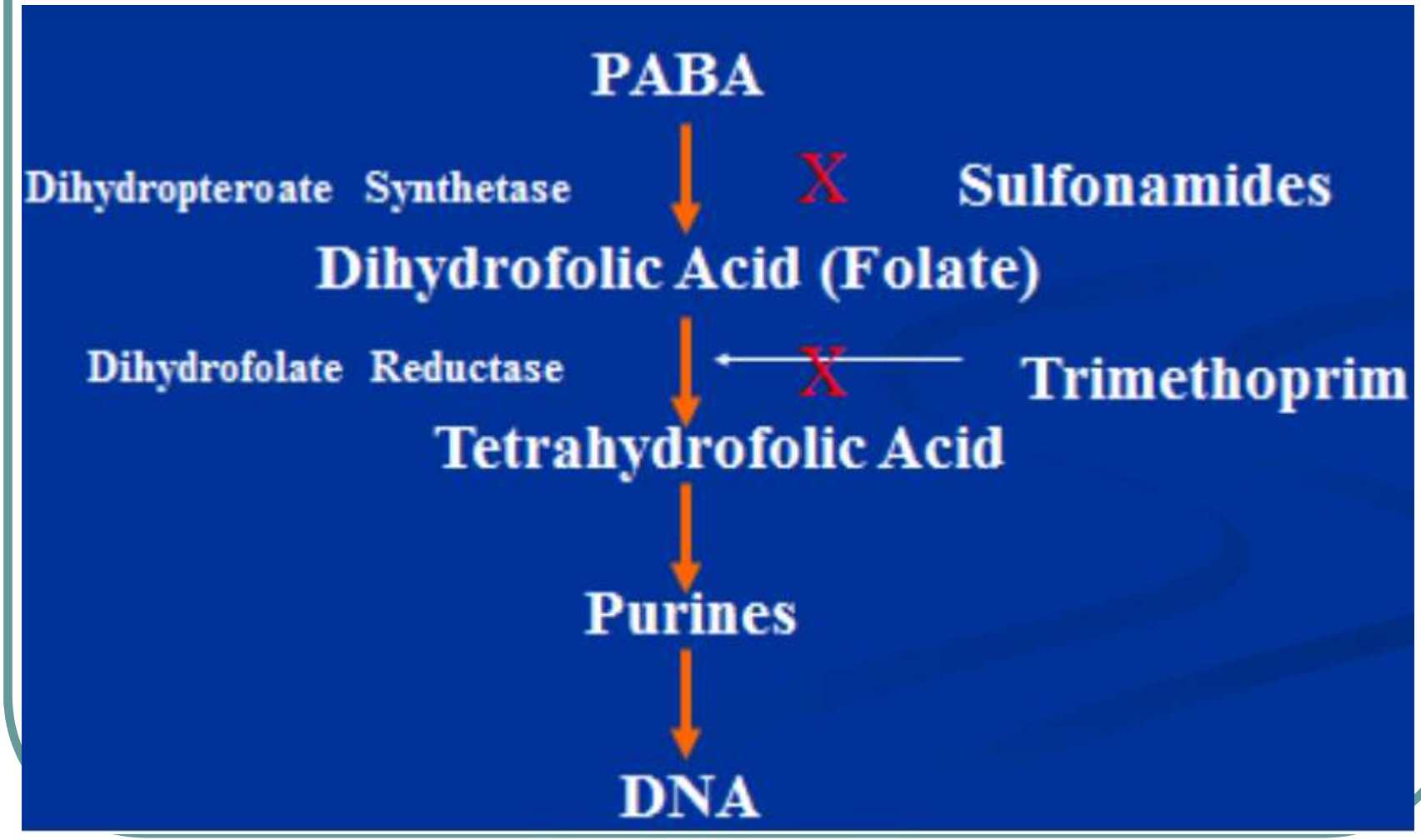
- **Combination of sulfonamide (sulfamethoxazole) and trimethoprim (diaminopyrimidine)**
- **Both substances interfere with the metabolism of folic acid at different levels - synergistic action and delay of the formation of resistence**
  Broad spectrum of antibakterial activity : Gram positive cocci (staphylococci), Gram negative bacteria - entrobacteria, *Haemophilus* spp, neisseria, *Nocardia* pp..*Pneumocystis jiroveci* *Toxoplasma gondii*

Structure



Trimethoprim (top) and **sulfamethoxazole** (bottom)

Mechanism of action



COTRIMOXASOLE – CLINICAL USE

- **UTI**

Respiratory infection (including Pneumocystis jirovecii)

Salmonellosis

Brucellosis

Nocardiosis

Toxoplasmosis…

Long-term prophylaxis of HIV-positive, organ transplant patients and other severely immunosuppressed patients

The most common side effect is various forms of allergies