

**Ministry of Public Health of Ukraine
Higher State Educational Institution
"Ukrainian Medical Stomatological Academy"**

"Approved"

at a meeting of the Department of Experimental
and Clinical Pharmacology with Clinical
Immunology and Allergology

Head of the department

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**METHODICAL GUIDANCE FOR STUDENTS' SELF-DIRECTED
WORK WHEN PREPARING FOR PRACTICAL SESSION**

Academic subject	Clinical Pharmacology
Topic 4	The clinico-pharmacological characteristic the antibacterial medicines
Year of study	5
Faculty	Foreign students training (Medical)

Poltava 2017

1. Relevance of theme:

Antibiotics - the substances, which have the high antimicrobial activity. Antibiotics widely are used in medicine. Last years all more frequent microorganisms serve as reason of development of inflammatory processes with natural and purchased resistance to the antibiotics are staphylococci, streptococci, gram-negative aerobic microorganisms and anaerobes.

It requires from doctor certain knowledge's in accordance with basic principles of rational using of antibacterial agents. Study of this theme will help future doctor to choose antibacterial agent, to identified dose, scheme of treatment, to administer combine therapy with help several medicinal agents, and also, if necessary, to realize correction of complication of pharmacological therapy with help antibiotics.

2. Learning objectives:

1. To capture skills effective and safe pharmacotherapy antibiotics.
2. To capture abilities of individual choice of antibiotics.
3. Able to conduct the correction of pharmacotherapy if necessary.

3. Basic knowledge, skills necessary for studying the subject (interdisciplinary integration)

Discipline	To know
Anatomy	Anatomic features of structure of organism of man (skeleton, vascular system, muscles).
Pathological physiology	Pathogenesis of infectious inflammatory process
Microbiology	Exciters which cause infectiously-inflammatory diseases
Pharmacology	Classification, pharmacokinetics, pharmacodynamics, side action of antibiotics
Therapy, pediatrics, the surgery	Symptomatology, clinic of infectious process, diagnostics
Aminoglycosides	BPO group, which is one of the most important places in the treatment of infectious diseases, drugs represented a broad spectrum, active against many gram-positive and gram-negative bacteria
Sulfonamide	synthetic antibacterial agents, broad spectrum
Nitrofurantoin	derivative group of drugs frequently used in surgical practice for local treatment, due to their aqueous solubility and persistence of antibacterial activity in the presence of pus and tissue decay products

4. Tasks for work during preparation for the classes.

4.1. The list of key terms, parameters, characteristics which the student is to assimilate while preparing for the class:

Term	Definition
Cephalosporin group	of highly efficient broad-spectrum agents, capable of treating almost all forms nozoolohichnyh
Penicillins	one of the most widely used and effective group of antibiotics, which is the advantage of low toxicity
Macrolides	effective BPO group, which has a high therapeutic activity, a broad antimicrobial spectrum of activity, low toxicity and little side effects

4.2. Theoretical questions for the class:

1. Classification of antibacterial drugs mechanism of action, and wide range of chemical structure.
2. General description of the pharmacological properties of the major groups of modern antibiotics (penicillins, cephalosporins, carbapenems aminoglycosides, macrolides, linkozamidiv etc.).
3. Overview of the main pharmacological properties of synthetic antimicrobial drugs (fluoroquinolones, CA, imidazole derivatives).
4. Name the side effects of antibacterial drugs.
5. Principles of control side effects of antibacterial agents.
6. Rational dosage of antibacterial drugs.
7. The principles of selection and rational use of antibacterial drugs and correction treatment

4.3. Practical tasks:

1. To learn the principles of the empirical use of antibacterial drugs.
2. Master the principles of choice and rational use of antibacterial drugs.

3. Master the principles of rational dosage of antibacterial drugs.
4. Master the principles kombinovannoho use of antibacterial drugs.

Content topics

Mechanisms of action of antibiotics

1. Violation of biosynthesis of cellular wall of microorganism. Preparations which operate thus usually cooperate with structurally important peptidoglycans. Penicillin's behave to such preparations, cefalosporins and bacitracin.

By the target of action all β -lactam antibiotics are membrane of microbial cell enzymes (transpeptidases and carboxypeptidases). These enzymes are named, proteins which promote bounding of penicillin's. These enzymes are tightly coupled with the cytoplasm membrane of microbial cell and participate in the synthesis of peptide-glycans. Peptidoglycans carry out formation of transversal bridges of cellular wall of microbes. β -lactam antibiotics has likeness with mureinic acid. Mureinic acid is used for the construction of peptide-glycans. The membrane of microorganism can maintain pressure in a few atmospheres.

In addition, β -lactam antibiotics violate the synthesis of protein, which promote adhesion (fixation) of microorganism on the cells of tissue macroorganism.

2. Violation of synthesis of albumens of microorganisms. It is carried out by many antibiotics. However much a mechanism of action of antibiotics can be different. Tetracyclines interfere in the function of RNA. Tetracyclines violate the synthesis of albumen at the level of 30 S of subunits of ribosomes.

Aminoglykosides interfere in the function of matrix RNA. Aminoglikozidy violate the synthesis of albumen at the level of 30 S and 50 S of subunits of ribosomes.

Levomycetine (chloramphenicol) cause inhibition of peptidiltraspherase. Levomycetine is violated synthesis of albumen at the level of 30 S and 50 S of s ribosomes.

Macrolides and lincasamides violate the synthesis of albumen at the level of 50 S of subunits of ribosomes. Erythromycin, lincomycin and clindomycin interfere in translocation.

3. Violation of synthesis of nucleic acids of microorganisms. It is carried out by many antibiotics. A mechanism of action can be different. Metronidazol and nitrofurantoin damage DNA. Quinolones induce decrease activity of DNA-hydrase. Rifampitsin induce decrease activity of RNA-polimerase. Sul'fanilamidy and trimethoprim cause inhibition of synthesis of folic acid.

CHEMOTHERAPEUTIC DRUGS

Types of anti-infective agents

Bacterial infections are readily treated in most instances by a wide variety of agents. Some antibacterial drugs are **bacteriostatic**; that is, they inhibit the growth of susceptible bacteria. Other antibacterials are truly **bactericidal**; that is, they kill susceptible bacteria. **Fungal infections**, in contrast to bacterial infections, generally are quite resistant to chemotherapy, and the number of useful agents for these infections is somewhat restricted. Fungal infections often occur as superinfections; that is, secondary infections superimposed on the original infection as a result of changes in the host flora. The drugs are divided in fungistats and functional medicaments. **Mycobacterial infections: Tuberculosis** is one of the few diseases which require a combination of antimicrobial drugs, which are named tuberculo-static and tuberculocidal drugs. **There is drug treatment of Helminthiasis, Protozoal infections, Viral infections.**

General principles of anti-infective therapy

1. Selection of an appropriate anti-infective agent includes: Identification of the infecting organism should precede antimicrobial therapy when possible.

2. Route of administration.

3. Optimal dose and concentration.

4. Rational antimicrobial combination therapy.

5. Therapeutic responses to drug therapy should be monitored clinically and microbiologically to detect the development of resistance or superinfections.

6. The duration of drug therapy required depends on the pathogen, the site of infection, and the immunocompetence of the patient.

7. Inhibition of bacterial growth which continues after antibiotic blood concentrations have fallen to low levels is called the **postantibiotic effect (PAE)**.

8. Changes in hepatic and renal function - and the use of dialysis - can influence the pharmacokinetics of antimicrobials and may necessitate dosage modifications.

9. Antimicrobial therapy during pregnancy and neonatal period requires special consideration. Tetracyclines cause tooth enamel dysplasia and inhibition of bone growth. Sulfonamides, by displacing bilirubin from serum albumin, may cause kernicterus in the neonate. *Laevomycetinum* may cause a gray baby syndrome.

ANTIBIOTICS

Antibiotics are chemotherapeutic drugs of biological nature inhibiting microorganism selectively.

Antibiotics are divided according chemical structure:

1. B-lactam antibiotics (penicillins, cephalosporins, monobactams, carbapenems);
2. Macrolides and azalides;
3. Aminoglycosides;
4. Tetracyclines;
5. Laevomycetines;
6. Polyenes;
7. Glycopeptide antibiotics;
8. Lincosamides;
9. Polymyxines;
10. Steroid structure antibiotics;
11. Antibiotics of different chemical groups.

Classification according to mechanism of action:

1. Antibiotics disturb synthesis of bacterial cell wall – β -lactam antibiotics, glycopeptides etc.;
2. Antibiotics disturb the initiation of protein synthesis – aminoglycosides antibiotics, tetracycline's, laevomycetines, macrolides, azalides, lincosamides, steroid structure antibiotics etc.;
3. Antibiotics impair permeability of cell wall - *polymyxinum*, polyene antibiotics etc.;
4. Antibiotics disturb nucleic acid synthesis - rifampicins etc.

Classifications according to types of action:

1. Bactericidal action - β -lactam antibiotics etc.;
2. Bacteriostatic action - tetracyclines, *laevomycetinum* etc.

Classification according to the spectrum of action:

3. Antibiotics influence on gram positive bacteria predominantly - native penicillins;
4. Antibiotics influence on gram negative bacteria predominantly - polymyxins;
5. Antibiotics of wide spectrum of action — *tetracyclinum* — *laevomycetinum*, half synthetic penicillines, cephalosporines, carbapenemes, macrolides of the second generation, *rifampicinum* etc.;
6. Antifungal antibiotics - *amphotericinum*, *nystatinum* etc.;
7. Anticancer antibiotics - *doxorubicinum* etc.

Classification in nature:

1. Microbial nature of mold fungi - *penicillinum-natrium* etc.;
2. Microbial nature of Streptomyces - aminoglycosides etc.;
3. Bacterial nature - *gramicidinum* etc.;
4. Plant nature - *novoinmaninum* etc.

B-Lactam Antibiotics

Penicillins, *monobactamum*, *carbapenemum* and *cephalosporins* are the major antibiotics which inhibit bacterial cell wall synthesis. They are called p-lactams because of the unusual four-member ring which is common to all their members. These four large classes of P-lactams include some of the most effective, widely used, and well-tolerated agents available for the treatment of microbial infections. The emergence of **microbial resistance** poses a constant challenge to the use of antimicrobial drugs. Mechanisms underlying microbial resistance to cell wall synthesis inhibitors include the production of antibiotic-inactivating enzymes, changes in the structure of target receptors, and decreases in the permeability of microbes' cellular membranes to antibiotics.

Mechanism of action: The P-lactam antibiotics are **bactericidal**. The P-lactam antibiotics inhibit key enzymes in bacterial cell wall synthesis. They are structurally resembled to the terminal d-alanyl-d-alanine (peptido-glycan-murein). Bacterial transpeptidase covalently bind p-lactam antibiotics on the enzyme active sites, the acyl-enzyme molecule is stable and inactive. They also appear to activate one or more cell-wall autolytic enzymes, causing lysis of the bacterium. **B-lactamases**, enzymes produced by many different bacteria, hydrolyze the P-lactam ring, inactivating the antibiotic. **Penicillinase** and cephalosporinase are β -lactamases with narrow substrate specificities. Initially sensitive bacterial strains can become permanently resistant to a particular antibiotic by acquiring plasmids or R (resistance) factors carrying the genetic code for a β -lactamase.

Penicillins

Classification of Penicillins

I. Native penicillins

- 1.1. Drugs of short acting - *Benzylpenicillinum-natrium*, *Benzylpenicil-linum-kalmm*;
- 1.2. Drugs of long-acting - *Penicillinum-novocainum*, *Bicillinum-1*, *Bi-cillinum-3*, *Bicillinum-5*;
- 1.3. Drugs for oral administration - *Penicillin G*, *Penicillin V* (*phenoxy-methylpenicillinum*);

II. Semisynthetic penicillins.

- 2.1. Penicillinase-resistant penicillins - *Methicillinum*, *Oxacillinum*, *Cloxacillinum*, *Naficillinum*, *Dicloxacillinum*;
- 2.2. "Broad-spectrum" penicillins - *Ampicillinum*, *Amoxicillinum*, *Bacampicillinum*, *Cyclacillinum*, *Hetacillinum*, *Pivampicillinum*;

Antipseudomonas penicillins - *Carbenicillinum*-*Carbenicillin in-danyl*, *Ticarcillinum*; *Ureidopenicillinums*-*Azlocillinum*, *Mezlocillinum*, *Piperacillinum*;

2.4. Combinations of penicillin and a (3-lactamase inhibitor *Amoxycillinum* with clavulanic acid - *Ampicillinum* with sulbactam, *amoxycillinum* with clavulanic acid, *Ticarcillinum* with clavulanic acid. **Pharmacokinetics:** Penicillins vary in their resistance to gastric acid and therefore vary in their oral bioavailability. They are polar compounds and are not metabolized extensively. They are usually excreted unchanged in the urine via glomerular filtration and tubular secretion, the latter process being inhibited by probenecid. *Ampicillinum* and *nafticillinum* are excreted partly in the bile. The plasma half-lives of most penicillins vary from one-half to 1 hour. *Benzylpenicillinum-natrium* is distributed widely throughout the body with about 60% reversibly bound to plasma albumin. It penetrates poorly into ocular, pericardial, and cerebrospinal fluids. Significant amount of the drug appears in the liver, intestine, and kidneys, as well as in bile, semen, and lymph. From 60%-90% of an intramuscular dose of *benzylpenicillinum-natrium* is excreted within 1 hour. Up to 99% of the dose is eliminated via the kidney; that is, about 90% by tubular secretion and 10% by glomerular filtration. *Novocainum* and benzathine forms of *penicillin G* are administered intramuscularly and have long plasma half-lives because the active drug is released very slowly into the bloodstream. Most penicillins cross the blood-brain barrier only when the meninges are inflamed. Because gastric acid inactivates **phenoxymethylpenicillinum**, only 30% of an oral dose is absorbed from the duodenum.

Mechanism of action: Penicillins inhibit the synthesis of bacterial cell walls and are considered **bactericidal**. They combine with and inactivate transpeptidase, which normally is responsible for cross-linking the linear glycopeptide strands of bacterial cell walls. Loss of cell wall rigidity in the presence of normal high intracellular osmotic pressure causes lysis of the bacterial membrane.

Pharmacologic effects and therapeutic uses: The various types of penicillins differ in their spectrum of activity and in their degree of efficacy against particular species or strains. In general, microbial sensitivity should be verified whenever possible. ***Benzylpenicillinum-natrium* and *kaliūm*** are highly effective against many strains of gram-positive cocci (strepto-coccal and staphylococcal) infections, *S. pneumoniae* (pneumococcal infections). They are the drug of first choice for treatment of pneumococcal pneumonia. For pneumococcal meningitis, *benzylpenicillinum natrium* is usually administered intravenously. Intrathecal administration is sometimes used, but arachnoiditis and encephalopathy can complicate this form of therapy. Other pneumococcal infections for which *benzylpenicillinum natrium* is the drug of first choice include suppurative arthritis, mastoiditis, endocarditis, pericarditis, and osteomyelitis, streptococcal pharyngitis and scarlet fever, otitis media. *Benzylpenicillinum natrium* and scarlet fever is the most effective treatment for all stages of syphilis, against many oral anaerobes, in gas gangrene, most strains of *Corynebacterium diphtheriae*, anthrax, actinomycosis, *Listeria* infections.

Benzylpenicillinum-novocainum action lasts 12 hours, *Benzatin benzylpenicillinum* (*Bicillinum 1*) - 7 days, *Bicillinum* - 3-7-10 days, *Bicillinum-5* till a month. **Semisynthetic penicillins** are derivatives of 6-amino-penicillin acid. They are divided into:

I. Drugs of narrow specter stable to penicillinase (*Oxacillinum*, *Doxacillinum*).

II. Drugs of wide specter.

2.1 *Ampicillinum*, *Amoxicillinum*, *Aminopenicillinum*.

2.2 *Carboxypenicillinum*, *Carbenicillinum*, *Carfecillinum*, *Ticarcillinum*.

2.3 *Ureidopenicillinum*, *Azlocillinum*, *Piperacillinum*, *Mezlocillinum*.

Pharmacokinetics: *Oxacillinum-natrium* is stable in acidic stomach environment. *Doxacillinum* has more absorption. They influence gram-positive organism stable to native penicillinum. It is called antistaphylococcus penicillinum. *Amoxicillinum* is absorbed better than ampicillinum and acts longer.

Pharmacodynamics: Penicillinase-resistant penicillins has very narrow spectrum. This subclass of penicillins includes ***methicillinum*** (the prototype), ***nafticillinum***, and ***oxacttlinum***. Their primary use is in the treatment of known or suspected staphylococcal infections. Methicillin-resistant staphylococci (MRSA) are resistant to other members of this subgroup and may be resistant to multiple antimicrobial drugs. ***Methicillinum*** has one-twentieth the potency of *Benzylpenicillinum-natrium*. It is not administered orally because of poor absorption via this route. ***Oxacillinum*** is acid-stable and, therefore, can be given orally as well as intravenously and intramuscularly. It is highly protein-bound in the plasma. It is up to eight times as potent as *methicillinum*. ***Cloxacillinum*** has pharmacologic and pharmacokinetic properties which are similar to those of *oxacillinum*. ***Nafticillinum*** can be given orally, intravenously, or intramuscularly. ***Dicloxacillinum***, because it is highly resistant to penicillinase and acid hydrolysis, is very effective when administered orally.

The broad-spectrum penicillins-ampicillinum, amoxicillinum, and their various derivatives (e.g. *bacampicillinum*, *pivampicillinum*, *hetacillinum*) - are effective against gram-positive organisms, some strains of *E. coli*, *H. influenzae*, *Salmonella*, and *Shigella*, and some *Proteus* species. When strains are sensitive, *ampicillinum* and *amoxicillinum* are used to treat some forms of gonorrhea, sinusitis and otitis media due to *H. influenzae*, pneumococci, or *S. pyogenes*, urinary tract infections due to *E. coli* or *P. mirabilis*, meningitis due to *H. influenzae*, meningococci, or pneumococci. *Amoxicillinum* influences more *Helicobacter pylori* and *S. pneumoniae*. **Broad-spectrum penicillins. Ampicillinum and amoxicillin.** These drugs comprise a penicillin subgroup which has a wider spectrum of antibacterial

activity than *benzylpenicillinum* but remains susceptible to penicillinases. Their clinical uses include indications similar to benzylpenicillin as well as infections due to enterococci, *Listeria monocytogenes*, *Escherichia coli*, *Proteus mirabilis*, *Haemophilus influenzae*, and *Moraxella catarrhalis*, though resistant strains occur. When used in combination with inhibitors of penicillinases (clavulanic acid etc.), their antibacterial activity is enhanced. In enterococcal and listerial infections ampicillin is synergistic with aminoglycosides.

"Antipseudomonas" penicillins are chiefly used to treat serious infections (bacteremia, pneumonia, burn infections) due to gram-negative organisms, particularly *P. aeruginosa*, indole-positive *Proteus*, and *Enterobacter*. **Carbenicillinum and ticarcillinum** have a spectrum of activity similar to that of *ampicillinum* and, in addition, are effective against indole-positive *Proteus* and *Pseudomonas*. *Ticarcillinum* is two to four times more active against *P. aeruginosa* than carbenicillin and may be preferable in serious *Pseudomonas* infections. The *carbenicillinum* congener, **carbenicillin indanyl**, accumulates rapidly in the urine and, thus, provides effective therapy for urinary tract infections caused by indole-positive *Proteus* or *Pseudomonas*. **Azlocillinum mezlocillinum, and piperacillinum** are known collectively as the **ureidopenicillins**. *Azlocillinum* and *piperacillinum* are ten times more active than carbenicillin against *Pseudomonas* organisms. *Mezlocillinum* and *piperacillinum* are more active than *carbenicillinum* against *Klebsiella*. When a *Pseudomonas* infection is life-threatening, antipseudomonas *penicillinum* is often used in combination with *gentamicinum*, *amikacinum*, or *tobramycinum*.

Combinations of penicillin and β -lactamase inhibitor Clavulanic acid is a β -lactamase inhibitor which is structurally related to the penicillins. Clavulanic acid extends the antibacterial spectrum of β -lactam antibiotics by irreversibly binding and, thus, inhibiting many bacterial β -lactamases. It extends in vitro activity of **amoxicillinum** to include β -lactamase-producing strains of *H. influenzae*; *E. coli*, *Proteus* species; *Klebsiella pneumoniae*; *Staphylococcus epidermidis* and *Staphylococcus saprophyticus*, as well as *S. aureus*; and *Branhamella catarrhalis*. It extends the in vitro activity of **ticarcillinum** to include an extremely wide variety of gram-negative and gram-positive organisms and anaerobes. The combination of **amoxicillinum and clavulanate** (*Amoxiclavum*) is used to treat infections caused by β -lactamase-producing strains of *H. influenzae*, *B. catarrhalis*, *S. aureus*, *E. coli*, *Klebsiella*, and *Enterobacter*. The combination of *ticarcillinum* and clavulanate is used to treat infections caused by β -lactamase-producing strains of *Klebsiella*, *E. coli*, *S. aureus*, *Pseudomonas*, *H. influenzae*, *Citrobacter*, *Enterobacter cloacae*, and *Serratia marcescens*.

Sulbactam is a penicillanic acid sulfone with limited antibacterial activity. Its principal action is to inactivate bacterial β -lactamases, thereby enhancing the antibacterial spectrum of *ampicillinum*. It extends in vitro activity of **ampicillinum** to include β -lactamase-producing strains of *H. influenzae*, *E. coli*, *Proteus* species, *K. pneumoniae*, *S. aureus*, *S. epidermidis*, *B. catarrhalis*, *Enterobacter aerogenes*, *Acinetobacter calcoaceticus*, *Neisseria*, and several anaerobes, including *B. fragilis*. The combination of **ampicillinum and sulbactam** has been useful in treating intra-abdominal and gynecologic infections. *Bicillinum-1*, 3, 5 have been shown to be effective for prophylaxis in the following conditions: rheumatic fever recurrences; syphilis; streptococcal infections (generalization).

Antipseudomonas penicillins. *Azlocillinum* is given intravenously. **Carbenicillinum, ticarcillinum, mezlocillinum, and piperacillinum** are given intravenously or intramuscularly. **Piperacillinum and ticarcillinum:** These drugs have activity against several gram-negative rods, including pseudomonas, enterobacter, and in some cases klebsiella species. More drugs in this subgroup have synergistic actions when used with aminoglycoside against such organisms. *Piperacillinum* and *ticarcillinum* are susceptible to penicillinases and are often used in combination with penicillinase inhibitors to enhance their activity. **Carbenicillinum indanyl** is acid-stable and is administered orally.

Combinations of penicillinum and β -lactamase inhibitor. **Amoxicillinum with clavulanate** is given orally. **Ticarcillinum with clavulanate** is given intravenously. **Ampicillinum with sulbactam** is given intravenously or intramuscularly.

Adverse effects. Hypersensitivity reactions to the penicillin occur in 5%-20% of patients receiving these drugs, and all forms of penicillin can cause hypersensitivity reactions. A reaction can occur in the absence of prior therapeutic penicillin administration. The reaction can range from a mild rash to life-threatening anaphylaxis and may persist 1-2 weeks after discontinuation of therapy. Hypersensitivity reactions include: skin rashes of all types. In severe cases, the Stevens-Johnson syndrome can occur. The highest incidence of skin rash (about 9%) occurs after *ampicillinum* administration. Fever, which disappears within 36 hours after termination of administration, eosinophilia, angioedema, serum sickness, anaphylactic reactions. One in 50,000 patients treated with penicillin dies from this type of reaction, which is the most common after parenteral administration, but it can occur after oral ingestion and with minute quantities of penicillin; recurrent reactions and cross-sensitivity. A hypersensitivity reaction to one form of penicillin places the affected patient at high risk of reaction. The risk of cross-reactions with other β -lactams is less clear. Penicillin-allergic individuals occasionally have allergic reactions to cephalosporins. In penicillin-allergic patients serious infections due to gram-positive organisms are often treated with *vancomycinum*. Alternatives for other infections include *erythromycinum*, *trimethoprim-sulfamethoxazole*, aminoglycosides, and *ciprofloxacinum*.

Gastrointestinal complications are more likely with orally administered preparations; an example is ampicillin-associated diarrhea. *Amoxicillinum* is thought to cause a lower incidence of diarrhea than *ampicillinum*.

Nephrotoxicity is very rare. Bone-marrow toxicity is uncommon. Agranulocytosis has been reported with

ampicillinum administration. Impairment of platelet aggregation has been reported with *Carbenicillinum* administration. Superinfection results from alterations in intestinal flora. A low incidence occurs with penicillin G administration. A higher incidence occurs with broad-spectrum penicillins, such as *ampicillinum* and *Carbenicillinum*.

Cephalosporins

The cephalosporins are derivatives of 7-aminocephalosporanic acid and contain the p-lactam ring structure and are semisynthetic.

Classification. The cephalosporins are typically classified by "generations", which roughly parallel to their chronologic development and their antimicrobial spectrum.

First-generation drugs: *Cefazolinum* (parenteral) and *cephalexinum* (oral), *cefadroxilum*, *cefalotinum*, *cefapirinum* are examples of this subgroup. They are active against gram-positive cocci, including staphylococci and common streptococci. Many strains of *E. coli* and *K. pneumoniae* are also sensitive. Clinical uses include treatment of infections caused by these organisms and surgical prophylaxis in selected conditions. These drugs have minimal activity against gram-negative cocci, enterococci methicillin-resistant staphylococci, and most gram-negative rods. **Second-generation drugs:** Drugs in this subgroup usually have less activity against gram-positive organisms than the first-generation drugs but have an extended gram-negative coverage. Marked differences in activity occur among the drugs in this subgroup. Examples of clinical uses include infections caused by *Bacteroides fragilis* (*cefotetanum*, *cefoxitinum*) and by *H. influenzae* or *Moraxella catarrhalis* (*cefuroximum*, *cefaclor* etc.). **Third-generation drugs:** Characteristic features of third-generation drugs (e.g. *cefoperazonum*, *ceftazidinum*, *cefpiramidum*, *cefpodoximum*, *ceftibutenum*, *moxalactamum*, *cefotaximum* etc.) include increased activity against gram-negative organisms resistant to other p-lactam drugs and ability to penetrate a blood-brain barrier (except cefoperazone and cefixime). Most are active against enterobacter, providencia, *Serratia marcescens*, and p-lactamase-producing strains of *H. influenzae* and neisseria. Individual drugs also have activity against *B. pseudomonas* (*ceftazidinum*) and *B. fragilis* (*ceftizoximum*). Drugs in this subclass should usually be reserved for treatment of serious infections, e.g. bacterial meningitis. *Ceftriaxonum* (parenteral) and *ceftiximum* (oral), currently drugs of choice in gonorrhea, are exceptions. Likewise, in acute otitis media, a single injection of ceftriaxone is as effective as a 10-day course of treatment with *amoxicillinum* or *cefaclor*. **Fourth-generation drugs:** *Cefipimum*, *cefpimomum*, *cefclidinum*, *cefluprenamum*, *cefosopranum*, *cefquinomum* are more resistant to P-lactamases produced by gram-negative organisms, including enterobacter, haemophilus, and neisseria. *Cefipimum* combines a gram-positive activity of first-generation agents with a wider gram-negative spectrum of third-generation cephalosporins.

Mechanism of action: Cephalosporins, like the penicillins, inhibit bacterial cell wall synthesis and are considered **bactericidal**. Cephalosporins are bactericidal against susceptible organisms. Structural differences from penicillins render cephalosporins less susceptible to penicillinases produced by staphylococci, but many bacteria are resistant through the production of other P-lactamases which can inactivate cephalosporins. Resistance can also result from damages in membrane permeability to cephalosporins and from changes in PBPs. Some bacteria elaborate a p-lactamase called **cephalosporinase** which acts on the cephalosporin nucleus to destroy its antibacterial activity, but many cephalosporins are resistant to the enzyme.

Pharmacokinetics: Most cephalosporins are administered parenterally; some, however, are well absorbed from the gastrointestinal tract and can be given orally. Several cephalosporins are available for oral use, but most are administered parenterally. Cephalosporins with side-chains may undergo hepatic metabolism, but the major elimination mechanism for drugs in this class is renal excretion via active tubular secretion. *Cefoperazonum* and *ceftriaxonum* are excreted mainly in the bile. Most first- and second generation cephalosporins do not enter the cerebrospinal fluid even when the meninges are inflamed. The cephalosporins become widely distributed throughout body tissues and fluids. The majority does not penetrate a blood-brain barrier and, thus, are not effective in the treatment of the CNS infections. Some cephalosporins are excreted via the bile, most are excreted in the urine via renal tubular secretion. *Probenecidum* blocks the tubular secretion of cephalosporins, often resulting in an increased half-life and elevated plasma concentration.

Pharmacologic effects: According to the generations all cephalosporins are active against different microorganisms.

Therapeutic uses: Diseases produced by *S. aureus*, both penicillin-sensitive and penicillin-resistant, including skin infections, osteomyelitis, and endocarditis, respond favorably to the cephalosporins. Cephalosporins are the drugs of first choice for *K. pneumoniae* infections. These drugs are used successfully in the treatment of pneumococcal pneumonia and in infections caused by *S. pyogenes*. Some of the parenteral cephalosporins are efficacious in the treatment of gonococcal disease which is resistant to other agents. Diseases caused by a number of gram-negative bacteria, including respiratory and urinary tract infections, respond well. The expanded-spectrum of activity of the cephalosporins includes effectiveness against *Proteus*, *B. fragilis*, *Serratia*, *Enterobacter*, and some activity against *Pseudomonas*. These agents are effective for the treatment of meningitis caused by susceptible strains.

First-generation cephalosporins are not effective against indole-positive *Proteus*, *Pseudomonas*, *Serratia*, *Enterobacter*, or *B. fragilis*. **Cephalexinum**. It is not well absorbed from the gastrointestinal tract. It is usually given intravenously. Intramuscular injection is painful. It is excreted principally via renal tubular secretion. **Cefazolinum**. It is

not well absorbed from the gastrointestinal tract and is administered intravenously or intramuscularly. Some 80% of the drug is reversibly bound to plasma proteins, substantially increasing its half-life. *Cefazolinum* is eliminated primarily by renal glomerular filtration; renal tubular secretion and biliary secretion play secondary roles. *Cephalexinum*. It is well absorbed from the gastrointestinal tract because of its high acid stability. It is available in oral capsules, suspensions, and pediatric drops. More than 90% of this drug is excreted unchanged in the urine; it is also excreted into bile. *Cephadrinum* is similar to *cephalexin*. It can be given orally, intravenously, or intramuscularly. *Cefadroxilum* is an orally active analogue of *cephalexin*. It is used in the treatment of urinary tract infections.

Second-generation cephalosporins. *Cefamandolum*. This expanded-spectrum cephalosporin is effective against indole-positive *Proteus* and P-lactamase-producing *H. influenzae*. It is administered parenterally only. *Cefoxitinum*. This expanded-spectrum cephalosporin is effective against indole-positive *Proteus* and *B. fragilis*. It has less activity against the gram-positive organisms. It is given parenterally. *Cefaclor* is similar to *cephalexin* but also is effective against P-lactamase-producing *H. influenzae*. It is given orally. *Cefonicidum* has an antibacterial spectrum similar to that of *cefamandole*. Its extended half-life allows once-a-day dosing; it is given parenterally. *Cefuroximium* is an expanded-spectrum cephalosporin which is useful for serious *H. influenzae* infections, particularly respiratory tract infections and otitis media. It is available for both parenteral and oral administration. *Ceforanidum* is similar in structure to *cefamandole* but is less active against *H. influenzae*. It is given parenterally. *Cefotetanum* has the in vitro spectrum similar to that of *cefoxitinum*, but it is less active against some anaerobes. It is given parenterally.

Third-generation cephalosporins. *Cefotaximum*, *ceftizoximum*, and *ceftriaxonum*. These relatively new, semisynthetic cephalosporins are more potent than the parent drug. They are given parenterally. *Ceftriaxonum*, because of its long half-life, can be administered once a day. It is particularly useful against penicillinase-producing strains of *Neisseria gonorrhoeae*. *Cefoperazonum* and *ceftazidimum* have greater activity against *P. aeruginosa* than the other third-generation cephalosporins but lesser activity against some other organisms. *Cefiximum* is effective against P-lactamase-producing strains of *H. influenzae*. It can be administered orally once a day.

Fourth generation cephalosporins. *Cefepimium* is effective to gram-positive and gram-negative microorganism. Only some strains of *Xanthomonas multiphilis* are stable to the drug.

Cefpironum (keiten) has analogic properties.

Adverse effects. Hypersensitivity reactions occur in about 5% of patients receiving cephalosporin therapy. Cephalosporins, like penicillins, elicit a spectrum of reactions which range from mild skin rash to anaphylaxis. A cross-sensitivity reaction to the cephalosporins occasionally occurs in individuals who are allergic to penicillin 1. Renal damage, although rare with normal doses of cephalosporins, can occur. Local tissue reactions can occur with parenteral administration. Intravenous administration can cause thrombophlebitis. Superinfections caused by gram-negative bacteria or yeasts can occur following administration of the cephalosporins.

Carbapenems Thienamum (Imipenemum and Cilastatinum) and meropenemum,

These drugs are **carbapenems** (chemically different from penicillins but retaining the p-lactam ring structure) with low susceptibility to p-lactamases. The drugs have ultrawide activity against gram-positive cocci (including some penicillin-resistant pneumococci), gram-negative rods, and anaerobes. They are administered parenterally and are especially useful for infections caused by organisms resistant to other antibiotics. They are currently the drug of choice for infections due to enterobacter. *Imipenemum* is inactivated by renal dehydropeptidase I and is administered in combination with cilastatinum, an inhibitor of this enzyme as *Thienamum*. *Thienamum* increases the plasma half-life of imipenemum and inhibits the formation of a potentially nephrotoxic metabolite.

Adverse effects of *Thienamum* include gastrointestinal distress, skin rash, and, at very high plasma levels, the CNS toxicity (confusion, encephalopathy, seizures). There is partial cross-allergenicity with the penicillins. *Meropenemum* is similar to imipenem except that it is not metabolized by renal dehydropeptidases and is less likely to cause seizures.

Pharmacologic effects: *Thienamum* and *meropenemum* have the broadest antimicrobial spectrum of all the P-lactam antibiotics. They are active against both gram-positive and gram-negative cocci (except methicillin-resistant staphylococci), Enterobacteriaceae, *P. aeruginosa*, and anaerobic bacteria, including *B. fragilis*. Gonococci and *H. influenzae* strains which are resistant to both penicillin and ampicillin are susceptible to them.

Therapeutic uses: Use of *Thienamum* and *Meropenemum* is limited to the treatment of serious hospital-acquired infections due to susceptible organisms. They are given intravenously. They are used in urinary tract, respiratory tract, skin, and soft tissue infections. It is effective for the treatment of osteomyelitis, septic arthritis, bacteremia, and gynecologic and intra-abdominal infections. Their usefulness in staphylococcal endocarditis has been established, but not in the CNS infections.

Adverse effects: *P. aeruginosa* may become resistant during carbopenems therapy. Allergic reactions. Patients allergic to penicillin should be considered allergic to them. Nausea, vomiting, and diarrhea occur.

Monobactams

Aztreonamum is a **monobactam** which is resistant to β -lactamases produced by certain gram-negative rods, including *Klebsiella*, *Pseudomonas*, and *Serratia*. The drug has no activity against gram-positive bacteria or anaerobes. It is an inhibitor of cell wall synthesis, preferentially binding to PBP3, and is synergistic with aminoglycosides.

Aztreonam is administered intravenously and is eliminated via renal tubular secretion. Its half-life is prolonged in renal failure. Adverse effects include gastrointestinal upset with possible superinfection, vertigo and headache, and rare hepatotoxicity. Though skin rash may occur, there is no cross-allergenicity with penicillins.

Mechanism of action: Like other p-lactams, *aztreonam* interferes with the synthesis of the bacterial cell wall.

Pharmacologic effects: *Aztreonam* is highly resistant to P-lactamases. It is highly active against aerobic gram-negative bacteria, including *P. aeruginosa* and penicillinase-producing strains of *H. influenzae* and gonococci. It shows poor activity against gram-positive cocci and anaerobic bacteria.

Therapeutic uses: *Aztreonam* is substituted by aminoglycosides in the treatment of urinary tract, lower respiratory tract, and skin and soft tissue infections. Additionally, osteomyelitis, gonorrhea, and gynecologic and intra-abdominal infections due to susceptible pathogens have been successfully treated. Because of its narrow spectrum *aztreonam* is often used in combination with another antimicrobial agent. *Aztreonam* is administered parenterally.

Adverse effects: Colonization and superinfection with gram-positive cocci can occur. Pseudomembranous colitis has been reported. *Aztreonam* shows little or no immunologic cross-reactivity with other P-lactams.

B-Lactamase Inhibitors: *Clavulanic acid*, *sulbactam*, and *tazobactam* are used in fixed combinations with certain hydrolyzable penicillins. They are most active against plasmid-encoded P-lactamases such as those produced by gonococci, streptococci, *E. coli*, and *H. influenzae*. They are not good inhibitors of inducible chromosomal p-lactamases formed by enterobacter and pseudomonas. There are combined drugs: *amoxiclavum* (*amoxycillinum* + clavulanic acid); *unasinum* (*ampicillinum* + sulbactam) etc.

Aminoglycosides

The aminoglycosides are compounds containing characteristic amino sugars joined to a hexose nucleus in glycosidic linkage. They are polycations and their polarity accounts for their pharmacokinetic properties. **Modes of antibacterial action:** in the treatment of microbial infections with antibiotics, multiple daily dosage regimens traditionally have been designed to maintain serum concentrations above the minimal inhibitory concentration (MIC) for as long as possible. Aminoglycosides are also capable of exerting a postantibiotic effect such that their killing action continues when their plasma levels have declined below measurable levels. Consequently, aminoglycosides have greater efficacy when administered as a single large dose than when given as multiple smaller doses. The toxicity (in contrast to the antibacterial efficacy) of aminoglycosides depends both on a critical plasma concentration and on the time which such a level exceeds.

Mechanism of action: Aminoglycosides are bactericidal inhibitors of protein synthesis. Their penetration through the bacterial cell envelope is partly dependent on oxygen-dependent active transport and they have little activity against strict anaerobes. Aminoglycoside transport can be enhanced by cell wall synthesis inhibitors, which may be the basis of antimicrobial synergism. Inside the cell aminoglycosides bind to the 30S ribosomal sub-unit and interfere with protein synthesis in at least three ways: they block formation of the initiation complex; they cause misreading of the code on the mRNA template; and they inhibit translocation. Aminoglycosides may also disrupt polysomal structure, resulting in nonfunctional monosomes. The aminoglycosides inhibit protein biosynthesis by acting directly on the ribosome. They interfere with the proper attachment of messenger RNA to ribosomes in the initiation of protein synthesis. They also cause misreading of the genetic code and, hence, cause decreased or abnormal protein synthesis. The aminoglycosides also appear to disrupt the bacterial cytoplasmic membrane. The rapid **bactericidal** effect of the aminoglycosides is not, however, adequately explained by any of their known actions. Aminoglycosides include 1) first generation - *streptomycinum*, *monomycinum*, *neomycinum*, and *kanamycinum*; 2) second generation - *gentamicinum*; 3) third generation - *tobramycinum*, *sisomicinum*, *netilmicinum*, and *amikacynum*; 4) fourth generation - *isopamycinum*, *dactinomycinum*, and *arbecacinum*.

Pharmacokinetics: Aminoglycosides are polar compounds polycationic structure and are not absorbed after oral administration. They must be given parenterally for systemic effect absorbed rapidly and have limited tissue penetration. They are distributed in all extracellular fluids, but tissue concentrations are low except in the kidney and ear. They cross a blood-brain barrier only if the meninges are inflamed.

Microbial resistance: The primary mechanism of resistance to aminoglycosides involves a plasmid-mediated formation of inactivating enzymes. *Amikacinum* and *netilmicinum* are not affected by most aminoglycoside-inactivating enzymes which cause bacterial resistance in some species.

Pharmacologic effects. *Streptomycinum*. High concentrations of *streptomycinum* are bactericidal; low concentrations are bacteriostatic. *Streptomycinum* is effective against the organisms which cause plague (*Yersinia pestis*) and tularemia (*Francisella tularensis*) and, in combination with *penicillinum*, against gram-positive enterococci and streptococci. In vivo, *streptomycinum* suppresses tubercle bacilli. *Neomycinum* is effective against many gram-negative species and is also effective against several gram-positive bacteria (e.g. *S. aureus*). Streptococci are generally resistant to *neomycinum*. *Gentamicinum* is bactericidal against a wide variety of gram-negative organisms, including indole-positive *Proteus*, *Pseudomonas*, and *Serratia* organisms. Some strains of *Staphylococcus* may be sensitive to *gentamicinum*. *Tobramycinum* has a spectrum of activity similar to that of *gentamicinum* but may be slightly more effective against *Pseudomonas*. *Amikacinum* has also a spectrum of activity similar to that of *gentamicinum* but often is

reserved for situations in which resistance to *gentamicin* emerged. **Netilmicin** has a spectrum of activity similar to that of *ami-kacinum* and may be active against bacteria which are resistant to *gentamicin*. **Kanamycin** has a more limited spectrum of activity than *gentamicin* has. It is ineffective against *Pseudomonas* and most gram-positive organisms. *Kanamycin*, *amikacin*, *streptomycin*, and *neomycin* all have some activity against *M. tuberculosis*. Anaerobic microorganisms are generally resistant to the aminoglycosides.

Therapeutic uses: *Streptomycin* is used very seldom. Sub-acute bacterial endocarditis caused by the viridans group of streptococci or by enterococci usually in combination with *benzylpenicillinum-natrium* or *oxacillinum*. Because of the frequent development of bacterial resistance, *streptomycin* is used alone to treat only two infections - tularemia and plague. Severe cases of brucellosis are treated with a combination of *streptomycin* and *tetracyclinum*. Urinary and respiratory tract infections, peritonitis, and bacterial meningitis may respond to *streptomycin* but are treated more effectively with other agents. Although *streptomycin* is no longer used alone in the treatment of pulmonary tuberculosis, it is often used in combination with other agents for the treatment of serious forms of tuberculosis. ***Gentamicin*, *tobramycin*, *amikacin*, and *netilmicin*.**

May be used in treatment of many infections can be treated successfully with these agents, but their toxicity restricts their use to situations involving life-threatening infections caused by: *P. aeruginosa*, *Serratia*, *Enterobacter*, and *Klebsiella*; methicillin-resistant staphylococci which are sensitive to *gentamicin*. These agents are sometimes used as part of an initial "blind therapy" for serious infections of unknown etiology, in which case a penicillinase-resistant *penicillinum* or a cephalosporin is administered in combination with an aminoglycoside, such as *gentamicin*.

Neomycin, because of its serious toxic effects when absorbed systemically, is used most frequently in dermatologic and ophthalmic ointments. In addition, *neomycin* can be used orally for surgery or for the management of hepatic coma. **Kanamycin** has also been largely superseded by less toxic, more effective agents.

Adverse effects: All of the aminoglycosides have a narrow therapeutic index which limits their parenteral usage. Ototoxicity and nephrotoxicity are the most serious side effects. Both labyrinthine damage and vestibular disturbances can occur. *Gentamicin* is the most nephrotoxic of the aminoglycosides. It can produce acute renal insufficiency and tubular necrosis. Neurotoxic effects include dysfunction of the optic nerve can occur with *streptomycin*, producing scotomas, neuritis, psychosis. Neuromuscular junction blockade may result when an aminoglycoside is given at high doses and in combination with curariform drugs. This apparently results from a decreased sensitivity of the postjunctional membrane to acetylcholine and decreased presynaptic release of the transmitter. Hypersensitivity reactions may occur. Superinfection and intestinal malabsorption may occur following oral administration of *neomycin*.

Tetracyclines

Tetracyclines are divided into

- 1) **natural** - *Oxy tetracyclinum*, *Tetracyclinum*;
- 2) **semisynthetic** - *Doxycyclinum*, *Methacyclinum*, *Minocyclinum*.

Tetracyclinum and its congeners are derivatives of the poly cyclic naph-thacenecarboxamide. *Tetracyclinum* are broad-spectrum antibiotics with

activity against gram-positive and gram-negative bacteria, rickettsia, chlamydia, mycoplasma, and some protozoa. Susceptible organisms accumulate *tetracyclinum* intracellularly via energy-dependent transport systems in their cell membranes. Plasmid-mediated resistance to *tetracyclinum* is widespread. Resistance mechanisms include decreased activity of the uptake systems and the development of mechanisms (efflux pumps) for active extrusion of *tetracyclinum*.

Mechanism of action: *Tetracyclinum* are primarily **bacteriostatic**, inhibiting protein synthesis by binding to 30S ribosomes. *Tetracyclinum* affects both eukaryotic and prokaryotic cells but apparently penetrates microbial membranes more readily due to the presence of active transport systems in microbes.

Pharmacokinetics: *Tetracyclinum* are adequately but incompletely absorbed from the gastrointestinal tract, particularly from the stomach and upper small intestine. Oral absorption is variable, especially for the older drugs, and may be impaired by food and multivalent cations (calcium, iron, aluminum). *Tetracyclinum* have a wide tissue distribution and cross the placental barrier. All of the *tetracyclinum* undergo enterohepatic cycling. *Doxycyclinum* is excreted mainly in feces; the other drugs are eliminated primarily in the urine. The half-lives of *doxycyclinum* and *minocyclinum* are longer than those of other *tetracyclinum*. Absorption is impaired by food, especially milk and milk products, by aluminum hydroxide gels and by calcium and magnesium salts. **Minocyclinum** and **doxycyclinum** are exceptions in that they chelate poorly with calcium, and food does not interfere with their absorption. Like other *tetracyclinum*, they do chelate with iron to form insoluble complexes. The *tetracyclinum* diffuses into body fluids and bind to plasma proteins to varying degrees, depending on the particular preparation. Concentrations in the cerebrospinal fluid are about 20% of serum levels unless the meninges are inflamed. The *tetracyclinum* are removed from the blood by the liver and are excreted into the intestine by way of the bile. They undergo enterohepatic circulation. Excretion occurs primarily via the kidneys, although there is some fecal excretion. Renal clearance of these drugs is by glomerular filtration. Gram-positive bacteria often become resistant to the *tetracyclinum*, limiting the usefulness of these drugs. **Pharmacologic effects:** *Tetracyclinum* are effective against many gram-positive and gram-negative

bacteria. The *tetracyclins* are effective against *Mycoplasma*, *Borrelia*, *Chlamydia*, and rickettsial species. They are useful secondary drugs against *Leptospira* and *Treponema* species. In high concentrations the tetracyclins inhibit the growth of the protozoan *Entamoeba histolytica*.

Therapeutic uses: The use of *tetracyclins* for treatment of infectious disease has declined because of increasing bacterial resistance and the development of newer, more effective antimicrobial agents. *Tetracyclins* are useful in the treatment of the following conditions. **Rickettsial infections.** *Tetracyclins* are the drugs of first choice for these diseases, which include: Rocky Mountain spotted fever, Brill's disease, murine and scrub typhus, rickettsialpox, Q fever. **Chlamydial infections:** lymphogranuloma venereum, psittacosis, inclusion conjunctivitis, trachoma. **Mycoplasmal infections. Bacillary infections:** brucellosis, tularemia, cholera, some *Shigella* and *Salmonella* infections. **Venereal infections:** gonorrhea, syphilis, chancroid, granuloma inguinale, chlamydial urethritis or cervicitis. **Amebiasis. Lyme disease,** a multisystem inflammatory disorder, is caused by the spirochete *Borrelia burgdorferi*, which is transmitted by ticks. Oral *tetracycline* or *doxycycline* for 10-20 days shortens the duration of symptoms and often prevents the development of more serious sequelae. Staphylococcal and streptococcal infections may respond to *tetracycline*. The drugs are third-line agents against these infections. In urinary tract infections, the use of *tetracycline* is limited because of the increasing number of resistant microorganisms. *Tetracycline* may be beneficial in the treatment of acne.

The various tetracyclins include: *Oxytetracycline*, *Tetracycline*, *Doxycycline*, *Methacycline*. **Minocycline** - absorption of this drug is not impaired by food or calcium ion. **Doxycycline:** increased absorption of *doxycycline* allows once-daily administration after the first day; as with *minocycline*, food and calcium ions do not affect absorption; as opposed to the other tetracycline 1,90% of this drug is excreted in the feces; therefore, it does not accumulate in the blood of patients with compromised renal function. Thus, it is one of the safest tetracycline 1 for use against extrarenal infections in patients with renal dysfunction. *Minocycline* penetrates through the BBB due to effective in meningitis. **Adverse effects:** Hypersensitivity reactions, including skin rash and drug fever, can occur. Cross-sensitivity among the various *tetracyclins* is common. When *tetracycline* are administered orally, gastrointestinal irritation is common. The intravenous administration of *tetracycline* often produces thrombophlebitis due to local irritation. Intramuscular injections are painful, cause local irritation, and result in poor absorption of the drugs. High doses of *tetracycline* can produce hepatic dysfunction. This reaction is exacerbated during pregnancy. Children receiving *tetracycline* may develop yellow-brown discoloration of the teeth and suffer depressed bone growth. The drugs are deposited in the teeth and bones because of their chelating properties and form a tetracycline-calcium orthophosphate complex. Discoloration of the permanent teeth can result, however, from the administration of *tetracycline* at any time between the ages of 2 months and 7 years, the period of tooth calcification. *Tetracycline* treatment during pregnancy can produce teratogenic effect. The ingestion of outdated and degraded tetracycline can result in Fanconi syndrome (renal tubular dysfunction, which can lead to renal failure). *Tetracycline* can cause increased intracranial pressure, especially in infants. Vestibular toxicity can occur in *minocycline* therapy. Disbacteriosis and superinfection is a significant problem, which can result in staphylococcal enterocolitis, intestinal candidiasis, and pseudomembranous colitis.

Laevomycetin (Chloramphenicol)

Laevomycetin is a nitrobenzene derivative, the antimicrobial drugs selectively inhibit bacterial protein synthesis, influence 50S ribosomes.

Mechanism of action: *Laevomycetin* inhibits protein synthesis by acting on the 50S ribosomal subunit, a site of action shared with macrolide antibiotics and clindamycin. *Laevomycetin* indirectly inhibits transpeptidation (catalyzed by peptidyl transferase) by blocking the binding of the aminoacyl moiety of the charged tRNA molecule to the acceptor site on the ribosome-mRNA complex. Thus, the peptide at the donor site cannot be transferred to its amino acid acceptor. This drug is primarily **bacteriostatic**, although it may be bactericidal to some strains. **Pharmacokinetics:** *Laevomycetin* is absorbed rapidly from the gastrointestinal tract. The drug undergoes enterohepatic cycling and a small fraction of the dose is excreted in the urine unchanged. Most of the drug is inactivated by a hepatic glucuronosyltransferase. It is widely distributed in body fluids and reaches therapeutic levels in cerebrospinal fluid. It is also present in bile, milk, and aqueous humor. *Laevomycetin* is metabolized in the liver by glucuronyl transferase. Its metabolites are excreted in the urine.

Pharmacologic effects: *Laevomycetin* has a fairly wide spectrum of antimicrobial activity, including: many gram-negative organisms (e.g. it is bactericidal for *H. influenzae*); anaerobic organisms, such as *Bacteroides* species (e.g. *B. fragilis*); some strains of *Streptococcus* and *Staphylococcus* (at a high antibiotic concentration); species of *Clostridium*, *Chlamydia*, and *Mycoplasma*; rickettsiae in which it suppresses growth. *P. aeruginosa* is resistant.

Therapeutic uses: Potentially severe toxicity limits the use of *laevo-mycetin* to those infections which cannot be treated effectively with other antibiotic agents. When another agent is as efficacious as *laevomycetin* and potentially less toxic, the other agent should be used, *laevomycetin* is the drug of choice for typhoid fever. Bacterial meningitis caused by *H. influenzae* is effectively treated. Most anaerobic infections respond to *laevomycetin*. Rickettsial diseases and brucellosis can be treated with *laevomycetin*; however, *tetracyclins* are the preferred

agents.

Adverse effects: Hypersensitivity reactions can occur. It may inhibit leucopoiesis and erythropoiesis. The most important effect, which may be related to hypersensitivity, is bone marrow depression, resulting in pancytopenia. Dose-dependent, reversible blood dyscrasias may also occur. Super-infections can occur, including oropharyngeal candidiasis and acute staphylococcal enterocolitis. Gastrointestinal upset can occur, and, as with many of the other broad-spectrum antibiotics, the possibility of diarrhea due to superinfection must be differentiated from local irritation effects. **Gray-baby syndrome** - this condition is seen in neonates, especially premature infants, who have been given relatively large doses of *laevomycetinum*. Cyanosis, respiratory irregularities, vasomotor collapse, abdominal distention, loose green stools, and an ashen-gray color characterize this often fatal syndrome. The condition develops because of the immature hepatic conjugating mechanism and the inadequate mechanism for renal excretion in neonates. The main drugs of laevomycetins are *laevomycetinum*, *laevomicetini stearas* (lacks bitter taste), *laevomycetini succinas* (for parenteral administration) *Linimentum synthomycini*, *laevomecolum*, *iruxolum* are designated for local administration.

Macrolides and Azalides

Macrolides and azalides are divided in two generations:

1. **First generation:** *Erythromycinum*, *Oleandomyciniphosphas*,
2. **Second generation:** *Azithromycinum* (azalide), *Clarithromycinum*, *Roxithromycinum*, *Spiramycinum*, *Diozamyacinum*, *Midecamycinum*.

The macrolide antibiotics (***erythromycinum*, *azithromycinum*, and *clarithromycinum***) are large cyclic lactone ring structures with attached sugars. *Erythromycinum*, *Oleandomycin sulfas*, *spiramycinum*, *djozamyacinum*, *midecamycinum* are native antibiotics. *Azithromycinum*, *clarithromycinum*, *roxithromycinum* are semisynthetic antibiotics. These group of antibiotics have low toxicity, may penetrate into cell. They have bacteriostatic type of action predominantly but in high concentrations they have bactericidal influence on gram-positive pneumococci, diphtheria and diphtheria pathogens. They have high activity on gram-positive cocci (streptococci, staphylococci) and intracellular microorganisms (chlamidia, mycoplasma). They can create high concentrations intracellular.

Erythromycinum is a macrolide antibiotic. *Erythromycinum* is absorbed slowly. Other drugs have good oral bioavailability, but *azithromycinum* absorption is impeded by food. Macrolides distribute to most body tissues, but *azithromycinum* is unique in that the levels achieved in tissues and in phagocytes are considerably higher (10-fold to 100-fold) than those in the plasma. The elimination of *erythromycinum* (via biliary excretion) and *clarithromycinum* (via hepatic metabolism and urinary excretion of intact drug) is fairly rapid (half-life 2-5 hours). *Azithromycinum* is eliminated slowly (half-life 2-4 days), mainly in the urine as unchanged drug. **Mechanism of action:** *Erythromycinum* and other macrolides inhibit bacterial protein synthesis by binding to 50S ribosomal subunits of sensitive microorganisms; they are usually **bacteriostatic** but can be bactericidal in certain situations. *Erythromycinum* has activity against many species of campylobacter, chlamydia, mycoplasma, legionella, gram-positive cocci, and some gram-negative organisms. The spectrums of activity of *azithromycinum* and *clarithromycinum* are similar but include greater activity against chlamydia, *M. avium* complex, and toxoplasma. *Clarithromycinum* influences *Helicobacter pylori*. *Azithromycinum* is more active against *H. influenzae*, *M. catarrhalis* and *Neisseria*, more active than *erythromycinum* according to gram-negative infections. Resistance to the macrolides in gram-positive organisms involves production of a methylase which adds a methyl group to the ribosomal binding site. Resistance in enterobacteria is the result of formation of drug-metabolizing esterases. Cross-resistance between the individual macrolides is complete. Macrolides blocks translocation of peptidyl-tRNA from the acceptor site to the donor site. Incoming charged tRNA cannot access the occupied acceptor site, so the next amino acid cannot be added to the nascent peptide chain. Macrolides may also block formation of the initiation complex. *Spiramycinum*, *djozamyacinum*, *midecamycinum* influence streptococci resistance to *erythromycinum*.

Therapeutic uses: Macrolides are useful for patients who are allergic to *penicillinum* when the infecting organism is sensitive to macrolides, particularly in cases of infection with group A *S. pyogenes* and *S. pneumoniae*, *Cornebacterium diphtheria*. Pneumonia due to *Mycoplasma* organisms is effectively treated. Legionnaires' disease is treated with *erythromycinum*. Topical *erythromycinum* preparations are used to treat acne. New macrolides have similar indications for use with some addition of oral uses. *Azithromycinum* is very active in the treatment of urogenital infections. *Clarithromycinum* is used in a combined therapy of ulcer diseases.

Adverse effects: *Erythromycinum* has a very low incidence of serious side effects. Cholestatic hepatitis occurs in adults treated for a week or longer with the estolate form. Hepatitis can also occur with the ethylsuccinate and possibly with the stearate. The hepatitis is uncommon and is reversible. Epigastric distress can occur. A high incidence of thrombophlebitis occurs when *erythromycinum* is administered intravenously, even when the drug is dissolved in a large fluid volume. Superinfection can occur. Transient deafness has been reported, especially with high doses. The macrolides may cause diarrhea and allergic reactions.

Lincosamides

The lincosamides include *lincomycinum* and *clindamycinum*, both of which inhibit protein synthesis. They bind to the 50S ribosomal subunit and block peptide bond formation.

Lincomycinum and *clindamycinum* have bacteriostatic type of action.

Pharmacokinetics: Though in high concentration may have bacteri-cide influence on gram-positive cocci. They penetrate most tissues including bone. They also concentrate in phagocytic cells, pass through the placental barrier. They are metabolized in liver and are excreted in the urine. If renal function is unpaired the amount of drugs is excreted with feces. **Pharmaco-dynamics:** They are very active against staphylococci and streptococci and obligate anaerobic pathogens. *Clindamycinum* is more active in influence on toxoplasma and PI. malariae.

Therapeutic uses: They are used to treat infections of respiratory organs, urinary tract, anaerobic abdominal infections caused bacteroids. *Clindamycinum* is also used in ulcer disease. *Spiramycinum* is also used in toxoplasmosis and gonorrhea.

Adverse effects: Pseudomembranous colitis can occur, resulting in diarrhea, abdominal pain, fever, and mucus and blood in the stools. They may cause allergic reactions. This potentially fatal condition, caused by *C. difficile*, can be treated with *vancomycinum*.

Glycopeptides

Vancomycinum is a bactericidal glycoprotein which binds to the D-Alu=I)-Ala terminal of the nascent peptidoglycan pentapeptide side chain and inhibits transglycosylation. This action prevents elongation of the peptidoglycan chain and interferes with cross-linking. **Pharmacokinetics:** *Vancomycinum* is not absorbed from the gastrointestinal tract and may be given orally for bacterial enterocolitis. When given parenterally, vancomycinum penetrates most tissues and is eliminated unchanged in the urine. Dosage modification is mandatory in patients with renal impairment. *Fosfomycinum* is excreted by the kidneys, with urinary levels exceeding the **minimal inhibitory concentrations (MICs)** for many urinary tract pathogens.

Pharmacodynamics: *Vancomycinum*, *Teicoplaninum*, *Fosfomycinum*, *Bacitracinum*, *Cydoserinum* are bacteriostatic against staphylococci, streptococci, and enterococci, *Corynebacterium diphtheriae*, *Clostridium tetani*, *Clostridium perfringens*. *Fosfomycinum* is an antimetabolite inhibitor of cytosolic enolpyruvate transferase. This action prevents the formation of JV-acetylmuramic acid, an essential precursor molecule for peptidoglycan chain formation. Resistance to fosfomycin occurs via decreased intracellular accumulation of the drug. *Bacitracinum* is a peptide antibiotic which interferes with a late stage in cell wall synthesis in gram-positive organisms. Because of its marked nephrotoxicity the drug is limited to topical use.

Bacitracinum is a cyclic peptide mixture. It is active against gram-positive microorganisms. *Fosfomycinum* inhibits in very early stage of bacterial cell wall synthesis, it is active against both gram-positive and gram-negative microorganisms.

Therapeutic uses: *Vancomycinum* is used for treatment infections caused by staphylococcus resistant to others antimicrobial drugs (pseudo-membranous enterocolitis caused by *Clostridium difficile*). *Teicoplaninum* is very similar vancomycinum in mechanism of action and antibacterium spectrum. *Bacitracinum* is used in skin and soft tissue infections. *Fosfomycinum* is used for monotherapy of lower urinary tract infection in women, it is safe in pregnancy.

Adverse effects of *vancomycinum* include chills, fever, thrombophlebitis, ototoxicity, nephrotoxicity, and hypersensitivity. Rapid intravenous infusion may cause diffuse flushing ("red man syndrome").

In a single dose, the drug is less effective than a 7-day course of treatment with fluoroquinolones. With multiple dosing, resistance emerges rapidly and diarrhea is common. *Fosfomycinum* may be synergistic with p-lac-tam and quinolone antibiotics in specific infections.

Cydoserinum: *Cydoserinum* is an antimetabolite which blocks the incorporation of D-Ala into the pentapeptide side chain of the peptidoglycan. Because of its potential neurotoxicity (tremors, seizures, psychosis), *Cydoserinum* is only used to treat tuberculosis caused by organisms resistant to first-line antituberculous drugs.

Polypeptides Polymyxins

Pharmacokinetics. *Polymixinum Msulfas* is for orally administration and *Polymyxinum B sulfas* is for parenteral administration. They influence gram-negative bactericidity. They are used in case of urinary and intestines infections. They may call allergy, toxic influence on kidneys.

Mechanisms: The polymyxins are polypeptides which are bactericidal against gram-negative bacteria. These drugs interact with a specific lipopoly-saccharide component of the outer cell membrane which is also a binding site for calcium. Membrane lipid structure is distorted with an increase in permeability to polar molecules, resulting in marked changes in cell metabolism.

Pharmacodynamics: The spectrum of action includes mainly the gram-negative bacteria (*P. aeruginosa*, salmonella, shigella, escherichia coli, pasteurilla, brucella, *H. mfluenzae* etc.). Gram-positive microorganisms, *Proteus* and *Neisseria* are resistant.

Therapeutic use: Because of toxicity, the clinical applications of the polymyxins are limited to topical therapy of resistant gram-negative infections, including those caused by enterobacter and pseudomonas. These drugs are occasionally administered into infected cavities, the joints and the pleural and peritoneal cavities.

Adverse effects: If absorbed into the systemic circulation, adverse effects include neurotoxicity (paresthesias, dizziness, ataxia) and acute renal tubular necrosis (hematuria, proteinuria, nitrogen retention).

Other Antibiotics

Fusidinum natrium has steroid structure, influences gram-positive microorganism (staphylococcus and

streptococcus). **Streptogramins** (*quinapristinum* and *dalfopristinuni*) are bactericidal for most susceptible organisms. They bind to the 50S ribosomal subunit, constricting the exit channel on the ribosome through which nascent polypeptides are extruded. In addition, transfer RNA (tRNA) synthetase activity is inhibited, leading to a decrease in free tRNA within the cell. They are used for treatment infections in caused by multiple drug resistant strains of pathogens. *Linezolidum* is a new class of synthetic antimicrobials (oxazolidinones).

Linezolidum is mainly bacteriostatic. The drug binds to a unique site on the 50S subunit, inhibiting initiation by blocking formation of the tRNA-ri-bosome-mRNA complex. It is active against gram-positive microorganisms. It exerts modest activity against Mycobacterium tuberculosis. It has high oral bioavailability.

Drug	Drug forms
Benzylpenicillinum-natrium	Flac. 250000 UA, 500000 UA, 1000000 UA
Bicillinum-1	Flac. 300000 UA, 600000 UA, 1200000 UA
Bicillinum-5	Flac. 1 500000 UA
Oxacillinum-natrium	Flac. 0,25, 0,5; tab. 0,25, 0,5
Ampicillini trihydraz	Tab. 0,25, 0,5
Ampicillinum-natrium	Flac. 0,25, 0,5
Amoxycillinum	Caps. 0,25, 0,5
Cefaloridinum	Flac. 0,25, 0,5, 1
Cefazolinum (Kefzol)	Flac. 0,25, 0,5, 1,2,4
Cefataximum (Claforan)	Flac. 0,5, 1,2
Cefpiromum (Keiten)	Flac. 1,0
Ceftriaxonum natrium	Flac. 1,0
Tienam	Flac. 60ml, 100ml
Asactam	Flac. 0,5, 1; Flac. 15ml, 100ml
Tetracyclinum	Tab. 0,05, 0,1,0,25
Tetracyclini hydrochloridum	Ung. 10,0; Flac. 0,1; tab. 0,1,0,25
Methacyclini hydrochloridum	Caps. 0,15, 0,3
Doxycylinum	Tab. 0,5, 0,1
Neomycini sulfas	Ung. 1%,2%- 15,30; Flac. 0,5; tab. 0,1,0,25
Gentamycini sulfas	Flac. 0,08; amp. 4% - 1, 2ml; ung. 0,1% -10
Erythromycinum	Tab. 0,1 (100000 UA); 0,25 (250000 UA); Caps. 0,1 (100000 UA), 0,2 (200000 UA); Ung. 3, 7, 10, 15, 30 (1,0 - 10000 UA)
Spiramycinum (Rovamycinum)	Tab. 1,5 (3000000 UA); Gran. 1500000 UA, 750000 UA, 375000 UA; Flac. 1 500000 UA
Azithromycinum	Tab. 0,5; Caps. 0,125, 0,25; Sirupus 0,02, 0,04 -1ml
Fusidinum-natrium	Tab. 0,125, 0,25
Lincomycini hydrochloridum	Caps. 0,25; Amp. 30% 1ml, 2ml
Polymyxini M sulfas	Flac. 500000 UA, 1000000 UA; Tab. 500000 UA; Linimentum 30 (1 - 10000)
Polymyxini B sulfas	Flac. 250000 UA, 500000 UA
Rifampicinum	Caps. 0,15, 0,3
Nystatinum	Tab. 500000 UA; Supp. 500000 UA; Ung. 15, 30 (100000 UA- 1,0)
Amphotericinum B	Flac. 50000 UA; ung. 15, 30 (30000 UA- 1,0)
Griseofulvinum	Tab. 0,25; Susp. 100 ml; Linimentum 2,5% - 30
Umcalor	Flac. 20, 50ml

Materials for students' self-directed work.

A. Tests for self-control:

Student must:

1. To expound classification of antibiotics in accordance with chemical structure, to the mechanism and character of action.
2. To expound the mechanism of antibacterial action of penicillins, cephalosporins, carbapenems.

3. To expound the mechanism of antibacterial action of macrolides, lincosamides.
4. To expound the mechanism of antibacterial action of tetracyclines.
5. To make the chart of treatment of odontogenic osteomyelitis.
6. To make the chart of treatment of infectious-inflammatory processes, caused by staphylococcus.
7. To make the chart of treatment of infectious-inflammatory processes, caused by gram-negative microflora.
8. To make the chart of treatment of infectious-inflammatory processes, caused by anaerobic microflora.

B. Tests for self-control:

1. Name preparation having bactericidal action:
 - a) ampicillinum;
 - b) erythromycinum;
 - c) furadoninum.
2. For the mechanism of action of what antibiotics depressing of synthesis of albumen is typical?
 - a) lincomycinum;
 - b) penicillin;
 - c) cephasolinum.
3. What antibacterial preparation influences negatively upon the function of kidneys:
 - a) polymixin B;
 - b) penicillin;
 - c) erythromycinum.
4. What antibacterial agents have expressed influence upon anaerobic microflora:
 - a) clindomycinum;
 - b) cephasolin;
 - c) ampicillin.
5. Name antibacterial agents which operate upon staphylococcus, which excrete penicillinase:
 - a) ampicillinum;
 - b) oxacillinum;
 - c) cephasolinum.
6. What antibiotics have the allergic reactions?
 - a) macrolides;
 - b) penicillins;
 - c) aminoglycosides.
7. To ground the choice of antibiotics for treatment of osteomyelitis.
8. What preparations have the potential hepatotoxic action?
 - a) streptomycinum;
 - b) penicillins;
 - c) tetracyclines;
 - d) cephalosporins.
9. Define antibacterial preparations which have anti-pseudomonas activity:
 - a) gentomycinum;
 - b) amycacinum;
 - c) ceftasidimum.
10. Define and ground rationality of combinations:
 - a) penicillins and aminoglycosides;
 - b) macrolides and tetracyclines;
 - c) cephalosporins and penicillins;
 - d) lincomycinum and macrolides.

Recommended literature:

Basic (studying):

1. Pharmacology: textbook / V.M. Bobyrov, T.O. Devyatkina, O.M. Vazhnicha, V.M. Khristyuk. – Vinnytsia: NOVA KNYHA Publishers, 2010. – 520 p.
2. Chekman I.S., Gorchacova N.O., Panasenko N.I., Bech P.O. Pharmacology. – Vinnytsia: NOVA KNYHA Publishers, 2006. – 384 p.
3. Samura B.B. Clinical pharmacology: Manual. - Vinnitsa, 2010. – 283 p.

Additional:

1. Basic and Clinical Pharmacology by Anthony J. Trevor, Bertram G. Katzung, Susan B. Masters, 2009.

2. Medical Pharmacology at a Glance by Michael J. Neal, 2009.
3. Introduction to Clinical Pharmacology by Marilyn W. Edmunds, 2009.
4. Introduction to Clinical Pharmacology by Marilyn W. Edmunds, 2009.
5. Introductory Clinical Pharmacology by Sally S. Roach, Susan M. Ford, 2008.

Web sources:

1. <http://cardio.medi.ru/66.htm/>
2. <http://eurheartj.oxfordjournals.org/>
3. <http://intl-ajrcm.atsjournals.org/>
4. <http://thorax.bmjournals.com/>
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21. <http://www.thoracic.org/>
<http://www.zheludok.ru/>

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