

POLTAVA STATE MEDICAL UNIVERSITY

Lecture

PHARMACOLOGY OF ANTIBIOTICS

ANTIBIOTICS: COMMON CONCEPTS

Antibiotics are substances produced by some microbes for their antagonism with other organisms.

The history of antibiotics.

The first antibiotic was penicillin. It was discovered by **Alexander Fleming** in 1928.

The second antibiotic streptomycin was discovered by **Selman Abraham Waksman**. He also proposed the name “antibiotics”.

Antibiotics are divided:

1. *On type of action*
 - bactericidal
 - bacteriostatic
2. *On spectrum of action*
 - antibiotics of wide spectrum
 - antibiotics of narrow spectrum
3. *On clinical use*
 - basis antibiotics (antibiotics of choice)
 - alternative antibiotics

MAIN PRINCIPLES OF THE THERAPY BY ANTIBIOTICS

- ❖ Early beginning of the treatment
- ❖ Choice of antibiotic on its spectrum of action
- ❖ Choice of antibiotic on sensitivity of microbes in this patient
- ❖ Use of wide spectrum antibiotic if the cause of infection is not known
- ❖ Duration of treatment no less than 5-7 days
- ❖ Usage of big doses of antibiotics
- ❖ Supporting of therapeutic concentration of the drug in the organism
- ❖ Combination of antibiotics with one another, as well as with drugs from other groups
- ❖ Discontinuation of the treatment in 2-3 days after the normalization of clinical status and body temperature
- ❖ Allergic test at the start of treatment
- ❖ Attention to age, physiological status of patient, concomitant diseases, location and severity of infection.

COMMON SIDE EFFECTS OF ANTIBIOTICS

- ❖ Allergy, anaphylactic shock. For prevention – allergic test before the first administration of the drug.
- ❖ Direct toxic influence
- ❖ Endotoxic reactions
- ❖ Dysbacteriasis. For prevention – antifungal drugs (nystatin, itraconazole) together with wide spectrum antibiotics.

ANTIBIOTICS:

CLASSIFICATION

A. Inhibitors of cell wall synthesis

1. Penicillins
2. Cephalosporins
3. Carbapenems and monobactams
4. Glycopeptides

B. Protein synthesis inhibitors acting on ribosomal subunits 30S

1. Aminoglycosides
2. Tetracyclines

C. Protein synthesis inhibitors acting on ribosomal subunits 50S

1. Macrolides and azalides
2. Chloramphenicols
3. Lincosamides

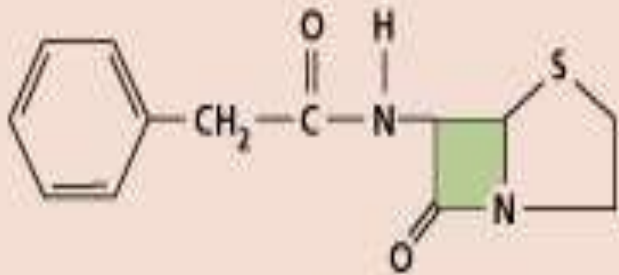
D. Antibiotics which disturb functions of nucleic acids

1. Rifampicins

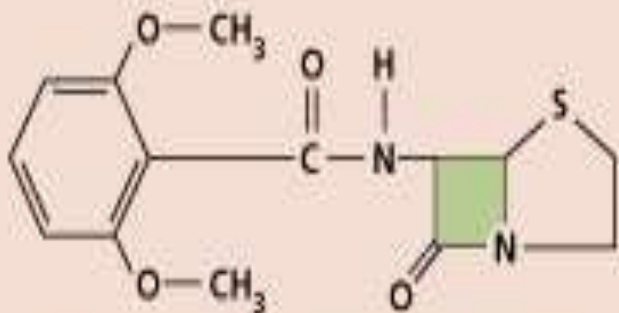
E. Antibiotics which disturb structure and functions of cell membranes

1. Polyenes
2. Cyclic polypeptides (polymyxins).

ANTIBIOTICS-INHIBITORS OF CELL WALL SYNTHESIS



Penicillin G (natural)



Methicillin (semisynthetic)

Penicillins



Cephalothin (semisynthetic)

Cephalosporin

PENICILLINS

Penicillins are derivatives of 6-aminopenicillanic acid.

CLASSIFICATION

A. Natural penicillins (benzylpenicillin, penicillin G)

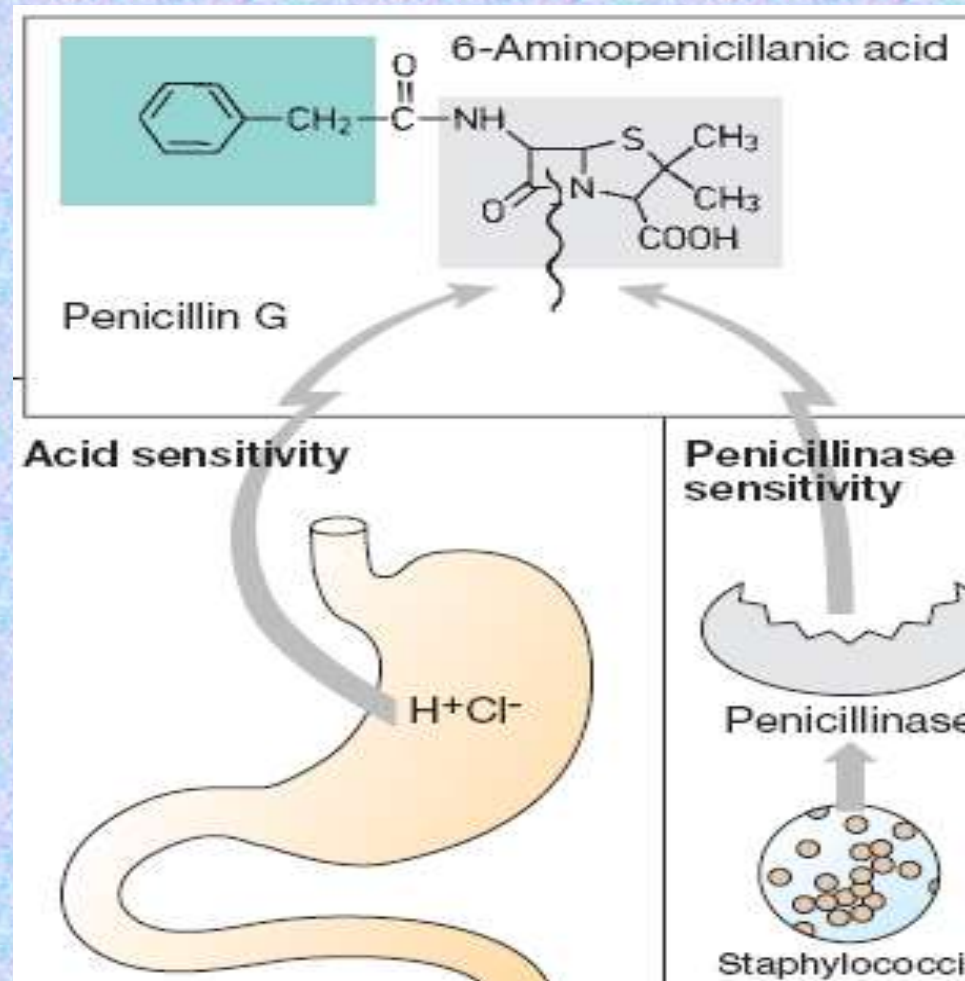
1. Short acting
 - Benzylpenicillin sodium (penicillin G)
 - Benzylpenicillin potassium
 - Phenoxymethylpenicillin
2. Long acting
 - Benzathine penicillin (Bicillin-1)
 - Bicillin-3
 - Bicillin-5

B. Semisynthetic penicillins

1. Penicillinase resistant
 - Oxacillin
2. Wide spectrum
 - Ampicillin
 - Amoxicillin
3. Combined penicillins
 - Ampiox
 - Amoxiclav (Augmentin).

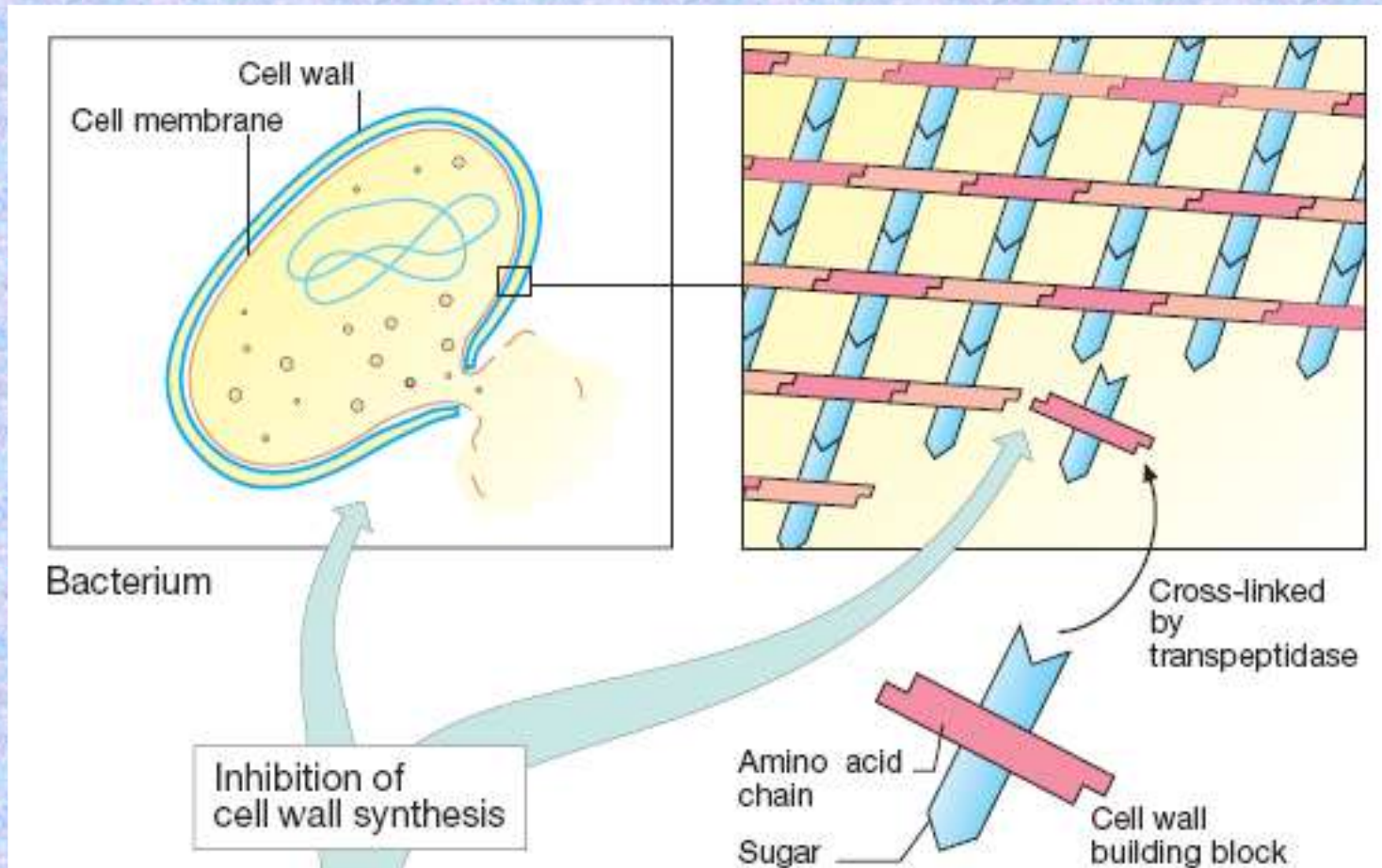
PENICILLINS:

**SITE OF THE CLEAVAGE OF PENICILLIN BY THE ACID
OR BY BACTERIAL PENICILLINASE**



PENICILLINS:

MECHANISM OF ACTION



PENICILLINS: SPECTRUM AND INDICATIONS

PNEUMOCOCCAL PNEUMONIA

- *Streptococcus pneumoniae* is a major cause of bacterial pneumonia in all age groups.
- Infection often occurs in an institutional setting in individuals who are ill from other causes.
- Resistance to *penicillin G* has greatly increased worldwide due to mutations in one or more of the bacterial penicillin-binding proteins.

Gram (+) cocci

*Streptococcus pneumoniae**
Streptococcus pyogenes
Streptococcus viridans group

*Resistant strains are increasingly seen

Gram (+) bacilli

Bacillus anthracis
Corynebacterium diphtheriae

Gram (-) cocci

Neisseria gonorrhoeae
Neisseria meningitidis

Spirochetes

Treponema pertenue (Yaws)
Treponema pallidum (Syphilis)

Anaerobic organisms

Clostridium perfringens

SYPHILIS

- A contagious venereal disease that progressively affects many tissues.
- A single treatment with *penicillin* is curative for primary and secondary syphilis. No antibiotic resistance has been reported.

GONORRHEA

- *Silver nitrate* drops in the eyes prevent gonococcal ophthalmia in newborns.
- Penicillinase-producing strains are treated using *ceftriaxone*, with *spectinomycin* as a backup.

CEPHALOSPORINS

Cephalosporins are derivatives of 7-aminocephalosporanic acid. They are wide spectrum antibiotics with bactericidal action. Mechanism of action is similar to the same of penicillins.

CLASSIFICATION

1. The 1st generation

- Cefazolin (Kefzol)
- Cephaloridine
- Cephalexin

2. The 2nd generation

- Cefamandole
- Cefuroxime
- Cefaclor

3. The 3rd generation

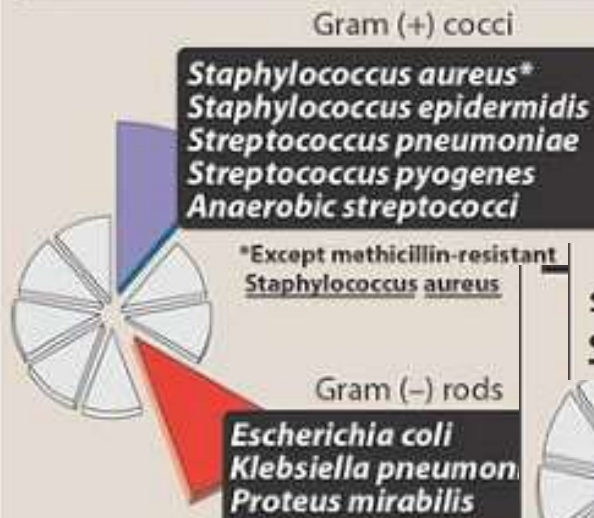
- Cefotaxime
- Ceftriaxone

4. The 4th generation

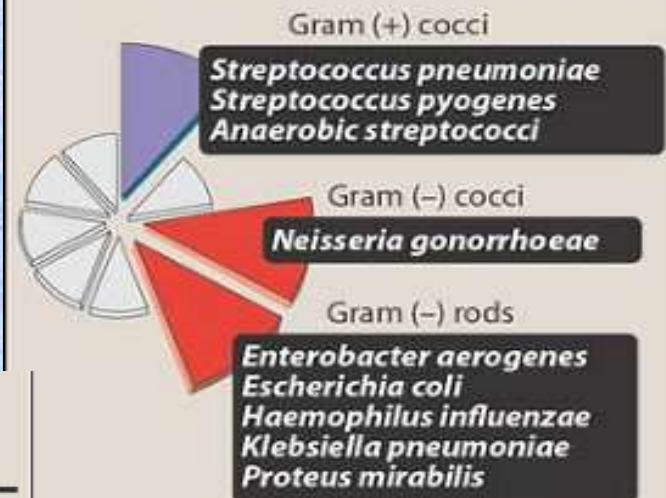
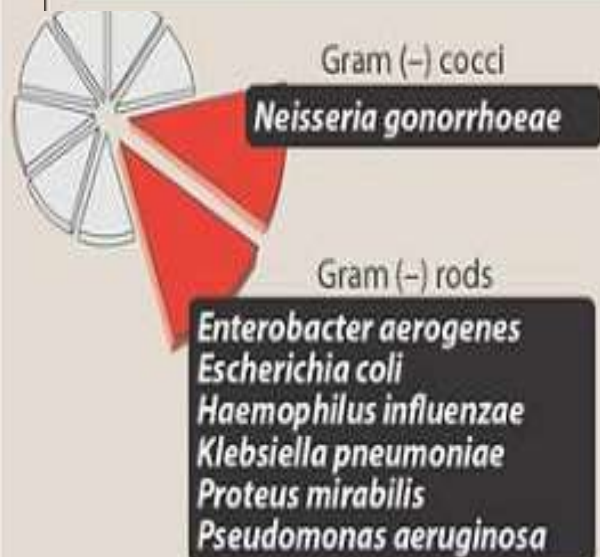
- Cefpirome
- Cefepime

CEPHALOSPORINS: SPECTRUM OF ACTION

First-generation cephalosporins



Second-generation cephalosporins



Third-generation cephalosporins

CEPHALOSPORINS:

INDICATIONS AND SIDE EFFECTS

Indications

- Severe respiratory infections
- Urinary tract infections
- Gynecologic infections
- Osteomyelitis
- Infections of skin and soft tissues
- Sepsis
- Peritonitis
- Prophylaxis of infectious complications of surgeries

Side effects

- Allergy
- Dyspepsia
- Renal disturbances (cephaloridine is the worst offender)
- Changes in the blood film, suppression of bone marrow
- A decrease in prothrombin amount in the blood
- Dysbacteriasis (for drugs administered orally).

CELL WALL SYNTHESIS INHIBITORS IN THE THERAPY OF DENTAL DISEASES

Semisynthetic penicillins of wide spectrum of action are used to treat acute infective inflammations of soft tissues and bones of maxillofacial area (periostitis, osteomyelitis, dento-alveolar abscess, phlegmon, odontogenous sepsis, actinomycosis, bacterial infections in oral cavity). **Natural penicillins** with short duration of action may be used topically.

Cephlosporins are used:

- to treat severe acute infective inflammations of soft tissues and bones of maxillofacial area (periostitis, osteomyelitis, dento-alveolar abscess, phlegmon, odontogenous sepsis)
- to prevent infective post-operative complications.

ANTIBIOTICS - PROTEIN SYNTHESIS INHIBITORS.

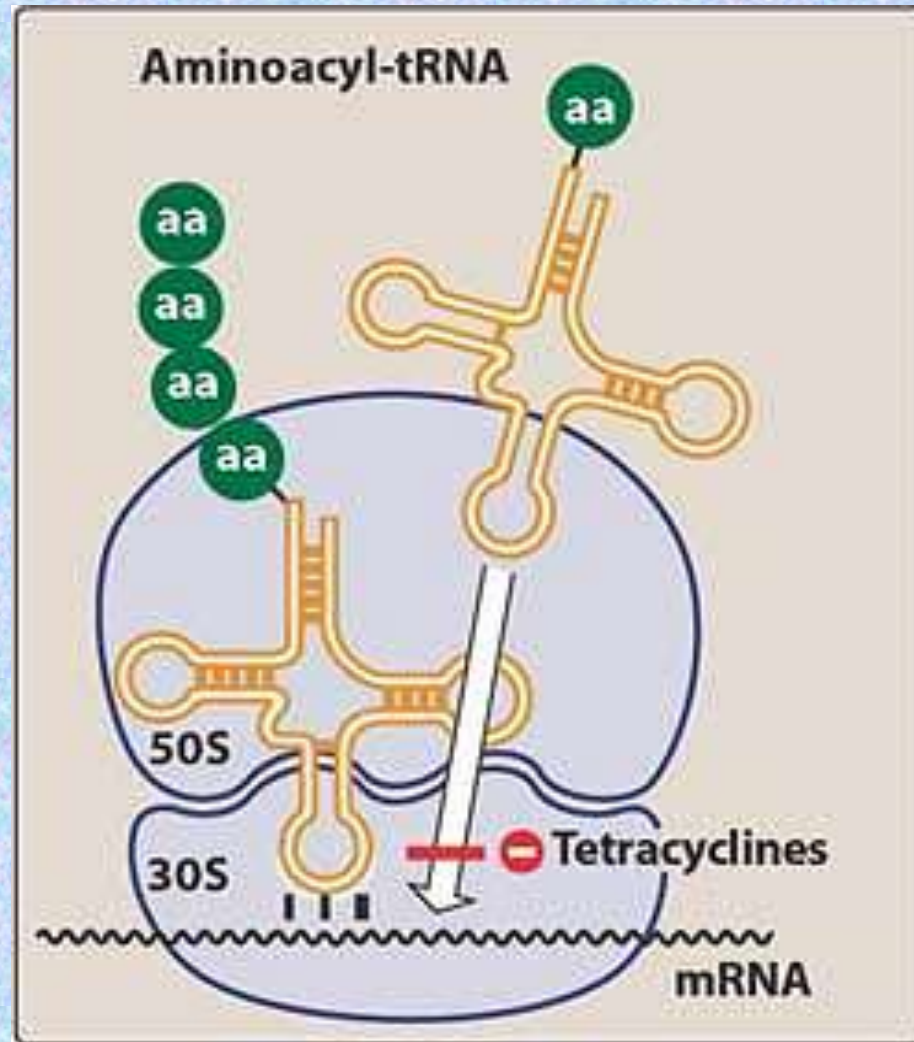
TETRACYCLINES

Tetracyclines contain 4 heterocyclic rings in their molecules.

CLASSIFICATION

1. Natural
 - Tetracycline
2. Semisynthetic
 - Doxycycline
 - Methacycline.

TETRACYCLINES: MECHANISM OF ACTION



TETRACYCLINES: SPECTRUM AND INDICATIONS

CHLAMYDIAL INFECTIONS

- *Chlamydia trachomatis* is the 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.

MYCOPLASMA PNEUMONIA

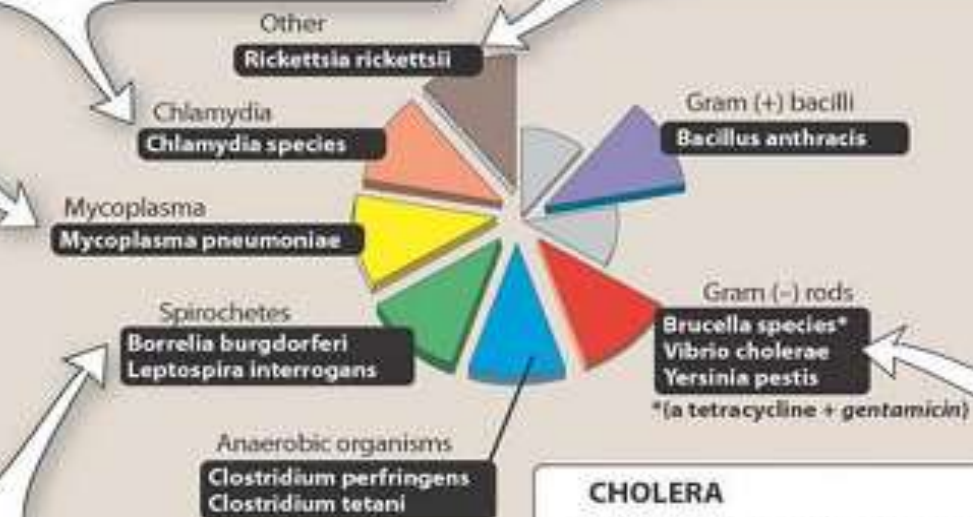
- *Mycoplasma pneumoniae* is a common cause of pneumonia in young adults and in people who live in close confines, such as in military camps.
- Treatment leads to a shorter duration of fever, cough, and malaise.
- Treatment with macrolides is also effective.

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 single, 200-mg dose of doxycycline, given within 72 hours after a tick bite, can prevent development of the disease.

CHOLERA

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



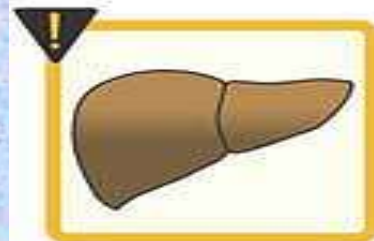
TETRACYCLINES: SIDE EFFECTS



GI disturbance



Deposition of
drug in bones
and teeth



Liver failure



Phototoxicity



Vertigo



Avoid in pregnancy

TETRACYCLINES:

SIDE EFFECTS (*TETRACYCLINE TEETH*)



AMINOGLYCOSIDES

Aminoglycosides are compounds containing amino sugars joined to a hexose nucleus in glycosidic linkage.

CLASSIFICATION

1. The 1st generation

- Streptomycin
- Neomycin

2. The 2nd generation

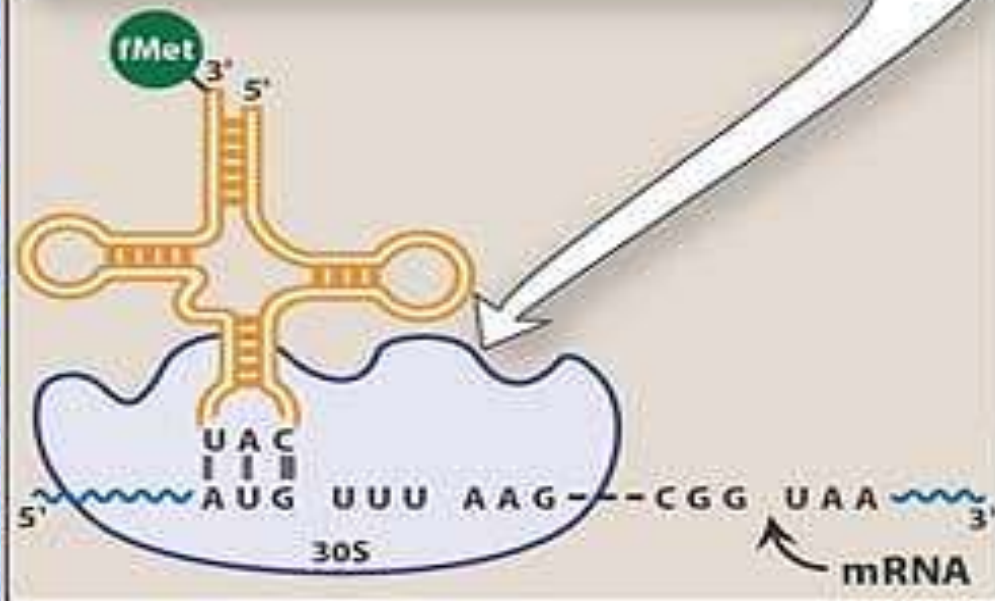
- Gentamycin

3. The 3rd generation

- Amikacyn.

AMINOGLYCOSIDES: MECHANISM OF ACTION

The aminoglycosides bind to the 30S ribosomal subunit and distort its structure, thus interfering with the initiation of protein synthesis. They also allow misreading of the mRNA, causing mutations or premature chain termination.



AMINOGLYCOSIDES: SPECTRUM AND INDICATIONS



AMINOGLYCOSIDES:

SIDE EFFECTS

Ototoxicity



Nephrotoxicity



Paralysis



Skin rash



MACROLIDES AND AZALIDES

Macrolides and azalides are the antibiotics that have a large lactone ring structure.

CLASSIFICATION

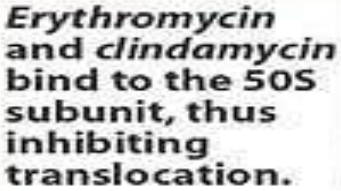
1. The 1st generation

- Erythromycin
- Oleandomycin

2. The 2nd generation

- Azithromycin
- Clarithromycin
- Spiramycin
- Roxithromycin
- Josamycin.

MECHANISM OF ACTION



MACROLIDES AND AZALIDES: SPECTRUM AND INDICATIONS

CHLAMYDIAL INFECTIONS

- *Azithromycin* is an alternative to *tetracycline* in treating uncomplicated urethral, endocervical, rectal, or epididymal infections due to *Chlamydia*.
- *Erythromycin* is the drug of choice for urogenital infections due to *Chlamydia* occurring during pregnancy.

Chlamydia

Chlamydia pneumoniae
Chlamydia psittaci
Chlamydia trachomatis

Mycoplasma

Mycoplasma pneumoniae
Ureaplasma urealyticum

Spirochetes

Treponema pallidum

MYCOPLASMAL PNEUMONIA

- Called "atypical" pneumonia because causative mycoplasma escape isolation by standard bacteriologic techniques.
- *Erythromycin* or *tetracycline* is effective.

SYPHILIS

- *Erythromycin* is used to treat syphilis in patients who are allergic to *penicillin G*.

Gram (+) cocci

Staphylococcus aureus
Streptococcus pyogenes
Streptococcus pneumoniae

Gram (+) bacilli

Corynebacterium diphtheriae

Gram (-) cocci

Moraxella catarrhalis
Neisseria gonorrhoeae

Gram (-) rods

Bordetella pertussis
Campylobacter jejuni
Haemophilus influenzae
Legionella pneumophila

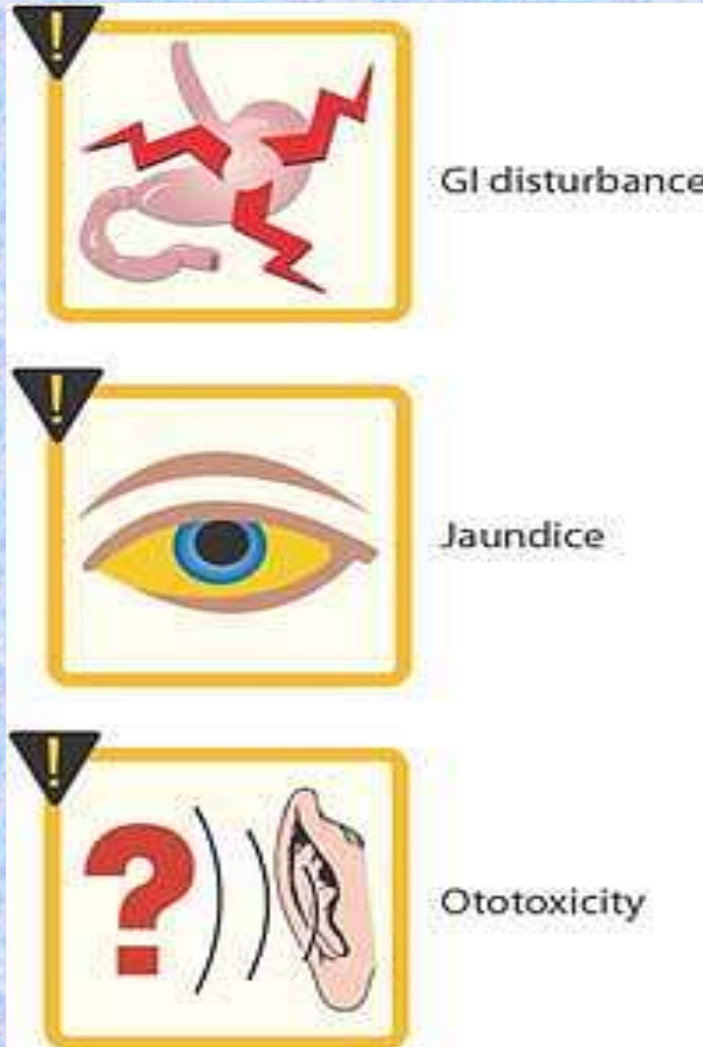
CORYNEBACTERIUM DIPHTHERIAE

- *Erythromycin* or *penicillin* is used to eliminate the carrier state.

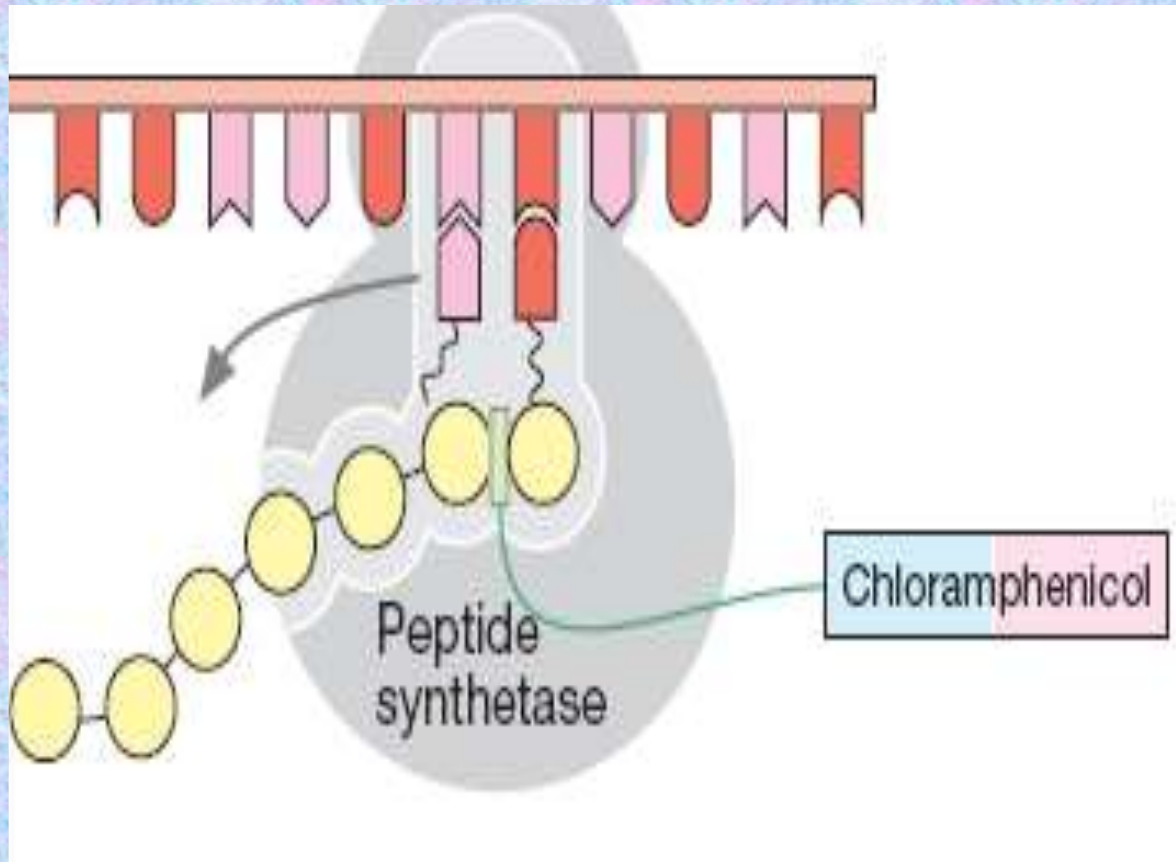
LEGIONNAIRES' DISEASE (LEGIONELLOSIS)

- Legionellosis represents 0.5 to 2.0 percent of all pneumonia in the United States. Undiagnosed or asymptomatic infections are common.
- *Azithromycin* is the therapy of choice.

MACROLIDES AND AZALIDES: SIDE EFFECTS



CHLORAMPHENICOL: MECHANISM OF ACTION



CHLORAMPHENICOL:

SPECTRUM, INDICATIONS, SIDE EFFECTS

Spectrum of action

Gram (-) organisms; anaerobic organisms (*Bacteroides* species); *Meningococcus*, some strains of *Streptococcus* and *Staphylococcus*; spirochetes, *Clostridium*, *Chlamydia*, *Mycoplasma*; rickettsiae.

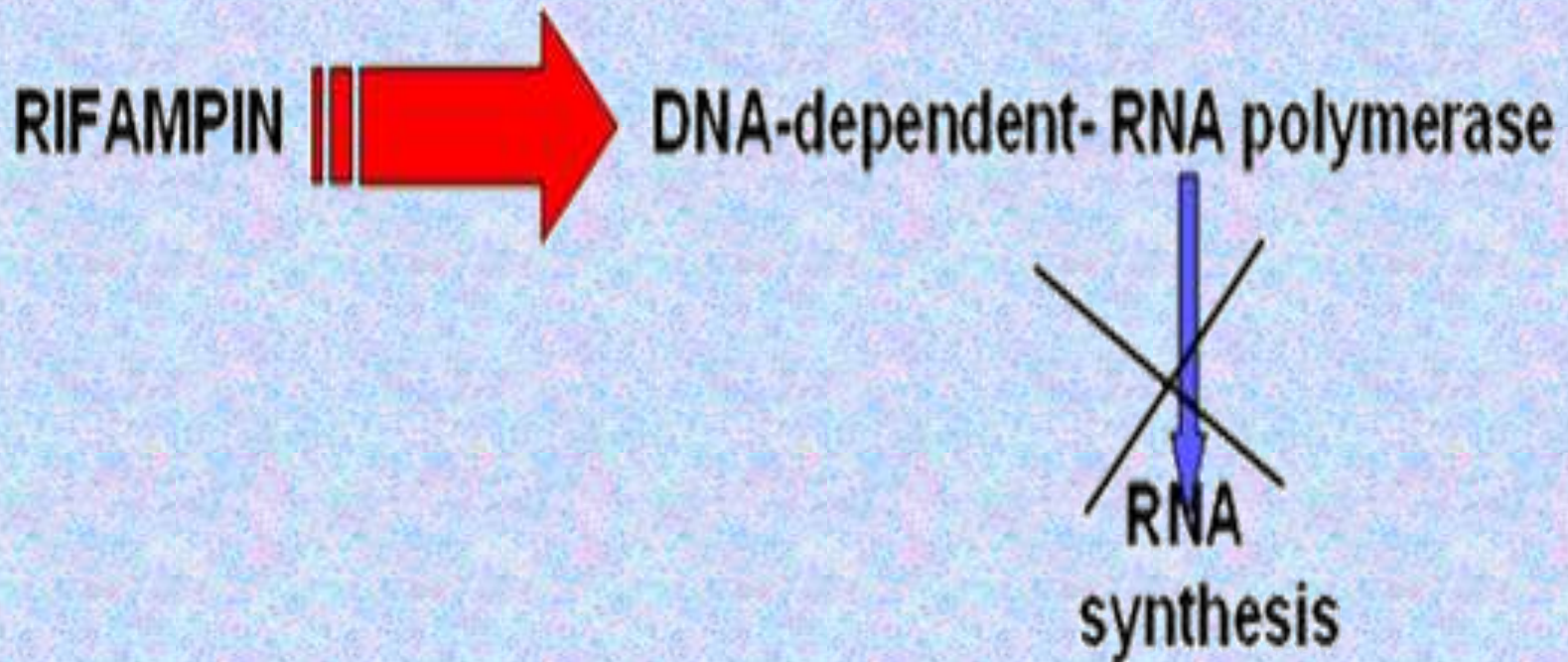
Indications

- Typhoid fever and Salmonella infections
- Bacterial meningitis
- Anaerobic infections
- Rickettsial diseases
- Brucellosis
- Infections of skin and soft tissues
- Bacterial conjunctivitis
- Chlamydial infections (trachoma).

Side effects

- Allergic reactions
- Inhibition of leukopoiesis and erythropoiesis → anemia, leukopenia
- Superinfections (candidiasis and acute staphylococcal enterocolitis)
- Gray-baby syndrome
- Endotoxic reactions.

ANTIBIOTICS WHICH DISTURB FUNCTIONS OF NUCLEIC ACIDS: RIFAMICINS



RIFAMICINS:

SPECTRUM, INDICATIONS, SIDE EFFECTS

Spectrum of action

Most Gram (+) and many Gram (-) microorganisms, *Mycobacterium tuberculosis*, *Mycobacterium leprae*.

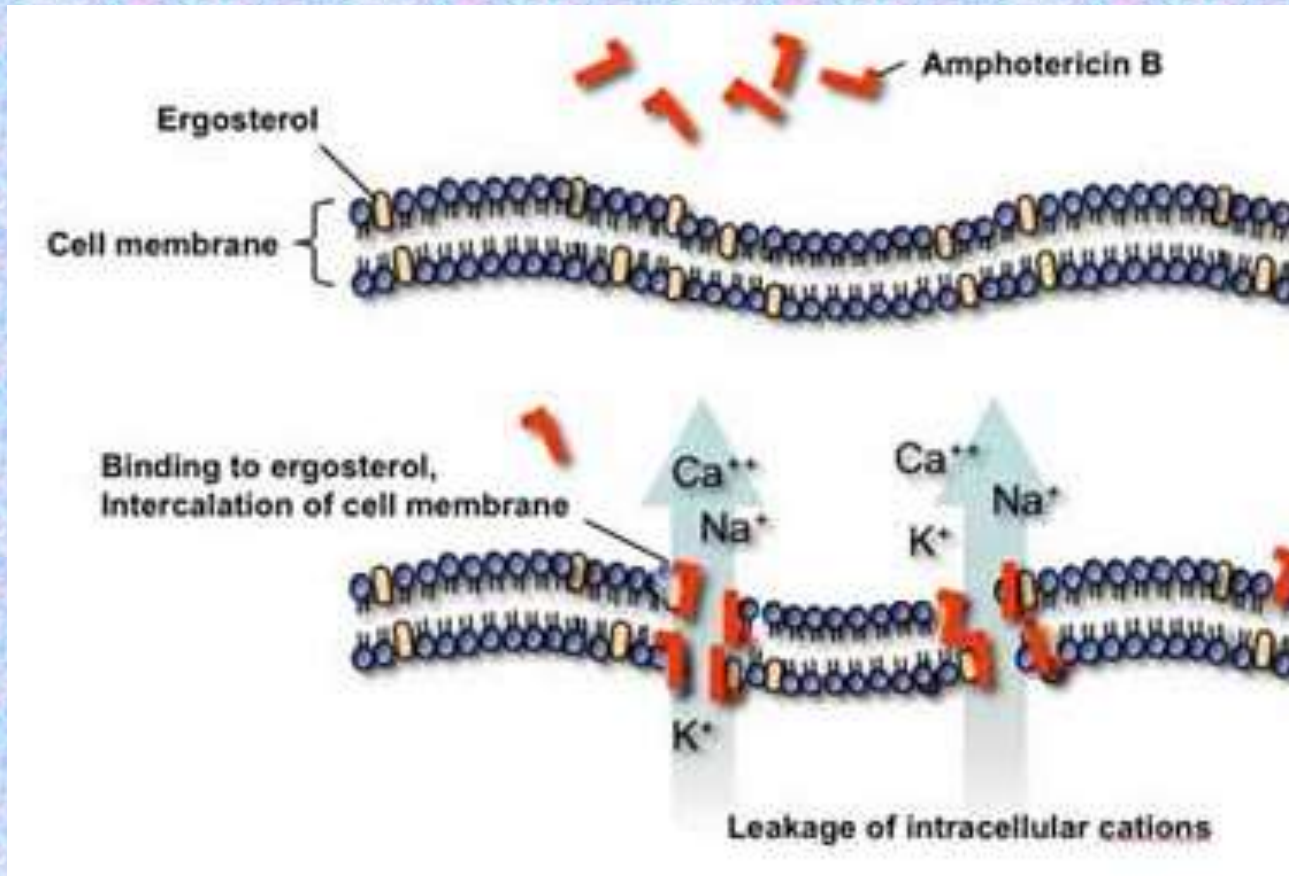
Indications

- Tuberculosis (in combination with other agents)
- Atypical mycobacterial infections
- Leprosy
- Bacterial infections caused by sensitive microbes: pneumonia, cholecystitis, osteomyelitis, etc (as alternative antibiotic).

Side effects

- 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
- Rash
- Gastrointestinal disturbances
- Renal damage
- Jaundice and severe hepatic dysfunction.

ANTIBIOTICS INFLUENCING STRUCTURE OF CELL MEMBRANES. POLYENES



POLYENES:

SPECTRUM, INDICATIONS, SIDE EFFECTS

Nystatin

- has narrow spectrum of action;
- influences *Candida 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*;
- is the most effective drug available for systemic fungal infections;
- is used for the treatment of life-threatening fungal infections in patient with impaired immunity; pulmonary, cutaneous, and disseminated forms of blastomycosis; acute pulmonary coccidioidomycosis; pulmonary histoplasmosis; *C. neoformans* infections, candidiasis;
- may cause hypersensitivity reactions, anaphylaxis, fever, chill, headache, gastrointestinal disturbances; decreased renal function, anemia and thrombophlebitis.

POLYPEPTIDES (POLYMYXINS)

Mechanism of action

Polymyxins interact with a specific lipopolysaccharide component of cell membrane.

Membrane lipid structure is distorted with an increase in permeability to polar molecules resulting in marked changes in cell metabolism.

Spectrum of action

The spectrum of action is narrow: Gram (-) bacteria (*P. aeruginosa*, *Salmonella*, *Shigella*, *E. coli*, *Pasteurella*, *Brucella*, *H. influenzae*, etc.)

Peculiarities of preparations

Polymyxin M is not absorbed in the GI tract; is administered orally (for action in the gut) and topically, is used to treat infected burns, wounds, skin diseases, intestinal infections, for sterilization of bowels before surgeries; topical administration of polymyxin M is not accompanied by denominated side-effects.

Polymyxin B is administered parenterally; is used in severe infections caused by Gram (-) bacilli: meningitis, sepsis, peritonitis; adverse effects include neurotoxicity (paresthesias, dizziness, ataxia) and acute renal tubular necrosis (hematuria, proteinuria, nitrogen retention).

PROTEIN SYNTHESIS INHIBITORS IN THE THERAPY OF DENTAL DISEASES

Tetracyclines are used to treat acute infective inflammations of soft tissues and bones of maxillofacial area (periostitis, osteomyelitis, alveolitis, parodontitis, arthritis of temporo-mandibular joint, abscess, phlegmon, odontogenous sepsis, bacterial infections in oral cavity, actinomycosis).

Aminoglycosides are indicated in infective inflammations in maxillofacial area caused by Gram (-) or mixed microflora.

Macrolides are used to treat acute infective inflammations of soft tissues and bones of maxillofacial area (periostitis, osteomyelitis, dento-alveolar abscess, phlegmon, odontogenous sepsis, bacterial infections in oral cavity).

Lincosamides are used to treat acute infective inflammations of bones in maxillofacial area (periostitis, osteomyelitis, alveolitis, odontogenous sepsis, parodontitis, arthritis of temporo-mandibular joint).

Chloramphenicols are used for treatment of purulent inflammations of mucous membrane in oral cavity (as ingredients of combined ointments).

TOPICAL APPLICATION OF ANTIBIOTICS-PROTEIN SYNTHESIS INHIBITORS IN DENTISTRY

<i>Neomycin</i>	– Instillations into parodontal pockets – Washing of dental root channels – Biological method of treatment of pulpitis
<i>Erythromycin</i>	– Heilitis (in the form of ointment) – Stomatitis (in the form of ointment)
<i>Chloramphenicol</i>	– Acute deep caries and pulpitis (as ingredient of stomatological paste) – Stomatitis, gingivitis, heilitis (in the form of combined ointment)
<i>Polymyxin M</i>	– Washing of dental root channels – Stomatitis, gingivitis, heilitis (in the form of ointment)

STEP 1

1. A child 5 years old with acute right-sided pneumonia. When sowing sputum revealed that pathogen is resistant to penicillin, but sensitive to macrolides. Which drug is most appropriate to use in this case?
 - A. Azithromycin
 - B. Ampicillin
 - C. Streptomycin
 - D. Tetracycline
 - E. Gentamicin

2. For the treatment of bacterial pneumonia was appointed penicillin sodium salt. What is the mechanism of antimicrobial action of the drug?
 - A. Inhibition of intracellular protein synthesis
 - B. Inhibition of the synthesis of the cell wall of microorganisms
 - C. Inhibition of cholinesterase activity
 - D. Inhibition of SH-groups of enzymes of microorganisms
 - E. Antagonism with parabens