Antibiotics
having a β-lactam ring.

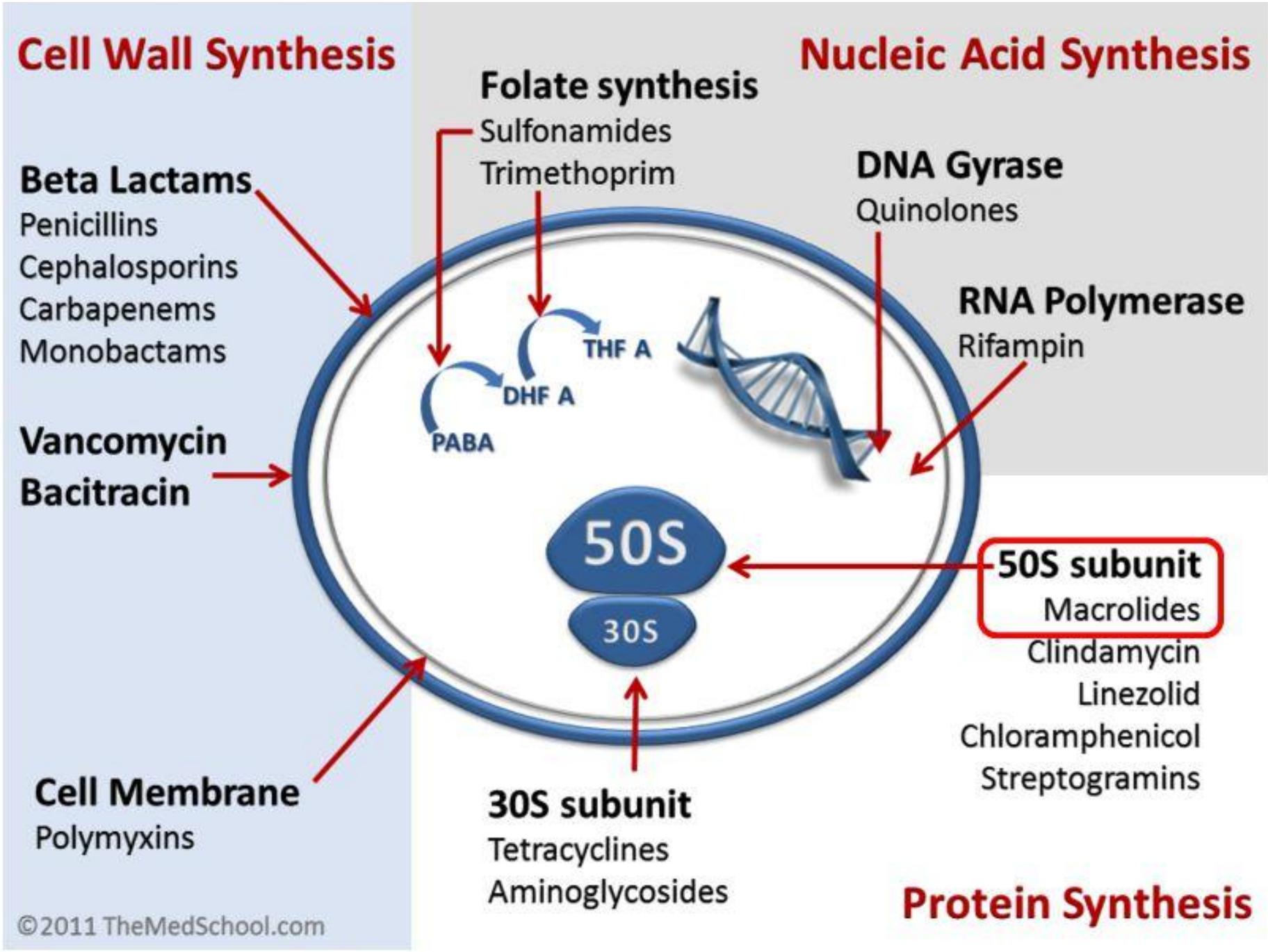
- Antibiotics - antimicrobial substances of natural origin, produced by certain types of fungi and bacteria. Usually they are used as chemotherapy drugs.
- There are antibiotics: antibacterial, antifungal, antineoplastic.
- Depending on the method of obtaining: natural and semi-synthetic.

Classification (chemical structure):

- **β-*Lactam antibiotics:*** Penicillins, Cephalosporins, Monobactams, Carbapenems;
- ***Macrolide antibiotics:*** Erythromycin, Clarithromycin, Azithromycin;
- ***Tetracyclines:*** Oxytetracycline, Doxycycline;
- ***Nitrobenzene derivative:*** Chloramphenicol;
- ***Aminoglycosides:*** Streptomycin, Gentamycin, Amikacin, Neomycin;
- ***Lincosamide antibiotics:*** Lincomycin, Clindamycin;
- ***Glycopeptide antibiotics:*** Vancomycin.

Mechanism of action:

- ***Inhibit cell wall synthesis:*** Penicillins, Cephalosporins, Vancomycin,
- ***Cause leakage from cell membranes:*** Polymyxins, Polyenes—Amphotericin B, Nystatin;
- ***Inhibit protein synthesis:*** Tetracyclines, Chloramphenicol, Erythromycin, Clindamycin,
- ***Cause misreading of m-RNA code and affect permeability:*** Aminoglycosides;
- ***Interfere with DNA function:*** Rifampicin


Cell Wall Synthesis
Nucleic Acid Synthesis
Folate synthesis
Sulfonamides
Trimethoprim
Beta Lactams
Penicillins
Cephalosporins
Carbapenems
Monobactams
DNA Gyrase
Quinolones
RNA Polymerase
Rifampin
THF A
DHF A
PABA
Vancomycin
Bacitracin
50S
30S
50S subunit
Macrolides
Clindamycin
Linezolid
Chloramphenicol
Streptogramins
Cell Membrane
Polymyxins
30S subunit
Tetracyclines
Aminoglycosides
Protein Synthesis
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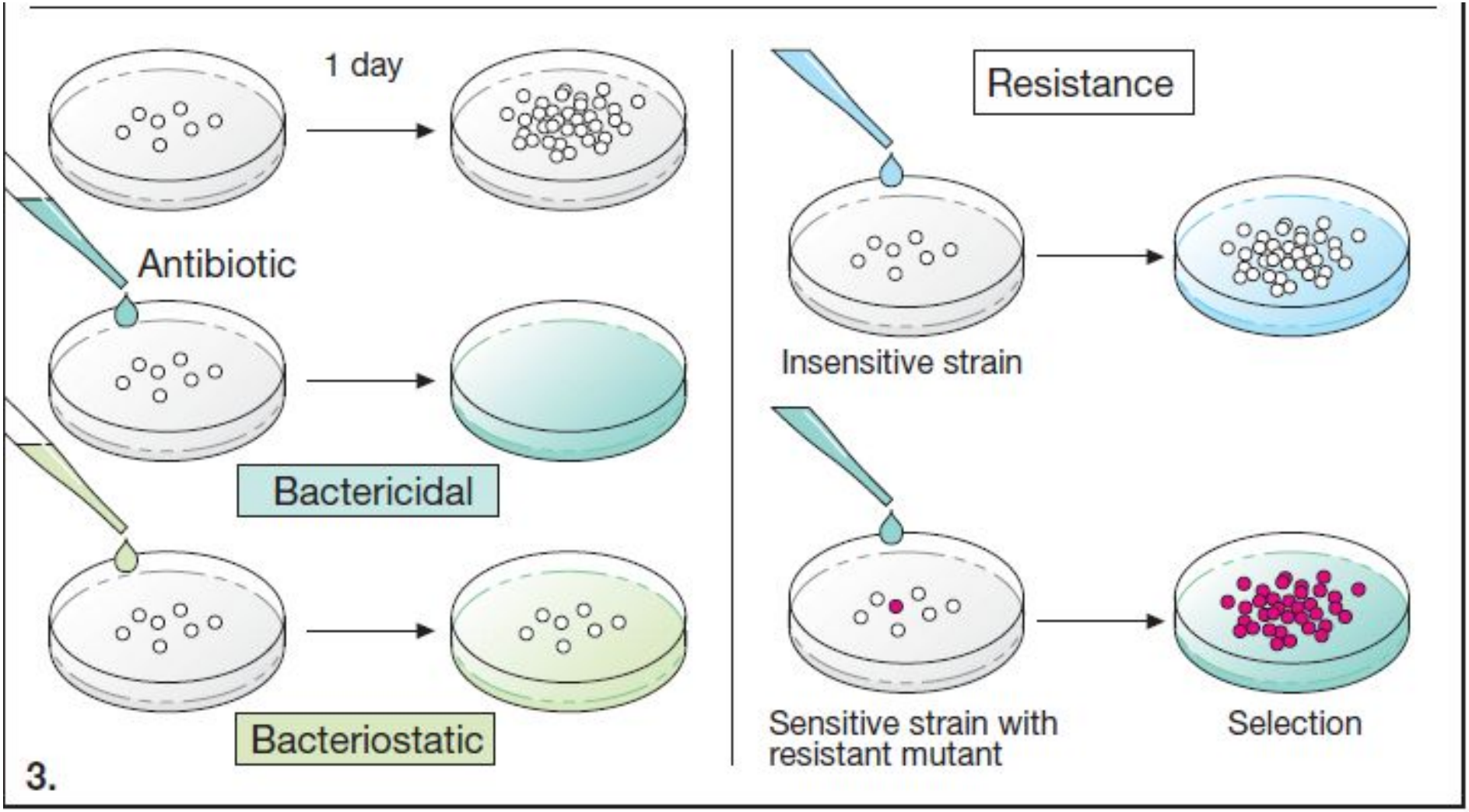
Type of antimicrobial action:

- *Bactericidal* (complete destruction of bacterial cells)
- *Bacteriostatic* (stopping of the growth and division of bacterial cells)

Spectrum of activity:

- *Narrow-spectrum:* Penicillin G, Erythromycin
- *Broad-spectrum:* Tetracyclines, Chloramphenicol


1 day
Antibiotic
Bactericidal
Bacteriostatic
3.
Resistance
Insensitive strain
Sensitive strain with resistant mutant
Selection

Toxicity and side effects:

- Practically all AMA, especially erythromycin, tetracyclines, certain cephalosporins and chloramphenicol are irritant.
- ***Systemic toxicity:*** Almost all AMAs produce dose related and predictable organ toxicities. Some have a ***high therapeutic index—doses up*** **to 100-fold range** may be given without apparent damage to host cells. These include penicillins, some cephalosporins and erythromycin.
- Others have a ***lower therapeutic index***—*doses* have to be individualized and toxicity watched for, e.g.:

Aminoglycosides: 8th cranial nerve and kidney toxicity.

Tetracyclines: liver and kidney damage.

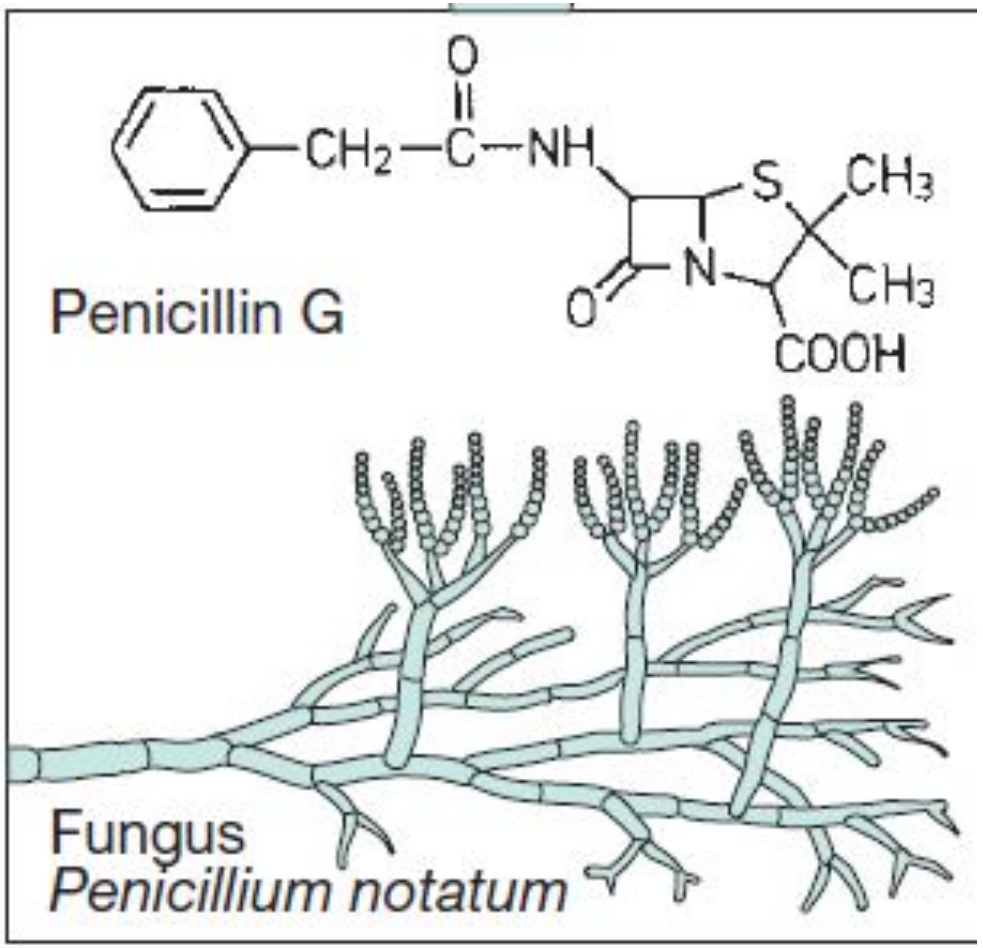
Chloramphenicol: bone marrow depression.

- Others have a ***very low therapeutic index***— use is highly restricted to conditions where no suitable alternative is available (Polymyxin B, Vancomycin, Amphotericin B)
- Practically all AMAs are capable of causing **hypersensitivity reactions.** These are unpredictable and unrelated to dose.
- **Drug resistance (**Natural resistance, Mutation, Gene transfer, Cross resistance)
- **Superinfection (Suprainfection).**

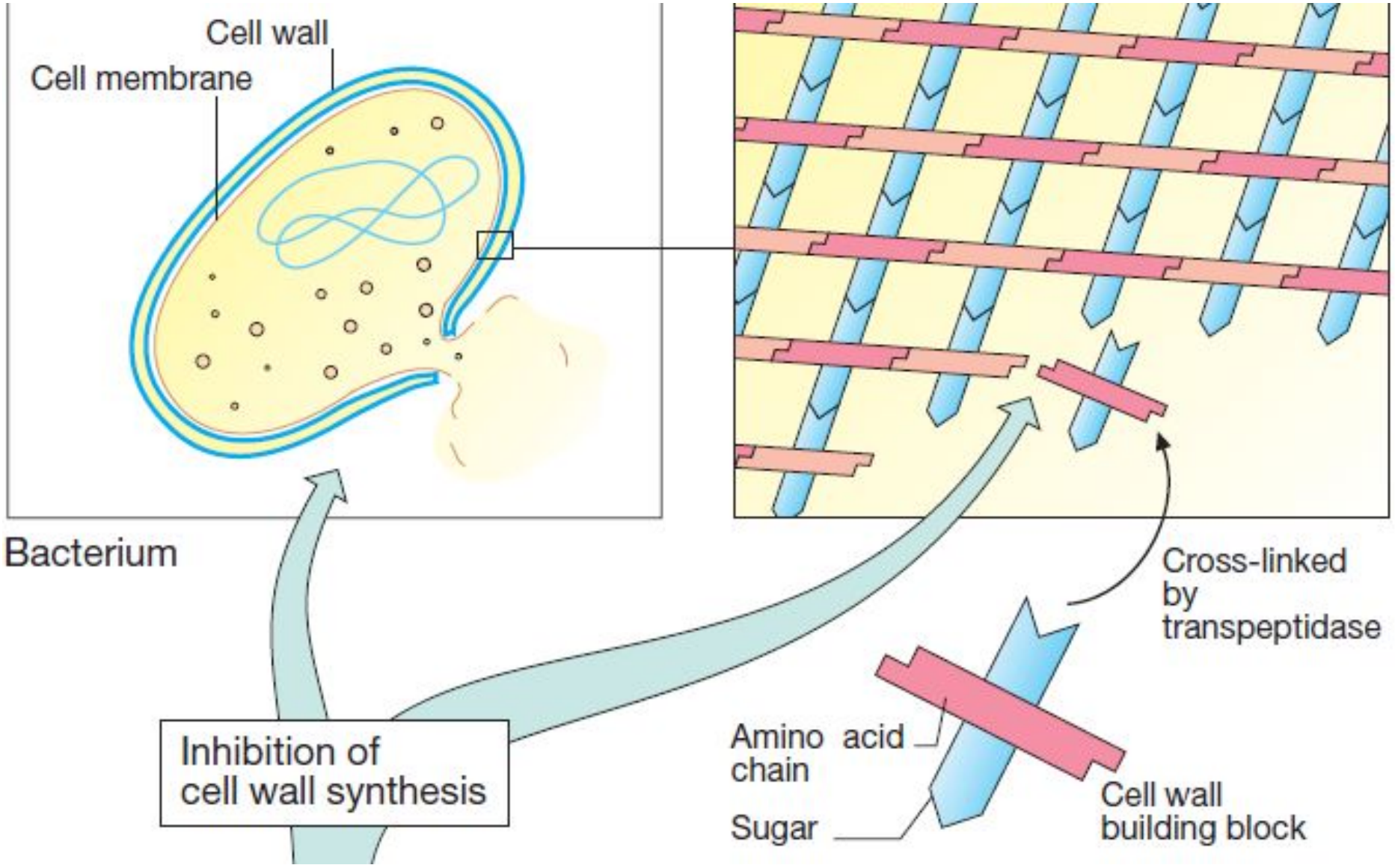
- **PENICILLIN** was the first antibiotic to be used clinically in 1941.

Chemical structure of penicillins:

- ❑ Thiazolidine ring;
- ❑ β-lactam ring;



- Ps. inhibit synthesis of the bacterial cell wall. The cell wall is composed of a polymer called peptidoglycan that consists of glycan units joined to each other by peptide cross-links.
- Ps. **inhibit transpeptidase, but activate production of autolysins**
- Ps. interfere with the last step of bacterial cell wall synthesis (transpeptidation or cross-linkage). Cell lysis can then occur, either through osmotic pressure or through the activation of autolysins. The type of action is bactericidal.


Cell wall
Cell membrane
Bacterium
Cross-linked by transpeptidase
Amino acid chain
Sugar
Cell wall building block
Inhibition of cell wall synthesis

Classification

Biosynthetic ps:

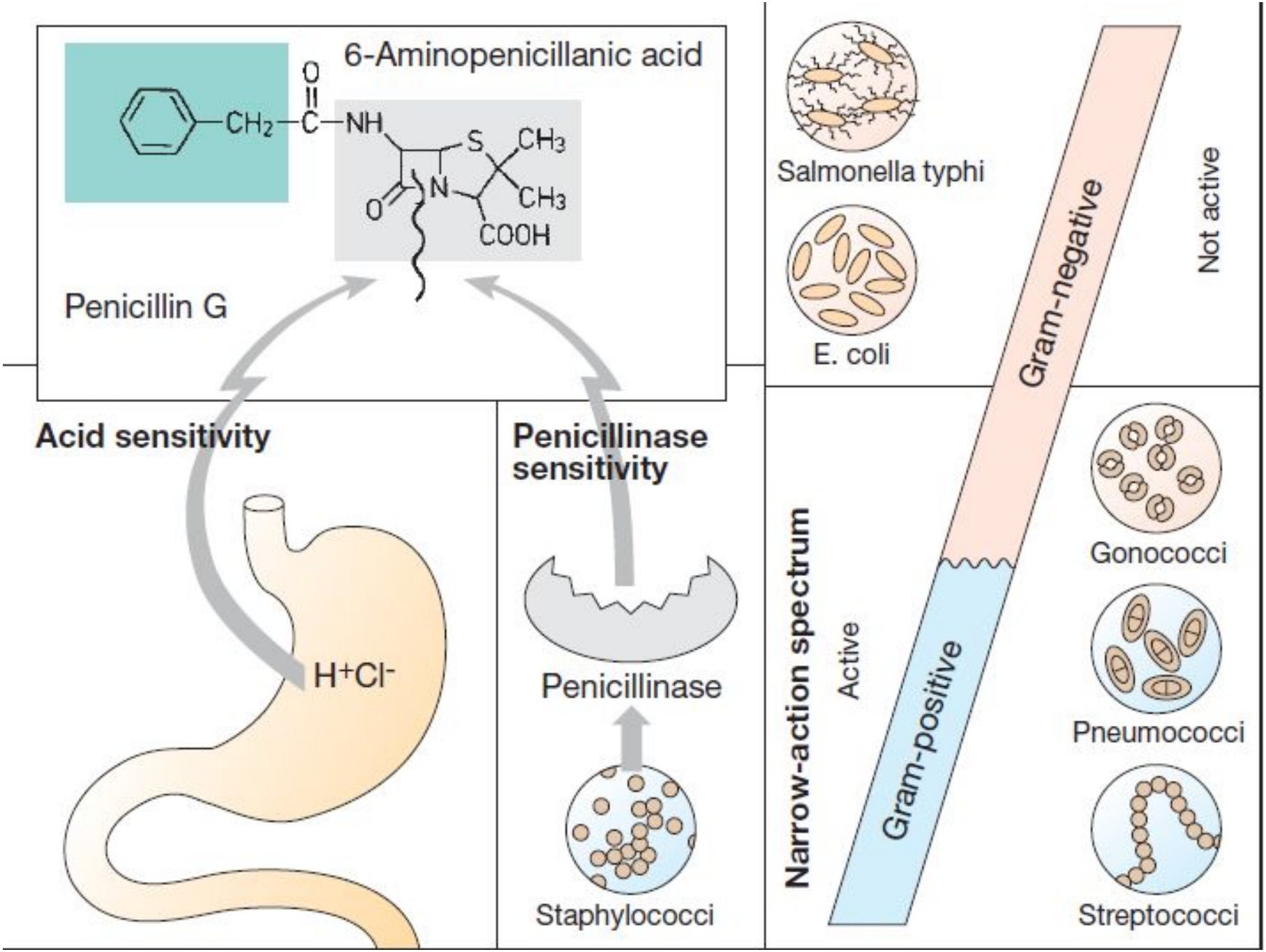
A. For parenteral use:

- Short acting: Benzylpenicillin
- Long acting: Procaine-benzylpenicillin, Benzylpenicillin-benzatine (bicilline 1), Bicilline-5

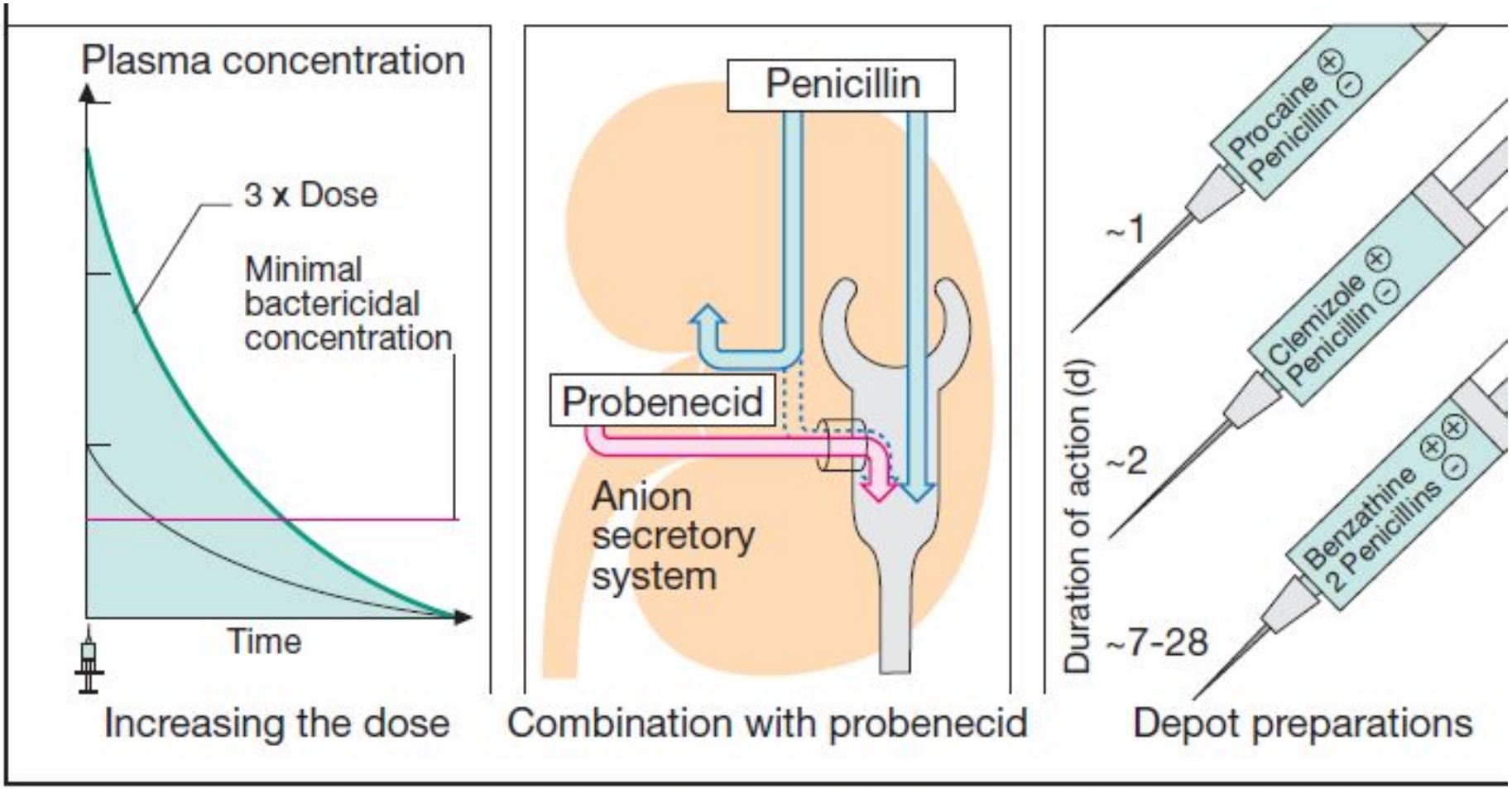
For oral use (acid-stable): phenoxymethylpenicillin

Antibacterial spectrum of biosynthetic ps.:

- Cocci: Streptococci, Pneumococci, Staphylococci, Neisseria gonorrhoeae and N. meningitidis;
- B. anthracis, Corynebacterium diphtheriae,
- Clostridia (tetani and others),
- Listeria, spirochetes (Treponema pallidum, Leptospira),
- Actinomyces
- **Staph. Aureus produces penicillinase (**a narrow spectrum β-lactamase which opens the β-lactam ring and inactivates P**s)**


6-Aminopenicillanic acid
Penicillin G
Acid sensitivity
H+Cl-
Penicillinase sensitivity
Penicillinase
Staphylococci
Salmonella typhi
E. coli
Gram-negative
Not active
Narrow-action spectrum
Active
Gram-positive
Gonococci
Pneumococci
Streptococci

- Benzylpenicillin is injected I.M. and I.V. 4-6 times a day. It penetrates well into the tissues, through BBB only in inflammation. It is excreted by the kidneys in the active form.
- Bicillins are poorly water soluble salts, they are administered only I.M. They are long-term acting drugs.
- Phenoxymethylpenicillin is acid-stable, its bioavailability is 30-60%. It is less active. It is used for respiratory infections.



A. Penicillin G: structure and origin; mode of action of penicillins; methods for prolonging duration of action

Uses:

- Streptococcal infections (pharyngitis, otitis media, scarlet fever, rheumatic fever)
- Pneumococcal infections
- Meningococcal infections (meningitis)
- Gonorrhoea
- Syphilis, Leptospirosis
- Diphtheria
- Tetanus and gas gangrene
- Prophylactic uses (Benzathine penicillin - bicillins): rheumatic fever, bacterial endocarditis

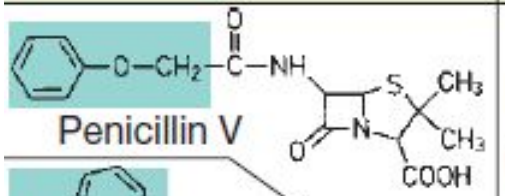
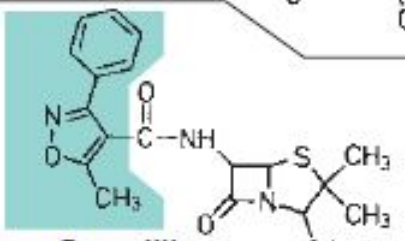
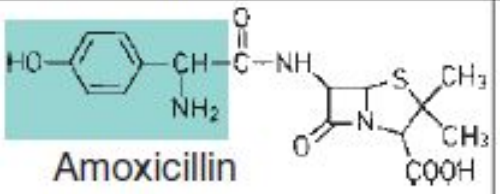
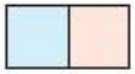
Classification of semysinthetic ps.

- *Penicillinase-resistant penicillins:* Methicillin, Oxacillin, Cloxacillin, Dicloxacillin.
- *Extended spectrum penicillins*

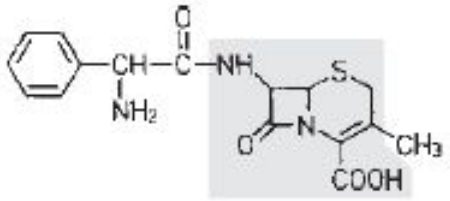
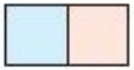
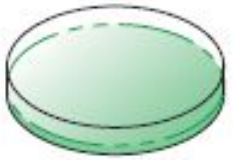
a) *Aminopenicillins:* Ampicillin, Amoxicillin.

b) *Act on Pseudomonas aeruginosa:* Carbenicillin, Ticarcillin, Piperacillin, Mezlocillin.

- β-*lactamase inhibitors:* Clavulanic acid, Sulbactam, Tazobactam

	Acid	Penicillinase	Spectrum	Concentration needed to inhibit penicillin G-sensitive bacteria
 Penicillin V	Resis-tant	Sensitive	 Narrow	
 Oxacillin	Resis-tant	Resistant	 Narrow	
 Amoxicillin	Resis-tant	Resistant	 Broad	

B. Derivatives of penicillin G

Cefalexin 	Resis-tant	Resistant, but sensitive to cephalosporinase	 Broad	

C. Cephalosporin

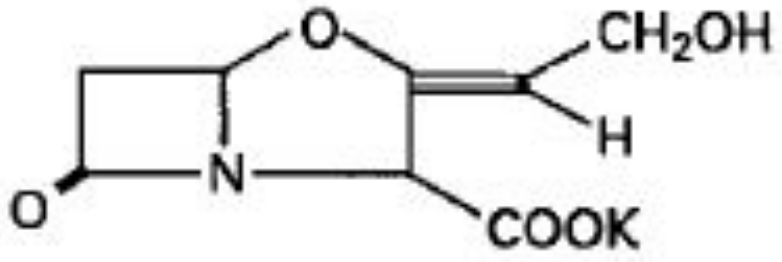
- Oxacillin, Cloxacillin, Dicloxacillin are highly penicillinase and acid resistant. Activity against PnG sensitive organisms is weaker. They do not effect on Treponema and Borrelia.
- They are incompletely absorbed from oral route, especially if taken in empty stomach. Elimination occurs primarily by kidney, also partly by liver. They are administered 4-6 times a day p/o, IV, IM.
- Uses: staphylococcal infections.

- Ampicillin, Amoxicillin inhibit ***H. influenzae, E. coli, Proteus, Salmonella, Shigella and Helicobacter pylori.*** They are active against all organisms sensitive to PnG (except treponema). They are destroyed by penicillinase and inactive against staphylococci
- They are absorbed from GIT (absorption of amoxicillin is better). They are eliminated by kidneys and they are partly excreted in bile and reabsorbed—enterohepatic circulation occurs.
- Ampicillin is used 4-6 times a day,
- Amoxicillin – 3 times a day.

Uses:

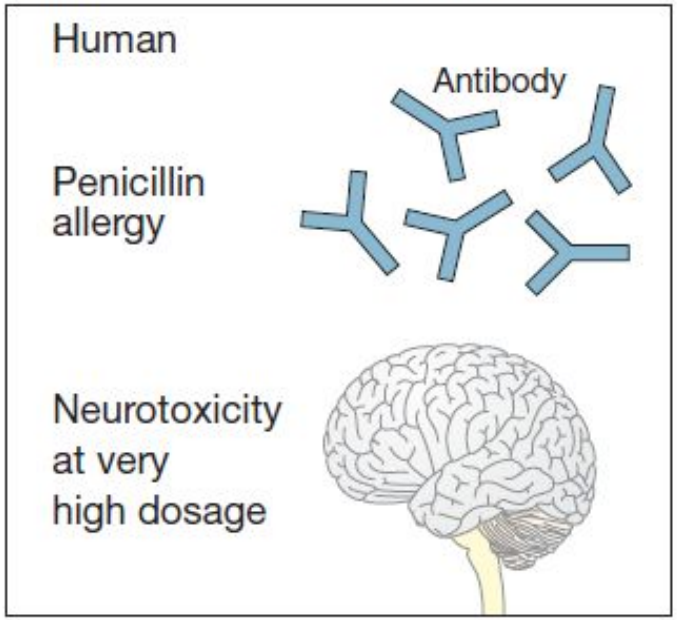
- Urinary tract infections;
- Respiratory tract infections: including bronchitis, sinusitis, otitis media;
- Gonorrhoea;
- Bacillary dysentery;
- Cholecystitis;
- H. pylori-infections (ulcer)
- Septicaemias and mixed infections

- **Carbenicillin, Ticarcillin, Piperacillin, Mezlocillin** are active against *Pseudomonas aeruginosa and indole positive Proteus, Bacteroides, many Enterobacteriaceae*, *Klebsiella,.*
- They are neither penicillinase-resistant nor acid resistant. They are inactive orally and are excreted rapidly in urine. They are used 4-6 times a day.
- Uses: serious infections caused by *Pseudomonas or Proteus,* e.g. burns, urinary tract infection, septicaemia.

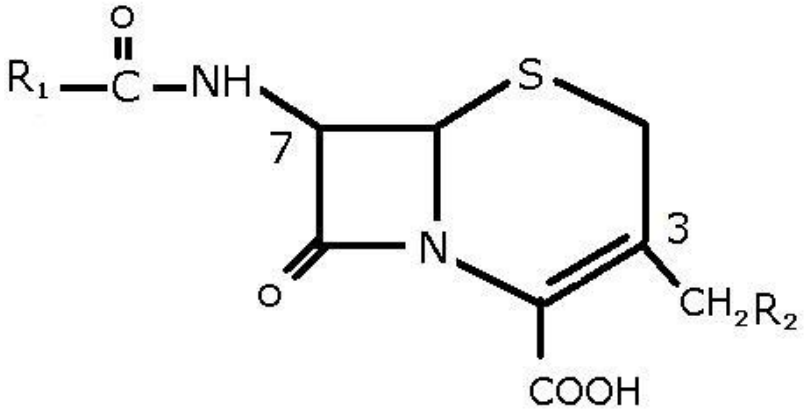


- Combination of drugs with inhibitors of β-lactamases (clavulanic acid, sulbactam, tazobactam): **amoxicillin + clavulanic acid**
- Clavulanic acid has a structural similarity with penicillins and it is subject to destruction. Antibiotic retains its structure.
- Uses: skin and soft tissue infections, intraabdominal and gynaecological sepsis, urinary, biliary and respiratory tract infections.

- **Allergic reactions** (urticaria, anaphylactic shock, fever, dermatitis)
- **Irritant effect** (gingivitis, stomatitis, dyspepsia, phlebitis, infiltrates)
- **Neurotoxicity** (seizures)
- **Dysbacteriosis, superinfection**
- **Resistance of microorganisms**
- **Thrombosis and embolism** (bicillin)
- ***Carboxypenicillins and Ureidopenicillins:*** violation of blood (leukopenia, thrombocytopenia), interstitial nephritis, disorders of coagulation



- The cephalosporins are β-lactam antibiotics. Most cephalosporins are produced semisynthetically by the chemical attachment of side chains to 7-aminocephalosporanic acid.



- They act bactericidally; inhibit transpeptidase, disrupt the synthesis of peptidoglycan, violate the synthesis of the cell wall.

- ✔ The first-generation cephalosporins act as *Pn G. They are resistant to the staphylococcal* penicillinase and also have activity against Proteus mirabilis, E. coli, and K. pneumoniae. These drugs are destroyed by cephalosporinase.
- ✔ Cephalexin (p/o), cefazolin (IM,IV) pass into the tissues, go through the BBB poorly, they are excreted by the kidneys by tubular secretion, appointed 3-6 times a day.

- The second-generation cephalosporins display greater activity against three additional gram-negative organisms: H. influenzae, Enterobacter aerogenes, and some Neisseria species, whereas activity against gram-positive organisms is weaker.
- Cefuroxime, cefaclor pass through the BBB in inflammation. They are excreted by the kidneys by filtration. They are appointed 3 times a day.

- Cefotaxime, ceftriaxone, ceftazidime, cefixime -drugs of 3 generation are less potent than first-generation cephalosporins against MSSA, have enhanced activity against gram-negative bacilli. They act on Pseudomonas aeruginosa, Bacteroides, they are resistant to cephalosporinase.
- They distribute very well into body fluids.
- Adequate therapeutic levels in the CSF, regardless of inflammation, are achieved.
- They are administered 1-2 times a day.

4: Cefepime. Cefpirome.

The spectrum is very wide (gram-negative and gram-positive), they are resistant to β-lactamases, but do not act on Bacteroides.

- They are administered IM, IV 2-4 times a day. They do not pass through the BBB. They are excreted by kidneys.

- 5. Ceftaroline and Ceftobiprole are active against MRSA and used for the treatment of serious infections. They are injected IV 2-3 times a day.

Uses:

- Respiratory, urinary and soft tissue infections caused by gram-negative organisms, especially *Klebsiella, Proteus, Enterobacter, Serratia;*
- Penicillinase producing staphylococcal infections;
- Septicaemias caused by gram-negative organisms;
- Surgical prophylaxis;
- Meningitis;
- Gonorrhoea;
- Mixed aerobic-anaerobic infections;
- Infections of GIT

Side effects:

- Allergic reactions: rash, anaphylactic shock;
- Local irritant effect: infiltrates, phlebitis, dyspeptic disorders;
- Nephrotoxicity (1 generation);
- Neurotoxicity (nystagmus, hallucinations, seizures);
- Hematotoxicity (thrombocytopenia, neutropenia, reduction of blood clotting);
- Alcohol intolerance(diarrhea, nausea, tachycardia, redness of the face);
- Dysbacteriosis. Diarrhoea.

MONOBACTAMS - Aztreonam

- Spectrum: gram-negative enteric bacilli, H.influenzae, Pseudomonas.
- Aztreonam is resistant to the action of most β-lactamases.
- It is administered IV and IM.
- Side effects: phlebitis, skin rash, abnormal liver function tests.
- This drug may be a safe alternative for treating patients who are allergic to other penicillins, cephalosporins, or carbapenems.

CARBAPENEMS

Imipenem-cilastatin, **Meropenem**

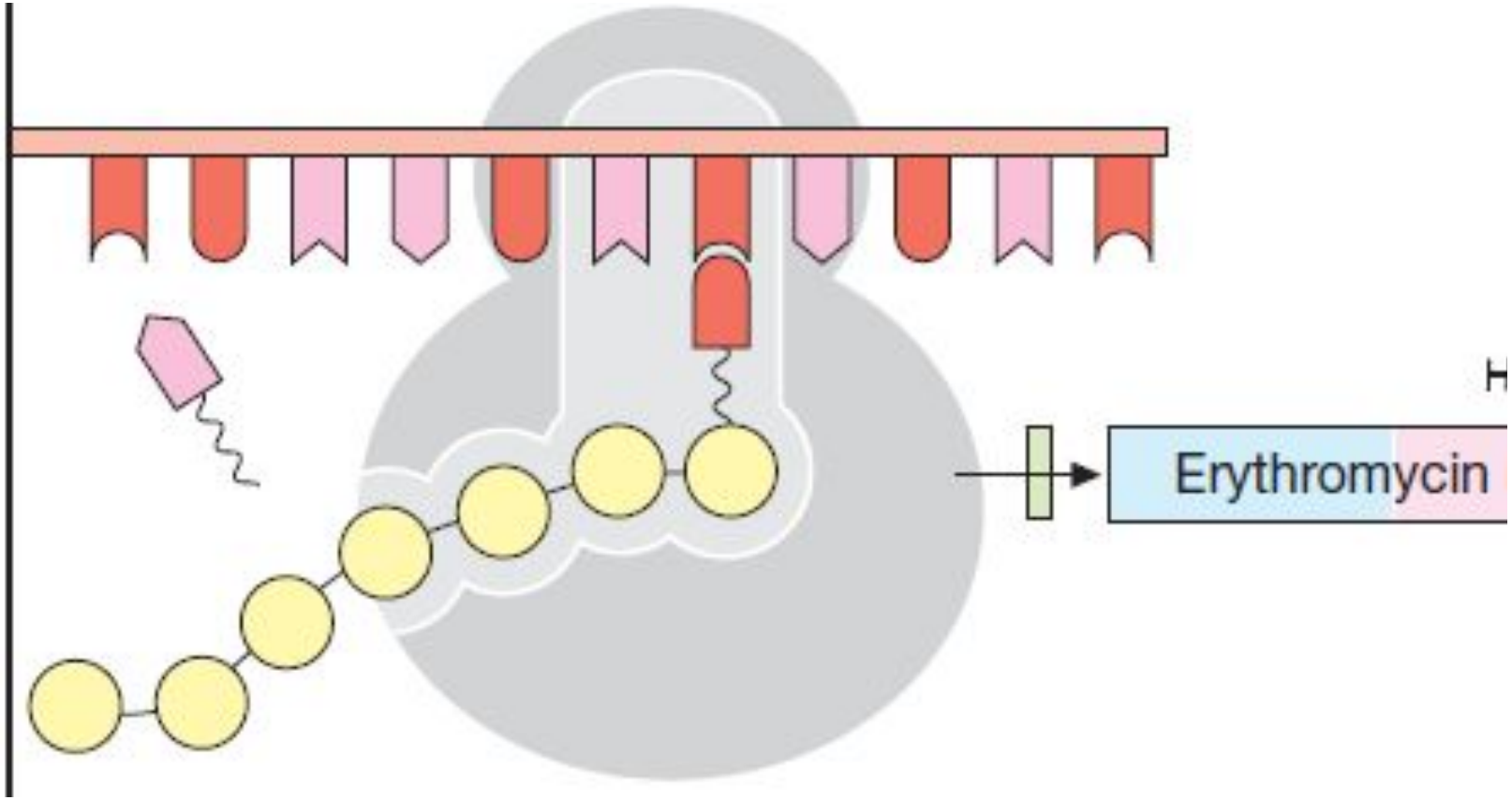
- Spectrum: gram-positive cocci, Enterobacteriaceae, Ps. aeruginosa, Listeria, Bact. fragilis., Cl.difficile.
- They are resistant to most β-lactamases; inhibit penicillinase producing staphylococci.
- Uses: serious hospital-acquired respiratory, urinary, abdominal, pelvic, skin and soft tissue infections.
- Side effects: nephrotoxicity, diarrhoea, vomiting, skin rashes and other hypersensitivity reactions.

The macrolides are a group of antibiotics with a macrocyclic lactone structure to which one or more sugars are attached.

- 1 generation - Erythromycin
- 2 generation - Clarithromycin, Roxithromycin, Spiramycin, Josamycin
- 3 generation (azalid) - Azithromycin (Sumamed)

- Type of action – bacteriostatic.

- The macrolides bind irreversibly to a site on the 50S subunit of the bacterial ribosome, thus inhibiting translocation steps of protein synthesis. They may also interfere with other steps, such as transpeptidation.



Erythromycin is active against:

- Str. pyogenes and Str. Pneumoniae, N. gonorrhoeae, Str. viridans, N. meningitidis
- Mycoplasma, H. influenzae, B. pertussis, Clostridia, C. diphtheriae and Listeria,
- Campylobacter, Legionella, Rickettsiae
- Gardnerella vaginalis
- Chlamydia trachomatis

- **2 generation** has activity similar to erythromycin, but it is also effective against Haemophilus influenzae, Helicobacter pylori, Moraxella, Legionella, Mycoplasma pneumoniae, toxoplasms.
- **Azithromycin:** H. influenzae, Mycoplasma, Chlamydia pneumoniae, Legionella, Moraxella, Campylobacter, Ch. trachomatis, Mycobacterium avium, N. gonorrhoeae.

- They are absorbed from the gastrointestinal tract, pass well into the tissue. They do not pass through the BBB They are excreted partially by the kidneys, partly by the liver (the bile).
- They are used: Erythromycin 4-6 times a day.
- 2 generation-2 times a day.
- Azithromycin is captured by leukocytes, passes with them into the focus of inflammation.
- Its concentration is higher in the focus of inflammation than that in the blood.
- It is eliminated slowly from the focus of inflammation and the body and used once a day.

Uses:

- Bronchitis, tonsillitis, otitis, sinusitis, diphtheria;
- Diseases of soft tissues (erysipelas, mastitis),
- Conjunctivitis,
- Pneumonia caused by chlamydia, Mycoplasma, Legionella, Moraxella),
- Sexually transmitted infections (syphilis, gonorrhea),
- Urogenital infection (prostatitis, adnexitis, urethritis, vaginitis).
- Cholecystitis, cholangitis.
- Ulcer.

Side effects:

- Dyspeptic disorders (nausea, vomiting, diarrhea),
- Stomatitis, gingivitis,
- Cholestasis, liver dysfunction,
- Allergic reaction,
- Arrhythmias,
- Deafness.

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