Lecture 11
Chemotherapeutic drugs. Antibacterial chemotherapeutic drugs (part 1).

- Pharmacokinetic and pharmacodynamic particularities of chemotherapeutic drugs.
- Antibacterial chemotherapeutic drugs:
  1. Inhibitors of bacterial cell wall synthesis (penicillins, cephalosporins, carbapenemes, monobactames, polypeptides, glycopeptides, phosphomycines, Cycloserine, Bacitracine, Ristocetine),
  2. Inhibitors of bacterial cell wall function (polymixines).

1. Pharmacokinetic and pharmacodynamic particularities of chemotherapeutic drugs.

History
- 1928: Alexander Fleming, a Scottish biologist, discovered the antibiotic effect of *Penicillum*.
  - He observed that *Penicillium notatum*, a common mold, had destroyed staphylococcus bacteria in culture
  - Fleming received Nobel price
- S. A. Waksman (1941): an antibiotic is a substance produced by a micro-organisme and has the capacity to inhibit the development of other micro-organismes and even to destroy them.
- 1946: started the industrial production of antibiotics.

Definitions
- **Antibiotics** = a natural substance produced by a micro-organism to kill another
- **Antiinfectives/Anti-microbial** = any agent (natural or synthetic) that kills pathogens (microbes)
  - Antibacterial chemotherapeutics
  - Antiviral chemotherapeutics
  - Antifungal chemotherapeutics
  - Antiparasitic chemotherapeutics
- **Key**: it needs to kill the microbial cell and not be toxic to normal healthy human cells
  - However, many bacteria are now resistant to antibiotics and some are resistant to all known agents.
- New drugs are continually being introduced to combat evolving patterns of resistance.

“**Biocide**” = a chemical agent (usually broad spectrum), that inactivates microorganisms. Because biocides range in antimicrobial activity, other terms may be more specific:
- “-static” = agents which inhibit growth (e.g., bacteriostatic, fungistatic, and sporistatic)
- “-cidal” = agents which kill the target organism (e.g., sporicidal, virucidal, and bactericidal).
Bacteriostatic vs Bactericidal
- **Bacteriostatic** allows for natural immunity to deal with the microbe (antibodies, phagocytosis etc)
- **Bactericidal** may lead to release of toxins and microbial contents leading to subsequent illness and inflammatory responses.

<table>
<thead>
<tr>
<th>Bacteriostatic</th>
<th>Bactericides</th>
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<tbody>
<tr>
<td>- tetracyclines;</td>
<td>- betalactams (penicillins, cephalosporins, carbapenems, monobactams);</td>
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<tr>
<td>- fenicoli;</td>
<td>- glycopeptides (vancomycin) or polypeptides (bacitracin)</td>
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<td>- macrolides*;</td>
<td>- polymyxins;</td>
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<td>- lincosamides*;</td>
<td>- aminoglycosides;</td>
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<td>- sulfonamides,</td>
<td>- ketolides;</td>
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<td>- trimethoprim.</td>
<td>- quinolones;</td>
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* According to the dose may be bactericidal for some organisms

Spectrum of Activity
- Relates to the number of microbes that are sensitive to the action of the drug
- Narrow (limited number) / Broad (wide)
  - Oxacillin is a narrow spectrum drug because it is only effective against Staphylococcus spp
  - Tetracyclines are broad spectrum drugs because they are effective against gram-positive and gram-negative microbes

*Note: Never confusion these terms with potency levels of the drugs or efficacy (Never confusion: Narrow are weak, Broad are strong)*

Indications for antibiotics
**Absolute indications:**
- in children, the elderly;
- before surgery (eg, gastrointestinal surgery, joint replacement) or antibacterial protection during surgery;
- people with valvular heart disease: to prevent bacterial endocarditis with S. aureus;
- person with severe chronic diseases or immunocompromised;
- prophylaxis of rheumatic fever.

**Relative indications:**
- prophylaxis of scarlet fever in contacts;
- prevention of meningococcal meningitis;
- the incubation period of some bacterial diseases (pertussis, tuberculosis, syphilis).

Associations of chemotherapics
- **Theoretically:** the treatment of bacterial infections should be in accordance with the culture and sensitivity testing or (second best) knowledge of these agents.
- **Practically:** the treatment of bacterial infections is empirical in:
  - mixed infections;
  - serious infection of unknown origin;
  - when there is the possibility of microbial resistance to chemotherapeutic groups;
  - long term traitemtes.

**The benefits:**
- widening the antibacterial spectrum;
- increase efficiency;
- delay emergence of resistance

- No associations are allowed between:
  - bacteriostatic with bactericidal;
  - aminoglycosides with polymyxins;
  - penicillins in high doses with nephrotoxic cephalosporins (generation I and II) or with aminoglycosides (gentamicin, kanamycin and others).

Criteria for the choice of chemotherapy
- The pharmacokinetic characteristics:
  - Absorption: depends on type of chemotherapy, gastrointestinal tract;
  - serum: absorption depends on the dose, the rate of administration, distribution in the tissue removal;
  - half-life and rate of administration;
  - diffusion in tissues (access to the site of infection, local conditions of infected tissue) is best in the inflamed organs by increasing blood flow, better chemotherapeutic diffuse low molecular weight, soluble and ionized;
  - metabolism: the liver and functional status and maturation;
  - excretion (renal / liver) and elimination of the form (active / inactive).

- The characteristics of chemotherapy:
  - spectrum of action, resistance, in vitro tests,
  - bactericidal / bacteriostatic chemotherapy.

- Particular physiological states: the newborn, adult, pregnancy, old.

Pharmacokinetic particularities
- Administration:
  - Oral administration is the most advantageous.
  - Food may affect the absorption.
  - iv: preferred in severe infections to reach higher concentrations in the body.

- Protein binding: Tetracyclines and lincomycin are highly bound to plasma proteins, this is why they are not used in patients on hemodialysis.

- Duration of treatment:
  - single dose:
    - for lower urinary primoinfections requiring a single dose of ampicillin,
    - gonococcal primary infection requiring a single dose of streptomycin.
  - long treatment: staphylococcal endocarditis (4 weeks) etc.

- Dose depends on many factors: the nature and severity of infection, weight, age, renal function and liver function of the patient.

- In severe liver disease
  - Reduce the dose or contraindicate: chloramphenicol, rifampicin.
  - No risk of acute toxicity: clindamycin, lincomycin, ampicillin, nafcillin, isoniazid.

- In case of severe renal impairment:
  - Reduce dose or contraindicate: aminoglycosides, polymyxin, vancomycin.
  - Tetracyclines: are contraindicated.

- During pregnancy: penicillins and cephalosporins reach high concentrations in the fetus, but no fetal toxicity problem.

- The active concentrations in the tissues:
  - There are necessary lower concentrations when the local immune mechanisms have a normal function
• There are required high concentrations when the local immune mechanisms are deficient.

- Entry into cells:
  • Possible when the cell has no cell wall. Required to destroy bacteria that survive in different cells, eg, phagocytes (Koch, Brucella, Legionella). Rifampicin or quinolones of the third generation are active on intracellular pathogens.

- The access of active substances to the site of infection
  • Infections in poorly perfused tissues are difficult to treat, when defense mechanisms are deficient, higher concentrations are needed.
  • penetration into the brain, eye, prostate, bone:
    - The classical cephalosporins can not reach bactericidal concentrations in CSF, but chloramphenicol penetrates through the meninges (faster when the meninges are inflamed);
    - staphylococcal osteomyelitis responds well to clindamycin (concentrated in the bones).

**Drugs concentrate in:**

- CNS, adipose tissue: Hexobarbital, Thiopental
- CSF: Metothrexate, Busulfan, benzodiazepines, antidepressant drugs, antiepileptic drugs (Carbamazepine, Phenytion, Ethesuximide)
- Bronchial secretions: Ampicilin, Cefalotin, Gentamicine
- Liver: vitamin B6, Dapsone (against leprosy);
- Bile: antibiotics (aminopenicillins, antistaphylococcal penicillins, macrolides, tetracyclines, cyclosporine, rifampicine, quinolones III-rd generation, cephalosporins III-rd and IV-th generation, aminoglycosides), antieoplastic drugs (Vincristine, Doxorubicine), barbiturics, benzodiazepines (with entero-hepatic cycle); opiates (Morphine natural, Hydromorfon, Oximorfon, Heroin – are intensive metabolized after first pass through liver), Spironolactone, Indapamide, digitalics.
- saliva: anticonvulsant drugs (Phenytoin, Carbamazepine, Valproic acid, Ethesuximide), Teophylline, Digoxin, Quinidine, lithium, illicit drugs (morphine, cocaine, amphetamine), benzodiazepine (Diazepam, Nitrazepam);
- salivary glands: Minocicline, quinoleines (Chlorchinaldol)
- tears: Rifampicine, anticonvulsant drugs, Minocicline;
- sweat: Rifampicine, amphetamine;
- milk: Phenobarbital, Theophylline, Morphyne, Phenclididine, nicotine, Penicillin G, aminoglycosides, barbiturates, ethanol, bromures, tetracyclines;
- hairr: quinolones III-rd generation (Temafloxacin, Ofloxacine, Norflonxacin, Ciprofloxacin), opiates, cocaine, amphetamine, Phenclididine, canabinoids, antipsychotic drugs (Haloperidol), nicotine, heavy metals;
- nails: antifungal drugs (Ketoconazole, Terbifencamine, Itraconazole, Griseofulvline), droguri (Metamphetamine, Cocaine), heavy metals;
- peritoneal liquid: Gentamicine, Vancomicine, Cefoxitin;
- interstitial liquid: Psoralens, Acitretin (used in dermatology);
- mucus cervical: nicotine;
- Prostate: quinolones III-rd generation, sulfonamides, Trimetoprim, Spectinomicine
- seminal fluid: cefalosporins, macrolides, quinolones, NSAIDs (salicitates, Sulfasalamzine, Mesalazine), Propranolol, Caffeine, Nicotine.
- vaginal fluid: quinolones III-rd generation, sulfonamid, Trimetoprin
- Bone, cartilages: tetracyclines, Lincosamine, quinolones III-rd generation, heavy metals.
  Phagocyte cells: rifampicina, quinolones III-rd generation.
• Thyroid gland: synthetic atiroidian drugs, quinolines (Clorchinol, Clorchinaldol)
• fetal blood and amniotic liquid: Ampicilline, Azlociline, anticonvulsant drugs, sedative-hipnotic drugs, betablockers, nicotine.

A bacterial cell structure
- the cell wall (cell maintains the structure) compound of peptidoglycan, a polymer of sugars and amino acids
- flagella (structures used for locomotion)
- plasma membrane (phospholipid bilayer surrounding the cell) contains proteins that play a role in the transport of ions, nutrients and waste
- nucleus
  • DNA (single double-stranded circular chromosome)
  • Plasmid (small circular chromosome) - can carry a gene for antibiotic resistance
- Ribosomes (site of protein synthesis)

Some characteristics of infectious bacteria
- Virulence factors: molecules produced by a pathogen that aid in its survival in a host
- capsule: surrounds the bacterial cell wall, protects the bacteria from phagocytosis
- pili: allows bacteria to attach and invade other cells in spite of mucus and cell turnover
- Enzymes: breaking the matrix between cells allows bacteria to spread into the tissues
- Toxins
  • Exotoxins: lysis of host cells because of some
  • enterotoxins: cause fluid secretion in the small intestine leads to vomiting and diarrhea
  • Endotoxin o: cell-bound lipopolysaccharide, fever and inflammation.

Bacterial resistance
- natural resistance:
  • relative resistance of Gram (-) to penicillin G;
  • Bacterial resistance to antifungal structure with polienique to chemotherapy etc..
- acquired resistance to drugs:
  • by mutations;
  • transfer (plasmid or extracromosomal) R factor (= resistance factor found in plasmids);
  • by the production of lytic enzymes;
  • by adaptation during antibacterial chemotherapy;
  • by changing the membrane permeability of bacteria.
- It can prevent the emergence of resistance: the fair, adequate doses of antibacterial agents, treatment monitoring, avoiding autotratamentelor.

Side effects of antibacterial agents
• Toxic reactions at therapeutic doses:
  • aminoglycosides are ototoxic and nephrotoxic
  • polimixines, cephalosporins generation I and II are nephrotoxic;
  • Rifampicin, Chloramphenicol, macrolides (Erythromycin, Azithromycin, Roxitromicina) are hepatotoxic;
  • Chloramphenicol is medulotoxic;
  • penicillins in high doses and polimixines are neurotoxic.
• The immunological reactions:
• Type I (IgE mediated): penicillins, cephalosporins, sulfonamides,
• Type III (mediated by IgG / IgM): penicillins, cephalosporins, sulfonamides.
• The biological reactions:
  • dismicrobism intestinal or superinfection with resistant organisms (after oral
    administration of broad-spectrum chemotherapy, long-term): tetracyclines, quinolones
    as IIIrd generation.

CLASSIFICATION OF ANTIBIOTICS CAN IN SEVERAL WAYS:
• Depending on their mechanism of action against the infecting organism (the most
  common criteria). Some antibiotics attack the cell wall, some disrupt the cell
  membrane, the majority inhibit the synthesis of nucleic acids and proteins, etc.
   1. Inhibitors of bacterial cell wall synthesis
   2. Inhibitors of the function of the bacterial cell wall (disruption of the cell
      membrane)
   3. Inhibitors of bacterial protein synthesis
   4. Inhibitors of nucleic acid synthesis
   5. Inhibitors of the synthesis of other structures bactérienes (interference with
      metabolic processes).
• According to which bacterial strains they affect: staphylococcus, streptococcus, E.
  coli, etc.
• Based on the chemical structure: penicillins, cephalosporins, aminoglycosides,
  tetracyclines, macrolides, sulfonamides, etc.
### Antibacterial chemotherapeutic drugs:

#### 1. Inhibitors of bacterial cell wall synthesis

Most bacteria possess a cell wall to protect from osmotic pressures. When microbe divides, they need to create a new cell wall. Interruption of this leads to new microbes being susceptible to external influences. Cell ruptures determines microbe death.

#### Classification

1. **Inhibitors of bacterial cell wall synthesis**

1.1. **Beta-lactam antibiotics:**

   1.1.1. **Penicillins:**
   - **Natural penicillins:** Benzylpenicillin (Penicillin G); Procainpenicillin; Benzathinpenicillin; Phenoxymethylpenicillin (Penicillin V).
   - **Semisynthetic penicillins:**
     - **Antistaphylococcal penicillins:** Oxacillin, Cloxacillin, Dicloxacillin; Methycillin; Nafcillin.
     - **Extended spectrum penicillins:**
       - **Aminopenicillins:** Ampicillin, Amoxicillin;
       - **Carboxipenicillins:** Carbenicillin, Ticarcillin;
       - **Ureidopenicillins:** Piperacillin, Mezlocillin, Azlocillin;
       - **Amidopenicillins:** Pivmecillinam, Furazlocillin.
   - **Beta-lactamase inhibitors:** Clavulanic acid; Sulbactam; Tazobactam.

   **Combinations**
   - Augmentin® = Amoxicillin + Clavulanic acid;
   - Timentin® = Ticarcillin + Clavulanic acid;
   - Zosyn® = Piperacillin + Tazobactam;
   - Unasyn® = Ampicillin + Sulbactam.

1.1.2. **Cephalosporins**

    **Cephalosporins 1st generation:**
    - oral administration: Cephradine, Cephalexin, Cefadroxil;
    - parenteral administration: Cephradine, Cefazolin, Cephalotin, Cephapirin.

    **Cephalosporins 2nd generation:**
    - oral administration: Cefuroxime, Cefaclor, Loracarbef, Cefotiam;
    - parenteral administration: Cefuroxime, Cefamandole, Cefmetazole, Cefotetan, Cefoxitin, Cefonicid, Ceforanid.

    **Cephalosporins 3rd generation:**
    - oral administration: Cefixime, Cefpodoxime;
    - parenteral administration: Ceftriaxone, Ceftazidime, Cefotaxime, Cefoperazone, Moxalactam, Ceftizoxime, Ceftibuten, Proxetil.

    **Cephalosporins 4th generation:**
    - parenteral administration: Cefepime, Ceftirome.
1.1.3. **Carbapenems:** Imipenem, Meropenem, Ertapenem;  
**Combinations:** Tienam® = Imipenem + Cilastatin

1.1.4. **Monobactams:** Aztreonam;

1.2. **Glycopeptide antibacterials:** Vancomycin, Teicoplanin;

1.3. **Phosphomycins:** Phosphomycin;

1.4. **Cycloserin:**

1.5. **Polypeptide antibacterials:** Bacitracin, Gramicidin, Tyrothricin;

1.6. **Ristocetin:**

1.7. **Daptomycin.**

**Structure**

Betalactams are the most important family (derived from 6-aminopenicillanic acid) with the structure:
- betalactam cycle
- tiazolidine cycle
- a second group R (which determines the antibacterial activity).

If the betalactam ring is enzymatically cleaved by bacterial beta-lactamases, results penicilloic acid, which lacks antibacterial activity, but determine allergic reactions.

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### PENICILLINS

**Sources**
- Are derived from *Penicillium chrysogenum.*
- Penicillin G and Penicillin V are unaltered products of *Penicillium fermentation.*
- Semi-synthetic penicillins are formed by addition of R groups to the main 6-aminopenicillanic acid ring.

The activity of penicillin G was originally defined in units. Semisynthetic penicillins are prescribed by weight rather than units.

**Mechanism of action:** inhibition of the synthesis of bacterial cell wall in three steps:
- covalent bind to specific receptors: penicillin binding proteins (PBP);
- inhibits transpeptidation;
- activation of autolisines.

**Bactericidal effect.**
- Effective only against rapidly growing organisms that synthesize peptidoglycan.  
  (Ineffective against mycobacteria.)

Penicillins bacterial resistance
- formation of a barrier that prevents access to receptors PBP - Gram (-);
- alteration of PBP receptors;
- inactivation under the action of beta-lactamases;
- lack bacterial cell wall.

**Pharmacokinetics**

**Administration:**
- only parenteral:
Benzylpenicillin (=Penicillin G) – administered i.v./i.m.;
Procaínpenicillin; Benzathinpenicillin – administered i.m. because are depot penicillins,
Methycillin, carboxipenicilins, ureidopenicilins, Furazlocilin;
- only oral: Penicillin V (because it is acid resistant), Pivmecilinam
- the others are administered either parenteral or oral.

- **Protein binding**: high to nafcillin, oxacillin very low. **T1 / 2**: Increases in renal failure.

- **crosses the blood-brain barrier**:
  - The penicillins: cross very difficult through normal meninges, but very easily through inflamed meninges;
  - High concentrations in CSF are neurotoxic (determine seizures, tremors, restlessness, nervousness).

- **Do not enter the host cell.**

- **Presents enterohepatic cycle**: Oxacillin, Cloxacillin, Dicloxacilin, Nafcilin, Ampicillin, Amoxicillin.

- **Concentrated in**: breast milk; sputum.

- **Elimination**: 90% is unchanged,
  - eliminated mainly renal (natural penicillins, carboxipeniciline, ureidopeniciline, methicillin):
    - Dosage adjustment in renal impairment;
    - There is competition between Penicillin G and Probenecid for the mechanism of renal tubular secretion;
  - mainly biliary (Izoxazolilpenicilline, Nafcilin, Aminopenicilins)
    - no adjustment of dosage in renal failure.

### NATURAL PENICILLINS

#### Classification
- Benzylpenicillin (= Penicillin G);
- Procaínpenicillin (is a natural penicillin composed of procaine and penicillin G);
- Benzathinpenicillin;
- Phenoxymethylenicillin (= Penicilina V).

#### Antibacterial spectrum of the natural penicillins:
- **most effective against Gram-positive bacteria, and less effective against Gram-negative organisms and ineffective against fungi**:
  - G(+) cocci: streptococci (including Streptococcus beta-hemolytic group A, pneumococcus, enterococcus, peptostreptococcus);
  - G(+) bacilli: Lysteria monocytogenes, Corynebacterium;
  - G(-) cocci: Neisseria meningitidis, Neisseria gonorhoeae;
  - G(-) bacilli: Bacteroides (without Bacteroides fragilis);
  - spirochetes: Treponema pallidum, Leptospira;
  - Actinomymes.

#### Indications
- **Penicillin G:**
  - Drugs of choice for:
    - pneumococcal pneumonia or bacteremia;
    - beta hemolytic streptococcal infection (pharyngitis, septicemia);
    - infections of the upper respiratory tract, skin and soft-tissue infections, scarlet fever, and erysipelas due to susceptible streptococci;
    - meningococcal meningitis or pneumonia;
    - syphilis;
    - leptospirosis;
    - bacteroides infections (oropharyngeal, other G(-) anaerobic), infections with Actinomyces or Clostridium (tetanus, gangrene);
    - meningitis, septicemia, endocarditis in combination with other chemotherapeutic antibacterial.
    - anaerobic infections, gonorrhea, ear infections, sinusitis.

  NOTE: Reports indicate an increasing number of strains of staphylococci resistant to penicillin G.

- **Procainpenicillin:** treatment of infections due to penicillin G-sensitive microorganisms;

- **Benzathinpenicillin** (retard type Penicillins):
  - prophylaxis of rheumatic fever
  - treatment of mild/moderate infections in the upper respiratory tract caused by Streptococcus sp.
  - treatment of syphilis.

- **Penicillin V**: minor infections of the respiratory tract.

**SEMISYNTHETIC PENICILLINS**

**Classification**

- **Antistaphylococcal penicillins (= narrow spectrum penicillins):**
  - izoxazolylpenicillins: Oxacillin, Cloxacillin, Dicloxacillin;
  - Methycillin;
  - Nafcillin.

- **Extended spectrum penicillins:**
  - **Aminopenicillins**: Ampicillin, Amoxicillin;
  - **Carboxipenicillins**: Carbenicillin, Ticarcillin;
  - **Ureidopenicillins**: Piperacillin, Mezlocillin, Azlocillin;
  - **Amidopenicillins**: Pivmecillinam, Mecillinam, Furazlocilin.

- **Beta-lactamase inhibitors**: Clavulanic acid; Sulbactam; Tazobactam.

- **Combinations:**
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  - Unasyn® = Ampicillin + Sulbactam.

**Antibacterial spectrum of:**

- **Antistaphylococcal penicillins**: G(+) cocci (staphylococci and streptococci)
Lecture 11: Chemotherapeutic drugs. Antibacterial chemotherapeutic drugs (part 1).

- are resistant to staphylococcal lactamases, resist degradation by penicillinase, useful for treating S. aureus infections.

**Broad and Extended spectrum penicillins**

- **Aminopenicillins (Broad spectrum):**
  - G(+) cocci: streptococci (including beta-hemolytic group A streptococcus, pneumococcus, enterococcus);
  - G(+) bacilli: Lysteria monocytogenes, some species of Chlamydia, Corynebacterium;
  - G (-) cocci: Neisseria meningitidis, Neisseria gonorrhoeae;
  - G (-) aerobic bacilli: H. influenzae, E. coli, Salmonella, Shigella, H. pylori etc.

- **Carboxipenicilins (Extended spectrum penicillins):**
  - They are less active bacteria G (+).
  - active against more G (-) aerobic bacilli, including Pseudomonas, Proteus, Serratia, Enterobacter.

- **Ureidopenicilins (Extended spectrum penicillins):** spectrum similar carboxypenicilins, but are more active on Klebsiella pneumoniae.

- **Carboxipenicilins and ureidopenicilins are also called anti-Pseudomonal penicillins.** Often used with aminoglycosides when treating Pseudomonal infections.

**Indications**

- **Antistaphylococcal penicillins**:
  - Drugs of choice for beta-lactamase staphylococcal infections;
  - infection with strains of streptococci (S. pneumoniae).

- **Aminopenicillins:**
  - respiratory tract infection (drugs of choice for pneumococcal pneumonia),
  - infection of the bile or urinary infections (E. coli, Proteus),
  - typhoid infections (Salmonella);
  - severe infections (septicemia, meningitis, etc.);
  - drugs of choice for infections with Lysteria, H. influenzae, gonococcal;
  - treatment for eradication H. pylory infection.

- **Carboxipenicilins, ureidopenicilins:**
  - Drugs of choice for nosocomial infections, particularly determined by Pseudomonas.

- **Aminopenicillins:**
  - Pivmecillinam: acute uncomplicated cystitis, chronic or recurrent bacteruria and salmonellosis.
  - Mecillinam: severe infections due to Gram negative enteric bacteria.

**Adverse reactions of penicillins**

- **Hypersensitivity reactions** (due to penicilloic acid in 1-10% of patients):
  - Type I: rash (most common), fever, pruritus, urticaria, angioedema, anaphylactic shock (rare, but very severe);

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1 Dicloxacillin: highest serum levels after oral administration; Nafcillin: preferred for parenteral administration; Methicillin: rarely used due to toxicity.
Type II: hemolytic anemia;
Type III: Stevens-Johnson syndrome.
Rashes - most common reaction. 50% do not have a recurrent rash.
- Herxheimer reaction: penicillin G (administered at high doses in syphilis);
- dysmicrobism, nausea, vomiting: for extended spectrum penicillins;
- pseudomembranous colitis: to ampicillin.
- neurotoxicity: penicillin (intrarahidian or high dose). In patients with renal failure, high
doses cause convulsions.
- hepatotoxicity: for oxacillin, carboxipeniciline.
- nephrotoxicity: for methicillin, carboxipeniciline.
- medulotoxicity (leukopenia, neutropenia, thrombocytopenia, hemolytic anemia and injuries
in those with severe renal impairment): for carboxipeniciline;
- severe granulocytopenia: for methicillin.
- systemic hypokalemic alkalosis: for Carbeniciline.
- bleeding disorders: for Carbeniciline.

**Contraindications**
- hypersensitivity reactions to penicillins
- Penicillin G sodium is contraindicated in heart failure, arrhythmias;
- Penicillin G potassium is contraindicated in renal failure and arrhythmias (risk of
arrhythmias).

**BETA-LACTAMASE INHIBITORS**

**Classification:**
- Clavulanic acid: produced by Streptomyces clavuligerus;
- Sulbactam;
- Tazobactam.

**Mechanism of action:** inhibitors of many (but not all bacterial lactamases) and protect
penicillins from inactivation by these enzymes.
**Bactericidal effect.**

**Indications:**
- drug of choice for gonorrhea, infections with bacteria that produce beta-lactamase;
- infection to other susceptible organisms.

**CEPHALOSPORINS**
Are chemical similar to penicillins (semisynthetic beta-lactams with 7-aminoccephalosporanic
acid ring). Generally, are more resistant to beta-lactamases.

**Classification of cephalosporins** is by generations:

- **Cephalosporins 1st generation:**
  - oral administration: Cephradine, Cephalexin, Cefadroxil;
  - parenteral administration: Cephradine, Cefazolin, Cephalotin, Cephapirin.

- **Cephalosporins 2nd generation:**
Lecture 11: Chemotherapeutic drugs. Antibacterial chemotherapeutic drugs (part 1).
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- **oral administration:** Cefuroxime, Cefaclor, Loracarbef, Cefotiam;
- **parenteral administration:** Cefuroxime, Cefamandole, Cefmetazole, Cefotetan, Cefoxitin, Cefonicid, Ceforanid.

**Cephalosporins 3rd generation:**
- **oral administration:** Cefixime, Cefpodoxime;
- **parenteral administration:** Ceftriaxone, Ceftazidime, Cefotaxime, Cefoperazone, Moxalactam, Ceftizoxime, Ceftibuten, Proxetil.

**Cephalosporins 4th generation:**
- **parenteral administration:** Cefepime, Cefpirome.

**Mechanism of action:** inhibition of the synthesis of bacterial cell wall in three steps:

**Antibacterial spectrum:**
- *first-generation compounds* have better activity against *G(+) organisms* and the later generation have improved activity against *beta-lactamase-producing strains* and against *G(-) aerobic organisms*.
- *first-generation cephalosporins*: good activity against *G(+) bacteria* and relatively modest activity against *G(-) bacteria* (active on *Escherichia coli*, *Klebsiella*);
- *2nd generation cephalosporins*: some activity against *G(+) bacteria* and somewhat increased activity against *G(-) bacteria* (*E. coli*, *Klebsiella*, *Proteus*, *Haemophilus influenzae*);
- *3rd generation cephalosporins*: less active than first-generation agents against *G(+) cocci*, but are much more active against *G(-) bacteria* (*E. coli*, *Klebsiella*, *Proteus*, *H. influenzae*, *Serratia*), including *beta-lactamase-producing strains*;

**Pharmacokinetics**
- *1st generation cephalosporins*:
  - do not cross the blood-brain barrier.
  - not effective systemic concentrations.
  - are highly nephrotoxic.
- *2nd generation cephalosporins*:
  - do not cross the blood-brain barrier (except cefuroxime).
  - determine effective systemic concentrations.
  - are highly nephrotoxic.
  - cefamandole is the only compound that is concentrated in bile.
- *cephalosporins 3rd and 4th generation*:
  - crosses the blood-brain barrier.
  - are hepatotoxic
  - are concentrated in bile, present enterohepatic cycle.

**Indications**
- *1st-generation cephalosporins*: excellent agents for skin and soft tissue infections (especially *S. aureus* and *S. pyogenes*), surgical prophylaxis for skin infections.
- *2nd-generation cephalosporins* are used to treat respiratory tract infections, intra-abdominal infections, pelvic inflammatory disease, diabetic foot infection and are preferred for prophylaxis for intestinal anaerobes (eg, colorectal surgery).
- *3rd-generation cephalosporins* are the drugs of choice for serious infections caused by *Klebsiella*, *Enterobacter*, *Proteus*, *Providencia*, *Serratia*, and *Haemophilus* spp, for treatment of community-acquired pneumonia, for initial treatment of meningitis in immunodepressed
patients. Ceftriaxone is the drug of choice for all forms of gonorrhea. Ceftazidime is active against Pseudomonas.

- **4\(^{th}\)-generation cephalosporins** are indicated for the empirical treatment of nosocomial infections where there is resistance to other antibiotics.

**Side effects**

- **hypersensitivity reactions** (15% of patients):
  - Type I: urticaria angioedema, anaphylaxis;
  - Type III: Stevens-Johnson syndrome.
- intestinal dysmotismus (after oral administration);
- disulfiram-like reactions: Moxalactam, Cefamandole, Cefotetan, Cefoperazone;
- anticoagulant-like effect (risk of bleeding): Cefamandole, Cefoperazone;
- hepatotoxicity: III and IV generation cephalosporins;
- nephrotoxicity: I and II generation cephalosporins.

**CARBAPENEMS**

Carbapenems: Imipenem, Meropenem, Ertaopenem

**Association:** imipenem + cilastatin (dehydropeptidase inhibitor) = Primaxin ®.

Are resistant to beta-lactamases, but are inactivated by metallo-beta-lactamase or dehidropeptidases from renal tubules.

**Mechanism of action:** inhibition of the synthesis of bacterial cell wall in three steps:

**Bactericidal effect.**

**Antibacterial spectrum** - very large (very active on anaerobes):
- G (+) cocci: except for Methicillin-resistant staphylococci;
- G (+) bacilli: Lysteria; G (-) bacilli: Pseudomonas, Enterobacter, H. influenzae etc.

**Indications:** polymicrobial infections or bacteria resistant to beta-lactams.

**Adverse reactions:**
- type I immunological reactions (allergies), local reactions (phlebitis, thrombophlebitis, erythema), nausea, vomiting, hypotension, sweating, dizziness, nephrotoxicity,
- convulsions (neurotoxicity) in the elderly, in alcoholics and in chronic renal failure.

**MONOBACTAMS**

Monobactams: Aztreonam

They are resistant to beta-lactamases.

**Bactericidal effect.**

**Mechanism of action:** inhibition of the synthesis of bacterial cell wall in three steps:

**Antibacterial spectrum** is narrow: only aerobic G (-) bacteria (including Pseudomonas, Serratia, Enterobacter, Haemophilus influenzae etc).

- Ineffective against gram positive and anaerobic organisms.

**Indications:**
- infections by G(-) bacteria resistant to other antibacterial chemotherapy (respiratory tract, skin, osteomyelitis);
- alternative for patients allergic to penicillins or cephalosporins.

**Adverse reactions:**
- nephrotoxicity;
- neurotoxicity;
- increase of serum transaminases;
- suprainfection with staphylococci, enterococci etc.
GLYCOPEPTIDES

Glycopeptides: Vancomycin, Teicoplanin
Mechanism of action: inhibition of the synthesis of bacterial cell wall in three steps:
Antibacterial spectrum: G(+) bacteria: staphylococci (including S. aureus and S. epidermidis resistant to methicillin), streptococci, enterococci, Clostridia.
Bactericidal effect.
Pharmacokinetics: Low concentrations in the CNS (only when the meninges are inflamed)
Excretion by glomerular filtration.
Synergy with aminoglycosides.
Indications:
- drug of choice for staphylococcal infections resistant to methicillin or and highly resistant to Streptoccocus species.
- drug of choice for pseudocolite membranous Clostridium difficile;
- infections with G(+) bacteria resistant to other antibacterial chemotherapics;
- Staphilcoccal infections in persons with allergies to penicillins and cephalosporins.
Adverse reactions:
- erythema on the neck (or red neck syndrome "red man"),
- nephrotoxicity,
- ototoxicity – may potentiate known ototoxic agents,
- phlebitis at the injection site.

FOSFOMYCINES

Fosfomycines: Fosfomycin
Bactericidal effect.
Mechanism of action: inhibition of the synthesis of bacterial cell wall in three steps:
Antibacterial spectrum: broad spectrum G (+) and G (-) bacteria.
Indications: lower urinary tract infection without complications, ENT infections
Contraindication:
- renal failure;
- breastfeeding.

CYCLOSERINE

Chemotherapeutic antibacterial produced by Streptomyces orchidaeus.
Bactericidal effect.
Mechanism of action: inhibition of the synthesis of bacterial cell wall in three steps:
Antibacterial spectrum: M. tuberculosis, G (+) and G (-) bacteria.
Pharmacokinetics
- widely distributed in tissues;
- most of the administered dose is excreted in the urine as active metabolite.
Indications: treatment of tuberculosis (in case of resistance to first-line antituberculosis treatment).
Adverse reactions:
- neurotoxicity (dose): headache, tremor, acute psychosis, seizures.
Note: therapeutic dose is 0.5 to 1 g/24 hours, divided into 2-3 partial doses. Doses of 0.75 g / 24 hours prevents the effects on the central nervous system.

**BACITRACIN**

Produced by *Bacillus subtilis*.

Antibacterial polypeptides: Bacitracin, Gramicidin, Tyrothricin

**Bactericidal effect.**

**Mechanism of action:** inhibition of the synthesis of bacterial cell wall in three steps:

**Antibacterial spectrum:** bacteria G (+) and G (-), including Neisseria.

Topical appliquation (because of increased toxicity when administered systemically).

**Indications only in topical use:**
- skin lesions or mucous membranes, suprainfected (as ointments, in combination with neomycin or polymyxin);
- irrigation of joints, wounds or pleural cavity (saline with bacitracin 100-200 units / ml).

**Adverse reactions:**
- nephrotoxicity: proteinuria, hematuria, nitrogen retention;
- immunological reactions of type I.

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**Antibacterial chemotherapeutic drugs:**

**2. Inhibitors of bacterial cell function**

Essentially, affect cell membrane transport: increasing the permeability of the membrane.
Note: These agents are more toxic than systemic agents that inhibit cell wall synthesis.

**Classification of polymyxins:**
- Colistin;
- Polymyxin B.

**Bactericidal effect.**

**Antibacterial spectrum:** G (-) bacteria (including Pseudomonas).
- Resistant to polymyxin: G (+) bacteria, Proteus, Neisseria.

**Mechanism of action:**
- as cationic detergents on bacterial cell membranes → blocks the transmembrane transport.

**Pharmacokinetics:**
- not absorbed through the intestinal cells, do not enter the liver.

**Indications:** uncomplicated skin lesions, superficial infected skin lesions.

**Contraindications:** renal failure, lactation.