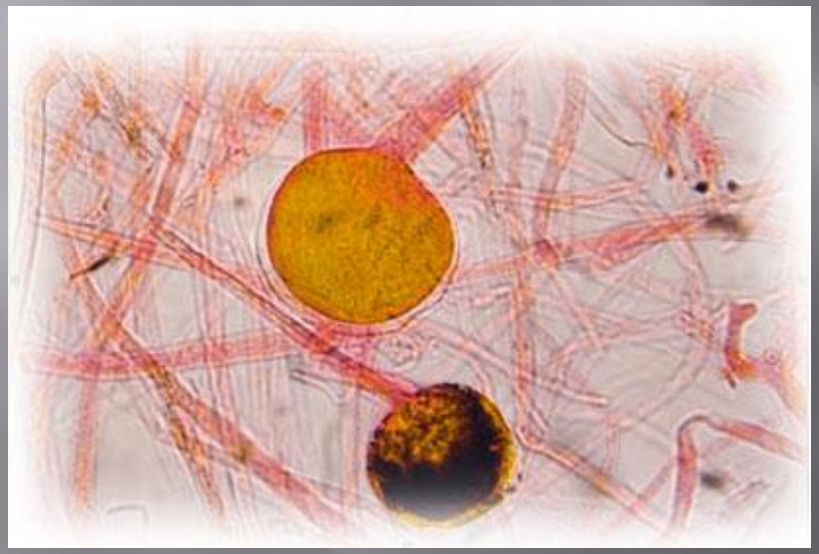
ZSMU PHARMACOLOGY DEPARTMENT

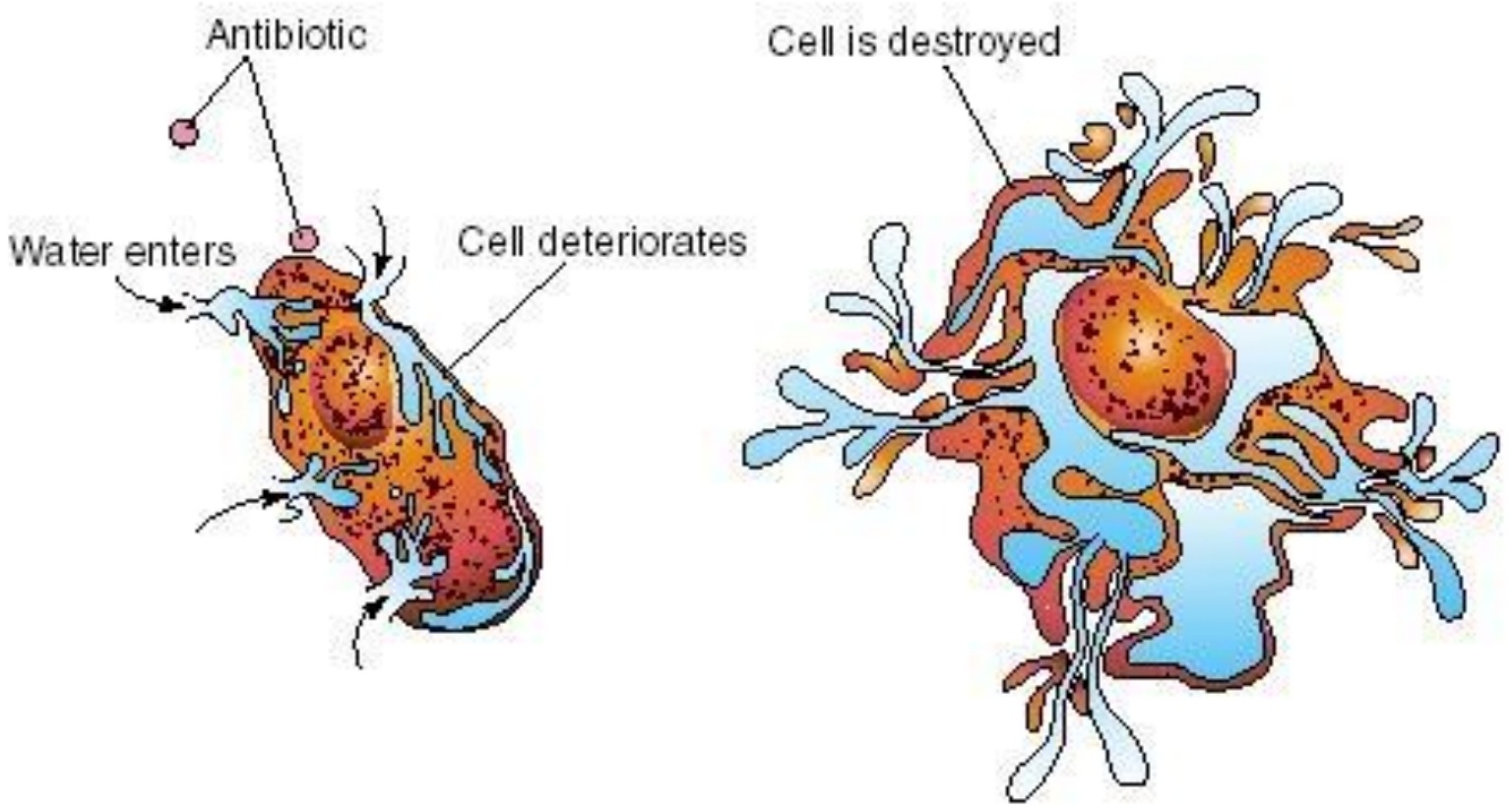
Lecture N 7

ANTIBIOTICS



ANTIBIOTICS — are chemical compounds of biologic origin that exert selective damaging or subversive effect on microorganisms.

There are antibiotics with Antibacterial, Antifungal and Antitumor actions .



Principles of Antimicrobial Therapy

1. Early beginning and selection of an appropriate drug: identification of the infecting organism should precede antimicrobial therapy if it is possible.
2. Selection of an optimal dose, rhythm and route of administration.
3. Careful clinical and microbiological monitoring to detect the development of resistance or superinfections.
4. Appropriate duration of antimicrobial therapy course (in acute cases the 5-10 day course, subacute – 2-3 weeks, chronic – several months. In prolonged treatment the antibiotic has to be changed after 7–10 days or earlier in case of its toxic action or inefficacy).
5. Antimicrobial therapy during pregnancy and neonatal period requires special consideration. E.g., *Tetracyclines* produce tooth enamel dysplasia and inhibition of bone growth.

I. Inhibitors of cell wall synthesis:

1. β-Lactam antibiotics:

- Penicillins
- Cephalosporins
- Carbapenems
- Monobactams

2. Others:

- Polypeptides
- Glycopeptides

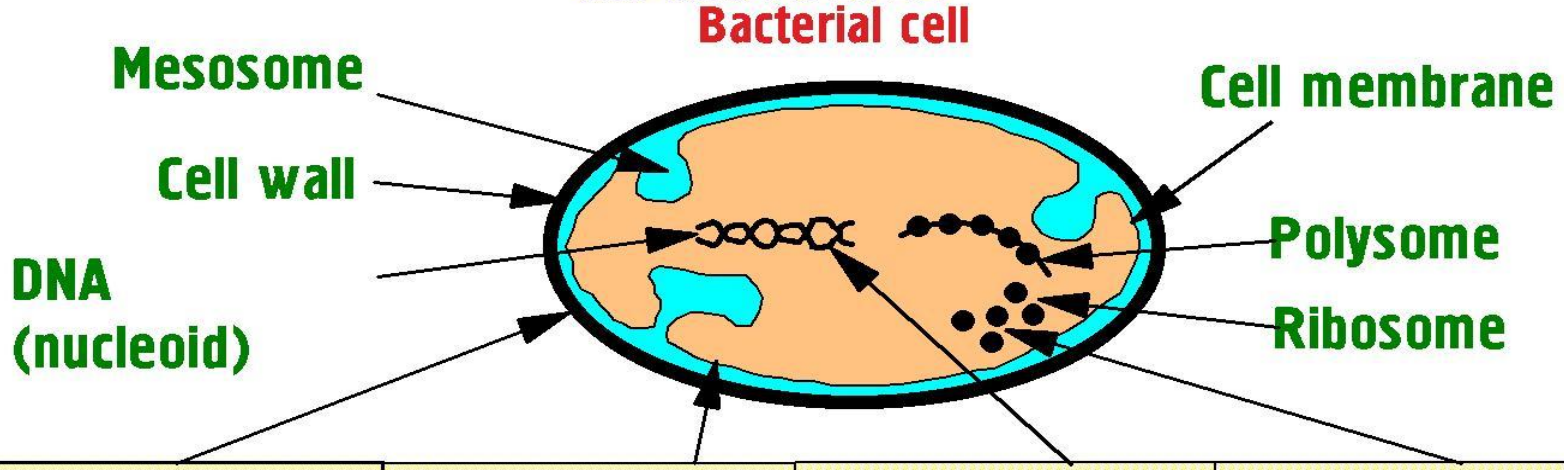
II. Producing disturbance in cell wall permeability:

Polypeptides (Polymyxins)

III Protein synthesis inhibitors:

- Macrolides
- Tetracyclines
- Aminoglicosides
- Chloramfenicols
- Lincosamides

Mechanisms of antimicrobial action of antibiotics



Impairment of synthesis of the cell wall	Impairment of permeability of the cell membrane	Impairment of synthesis of RNA and DNA*	Impairment of protein synthesis in ribosomes
Penicillins, Cephalosporins, Carbapenems, Monobactams, Glycopeptides, Cycloserine	Polymyxines, Antifungal polyene macrolides,	Rifamycins, Antitumoral antibiotics, Fluorquinolones*	Tetracyclines, Chloramphenicol Macrolides, Lincosamides, Aminoglycosides, Streptogramines

1. Narrow spectrum:

Gram(+) bacteria:

Benzylpenicillins

Oxacillin

Erythromycin

Gram(-) bacteria:

Polymyxins

2. Broad Spectrum:

Tetracyclines

Aminoglycosides

Semi-synthetic Penicillins of Broad-spectrum

Carbapenems

Cephalosporins

Levomycetin (*Chloramphenicol*)

Rifampicin

PENICILLINS

I. Biosynthetical Penicillins: Narrow Spectrum Gram(+)

A. For parenteral introduction:

Short acting (3-4 hs):

Benzylpenicillin-natrium (*Sodium Penicillin G*)

Benzylpenicillin-kalium (*Potassium Penicillin G*)

Long acting:

Benzylpenicillin-Novocain (12 hs)

Bicillin-1 (once a week)

Bicillin-5 (once a month)

B. For enteral introduction:

Phenoxymethylpenicillin (4-6 hs)

Penicillinase is an enzyme β-lactamase produced by certain bacteria which opens β-lactam ring and inactivates penicillins and some closely related congeners.

Majority of *Staphylococci* and some strains of gonococci, *E. coli, H. influenzae* and other bacteria produce penicillinase.

The Gram+ penicillinase producers elaborate the enzyme which diffuses into the surroundings and can protect other bacteria.

In Gram– bacteria, penicillinase is located in the lipoprotein and peptidoglycan layers of the cell wall.

Staphylococcal penicillinase is inducible –

Methicilin is an important inducer.

Acid-resistant penicillins are relatively resistant to inactivation by gastric juice and hence, may be given orally.

II. Semisynthetic Penicillins:

A. For **parenteral** and **enteral** introduction (*acid-resistant*):

1. Penicillinase-resistant:

Oxacillin
Cloxacillin
Flucloxacillin
Methicillin

2. Extended spectrum:

· Aminopenicillins:

Amoxicillin
Ampicillin
Bacampicillin

B. For **parenteral** introduction:

Broad spectrum including blue pus bacilli *Pseudomonas aeruginosa*:

· Carboxy penicillins:

Carbenicillin disodium
Ticarcillin

· Ureidopenicillins:

Piperacillin
Azlocillin
Mezlocillin

C. For **enteral** introduction (*acid-resistant*):

Carbenicillin-indanyl
Carbenicillin phenyl
Carfecillin

Semisynthetic penicillins (3):

Drugs which have extended spectrum of action and are penicillinase resistant (combined drugs):

- → Combinations of ampicillin and oxacillin - Ampiox.
- → Combinations of a semisynthetic penicillin and a penicillinase inhibitor (Clavulanic acid, Sulbactam, Tazobactam) - "Protected penicillins":
  - Sultamicillin (ampicillin + sulbactam).
  - Amoxicillin clavulanate (amoxicillin + clavulanic acid).
  - Timentin (ticarcillin + clavulanic acid).
  - Tazocin (piperacillin + tazobactam).

A cell wall surrounds the bacterial cell like a rigid shell that protects against outside influences.

The stability of the cell wall is due to the **murein** (*peptidoglycan*) **lattice** consisting of building blocks linked together to form a macromolecule.

The blocks are synthesized in the bacterium, transported outward through the membrane and assembled.

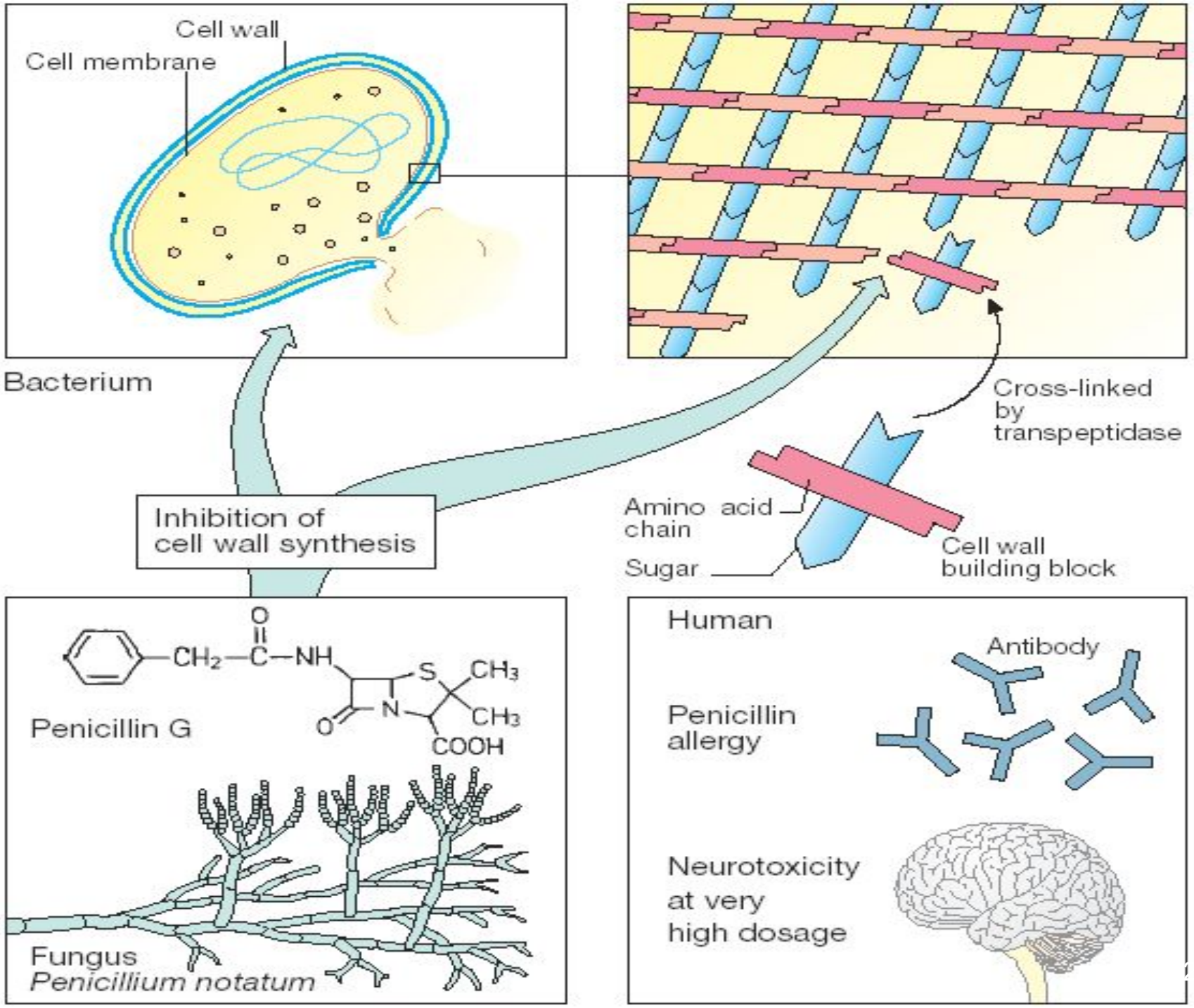
Each block contains 2 linked amino sugars *N-acetyl glucosamine* and *N-acetyl muramyl acid*, the latter bears a peptide chain.

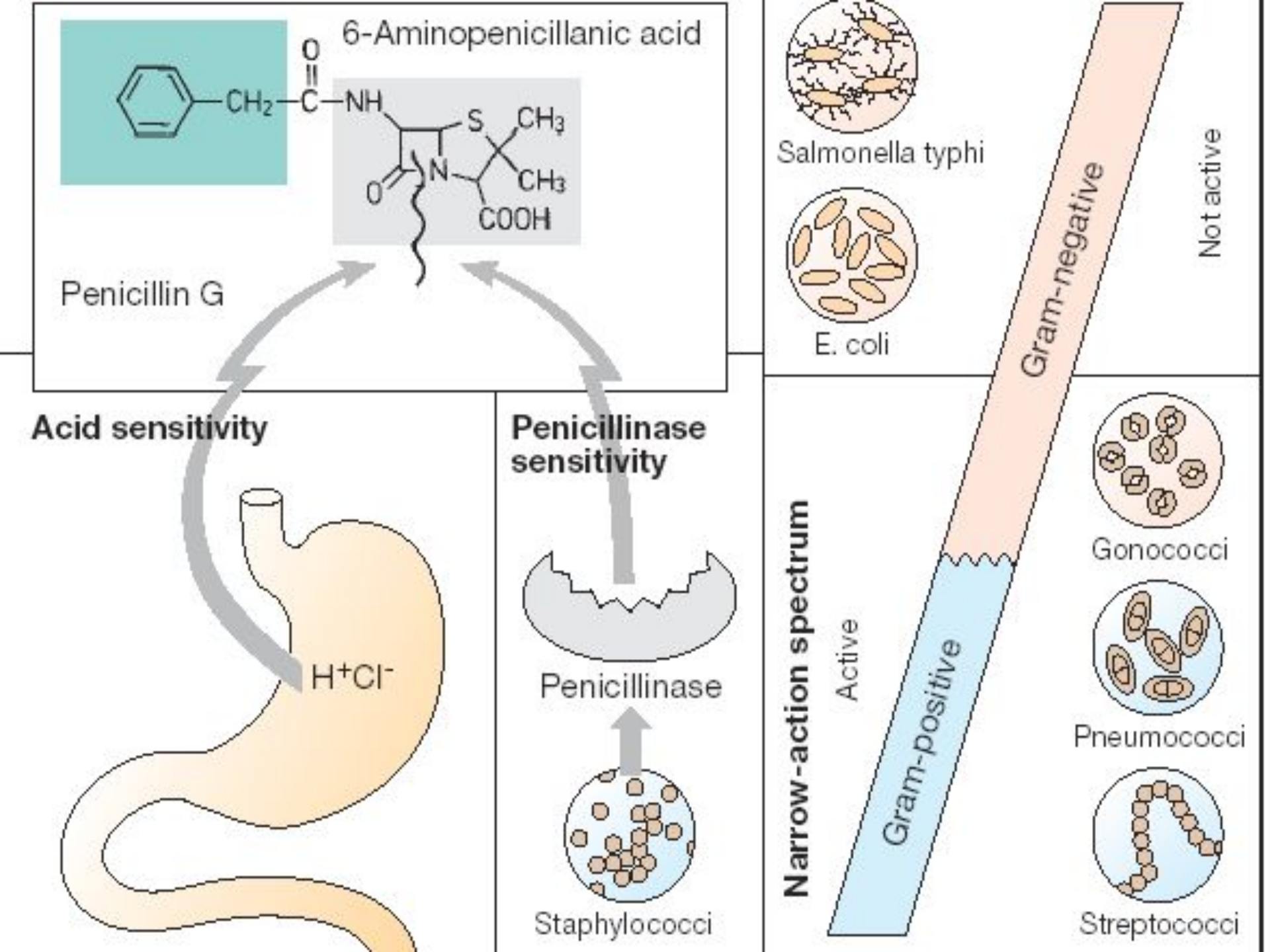
The enzyme **transpeptidase** cross-links the peptide chains, the final step in the bacterial cell wall synthesis, by a process called **transpeptidation**

Mechanism of action of PENICILLINS

Penicillins and cephalosporins are structurally similar to the terminal portion of the peptidoglycan strands and can compete and bind to penicillin-binding proteins and prevent transpeptidation and cross-linking.

=> the formation of a weakened cell wall, oddly shaped bacteria, and ultimately, death.


Cell wall
Cell membrane
Bacterium
Cross-linked by transpeptidase
Amino acid chain
Sugar
Cell wall building block
Inhibition of cell wall synthesis
Penicillin G
Fungus
Penicillium notatum
Human
Antibody
Penicillin allergy
Neurotoxicity at very high dosage


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

CLINICAL USE of PENICILLINS

- **Bacterial Meningitis:** ***Benzylpenicillin***, high doses IV
- **Bone and Joint Infections**

  (e.g. with *Staphylococcus aureus*): ***Flucloxacillin***
- **Skin and Soft Tissue Infections**

  (e.g. with *Streptococcus pyogenes* or *S. aureus*): ***Benzylpenicillin, Flucloxacillin***

  animal bites: ***Coamoxiclav***
- **Pharyngitis** (*S.pyogenes*) - ***Phenoximethylpenicillin***
- **Bronchitis** (mixed infections common) and **Pneumonia**: ***Amoxicillin***
- **Gonorrhea**: ***Amoxicillin*** (plus ***Probenecid***)
- **Syphylis**: ***Procain Benzylpenicillin***
- **Endocarditis** (e.g. with *Streptococcus viridans* or *Enterococcus faecalis*)

Benzylpenicillin-natrium (vial 500,000 and 1,000,000 UA) - biosynthetical penicillin of narrow spectrum **(Gram+).**

It is the drug of choice for infections caused by:

Streptococci, Meningococci, Enterococci,
Penicillin-susceptible Pneumococci,
non-beta-lactamase-producing Staphylococci,
Treponema Pallidum and many other ***Spirochetes***,
Bacillus Antracis, Clostridium Species,
Actinomyces and other **Gram+** rods,

Non-beta-lactamase-producing **Anaerobic organisms**

Depending upon the organism, the site, and the severity of infection, effective doses range between **4** and **24 mln Units** per day administered IV in **4-6** divided doses.

Bicillin-5 –

1 part of Benzylpenicillin-novocaine (300,000 UA)

4 parts of Biccilin-1 (1,200,000 UA)

The drug is used as suspension only IM once 4 weeks.

The drug provides high concentrations in the plasma for long period of time (ad 4 weeks).

Effective against *Streptococci, Pneumococci, Staphylococci* etc.

Bicillin-5 is especially useful for permanent (whole-year) prophylaxis of rheumatism relapses.

Amoxicillin (tab. and caps. 250 and 500 mg)

a semisynthetic bactericidal antibiotic of *broad-spectrum* action (Gram+ and some Gram-).

The drug adheres to bacterial *penicillin-binding* proteins, thus inhibiting bacterial cell synthesis.

- **Systemic Infections, Urinary or Respiratory Tract Infections,**
- **Oral prophylaxis of Bacterial Endocarditis,**
- **Uncomplicated Gonorrhea** (3 g PO as a single dose),
- **Ulcer of the stomach and duodenum** associating with *Helicobacter pylori* infection in combination with base agents (*inhibiting secretion* and *antacids*).

Adults: usually 500 mg (in severe cases 1 g) PO q 8 hours.

Unwanted reactions: Hypersensitivity Reactions, Seizures, Agranulocytosis, Hemolytic Anemia, Thrombocytopenia, Eosinophilia, Leukopenia, Interstitial Nephritis, Nephropathy, Enterocolitis

Cephalosporins

I Generation:

Parenteral cephalosporins: Cefazolin, Cefalotin

Enteral (PO) cephalosporins: Cephalexin

II Generation:

Parenteral cephalosporins: Cefuroxim, Cefamandole

Enteral cephalosporins: Cefaclor

III Generation:

Parenteral cephalosporins:

Ceftriaxone, Cefotaxime, Ceftazidime

Enteral cephalosporins: Cefixim

IV Generation:

Parenteral cephalosporins: Cefepime, Cefpirome

Ceftriaxone (vial 0.5 and 1.0) – a 3d-generation cephalosporin, acts bactericidally by adhering to bacterial *penicillin-binding proteins*, inhibiting cell wall synthesis.

Ceftriaxon (as a single 250 mg IM) and Cefixim (as a single 400 mg PO) are 1st line drugs for treatment of Gonorrhea

Indications: Bacteremia, septicemia, endocarditis;

respiratory, bone, joint, urinary, gynecologic, intra-abdominal, and skin infections from susceptible organisms;

gonorrhea, gonococcal meningitis, syphilis, Lyme disease,.

3d-generation cephalosporins influence on hemostatic properties since they possess coumarin-like action, may induce bleeding disorders by decreasing level of plasma coagulation factors (II, VII, IX, X);

inducing hypoprothrombinemia.

Vitamin K 10 mg twice weekly can prevent this.

Combined drugs:

- → With inhibitors of β-lactamases:
  - Cefoperazone + Sulbactam.
  - Ceftazidime + Clavulanic acid.
- → With fluorquinolones (quinolactams):
  - Ceftazidime + Fleroxacin.

Carbapenems:

Imipenem, Tienam (Imipenem + Cilastatin), Meropenem, Carbapenem

Mechanism of action: inhibition of synthesis of the bacterial cell wall components. Imipenem is inactivated by dehydropeptidase-1 in renal tubules.

The type of action - bactericidal.

Gram-positive: Corynobacterium diphtheriе, Staphilococci, Streptococci.

Gram-negative: Achromobacter, Acinetobacter, Aeromonas, Brucella melitensis, Citrobacter, Enterobacter, Escherichia coli, Haemophylus, Helicobacter pylori, Klebsiella, Moraxella, Neisseria, Proteus, Pseudomonas, Salmonella, Serratia, Shigella, Vibrio cholerae, Yersinia, Anaerobic microorganisms.

For treatment of polyresistant infections - pneumonia, nosocomial infections, urinary tract infections, infections of abdominal cavity, septicemia.

Toxicity is relatively low. Allergic reactions, nephrotoxicy, dispeptic disorders, local irritation, superinfection, coloring of the urine red.

Monobactams:

Aztreonam

Mechanism of action: inhibition of synthesis of the bacterial cell wall components. Relatively resistant to β-lactamases.

The type of action - bactericidal.

Gram-negative: Meningococci, Gonococci, Escherichia coli, Klebsiella, Morganiella, Proteus, Pseudomonas, Salmonella, Serratia, Shigella, Yersinia, Bacteroides.

For treatment of infections resistant to another drugs - hospital infections, urinary tract infections, infections of abdominal cavity, septicemia.

Toxicity is relatively low. Allergic reactions, nephrotoxicy, hepatotoxicy, dispeptic disorders, local irritation, superinfection.

Glycopeptides:

Vancomycin

Mechanism of action: inhibition of synthesis of the bacterial cell wall components.

The type of action - bactericidic.

Gram-positive: Streptococci, Staphylococci.

For treatment of penicilline and cephalosporine resistant infections.

Toxicity is high. Allergic reactions, nephrotoxicy and neurotoxicy, dispeptic disorders.

Macrolides-azalids and Macrolides-ketolids:

Mechanism of action: irreversible inhibition of protein synthesis in the rybosomes of mycro-organisms.

The type of action - bactericidic.

Macrolides-azalids: Azithromycin.

Gram-positive: Cocci (Streptococci, Staphylococci, Pneumococci).

Gram-negative: Cocci (Neisseria gonorrhoeae, Meningococci), Corynebacterium diphtheriae, Bacillus anthracis, Clostridium perfringens, Clostridium tetani, Actinomyces, Treponema pallidum, microorganisms which causes respiratory deseases (Haemophilius influenzae, Moxarella catarrhalis, Bordetella pertussis, legionella pneumophila) Chlamidia, Mycoplasma, Ureaplasma.

Macrolides-ketolids: Erythromycin acistrate.

+ Streptococcus pneumonie, Streptococcus pyogenes, Enterococci, Gonococci, Meningococci, Mycobacterium avium.

For treatment of tonsilitis, bronchitis, pneumonia, gonorrhea, chlamidiasis.

Toxicity is relatively low. Allergic reactions, dispeptic disorders.

Azithromycin **(*Sumamed* tab. 0.5, caps 0.25 g) binds to the 50S subunit of ribosomes, blocking Protein Synthesis.**

Active against respiratory infections due to *Haemophilus influenzae* and *Moraxella catarrhalis*.

Has excellent action against *Toxoplasma gondii*

It is now preferred therapy for urethritis caused by *Chlamidia Trachomatis*.

- **Penetrates into most tissues (except cerebrospinal fluid) with Tissue >> Plasma Concentration by 10-100-folds.**

Community-acquired Pneumonia can be treated with *Azithromycin* given as 500 mg loading dose, followed by a 250 mg singly daily dose for the next 4 days.

Tetracyclines:

- **Biosynthetic:** Tetracycline, Oxytetracycline, Demeclocycline.
- **Semisynthetic:** Doxycycline, Methacycline, Minocycline, Glycil-cycline.

Mechanism of action: inhibition of protein synthesis in the rybosomes of mycro-organisms and binding to Ca^{++} and Mg^{++} ions with the formation of chelate complexes.

The type of action - bacteriostatic.

Gram-positive: Staphilococci, Streptococci.

Gram-negative: Salmonella, Shigellsa, Pasteurella tularensis, Pasteurella pestis, Vibrio cholerae, Anaerobes, Rickettsiae, Chlamidiae, Mycoplasmas, Amebas.

For treatment of cholera, rickettsiosis, plague, brucellosis, tularemia.

Toxicity is high. Teratogenity (violation of skeleton and teeth development), allergic reactions, hepatotoxicy, dispeptic disorders, local irritation, dysbacteriosys, candidomycosis, superinfection, accumulation in the bone tissue.

Aminoglycossides:

- First-generation: Streptomycin, Monomycin, Neomycin, Kanamycin,
- Second-generation: Gentamycin.
- Third-generation: Tobramycin, Sisomycin, Netilmycin, Amikacin.
- Forth generation: Arbecacin, Isepamycin, Dactimycin.

Mechanism of action: irreversible inhibition of protein synthesis in the rybosomes

The type of action - bactericidic.

Gram-positive: Staphilococci, Streptococci.

Gram-negative: Mycobacterium tuberculosis, Pasteurella tularensis, Pasteurella pestis, Pseudomonas aeruginosa, Proteus, Escherichia coli, Seratia, Entherobacter.

For treatment of tuberculosis and other sensitive infections.

Toxicity is high. Allergic reactions, affection of the vestibular and acustic rames of the VIII pair of the cranial nerves (Calcium pantotenate should be used) nephrotoxicy, dispeptic disorders, local irritation, superinfection.

Chloramphenicoles:

Mechanism of action: irreversible inhibition of protein synthesis in the rybosomes of mycro-organisms.

The type of action - bacteriostatic.

Laevomycetinum, Laevomycetinum stearas, Laevomycetinum-natrium succinate, Syntomycinum.

Gram-positive: Cocci (Streptococci, Staphylococci, Pneumococci).

Gram-negative: Escherichia coli, Salmonella, Shigella, Haemophilius influenzae, Rickettsiae, Chlamidiae, Brucella, Pasteurella tularensis, Pasteurella pestis.

As alternative antibiotics for treatment of abdominal typhoid, rickettsiosis, salmonellosis.

Toxicity is high. Allergic reactions, dispeptic disorders, hematotoxicy ("gray baby syndrome"), dysbacteriosys, candidomycosis, superinfection.

Lincosamides:

Mechanism of action: irreversible inhibition of protein synthesis in the rybosomes of mycro-organisms.

The type of action - bacteriostatic (in high doses bactericidic).

Lincomycin, Clindamycin.

Gram-positive: Cocci (Streptococci, Staphylococci, Pneumococci).

Gram-negative: Anaerobes (Bacterioides, Clostridia, Fusobacterium, Actinomyces).

For treatment of abdominal cavity and anaerobic infections, pneumonias, osteomyelitis, purulent meningitis.

Toxicity is relatively low. Allergic reactions, dispeptic disorders, glossitis, stomatitis, phlebites.

Pseudomembranous Colitis –

the most serious potentially fatal adverse effect of **Clindamycin** and **Lincomycin** caused by overgrowth of *Clostridium difficile* (superinfection development) which elaborates necrotizing toxins .

- The patient develops profuse, watery diarrhea, fever, abdominal pain, leukocytosis.
- *Clostridium difficile* infection is confirmed.

Treatment: Metronidazole (PO 0.5 g tid) or

Vancomycin is effective

in controlling this serious problem.

ЗАПОРІЗЬКИЙ ДЕРЖАВНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ

Thank You for Attention!