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Sumy State University

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CHEMOTHERAPEUTIC DRUGS

Course of Lectures on Pharmacology

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Antiseptics and Disinfectant Drugs

According to statistics, about 40–50 % of all human diseases are caused by different parasites (bacteria, spirochetes, rickettsia, chlamydia, fungi, viruses, and protozoa which account about 1,000 cpecies). Besides, diseases may be caused by helminths and arthropods. Drugs, which are used to combat human pathogens, are divided into 2 groups:

– antiseptics and disinfectant drugs;

– chemotherapeutic drugs.

Antiseptics are used to combat human pathogens on the body surface (skin and mucosa). Sometimes, antiseptics are used to combat human pathogens in gastrointestinal and urinary tracts.

Disinfectant drugs are used to destruct pathogens in the environment: disinfection of medical instruments, medical supplies for nurses, dishes, clothes, rooms, and patient care equipment.

Antiseptics and disinfectants should have marked antibacterial and antiparasital effect. Simultaneously, these agents should be safe for human, don't irritate tissues, and don't damage instruments.

Division of drugs into antiseptics and disinfectants is somewhat relative, because some antiseptics in high concentrations are used for disinfection of the environment.

Chemotherapeutic agents are used to combat human pathogens into the organism. These drugs have high selective action upon certain species of microorganisms. Chemotherapeutic drugs should not affect the main functions of human organism. These drugs are used to prevent and treat infections. It should be noted that some chemotherapeutic drugs may be used as antiseptics (e.g., furacilinum).

According to chemical structure, antiseptics and disinfectants are classified into the following groups:

1. Detergents: *cerigelum, aetonium, chlorhexidine, benzalconium chloride*, etc.

2. Nitrofuran derivatives: *furacilinum (nitrofural).*

3. Phenol group: *phenol, resorcin, lysol, wood-tar,* and *ichthyol*.

4. Stains: *brilliant green, methylene blue,* and *ethacridine lactate (Rivanol).*

5. Halogens:

– chlorine compounds: *bleaching powder, chloramine B,* and *pantocide*;

– iodine compounds: *alcohol solution of iodine, Lugol's solution, iodinol,* and *iodovidonum*.

6. Oxidisers: *hydrogen peroxide* and *potassium permanganate*.

7. Heavy metal compounds:

– silver-containing drugs: *silver nitrate, Protargolum,* and *Collargolum*;

– zinc-containing drugs: *zinc sulfate* and *zinc oxide*;

– copper-containing drugs: *copper sulfate*;

– mercury-containing drugs: *mercury bichloride, yellow mercury oxide,* and *mercury ammonium chloride*;

– bismuth-containing drugs: *bismuth nitrate, xeroform,* and *dermatol*.

8. Alcohols: *ethanol*.

9. Aldehydes: *formaldehyde* and *hexamethylenetetramine (urotropine).*

10. Acids and alkalies: *boric acid, salicylic acid, aqueous ammonium solution,* and *sodium hydrocarbonate solution*.

Detergents

Detergents are synthetic compounds with high surface activity which exhibit the marked antiseptic and detergent (washing) properties. Detergent drugs include organic substances containing two positively charged nitrogen atoms (cationic detergents) and some negatively charged compounds (anionic detergents). Detergent molecules accumulate on the surface of the phase separation. Antibacterial activity of detergents is due to their ability to decrease the surface tension that leads to disruption of cell membrane permeability of microorganisms. The ensuing disturbances of osmotic balance lead to death of microorganisms.

Anionic detergents include such agents as *green soap* and *laundry soap*. These agents are sodium or potassium salts of fatty acids with long hydrocarbon chain. Anionic detergents are less active than cationic detergents. Anionic detergents are used for laundry, wet cleaning, handwashing, disinfection, etc. Green soap is a component of Wilkinson's ointment.

Cationic detergents exhibit bactericidal effect against bacteria, fungi, viruses, and some protozoa. It should be noted that activity of cationic detergents decreases in protein environment (e.g., presence of pus). Cationic detergents include such agents as *cerigelum, miramistin,*

chlorhexidine, etc. These agents are used for surgical hand preparation; disinfection of operative field and instruments; washing bladder, wounds, infected cavities, etc. Cationic detergents cannot be combined with anionic ones, because the antimicrobial activity reduces due to such combination.

Nitrofuran Derivatives

Nitrofuran derivatives exhibit high antimicrobial activity and low toxicity. Thereby, these agents are used as both antiseptics and chemotherapeutic drugs. Drugs exhibit bacteriostatic or bactericidal effects depending on the doses used. Mechanism of nitrofuran's action is based on ability of their nitro groups to reduce into amino groups. Nitrofurans compete with natural hydrogen acceptors of microbial cells. Due to this ability, the agents slow down the cellular respiration and destroy energetic balance of microorganisms. Spectrum of antimicrobial action of nitrofurans includes gram-positive and gram-negative bacteria, fungi, and protozoa (chlamydia, giardia, and trichomonas).

Furacilinum (nitrofural) and *furazolidone* are derivatives of nitrofuran used as antiseptics. Water solution of furacilinum is used to treat wounds, burns, otitis; for nasal and pleural lavage. Eye drops with furacilinum are used to treat conjunctivitis and blepharitis. Sometimes, furacilinum is used in dysentery treatment. Furacilinum is a component of such drugs as *Furaplastum* and *Liphuzol*. Furaplastum is used to treat wounds and minor skin injuries (bruises, scratches, cracks, etc.). The agent forms protective layer on the damaged surface and improves healing. Liphuzol, the drug aerosol, is used to treat wounds.

Antibacterial activity of *furazolidone* against gram-negative bacteria, giardia, and trichomonas is significantly higher than activity of furacilinum. Furazolidone is used mainly as chemotherapeutic agent.

Side effects of nitrofurans are dyspepsia, headache, disiness, and allergic reactions.

Phenol Group

Phenol is the oldest antiseptic agent. It is used as a standard to estimatie activity of other antiseptics and disinfectants. Phenol in low concentrations exhibits bacteriostatic effect. Phenol in high (1–5 %) concentrations has bactericidal effect. Phenol destroys the permeability of the cell membrane and blocks the activity of dehydrogenase. The agent has a wide spectrum of action. Proteins do not reduce the activity of phenol.

Phenol easily penetrates through skin and mucous memranes. Poisoning by phenol is manifested by disiness, weekness, dyspnea, tachycardia, sweating, and sonitus. Collapse and significant disturbances of respiration develop in severe cases. If phenol was taken perorally, a poisoned patient needs gastric lavage with vegetable oil. Affected regions of skin should be washed by 50 % ethyl alcohol or vegetable oil. In case of central nervous system depression, stimulating agents should be administered.

Phenol in form of 2–5 % carbolic-soap mixture is used to disinfect rooms, supplies for nurses, clothes, and places contaminated with feces. With the same end in view, lysol and tricresol are used in medicine.

Vagothyl is a 36 % water solution of polyethylene-metacresol-sulfonic acid. The drug exhibits bactericidal effect and high activity against trichomonads. Vagothyl is used to treat cervical erosion, bladder diseases, and ulcers of lower extrimities.

Phenyl salicylate is a phenyl ester of salicylic acid. In intestine, this agent is cleft with formation of phenol and salicylic acid. The drug is used to treat infective diseases of bowels, bile ducts, and urinary tract.

Resorcin is a derivative of phenol. Resorcin exhibits both keratoplastic (in concentrations about 2 %) and keratolytic (in concentrations about 20 %) effects. The drug is used to treat seborrhea, eczema, herpes, ringworm, etc.

Wood tar and *ichthyol* are agents which are also containing phenol and its derivatives. These drugs are widely used to treat bacterial and parasitic skin diseases. Ointments and liniments with wood tar are used to treat eczema, psoriasis, furunculosis, etc. Wood tar is included in *Vishnevsky ointment* (tretment of wounds, burns, ulcers, and bedsores) and *Wilkinson ointment* (treatment for scab and fungal diseases).

Thymol is a phenol derivative which is included in aerosol *Gexaspray* and in pastilles *Septolete* and *Hexadreps*. These drugs are used to treat the diseases of throat and pharynx.

Dyes

Soluble dyes include such colouring agents as *brilliant green, ethacridine lactate,* and *methylene blue (Rivanol).* Dyes occupy the intermediate position between antiseptics and chemotherapeutic drugs. Dyes have certain selectivity against microorganisms and are sometimes used for resorptive action. All agents are effective in treatment for coccal

infections. The dyes are characterised by low toxicity. They affect the permeability of bacterial cell membranes which causes osmotic disbalance and lysis of microorganisms. Besides, dyes inhibit the activity of catalase, galactosidases, and other enzymes.

Brilliant green is active against staphylococci, corynebacterium diphtheriae, and other gramm-positive bacteria. This agent is used as 1–2 % alcoholic (or water) solution for the lubrication of wounds, pustular skin lesions, blepharitis, etc.

Methylene blue is characterised by less antibacterial activity than brilliant green. But the agent exhibits antimycotic activity. Ability of methylene blue to attach and release hydrogen atoms is used in the treatment of poisoning by cyanides. In this case, 50–100 ml of a 1 % solution of the drug is administered intravenously. Methylene blue transforms hemoglobin into methemoglobin. The latter substance interacts with cyanides to form non-toxic cyanmethemoglobin. Also, methylene blue is used to treat burns, cystitis, uretritis, to wash body cavities, etc.

Ethacridine lactate (Rivanol) is a bacteriostatic agent with slowly developing effect. Rivanol is used in ointments, pastes, and solutions for external application. Therapeutic indications for Rivanol are purulent wounds, burns, washing body cavities, etc. Ethacridine lactate is a non-toxic agent.

Halogen-Containing Drugs:

Chlorine-Containing Drugs

Chlorine-releasing agents are *chloramine B*, *chlorhexidine*, and *household bleach*. These agents have high antimicrobial activity and broad spectrum of action. Chlorine-containing drugs are active against bacteria, viruses, and amoeba. Acid-fast bacilli (e.g., *Mycobacterium tuberculosis*) are less sensitive to chlorine-containing drugs. In an aqueous environment, chlorine-containing compounds decompose with the release of atomic chlorine which interacts with cytoplasmatic proteins of microorganisms. In proteins, chlorine ions replace the hydrogen ions that makes hydrogen bond formation between polypeptide chains impossible. Due to this fact, secondary structure of proteins is disrupted. Chlorine-releasing agents also have deodorizing properties. Most agents are used as disinfectants.

Chloramine B is used as an antiseptic. Its effect develops slowly and lasts for a long time. Chloramine B has also antimycotic activity. The agent

is used to wash infected wounds, operative field, and hands. Chloramine B is also used in disinfection of instruments and rooms.

Chlorhexidine is one of the most effective antiseptics. Water and alcoholic solutions of chlorhexidine are used to sterilize instruments, wash wounds, burns, bladder, and hands. The agent is also used in room disinfection.

Iodine-Containing Drugs

Action mechanism of iodine-containing drugs develops due to interaction of N-groups of proteins with iodine. This interaction leads to coagulation of microorganism proteins. Antibacterial spectrum of iodine-containing drugs is very broad. Iodine-containing drugs are used as both antiseptics and agents for resorptive action. Thus, radioactive iodine is used in diagnostics and treatment of thyroid gland diseases. Radioactive iodine compounds are used to diagnose liver, kidney, bronchi, uterus, and vessels diseases.

Alcoholic iodine solution is used in disinfection of a surgeon's hands and an operative area, in the fungal diseases treatment, and in lubrication of wounds. Besides, distracting effect of this agent is used in treatment for myositis and neuralgia.

Lugol's solution contains iodine in water solution of potassium iodide. The drug is used in mucous membranes of pharynx and larynx treatment.

Today, complex compounds of iodine with macromolecular surfactants are introduced in medicine: *Iodinol, Iodovidonum, Iodonatum*, etc. These compounds are called iodophors. Their advantage over alcoholic iodine solution is that these agents are water-soluble and have high bactericidal and absorptive activity, don't irritate skin and don't provoke the allergic reactions. Iodophores are used to cleanse mucous membranes of mouth and nasopharynx, to disinfect an operative area, treat wounds, burns, ulcers, etc.

Ioddicerinum is a mixture of iodine, dimexidum, and glycerine. The drug has a broad spectrum of antimicrobial actions. Ioddicerinum is used in the treatment of infections of skin, mucous membranes, wounds, etc., caused by *Staphylococcus*, meningococci, *Neisseria gonorrhoeae*, *Klebsiella*, *Shigella*, *Proteus*, virus of herpes and varicella zoster, *Chlamydia*, etc.

Oxidizers

Group of oxidizers contains *hydrogen peroxide* and *potassium permanganate*. Oxidizers change redox potential and therefore violate the normal physiological redox processes in microorganisms.

Under the influence of catalase, hydrogen peroxide decomposes with the release of molecular oxygen which exhibits low antimicrobial activity. Also, the process of decomposition is accompanied by formation of significant amount of foam. This foam washes away pus, blood clots, and dead tissue from the wounds. Therefore, hydrogen peroxide cleans the wounds. A 3% hydrogen peroxide solution is used to rins the mouth and throat, in treatment of purulent otitis media, and to stop nasal bleeding (release of oxygen accelerates the transformation of fibrinogen into fibrin).

Potassium permanganate exhibits higher antiseptic activity because it releases atomic oxigen which oxidizes biological substances. Also, potassium permanganate causes astringent, irritative, deodorant, and cauterizing effects. Potassium permanganate is used in gastric lavage in treatment of poisoning (0.02–0.1 % solutions) caused by poisons which are oxidized by potassium permanganate (e.g., morphine); in cleaning wounds, washinh urethra and vagina (0.01–0.5 % water solutions); in treatment of burns (2–5 % water solutions).

Heavy Metal Compounds

Heavy metals (silver, mercury, copper, bismuth, etc.) interact with proteins of microbial cells with the formation of albuminates. Heavy metals preparations exhibit the fast and marked bactericidal effect. Some drugs have atypical for other antiseptics activity against certain microorganisms. Thus, mercury and bismuth preparations are active against Treponema pallidum, silver preparations – against cocci.

Mechanism of action of heavy metal preparations is the following: ions of metal interact with SH_2-groups of proteins. Inactivation of SH-containing enzymes needs significantly less metal concentrations in cells than necessary for protein coagulation. This inactivation results in disruption of bacterial cell metabolism and growth inhibition of microorganisms. Besides, heavy metal salts influence proteins of skin and mucous membranes. Depending on concentration and the type of metal, the following effects can develop on the place of drug application: astringent, irritative, or cauterizing. These effects are based on the ability of salts to interact with tissue proteins with the formation of albiminates. The

interation with only superficial layers of skin and mucosa is accompanied by formation of dense albuminates preventing the penetration of ions into the deep layers of tissues. In this case, the astringent effect develops. In case of loose albuminate formation, metal ions penetrate into the deep layers of tissues that results in cauterizing effect on the tissue, accompanied by tissue damage (necrosis). Prof. Schmiedeberg made up a list of metals based on albuminate density:

Pb, Al, ... Fe, Cu, Zn, ... Ag, Hg.

Metals which are located in the left part of this list have mainly astringent and irritative actions. Metals which are located in the right part of Schmiedeberg's list have cauterizing action. Metals which are located in the middle part of the list can exhibit all these actions in dependence on their concentration.

In the human organism, salts of heavy metals are distributed irregularly: the most of the drug is accumulated in bones, liver, kidneys, and bone marrow. Slow ellimination of heavy metal salts is carried out by kidneys, sweat and salivary glands, and gastrointestinal mucosa.

Silver-containing drugs are *silver nitrate, protargolum (silver proteinate)*, and *colargolum (colloidal silver)*. These drugs have antibacterial, astringent, and anti-inflammatory actions.

Silver nitrate 1–2 % solution is used in the treatment for conjunctivitis. Silver nitrate 5–10 % solution or sticks are used in the treatment of trachoma, skin ulcers, erosion, and hypersarcosis. Protargolum and colargolum are used to treat conjunctivitis, rhinitis, urethritis, and chronic cystitis.

Zinc and copper salts have astringent, iritative, cauterizing, and antibacterial actions. *Copper sulfate* is used to treat conjunctivitis, uretritis, and vaginitis. Ophthalmic pencils with copper sulfate are used in the treatment of trachoma. Eye drops with *zinc sulfate* and *copper sulfate* are used in the treatment of conjunctivitis. Also, zinc sulfate solutions are used in the treatment for laryngitis, vaginitis, and urethritis. Zinc sulfate is the part of the dusting powders, ointments, and pastes.

Water-soluble aluminum preparations have an astringent, anti-inflammatory, and antibacterial actions. Insoluble aluminum salts have an absorptive capacity.

The preparations of lead are used as astringent and antibacterial agents in the treatment for pyderma, furunculosis, and carbuncles.

Mercury dichloride and *yellow mercury oxide* are used as antiseptics. Mercury dichloride is easily soluble in water and has high antibacterial activity. The agent is used to disinfect dishes, premises, etc. Mercury dichloride isn't used to disinfect metal surfaces because it causes metal corrosion. For skin disinfection, mercury dichloride is used seldom due to high irritant effect. Eye ointment with yellow mercury oxide is used to treat conjunctivitis and keratitis.

Bismuth preparations have no astringent and cauterizing effects. Antibacterial effect of bismuth salts is manifested due to blockage of HS-groups of bacterial enzymes. Bismuth, also, has an antidiarrheal effect due to its ability to bind hydrogen sulfide in the intestine. Bismuth-containing drugs (*dermatol* and *xeroform*) are used for treatment of the skin diseases (ulcers, eczema, and dermatitis). Also, bismuth-containing drugs are used as chemotherapeutic agents to treat stomach ulcer and syphilis.

At present, heavy metal salts are used seldom.

High concentrations of heavy metal salts can cause acute poisoning with the initial excitation replaced by inhibition in the central nervous system. Simultaneously, the cardiac depression and paralytic dilation of capillaries are observed (especially caused in abdominal cavity).

Chronic poisoning may be caused due to constant intake of heavy metal salts.

The constant contact with lead or its salts can cause the chronic poisoning (saturnism) due to the accumulation of lead, mainly in bone tissue. Interaction between lead and hydrogen sulfide in the oral cavity causes formation of lead sulfide which forms the gray film on the gums. Later, blood disorders (anemia), abdominal pain attacks (lead colic), and damage to the peripheral nervous system (lead polyneuropathy) are observed. Lead polyneuropathy is characterized by a primary lesion of the motor fibers of peripheral nerves with the development of lead paralysis. The antidote – metal-complexing agent tetacinum-calcium – is used to treat lead poisoning. The drug is administered intravenously drop-by-drop. Besides, the drug is taken orally in dose 0.5 g 4 times a day. The treatment of acute lead poisoning includes subcutaneous administration of atropine sulfate solution 0.1 %, subcutaneous omnoponum, intravenous sodium bromide, and rectal delivery of magnesium sulfate.

Acute poisoning by mercury dichloride is accompanied by abdominal pain, vomiting, diarrhea, excitation of central nervous system with the following depression, and acute cardiovascular failure. In 2–4 days, the

renal failure and lesions of gastrointestinal tract are observed. Unithiol is an antidote to the toxicity of mercury chloride. The drug is administered intramuscularly or subcutaneously. Saline laxatives, activated carbon, astringent agents, milk, and egg white are taken orally. The treatment also includes gastric lavage, forced diuresis, and hemodialisis.

Chronic poisoning by mercury salts is called mercurialism. The following are symptoms of mercurialism: disorders of central nervous system (dementia, tremor), stomatitis, anemia, etc. The treatment of chronic poisoning includes the administration of antidotes (unithiol, tetacinum-calcium, or sodium thiosulfate), the actions to remove the mercury salt from the organism, and symptomatic therapy.

Alcohols

Ethyl alcohol is used in medicine as an antiseptic and disinfectant agent. Ethanol antibacterial activity is defined due to its ability to cause dehydration and denaturation of proteins. Ethyl alcohol is used to disinfect hands of the surger, surgical field, and medical instruments. Disinfection of the skin is more effective if 70 % ethanol is used. Higher concentrations of ethanol have less antibacterial activity in this case because concentrated ethanol seals the epidermis that prevents its diffusion into the ducts of sweat and sebaceous glands. 20–40 % ethanol solutions significantly irritate the skin and, therefore, they are used in compresses and grinding. A 90–95 % ethanol is used to sterilize medical instruments.

Aldehydes

Formaldehyde is a water-soluble gas with a pungent irritating odor. The agent has high antibacterial activity against vegetative and spore forms of bacteria. Formaldehyde interacts with aminogroups of bacterial proteins that results in their dehydration. Formaldehyde (gas and solutions) is used to disinfect rooms, clothes, etc. Dehydrating effects of formaldehyde cause epithelial cell irritation. Mucous membranes are especially sensitive to formaldehyde. Formaldehyde affects the sweat glands and causes dry skin.

Formalin and *hexamethylenetetramine (methenamine, urotropin)* are drugs which contain formaldehyde.

Formalin is a 36.5–37.5 % water solution of formaldehyde. The drug is used to dry the skin of hands, in increased sweating of legs

(0.5–1 % solutions), to sterilize instruments (0.5 %), and to preserve cadaveric material.

Urotropine converts into formaldehyde in an acidic environment. The drug is taken orally (0.05–1.0 g 5 times a day after meal) or administered intravenously (5–10 ml of 40 % solution) for treatment of urinary tract infections. The activity of urotropin against Gram-negative bacteria is restricted. Also, hexamethylenetetramine (Urotropine) is a part of tablets *Calcex*.

Inhalation of concentrated formaldehyde vapors can cause the acute poisoning with lacrimation, sharp cough, and the feeling of chest tightness. Oral intake of formaldehyde results in drooling, epigastric burning, gastric pain, nausea, vomiting, diarrhea, inflammation of the kidneys, loss of consciousness, and convulsions with the following inhibition of nerve centres. The treatment of poisoning includes the gastric lavage with weak *ammonia solution* and intake of covering agents (milk or egg white).

Acids and Alkalis

Antibacterial effect of acids and alkalis manifests itself due to their ability to penetrate (in the form of undissociated molecules) into bacterial cells. In bacterial cells, molecules of acids and alkalis dissociate and cause the denaturation of bacterial proteins. *Boric acid* and *salicylic acid* are used as anticeptics in medicine.

Boric acid is used to treat conjunctivitis, otitis, eczema, dermatitis, colpitis, pyoderma, etc. The following medicinal forms of boric acid are used in medicine: water, alcohol, and glycerol solutions, eye drops, ointments, pastes, and antiseptic powders for external use.

Preparations of salicylic acid have antiseptic, irritating, keratoplastic (in concentrations up to 5 %) or keratolytic (in concentrations 5–10 %) effects. Water and alcohol solutions, ointments and pastes with salicylic acid are used in the treatment of different inflammatory and infectious skin diseases. Indications for its use include burns, blisters, warts, hyperkeratosis, excessive sweating of the feet, hair loss, psoriasis, acne vulgaris, seborrheic dermatitis, eczema, ichthyosis vulgaris, otitis media, etc.

Ammonia solution (contains 10 % ammonia) and sodium hydrocarbonate are alkalis that act as antiseptics. Ammonia solution is used in surgical hand antisepsis. The irritating activity of ammonia solution and ability reflexively stimulate the respiratory center give grounds for use in

syncope. Sodium hydrocarbonate solution has an expressed detergency. The drug is used to rinse mouth and throat in tonsilitis, to wash eyes, and sterilize instruments.

Table 1 – Drugs for prescription

Drug name (Latin)	**Single dose and mode of administration**	**Drug product**
Chlorhexidini bigluconas	For disinfection of skin or mucous membranes 0.05 %, 0.2 %, or 0. solution; for disinfection of surgical field 0.5 % aqueous-alcoholic solution; for disinfection of wounds and burns 0.5 % water solution; for hand disinfection 0.5 % alcoholic or 1 % water solution	0.05 % water solution in bottles 100 ml; 20 % water solution in bottles 100 or 500 ml
Aethonium	For treatment of wounds and ulcers: 0.02–1 % solution or 0.5–2 % ointment; for treatment of keratitis, corneal ulcers, and other eye lesions: 0.1 % eye drops; for treatment of stomatitis: 0.5 % solution; for treatment of dermatitis and burns: 0.5–2 % ointment	Pouder for solution preparation; ointment 0.5 % or 1 % – 25 g
Sol. Iodi spirituosae	For external use	5 % solution in bottles 10, 15 or 25 ml
Ioddicerinum	For external use	Bottles 15 ml
Spiritus aethylicus	For skin preparation 70 % solution; for processing surgical instruments 90 %	Bottles 100 ml
Acidum boricum	Solution or ointment for external use	2–4 % solution; 5–10 % ointment
Sol. Viridis nitentis spirituosae	For external use	1 % or 2 % spirituous solutions

Continuation of Table 1

Drug name (Latin)	Single dose and route of administration	Drug product
Zinci sulfas	1–2 drops in eyes 3–4 times daily	0.25 % or 0.5 % solution of eye drops
Furacilinum	Orally 0.1 g 4 times a day; ointment for external use; solution for washing infected cavities and mucous membranes	Tablets 0.1 g (for oral intake); tablets 0.02 g (for preparation of solutions); ointment 0.2 % – 25 g; water solution 1:5000 (1 part of Furacilinum to 5000 parts of water); alcoholic solution 1:1500
Sol. Hydrogenii peroxydi diluta	For external use	3 % solution in bottles 50 ml
Kalii permanganas	0.1–0.5 % solution for processing of wounds; 2–5 % solution for processing of burns; 0.02–0.05 % solution for gastric lavage	Solutions with different concentrations
Aethacridini lactas	Solutions, ointment and aspersion for external use	0.1 % or 0.2 % solutions; 3 % ointment; 3 % aspersion; 5–10 % paste
Unithiolum	Intramuscularly 0.25–0.5 g 2–4 times daily	Ampoules 5 ml of 5 % solution

Chemotherapeutic Drugs

Antibiotics

Paul Ehrlich is the founder of the modern chemotherapy. In 1907, he suggested the first effective agent for syphilis treatment – salvarsan. In 1932, Gerhard Domagk discovered the antibacterial properties of red streptocid.

The first antibiotic penicillin was discovered by Sir Alexander Fleming in 1929. In 1940, Sir Howard Walter Florey and Ernst Boris Chain produced a pure form of penicillin. In the USSR, the pure penicillin was

produced by Z. V. Yermolyeva and T. I. Balyazina in 1942. The significant amount of natural and synthetic antibacterial drugs have been created in succeeding years. The synthesis of new antibacterial drugs is presently going on.

Chemotherapeutic drugs are characterized by definite spectrum of antibacterial action. One of the requirements for drugs is their low toxicity for humans and animals.

There are the following main principles of chemotherapy:

1. It is necessary to make the precise diagnosis and identify the pathogen and its antibiotic sensitivity.

2. It is necessary to start treatment as early as possible, yet the number of agent is low and the serious lesions of internal organs do not develop.

3. The route of drug administration should be optimal that provides the best drug – pathogen interaction.

4. The drug concentration in human organism should be effective and stable throughout the whole therapy. Sometimes, the knockout dose is prescribed in early treatment to create a necessary effective concentration of the antibacterial agent.

5. The duration of antibacterial therapy should be optimal (the therapy lasts 3–5 days after clinical recovery.

6. The measures to support the body's defences should be provided together with chemotherapy (vitamins, immunomodulators, drugs that support the hepatic and renal functions, etc.).

Chemotherapeutic drugs include the following drug groups:

1. Antibiotics.
2. Sulfonamides.
3. Synthetic antibacterial drugs with different chemical structure (quinolones, fluoroquinolones, hydroxyquinolines, nitroimidazole derivatives, and nitrofurane derivatives).
4. Antifungal drugs.
5. Antiviral drugs.
6. Antiprotozoal drugs.
7. Antisyphylitic drugs.
8. Antituberculosis drugs.
9. Anthelmintic drugs.

Antibiotics are drugs of bacterial origin and their semi-synthetic and synthetic analogues which selectively damage or kill certain microbial species. Antibiotics are classified according to their origin, chemical

structure, mechanism of action, and character of the influence upon bacteria.

Antibiotic classification according to chemical structure is the following:

1. β-lactam antibiotics: penicillins, cephalosporins, monobactams, and carbapenems.
2. Antibiotics containing the macrocyclic lactone rings in molecules: macrolides and azalides.
3. Tetracyclines (antibiotics containing four condensed six-membered rings in molecules).
4. Chloramphenicol drug group.
5. Aminoglycosides (antibiotics containing the aminosugars in molecules).
6. Polypeptides (polymyxins and gramicidin C).
7. Polyenes (amphotericin B, nystatin, and levorin).
8. Glycopeptides (vancomycin and ristomycin).
9. Lincosamides (lincomycin and clindamycin).
10. Ansamycins (rifampicin and rifamycin).
11. Antibiotics with steroidal structure (fuzidin-sodium).
12. Different antibiotics (fusafungine).

According to mechanism of action, antibiotics are classified into the following groups:

1. Antibiotics affecting the synthesis of bacterial cell wall: β-lactams and glycopeptides.

2. Antibiotics affecting the function of bacterial cytoplasmic membrane: polypeptides and polyenes.

3. Antibiotics affecting the synthesis of bacterial proteins: aminoglycosides, tetracyclines, chloramphenicols, macrolides, and lincosamides.

4. Antibiotics affecting the synthesis of nucleic acids: ansamycins.

There are two types of antibacterial action of antibiotics: bactericidal and bacteriostatic. Bactericidal antibiotics affect the synthesis of bacterial cell wall or the function of cytoplasmic membrane; these agents kill the bacteria. Bactericidal antibiotics include β-lactams, glycopeptides, polypeptides, and polyenes. Besides, high doses of aminoglycosides, rifampicin, and chloramphenicol are cases of bactericidal action. Tetracyclines, macrolides, ansamycins, lincosamides, etc. have the

bacteriostatic effect. Bacteriostatic antibiotics affect the growth and division of bacteria.

Depending on the number of bacteria species affected by a drug, antibiotics are divided into the drugs of broad spectrum and the agents of narrow spectrum. The antibiotics of broad spectrum of antibacterial activity include tetracyclines, chloramphenicol, aminoglycosides, cephalosporins, and semisynthetic penicillins, azalides, and macrolides. Narrow spectrum is typical for biosynthetic penicillins, macrolides, lincosamides (these groups are active against gram-positive bacteria), and polymyxines (active against gram-negative flora).

β-Lactam Antibiotics

It is the dominant group of modern antibiotics which includes penicillins, cephalosporins, carbapenems, and monobactams. B-lactams are bactericidal antibiotics. They work by inhibiting cell wall synthesis due to the blockage of transpeptidase (an enzyme that cross-links the peptidoglycan chains to form rigid cell walls). It results in lysis of bacterial cells.

Penicillins

Penicillins are a type of antibiotics that contain the 6-aminopenicillanic acid in the molecules. Natural penicillins are produced by *Penicillium* molds. The semisynthetic penicillins are synthezied due to chemical modification of 6-aminopenicillanic acid.

Penicillins can be classified as follows:

1. Biosynthetic penicillins.

1.1. Drugs for parenteral administration:

- short-acting penicillins: *benzylpenicillin-sodium* and *benzylpenicillin-potassium*;
- long-acting penicillins: *benzylpenicillin novocaine salt, bicillin-1,* and *bicillin-5*.

1.2. Drugs for enteral administration: *phenoxymethylpenicillin*.

2. Semisynthetic penicillins.

2.1. Drugs for both parenteral and enteral administration:

- drugs stable to penicillinase: *oxacillin* and *nafcillin*;
- drugs of broad spectrum (aminopenicillins): *ampicillin* and *amoxicillin*.

2.2. Drugs of broad spectrum for parenteral administration:

– carboxypenicillins: *carbenicillin-disodium* and *ticarcillin*;
– ureidopenicillins: *azlocillin, piperacillin,* and *mezlocillin*.

2.3. Drugs for enteral administration of broad spectrum:
– carboxypenicillins: *carbenicillin indanyl sodium* and *carfecillin*.

Biosynthetic Penicillins

Biosynthetic penicillins are drugs of narrow antibacterial spectrum which include mainly Gram-positive bacteria. The following bacteria are sensitive to biosynthetic penicillins: staphylococci, streptococci, pneumococci, gonococci, meningococci, *Clostridia* (the causative agents of gas gangrene and tetanus), *Corynebacterium diphtheria*, *Bacillus antracis*, spirochetes (the causative agents of syphilis, relapsing fever, and leptospirosis), and actinomycetes.

Benzylpenicillin-sodium and *benzylpenicillin-potassium* are the water-soluble salts of monobasic acid. In case of oral intake, these drugs are dystroyed by hydrochloric acid, therefore they are administered parenterally, mainly intramuscularly. Duration of benzylpenicillin action is 3–4 hours, therefore drugs are administered 6 times a day. In special cases, benzylpenicillin is administered intravenously, intra-arterially, into the spinal canal (only sodium salt), joint capsules, and serous cavities, or it is used in inhalations. Nearly 60–70 % of administered benzylpenicillin is excreted through kidneys in non-modified form. Insignificant part of the drug is secreted into biliary ducts and excreted through intestine. The rate of drug elimination depends on renal and hepatic functions. The elimination of benzylpenicillin in patients with simultaneous damage of renal and hepatic functions can be slowed down 10 times.

There are benzylpenicillin preparations of prolonged action: *benzylpenicillin novocaine, bicillin-1*, and *bicillin-5*. Water suspensions of these drugs are administered intramuscularly. Benzylpenicillin novocaine is administered twice a day, bicillin-1 – once in 1–2 weaks, and bicillin-5 – once a month. Long-acting drugs are prescribed only if it is known that a patient has no allergy to penicillins and causative agent has high sensitivity to a prescribed drug. Therapeutic indications for the long-acting biosynthetic penicillins are rheumatism and syphilis.

Phenoxymethylpenicillin is an acid-stable penicillin because its molecules contain the phenoxymethyl groups. Antibacterial spectrum of phenoxymethylpenicillin is identical to antibacterial spectrum of

benzylpenicillin. The drug is easily absorbed in gastrointestinal tract but its blood concentration is not high. Therefore, phenoxymethylpenicillin is not used in treatment of severe infections. The drug is prescribed for oral intake 4–6 times a day for the teatment of mild to moderate infections, such as pharyngitis, tonsillitis, sinusitis, otitis, bronchitis, pneumonia, erysipelas, erysipeloid, erythema migrans, lymphadenitis, lymphangitis, scarlet fever, etc.

Semisynthetic Penicillins

Semisynthetic penicillins are synthesized by the acylation of 6-aminopenicillanic acid.

Oxacillin and *nafcillin* are known as antistaphylococcal penicillins. The antibacterial spectrum of these drugs is similar to the spectrum of benzylpenicillin. But these drugs are stable to penicillinase action, therefore they are highly active against different strains of *Staphylococci*, including penicillinase producing strains.

Oxacillin is taken orally or administered parenterally 4–6 times a day. The degree of drug binding to plasma proteins is 90–95%. Oxacillin does not penetrate through the blood-brain barrier. The main route of the drug excretion is through the kidneys.

Nafcillin has high antibacterial activity. Nafcillin is administered both orally and parenterally. The drug easily penetrates through the blood-brain barrier. The drug is mainly excreted with bile.

Ampicillin and *amoxicillin* are aminopenicillins. The drugs have the broad spectrum of antibacterial action but are broken by penicillinase. The spectrum of antibacterial action of aminopenicillins includes Gram-positive and Gram-negative bacteria. Aminopenicillins are active against *Enterococcus*, *Salmonella*, *Shigella*, *Escherichia coli*, some strains of *Proteus*, etc. It is significant that activity of aminopenicillins against Gram-positive bacteria is 3–4 times less than the activity of biosynthetic penicillins. But their activity against Gram-negative bacteria is higher than the activity of tetracyclines and chloramphenicol. Aminopenicillins are not active against *Pseudomonas aureginosa*.

Ampicillin is an acid-stable antibiotic which is easily absorbed in gastro-intestinal tract. The degree of binding to plasma proteins is low. The drug is excreted from the body through the kidneys and liver and creates the high concentration in urine and bile. This allows its use for treatment for infections of urinary and biliary tracts. Ampicillin badly penetrates through

the blood-brain barrier. The drug is taken orally 3–4 times a day or administered intramuscularly 4–6 times a day. Toxicity of ampicillin is low.

Amoxicillin is similar to ampicillin. But the drug is better absorbed in gastrointestinal tract with high concentrations in plasma and tissues.

There are combined penicillin preparations such as *Ampiox* (combination of ampicillin with oxacillin in ratio 2:1).

Carbenicillin is a broad-spectrum semisynthetic penicillin of carboxypenicillin group. The drug is active against many Gram-positive and Gram-negative bacteria including *Pseudomonas aureginosa*, Proteus, and some bacteroides. Beta-lactamase breaks up carbenicillin, therefore it does not influence staphylococci producing penicillinase. Carbenicillin is used mainly as a reserve antibiotic in treatment of infectious diseases caused by *P. aureginosa*.

Carbenicillin is an acid-labile antibiotic, therefore it is administered intramuscularly or intravenously. The drug permeability through the blood-brain barrier is low. The main route of excretion is through the kidneys. Duration of carbenicillin action is 4–6 hours. Carbenicillin indanyl sodium is an acid-stable form of carbenicillin which is administered orally mainly in treatment of urinary tract infections.

Ticarcillin is carboxypenicillin with high activity against *Pseudomonas aureginosa*. The drug is administered parenterally. Such carboxypenicillins as carfecillin and carindacillin are to be given orally. Their bioavailability in oral intake is above 40 %.

A group of ureidopenicillins includes such medications as *azlocillin*, *mezlocillin*, and *piperacillin*. Ureidopenicillins are characterized by high activity against *P. aureginosa* and fast development of bacterial resistance. These drugs are administered only parenterally 3 times a day.

There are inhibitors of β-lactamase that prevent the destruction of penicillins by penicillinase: *clavulanic acid*, *sulbactam*, and *tazobactam*. These agents are used in combination with penicillins. For example, augmentin consists of amoxicillin and clavulanic acid. The drug is administered once a day for treatment of infectious diseases of respiratory and urinary tracts, joints, bones, sepsis, etc. Another group of combination drugs includes unazinum (ampicillin with sulbactam), co-amoxiclav (amoxicillin with clavulanic acid), and tazocin (piperacillin with tazobactam).

Despite low toxicity and inability to accumulate in the organism, penicillins have many side effects.

Allergic reactions (skin rash, bronchospasm, and anaphylactic shock) are the most common side effect of penicillins. To prevent allergy, the test for sensitivity to penicillins shoud be performed before the drug administration. In the case of anaphylactic shock, intramuscular adrenaline, intravenous glucocorticoids and calcium chloride must be administered very quickly.

Other side effects of penicillins are painful injections, infiltrates, and aseptic necrosis in the injection site. Oral drug intake can cause nausea, diarrhea, stomatitis, and glossitis. Intravenous administration can cause phlebitis and trombophlebitis. Large doses of penicillins or their use in patients with renal failure can result in development of neurotoxic effects. Sometimes, penicillins cause disturbances of cardiac activity and inhibition of hepatic enzymes. Semisynthetic broad-spectrum penicillins can cause disbiosis and superinfection.

Cephalosporins

Cephalosporins are semisynthetic antibiotics with β-lactame ring in molecules. Mechanism of cephalosporins' action is associated with affection of bacterial cell wall synthesis due to inhibition of transpeptidase. Cephalosporins have the bactericidal effect and are broad-spectrum antibiotics. The drugs are stable to staphyloccocal β-lactamase, but β-lactamases of Gram-negative bacteria can affect some cephalosporins.

Cephalosporins are grouped into four generations:

1. Cephalosporins, 1st generation.

1.1. Drugs for parenteral administration: *cephaloridine, cefalotin, cefazolin, cefradine,* and *cefapirine*.

1.2. Drugs for enteral use: *cephalexin, cephradine,* and *cefadroxil*.

2. Cephalosporins, 2nd generation.

2.1. Drugs for parenteral administration: *cefuroxime, cefamandole, cefoxitin, cefmetazole,* and *ceforanide*.

2.2. Drugs for enteral use: *cefaclor, cefuroxime,* and *loracarbef*.

3. Cephalosporins, 3rd generation.

3.1. Drugs for parenteral administration: *cefotaxime, ceftriaxone, ceftazidime, cefoperazone, cefmenoxime,* and *moxalactam*.

3.2. Drugs for enteral use: *cefixime, ceftibuten,* and *cefpodoxime*.

4. The 4th generation cephalosporins are the drugs for parenteral administration: *cefepime, cefpirome, cefclidine,* and *cefozopran*.

First-Generation Cephalosporins

First-generation cephalosporins are antibiotics with high activity against Gram-positive bacteria. Also, some Gram-negative bacteria are sensitive to these drugs. Antibacterial spectrum of 1st-generation cephalosporins includes staphylococci, streptococci, pneumococci, meningococci, gonococci, *Corynebacterium diphtheria*, *Clostridium*, actinomycetes, *Proteus mirabilis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella*, and *Shigella*. First-generation cephalosporins have no activity against methicillin-resistant staphylococci, *Pseudomonas*, indole-positive *Proteus*, *Bacteroides*, *Enterococcus*, *Enterobacter*, etc.

Therapeutic indications for 1st-generation drugs are infectious diseases of respiratory tract, pneumonia, peritonitis, osteomyelitis, otitis, furunculosis, infected wounds, infections of urinary tract, prevention of surgical infections, etc.

Cefazolin is 1st-generation cephalosporin for parenteral administration. The drug is administered intramuscularly or intravenously 3–4 times a day. Cefazolin has high antibacterial activity and penetrates in the tissues better than other 1st-generation drugs. The high drug concentration is created in bile and urine. The nephrotoxicity of cefazolin is low. There are the following side effects of the drug: superinfection caused by *Candida* or *Pseudomonas aeruginosa*, allergic reactions, leukopenia, pain and infiltrations in the injection site.

Cephalexin is easily absorbable in the gastrointestinal tract. The drug is taken orally 4 times a day. Cephalexin is available in the following medical forms: capsules, tablets and suspension for oral intake. The drug is used to treat infectious diseases of moderate severity. Side effects of cephalexin are as follows: disbiosis and leukopenia.

Second-Generation Cephalosporins

The antibacterial spectrum of 2nd-generation cephalosporins is similar to the 1st-generation cephalosporins. But 2nd-generation has higher activity against Gram-negative bacteria and it is less active against Gram-positive flora. These drugs are not active against *Pseudomonas aeruginosa*. Second-generation cephalosporins are used to treat infectious diseases of respiratory tract, abdominal and gynecological infections, septicemia, endocarditis, urinary tract infections, infections of bones, joints, skin and soft tissues, to prevent postoperative infections.

Cefoxitin is active against bacteroids. It is highly active against other Gram-negative bacteria (*Escherichia coli, Haemophilus influenzae, Salmonella, Shigella, Proteus mirabilis*, gonococci). Cefoxitin is also active against Gram-positive bacteria (*Staphylococcus*, *Streptococcus*) and against some anaerobic bacteria. The drug is resistant to β-lactamase. Pseudomonas aeruginosa, Listeria, many strains of enterococci and methicillin-resistant staphylococci, and others are insensitive to cefoxitin. The drug is administered intramuscularly or intravenously 2–3 times a day.

Cefaclor is the 2nd-generation cephalosporin for peroral use. The drug is taken orally 3 times a day. The drug is highly active against Gram-negative bacteria (*Escherichia coli, Haemophilus influenzae, Salmonella, Shigella, Proteus mirabilis, Klebsiella, Neisseria gonorrhoeae, Citrobacter*). Besides, cefaclor is active against Gram-positive bacteria. The drug has no activity against anaerobic microorganisms (*Bacteroides*, etc.), *Pseudomonas, Enterococcus, Listeria, Serratia,* etc.

Cefuroxime is available both for peroral and parenteral administration. The drug has a higher ability to penetrate through the blood-brain barrier than other drugs of the 2nd-generation, and it is used to treat meningitis. The drug is administered parenterally or taken orally 2–3 times a day.

Third-Generation Cephalosporins

Antibacterial spectrum of these drugs is wider, and their activity against Gram-negative bacteria is higher compared to preceding drugs. Third-generation cephalosporins are stable to Gram-negative β-lactamases. *Ceftazidime*, *cefotaxime*, and *cefoperazone* are active agaisnt *Pseudomonas aeruginosa*.

All third-generation cephalosporins (except cefoperazone) easily penetrate into tissues, including central nervous system. Most of the drugs

are excreted through the kidneys in unchanged form. Only ceftriaxone and cefoperazone are excreted mainly with bile. Therapeutic indications for the third-generation cephalosporins are infections of respiratory tract, bones, soft tissues, abdominal cavity, and urinary tract, sepsis, meningitis, endocarditis, etc. The drugs should be taken 2–3 times a day, but ceftriaxone and cefoperazone – 1–2 times a day.

Fourth-Generation Cephalosporins

All forth-generation cephalosporins are administered only parenterally. These drugs have the extended antibacterial spectrum and high activity against both Gram-positive and Gram-negative bacteria. These drugs have a greater resistance to β-lactamases than the 3rd-generation cephalosporins. Fourth-generation cephalosporins affect bacteria insensitive to other antibiotics (including carbapenems). It is due to drug ability to penetrate through cell membranes and to bind to bacterial penicillin-binding proteins. Besides, the 4th-generation cephalosporins create high concentrations in periplasmic space. But these drugs are inactive against bacteroides, therefore, for expansion of antibacterial spectrum, they are combined with metronidazole, carboxypenicillins, and ureidopenicillins. Secondary resistance of bacteria to these drugs develops slowly. The therapeutic indications for the 4th-generation cephalosporins are infections of respiratory and urinary tracts, sepsis, surgical infections, meningitis, etc. Cefepime and cefpirome are administered twice a day.

Therapy with cephalosporins may be accompanied by allergic reactions. Cephalosporins are contraindicated to patients with allergy to penicillins in anamnesis. Nephrotoxicity is typical mainly for the 1st-generation cephalosporins. Neurotoxicity (hallucinations, convulsions, nystagmus) is due to antagonism between cephalosporins and γ-aminobutyric acid. Hematotoxicity (leukopenia, thrombocytopenia, neutropeniza) can develop in patients with renal failure or in the case of parenteral administration of high doses of cephalosporins. Therapy by cephalosporins can be accompanied by elevated liver enzymes in blood. Enteral cephalosporin intake can cause disbiosis. Patients treated with cephalosporins should avoid alcohol consumption because the drugs have Antabuse-like effect. In this case, alcohol intake can result in nausea, vomiting, diarrhea, tachycardia, etc.

Monobactams

Monobactams are β-lactam antibiotics which are active only against aerobic Gram-negative bacteria (e.g., *Escherichia coli*, *Enterobacter*, Neisseria, Pseudomonas, Proteus, Serratia, Morganella, Salmonella, *Shigella*, *Klebsiella*, etc.). The representative of monobactams is *aztreonam*. The drug has high stability to β-lactamases of Gram-negative bacteria, but it is destroyed by β-lacatamases of Gram-positive microorganisms. Therefore, aztreonam has no activity against Gram-positive bacteria, bacteroides, and other anaerobes. The therapeutic indications of aztreonam are severe infections of urinary and respiratiry tracts, abdominal cavity, soft tissues, meningitis, sepsis, etc. The drug is administered intramuscularly or intravenously 2–3 times a day. The side effects of aztreonam are allergic reactions, dysbiosis, dyspepsia, and phlebitis.

Carbapenems

It is a modern group of β-lactame antibiotics with high stability to β-lactamases and broad antibacterial spectrum. Carbapenems are active against both Gram-positive and Gram-negative aerobic and anaerobic bacteria, including Pseudomonas aeruginosa. The mechanism of carbapenems' action is identical to other β-lactame antibiotics. These drugs are divided into two generations:

– 1st generation: *imipenem, tienam, primaxin*;

– 2nd generation: *meropenem*.

Imipenem is a semisynthetic antibiotic with broad spectrum of action. The drug is stable to β-lactamases, but is destroyed by dehydropeptidase-I (enzyme of proximal tubules of nephron). *Tienam* and *primaxin* are combined drugs which contain imienem and cilastatin in ration 1:1. Cilastatin is inhibitor of dehydropeptidase-I.

Meropenem is stable to dehydropeptidase-I, therefore it does not require the combination with cilastatin. Also, antibiotic is stable to β-lactamase action. Antistaphylococcal activity of meropenem is 2–4 times less than the activity of tienam. On the other hand, the drug activity against Gram-negative enterobacteria and Pseudomonas is higher 2–8 times.

There are microorganisms with natural resistance to carbapenems. They are *Chlamydia*, *Mycoplasma*, *Corynebacterium*, *Mycobacterium*, *Flavobacterium*, methicillin-resistant staphylococci, fungi, and protozoa.

Carabapenems are administered only parenterally. Tienam is administered intravenously 4 times a day or intramascularly 2 times a day. Meropenem is administered intravenously 3 times a day. Carbapenems are reserve antibiotics which are used in treatment of severe infections in case of ineffectiveness of other antibiotics. There are the following therapeutic indications for carbapenems:

– intraperitoneal surgical infections;
– gynecological infections after labor, cesarean section, and surgery;
– intensive therapy for newborns;
– complicated infections of urinary tract;
– complicated infections of bones, joints, skin, and soft tissues;
– sepsis;
– pulmonary infections;
– infectious diseases in patients with neutropenia;
– meningitis (meropenem is a drug of choice due to higher permeability through the blood-brain barrier and less neurotoxicity).

Side effects of carbapenems are as follows:

– pain, thrombophlebitis, and sealing the injection site;
– allergic reactions;
– superinfections;
– nephrotoxicity (more common for imipenem);
– neurotoxicity: tremor, muscular hypertone, paresthesia, encephalopaty, convulsions (in the case of intravenous administration of tienam or primaxin, but meropenem).

Macrolides and Azalides

Macrolides are antibiotics containing macrocyclic lactone rings in molecules.

There are three generations of macrolides:

1st generation: *erythromycin* and *oleandomycin*;

2nd generation: *spiramycin, roxithromycin, clarithromycin,* and *midecamycin*.

3rd generation (azalides): *azithromycin*.

Mechanism of macrolide action is as follows. Drugs bind to 50S ribosomal subunit that results in violation of ribosome translocation along mRNA and inhibition of protein synthesis. The macrolides are bacteriostatic antibiotics.

First-generation macrolides are drugs with narrow antibacterial spectrum. These drugs are active mainly against Gram-positive bacteria (streptococci, staphylococci, pneumococci, *Corynebacterium diphtheriae*, etc.). Besides, gonococci, *Mycoplasma*, *Chlamydia*, *Legionella*, spirochetes, certain strains of *Brucella* and *Mycobacteria* are sensitive to 1st-generation macrolides. But most Gram-negative microorganisms have high resistance to these drugs.

The second- and third-generation macrolides have the broad antibacterial spectrum. These drugs are active against enterococci, *Escherichia coli*, *Haemophilus influenzae*, *Shigella*, *Salmonella*, *Bacteroides*, *Helicobacter pylori*, etc. Azithromycin has high activity against bacteria – causative agents of genital infections (*Neisseria gonorrhoeae*, *Chlamydia*, spirochetes, and *Trichomonas vaginalis*).

Macrolide resistance of bacteria develops readily, therefore a course of treatment should not exceed 7 days.

Erythromycin is a low toxic antibiotic for oral intake. The drug is slowly absorbed in gastrointestinal tract. Erythromycin is partly degraded by gastric juice, therefore the drug is used in capsules or specially-coated tablets. The bioavailability of erythromycin is higher if taken before a meal. The drug esealy penetrates into tissues and body fluids (except central nervous system). High concentrations of the drug are created in lungs, liver, prostate, and urinary tract. About 60–70 % of the administered dose undergo hepatic metabolism. Erythromycin is taken 4–6 times a day before a meal or used locally in ointments. Erythromycin phosphate is used in intravenous administration 2–3 times a day in a dose of 0.2 g.

Oleandomycin has lower antibacterial activity than erythromycin, but irritative ability of oleandomycin is higher. The drug is taken orally 4 times a day. Presently, oleandomycin is not used in monotherapy. It is most commonly combined with tetracyclines (oletetrin, tetraolean, etc.).

Clarithromycin is 2–4 times more active against staphylococci and streptococci than erythromycin. The drug is used in treatment of infectious diseases caused by *Mycoplasma*, *Chlamydia*, *Toxoplasma*, and *Helicobacter pylori*. Clarithromycin is easily absorbed in gastrointestinal tract. The drug undergoes hepatic metabolism and is excreted through the kidneys. Clarithromycin is taken 2 times a day. Course of treatment is 5–14 days. Side effects are abdominal pain, diarrhea, and nausea.

In comparison with the 1st and 2nd generations, molecules of the 3rd-generation macrolides have aromatic group in the structure of

macrocyclic lactone ring, and due to this they have new properties. In contrast with erythromycin, *azithromycin* is 2–4 times less active against Gram-positive cocci. But drug activity against Gram-negative bacteria is higher. The bioavailability of azithromycin in gastrointestinal tract is low. The drug can accumulate in the cells (intracellular concentration may be higher than plasma concentration 10–100 times). Azithromycin does not penetrate through the blood-brain barrier. The drug is excreted through the kidneys in unchanged form. Azithromycin is taken orally once a day. The first dose is twice higher than subsequent doses. Therapeutic indications for azithromycin are bronchitis, otitis, sinusitis, erysipelas, mastitis, whooping cough, diphtheria, chlamydial conjunctivitis, chlamydial pneumonia of newborns, pneumonia caused by *Mycoplasma pneumoniae*, lobar pneumonia caused by *Legionella pneumophila* and *Moraxella catarrhalis*, primary syphilis, gonorrhea, cholecystitis, enteritis, colitis, toxoplasmosis, urogenital infections, and ulcer diseases of stomach and duodenum.

New macrolide antibiotic *josamycin* is approved in medicine. The drug has broad antibacterial spectrum and causes bacteriostatic or bactericidal (in high doses) effect. The resistance of bacteria to josamycin develops seldom.

Tetracyclines

Tetracyclines are antibiotics with four condensed 6-member cycles in molecules. A classification of tetracycline is as follows:

1. Biosynthetic tetracyclines: *oxytetracycline, tetracycline,* and *demeclocycline*.

2. Semisynthetic tetracyclines: *methacycline (rondomycine), doxycycline (vibramycin),* and *minocycline*.

The antibacterial spectrum of tetracyclines is broad and includes such microorganisms as Gram-positive and Gram-negative cocci, *Escherichia coli*, *Chlamydia*, *Rickettsia*, *Mycoplasma*, *Ameba*, *Plasmodium*, *Helicobacter pylori*, *Klebsiella*, *Enterobacter*, Spirochaetales, *Vibrio cholerae*, *Yersinia pestis*, *Francisella tularensis*, *Brucella*, *Shigella*, *Salmonella*, etc. Tetracyclines have no activity against *Proteus*, *Pseudomonas aeruginosa*, viruses, and fungi. Bacterial resistance to tetracyclines develops slowly and can be characterized by cross-resistance.

Tetracyclines block protein synthesis in bacterial cells. The drugs bind to 30S ribosomal subunits and affect the binding of tRNA to them. That stops protein synthesis. Besides, tetracyclines form the compounds with

biologically active two valence metals (iron, calcium, zink, etc.). Tetracyclines have the bacteriostatic effect.

Tetracyclines are liposoluble agents, therefore they are easily absorbed in gastrointestinal tract. Also, tetracyclines easily penetrate through tissue barriers and accumulated in the tissues. It is necessary to notice that the drug permeability into mother's milk and amniotic fluid is better than into the skin, cerebrospinal fluid, and saliva. The degree of binding to proteins for biosynthetic tetracyclines is 20–40 % and for semisynthetic drugs – 60–95 %. Tetracyclines undergo partial biotransformation in the liver and are excreted with urine and bile. The drugs are taken orally. Their absorption is higher if the drug is taken 1–1.5 hours before a meal or 3 hours after the meal. It is necessary to notice that milk significantly reduces the absorption of tetracyclines due to formation of complexes between the drug and two valence metals. Semisynthetic tetracyclines are less capable to form such compounds, therefore their bioavailability at oral intake is closer to 100 %. Oxytetracycline and tetracycline are also used in ointments. Tetracycline is administered intramuscularly, and doxycycline – intravenously. Oxytetracycline and tetracycline are prescribed to take 4 times a day, methacycline – 2–3 times, doxycycline and minocycline – 1–2 times, and demeclocycline – once a day.

Therapeutic indications for tetracyclines are as follows: putrid fever, Q fever, trachoma, psittacosis, ornithosis, urogenital chlamydiosis, dysentery, leptospirosis, plague, brucellosis, tularemia, anthrax, cholera, bronchitis, pneumonia, tonsilitis, otitis, sinusitis, infections of urinary and biliary tracts, osteomyelitis, syphilis, gonorrhea, ulcer diseases of stomach and duodenum (doxycycline), intestinal amebiasis, etc.

Presently, *tigecycline*, a new tetracycline derivative, is approved in medicine. The drug has high activity against Gram-positive and Gram-negative bacteria. Tigecycline is used as a reserve antibiotic when other antibiotics are ineffective. The drug is administered intravenously, drop-by-drop, twice a day.

It is necessary to notice that tetracyclines affect cell division both in microorganisms and in a human organism. Due to this, drugs affect the epithelization of the intestine (dyspesia, erosions, ulcers, glossitis) and the skin (dermatitis, photosensitization) and suppress the hemopoiesis (leukopenia, anemia, thrombocytopenia). Catabolic effect of tetracyclines results in inhibition of protein synthesis and immunity.

Tetracyclines are hepatotoxic and teratogenic drugs.

Tetracyclines form the chelates with calcium phosphate in teeth and bones that results in the delay of skeletal growth in children, yellow coloration of teeth, violation of tooth enamel formation, and caries. Due to this, tetracyclines are contraindicated in children aged under 12 years, pregnant woman, and nursing mothers.

Expired tetracyclines form toxic substances. In this case, the following intake of expired tetracyclines causes an acute kidney injury (Fanconi's syndrome).

Tetracycline in young children can cause the increase of intracranial pressure along with development of meningeal symptoms (headache, vomiting, etc.).

Tetracyclines can cause disbiosis, hypovitaminosis B, candidiasis, and enterocolitis. Fast intravenous administration of doxycycline can cause the development of acute heart failure. Minocycline causes vestibular disturbances. Tetracycline therapy can cause allergic reactions.

Chloramphenicol Group

Levomycetin (chloramphenicol) is the main representative of this group. Such drugs as levomycetin, levomycetin stearate, levomycetin palmitate, and levomycetin succinate are the most commonly used in medicine.

Levomycetin inhibits the protein synthesis in bacterial cells due to binding to 50S subunit of ribosomes. Also, the drug inhibits peptidyl transferase activity that impedes prolongation of polypeptides. Chloramphenicol has a bacteriostatic effect.

Levomycetin is a broad-spectrum antibiotic. Unfortunately practical realization of the drug potential in medicine is impossible due to high drug toxicity. Therefore, levomycetin is used as a reserve antibiotic. Levomycetin inhibits the growth of the most strains of staphylococci, pneumococci, streptococci, meningococci, *Haemophilus influenzae*, *Brucella*, *Rickettsia*, *Chlamydia*, *Mycoplasma*, *Vibrio cholerae*, *Escherichia coli*, *Shigella*, *Salmonella*, and *Enterobacter*. It is important that chloramphenicol inhibits the growth of such anaerobes as bacteroides, anaerobic cocci, and fusobacteriales. The resistance of bacteria to chloramphenicol develops slowly.

Levomycetin is prescribed mainly for oral intake. Levomycetin succinate is administered intravenously (seldom – intramuscularly or in the

form of an aerosol in lungs). Sometimes levomycetin is administered rectally.

The drug bioavailability in gastrointestinal tract is more than 90 %. Parenteral administration of levomycetin is used in treatment of meningitis. The degree of drug binding to plasma proteins is 50–60 %. Chloramphenicol easily penetrates into different tissues and fluids of the body. Nearly 90 % of administered chloramphenicol dose are metabolized in the liver. Unchanged 10 % of chloramphenicol is excreted through the kidneys that provides the antibacterial effect in the urinary tract.

Levomycetin is used only in treatment for severe infections caused by sensitive to levomycetin bacteria. Therapeutic indications for levomycetin are brain abscess, systemic salmonolesis, dysentery, richettsiosis, intrzoccular infections (eye burns, trachoma), brucellosis, tularemia, reactive arthritis, meningitis caused by *Haemophilus influenzae*, meningococci, and pneumococci. Aerosol thiamphenicol glycinate asetylcysteinate (combined levomycetin preparation) is used in treatment of respiratory tract infections.

Chloramphenicol for oral intake is prescribed at 0.25–0.5 g dose given 4 times a day. A 20 % solution of levomycetin succinate is administered parenterally 2–3 times a day. Levomycetin liniment 10 %, or synthomycin liniment 10%, is used in treatment of skin infections, burns, fissures, etc. Levomycetin is a component of different ointments (“*Levomekol*”, “*Levosin*”) and aerosols (“*Levovinisol*”, “*Olazol*”).

An accurate calculation of the dosage is based on the body weight of the patient in cases of enteral and parenteral administration of chloramphenicol. Course of treatment should not exceed 10–14 days. Control of the blood and liver function is required.

Levomycetin is a toxic antibiotic with narrow therapeutic action. The drug inhibits haematopoiesis that results in anemia, leukopenia, and thrombocytopenia. Chloramphenicol can cause acute drug-induced hemolysis in patients with genetically determined deficiency of glucose-6-phosphate dehydrogenase. Non-hemolytic anemia can develop in patients with genetically determined deficiency of uridine-diphosphoglucuronic transferase. Levomycetin blocks mitochondrial ferrochelatase (enzyme which provides the iron inclusion in the structure of heme) that results in iron deficiency anemia, myodystrophy, and hypotrophy.

Gray baby syndrome is one of the possible complications caused by levomycetin in newborn infants and babies under 3 months. The gray baby

syndrome is manifested by respiratory disturbances, severe metabolic acidosis, and vascular collapse. This complication is caused by insufficiency of mitochondrial respiratory enzymes in myocardium, slow excretion of drug with urine, and insufficiency of hepatic enzymes.

Sometimes the complications caused by chemotherapeutic effect of levomycetin are possible: aggravation of disease due to massive degradation of bacterial cells and release of endotoxins, dysbiosis, candidiasis, superinfection caused by *Pseudomonas aeruginosa*, resistant strains of staphylococci, and *Proteus*.

Aminoglycosides

Aminoglycosides are antibiotics containing aminosugars in molecules. These antibiotics are grouped into 4 generations:

– 1st generation: *streptomycin, neomycin, kanamycin, monomycin*.

– 2nd generation: *gentamicin*.

– 3rd generation: *tobramycin, sisomicin, amikacin, netilmicin*.

– 4th generation: *isepamicin*.

Aminoglycosides irreversibly inhibit 30S subunits of ribosomes that results in incorrect reading of mRNA and incorporation of mistaken amino acids in the protein structure. Also, aminoglycosides affect the structure and function of bacterial cytoplasmic membrane. Aminoglycosides are bactericidal antibiotics.

Aminoglycosides are broad-spectrum antibiotics. These drugs are active against Gram-negative aerobic (*Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella*, *Shigella*, *Proteus*, and enterobacteria) and Gram-positive coccal flora (staphylococci, streptococci, and pneumococci). Besides, gentamycin is active against *Francisella tularensis*; streptomycin, amikacin, and kanamycin – against *Mycobacterium tuberculosis*; monomycin – against *Entamoeba histolytica*, *Leishmania*, and *Trichomonas*. Isepamicin, besides the above mentioned flora, is active against *Citrobacter*, *Acinetobacter*, *Morganella*, *Listeria*, and *Nocardia*.

The bacterial resistance to aminoglycosides develops quickly due to the ability of bacteria to synthesize the enzymes which destroy aminoglycosides. There are 15 known enzymes that destroy aminoglycosides of the 1st generation, 10 enzymes that destroy 2nd-generation drugs, and only 3 enzymes that destroy aminoglycosides of the 3rd and 4th generations.

The main routes for aminoglycoside administration are intramuscular and intravenous (bolus or drop-by-drop). Aminoglycosides have poor solubility in lipids and their degree of absorption in gastrointestinal tract is low. The degree of aminoglycoside binding to plasma proteins is 10–30 %. These drugs have low ability to penetrate inside of the cells. But aminoglycosides easily penetrate through placenta, accumulate in the inner ear and adrenal cortex. Aminoglycosides do not undergo metabolism in the body and are excreted unchanged.

Presently, clinical use of the 1st-generation aminoglycosides is restricted due to bacterial resistance and high drug toxocity. Thus, streptomycin is used only in treatment of tuberculosis, tularemia, and plaque. Widely used in the past combination of streptomycin and benzylpenicillin, nowadays, is used only in treatment of enterococcal endocarditis, due to high toxicity. Monomycin is used only in treatment of skin leishmaniasis. Tablets of kanamycin and neomycin are used in treatment of gastrointestinal infections (enterocolitis and dysentery) and for sanitation of intestine before surgery. Also, both agents are used externaly in treatment of dermatitis and infectious inflammatory diseases of skin. Kanamycin sulfate for parenteral administration is used in treatment of tuberculosis.

Gentamicin is a broad-spectrum aminoglycoside antibiotic of the 2nd generation. The most important is its activity against *Pseudomonas aeruginosa*, *Proteus*, *Escherichia coli*, *Enterobacter*, *Klebsiella*, and number of other bacteria, including staphylococci, resistant to the 1st-generation aminoglycosides and benzylpenicillin. Bacterial resistance to gentamicin develops slowly. Normally, gentamicin does not penetrate through the blood-brain barrier, but in patients with meningitis the permeability of the blood-brain barrier is increased. The therapeutic indications for gentamicin are sepsis, urogenital infections, pneumonia, bronchitis, infections of central nervous system (including meningitis), osteomyelitis, peritonitis, postsurgical infections, infected wounds and burns, etc. The drug is administered intramuscularly or intravenously 2–3 times a day. Also, gentamicin is used topically in treatment of skin and eye infections caused by sensitive flora.

Third-generation aminoglycosides are characterizied by higher activity against *Pseudomonas aeruginosa*, different strains of *Proteus*, *Klebsiella*, and *Enterobacter*. Amikacin also is active against *Mycobacterium*

tuberculosis. Secondary resistance of bacteria to gentamicin develops significantly slowly than to gentamicin.

Fourth-generation aminoglycoside isepamicin has longer duration of action than previous drugs. Isepamicin is administered intramuscularly or intravenously once a day. Toxicity of isepamicin is low.

Aminoglycoside therapy may be accompannied by development of serious side effects and complications.

Ototoxicity. Aminoglycosides accumulate in the outer and inner hair cells within the organ of Corti that results in degenerative changes of hair cells. Sensitive nerve fibers of the inner ear also degenerate. In case of streptomycin and gentamicin therapy vestibular disfunction develops initially. Other aminoglycosides may cause the initial hearing loss.

Nephrotoxicity occurs due to aminoglycoside accumulation in proximal convoluted tubules and functional disturbances of many enzymes that cause the development of interstitial nephritis, impaired concentration of urine, proteinuria, and leukocyturia.

Blockage of neuromuscular synapses is accompanied by weakness of diaphragm and other respiratory muscles that can cause respiratory paralysis.

Aminoglycosides inhibit the absorption of nutrients in gastrointestinal tract. Other possible side effects of aminoglycosides include allergic reactions, polyneuritis, and phlebitis in case of intravenous administration.

Polymyxins (Cyclic Polypeptides)

The group is represented by such drugs as *polymyxin M*, *polymyxin B*, and *polymyxin E*.

Polymyxins affect the functions of cytoplasmatic membranes of bacteria. Antibiotics interact with phospholipids of membranes that results in the increase of membrane permeability. Polymyxins have a bactericidal action.

Antibacterial spectrum of polymyxins is narrow and includes Gram-negative bacteria: *Escherichia coli*, *Shigella*, *Salmonella*, *Klebsiella*, *Enterobacter*, *Vibrio cholerae*, and most strains of *Pseudomonas aeruginosa*.

Polymyxin M is taken orally or used topically. The degree of the drug absorption in the gastrointestinal tract is about 1–2 %, but in patients with intestinal infections drug absorption increases up to 10–15 %. This

fact should be considered because polymyxins are drugs with narrow therapeutic margin.

Polymyxin B and *polymyxin E* are administered intramuscularly, intravenously, into body cavities, and in aerosols for inhalation. The drugs have low degree of binding to plasma proteins. Polymyxins penetrate through cell membranes and into pleural and peritoneal fluids poorly. Therefore, in relevant cases these drugs are administered directly into the foci of the infection or intrathecally. Only 2–4 % of administered dose undergoes biotransformation. About 90 % of the dose is excreted unchanged through the kidneys. Polymyxins are active in the urinary tract only in the acidic urine. The drugs are prescribed to be taken 3–4 times a day. For newborn infants, polymyxins should be taken only once a day.

Therapeutic indications for polymyxins are infections of intestine and urinary tract, pneumonia, endocarditis, and sepsis caused by sensitive flora. Also, polymyxins are used in treatment of purulent wounds, burns, purulent otitis and conjunctivitis, etc.

Polymyxins have the marked neurotoxicity and nephrotoxicity. These drugs can affect neuromuscular transmission (muscular weakness, and respiratory disturbances), vision, speech, and hearing. Therapy with polymyxins may be accompanied by drowsiness and irritability. Proteins, cylinders, and erythrocytes in the urine are manifestations of polymyxin nephrotoxicity.

Daptomycin is a new antibiotic with chemical structure similar to polymyxins. Daptomycin is a semisynthetic antibiotic active against Gram-positive and Gram-negative bacteria. Therapeutic indications for daptomycin include complicated infections of the skin and soft tissues and bacteremia caused by *Staphylococcus aureus* (including endocarditis). The drug is used only in the treatment of adults. The drug is administered intravenously once daily. Side effects are nausea, vomiting, muscular pain, etc.

Rifamycins

Rifamycin group includes such drugs as *rifamycin* (natural antibiotic) and *rifampicin* (semisynthetic antibiotic).

Rifamycins block the synthesis of RNA due to inhibition of DNA-dependent RNA-polymerase. Antibacterial effect of rifamycins is bacteriostatic. Spectrum of activity includes mainly Gram-positive bacteria: *Mycobacterium tuberculosis*, staphylococci, streptococci, pneumococci,

meningococci, enterococci, gonococci, *Haemophilus influenzae*, *Mycobacterium leprae*, *Bacillus anthrax*, etc. Large doses of rifamycins affect also Gram-negative bacteria: *Escherichia coli*, *Shigella*, *Salmonella*, *Rickettsia*, *Klebsiella*, *Chlamydia*, *Brucella*, some strains of *Pseudomonas aeruginosa* and *Proteus*, etc. The bacterial resistance to rifamycins develops readily (in few days after the start of treatment).

Rifampicin is taken orally or administered intramuscularly or intravenously. The drug is easily absorbed in gastrointestinal tract. Rifampicin penetrates through tissue barrier, creates high concentrations in lungs, pleural cavity, peritoneal exudate, liquor, and bones. About 70 % of administered dose is metabolized in the liver. A part of rifampicin dose is excreted with bile into intestine where it is absorbed in the blood. About 30 % of the dose is excreted with the urine unchanged.

Rifampicin is mainly used to treat tuberculosis. Besides, the drug is prescribed to treat leprae, pneumonia, osteomielitis, urinary and biliary tract infections, acute gonorrhea, etc. The drug is also used to prevent rabies encephalitis in humans and meningitis in the carriers of meningococcal infection.

Rifampicin is a low-toxic antibiotic. Side effects of rifampicin include hepatotoxicity, leukopenia, thrombocytopenia, allergic reactions, and dispepsia. It is necessary to notice, that rifampicin turns the saliva, urine, sweat, feces, and tears an orange-red color. Rifampicin is not recommended for intake during first three months of pregnancy.

Lincosamides

The group includes such antibiotics as *lincomycin* and *clindamycin*.

Lincosamides inhibit the protein synthesis on the level of 50S subunit of bacterial ribosome. Lincosamides exhibit the bacteriostatic effect.

Antibacterial spectrum of lincosamides is broad, but preferably directed against Gram-positive bacteria: staphylococci, streptococci, pneumococci, *Corynebacterium diphtheriae*, and anaerobes (bacteroides, *Clostridium*, *Fusobacterium*). The activity of lincosamides against Gram-negative bacteria is less expressed. The following Gram-negative bacteria are sensitive to lincosamides: meningococci, gonococci, some strains of *Haemophilus influenzae*, and *Mycoplasma*. Clindamycin is also active against *Toxoplasma gondii*, *Plasmodium*, and some strains of

Pneumocystis. Clindamycin is 50 times more active against bacteroides than lincomycin.

Secondary bacterial resistance to lincosamides develops slowly.

Lincosamides are administered intramuscularly and intravenously or taken orally. Bioavailability of the drugs is 50 %. The degree of binding to plasma proteins is about 50 %. Lincosamides easily penetrate into different tissues and fluids of the body, except cerebrospinal fluid. Also, lincosamides are known to accumulate in bones. Nearly 80–90 % of administered dose is excreted in inactivated form with bile. Only 10–20 % of dose is excreted in unchanged form through the kidneys. Lincosamides exhibit the highest activity in alkaline environment. The drugs are prescribed to be taken 3–4 times a day.

Lincosamides are reserve antibiotics. The therapeutic indications for lincosamides are sepsis, endocariditis, artritis, osteomyelitis, lower respiratory tract infections, otitis, infected wounds, diabetic foot, toxoplasmosis, and tropical malaria. These drugs are also used to prevent infections after surgery in abdomynal cavity and on the pelvic organs.

Side effects of lincosamides are nausea, vomiting, abdominal pain, allergic reactions, leukopenia, and thrombocytopenia. Fast intravenous administration of the drugs can cause a decrease in blood pressure, dizziness, and a decrease in skeletal muscle tone. Lincosamides are contraindicated during pregnancy and in patients with severe hepatic and renal diseases.

Glycopeptides

The main representatives of this group are *vancomycin* and *teicoplanin (Targocid).*

Glycopetides inhibit the synthesis of bacterial cell wall and simultaneously affect the function of bacterial cytoplasmatic membrane. Glycopeptides are antibiotics with bactericidal activity.

Antibacterial spectrum includes Staphylococcus (including strains with resistance to other antibiotics), Streptococcus, Enterococcus, *Clostridium difficile,* and some other microorganisms.

Vancomycin is used in treatment of infections caused by Gram-positive bacteria: sepsis, endocarditis, meningitis, osteomyelitis, pneumonia, and enterocolitis (including pseudomembranous colitis). The drug is administered intravenously drop-by-drop 3–4 times a day.

Vancomycin is an antibiotic with high nephro- and ototoxicity. The fast drug administration can cause a massive release of histamine from basophils that results in low blood pressure and skin rashes. Vancomycin can cause phlebitis, neutropenia, and thrombocytopenia.

Teicoplanin has similar antibacterial spectrum with vancomycin. The drug is used in treatment of serious infections caused by sensitive bacterial flora (severe infections of respiratory and urinary systems, sepsis, peritonitis, etc.). Teicoplanin is administered intramuscularly or intravenously once a day.

Table 2 – ***Drugs for prescription***

Drug name (Latin)	**Single dose and route of administration**	**Drug product**
Benzylpenicillinum-natrium	Intramuscularly 250,000–1,000,000 IU 4–6 times a day; intravenously slowly 1,000,000–2,000,000 IU; intravenously drop-by-drop 2,000,000–5,000,000 IU	Vials 250,000; 500,000 or 1,000,000 IU, powder for injection
Benzylpenicillinum-kalium	Intramuscularly 250,000–500,000 IU 4–6 times a day	Vials 250,000; 500,000 or 1,000,000 IU, powder for injection
Benzylpenicillinum-novocainum	Intramuscularly 300,000–600,000IU 2–3 times a day	Vials 300,000 or 600,000 IU, powder for injection
Bicillinum-5	Intramuscularly 1,500,000 IU once a month	Vials 1,500,000 IU, powder for injection
Oxacillinum-natrium	Orally, intramuscularly or intravenously 0.25–0.5 g 4–6 times a day	Tablets 0.25 or 0.5 g; capsules 0.25 g; vials 0.25 or 0.5 g of powder for parenteral administration
Ampicillinum	Orally 0.5 g 3–6 times a day	Capsules and tablets 0.25 g
Amoxicillinum	Orally 0.25–1.0 g 3 times a day; intramuscularly or intravenously 1.0 g 2 times a day	Coated tablets 1.0 g; capsules 0.25 or 0.5 g; vials 1.0 g of powder for injection
Cefalexinum	Orally 0.25–0.5 g 4 times a day	Capsules 0.25 g; tablets 0.5 g

Continuation of Table 2

Drug name (Latin)	Single dose and route of administration	Drug product
Cefotaximum	Intramuscularly or intravenously 0.5–1.0 g 2–3 times a day	Vials 0.5, 1.0 or 2.0 g of powder for injection
Cefoxitinum	Intramuscularly or intravenously 1–2 g 2–4 times a day	Vials 1.0 or 2.0 g of powder for injection
Ceftriaxone	Intramuscularly or intravenously 1–2 g once a day or 0.5–1.0 g twice a day	Vials 0.5, 1.0 or 2.0 g of powder for injection
Erythromycinum	Orally 0.1–0.25 g 4–6 times a day; into the lower eyelid pocket 1 % ointment up to 6 times a day	Tablets 0.1 or 0.25 g; 1 % ophthalmic ointment 7 g
Azithromycinum	Orally 0.25–1.0 g once a day	Capsules 0.125 or 0.25 g; tablets 0.5 g
Tetracyclinum	Orally 0.2–0.25 g 4 times a day; into the lower eyelid pocket 1 % ointment ointment 2–6 times daily	Coated tablets 0.05, 0.1 or 0.25 g; 1 % ophthalmic ointment 3.0 or 10.0 g
Methacyclini hydrochloridum	Orally 0.3 g 2 times a day	Capsules 0.15 or 0.3 g
Doxycyclinum	Orally 0.1 g 1–2 times a day or 0.2 g once a day	Capsules 0.1 g
Laevomycetinum	Orally 0.25–0.5 g 3–4 times a day; 1–2 drops of 0.25 % solution into the eye	Tablets 0.25 or 0.5 g; capsules 0.1, 0.25 or 0.5 g; vials 10 ml of 0.25 % solution
Synthomycinum	1–10 % topically	1 %, 5 % or 10 % liniment
Streptomycini sulfas	Intramuscularly 0.5 g 2 times a day	Vials 0.25, 0.5 or 1.0 g of powder for injection

Continuation of Table 2

Drug name (Latin)	Single dose and route of administration	Drug product
Gentamycini sulfas	Intramuscularly or intravenously 0.0004–0.001 g/kg 2–3 times daily; 1–2 drops of 0.3 % solution into the affected eye(s)	Ampoules 1 or 2 ml of 4 % solution; vials 0.08 g of powder for injection (for parenteral administration, it should be dissolved before using); ophthalmic solution: 0.3 % – 10 ml
Amikacini sulfas	Intramuscularly or intravenously (slowly or drop-by-drop) 0.0075 g/kg twice a day or 0.005 g/kg 3 times a day	Vials 0.25, 0.5 or 1 g of powder for injection; ampoules 2 ml of 5 % or 25 % solution
Polymyxini M sulfas	Orally 500,000 IU 3–4 times daily; topically, in liniment (10,000 IU/1 g) or in solution (10,000–20,000 IU/ml) to treat wounds	Tablets 500,000 IU; vials 500,000 or 1,000,000 IU of powder (to prepare solution for external use); liniment 30,0 g (10,000 IU in 1 g)

Sulfonamides

Sulfonamides are synthetic chemotherapeutic drugs – derivatives of sulfanilic acid.

Sulfonamides are classified as follows:

1. Resorptive sulfonamides.

1.1. Short-acting drugs: *streptocid*, *norsulfazol*, *etazol*, *sulfadiazine*, and *sulfadimezine*.

1.2. Intermediate-acting drugs: *sulfamethoxazole* and *sulfazine*.

1.3. Long-acting drugs: *sulfapyridazine* and *sulfadimethoxine*.

1.4. Ultra-long-acting drugs: *sulfalen* and *sulfadoxine*.

2. Sulfonamides acting in the intestinal lumen:

– *phthalazolum (phthalylsulfathiazole)*, *phthazinum (phthalylsulfapyridazine)*, and *sulginum (sulfaguanidine)*;

– combined drugs of sulfonamides and 5-aminosalicylic acid: *salazopyridazine (mesalazine)* and *salazodimethoxine*.

3. Sulfonamides for topical application: *sulfacyl sodium* and *silver sulfadiazine*.

Chemical structure of sulfonamides is similar to the structure of para-aminobenzoic acid (PABA). PABA is a component of folic acid. Folic acid participates in synthesis of nucleic acids and proteins (transfers the one-carbon radicals). A significant number of bacteria synthesize folic acid. Due to structural resemblance, sulfonamides are competitive antagonists of PABA. When concentration of sulfonamides in environment is higher than PABA concentration, bacterial cells absorb molecules of sulfonamides instead of molecules of PABA. Also, sulfonamides are competitive inhibitors of dihydropteroate synthase – a bacterial enzyme involved in folate synthesis. As a result, the synthesis of folic acid is violated with the following inhibition of protein and nucleic acid synthesis. Sulfonamides are bacteriostatic agents.

It is necessary to notice that human cells do not synthesize folic acid but require its dietary intake in the form of vitamin B_c, therefore, sulfonamides are not antimetabolites for human organism.

Sulfonamides have the broad spectrum of antibacterial action. These drugs are active against both Gram-positive and Gram-negative cocci (staphylococci, streptococci, pneumococci, meningococci, gonococci), as well as against *Haemophilus influenza*, *Bacillus anthracis*, *Jersinia pestis*, Brucella, *Vibrio cholerae*, *Corinebacterium diphtheriae*, *Shigella*, *Chlamidia*, *Toxoplasma*, *Plasmodium*, *Pneumocystis*, Actinomycetes, etc.

Resorptive sulfonamides are readily absorbed in gastrointestinal tract. The degree of plasma protein binding ranges from 20 % up to 90 %. The main step of drug metabolism, acetylation, take place in the liver. Acetylated forms have a higher ability to bind to plasma proteins and a low ability to penetrate into tissues. Acetylated sulfonamides do not have antibacterial properties. These metabolites are excreted through the kidneys without the following reabsorption.

Acetylated forms are badly dissolved in water and can form precipitate in the acid urine with the obstruction of renal tubules. This complication may be prevented by intake of sodium hydrocarbonate or alkaline mineral water (alkalinization of urine).

Sulfonamides easily penetrate through the blood-brain barrier. Significant drug concentrations are observed in kidneys, lungs, liver, skin,

peritoneal and pleural fluids, milk, saliva, bile, urine, etc. Sulfonamides do not accumulate in the bones.

Long-acting and ultra-long-acting sulfonamides are slowly inactivated in organism. These drugs undergo a significant reabsorption in distal convoluted tubules. Therefore, these drugs have long duration of action.

Short-acting sulfonamides are prescribed to be taken 4–6 times a day in a daily dose 4–6 g. Intermediate-acting drugs are prescribed for 2 times a day intake in a daily dose 1–3 g. Short-acting and intermediate-acting sulfonamides are used to treat acute infections. Long-acting sulfonamides are prescribed to take once a day for treatment of chronic infections. Ultra-long-acting drugs are prescribed to be taken by the scheme (as a rule once a week).

Therapeutic indications for sulfonamides are infections of urinary, respiratory or biliary tracts, intestinal infections, infections of skin and soft tissues, etc.

Sulfonamides acting in intestinal lumen are prescribed for 4 times a day intake in a daily dose 4–6 g.

Combined sulfonamides with 5-aminosalicylic acid are called salazosulfonamides. *Salazopyridazine* (*mesalazine*) is the most commonly used among them. Under the influence of bacterial enzymes in large intestine, salazosulfonamides are decomposed to sulfonamide and 5-aminosalicylic acid that provides the anti-inflammatory effect. Salazosulfonamides are used to treat nonspecific ulcerative colitis and Crohn's disease.

Sulfonamides for topical application are used in solutions, eye drops, ointments, pastes, antiseptic powders, or aerosols. Before drug application, skin breaks, wounds, or burns should be cleaned from the pus because it reduces sulfonamide activity owing to presence of PABA. Eye drops of sodium sulfacyl are used in treatment of blepharitis, corneal ulcers, and blennophthalmia.

Sulfonamides seldom cause the development of side effects. As a rule, undesirable phenomena develop due to overdose and include the following symptoms: central nervous system intoxication (dizziness, headache, depression of consciousness, nausea, and vomiting), hemolytic or aplastic anemia, granulocytopenia, thrombocytopenia, allergic reactions (dermatitis and skin rashes), and nephrotoxicity (proteinuria, erythrocytes and drug microcrystals in urine, and low back pain). The formation of microcrystals may be prevented by intake of alkaline liquids, because in alkaline

environment the ability of sulfonamides and their acetylated metabolites to precipitate is low. Sulfonamides should be prescribed with caution for patients with diseases of liver and kidney.

Sulfonamide and Trimethoprim Combinations

There is a number of drug combinations comprising sulfonamides and trimethoprim: *Co-trimoxazole (Biseptol, Bactrim, Groseptol), Sulfaton, Lidaprim, Poteseptil,* etc. The optimal ratio of trimethoprim to sulfonamide is 1:5. Thus, the most commonly used drug Biseptol contains 400 mg of *sulfamethoxazole* and 80 mg of *trimethoprim*.

A combination of sulfonamides with trimethoprim provides the possibility to block the synthesis of tetrahydrofolic acid in two steps:

– sulfonamide compete with PABA;

– trimethoprim blocks the enzyme, providing transformation of dihydrofolic acid into tetrahydrofolic acid – dihydrofolate reductase.

Due to this mechanism, combination drugs have bactericidal effect. The bacterial resistance to combination drugs develops slowly.

It is necessary to notice that human dihydrofolate reductase is 50,000 times less sensitive to trimethoprim than bacterial enzyme.

Trimethoprim is readily absorbed in gastrointestinal tract and easily penetrates into tissues and fluids of the body. Nearly 50–60 % of the administered dose is exscreted from the body with urine. The rest is excreted with bile, sputum, etc.

Biseptol is used to treat infections of moderate severity. Children older than 12 eyars and adult patients should take 2 tablets of Biseptol twice a day. There are Bactrim or Septrin solutions in ampoules for intravenous infusion. The content of the ampule should be diluted with 5% dextrose in water and administered intravenously drop-by-drop.

Therapeutic indications for Biseptol are as follows: respiratory tract infections (acute bronchitis, pneumonia, icluding pneumonia caused by Pneumocystes), urinary tract infections, enteritis, colitis, otitis, meningitis, sepsis, toxoplasmosis, and tropical malaria.

Side effects of combination drugs are allergic reactions, nephrotoxicity, hepatotoxicity, methemoglobinemia, hemolytic anemia, neuritis, teratogenicity, porphyria (in patients with hereditary metabolic disorders), superinfection, deficiency of folic acid that results in anemia, hypotrophy, dyspepsia, and disturbances in spermatogenesis.

Combination drugs are contraindicated to children under 6 years of age, pregnant women, patients with disturbances in haematopoiesis, and in diseases of liver and kidneys.

Synthetic Antibacterial Drugs with Different Chemical Structure

This group includes antimicrobial drugs with different chemical structure which are classified into different groups:

1. Quinolone derivatives.
2. Nitrofuran derivatives.
3. Quinoxaline derivatives.
4. Oxazolidinones.

Quinolones

There are three generations of quinolones which differ by their antibacterial spectrum, activity, and toxicity.

First-Generation Quinolones

First-generation quinolones are *nitroxolinum, intestopan, chiniofonum, enteroseptol,* and *chlorchinaldolum*. There are combination drugs containing enteroseptol: *Mexaform* (contains *enteroseptol, entobex,* and *oxyphenonium bromide*) and *Mexasa* (*enteroseptol, entobex, bile acids, pancreatin,* and *bromelain)*. Oxyphenonium bromide is a drug with antispasmodic activity. Bromelain is a proteolytic enzyme contained in a pineapple.

First-generation quinolones affect the activity of metal-containing bacterial enzymes and inhibit the synthesis of bacterial DNA. Besides, molecules of these drugs contain the atoms of I, Cl, or Br and cause the denaturation of bacterial proteins. Pharmacological effect of the 1st-generation quinolones is bactericidal.

Antibacterial spectrum of the 1st-generation drugs is broad and includes Gram-positive and Gram-negative bacteria, protozoa (amoeba, lamblia), and *Candida*. One should have in view that microorganisms become resistant to the 1st-generation quinolones very quickly.

All drugs (except nitroxoline) are almost not absorbed from gastrointestinal tract, therefore they act only on microflora of the

gastrointestinal tract. Most 1st-generation drugs are taken orally 4 times a day.

About 50 % of orally taken *nitroxoline* is absorbed in the blood. Nitroxoline binds to plasma proteins, poorly penetrates into fluids and tissues of the body (except renal tissue and prostate), and is excreted through the kidneys unchanged. Nitroxoline is used in treatment for urinary tract infections. The toxicity of nitroxoline is low. Side effects are allergic reactions and dispeptic disorders. The drug turns the urine violent yellow.

Chiniofonum is used mainly to treat amoebic dysentery. *Intestopan, enteroseptol,* and *chlorchinaldolum* are used to treat intestinal infections (dysentery, salmonellosis, intestinal disorders caused by staphylococci, Proteus, enterobacteria, etc.). *Mexaform* is a drug of choice in case a patient is concerned about painful spasms of intestinal smooth muscles. In case of meteorism, *Mexasa* is preferable. Iodine-containing drugs are contraindicated to patients with hyperthyreosis.

Second-Generation Quinolones

Second-generation quinolones are *nalidixic acid, oxolinic acid (gramurin),* and *pipemidic acid (palin)*. These drugs inhibit metal-containing enzymes of bacterial cells. Depending on concentration, the 2nd-generation quinolones cause bacteriostatic or bactericidal effect.

Antibacterial spectrum of the 2nd-generation quinolones directs upon Gram-negative bacteria (*Escherichia, Shigella, Salmonella, Klebsiella,* and *Proteus*). *Pseudomonas aeruginosa* is resistant to the 2nd-generation drugs. Bacteria quickly develop secondary resistance to these drugs.

The second-generation quinolones are prodrugs, which after hydroxylation in liver, are transformed into pharmacologically active substances.

The drugs are taken orally because they have high bioavailability in the gastrointestinal tract. The 2nd-generation drugs poorly penetrate into tissues and fluids of the body, being excreted through the kidneys. These drugs are prescribed to be taken 4 times a day. Therapeutic indications for the 2nd-generation quinolones are acute and chronic infections of urinary tract. It is necessary to acidify the urine during treatment with these drugs.

Side effects of the 2nd-generation quinolones are allergic reactions, dispetic disorders, headache, photodermatosis, and isomnia. The drugs are contraindicated for patients with severe violations of hepatic and renal

functions, for pregnant women in first 3 months of pregnancy, and for children under 2 years of age.

Third-Generation Quinolones (Fluoroquinolones or Systemic Quinolones)

Molecules of these drugs contain fluorine and piperidine radicals that significantly influence upon their antibacterial spectrum and pharmacological properties. Fluoroquinolones are classified into the following groups:

– monofluoroquinolones: *norfloxacin (floxacin), pefloxacin (abactal), enoxacin, ofloxacin (tarivid), ciprofloxacin (ciprobay), pufloxacin*;

– difluoroquinolones: *lomefloxacin (maxacvin), sparfloxacin (zagam)*;

– trifluoroquinolones: *tosufloxacin, fleroxacin (Quinodis)*.

Fluoroquinolones inhibit DNA gyrase (also known as topoisomerase II) activity – an enzyme essential for bacteria viability. DNA gyrase paticipates in the process of DNA replication. DNA gyrase provides the formation of negative supercoiling in the relaxed circular prokaryotic DNA molecules. Interaction between gyrase and DNA leads to DNA winding around the enzyme. There is a positive supercoiling in places of DNA which is associated with gyrase. Thereafter, the enzyme makes a double-stranded break in DNA, moves a double strand from inside to outside, and stitches segments back together. Thus positive supercoiling of DNA transformes into negative supercoiling that promotes the movement of DNA polymerase along DNA.

Bacterial DNA gyrase essentially differs from human DNA gyrase. This provides the high selectivity of fluoroquinolones against microorganisms and their low toxicity for humans.

Some fluoroquinolones (ofloxacin, ciprofloxacin, and lomefloxacin) have an ability to inhibit the enzyme that provides the synthesis of the SOS-system proteins. These proteins protect the bacterial cell from unfavorable external factors and are responsible for changes of the rod-shaped bacteria (filament forms) before cell division. Fluoroquinolones are bactericidal agents.

Fluoroquinolones are ultra-broad-spectrum antibacterial agents. Gram-negative microflora is more sensitive than Gram-positive bacteria to these drugs. Fluoroquinolones are active against gonococci, *Escherichia coli,*

Shigella, *Salmonella*, *Klebsiella*, *Enterobacter*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Mycoplasma*, *Chlamidia*, etc. There are resistsnt bacteria to fluoroquinolones: Spirochaetales, fecal enterococci, and anaerobes. It is necessary to notice that sparfloxacin has the highest activity against Gram-positive cocci, *Chlamidia*, *Mycoplasma*, *M. tuberculosis* and *M. leprae*.

Moxifloxacin (Avelox, Avalox) exhibits the high activity against streptococci, staphylococci, *Chlamydia*, *Mycoplasma*, *Ureaplasma*, and anaerobes. In activity against anaerobes, moxifloxacin is similar to metronidazole and imipenem.

Bacteria slowly develop the secondary resistance to fluoroquinolones. As soon as bacterial resistance is developed, it spreads to the 1st- and the 2nd-generation quinolones and a significant amount of antibiotics (tetracyclines, chloramphenicol, and β-lactam antibiotics). Therefore fluoroquinolones should be used only as reserve drugs.

There are known such new fluoroquinolones as *gatifloxacin*, *gemifloxacin*, and *levofloxacin*. The drugs have high activity against Gram-positive and Gram-negative bacteria, especially against pathogens causing respiratory tract infection and tuberculosis. These new agents are taken orally.

Fluoroquinolones are taken orally, administered intravenously, or used externally. For intravenous administration, the drug (e.g. ciprofloxacin, pefloxacin) is diluted ex tempore. Solutions should be protected from light.

Fluoroquinolones are readily absorbed in the gastrointestinal tract. Simultaneous intake of fluoroquinolones with antacids and iron-containing drugs should be avoided, because the bioavailability of fluoroquinolones is reduced. The degree of fluoroquinolone binding to plasma proteins is about 40 %. Fluoroquinolones readily penetrate into main tissues and fluids of the body, but only some drugs (ofloxacin, pefloxacin, and ciprofloxacin) can penetrate through the blood-brain barrier. The main route of drug elimination is kidneys. Fluoroquinolones are prescribed to be taken 1–2 times a day.

Fluoroquinolones should be prescribed only in cases when broad-spectrum antibiotics are ineffective. The therapeutic indications for fluoroquinolones are infections of urinary tract (foremost caused by *Pseudomonas aeruginosa*), respiratory system, gastrointestinal tract, severe purulent surgical infections caused by multiresistant microflora or

Staphylococcus aureus, treatment and prevention of infections in patients with neutropenia, oncological diseases, and immunodeficiency.

Fluoroquinolones are low-toxic drugs. Their side effects are dyspepsia, skin rash and other allergic reactions, headache, dizziness, insomnia, photosensitization, temporal arthralgia, disbiosis, and disturbances of renal and hepatic functions.

Nitrofurans

Nitrofurans include such drugs as *furacilinum (nitrofural, nitrofurazone), furazolidone, furadoninum (nitrofurantoin), furaginum (furazidin),* and *furazolinum*.

Nitrofurans form the complex compound with bacterial DNA, affect the transport of electrons in respiratory chain, violate the redox processes in citric acid cycle. It results in the disturbances of cytoplasmic membrane function and destruction of bacterial cell wall. Depending on a dose, nitrofurans exhibit bacteriostatic or bactericidal effect. Unlike other antibacterial drugs which inhibit immunity, nitrofurans slightly increase the resistance of macroorganisms to infection (nitrofurans stimulate phagocytosis, etc.). Under the nitrofuran influence, the production of toxins by bacteria is reduced. Nitrofurans keep their activity in precence of pus and other products of tissue disintegration.

Nitrofuran antibacterial spectrum is broad and includes such microorganisms as Gram-positive and Gram-negative bacteria (staphylococci, pneumococci, streptococci, *Klebsiella*, *Proteus*, *Enterobacter*, meningococci, gonococci, etc.) and protosoa (*Trichomonas* and *Giardia lamblia*).

The bacterial resistance to nitrofurans develops slowly and is not cross-reactive with sulfonamides and antibiotics.

Nitrofurans are taken orally after a meal. Furaginum is also used for intravenous administration. Furacilinum and furaginum are used topically. The degree of nitrofuran absorption in gastrointestinal tract is about 50 % (for furazolidone – only 30 %). The degree of binding with plasma proteins is very low. Nitrofurans readily penetrate into lymph and accumulate in the bile duct. Only 10 % of administered nitrofuran dose undergoes biotransformation. Nitrofurans are excreted from the body through the kidneys. The intensity of excretion is higher in alkaline urine. In acid urine, nitrofurans undergo reabsorption that provides for their accumulation. Nitrofurans are prescribed to be taken 4 times a day.

Furadoninum (nitrofurantoin) is mainly used in treatment of urinary tract infections (pyelonephritis, cystitis, and uretritis). Also, furadoninum is used to prevent infection in cystoscopy and prolonged catheterization.

Furazolidone is poorly absorbed in the gastrointestinal tract that allows it to be used in enterocolitis treatment. The drug is also used to treat lambliasis and colpitis caused by Trichomonas. Furazolidone is taken orally and applied intravaginally or rectally.

Furacilinum (nitrofural) is known as antiseptic for external use. The drug is used for antiseptic rinsing, washing of wounds, burns, and bedsores. Also, furacilin is used in form of eye and ear drops.

Side effects of nitrofurans are expressed by loss of appetite, nausea, epigastric pain, allergic reactions (skin rash, bronchospasm, fever, etc.), disturbances of renal function, neuritis, and methemoglobinemia. Drinking plenty of fluids and taking in H_2-receptor antagonists and vitamins of group B are prescribed when treating by nitrofurans to prevent or diminish their side effects.

Quinoxaline Derivatives

Quinoxaline derivatives are *quinoxidine* and *dioxidine*. Quinoxalines are synthetic agents with bactericidal effect. The mechanism of their action is poorly understood. Antibacterial spectrum includes *Proteus*, *Pseudomonas aeruginosa*, *Klebsiella*, *Escherichia coli*, *Shigella*, *Salmonella*, staphylococci, streptococci, *Clostridium*, and *Bacteroides*. Bacteria slowly develop secondary resistance to quinoxalines.

Quinoxidine is taken orally 3–4 times a day after a meal. The drug is readily absorbed in the gastrointestinal tract. Dioxidine is administered intravenously drop-by-drop (0.1–0.2 % sterile solutions) or administered in body cavities. Also, solutions or ointments with dioxidine are used topically. Quinoxaline derivatives are excreted through the kidneys unchanged.

Quinoxaline derivatives are used as reserve drugs in treatment of purulent inflammatory processes of different localization: purulent pleuritis, lung abscess, peritonitis, pyelonephritis, cholecystitis, and severe sepsis.

Quinoxalines are quite toxic drugs. Their side effects are expressed by dispepsia, dizziness, headache, allergic reactions, candidiasis, muscle twitching, carcinogenesis, teratogenicity, etc.

Oxazolidinones

The representative of this new antibacterial group is *linezolid (Zyvox)*. Linezolid affects the syntheisis of nucleic acids and protein synthesis on ribosomes. As a rule, linezolid exhibits bacteriostatic effect, but against Gram-positive cocci the drug can produce the bactericidal effect.

Antibacterial spectrum of linezolid is broad and includes such microorganisms as aerobic Gram-positive bacteria and cocci, some Gram-negative bacteria, Mycobacterium tuberculosis, and many anaerobes.

Linezolid is administered intravenously or taken orally 1–2 times a day. The drug is readily absorbed in the gastrointestinal tract. Its bioavailability is about 100 %. The degree of binding to plasma proteins is about 30 %. Inactivated linezolid is excreted through the kidneys (30 %) and liver (70 %).

The therapeutic indications for linezolid are sepsis, endocarditis, pneumonia, infections of skin and soft tissues, and other severe infections caused by Gram-positive cocci.

The side effects of linezolid are dysbiosis, candidiasis, nausea, vomiting, headache, and changes in gustatory perception. The prolonged drug use can cause thrombocytopenia, peripheral neuropathy (including optic nerve), allergic reactions, pancreatitis, and liver damage.

Table 3 – ***Drugs for prescription***

Drug name (Latin)	Single dose and route of administration	Drug product
Sulfadimezinum	Orally 1st administration – 2.0 g; all subsequent administrations 1.0 g 4–6 times daily	Tablets 0.25 or 0.5 g
Aethazolum	Orally 1.0 g 4–6 times daily	Tablets 0.25 or 0.5 g
Sulfacylum-natrium	Intravenously slowly 3–5 ml of 30 % solution twice a day; 1–2 drops into eyes 2–6 times daily	Ampoules 5 ml of 30 % solution; eye drops: bottles 10 ml of 20 % or 30 % solution
Sulfadimethoxinum	Orally 1st administration – 1.0–2.0 g; all subsequent administrations 0.5–1.0 g 1–2 times a day	Tablets 0.2 or 0.5 g

Continuation of Table 3

Drug name (Latin)	Single dose and route of administration	Drug product
Phthalazolum	Orally 1.0 g 4–6 times daily	Tablets 0.5 g
Biseptol-480	Orally 2 tablets 2 times daily; intravenously drop-by-drop 10 ml deluted in 250 ml of isotonic solution of NaCl twice a day	Tablets containing 0.4 g of sulfamethoxazole and 0.08 g of trimethoprom; ampoules 5 ml
Nitroxolinum	Orally 0.1 g 4 times a day	Coated tablets 0.05 g
Acidum nalidixicum	Orally 0.5–1.0 g 4 times daily	Tablets or capsules 0.5 g
Ciprofloxacinum	Orally 0.25–0.75 g 2 times daily; intravenously drop-by-drop 0.2–0.4 g with 50 ml of isotonic sodium chloride solution 2 times a day	Tablets 0.25; 0.5 or 0.75 g; ampoules 10 ml of 1 % solution
Furazolidonum	Orally 0.1 g 4 times daily	Tablets 0.05 g

Antisyphylitic Drugs

Antisyphylitic drugs are used to treat syphilis. The infectious agent causing syphilis is *Treponema pallidum*. The antisyphylitic therapy is complex and requires pill-dosing regimen.

Presently, three groups of drugs are most commonly used to treat syphilis: antibiotics, fluoroquinolones, and bismuth preparations.

Classification of antisyphylitic drugs is as follows:

1. Antibiotics:

– penicillins: *benzylpenicillin sodium, benzylpenicillin potassium, benzylpenicillin novocaine salt, bicillin-1, bicillin-5, ampicillin, oxacillin*;

– macrolides and azalides: *erythromycin, oleandomycin, azithromycin*;

– cephalosporines: *cefazolin, ceftriaxone*, etc.;

– tetracyclines: *doxycycline, tetracycline*.

2. Fluoroquiniolones: *ofloxacin*, etc.

3. Bismuth-containing drugs: *biiochinol, bismoverol*.

Both short-acting and long-acting penicillins are used to treat syphilis. Penicillins are the most efficient drugs for syphilis therapy and are active against *Treponema palidum* in all stages of the disease. Penicillins are especially effective if used in combination with bismuth preparations.

In case of individual intolerance to penicillins, other effective antibiotics (macrolides, tetracyclines, and cephalosporins) are prescribed for syphilis treatment. But all of them are less active against *Treponema pallidum*.

Bismuth-containing drugs are biiochinolum and bismoverolum. Both drugs are the suspensions of bismuth-containing substances in peach-kernel oil. These drugs are active only against *Treponema pallidum*. Bismuth blocks the thiol enzymes of *Treponema*. The activity of bismuth-containing drugs is less then penicillin activity, and their effect develops slower. Bismuth-containing drugs are especially effective in neurosyphilis. Both drugs are non-absorbable in gastrointestinal tract, therefore they are administered intramuscularly. Bismuth-containing drugs accumulate in the body with a significant accumulation in the bones, kidneys, liver, and nervous tissue. The routes of drug excretion are kidneys and intestine. Bismuth-containing drugs are used in treatment of all forms of syphilis.

The common complication of bismuth therapy is so-called "bismuth flu": generalized weakness, fever, and fatigue. These symptoms appear right after drug administration: gray colored border around the edge of the gums, dermatitis, gingivitis, colitis, stomatitis, and dark spots on the cheeks appear subsequently. Sometimes, leukopenia and disturbances of hepatic and renal functions are observed.

Iodine preparations are used in resorption of intracranial gummas in the tertiary stage of syphilis.

Table 4 – ***Drugs for prescription***

Drug name (Latin)	**Single dose and route of administration**	**Drug product**
Benzylpenicillinum-natrium	Intramuscularly 250,000–1,000,000 IU 4–6 times daily	Vials 250,000; 500,000 or 1,000,000 IU of powder for injection
Bicillinum-5	Intramuscularly 1,500,000 IU 1 time per month	Vials 1,500,000 IU of powder for injection
Biiochinolum	Intramuscularly 2–3 ml 1 time per 3 days	Vials 100 ml
Bismoverolum	Intramuscularly 1.5 ml 2 times per week	Vials 100 ml

Antituberculosis Drugs

Tuberculosis is an infective disease caused by three species of Mycobacterium: *M. tuberculosis, M. bolis* and *M. avium*. *M. tuberculosis* is a so-called "human" specie which is transmitted only from human to human. *M. bolis* and *M. avium* (bovine and avian species) can infect both humans and animals.

Modern tuberculosis is characterized by mainly bronchopulmonary localization (about 80 % of cases). According to WHO, there are about 20 million sick people with active tuberculosis around the world. Annually, from 50 to 100 million people are infected and more than 3 million people die. The risk of falling ill is significantly increased in people with immunodeficiency: AIDS/HIV patients, smokers, patients with chronic bronchopulmonary diseases, and in malnutrition. The stress is not the least among health risk factors. Thus, the incidence of tuberculosis is sharply increased in times of crises and wars.

Antituberculosis drugs include both antibiotics and synthetic agents. Synthetic drugs are active only against species of *Mycobacterium* causing tuberculosis. Some of them are also active against *Mycobacterium leprae*. Antibiotics which are used to treat tuberculosis are broad spectrum antibiotics of rifamycin and aminoglycoside groups.

According to reccomendations of the International Union Against Tuberculosis and Lung Disease (1997), antituberculosis drugs are classified into the following groups based on their activity:

1. Most effective antituberculosis drugs.
1.1. Isonicotinic acid derivatives: *isoniazid, ftivazide, saluzidum*.
1.2. Rifamicins: *rifampicin, rifabutin, rifaximin*.
2. Drugs with high antituberculosis activity:
2.1. Aminoglycosides: *streptomycin, kanamycin, amikacin*.
2.2. Isonicotinic acid derivatives: *ethionamide, prothionamide, pyrazinamide*.
2.3. Aminobutanol derivatives: *ethambutol*.
2.4. Fluoroquinolones: *ofloxacin, lomefloxacin, ciprofloxacin, sparfloxacin*.
2.5. Antibiotics of different groups: *cycloserine, capreomycin, florimycin*.
3. Drugs with moderate antituberculosis activity:

3.1. Para-aminobenzoic acid derivatives: *sodium para-aminosalicylate (PAS)* and *calcium para-petrolyl-aminosalicylate (Bepascum)*.

3.2. Thiosemicarbazone derivatives: *thioacetazone*.

According to the degree and reliability of action upon Mycobacteria, antituberculosis drugs are divided into two groups:

1. First-line drugs: *isoniazid, rifampicin, ethambutol, pyrazinamide,* and *streptomycin*.
2. Second-line drugs: *ethionamide, prothionamide, cycloserine, florimycin, capreomycin, amikacin, kanamycin, lomefloxacin, ofloxacin, ciprofloxacin,* and *PAS*.

There are several populations of *M. tuberculosis*. First-population mycobacteria are located outside the cells, have intensive metabolism and rapidly grow in the acidic environment. This population is predominant in acute phase of disease. Moreover, bacteria are highly sensitive to antituberculosis drugs; the resistant strains are often found between them. Therefore, the treatment of tuberculosis starts with the use of 3–5 drugs.

Second-population mycobacteria are located inside the cells (mainly within macrophages) and characterized by low metabolic rate and slow growth in the acidic environment. This population is typical for chronic forms of tuberculosis. Second-population mycobacteria are sensitive to pyrazinamide, isoniazid, and rifampicin. Aminoglycosides do not penetrate into the cells, therefore, they do not significantly affect this population.

Third-population mycobacteria are characterized by slow growth and location in caseous foci. This population is sensitive only to pyrazinamide and rifampicin. Second- and third-population mycobacterium can transform into latent forms. In unfavourable conditions (reduction of immunity, deterioration of the living conditions of the patient), these latent forms cause the disease recurrence. The latent forms of mycobacteria are sensitive to rifampicin and pyrazinamide.

There are some peculiarities of tuberculosis treatment. It is necessary to choose the drugs to which mycobacteria are sensitive. The course of treatment can take from several months to several years. Pharmacotherapy includes simultaneous intake of several drugs. A prolonged antituberculosis therapy is accompanied by the development of bacterial resistance and toxic effects in the human body. The combined pharmacotherapy with 3–5 antituberculosis drugs prevents the bacterial resistance. The efficacy of

tuberculosis therapy increases if antituberculosis drugs are used together with immunomodulators. Also ambenum is used because this drug prevents the lungs' fibrosis. In prolonged antituberculosis therapy, such agents as insulin (8 IU a day), glucocorticoids (20 mg a day), folic acid, and stimulator of phagocytosis flurenizid are used. Hepatoprotectors are prescribed to prevent liver damage (LIV 52, Essentiale, Solcoseryl, etc.).

From the clinical point of view, all tuberculosis patients are divided into 4 groups. The first group includes the patients who release mycobacteria into the external environment. The short-term therapeutic regimen (during 6 months) is used to treat such patients. The treatment is performed in two phases. A combination of four drugs is prescribed in the initial phase of treatment. This combination includes isoniazid, rifampicin, pyrazinamide, and ethambutol or streptomycin. The duration of this phase is 2 months. The second phase lasts four months. Two drugs – isoniazid and rifampicin – are prescribed in this phase. As a result of therapy, the release of mycobacteria is terminated in 100 % of patients and closing of caverns is observed in 89 %.

The second group includes tuberculosis patients who do not release mycobacteria. These patients are treated by 4-drug combination (isoniazid, rifampicin, pyrazinamide, and ethambutol or streptomycin) during four months.

The third group includes elderly patients. A so-called "mild" regimen of intermittent therapy is used in their treatment. According to this regimen, three drugs are prescribed to be taken two times a week during the first half-year.

The fourth group includes healthy people at high risk for tuberculosis: persons who contact sick people releasing mycobacteria, patients with hyperergic tuberculin reaction (more than 6 mm), healthcare workers of TB dispensary, etc. They take isoniazid once a day after a meal during 2–3 moonths or three times a week (intermittent method).

Most Effective Antituberculosis Drugs:

Isonicotinic Acid Derivatives

Hydrazides of isonicotinic acids include such drugs as *isoniazid, ftivazide, saluzidum, ethionamide,* and *prothionamide*.

Isoniazid is most commonly used among them. The drug has high activity against *Mycobacterium tuberculosis*. Isoniazid acts upon both extracellular and intracellular mycobacteria.

A mechanism of isoniazid action is not clear enough. The drug affects synthesis of mycolic acids which are essential for the cell wall of mycobacteria, because mycolic acids are structural components of the cell wall only for mycobacteria, therefore isoniazid action is highly specific and it is active only against mycobacteria. Besides, there is a viewpoint that isoniazid also inhibits the nucleic acid synthesis. Effect of isoniazid is bactericidal.

Isoniazid is taken orally or administered intramuscularly, intravenoulsly, by inhalation, and into cavernas. Orally, isoniazid is taken 1–3 times a day after a meal. The drug is readily absorbed in the gastrointestinal tract. Isoniazid easily penetrates through tissue barriers including the blood-brain barrier.

The rate of isoniazid inactivation (hepatic acetylation) significantly differs in different patients. This fact should be taken into account for drug dosing. The speed of hepatic acetylation is genetically determined, and about 50% of European population has a low speed of this reaction. In these patients (so-called "slow acetylators"), plasma drug concentration reduces 2–2.5 times slower than in "fast acetylators". The main route of isoniazid excretion is kidneys.

Intramuscular or intravenous routes of isoniazid administration are used in severe forms of tuberculosis. After intravenous drug administration, a patient should lie at least during 1–1.5 hours. As a rule, intravenous administration of isoniazid improves the pulmonary blood circulation.

Therapy with isoniazid is accompanied by significant side effects and complications. Neurotic effects are the first among them: neuritis, damage of ocular nerve, insomnia, psychic disturbances, dizziness, and memory loss. Nausea, vomiting, constipation, dry mouth, and allergic skin rash are possible due to the drug intake. Isoniazid affects the synthesis of vitamin B_6 active form – pyridoxal phosphate. The last one is the essential co-enzyme for deamination and transamination of amino acids and participates in protein synthesis. Therefore, isoniazid can cause disturbances of protein synthesis with the following muscular atrophy and anemia. Also, gynecomastia in males and menorrhagia in females are possible side effects of isoniazid. Pyridoxine, glutamic acid, thiamine, and ATP-Long are used for reduction of isoniazid toxicity.

Isoniazid contraindications are epilepsy and other convulsive diseases, disturbances of hepatic and renal functions, marked atherosclerosis, and phlebitis.

Other derivatives of isonicotinic acid (ftivazide, saluzid, ethionamide, prothionamide) are less active in comparison with isoniazid. These drugs are used in case of isoniazid intolerance.

Rifamicins

The main representative of this antibiotic group is *rifampicin*. This broad spectrum antibiotic is active against mycobacteria, Gram-positive and Gram-negative bacteria, including some strains of *Pseudomonas aeruginosa*, *Proteus*, and capsular bacteria.

Rifampicin inhibits the RNA synthesis due to blockage of DNA-dependent RNA-polymerase. Depending on the used dose, antibacterial effect of rifampicin is either bacteriostatic or bactericidal. Bacterial resistance to rifampicin develops quickly.

Rifampicin is taken orally 1–2 times a day 0.5–1 hour before a meal. The drug is easily absorbed from gastrointestinal tract. Maximum blood concentration is achieved in 2–2.5 hours. Also, rifampicin is administered intravenously drop-by-drop (only for adults). Duration of the drug action is 8–12 hours. Rifampicin readily penetrates through the histohematic barrier and is excreted with bile, urine, and bronchial secret. The drug can turn urine, tears, saliva, and other body fluids red.

As a rule, rifampicin is prescribed together with other antituberculosis agents. Also, rifampicin is used as a reserve drug for treatment of other infectious diseases. Sometimes, rifampicin is used to treat lepra and rabies (in incubation period, because the drug inhibits the development of rabies encephalitis).

Rifampicin is hepatotoxic and immunosupressive agent. To prevent immunodeficiency, immunocorrectors (levamisole, T-activin, etc.) are used during therapy with rifampicin.

Rifampicin therapy may be complicated by leukopenia, dyspepsia, and allergic reactions. The drug is contraindicated for pregnant women, infants, and in severe hepatic and renal diseases.

Drugs with High Antituberculosis Activity:

Aminoglycosides

Streptomycin is an antibiotic of broad antibacterial spectrum. The drug is active against mycobacteria and most Gram-positive and Gram-

negative bacteria. Anaerobes, spirochetes, rickettsia, viruses, fungi, and protozoa are not sensitive to streptomycin.

Streptomycin inhibits the protein synthesis and affects the permeability of the bacterial cell membrane. Streptomycin is a bactericidal medication.

Streptomycin is badly absorbed in the gastrointestinal tract and therefore it is administered intramuscularly. Maximum blood concentration of streptomycin is achieved in 1–2 hours after administration. For tuberculosis treatment, the drug is administered 1–2 times a day. For treatment of other infections, streptomycin may be administered 3–4 times a day. Sometimes, streptomycin is administered intratrachealy (aerosol) or into cavernas (10 % solution, once a day, only in hospital). Streptomycin is excreted unchanged through the kidneys.

Ototoxic effect of streptomycin arises due to the damage to the vestibular branch of the 8th cranial nerve (vestibulocochlear nerve). The auditory branch is affected less frequently. The disturbances start from noise in ears. At that moment, the drug use should be stopped.

Streptomycin is a nephrotoxic agent. Also, the drug inhibits neuromyscular transmission that can result in respiratory depression.

Streptomycin is contraindicated in severe forms of cardiovascular failure, renal failure, disorders of cerebrovascular circulation, myasthenia gravis, and diseases of vestibulocochlear nerve.

Vitamins of A, B group, and C are prescribed for prevention or reduction of streptomycin neurotoxicity. Also, streptomycin pantotenate or streptomycin ascorbate are used with the same purpose. Streptomycin is prescribed only for inpatients.

Kanamycin is another representative of aminoglycosides. The drug has broad antibacterial spectrum of action. Kanamycin is used in tuberculosis treatment in the case when other antituberculous drugs are ineffective.

Other Antibiotics

Cycloserine is an antibiotic with broad antibacterial spectrum, including Gram-positive and Gram-negative bacteria. The most valuable property of cycloserine is its activity against mycobacteria. The drug is active against both extracellular and intracellular mycobacteria. Cycloserine is used to treat tuberculosis as a reserve agent when other antituberculosis drugs become ineffective. Cycloserine is the drug with

high neurotoxicity. Side effects of the drug are headache, dizziness, insomnia, irritability, memory loss, paresthesia, peripheral neuritis, anxiety, psychasthenic state (a condition characterized by rapid mood changes, suicidality, depression, etc.), epileptiform seizures, loss of consciousness, etc.

Florimycin (viomycin) is a polypeptide antibiotic. Florimycin affects protein synthesis that results in bacteriostatic effect. The drug is characterized by low absorbability in the gastrointestinal tract, therefore it is administered intramuscularly. Florimycin easily penetrates through the tissue barriers. Viomycin is used to treat different forms of tuberculosis when other drugs are ineffective. The side effects of florimycin are the damage to 8th cranial nerve, disturbances of renal function, allergic reactions, and electrolyte disturbances.

Synthetic Drugs

Ethambutol is a synthetic agent with high antituberculosis activity. The drug affects only mycobacteria and is active in cases of bacterial resistance to isoniazid, streptomycin, and other drugs. Mechanism of action is based on ethambutol ability to inhibit the synthesis of RNA and proteins and the ability to interact with divalent metal ions. Also, ethambutol affects the ribosome structure. Ethambutol is bacteriostatic antitubercular agent. The drug is taken orally once a day after a meal. Ethambutol is easily absorbed from the gastrointestinal tract and excreted unchanged through the kidneys. Insignificant amount of the drug is excreted unchanged in feces.

Ethambutol is used in combination with other antituberculosis agents in treatment of different forms of tuberculosis. Side effects of ethambutol are dispepsia, dizziness, depression, allergic reactions, and visual field loss. Drug intake during 2–6 months may be accompanied by disturbances of color vision (especially perception of red and green colors). The vision is restored after drug removal.

Pyrazinamide is a derivative of pyrazincarbonic acid. The value of the drug is its ability to affect mycobacteria with resistance to other antituberculosis drugs. Antituberculosis activity of pyrazinamide is lower than the activity of isoniazid, rifampicin and aminoglycosides. Mechanism of pyrazinamide action is not completely known. It is apparent that the drug inhibits mycobacteria development on the stage of intracellular division.

Pyrazinamide is easily absorbed in the gastrointestinal tract, penetrates into tuberculous foci and exhibits high activity in the acidic environment of

caseous masses. Pyrazinamide is excreted through the kidneys. The drug is taken orally 3–4 times a day after a meal. Bacterial resistance to pyrazinamide develops readily. The drug is used to treat tuberculosis in combination with other antituberculosis drugs. Side effects are dispepsia, disturbances of liver functions, allergic reactions, artralgia, gout exacerbation, and photosensitization. Cyanocobalamin, methionine, and glucose are used to diminish pyrazinamide toxicity.

Ethionamide and *prothionamide* are isonicotinic acid derivatives. The properties of these drugs are close to the properties of isoniazid, but antituberculosis activity is low. The value of these drugs is their ability to affect mycobacteria which are isoniazid-resistant. The mechanism of action is the same as that with isoniazid. Ethionamide and prothionamide are bacteriostatic agents, they are active against both extracellular and intracellular mycobacteria. Both drugs stimulate phagocytosis in the inflammatory foci. The drugs are taken orally or administered rectally 3–4 times a day, but in case of poor tolerance – 2 times a day. It is necessary to notice that patients tolerate prothionamide better. The side effects of ethionamide and prothionamide are nausea, vomiting, diarrhea, liver function disturbances, allergic reactions, insomnia, and orthostatic hypotension. For prevention or reduction of these side effects, pyridoxine and nicotinamide are used. Ethionamide and prothionamide are contraindicated in pregnancy.

Drugs with Moderate Antituberculosis Activity:

Para-Aminosalycilic Acid Derivatives

Sodium para-aminosalicylate (PAS) and *calcium para-petrolylaminosalicylate (Bepascum)* exhibit bacteriostatic effect against mycobacteria. The molecular structure of these drugs is similar to the structure of para-aminobenzoic acid (PABA). Therefore, para-aminosalycilic acid derivatives are competitive antagonists of PABA. It is known that PABA is used by mycobacteria for protein synthesis. Inhibition of protein synthesis by PAS and Bepascum slows down the growth and division of bacteria.

PAS is taken orally after meal (with milk or alkaline mineral water). The drug is easily absorbed from the gastrointestinal tract. After absorption, the drug quickly penetrates into tissues of the internal organs. About 90 % of the taken dose is excreted through the kidneys, 10 % – with bile in an

inactive form. The main route of PAS inactivation is acetylation. Sometimes PASA is administered intravenously drop-by-drop.

Bepascum is a drug with prolonged action which releases para-aminosalycilic acid. The drug is taken orally.

Both drugs can cause such side effects as dispepsia (nausea, vomiting, diarrhea, and abdominal pain), allergic reactions (skin rash), hepatotoxicity, crystalluria, agranulocytosis, increased growth of the thyroid gland, and hypothiroidism.

Thiosemicarbazone Derivatives

Thiacetazone is a synthetic agent which is active against mycobacteria tuberculosis and leprosy. The drug exerts its bacteriostatic activity. Thiacetazone is taken orally after a meal. The clinical use of thiacetazone is restricted by its high toxicity. The drug is used only in combination with other antituberculosis agents in treatment of extrapulmonary tuberculosis: tuberculosis of mucous and serous membranes, lymphadenitis, specific fistulas, etc.

Side effects of thiacetazone are headache, nausea, dermatitis, blood dyscrasias (anemia, thrombocytopenia, leukopenia, and agranulocytosis), and disturbances of liver and renal functions.

Table 5 – ***Drugs for prescription***

Drug name (Latin)	**Single dose and route of administration**	**Drug product**
Isoniazidum	Orally 0.3 g 2–3 times daily; intramuscularly 0.3–0.9 g or intravenously drop-by-drop 0.01 g/kg (as 0.2 % solution) daily	Tablets 0.1 or 0.3 g; ampoules 5 ml of 10 % solution
Rifampicinum	Orally 0.45 g daily; intravenously drop-by-drop 0.45 g daily	Capsules 0.15 g; ampoules 0.15 g of powder
Natrii para-aminosalicylas	Orally 3–4 g 3–4 times daily (1–2 teaspoons of granules); intravenously drop-by-drop 7.5–15 g daily (as 3 % solution)	Tablets 0.5 g; granules 100 g; vials 250 or 500 ml of 3 % solution
Ethambutolum	Orally 0.025 g/kg daily	Tablets 0.1 or 0.4 g

Continuation of Table 5

Drug name (Latin)	Single dose and route of administration	Drug product
Streptomycini sulfas	Intramuscularly 0.5 g 2 times daily	Vials 0.5 g of powder
Pirazinamidum	Orally 0.015–0.025 g/kg once a day or 0.05–0.07 g/kg 2–3 times per week	Tablets 0.5 or 0.75 g

Antiviral Drugs

Antiviral drugs are agents of different chemical structure which interfere with viral penetration into the cells, synthesis of viral nucleic acids and proteins, and viral replication.

The following mechanisms of action are typical for different antiviral drugs:

1) inhibition of viral absorption and penetration into the host cell: *γ-globulin, enfuvirtide*;

2) impairment of the efficient release of the viral genome: *amantadine (midantanum), rimantadine*;

3) violation of viral protein synthesis: *guanidine, saquinavir*;

4) violation of nucleic acid synthesis: *zidovudine, acyclovir, vidarabine, idoxuridine*;

5) violation of the virion assembly: *metisazon*.

Nowadays, about 30 antiviral drugs are used in medicine. Except interferons, all of them are synthetic agents.

There are the following groups of antiviral drugs:

– drugs for influenza treatment;

– drugs active against herpes simplex virus and against cytomegalovirus;

– drugs active against human immunodeficiency virus (HIV);

– drugs active against retrovirus and picornavirus;

– drugs affecting variola virus;

– drugs active against Hepatitis B and Hepatitis C viruses.

Drugs for Influenza Treatment

This group includes the following drugs:

1. Drugs which block viral M_2 proton channel: *rimantadine,* *amantadine,* and *adaprominum*.

2. Drugs which inhibit viral enzyme neuraminidase: *zanamivir,* *oseltamivir*.

3. Drugs which inhibit viral RNA-polymerase: *ribavirin*.

4. Other drugs: *arbidol, oxoline*.

The Matrix-2 (M_2) protein is a specific protein of influenza virus. This protein is located in viral membrane and functions as an ionic channel. Drugs blocking this protein affect the disassembling of the virus and prevent the release of the viral genome in the host cells. Due to this, viral replication is abolished.

Amantadine (midantanum) is used to prevent influenza type A. However, the drug has low efficiancy to use it with that end in view. The drug is taken in dose 100 mg twice a day (every 12 hours). Amantadine is readily absorbed in the gastrointestinal tract and excreted from the body with urine.

Adapromine and *rimantadine* are more effective agents. Rimantadine is active against influenza type A virus (especially type A_2). Adapromine is active against influenza A and B type viruses. Also, rimantadine affects the tick borne encephalitis virus. For prevention of influenza, rimantadine is taken orally in dose 0.05 g, adapromine – in dose 0.1 g once a day during 10–20 days. Timely drug intake reduces the frequency of the disease incidence by 50 % and more. In case of taking influenza, it is mild. It is necessary to notice that intake of the drugs in 2–3 days after the disease onset has low efficiency. The drug intake in 5 days after the start of the disease is completly ineffective. For prevention of tick borne encephalitis, rimantadine is taken twice a day in dose 0.1 g during 3–5 days. Preventive drug intake starts immediately after a tick bite. Rimantadine is readily absorbed in the gastrointestinal tract, metabolized in the liver, and excreted through the kidneys. As a rule, the drug is well tolerated by patients. Side effects include dyspepsia, headache, insomnia, dizziness, and irritability. Rimantadine has teratogenic and embryotoxic effects. Adapromine is a less toxic agent. Both drugs are contraindicated in acute hepatic and renal diseases and during pregnancy.

Influenza viruses quickly develop resistance to the drugs of this group.

Neuraminidase is a glycoprotein which is located on the surface of the influenza viruses types A and B. The enzyme promotes penetration of the virus into the target cells in the respiratory tract. The drugs, blocking neuraminidase, violate the virus propagation and affect the viral replication. *Zanamivir* and *oseltamivir* are drugs with such mechanism of action.

Zanamivir is used for intranasal application or for inhalations. About 15 % of administered dose of zanamivir penetrates into the systemic blood circulation. The drug is excreted through the kidneys.

Oseltamivir (Tamiflu) is taken orally. The drug is active against influenza viruses types A and B, including virus AH4N2. Oseltamivir is readily absorbed in the gastrointestinal tract. The drug undergoes fast hydrolysis in the intestine, liver, and blood. Bioavailability of its active metabolites is about 80 %. The main route of excretion is the kidneys. The half-life period is 6–10 hours. Side effects of oseltamivir are nausea, vomiting, and nephrotoxicity.

Ribavirin is a derivative of guanosine. The drug is phosphorylated in the body into ribavirin monophosphate and ribavirin triphosphate. Ribavirin monophosphate inhibits the synthesis of guanine nucleotides. Ribavirin triphosphate inhibits viral RNA-polymerase and affects the formation of iRNA. Ribavirin is active against influenza viruses A and B. Also, the drug is used in treatment of severe infections caused by respiratory syncytial virus and hemorrhagic fever with renal syndrome. Side effects of ribavirin are skin rash and conjunctivitis. Ribavirin has mutagenic, teratogenic, and cancerogenic properties.

Arbidol is used to prevent and treat influenza type A and B, acute respiratory viral infections, and herpes recurrent infection. Arbidol exhibits interferonogenic activity, stimulates cellular and humoral immunity. The drug is taken orally and tolerated by patients well.

Oxoline is used to prevent influenza and to treat viral rhinitis, adenoviral keratoconjunctivitis, herpetic keratitis, and some viral skin diseases (shingles, etc.). Oxolinic ointment is used to lubricate nasal mucosa, to apply over the lower eyelid, or on the skin.

Antiherpethetical Drugs and Drugs for Cytomegalovirus Infection Treatment

The following drugs are used to treat herpes:

1. Drugs for resorbtive action: *acyclovir, valacyclovir, famcyclovir, vidarabine*.

2. Drugs for topical use: *trifluridine, idoxuridine, megosin, gossypol*.

Acyclovir (Zovirax) is a drug of high activity. It is a synthetic purine nucleoside analogue. In a human body, acyclovir is phosphorylated with active metabolite formation. Phosphorylated acyclovir inhibits DNA-polymerase. It results in violation of nucleic acid synthesis and inhibition of viral replication. Viral DNA-polymerase is 100 times more sensitive to acyclovir action than human DNA-polymerase. The oral bioavailability of acyclovir is about 20 %. Acyclovir has satisfactory permeability through the blood-brain barrier. The therapeutic indications for acyclovir are herpes simplex, herpetic lesions of eyes and genitalia, and cytomegalovirus infection. The drug is taken orally, administered intravenously, or applied topically (5 % skin cream, or 3 % ophthalmic ointment which are used 5 times a day). In case of significant skin damage, acyclovir is taken orally 5 times a day in dose 0.2–0.4 g. Intravenous acyclovir is used to treat herpetic infections in patients with immunodeficiency or to treat severe herpetic lesions of genitalia. Side effects develop seldom. During acyclovir therapy the following side effects are observed: nausea, vomiting, diarrhea, headache, and allergic reactions. Intravenous acyclovir administration can cause the reversible neurological complications (hallucination, excitement, and confusion), renal dysfunction, phlebitis, and skin rash. External acyclovir application can cause dry and peeling skin.

Valacyclovir is a new agent for treatment of herpetic infection. Oral bioavailability of valacyclovir is about 54 %. It is necessary to notice that valacyclovir has no antiviral activity. Valacyclovir is converted to acyclovir in the intestine and liver.

Famcyclovir and *gancyclovir* are similar to acyclovir.

Vidarabine is phosphorylated by kinases into the active metabolite. Phosphorylated metabolite inhibits viral DNA-polymerase and suppresses the virus replication. Vidarabine is used to treat herpetic encephalitis. The drug decreases the mortality from this disease by 30–70 %. Sometimes, vidarabine is used to treat shingles and herpetic keratoconjunctivitis. Also, vidarabine is used to treat patients suffering from allergic reactions to idoxuridine. Side effects of vidarabine are dyspepsia, tremor, psychosis, allergic reactions, blood clots on the injection site.

Idoxuridine and *trifluridine* are antiherpetic drugs which are used topically. Therapeutic indications for their use are herpetic keratitis and

keratoconjunctivitis. Side effects are irritation of mucous membranes and eyelid oedema.

Gancyclovir, valgancyclovir, foscarnet, and *Vitravene (fomivirsen)* are drugs for treatment of cytomegalovirus infection.

Mechanism of action of gancyclovir is similar to acyclovir. The drug is used to treat cytomegalovirus retinitis, colitis, esophagitis, pneumonia, etc. Gancyclovir is administered intravenously or used topically in conjunctival cavity. The side effects of gancyclovir are headache, psychosis, convulsions, granulocytopenia, thrombocytopenia, skin rash, and liver damage. Gancyclovir is a drug with teratogenic activity.

Valgancyclovir is metabolized to gancyclovir in the intestine and liver. The bioavailability of valgancyclovir is about 60 % (in 10–12 times higher than gancyclovir).

Foscarnet is a drug with the same mechanism of action. The drug is used to treat cytomegalovirus retinitis in patients with AIDS. Also, foscarnet may be used as an alternative to acyclovir to treat herpes simplex and shingles. Foscarnet is administered intravenously or applied topically in ointment. The toxicity of foscarnet is higher than gancyclovir toxicity. But foscarnet inhibits the leukopoiesis to a lesser degree than gancyclovir. Side effects of foscarnet are fever, headache, convulsions, nephrotoxicity, cardiac arrhythmias, encephalopathy, disturbances of mineral and electrolyte balance, etc.

Vitraven is used to treat cytomegalovirus rhinitis and retinitis.

Drugs Active Against Human Immunodeficiency Virus (Antiretroviral Drugs)

The following drugs are used to treat HIV-infection:

1. Reverse transcriptase inhibitors.

1.1. Nucleosides: *zidovudine, didanosine, stavudine,* and *zalcitabine*.

1.2. Non-nucleoside compounds: *nevirapine, delavirdine,* and *efavirenz*.

2. HIV protease inhibitors: *indinavir, ritonavir, saquinavir,* and *nelfinavir*.

The synthesis of viral DNA on the matrix (viral RNA) occurs after penetration of AIDS virus into lymphocytes. This synthesis is controlled by reverse transcriptase. After phosphorylation, zidovudine blocks reverse transcriptase and inhibits DNA synthesis. This results in inhibition of

iRNA and viral protein synthesis. *Zidovudine* is effective mainly against virus carriers (before the appearance of AIDS symptoms). In sick patients, zidovudine slows down the disease progression, prolongs the duration of life, and reduces the frequency and severity of infectious complications. But recovery does not complete. Zidovudine is taken orally 0.1 g 5–6 times a day or 0.2 g 3 times a day. The drug is readily absorbed in the gastrointestinal tract. Zidovudine readily penetrates through the blood-brain barrier. About 75 % of administered dose is metabolized in the liver. The main route of zidovudine excretion is through the kidneys. The prolonged therapy with zidovudine (more than 6 months) results in development of antiviral drug resistance. Side effects of zidovudine are anemia, neutropenia, thrombocytopenia, pancytopenia, headache, diarrhea, fever, and renal dysfunction. After prolonged use of zidovudine, the following drugs may be prescribed to a patient: didanozine, zalcitabine, stavudine, lamivudine, or abacavir. These drugs have an identical mechanism of action with zidovudine. All drugs are taken orally and undergo hepatic metabolism with the subsequent renal excretion. Hematotoxicity (anemia, leukopenia, and thrombocytopenia), neurotoxicity (headache and insomnia), and renal, pancreatic and hepatic dysfunctions are typical side effects of these drugs.

The non-nucleoside agents for AIDS treatment are *nevirapine, delavirdine,* and *efavirenz*. These drugs also block reverse transcriptase, but bind to enzyme in another site than nucleosides. There is an evidence that these drugs also simultaneously inhibit DNA-polymerase. Non-nucleoside drugs are taken orally and used only in HIV-1 infection.

HIV protease inhibitors (*indinavir, ritonavir, saquinavir, nelfinavir*) block enzymes regulating formation of structural proteins and enzymes which are necessary for virus replication. The deficit of these proteins results in formation of virus immature precursors and slows down the development of infection. Saquinavir is the most commonly used HIV protease inhibitor. The drug is effective against both HIV-1 and HIV-2 infections. Saquinavir is taken orally. The bioavailability of the drug is very low (about 4 %), but blood concentration of the drug is enough to inhibit retroviral replication. The side effects of saquinavir are dyspepsia, disturbances of lipid and carbohydrate metabolism, anemia, and dysuria. The prolonged drug intake causes the development of antiviral drug resistance.

Combined drug use is the most effective in HIV therapy: zidovudine + zalcitabine + saquinavir, zidovudine + saquinavir, etc.

Drugs Active Against Variola Virus

Metisazon is used to prevent smallpox and to decrease the risk of vaccine complication. Metisazon may act by inhibiting viral structural protein synthesis or blocking late stages of virus assembly. The drug is taken orally. Side effects include dyspeptic disorders and dizziness.

Broad Spectrum Antiviral Drugs (Including Hepatitis B and C Viruses)

Interferons are recovered from the cultures of human leukocytes (*α-interferon*), fibroblasts (*β-interferon*), or lymphocytes (*γ-interferon*). Recombinant interferons are derived by means of implantation of correspondent human genes to *Escherichia coli*.

Interferons are species-specific low molecular weight glycoproteins. Interferons are not themselves antiviral active. Interferon interacts with a specific receptor located on the cellular surface that results in activation of protein kinase and formation of low-molecular inhibitor of protein synthesis. This inhibitor acts due to stimulation of enzymes which destroy RNA of viruses and host cells.

Besides antiviral and antibacterial effects, interferons also activate the immunity (phagocytic activity of macrophages and toxicity of killers increase), exhibit antitumor and radioprotective activity, and influence functions of different systems of the body, including CNS.

There is the following classification of interferon preparations:

– α-2A-interferons: *Reaferon, Roferon-A, Laferon*;
– α-2B-inteferons: *Intron-A, Viferon*;
– α-2C-interferons: *Berofor, Wellferon*;
– β-interferons: *Betaseron (Betaferon), Feron*;
– γ-interferons: *Gammaferon, Imunoferon*.

Alfa-interferons (α-2A, α-2B) are used mainly as antiviral drugs. These drugs are effective in treatment of herpetic keratitis, herpetic lessions of the skin and sex organs, acute respiratory viral infection, shingles, viral hepatitis B and C, and AIDS.

Laferon and *Reaferon* are used topically as nasal or eye drops (to prevent a disease – 2–3 drops in nose or in conjunctival cavity 1–2 times a day; to treat the disease – 4–6 times a day). The drugs are also used topically to treat shingles.

There are high-purified interferons (1 mg – 5,000,000 IU) for oral intake or for parenteral administration (intravenously, intramuscularly,

intraosseously, endolumbarly, and endolymphatically). Interferons are quickly inactivated, therefore they are administered 4-6 times a day. High-purified interferons are used in treatment for systemic viral infections or malignant neoplasms. Recombinant interferons (*Reaferon, Roferon, Intron-A, Viferon,* and *Wellferon*) are administered 2–3 times a day. Moreover, the drugs may be administered rectally. Side effects are possible in case of parenteral interferon administration and include fever, headache, muscular pain, reduction of blood pressure, cardiac arrhythmias, paresis and paralisis, blood dyscrasias, and dyspepsia.

A disadvantage of interferon therapy is the development of drug resistance after 1–2 injections. The combined use of several inductors of interferons is recommended to prevent it.

Interferon inductors are drugs which stimulate the formation of interferons. There are natural (bacteria, viruses, rickettsia, fungi, etc.) and synthetic (vitamins, synthetic polynucleotides, polyanions, and some low-molecular-wheight and high-molecular-wheigh compounds). The representatives of synthetic low-molecular-wheight interferon inductors are *Amixin (tilorone), megosin, mefenamic acid,* etc. The representative of high-molecular-wheight interferon inductors is *poludanum*. Poludanum is used in eye drops for treatment of viral lesions of mucous membranes of the eyes. Also, poludanum is administered subcutaneously once a week in treatment for chronic hepatitis C. Mefenamic acid is used to treat influenza. Megosin is applied topically to treat viral skin diseases. Tilorone is used to treat influenza, acute respiratory viral diseases, hepatitis B and C, herpes, cytomegalovirus infections, neurotropic viral infections, tuberculosis, and chlamydiosis. This drug is contraindicated for pregnant women.

Some drugs of other pharmacological groups also exhibit the property to induce interferon formation. They are *levamisole, isoprinozin, dipyradamole, theophylline, Trental (pentoxifylline), dibazol (bendazol),* etc.

Beta-interferon is used in treatment of multiple sclerosis. It is a disease caused by demyelination of nervous fibers in the central nervous system. Multiple sclerosis occurs to young people, progressively worses, and results in disability. Recently, *Betaseron* was established by means of gene engineering. The drug significantly reduces the frequency and severity of the exacerbations and slows down the disease progressing. Betaseron is administered subcutaneously once every 48 hours. Side effects of betaseron

are pain and redness on the injection site, fever, weakness, muscle pain, anemia, thrombocytopenia, neutropenia, lymphopenia, and menstrual irregularities.

Table 6 – ***Drugs for prescription***

Drug name (Latin)	Single dose and route of administration	Drug product
Oxolinum	Topically to apply to the nasal mucosa 2 times daily; 1–2 drops into each eye 5–6 times daily	Ointment 0.25 % or 0.5 % 10.0 or 15.0 g; eye drops: 0.1 % solution 10 ml
Remantadinum	Orally 0.1 g 1–3 times daily	Tablets 0.05 g
Azidothimidinum (Zidovudine)	Orally 0.1–0.25 g twice a day	Capsules 0.1 or 0.25 g
Aciclovir	Orally 0.2–0.8 g 4–5 times a day; intravenously slowly 0.0005–0.001 g/kg 3 times daily; topically to treat skin infections; for instillation into a lower conjunctival sac 5 times a day	Tablets 0.2; 0.4 or 0.8 g; vials 0.25 g of powder for injections; ointment 5 % 5 g; eye ointment 3 % 4.5 g or 5 g
Laferon	For instillation into the nose (3–6 drops) or eyes (1–2 drops) (before using, the powder of the ampoule should be dissolved in 2 ml of sterile water) 3–6 times daily; intramuscularly, subcutaneously or intravenously 1,000,000–5,000,000 IU 1–2 times daily	Ampoules or vials with powder 1,000,000; 3,000,000 or 5,000,000 IU (dissolved before administration)

Antileprosy Drugs

Leprosy is an infectious disease caused by *Mycobacterium leprae* (Hansen's bacillus). Drugs for leprosy treatment (antileprosy drugs) are classified into the following groups:

1. Derivatives of aromatic sulfones: DDS – *diaminophenyl sulfone (dapsone, avlosulfon), solusulfonum (sulphedrone, cimedone), dimociphone, diuciphone*.

2. Antibiotics:
   – rifamicins*: rifampicin*;
   – macrolides: *clarithromycin*;
   – tetracyclines: *minocycline*.
3. Fluoroquinolones: *ofloxacin (Tarivid)*.
4. Synthetic antituberculosis drugs: *ethionamide, prothionamide, thioacetazone*.
5. Phenazine derivatives: *clofazimine (lamprene)*.

Diaphenylsulfone (dapsone) is one of the main drugs for leprosy treatment. Dapsone is a competitive antagonist of para-aminobenzoic acid and due to this fact it influences the synthesis of folic acid by *Mycobacterium leprae*. Also, the drug activates lysosomes of macrophages. The drug is taken 0.05–0.1 g once a day six days a week. The drug is rapidly and almost completely absorbed from the gastrointestinal tract. The half-live for dapsone in the body is 24 hours. Side effects of dapsone are weakness, headache, dyspepsia, toxic hepatitis, precordialgia, hemolysis, and agranulocytosis. The toxicity of the drug is limited due to reduction of the dose and intake of B group vitamins and iron-preparations.

Diuciphone is a diphenyl sulfone derivative containing two residues of methyluracil. The drug has antileprosy and immunomodulating effects.

As a rule, antibiotics, ofloxacin, and synthetic antituberculosis agents in combination with sulfones are used to treat leprosy. The rapid effect is typical for rifampicin. Rifampicin is taken every day or twice a week (in combination with other antileprosy agents). Being located in the skin, *Mycobacterium leprae* lose their viability in 5 days. Synthetic antituberculosis drugs are less effective in leprosy treatment, but more toxic.

Clofazimine is a lipid-soluble phenazine derivative. The drug accumulates in the skin, gastrointestinal tract, and in the cells of monocyte macrophage sprout. Side effects are skin dyschromia (red-brown skin), ichthyosis, diarrhea, intestinal colic, etc. Clofazimine is contraindicated in pregnancy.

The chemotherapy of leprosy is a long-term cure. *Mycobacterium leprae* resistance and disease relaspse are common problems. A relapse in leprosy occurs due to persistent *Mycobacterium leprae* in bone marrow, nervous and muscular tissues. The combined antileprosy chemotherapy by means of 2–3 drugs with different chemical structure is used to prevent leprosy prolapse and antileprosy drug resistance. The most common drug

combination includes diphenyl sulfone, rifampicin, and clofazimine. Besides, the use of immunomodulators and vitamins in treatment of leprosy is advisable.

Antiprotozoal Drugs

It is known that more than 1000 species of protozoa are pathogenic for humans. Antiprotozoal drugs are selectively active against protozoa – causative agents of malaria, amoebiasis, giardiasis, toxoplasmosis, leishmaniasis, trichomoniasis, and balantidiasis. Antiprotozoal drugs include synthetic agents and some antibiotics, and they are classified into the following groups:

1. Antimalarial drugs.
2. Drugs for giardiasis treatment.
3. Drugs for toxoplasmosis treatment.
4. Drugs for balatidiasis treatment.
5. Drugs for trichomoniasis treatment.
6. Drugs for leishmaniasis treatment.

Antimalarial Drugs

In the past, malaria was one of the most common diseases in the world. About one million peple were dying every year. In 50–60-s of the 20^{th} century, malaria morbidity was significantly reduced due to the broadest antimalarial actions under UN auspices. Unfortunatelly, last years the formation of drug resistant strains of *Plasmodium* results in the increase of malaria morbidity.

A source of malaria infection is the sick person or a gamete carrier. A person can get infection through the bite of infected mosquitoes (seldom – due to blood transfusion from the sick person). Thus malaria parasites enter the blood.

There are 4 species of malaria parasites:

– *Plasmodium vivax*, and *Plasmodium ovale* – the causative agents of vivax (three-day malaria);

– *Plasmodium malaria* – the causative agent of quartan (four-day malaria);

– *Plasmodium falciparum* – the causative agent of tropical malaria.

Plasmodium ovale is found only in the tropics.

The Plasmodium parasite undergoes two cycles of replication: asexual cycle (schizogony) takes place in the human body, and sexual cycle (sporogony) occurs in the mosquito. Due to infected mosquito bite, the sporozoites enter the blood of the person, then quickly enter hepatocytes. Inside hepatocites multiplication occurs: pre-erythrocytic or exo-erythrocytic schizogony stage. Tens of thousands of merozoites are formed due to multiple division of one sporozoit. Pre-erythrocytic schizogony is asymptomatic. After completion of pre-erythrocytic schizogony, merozoites penetrate into erythrocytes and undergo the stage of erythrocytic schizogony. This stage is accompanied by erythrocyte rupture and fever attacks. Erythrocytic merozoites again penetrate into erythrocytes and repeat the erythrocytic cycle. In infection with *Pl. vivax* and *Pl. ovale*, these cyclical fevers occur every 48 hours, in infection with *Pl. falciparum* – every 6 hours, and in infection with *Pl. malarie* – every 72 hours. Along with asexual division, the sexual forms of Plasmodium are formed in the human blood. These sexual forms are called gametocytes (gamonts). Their presence in the blood is not accompanied by the disease symptoms, but gamonts are dangerous in the context of epidemiology. Such patients are the source of mosquito infection.

In the tropical and four-day malaria, after the completion of pre-erythrocytic schizogony, merozoites enter the blood and their following development occurs only in the erythrocytes. In the three-day malaria, the infection by genetically heterogeneous set of parasites occurs. A part of them (tachysporozoites or primary forms) pass the stage of tissue schizogony after penetration into hepatocytes and are released from the liver after completion of this stage. Another part of sporozoites (bradysporozoites or secondary forms) are capable to be in liver in dormant form from 8–9 months up to 2 years. After completion of the latent period, these dormant sporozoites undergo exoerythrocytic schizogony which finishes when parasites enter the blood and develop primary malaria or its relapse.

The duration of sporogony, exo- and erythrocytic schizogony, the ability of drug-resistant Plasmodium to appear are different for different species of Plasmodium.

Presently, the following chemical groups of drugs are used to treat malaria:

1. Quinoline derivatives: *quinine, chingaminum (chloroquine), mefloquine, primaquine,* and *quinocide*.

2. Biguanides: *bigumal*.
3. Pyrimidine derivatives: *chloridinum (pyrimethamine)*.
4. 9-aminoacridine derivatives: *quinacrine*.
5. Sulfonamides.
6. Sulfones.
7. Tetracyclines.

Pharmaceutical industry produces a lot of combined drugs: *Metakelfin* (contains *pyrimethamine* and *sulfalen*), *Fansidar* (contains *pyrimethamine* and *sulfadoxine*), *Fansimef* (contains *mefloquine, sulfadoxine,* and *pyrimethamine*), etc.

According to antimalarial action, the drugs are divided into the following groups:

1. Blood schizonticides are the drugs active against erythrocytic forms of Plasmodium: *chingaminum (chloroquine), mefloquine, quinine*. Also, the following agents are used in combined drugs: *hydroxychloroquine, chloridinum, bigumal, sulfadoxine,* and *doxycycline*.

These drugs eliminate schizonts from the peripheral blood after 3–5 days treatment. These drugs prevent and interrupt malaria attacks in the acute phase of the disease.

2. Tissue schizonticides are the drugs which affect tissue forms of Plasmodium. These drugs are divided into two groups:

– tachysporozoites are tissue schizonticides which are active against pre-erythrocytic forms: *bigumal* and *chloridinum*; these drugs are used to prevent malaria;

– bradysporozoites are tissue schizonticides which are active against para-erythrocytic forms of Plasmodium: *primaquine* and *quinocide*; these drugs are used to prevent malaria relapses.

3. Gametocides are the drugs which are active against sexual forms of Plasmodium. These drugs are divided into two groups:

– gametocides acting upon sexual forms of Plasmodium in human erythrocytes: *primaquine* and *quinocide*;

– drugs inhibiting the sporogony in the body of mosquito: *bigumal* and *chloridinum*.

These drugs are used for collective protection against malaria – prevention of disease transmission from the sick to healthy person through

a mosquito bite. Due to the use of these agents, sporozoites are not formed in the mosquito body.

Blood Schizonticides

Quinine is an alkaloid found in the bark of the cinchona tree. Different species of cinchona tree are native to South America. In the 17th century, the bark of the cinchona tree was brought to Europe and since then it was used to treat malaria as well as fever. In 1816 quinine was isolated from the bark by J. E. F. Giese. Other antimalarial drugs were synthezied later on.

Quinine affects erythrocytic schizonts of Plasmodium, gamonts, pre-erythrocytic forms of *P. falciparum*, and the causative agent of toxoplasmosis. The drug is readily absorbed from the gastrointestinal tract and quickly excreted from the body. Quinine inhibits the center of thermoregulation and decreases the body temperature in fever. Also, quinine inhibits the excitability of myocardium, exhibits negative chronotropic effect, stimulates uterine contractions in pregnant women, and stimulates the spleen to contract. Mechanism of action of quinine is identical with chingaminum, primaquine, quinocide, and mefloquine. This mechanism is associated with violation of DNA synthesis both in Plasmodium cells and in host cells. Besides, quinine seals the lysosomal membranes, resulting in impaired assimilation of hemoglobin by Plasmodium.

Therapy with quinine is commonly accompanied by side effects: dizziness, vomiting, headache, collapse, tinnitus, etc. Presently, quinine is once again being used to treat tropical malaria, because Plasmodium infections became resistant to other drugs.

Chingaminum (chloroquine) hes been suggested for malaria treatment in 1943. The drug is one of the best blood schizonticides. Chloroquine interrupts the acute malarial fever within 24–48 hours. Plasmodium infections disappear from the peripheral blood in 2–3 weeks after the start of therapy with chingaminum. The drug is used to prevent and treat all types of malaria.

Along with antimalarial effect, chloroquine exhibits the anti-inflammatory activity and is widely used to treat polyarthritis, systemic lupus erythematosus, scleroderma, and other collagen-vascular diseases. Also, chingaminum is used to treat amebiasis.

Chingaminum is taken orally and administered intramuscularly or intravenously. The drug is readily absorbed from the gastrointestinal tract. About 50 % of the drug bind to plasma proteins. The elimination rate for the drug is low. Kidneys are the main route of chingaminum excretion. Chloroquine side effects are headache, nausea, dermatitis, and loss of appetite. Overdose of chingaminum can cause dystrophy of myocardium and liver, disturbances of accommodation, tinnitus, and leukopenia.

Mefloquine is an active antimalarial agent. In tropical malaria, the single use of the drug interrupts malarial fever and kills chloroquine-resistant strains of Plasmodium. Mefloquine is also effective in three-day malaria but does not prevent relapse. The toxicity of mefloquine is low. Sometimes, therapy with mefloquine can result in nausea, vomiting, abdominal pain, and drowsiness. Central nervous system disorders are seldom possible (depression, halucinations, convulsions, and disorientation).

Chloridinum (pyrimethamine) is a synthetic agent – derivative of pyrimidine. The drug violates the synthesis of dihydrofolic acid due to the inhibition of dihydrofolate reductase. Pyrimethamine is active against erythrocytic and pre-erythrocytic forms of Plasmodium, and also inhibits the sporogony in the body of mosquito. Pyrimethamine is taken orally and easily absorbed from the gastrointestinal tract. The drug is able to accumulate in tissues and, therefore, has the prolonged effect. The therapeutic indications for chloridinum are treatment of malaria, toxoplasmosis, and leishmaniasis. Also, the drug is used for personal protection against malaria. The side effects include headache, dizziness, discomfort in the heart area, hepatic disfunction, megaloblastic anemia, leukopenia, and teratogenic effect.

Sulfonamides and sulfones are also blood schizonticides. These drugs affect utilization of benzoic acid by Plasmodium. The activity of these agents are relatively low and their antimalarial effect develops slowly. Sulfonamides and sulfones in combination with other drugs are used to treat malaria.

Tissue Schizonticides

Chloridinum (pyrimethamine) and bigumal are active against pre-erythrocytic forms (tachysporozoites). Both drugs inhibit dihydrofolic acid reductase that results in violation of terahydrofolic acid and nucleic acid synthesis.

Bigumal is a biguanide derivative. The drug is active against pre-erythrocytic forms and gamonts of Plasmodium. The activity of bigumal is lower than the activity of chloridinum. Bigumal is taken orally, readily absorbed from the gastrointestinal tract, and is readily excreted from the body. The therapeutic effect of bigumal develops slowly. The side effects are leukocytosis and erythrocyturia. It is necessary to notice that Plasmodium quickly develops the tolerance to bigumal.

Primaquine and *quinocide* are tissue schizonticides which are active against para-erythrocytic forms of Plasmodium (bradysporozoites). Primaquine affects bradysporozoites of *Plasmodium vivax* and *Plasmodium ovale* which cause the relapse. Also, primaquine affects the sexual forms of *Pl. vivax, Pl. ovale,* and *Pl. falciparum* in human erythrocytes. Primaquine is taken orally and well absorbed from the gastrointestinal tract. Maximal concentration in the blood is observed in 2 hours after drug intake. The drug is metabolized in the body and excreted through the kidneys. Therapeutic indications for primaquine are prevention of relapses of three-day malaria and prevention of malaria spreading through the carrier. Primaquine is commonly combined with other antimalarial drugs. Side effects of primaquine are dyspepsia, methemoglobinemia, leukocytosis or leukopenia.

Quinocide is more toxic than primaquine. Other antimalarial agents increase its toxicity, therefore, combined use of quinocide with them is impossible. Quinocide is taken orally 1–2 times a day after a meal. Side effects of quinocide are nausea, cyanosis, fever, irritation of bladder, leukopenia or leukocytosis. These complications disappear after giving up the drug.

Gametocides

Gametocides are drugs which are active against sexual forms of Plasmodium. Gametocides which inhibit the sexual forms of Plasmodium in human erythrocytes are *primaquine* and *quinocide*. Gametocides inhibiting the sporogony in the body of mosquito are bigumal and chloridinum. Pharmacology of these drugs is described above.

Selection Criteria for Antimalarial Drugs

Antimalarial drugs are used to treat and prevent malaria. In acute period (malarial fever, malarial coma), blood schizonticides are used (chingaminum (chloroquine), mefloquine, quinine, etc.). These drugs

readily penetrate human erythrocytes and facilitate the fast improvement in clinical findings. The resistance of Plasmodium to these drugs develops relatively slow. In malarial coma, chloroquine and quinine are administered parenterally.

The reserve group (used in case of Plasmodium resistance to the main drugs) includes such drugs as pyrimethamine, bigumal, primaquine, quinocide, sulfonamides, sulfones, and tetracyclines. These drugs are less effective in comparison with main drugs. Their effect develops slowly, while resistance of Plasmodium develops quickly. Therefore, drug combinations with different mechanism of action are commonly used.

Primaquine is used to prevent relapse of three-day and four-day malaria.

The drugs influencing upon pre-erythrocytic forms of Plasmodium (for instance, pyrimethamine) are used for individual preventive chemotherapy in people who live in or travel to malaria risk areas. Blood schizonticides (chloroquine, mefloquine, etc.) are also sometimes used with this end in view.

The total preventive chemotherapy of malaria suggests the prevention of malaria transmission from the sick person to healthy people through mosquito bite. Gametocides (primaquine, pyrimethamine, and quinocide) are used for this purpose – to prevent formation of sporozoites in mosquito.

Drugs for Amebiasis Treatment

The causative agent of amebiasis is *Entamoeba histolytica*, which exists in two forms: vegetative and cystic. The transformation of vegetative form into cystic occurs in the presence of anaerobic bacterial flora (clostridium). Cystic forms, in turn, transform into vegetative amoeba, living in the intestinal lumen (without symptoms) and feeding on the organic wastes of bacterial origin. Under the influence of aerobic bacteria (E. coli), amoeba takes on pathogenic properties. Vegetative forms of amoeba secrete proteolytic enzyme which dissolves tissues. It provides the formation of invasive forms of amoeba – hematophagous amoebas. A significant amount of erythrocytes is observed in the endoplasma of invasive forms of amoeba. At this stage, the invasive amoebiasis develops when amoeba is present both in the intestinal lumen and in the intestinal wall. By hematogenic way, amoeba can penetrate into the liver, lungs, and other organs.

Treatment of amebiasis differs depending on amoeba localization.

The drugs which are used to treat amoebiasis are classified as follows:

1. Drugs which are effective in any localization of amoeba: *metronidazole*.
2. Drugs of dirrect action which are effective against amoeba localized in the intestinal lumen: *chiniofonum* and *intetrix*.
3. Drugs of indirect action which are effective against amoeba localized in the both intestinal lumen and intestinal wall: *tetracyclines*.
4. Drugs acting upon amoeba which is mainly located in the intestinal wall and liver: *emetine hydrochloride*.
5. Drugs which are mainly effective against amoeba localized in the liver: *chloroquine*.

Metronidazole is a drug which is effective in any localization of amoeba. The drug was introduced in the medical practice in 1951 as an agent for the treatment of trichomoniasis. Metronidazole is also active against amoeba, giardia, balantidium, and *Helicobacter pylori*. Metronidazole is not active against cystic forms of amoeba. The drug is taken orally 0.25–0.5 g three times a day after a meal. Metronidazole is readily absorbed from the gastrointestinal tract and is well metabolized. The main route for drug excretion is via kidneys. Insignificant amount of metronidazole is excreted by salivary glands, intestine, and mammary glands. Metronidazole is manufactured in tablets, solution for intravenous administration, and vaginal suppositories. Side effects of metronidazole are nausea, diarrhea, metallic taste in mouth, appetite loss, tremor, and disturbances of accommodation. Sometime, lesions of skin and mucous membranes are possible. Efficacy of metronidazole is low in localization of amoeba in the intestinal lumen. In this case, metronidazole is combined with chiniofonum. It is necessary to notice that metronidazole inhibits the activity of acetaldehyde dehydrogenase and causes accumulation of acetaldehyde that results in alcohol intolerance.

Chiniofonum (yatren) affects the vegetative and cystic forms of amoeba located in the intestinal lumen. The drug is taken orally. Gastrointestinal absorption of chiniofonum is low (about 10–15 %), therefore, high drug concentration is created in the intestinal lumen. Toxicity of yatren is low. Chiniofonum also exhibits significant antibacterial and antifungal activity. The drug is used to treat amebic dysentery, colitis, and uretritis. Ointments and solutions of chiniofonum are used externally in treatment for purulent wound, burns, ulcers, etc.

Intetrix is active against amoeba, *Candida*, Gram-positive and Gram-negative bacteria. The drug is used in treatment of intestinal amoebiasis and diarrhea. Toxicity of intetrix is low.

Tetracycline is an antibiotic which has indirect influence upon amoeba. Tetracycline affects the bacterial intestinal microflora which utilizes oxygen. Since species of amoeba are anaerobic, they can not live in the presense of oxigen. Therefore, tetracycline is an indirect amoebicide. Efficacy of tetracycline is lower than the efficacy of direct amoebicides. Aminoglycoside *monomicine* is also used to treat acute intestinal amoebiasis.

Emetine hydrochloride is an alkaloid of ipecacuanha. In therapeutic doses, emetine inhibits vegetative forms of amoeba but practically does not influence upon its cystic forms. The drug quickly eliminates the symptoms of amoebic dysentery, but does not prevent the relapses. Emetine is administered intramuscularly because oral intake of emetine significantly irritates the gastrointestinal mucosa. Emetine is eliminated very slowly (more than a month), therefore, the drug is able to acummulate in the body. The main sites of emetine accumulation are the liver, lungs, and intestinal wall. Emetine does not penetrate the blood-brain barrier. Emetine is used in treatment for hepatic, pulmonary, and intestinal amoebiasis. The drug does not influence upon amoeba which is located in the intestinal lumen or in the brain. The side effects of emetine are nausea, vomiting, diarrhea, tachycardia, hypotension, precordialgia, polyneuritis, abnormal hepatic and renal functions, etc.

Chingaminum (chloroquine) is active against amoeba which is located in the liver, bacause the liver can accumulate a high concentration of the drug. The characteristics of chingaminum are given in subsection “Antimalarial drugs”.

Drugs for Lambliasis Treatment

Lambliasis (guardiasis) is caused by *Lamblia intestinalis*. Parasites can damage the intestine with the following development of duodenitis and enteritis. Also, Lamblia can penetrate into the bile and pancreatic ducts. The following drugs are used to treat lambliasis: *metronidazole, furazolidone, aminoquinol,* and *albendazole (Vormil)*.

Aminoquinol is a derivative of quinoline. The drug is used in treatment of lambliosis, toxoplasmosis, skin leishmaniasis, and systemic collagenosis. In lambliasis, aminoquinol is taken orally 20–30 minutes after

a meal. After absorption, the drug is excreted with bile into the intestine. Simple drug intake results in excretion of the agent with bile during one month. The side effects of aminoquinol are dyspepsia, weakness, headache, tinnitus, insomnia, leukopenia, liver and kidney failure.

Pharmacology of albendazole is given in "Anthelmintic drugs".

Drugs for Trichomoniasis Treatment

A causative agent of trichomoniasis is *Trichomonas vaginalis*. The disease occurs in the form of colpitis or vulvovaginitis (in women), cystitis, stomatitis, colitis, and urethritis. The following drugs are used for trichomoniasis treatment:

– nitroimidazole derivatives: *metronidazole, tinidazole, ornidazole*;

– aminoquinoline derivatives: *trichomonacide*;

– imidazole derivatives: *econazole, miconazole, clotrimazole, nitazole*;

– nitrofuran derivatives: *furazolidone*.

Tinidazole (Fasigyn) exhibits high activity against *Trichomonas vaginalis*. Besides, the drug is active against obligate anaerobes. Tinidazole is readily absorbed from the gastrointestinal tract. The blood concentration of tinidazole is higher than the concentration of metronidazole. The duration of tinidazole action is much longer.

Trichomonacide has high activity against *Trichomonas vaginalis*. The drug is readily absorbed from the gastrointestinal tract. Trichomonacide is mainly used in treatment of urogenital trichomoniasis. The drug is taken orally or used topically in the form of suppositories or globules. Trichomonacide irritates the mucous membranes.

The pharmacological characteristics of imidazole derivatives (ornidazole, miconazole, econazole, clotrimazole) is given in "Antifungal drugs". Pharmacology of furazolidone is described in "Nitrofuranes".

Drugs for Toxoplasmosis Treatment

A causative agent of toxoplasmosis is *Toxoplasma gondii*. There are several forms of the disease which are accompanied by lessions of lymph nodes, intestine, lungs, eyes, central nervous system, and other organs. Toxoplasmosis can result in premature labor, abortion, congenital malformations, and stillbirth. To prevent congenital toxoplasmosis, *chloridinum* and *aminoquinol* in combination with *sulfonamides* are

prescribed to pregnant women. Preventive use of chloridinum and aminoquinole is contraindicated during the first 9 weeks of pregnancy due to their toxic influence upon the fetus. During this period, sulfonamides are used for prevention of fetal infection. *Chingaminum* and *pentamidine* are also used to treat toxoplasmosis.

Drugs for Balantidiasis Treatment

A causative agent of balantidiasis is infusorium *Balantidium coli* parasitizing the large intestine. *Tetracyclines* and *chiniofonum* are used to treat balantidiasis. Pharmacological characteristics of these agents are given in the corresponding sections.

Drugs for Leishmaniasis Treatment

Leishmaniasis is a protozoal disease which is caused by *Leishmania donovani* (the causative agent of visceral leishmaniasis – kalaazar) and *Leishmania tronica* (the causative agent of skin leishmaniasis). Visceral leishmaniasis is accompanied by high temperature, anemia, leukopenia, and splenomegaly. Initialy, leishmania parasites cause skin sores or ulcers at the site of the bite. If the disease progressies, it attacks the immune system.

Solusurminum is the most commonly used agent to treat visceral leishmaniasis. It is a preparation of pentavalent antimony. The drug is administered intravenously. Solusurminum blocks thiol groups of Leishmania enzymes that affects their growth and division. Side effects of solusurminum are nausea, headache, skin rash, and agranulocytosis. After an overdose of solusurminum, unithiol is administered as an antidote.

Sodium stibogluconate is also a preparation of pentavalent antimony. The drug is administered intramuscularly or intravenously. Its side effects are dyspepsia, vomiting, appetite loss, arterial hypotension, and chest pain.

Glukantim, pentakarinate (pentamidine), neostibazine, and *pentostim* are also preparations of pentavalent antimony for visceral leishmaniasis treatment.

Pentakarinat (pentamidine) is administered intramuscularly and in inhalations. Mechanism of drug action is associated with blocking thymidylate synthetase that inhibits of DNA synthesis. Pentakarinat is used to treat visceral and skin leishmaniasis, to prevent pneumonia in AIDS patients, and to treat trypanosomiasis, also known as African sleeping sickness. Side effects of pentakarinat are cough, dyspnea, bronchospasm,

skin rash, metallic taste in the mouth, dizziness, arterial hypotension, acute pancreatitis, anemia, leukopenia, thrombocytopenia, increased blood urea nitrogen level and creatinine.

All above preparations of pentavalent antimony may be used to treat skin leishmaniasis. Also, the following agents are used to treat skin leishmaniasis: *quinacrine, monomycin, neomycin, metronidazole,* and *aminoquinol*.

Drugs for Trypanosomiasis Treatment

Causative agents of trypanosomosis are *Tripanosoma gambiense* and *Trypanosoma brucei rhodesiense* (sleeping sickness) and *Trypanosoma cruzi* (Chagas disease).

Melarsoprol is used as a primery agent for treatment of sleeping sickness. It is arsenicum derivative which easily penetrates through blood-brain barrier. Besides, pentakarinat (pentamidine) and suramin are used to treat African trypanosomosis. But these drugs do not penetrate into the central nervous system and, therefore, are effective only at early stages of the disease (when the brain is not affected by *Trypanosoma*). All these drugs are toxic and cause a large number of side effects.

To treat Chagas disease (spread in South America), primaquine and antibiotic puromycin are used.

Drugs for Chlamydiosis Treatment

Chlamydia are intracellular parasites of humans and animals. There are three species of Chlamydia which are causative agents for humans: *Chlamydia trachomatis, Chlamydia psittici* and *Chlamydia pneumonia*. *Chlamydia trachomatis* is the most common sexually transmitted infection. *Chlamydia pneumonia* causes pneumonia. *Chlamydia psittici* mainly affects birds.

Chlamydia trachomatis can cause a recurrent ocular infection – trachoma. Other serological forms of *Chlamydia* cause lymphogranuloma venereum, conjunctivitis, child pneumonia, urethritis, endometritis, salpingitis, cervicitis, and epididymitis (inflammation of the epididymis). During pregnancy, *Chlamydia* can commonly cause premature labor and endometritis. Moreover, chlamydial infection may be associated with septic arthritis.

To treat chlamydiosis, *tetracycline* and *erythromycin* are aminly used. Penicillin is ineffective in that disease. Also, *rifampicin,*

chloramphenicol, and *sulfonamides* are used. *Doxycycline* and *azithromycin* are drugs of choice for the treatment of urogenital chlamydiosis.

Table 7 – ***Drugs for prescription***

Drug name (Latin)	Single dose and route of administration	Drug product
Chingaminum	Orally 0.25–0.5 g 1–2 times daily; intramuscularly or intravenously 0.5 g	Tablets 0.25 g; ampoules 5 ml of 5 % solution
Chloridinum	0.01 g 3 times daily (for malaria treatment); 0.025 g 2–3 times daily (for toxoplasmosis treatment)	Tablets 0.01 or 0.025 g
Chinini hydrochloridum	Orally 0.5 g 2 times daily; subcutaneously 1.0 g 2 times daily; intravenously 1 ml in 20 ml of 40 % glucose solution	Tablets 0.25 or 0.5 g; ampoules 1 ml of 50 % solution
Primachinum	Orally 0.009 g 3 times daily	Tablets 0.009 g
Metronidazolum	Orally 0.25–0.5 g 2–3 times daily; intravenously drop-by-drop 0.5 g 3 times daily	Tablets 0.25 g; bottles 100 ml of 0.5 % solution
Emethini hydrochloridum	Intramuscularly or subcutaneously 0.015 g twice a day	Ampoules 1 ml of 1 % solution
Furazolidonum	Orally 0.1 g 4 times daily	Tablets 0.05 g
Solusurminum	Intravenously slowly, intramuscularly or subcutaneously 0.1–0.12 g/kg once a day	Ampoules 10 ml of 20 % solution

Antifungal Drugs

Fungal infections (mycoses) are very common. Sick people, animals, and environment (plants, soil, etc.) can be the source of infection. Infection occurs through the injured skin, gastrointestinal tract, respiratory tract. Besides, potential pathogens, especially of the genus *Candida,* are located

on the skin, in the upper respiratory system, on the mucous membranes of sex organs, and in the gastrointestinal tract. The cause of saprophytic flora transformation into pathogens is the reduction of the human body resistance due to immunodeficiency (at severe diseases, hormonal therapy, and the use of cytostatic drugs or some antibiotics).

Antifungal drugs are classified into the following groups:

1. Drugs for treatment of systemic or deep mycoses:
– antibiotics: *amphotericin B, mycogeptin,* and *amphoglucaminum*;
– azole derivatives: *miconazole, ketoconazole (nizoral), clotrimazole, itraconazole,* and *fluconazole*;
2. Drugs for treatment of dermatomycoses:
– antibiotics: *griseofulvin*;
– azole derivatives: *ketoconazole (nizoral), itraconazole, miconazole, fluconazole,* and *clotrimazole*;
– N-methylnaphthaline derivatives: *terbinafine (Lamisil)*;
– nitrophenol derivatives: *nitrofungin*;
– thiocarbamate derivatives: *chinofungin*;
– undecylenic acid derivatives: ointments *"Zincundanum"* and *"Undecinum"*;
– iodine preparations: *alcohol solution of iodine* and *potassium iodide*.
3. Drugs for treatment of mycoses caused by fungi Candida:
– antibiotics: *nystatin, levorin, amphotericin B,* and *natamycin (Pimafucin)*;
– azole derivatives: *itraconazole, clotrimazole, ketoconazole,* and *miconazole*;
– bis-quaternary ammonium salts: *decaminum*;
– halogens, non-organic acids, and alkalis.

Drugs for Systemic or Deep Mycosis Treatment

Systemic or deep mycoses affect the liver, bones and joints, gastrointestinal tract, brain and meninges, lymph nodes, etc. Sometimes, systemic mycoses develop in septic form. The deep mycoses are rare and difficult to treat. More than half of them are caused by saprophytic Candida activity. Lesser are deep mycoses caused by the causative agents of coccidioidomycosis, paracoccidioidomycosis, histoplasmosis, cryptococcosis, blastomycosis, etc.

Amphotericin B is one of the main drugs for treatment of deep mycoses. It is a polyen antibiotic which is produced by *Streptomyces nodosum*. Amphotericin B does not affect bacteria, rickettsia, and viruses. Mechanism of action is associated with violation of transport function and permeability of fungi cell membrane. Selectivity of antifungal action occurs due to the fact that amphotericin B interacts with the main lipid of fungal cell wall – ergosterol. The main lipid of human and bacterial cells is cholesterol. Antifungal effect of amphotericin B is characterized as fungistatic. This antibiotic is practically not absorbed in the gastrointestinal tract. Amphotericin B is administered intravenously and into body cavities, applied topically, and used in inhalations. The drug does not penetrate through the blood-brain barrier. About 95 % of the drug, circulating in the blood, bind to plasma proteins. The main organ of amphotericin B biotransformation is the liver. The drug elimination from the body is slow (about 20–40 % of administered dose during a week). The therapeutic indications for amphotericin B are hystomycosis, coccidioidomycosis, visceral candidomycosis, blastomycosis, and deep generalized trichophytosis.

Amphotericin B is a very toxic drug. Therefore, the drug is administered intravenously only in cases of life threatening mycosis. Amphotericin B is dissolved by 5 % glucose solution and administered intravenously drop-by-drop during 3–6 hours. The drug is administered once in two days or twice a week. Side effects are headache, fever, dyspepsia, hypotension, nephrotoxicity, anemia, hypokalemia, disturbances of hepatic function, nephrotoxicity, thrombophlebitis, and allergic reactions. Amphotericin B is contraindicated in hepatic and renal diseases.

Despite identical mechanism of action, *amphoglucaminum* is a less toxic drug than amphotericin B. Amphoglucaminum is used to treat mycoses of the urinary, gastrointestinal, and respiratory tracts. The drug is administered during 10–14 days. To treat chronic (granulomatous) candidiasis and deep mycoses, amphoglucaminum is used during 3–4 weeks. Amphoglucaminum is taken orally. The drug is gradually absorbed from the gastrointestinal tract with maximum blood concentration in 2–3 days. Amphoglucaminum is excreted with urine during 10 days. Side effects are identical with amphotericin B but less expressed.

Mycogeptin has similar properties with amphotericin B. Mycogeptin is taken orally during 10–14 days or applied topically. The drug is partially absorbed in the gastrointestinal tract and excreted with urine. The

therapeutic indications for mycogeptin are visceral mycoses, sepsis caused by Candida, aspergilosis, and geotrichosis. Side effects are gastrointestinal distress, renal disfunction, and allergic reactions.

Miconazole is a derivative of imidazole. The drug is taken orally and administered intravenously or subarachnoidally to treat deep mycoses. Also, miconazole is applied topically to treat vaginal mucosa damage caused by Candida and for the treatment of dermatomycoses. The side effects of miconazole are thrombophlebitis, nausea, anemia, hyperlipidemia, hyponatremia, leukopenia, and allergic reactions.

Ketoconazole (Nizoral) is readily absorbed from the gastrointestinal tract. About 90 % of the absorbed drug bind to plasma proteins. The permeability of the drug through the blood-brain barrier is low. Ketoconazole is metabolized in the liver and excreted with urine and bile. The drug is used to treat deep mycoses and lesions of mucous membranes by Candida. Mechanism of action is associated with inhibition of ergosterol, triglyceride, and phospholipid biosynthesis that violates the structure of the fungal cell membrane. Side effects of ketoconazole are dyspepsia and hepatic dysfunction.

Itraconazole is a triazole derivative. The drug is taken orally. The drug absorption from the gastrointestinal tract is high, but permeability through the blood-brain barrier is low. Itraconazole is extensively metabolized by the liver. A large number of metabolites and unchanged itraconazole are excreted through the kidneys. Side effects are dyspepsia, headache, hepatic dysfunction, and allergic reactions.

Fluconazole is also a derivative of triazole. Fluconazole is one the most effective antifungal drugs. The drug is taken orally. Fluconazole easily penetrates through the blood-brain barrier. Unchanged fluconazole is excreted from the body through the kidneys. The therapeutic indications for fluconazole are fungal meningitis, coccidioidomycosis, candidomycosis, etc. Side effects of fluconazole are dyspepsia, hepatotoxicity, and skin allergy.

Drugs for Dermatomycosis Treatment

In dermatomycoses, the skin, nails, and hair are affected. The causative agents of dermatomycoses are *Trichophyton violaceum, Microsporum lanosum, Achorion schonlein,* different species of Epidermophyton, etc. Onichomycoses (fungal lesions of nails) are widely spreaded. Onichomycoses are caused by dermatophytes (most commonly

by *Trichophyton rubrum*), Candida, and mild fungi (*Scopulariopsis brevicaulis, Aspergillus spp*., etc.). The fungi of the genus Candida and sometimes molds (causative agents of aspergillosis) are the most common pathogens among saprophytic fungi.

The most effective drugs for dermatomycoses treatment are *terbinafine (Lamisil), itraconazole, ketoconazole (Nizoral),* and *griseofulvin*. *Micospor, cyclopirox, amorolfine,* and *tioconazole* are used topically.

Griseofulvin is an antibiotic which is produced by mold-forming fungi Penicillium nigricans. The drug has narrow antifungal spectrum and is active against such causative agents of dermatomycoses as Trichophyton, epidermofiton, mikrosporum, and favus. Griseofulvin is ineffective against Candida and causative agents of deep mycoses. Mechanism of action is associated with violation of nucleic acid synthesis due to griseofulvin interaction with guanidine bases of RNA. The fungal resistance to griseofulvin does not develop in general. Griseofulvin is taken orally. The drug is readily absorbed from the gastrointestinal tract. Griseofulvin accumulates in the tissues, synthesizing keratin. Therefore, stratum corneum, nails, and hair become resistant to dermatomycetes. But in the upper epidermal layers, griseofulvin is determined only in 1–2 months after the start of therapy. Moreover, griseofulvin does not penetrate into the nail plates. Therefore, nail avulsion involves application of keratolytic agents. The daily dose of griseofulvin is divided into 4 intakes to provide the stable high drug concentration in the blood. Although a single drug intake of the daily dose is also possible. The duration of treatment with griseofulvin is 1–8 months. Also, liniment with griseofulvin is used topically.

The main routes of griseofulvin excretion from the body are kidneys and an intestine. A main part of the antibiotic dose undergoes the drug biotransformation in the liver.

The side effects of griseofulvin are headache, nausea, insomnia, disorientation, photodermatosis, fear, leukopenia, eosinophilia, etc. It is necessary to notice that nowadays the clinical use of griseofulvin is significantly restricted due to its cancerogenic property.

Terbinafine (Lamisil) is a derivative of N-methylnaphthalene. The drug affects ergosterol synthesis and formation of fungal membranes due to the influence upon the early steps of synthesis and violation of squalene accumulation. Lamisil exhibits the fungicidal effect. The spectrum of antifungal action includes dermatophytes and *Candida*. Terbinafine is taken

orally. The drug is readily absorbed from the gastrointestinal tract and accumulates in the skin, subcutaneous fat, nail plates, hair follicles, and sebaceous glands. Terbinafine is metabolized in the liver and excreted through the kidneys. Lamisil cream is used topically twice a day.

The therapeutic indications for terbinafine are dermatomycosis of different localization and candidiasis. Most commonly the drug is used to treat onychomycosis and candidiasis of mucous membranes. The course of treatment lasts from 2 to 6 months. Lamisil is not recommended for pregnant women and for nursing mothers. The side effects of terbinafine are dyspepsia and allergic reactions. External drug use can cause itching and red skin.

Nitrofungin is a nitrophenol derivative. The drug is used topically as an alcoholic solution. Antifungal activity of nitrofungin is low.

The following drugs are also used topically for treatment of mycoses: *miconazole, clotrimazole*, preparations of undecylenic acid (ointments *"Zincundanum", "Mycoseptin", "Undecinum"*), and iodine preparations (*alcoholic iodine solution,* and *potassium iodide*).

Drugs for Candidiasis Treatment

Candidiasis most commonly affects mucous membranes of the gastrointestinal tract, bronchi, sex organs, and skin. The main causative agent of candidiasis is *Candida albicans.*

Antibiotics *nystatin* and *levorin* exhibit fungiostatic and fungicidal effects. These drugs violate permeability of the fungal cell membrane. These drugs are characterized by low intestinal absorption. Nystatin and levorin are used orally to treat gastrointestinal candidiasis or to prevent candidiasis in patients treated by antibacterial drugs of broad spectrum. To treat candidiasis of oral cavity of sex organs, nystatin and levorin are used in solutions for syringing or in suppositories.

Toxicity of nystatin is very low. Its side effects are dyspepsia and allergic reactions. Levorin has a higher toxicity. But resistance of Candida to levorin develops more slowly. Levorin is also used in treatment of trichomoniasis and in therapy of patients with prostate adenoma.

Natamycin (pimafucin) is a polyene antibiotic with broad spectrum of antifungal action. Candida is especially highly sensitive to natamycin. Dermatophytes are less sensitive to natamycin. Pimafucin is used topically in treatment for candidiasis of the skin and mucous membranes. Suppositories with natamycin are used in treatment for vaginal

candidiasis, and tablets – in treatment for intestinal candidiasis (drug is taken orally 4 times a day). To treat dermatomycoses, pimafucin is used in combination with griseofulvin. Toxicity of pimafucin is low. The side effects are dyspepsia and irritation and burning in case of local use.

Clotrimazole is imidazole derivative. It is a highly toxic agent which is used topically to treat candidiasis, resistant to polyene antibiotics.

Decaminum is bis-quaternary ammonium salt. It is a detergent with high surface activity. Decaminum violates permeability of fungal cytoplasmic membrane and due to this exhibits bactericidal, fungistatic, and fungicidal effects. The ointment with decaminum is used to treat fungal lesions of skin 1–2 times a day during 2–3 weeks. Decaminum is also effective in inflammatory lesions of the oral cavity, throat, and vagina.

Table 8 – ***Drugs for prescription***

Drug name (Latin)	**Single dose and route of administration**	**Drug product**
Nystatinum	Orally 500,000 IU 3–4 times daily; for rectal or vaginal introduction 1 suppository 2 times daily; ointment for applying on the skin	Tablets 250,000 or 500,000 IU; suppositories 250,000 or 500,000 IU; ointment 1 % – 15.0 g
Amphotericinum B	Intravenously drop-by-drop 100–1,000 IU/kg (in 450 ml of 5 % glucose solution) 2–3 times per week; ointment for applying on injured parts of the skin	Vials with 50,000 IU of powder for injection; ointment 15.0 or 30.0 g (1 g contains 30,000 IU of amphotericinum B)
Griseofulvinum	Orally 1 tablet 4 times daily; liniment for applying on injured parts of the skin	Tablets 0.125 g; liniment 2.5 % – 30.0 g
Fluconazole	Orally or intravenously drop-by-drop 0.05–0.4 g once a day	Capsules 0.05; 0.1; 0.2 g; vials 50; 100 or 200 ml of 0.2 % solution
Ketoconazole	Orally 0.2–0.4 g once a day	Tablets 0.2 g
Itraconazole	Orally 0.1–0.2 g once a day	Capsules 0.1 g

Anthelmintic Drugs

More than 250 species of worms can parasitize in a human body. The worms cause an enormous damage for the host organism due to the release of toxins and mechanical damage of the internal organs. Helminthiases can cause anemia, allergic reactions, disordes of the central nervous system activity, gastrointestinal distress, functional disturbances of the liver, lungs, eyes, blood and lymphatic vessels, etc. The incidence of worm infections is quite high.

Depending on localization of worms in the human organism, there are intestinal and extraintestinal helminthiases. Depending on the types of worms, which cause the disease, helminthiases are divided into nematodiasis (causative agents are roundworms or nematodes), cestodiasis (causative agents are flatworms or cestodes), and trematodiasis (causative agents are flukes or trematodes).

Drugs for Intestinal Helminthiasis Treatment

Drugs for Intestinal Nematodiasis Treatment

The following drugs are used to treat intestinal nematodiasis: *mebendazole, albendazole, medamin, levamisole, piperazine, naftamon, pervinium pamoate,* and *pyrantel pamoate*.

Mebendazole (Vermox) is a benzimidazole derivative. The drug has a broad spectrum of anthelmintic action which includes main types of roundworms: *Ascaris lumbricoides* (causative agent of ascariasis), *Enterobius vermicularis* (enterobiasis), *Trichocephalus trichiurus* (trichocephaliasis), *Ancylostoma duodenale* (ankylostomiasis), and *Strongyloides stercoralis* (strongyloidiasis). Mebendazole is active against infections, caused by cestodes *Taeniarhynchus saginatus* (bovine tapeworm), *Hymenolepis nana* (dwarf tapeworm), and *Taenia solium* (pork tapeworm). Vermox affects both worms and their eggs.

The mechanism of mebendazole action is associated with violation of glucose absorption by worms that results in disturbances of energy metabolism. At the same time, the violation of glucose absorption by mammalian cells is not observed. The inhibition of motor activity and death of helminths develop gradually. The excretion of dead parasites with feces is observed during several days.

Mebendazole is taken orally during or after meals. Gastrointestinal absorption of mebendazole is low (not more than 10 %). The absorbed part

of the drug undergoes hepatic metabolism and is excreted by the kidneys within 1–2 days. For better absorption, an intake of mebendazole suspension in sunflower oil is recommended. The treatment with mebendazole does not require a special diet. The single mebendazole intake is used in case of invasion by *Ascaris lumbricoides* or *Enterobius vermicularis*. Repeated intake of the drug is recommended in two weeks. To treat other helminthiases, the course of treatment with mebendazole varies depending on the type of helminth.

The therapeutic indications for mebendazole are intestinal nematodiasis (ascariasis, enterobiasis, ankylostomiasis, trichocephaliasis, and strongyloidiasis), intestinal cestodiasis (teniasis, teniarinchiasis, and hymenolepiasis), extraintestinal nematodiasis (filariasis and trichinelliasis), and extraintestinal cestodiasis (cysticercosis and echinococcosis).

Albendazole (Vormil) is effective in intestinal nematodiasis, cysticercosis, and echinococcosis. Vormil also affects the eggs of *Ascaris lumbricoides*, *Ancylostoma duodenale*, and *Trichocephalus trichiurus* (whipworm). The drug violates glucose utilization by helminths. Taken orally, albendazole is easily absorbed from the gastrointestinal tract and metabolized in the liver. The drug metabolites are excreted mainly by the kidneys. The side effects of albendazole are headache, diarrhea, dizziness, and insomnia. Prolonged intake of albendazole can cause leukopenia, vomiting, skin rash, abdominal pain, and alopecia.

Pyrantel pamoate is a pyrimidine derivative. The drug is used at invasion by roundworms. Pyrantel violates neuro-muscular transmission due to cholinesterase inhibition. It results in spastic paralysis of helminths. Pyrantel is taken orally. The degree of intestinal drug absorption is about 50 %. The main route of excretion is the intestine. The therapeutic indications for pyrantel are ascariasis, enterobiasis, ancylostomiasis, and trichostrongyliasis. Side effects of pyrantel are dyspepsia, loss of appetite, and headache.

Levamisole (decaris) is commonly used in ascariasis treatment. The drug causes depolarization of helminth muscular membranes that results in muscular paralysis. Besides, levamisole inhibits the activity of fumaratereductase and violates metabolism of the helminths. Simple drug intake provides the full dehelminthization in 90–100 % of patients with ascariasis. Levamisole activity is lower in ancylostomiasis and

strongyloidiasis. Levamisole effects positively in patients with extraintestinal helminthiasis, for instance with filariasis.

The side effects of levamisole are abdominal pain, nausea, vomiting, and headache.

Levamisole also has immunomodulatory effect. The drug normalizes function of macrophages and T-lymphocytes in patients with immunodeficiency. The course of treatment with levamisole lasts from 2–3 weeks up to a year. Prolonged therapy with levamisole can be aggreveted by a lot of serious side effects: insomnia, disorders of taste and smell, skin rash, and agranulocytosis.

Pyperazine adipinate is widely used to treat ascariasis and enterobiasis. Pyperazine paralyzes the neuromuscular systems of helminths that prevents their movement through the intestine and penetration into the bile ducts. Also, pyperazine stimulates the intestinal peristalsis that provides favorable conditions for evacuation of helminths from the intestine. The drug is readily absorbed from the intestine, its metabolites are excreted with the urine. The treatment with pyperasine does not require a special diet and intake of laxative drugs. An efficacy of pyperazine in ascariasis is 90–100 %. Pyperazine is a low toxic drug. Its side effects are dyspepsia and headache.

Naftamon is a monoquaternary ammonium compound. The drug is highly effective in ascariasis, enterobiasis, ankylostomiasis, and trichostrongyliasis. Mechanism of action is associated with inhibition of neuromuscular transmission of helminths. Naftamon is characterized by low ability to absorb from gastrointestinal tract and laxative activity. A very bitter taste of naftamon is the cause of nausea and vomiting. Naftamon is prescribed for oral intake for 1–2 hours before a meal.

Pervinium pamoate is mainly used to treat enterobiasis and strongyloidiasis. The drug inhibits aerobic respiration of helminths and violates the utilization of exogenic glucose. The absorption from gastrointestinal tract is low. Pervinium seldom causes the side effects.

Drugs for Intestinal Cestodiasis Treatment

The drugs to treat intestinal cestodiasis are *praziquantel, niclosamide (phenasalum), extract of male fern, pumpkin seeds*, etc.

Niclosamide (phenasalum) is active against *Taenia solium, Taeniarincus saginatus, Diphyllobothrium latum*, etc. The drug inhibits

phosphorylation in mitochondria of cestodes, utilization of oxigen and glucose by helminths, and paralyzes their neuromuscular system. Besides, niclosamide decreases the resistance of helminths to proteolytic enzymes of the gastrointestinal tract that provokes degradation of the coating tissues of helminths. The treatment with niclosamide requires a specific patient preparation – carbohydrate diet because proteins bind to drug and inactivate it. Overnight, the patient drinks only tea and fruit juice and gets an enema. Niclosamide is taken in the morning on an empty stomach. Laxative drugs are given only in case of teniasis (to prevent cysticercosis). Niclosamide is readily absorbed from the gastrointestinal tract. About 25–30 % of the drug is excreted from the body in urine, another part – in feces. Side effects of niclosamide are nausea, vomiting, and abdominal pain.

Praziquantel (biltricide) is highly effective drug to treat intestinal cestodiasis (teniasis, diphyllobothriasis, teniarinchiasis, and hymenolepiasis), extraintestinal trematodiasis, and cysticercosis. Praziquantel increases permeability of calcium in helminthic cell membranes. Calcium entrance causes a short-time increase of muscular activity which is replaced by spastic paralysis of helminths. Praziquantel is readily absorbed from the gastrointestinal tract, undergoes fast hepatic metabolism, and is being excreted by the kidneys. Side effects of praziquantel are dyspepsia, headache, and skin rash. The drug is contraindicated in first trimester of pregnancy and for nursing mothers.

The *extract of the male fern* is obtained from the rhizome of this plant. The extract contains dezaspidin, dezaspidiol, and other derivatives of phloroglucinol. The taken orally drug is practically not absorbed from the gastrointestinal tract. However, the presence of fats can increase the gastrointestinal absorption of the extract that results in poisoning. The extract of the male fern causes the muscular paralysis in helminths, therefore, parasites can not attach to the intestinal wall. The extract of the male fern is used to treat teniasis, diphyllobothriasis, teniarinchiasis, and hymenolepiasis. Due to high toxicity, the treatment by the extract of the male fern is carried out according to certain regimen and only in the hospital. Two days before treatment, a special diet with easily digestible meatless products is prescribed to a patient. In the evening before the drug intake, a patient drinks a cup of tea with rusk. The laxative drug is prescribed for the night. In the morning, the patient receives the cleansing enema and takes the drug (required number of capsules within 30 minutes). The capsules are washed down by a solution of sodium hydrocarbonate. It

is necessary for pyloric relaxation and increase of drug evacuation rate from the stomach into the intestine. After 1–1.5 hours, the patient receives the laxative drug. If laxative effect does not develop in 3 hours, the patient receives the cleansing enema. Side effects of the extract of the male fern are headache, vomiting, diarrhea, convulsions, paralysis, respiratory depression, atrophy of the optic nerve, heart disorders, and collapse. Due to high toxicity, the extract of the male fern is used seldom.

Mebendazole may be used to treat some cases of cysticercosis.

Drugs for Intestinal Trematodiasis Treatment

Ethylene tetrachloride and *praziquantel* are used to treat metagonimosis (caused by *Metagonimus yokogawai*).

Ethylene tetrachloride is taken orally. The drug absorption from the gastrointestinal tract is low. The special fat-free and carbohydrate-rich diet should bt used during 1–2 days to prepare a patient to treatment. Also, alcohol is contraindicated during this time. In 15–20 minutes after ethylene tetrachloride intake, the patient receives saline laxative drug. Ethylene tetrachloride is also effective in ancylostomiasis.

Drugs for Extraintestinal Helminthiasis Treatment

Drugs for Extraintestinal Nematodiasis Treatment

Filariasis is the most common extraintestinal nematodiasis. There are several causative agents of filariasis: *Wucherichia Bancrofti* and *Brugia malayi* affect the lymphatic system; *Loa Loa* parasitizes in the subcutaneous fat; *Onchocerca volvulus* parasitizes in the subcutaneous fat and in the eyes. Other widely spread extraintestinal nematodiasis is trichinelliasis at which *Trichinella spiralis* affects the skeletal muscles (larval stage) and the intestine (mature stage).

To treat extraintestinal nematodiasis, *diethylcarbamazine (ditrazinum)* and *ivermectin* are used.

Diethylcarbamazine is an effective drug for filariasis treatment (the highest activity against microfilariae). The drug is easily absorbed from the gastrointestinal tract, it undergoes partial biotransformation and is excreted in the urine within 2 days. Ditrazinum inhibits the ability of microfilariae to resist phagocytosis. Ditrazinum exhibits a nematicidal effect. However diethylcarbamazine provides the marked therapeutic effect only at early stages of the disease. The side effects of diethylcarbamazine

are headache, weakness, nausea, and vomiting. These complications are caused by toxic influence of decomposition products of microfilariae and rapidly disappear.

Ivermectin is highly active againt microfilariae and Strongyloides stercolaris, but not active against macrofilariae. Ivermectin is semisynthetic macrocyclic lactone compound. The drug is taken orally. Therapeutic effect develops after a single intake. Ivermectin causes the flaccid paralysis of helminths due to inhibition of GABA. The highest drug activity develops when treating onchocercosis (blinding filarial disease or river blindness). The side effects of ivermectin are fever, drowsiness, dizziness, headache, bronchospasm, etc.

There are no effective drugs for trichinelliasis treatment. Certain positive effect in this case is possible for *mebendazole*.

Drugs for Extraintestinal Trematodiasis Treatment

Schistosomiasis is the most common extraintestinal trematodiasis. The causative agents of schistosomiasis are *Schistosoma mansoni*, *Schistosoma haematobium*, and *Schistosoma japonicum*. These parazites affect the blood vessels that results in disorders of internal organs (intestine, liver, lungs, spleen, urogenital system, etc.).

The most effective drug for schistosomiasis treatment is *praziquantel (biltricid)*. The drug is also effective in other extraintestinal trematodoses:

– opisthorchiasis (causative agent is *Opisthorchis felineus* which affects the liver and pancreas);

– clonorchiosis (*Clonorchis sinensis* parasitizes also in the liver and pancreas);

– paragonimiasis (*Paragonimus Westermani* affects the brain, lungs, and lymphatic system);

– fascioliasis (*Fasciola hepatica* parasitizes in the liver and gallbladder).

Besides, praziquantel is used to treat metagonimiasis. The pharmacological characteristics of praziquantel is given above.

Antimony sodium tartrate is a drug containing antimony. The drug is administered intravenously, slowly, daily during 20 days. Antimony sodium destroys helminth larvae which are located in eggs. Also, the drug interacts with thiol groups of enzymes, and due to this, inhibits the vital functions of helminths. Antimony sodium tartrate is a toxic agent and

commonly causes side effects. The drug may cause phlebitis. Accidental subcutaneous administration of its solution causes sharp pain and tissue oedema. Weakness, headache, extrasystoles, metallic taste, nausea, muscular and joint pain, hypotension, insomnia, skin rash, cough, chest pain, and anaphylaxis are also possible side effects of antimony sodium tartrate. The drug is contraindicated in patients with diseases of heart, liver, and kidneys, in pregnant women, and during menses. In case of drug overdose, unithiol is used as an antidote.

Chloxilum is an effective agent in treatment for opisthorchiasis and fascioliasis in which helminths affect the liver, bile ducts, and pancreas. Chloxilum reduces the helminth resistance to the action of helminth proteolytic enzymes that results in death of helminths. The drug is taken orally. Patient preparation to treatment lasts 1–2 days, and duration of therapy with chloxilum is 2 days. Within this time, a patient adheres to the fat-free diet and excludes alcohol. Therapeutic efficacy of chloxilum is 35–40 %. In significant number of patients, only reduction in invasion severity is observed. The helminth eggs can be released from the body during 3 months after treatment. Taken orally chloxilum is slowly and incompletely absorbed from the intestine. A main part of the taken dose is excreted from the intestine in feces during the first day. Another part of the drug, which has reached the systemic blood circulation, is accumulated in the body and excreted within 6–28 days. The side effects of chloxilum are headache, light inebriation, drowsiness, pain in the liver and heart, and allergic reactions. Chloxilum is contraindicated in patients with diseases of heart, liver, and in pregnant women.

Bithionol and emetine hydrochloride are used for treatment of fascioliasis.

Bithionol is a drug of choice for paragonimiasis treatment. Typical side effect of this drug is diarrhea.

Drugs for Extraintestinal Cestodiasis Treatment

In extraintestinal cestodiasis treatment, some success has been recently achieved. Thus, therapy with *mebendazole* and *albendazole* exhibits positive results in treatment for echinococcosis and cysticercosis. *Praziquantel* is used to treat cysticercosis, but the drug is ineffective when helminths depoint in the spinal cord and into the cerebral ventricles.

Table 9 – ***Drugs for prescription***

Drug name (Latin)	Single dose and route of administration	Drug product
Mebendazolum	Orally 0.1 g once (only for treatment of enterobiasis) or 0.1–0.4 g 2–3 times a day	Tablets 0.1 g
Piperazini adipinas	Orally 1.5–2.0 g 2 times a day	Tablets 0.2 or 0.5 g
Phenasalum	Orally 2.0 g	Tablets 0.25 g
Ditrazini citras	Orally 0.002 g/kg 3 times a day	Tablets 0.05 or 0.1 g
Praziquantel	Orally 0.025–0.04 g/kg	Tablets 0.6 g
Chloxilum	Orally 0.06 g/kg	Powder

Antitumoral Drugs

Antitumoral drugs are agents with different chemical structure which are able to inhibit the division of malignant cells in various stages of cell cycle. These drugs are used in chemotherapy for different oncological diseases. According to medical statistics, malignant solid tumors and blood diseases rank second among the causes of human death.

Nowadays, about 200 antitumoral drugs are used in oncology. But drugs which are fatally toxic for malignant cells and simultaneously safe for normal body cells are still not developed. Therefore, one of the most important principles for modern chemotherapy is a simultaneous use of several drugs with different chemical structures and mechanisms of action. This enables to increase antitumoral activity and to reduce the toxicity of the drugs.

Classification of antitumoral drugs is as follows:

1. Cytotoxic drugs.

1.1. Alkylating agents:

– chloroethylamines: *embichine (chlormethine), sarcolysin (melphalan), dopanum (uramustine, chlorethylamino-uracil), chlorbutinum (chlorambucil), cyclophosphane (cyclophosphamide),* and *prospidine*;

– ethylenimines: *thiophosphamide (ThioTEPA)*, and *thiodipine*;
– methanesulphonic acid derivatives: *myelosanum (busulfan)*, and *myelobromol*;
– nitrosourea derivatives: *nitrosomethylurea*, *lomustine*, and *carmustine*.

1.2. Antimetabolites:
– folic acid antagonists: *methotrexate*;
– purine antagonists: *mercaptopurine*;
– pyrimidine antagonists: *phthoruracilum (fluorouracil)*, *cytarabine*, and *ftorafur (tegafur)*.

1.3. Cytotoxic antibiotics: *dactinomycin*, *rubomycin*, *carminomycin*, *olivomycin*, *bruneomycin*, *bleomycin*, *epirubicin*, and *mitomycin*.

1.4. Cytotoxic drugs of plant origin:
– Vinca rosea alkaloids: *vinblastine* and *vincristine*;
– taxanes (alkaloids of yew-free): *paclitaxel (taxol)*, *docetaxel*, and *taxotere*;
– podophyllotoxin (obteined from Podophyllum peltatum): *etoposide*, *teniposide*, and *podophylline*;
– alkaloids of Colchicum autumnale: *colchamine* and *colchicine*.

1.5. Other synthetic cytotoxic drugs: *cisplatin*, *carboplatin*, *dacarbazine*, and *procarbazine*.

2. Hormones and their antagonists:
– androgens: *testosterone propionate*, *testenate*, *tetrasterone*, and *medrotestrone propionate*;
– antiandrogens: *flutamide* and *cyproterone (androcur)*;
– estrogens: *fosfestrol*, *diethylstilbestrol*, and *ethinyl estradiol*;
– antiestrogens: *tamoxifen* and *toremifene*;
– progestins: *oxyprogesterone capronate* and *medroxyprogesterone acetate*;
– analogues of gonadotropin-releasing hormone: *goserelin* and *leuprorelin*;
– inhibitors of aromatase: *aminoglutethimide* and *letrozole*.
– glucocorticoids: *prednisolone* and *dexamethasone*.

3. Enzymes: *L-asparaginase*.

4. Cytokins:
   – interferons: *α-interferon*;
   – interleukins: *aldesleukin*.
5. Monoclonal antibodies: *herceptin*.
6. Tyrosine kinase inhibitors: *imatinib*, *gefitinib*, and *erlotinib*.

Most antitumoral drugs cause multiple side effects which restrict their clinical use. To prevent or reduce these side effects, the following drugs are used:

1. Drugs stimulating hemopoiesis (colony-stimulating factors).
1.1. Drugs stimulating leucopoiesis: *molgramostim (Leucomax)* and *filgrastim*.
1.2. Drugs stimulating erythropoiesis: erythropoietins (*epoetin alfa* and *epoetin beta*).
2. Antiemetic drugs: *ondansetron*, *tropisetron*, and *metoclopramide*.
3. Immunomodulators: *interferons*, *interleukins*, *thymus preparations*, and *levamisole*.
4. Drugs which inhibit manifestations of carcinoid syndrome associated with malignant neuroendocrine tumors: *ortreotide*.
5. Drugs which prevent osteoporosis associated with tumor metastasis spread to bones: bisphosphonates (*pamidronate*, *clodronate*, and *zoledronate*).

Alkylating Drugs

Alkylating drugs include cytotoxic agents of different chemical strucrure with identical mechanism of action. It is believed that radicals of alkylating drugs form covalent bonds with different molecules of the cell. The bonds with guanine of DNA are the most important. As a result, the cross-linking of DNA strands occurs. DNA double helix loses its ability to diverge, gene mutations occur, and replication is violated.

Embichin (chlormethine) is the first drug of chloroethylamine subgroup. Like most drugs of this group, embochin is used to treat hemoblastoses (chronic leukemia, lymphogranulematosis, lymphosarcoma, reticulosarcoma, etc.).

Sarcolysin (melphalan) is chloroethylamine derivative. The drug is used in lymphosarcoma, reticulosarcoma, multiple myeloma, and some solid tumors (testicular seminoma, and Ewing sarcoma). In testicular

seminoma, sarcolysin is effective even in the presence of metastases. Sarcolysin is administered parenterally or taken orally.

Cyclophosphane (cyclophosphamide) is the most effective drug within chloroethylamine derivatives. It is a prodrug which is transformed in the human body into the metabolites with antitumoral activity. Cyclophosphane is used to treat hemoblastoses, multiple myeloma, testicular cancer, breast cancer, and small-cell lung cancer (small-cell carcinoma). Cyclophosphane causes a long-term remission in patients with lymphoid leukosis. The drug is administered parenterally and taken orally.

Dopanum (uramustine) and *chlorbutinum (chlorambucil)* are also used to treat hemoblastoses. Both drugs are taken orally.

Prospidine is chlorethylamine derivative which is used in laryngeal cancer treatment.

Thiophosphamide (ThioTEPA) is ethylenimine derivative which is used in treatment for hemoblastoses (chronic leukemia, lymphogranulomatosis, lymphosarcoma, reticulosarcoma) and solid tumors (testicular cancer and breast cancer).

Methanesulphonic acid derivatives *myelosanum (busulfan)* and *myelobromol* are used in exacerbation of chronic myeloid leukemia. Both drugs are taken orally.

Nitrosourea derivatives include such drugs as *nitrosomethylurea*, *lomustine*, and *carmustine*. Nitrosomethylurea is effective at small-cell carcinoma and lymphogranulomatosis. Other drugs are used in treatment for brain cancer, colon and rectal carcer, Hodgkin's disease, and other lymphomas. Another representative of nitrosourea derivatives is *fotemustine*. The drug is used to treat malignant melanoma and primary brain tumors.

Also in melanoma treatment, *dacarbazine* and *procarbazine* are used. These drugs are cytotoxic agents – derivatives of triazenes.

Cisplatin is platinum compound which is used to treat testicular tumors, ovary cancer, bladder cancer, squamous head and neck cancer, endometrial cancer, lymphomas, and non-small cell lung cancer. Like alkylating drugs, cisplatin chemically interact with DNA that results in violation of DNA function.

All alkylating drugs are characterized by high toxicity. Therapy by these drugs is accompanied by nausea, vomiting, hemopoiesis depression (anemia, thrombocytopenia, and neutropenia), ulceration of gastrointestinal tract and bladder, etc. Intravenous administration of alkylating drugs can

cause thromoflebitis. Amenorea, impotention, and hair loss are also possible. At present, cytokins (filgrastim and molgrastim), erythropoietin, and some interleukins are used to stimulate hemopoiesis. Antibiotics are used to prevent and treat various infections.

Antimetabolites

Antimetabolites are structural analogues of natural metabolites: folic acid, purines, and pyrimidines. The mechanism of their action is based on the drug ability to compete with natural metabolites and replace them in the body compounds. Since antimetabolites cannot fulfil the normal physiological functions, their incorporation in molecules of nucleic acid blocks its normal synthesis. Antimetabolites are active only against dividing malignant cells. These drugs do not influence dormant stem cells of tumors.

Folic acid antagonist *methotrexate* and purine antagonist *mercaptopurine* are mainly used in acute lymphoblastic leukemia treatment. Methotrexate has higher activity in children, but mercaptopurine – in adult patients. Besides, both drugs are used in uterine horionepitelioma. Methotrexate is also used in chemotherapy for such solid tumors as breast cancer. Both drugs are taken orally, and methotrexate is administered parenterally.

Phthoruracilum (fluorouracil) is a pyrimidine antagonist. The drug is used in therapy of solid tumors: cancer of stomach, pancreas, breast, and colon. Fluorouracil causes temporal tumor regression in some patients. Fluorouracil is administered intravenously. For peroral intake, capecitabine was created. It is a prodrug which, under the influence of thymidine phosphorylase, is transformed into fluorouracil.

Ftorafur (tegafur) is a less toxic drug than fluorouracil. The drug is used in breast cancer, cancer of stomach, colon, and rectum.

Cytarabine and *thioguanine* are used in chemotherapy for acute myeloid and lymphoid leukemia.

Antimetabolites are highly toxic drugs. Their side effects are nausea, vomiting, inhibition of hemopoiesis, lesions of gastrointestinal tract, hair loss, etc. Only mercaptopurine and thioguanine are relatively well tolerated by patients.

Cytotoxic Antibiotics

Cytotoxic antibiotics are produced by different species of Streptomyces and Actinomycetes. These drugs have different chemical structure. Mechanism of action is associated with inhibition of synthesis and function of nucleic acids that results in suppression of cell division.

Dactinomycin is produced by actinomycetes. The drug is used in chemotherapy for horionepitelioma, Wilms' tumor (nephroblastoma) of children, and lymphogranulomatosis. Dactinomycin is administered intravenously or into the body cavities.

Olivomycin is a derivative of aureolic acid which is produced by actinomycetes. Olivomycin is used in the treatment for seminoma, teratoblastoma, embryonal carcinoma, lymphoepithelioma, reticulosarcoma, and melanoma. The drug is administered intravenously or applied topically in ointments.

Rubomycin, doxorubicin (Adriamycin), carminomycin are anthracycline antitumor antibiotics. These drugs are used in the treatment for sarcomas of mesenchymal origin. Also, doxorubicin is used in bone sarcoma, breast, lungs', bladder, thyroid, and ovarian cancer, etc. Rubomycin is used in treatment for acute leucosis, reticulosarcoma, and uterine horionepitelioma.

Bleomycin is cytotoxic glycopeptide antibiotic produced by *Streptomyces verticillus*. The drug is used in treatment for squamous cell carcinoma of the oral mucosa, tongue, tonsil, skin, and uterus. Also, bleomycin is used in lymphogranulomatosis and penile cancer.

Bruneomycin is used in treatment for lymphogranulomatosis, reticulo- and lymphosarcoma, and chronic lymphocytic leukemia.

Cytotoxic antibiotics may be combined with other antitumoral drugs, except alkylating drugs and antimetabolites.

It is necessary to notice that all cytotoxic antibiotics have also antibacterial activity, but it has no practical value.

Cytotoxic antibiotics are drugs with high toxicity. Chemotherapy with them is accompanied by numerous side effects: appetite loss, nausea, vomiting, diarrhea, candidiasis, inhibition of hemopoiesis, hair loss, fever, hypotension, cardiotoxicity, allergic reactions, and anaphylactic shock.

Antitumoral Drugs of Plant Origin

Vinblastine and *vincristine* are alkaloids of *Vinca rosea.* Their mechanism of action is associated with metaphase-blockage mitosis due to

disruption in formation and function of the microtubule spindle. It results in violation of DNA divergence to the poles of the cell, the following degradation of DNA strands, and cell death.

Both drugs are used in the treatment for hemoblastoses (acute leukemia, reticulo- and lymphosarcoma, etc.), lymphogranulomatosis, breast cancer, neuroblastoma, etc. *Vinca rosea* alkaloids are commonly combined with other antitumoral drugs. Both drugs are administered intravenously. Their side effects are inhibition of hemopoiesis, nephrotoxicity, neurological disturbances (ataxia, violation of neuro-muscular transmission), alopecia, jaundice, etc.

Yew-tree (*Taxus*) preparations are *paclitaxel (taxol)* and *docetaxel (Taxotere)*. These drugs exhibit antimitotic activity due to interaction with tubulin. Taxones are used in the treatment for breast and ovarian cancer, small cell lung cancer, and epithelial tumors of the head and neck. The side effects of taxones are nausea, vomiting, diarrhea, neutropenia, thrombocytopenia, hypotension, etc.

Podophyllum peltatum (mayapple) preparations are *etoposide, teniposide,* and *podophylline*. These drugs are used in the treatment for laryngeal and bladder papillomatosis, small cell lung cancer, Ewing's sarcoma, etc.

Colchamine and *colchicine* are alkaloids of *Colchicum autumnale* and *Colchicum speciosum*. Colchamine is used topically in ointment in the treatment for skin cancer, esophagus, and stomach cancer (in the combination with sarcolysin). Colchamine kills malignant cells practically without damage of normal epithelial cells. Colchamine can cause skin rashes. After removing necrotic tissue, wounds may be healed with good cosmetic result.

Besides, the following plant preparations are used as antitumoral agents: befungin, drugs of celandine, calendula, wild poppy, plantain, etc.

Enzymes

L-asparaginase is enzyme which is used in the treatment for acute lymphoblastic leukemia and lymphosarcoma. This enzyme distroys L-asparagine. L-asparagine is amino acid which is required for the synthesis of proteins, RNA, and DNA. Side effects of L-asparaginase are neuro-, nephro- and hepatotoxicity, and affection of pancreas.

Hormonal Drugs and Their Analogues

This group includes male and female sex hormones and their antagonists, and also glucocorticoids which play complementary role. Sex hormones are used in the treatment for malignant neoplasms of ovaries, uterus, prostate, and breast. There are evidences that under the influence of sex hormones, malignant cells do not die because hormonal drugs only slow down their division and metastasis.

As a rule, chemotherapy with sex hormones is combined with surgical and radiation treatments.

Androgens (*testosterone propionate, testenate, tetrasterone, medrotestrone propionate*) are used to treat breast cancer in women with menstrual cycle and in the first 5 years after menopause. In these cases, androgens inhibit production of estrogens. The use of high androgen doses is accompanied by virilization (excess facial and body hair, baldness, acne, deepening of the voice, increased muscularity), dizziness, nausea, etc.

Antiandrogens include such drugs as *flutamide* and *cyproterone (androcur)*. Their mechanism of action is associated with the inhibition of transport and binding of dihydrotestosterone with receptors in the prostatic cells. It results in slowing down tumoral cell growth in the prostate. Both drugs are taken orally. Antiandrogens exhibit high efficacy in prostate cancer and cause prolonged remission in the majority of patients. The drugs are well tolerated by patients. Prolonged anti-androgen therapy may be accompanied by the development of gynecomastia, but it does not affect sexual function.

Estrogens (*fosfestrol, diethylstilbestrol, ethinylestradiol*) are used to treat breast cancer in women with menopause which lasts more than 5 years. In these patients, estrogens inhibit the production of pituitary gonadotropins which indirectly stimulate the growth of tumoral cells.

Besides, estrogens are used in the treatment for prostate cancer. In this case, estrogens inhibit the function of natural androgens. One of the drugs for prostate cancer treatment is fosfestrol (sodium salt of diphosphoric ether of diethylstilbestrol). Under the influence of acid phosphatase of tumoral cells, fosfestrol is transformed into diethylstilbestrol. Fosfestrol is taken orally or administered intravenously. Fosfestrol is characterized by fast efficacy development and low toxicity in contrast to diethylstilbestrol. The use of estrogens in males can cause feminization, dyspepsia, itchy skin, and

hemorrhagic rash. In 1–2 years of estrogen use, malignant cells lose the sensitivity to these agents.

Antiestrogens (*tamoxifen, toremifene*) bind to estrogen receptors of neoplastic cells of the breast and prevent estrogen-induced tumor growth. Antiestrogens are used to treat estrogen-induced breast cancer, especially in postmenopausal women. The side effects of these drugs are vaginal hemorrhage, redness of the skin, vomiting, dermatitis, etc.

At present, drugs inhibiting the synthesis of androgens are introduced in the medical practice. These drugs are aromatase inhibitors. In postmenopausal period, estrogens are synthesized from androgens which are produced by adrenal cortex. This process is regulated by enzyme aromatase. Inhibition of aromatase results in violation of estrogen synthesis.

A group of aromatase inhibitors includes such drugs as *letrozole (Femara), anastrozole (Arimidex), aminoglutethimide (Cytadren)*, etc. Aromatase inhibitors are used to treat breast cancer and ovarian cancer in postmenopausal women and gynecomastia in men. Their side effects are headache, dyspepsia, skin rash, weakness, vaginal bleeding, etc.

Progestins (*oxyprogesterone caproate, medroxyprogesterone acetate*) are used to treat uterine cancer. Progestins cause the cancer regression in significant number of patients.

Analogues of gonadotropin-releasing hormone (*goserelin, leuprorelin*) also exhibit the antitumoral activity. In case of continuous use, these drugs reduce the secretion of gonadotropins by the anterior pituitary and exhibit therapeutic effect in patients with prostate cancer.

Glucocorticoids and preparations of *adrenocorticotropin* are commonly used to treat acute leukemia in children, lymphogranulomatosis, chronic lymphocytic leukemia, and lymphosarcoma.

Cytokines

Cytokines include interferons and interleukins.

Recombinant human interferon α is interferon which is used in the complex treatment for some tumors. The drug activates macrophages, T-lymphocytes, and T-killer cells. Recombinant human interferon α is effective in multiple myeloma, Kaposi's sarcoma, renal cell carcinoma, etc. The drug is administered parenterally. Side effects of this drug are

headache, fever, myalgia, arthralgia, dyspepsia, blood dyscrasias, thyroid dysfunction, etc.

Interleukin-2 (proleukin) stimulates proliferation and differentiation of T-helpers and cytotoxic T-lymphocytes, activates macrophages, stimulates proliferation of B-lymphocytes. Proleukin is derived by genetic engineering. The drug is administered parenterally. Side effects are hypotension, pulmonary oedema, inhibition of hematopoiesis, nephrotoxicity, lesions of the central nervous system, and allergic reactions.

Monoclonal Antibodies

Monoclonal antibodies include *trastuzumab (Herceptin)* and *rituximab (Mabthera)*. These drugs are produced by genetic engineering. Both drugs are administered intravenously. Monoclonal antibodies are used in complex chemotherapy for some oncological diseases.

Herceptin is an antibody against antigenic HER2-receptors of the breast malignant cells that results in cytotoxic effect. Overexpression of these receptors leads to proliferation and malignant transformation of the cells. Overexpression of HER2-protein is observed in 20–30 % of patients with breast cancer. Therapeutic indication for trastuzumab is metastatic breast cancer with HER2-protein overexpression.

Rituximab interacts with protein CD20 which is an antigen located on the membranes of B-cells of non-Hodgkin's lymphomas.

Bevacizumab (Avastin) is a monoclonal antibody preparation which blocks the vascular endothelial growth factor. The drug inhibits the growth of tumor vessels that violates its blood supply and slows down the tumoral growth. Avastin is administered intravenously. Bevacizumab is used in complex chemotherapy for colorectal cancer.

The side effects of monoclonal antibodies are fever, nausea, vomiting, skin rash, headache, hypo- or hypertension, nephrotoxicity, oedemas, bronchospasms, a cough, lymphopenia, leukopenia, etc.

Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors include *imatinib, gefitinib,* and *erlotinib*. It is a new group of antitumoral drugs. Tyrosine kinase is an important functional element of membrane receptors – growth factors of thrombocytes, epithelium, stem cells, vascular endothelium, nerves, etc. Besides, there are tyrosine kinases of the cytoplasmic and nuclear

localization. Tyrosine kinase regulates the growth and differentiation of cells and their apoptosis.

The first representative of this group is *imatinib*. The drug blocks tyrosine kinase of the receptors for platelet-derived growth factor, stem cell factor, and cytoplasmic tyrosine kinase. Imatinib is used to treat chronic myelogenous leukemia and gastrointestinal stromal tumors. The drug is taken orally. Side effects of imatinib are nausea, vomiting, neutropenia, skin rash, etc.

Gefitinib blocks tyrosine kinase of the receptor for epidermal growth factor. The drug is used to treat non-small cell lung cancer and head cancer.

Erlotinib blocks several receptor tyrosine kinases, and it is used to treat non-small cell lung cancer.

Sunitinib is used to treat gastrointestinal stromal tumors and a clear-cell subtype of renal cell carcinoma.

Table 10 – ***Drugs for prescription***

Drug name (Latin)	**Single dose and route of administration**	**Drug product**
Cyclophosphanum	Orally, intramuscularly or intravenously 0.2 g once a day; 0.4 g once every 2 days	Coated tablets 0.05 g; ampoules 0.1 or 0.2 g of powder for solution
Chlorbutinum	Orally 0.002–0.01 g once a day	Tablets 0.002 or 0.005 g
Myelosanum	Orally 0.002–0.01 g once a day	Tablets 0.002 g
Mercaptopurinum	Orally 0.001–0.00125 g/kg once a day	Tablets 0.05 g
Methotrexatum	Orally, intramuscularly or intravenously 0.03 g 2 times in a week, or 0.05 g once in five days	Coated tablets 0.0025 g; ampoules 0.005, 0.05 or 0.1 g of powder for solution
Phthoruracilum	Intravenously slowly or drop-by-drop 0.01–0.015 g/kg once a day or once every 2 days	Ampoules 5 ml of 5 % solution
Vinblastinum (Rosevinum)	Intravenously 0.00015–0.0003 g/kg once per week	Ampoules 0.005 or 0.01 g of powder for solution
Vincristinum	Intravenously 0.00001–0.00003 g/kg once per week	Ampoules 1 or 5 ml of 0.1 % solution; vials 0.0005 or 0.001 g of powder for solution

Radioprotectors. Radionuclide Decorporation Drugs

Radioprotectors are drugs which are used in case of radiation threat, during radiotherapy of cancer patients, and in work with radionuclides. Radioprotectors reduce or prevent the destructive action of ionizing radiation.

Radioprotectors are classified as follows:

1. Sulfur-containing drugs.
1.1. Sulfur-containing amino acids and their derivatives: *cysteine, methionine, cysteamine hydrochloride, taurine, acetylcysteine*.
1.2. Other groups of sulfur-containing drugs: *unithiol, β-mercaptoethylamide, β-aminoethyl, isothiuronyl, cystophos, gamaphos*.
2. Biogenic amines: *serotonin adipate, mexamine, adrenaline*.
3. Amino acids and their derivatives: *glutamic acid, asparaginic acid, asparcam, panangin*.
4. Derivatives of nucleotides and nucleosides: *sodium nucleinate, methyluracil, riboxinum, phosphadenum, ATP*.
5. Alcohols: *butyl alcohol*.
6. Vitamins: *rutin, ascorbic acid, pyridoxine, tocopherol, nicotinamide, methylmethionine sulfonium*.
7. Antioxidants.
7.1. Antioxidants of direct action: *tocopherol, ubiquinone*.
7.2. Antioxidants of indirect action: *selenium-containing drugs, amino acids, zinc-containing drugs, copper-containing drugs, caffeine*.
8. Biopolymers: *zymosan*.
9. Estrogens: *estradiol*.
10. Polysacharides: *prodigiozan*.
11. Complexones: *pentacinum, tetacinum-calcium*.
12. Sorbents: *enterosorbent CKN, silica gel, activated carbon, carbolong, carbalose*.
13. Herbal preparations: *liquid extract and tincture of ginseng, tinctures of Aralia, Chinese schizandra, Eleutherococcus, polyphenolic compounds*.
14. Methemoglobin-forming drugs: *sodium nitrite, methylene blue*.

According to duration of action, there are short-acting and long-acting radioprotectors. Short-acting radioprotectors develop effect in 0.5–4 hours after administration. These drugs protect from single radiation or short-term high-level radiation. Short-acting radioprotectors are administered in maximal doses. This group includes sulfur-containing compounds, biogenic amines, and methemoglobin-forming drugs which disrupt tissue oxygenation.

Long-acting radioprotectors are used to protect human body from a long-term effects of low-level radiation. These drugs are divided into drugs with hypoxic mechanism of action and drugs with non-hypoxic mechanism of action. Drugs with hypoxic mechanism of action are biogenic amines and methemoglobin-forming drugs. Drugs with non-hypoxic mechanism of action include sulfur-contaning compounds and drugs of other groups.

Mexamine and *cysteamine hydrochloride* are drugs which are most commonly used to prevent and treat radiation sickness.

The damaging effect of ionizing radiation is lower in hypoxia. The drugs causing vasoconstriction and reducing oxygen blood concentration cause hypoxia and inhibit lipid peroxidation. These properties are typical for biogenic amines. These drugs are used to treat and prevent radiation sickness.

Mexamine is a biogenic amine which has a similar chemical structure to serotonin. Mexamine causes contraction of smooth muscles and provides sedating effect on the central nervous system. The drug is taken orally 30–40 minutes prior to radiation therapy. Mexamine is well tolerated by patients.

Sulfur-containing drugs contain SH_2-groups and are the most active radioprotectors. Sulfur-containing drugs inhibit free radicals in cell bodies, form compounds of heavy metals, normalize protein metabolism on the DNA level, and increase cAMP concentration.

Cysteamine hydrochloride is taken orally 1 hour prior to radiation therapy. The duration of the effect is 5 hours. The drug is used to prevent and treat chronic radiation sickness. Cysteamine hydrochloride is ineffective in cases of acute radiation sickness.

Cyanides also exhibit radioprotective effect due to blockage of respiratory enzyme cytochrome oxidase which provides transport of the electrons from cytochrome to oxygen.

Estrogens increase human body resistance to ionizing radiation. These drugs protect the bone marrow, thyroid gland, decrease catabolic action of ionizing radiation, and activate the immunity (phagocytosis).

Some macromolecular substances also have radioprotective activity (polysaccharides, nucleic acids, alcohols, and synthetic polymers). Their radioprotective effect arises 0.5–2 hours after intake and lasts up to 3 days. Mechanism of their action is based on stimulation of nucleic acid synthesis and bone marrow cell regeneration. Among glycans, *zymosan* is characterised by the highest radioprotective activity. Zymosan protects hematopoiesis from negative influence of antitumoral drugs and ionizing radiation. The drug is administered intramuscularly in dose 1–2 ml on alternate days. The treatment course is 5–10 injections.

Batilol protects leukocyte and erythrocyte sprouts from ionixing radiation within 4–6 weeks. The drug is taken orally together with butter or vegetable oil which improve batilol absorption.

Thesanum is used in skin protection from ionizing radiation. Liniment of thesanum is applied on the skin prior to radiation session.

Direct antioxidants are drugs with radiprotective properties: *tocopherol, ascorbic acid, nicotinamide, riboflavin, pyridoxine*, preparations of *ginceng, Chinese magnolia, Manchurian Aralia, Eleutherococcus*, etc.

Selenium preparations are drugs with indirect antioxidant activity. Selenium stimulates enzymes of the antioxidant cellular system (activates glutathione peroxidase, and promotes synthesis of cytochrome C and ubiquinone).

Besides, antioxidant properties are typical for compounds of zinc and copper, glutathione precursors, linoleic acid, and caffeine.

Stimulators of leukopoiesis (*sodium nucleinate* and *methyluracil*) also provide radioprotective effect. Some radioprotective activity is typical for vasopressin, prostaglandins, and acetylcholine.

Chelators (*pentacinum, tetacinum-calcium,* and *alginates*), sorbents (*activated carbon, carbolong, enterosorbent SKN, silica gel*, etc.), pectins, vegetable fibers, and carboxymethyl cellulose bind radionuclides and provide their elimination from the body.

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