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LECTURE No. 1. CLINICAL PHARMACOLOGY AS A SCIENCE, ITS TASKS AND BASIC PROVISIONS

Target:
After studying the topic, the student should have an idea of the main stages of development of clinical pharmacology (CP) and know:
• the concept of "clinical pharmacology";
• its subject and objectives;
• the importance of CF for the practical activities of a doctor
• the concepts of "medicine" and "dosage form".

Lecture abstracts

Main stages in the development of clinical pharmacology
CF was formed as an independent science in the second half of the 20th century.
Since the 30s of the last century, the development of the scientific foundations of CF began. This coincides with fundamental discoveries and the beginning of the use of sulfonamides, H1 receptor blockers, organophosphates, antihypertensive drugs (rauwolfin), phenytoin and other drugs.
Many outstanding domestic and foreign scientists have made a certain contribution to the development of ideas about individual pharmacotherapy (PT). The development of medicinal toxicology as the science of pharmacokinetics (PK) and pharmacodynamics (PD) of drugs and poisons was facilitated by A.P. Nelyubin (1785-1858).
In the 40s, penicillins, tetracyclines, streptomycin, aminosalicylic acid, anti-blastoma drugs, ganglion blockers, muscle relaxants and glucocorticoids were discovered and created. In the 50s, psychotropic drugs (chlorpromazine, haloperidol, reserpine, imipramine, diazepam) were introduced into clinical practice, literally giving mentally ill patients a free hand. During these years, new methods and means of treating diabetes mellitus (DM), hypertension, tumor and a number of infectious diseases, hormonal disorders, bronchial asthma (BA), and drugs for combined anesthesia and anesthesia were created.
In the last decades of the last century, marked by the progress of medical technology, the introduction into the practice of doctors of subtle biochemical, cytological, microbiological, electrophysiological, immunological and other methods, there was an accumulation of a huge arsenal of information about the behavior of drugs in the body of patients, their FC, interaction, methods of administering drugs to the patient's body, monitoring the effectiveness and safety of medications, etc.

Subject and tasks of clinical pharmacology

CP is a science that studies drugs as applied to humans (WHO definition). Its goal is to optimize drug therapy, i.e. achieving maximum efficiency and safety.
CF consists of two main parts: pharmacology and therapeutic evaluation (determining the clinical value of the drug and the method of its optimal use).
• Pharmacology:
- FDynamics - study of the isolated and combined (with other drugs) effects of drugs on the body of a young, elderly, healthy and sick person;
- Phkinetics - study of absorption, distribution, metabolism and excretion of drugs (i.e., the influence of a healthy or sick organism on drugs).
• Therapeutic assessment of drugs:

- official (formal) controlled therapeutic studies;
- monitoring the effectiveness and undesirable effects of drugs

Objectives of the CF

• Organization and conduct of clinical trials of new and old drugs.
• Development of methods for effective and safe FT.
• Organization of information and advisory work in medical institutions, pharmacies and among the population; training of students, doctors and pharmacists.

The relevance of the study of clinical pharmacology for the practical activities of a doctor

The need for medical personnel to know the basics of CF is due to the steady increase in the number of new drugs produced by the global pharmaceutical industry. It is known that currently the total number of drugs in different countries of the world exceeds more than 20 thousand items. It is important to recognize that the choice of drug and its safe and effective use depends on information that can only be obtained through systematic study of the drug in a clinical setting. Unfortunately, at present, drugs are often prescribed unjustifiably and uncontrolled, which leads to the development of unwanted side effects and complications that reduce the effectiveness of treatment. That is why every medical worker must have sufficient knowledge of CF.

Name of the drug and dosage form

A drug is any substance that, after being introduced into a living organism, changes its functioning (WHO, 1969). An individual chemical substance (the active ingredient of a drug) may contain many other substances that ensure the stability of the dosage form (DF) prescribed to the patient. In our country, drugs are drugs approved for use in accordance with the established procedure (Pharmacological and Pharmacopoeial committees). The terms "drug" and "drug" are usually used interchangeably.

Classification and name of drugs

The classification of drugs is based on the following principles.

• Medicinal use: antihypertensive, antianginal, antiarrhythmic, etc.
• Mechanism or site of action:
- molecular - receptor blockers (α- and β-adrenergic blockers, etc.), enzyme inhibitors (for example, angiotensin-converting enzyme), etc.;
- intraorgan - loop diuretics (act in the kidney at the level of the loop of Henle), etc.;
- physiological system - vasodilators, hypolipidemic, anticoagulants, etc.
• Molecular structure: barbiturates, glycosides, etc.

The names (nomenclature) of drugs can be of three types.

• Full chemical name: usually not used in medical practice and used in special reference publications and annotations for drugs.
• Nonproprietary (international) name: a single name, officially accepted in pharmacopoeias of different countries (for example, propranolol, verapamil, isosorbide dinitrate, etc.).
• Patented (commercial) name: assigned by pharmaceutical companies; serves as their commercial property, a trademark (for verapamil - finoptin♠, isoptin♠, etc.; for isosorbide dinitrate - isoket♠, etc.).

Generic drug names must meet three main requirements: have a clear sound and spelling, a distinct difference from other already existing non-branded or branded names, and be close to the names of drugs that are similar in structure or mechanism of action, i.e. belonging to the same group. For

example, the common final part of the name is often used: “olol” - for β-blockers (propranolol, acebutolol, nadolol, etc.); “statin” - for one of the groups of lipid-lowering drugs (lovastatin, pravastatin, simvastatin; recently this group of drugs has been simplified to be called “statins”, which is accepted even in the scientific clinical and pharmacological literature). The creation of proprietary names has another goal: to distinguish (separate) the drug as much as possible from similar generic products produced by other companies. Often, a certain part is introduced into such a name, indicating that the drug belongs to a specific company (for example, at the end of the name - “ket”, “poppy”, etc.). Recently, words, numbers or endings are often introduced into the name, indicating the features of the LF:
• “spray” - inhalation form;
• “long” or “SR” - for long-acting drugs, etc.;
• numbers indicating the dose (in milligrams) - isoptin* 80, isoptin* 240 or isoket* 20, isoket* 60, isoket* 120;
• to isolate a dose of the same drug in tablets or dragees (a large dose - “forte”, a small dose - “mite”).

Dosage forms

LF is a state imparted to a medicinal substance and making it convenient for practical use, in which the necessary therapeutic or prophylactic effect is achieved. In other words, LF is a method of releasing drugs.

Depending on the method of administration, LF is divided into:
• sublingual - granules, tablets and similar ones;
• aerosols (sprays) - dosage forms for administration into the oral cavity (for example, nitroglycerin);
• buccal - plates and tablets with adhesive properties for placement on the oral mucosa (for example, Trinitrolong♠, Dinitrosorbilong♠ plates; Susadrinap tablets, etc.);
• oral (oral) - for oral administration in the form of tablets, dragees, capsules, rarely - wafers and solutions;
• parenteral - for intravenous, intramuscular or subcutaneous administration (solutions in ampoules, vials);
• transdermal (cutaneous) - ointments, patches or discs (for example, with nitroglycerin).

It is fundamentally important to distinguish between LF:

• normal duration of action (characteristic of a specific chemical compound);
• prolonged action, obtained through the use of various systems of controlled long-term release (microencapsulation method, attachment to polymers), complex systems for a very long prolongation of the effect (plasters or disks, depot forms), due to the dissolution of the drug substance in oil, gelatin, synthetic medium .

The concept of pharmacotherapy and pharmacoprophylaxis

PT is the doctrine of treating diseases with the help of drugs. Pharmacoprophylaxis is the study of preventing diseases with the help of drugs.

Due to practical necessity, a new direction is currently being formed - pharmacovaleology (valeology - the science of health), designed to improve people's health with the help of drugs with adaptogenic and antioxidant effects.
The scientifically sound use of drugs for the treatment and prevention of diseases is based on knowledge of the mechanisms of disease development, the protective and compensatory reserves of the body. The success of PT depends on knowledge of PD, PK and drug metabolism.

The following main types of drug treatment are distinguished.

Etiotropic therapy (from the Greek aetia - cause, tropo - direct) is aimed at eliminating or weakening the effect of the causative factor of the disease (for example, in infectious diseases and poisoning).
Medicines with etiotropic action include antimicrobial drugs (disinfectants, antiseptics, chemotherapeutic drugs), therapeutic serums containing antibodies to antigens of certain types of bacteria, as well as various antidotes that come into strong contact with toxic substances. This type of treatment is the most effective.
Pathogenetic therapy (from the Greek pathos - disease, genesis - origin) is aimed at eliminating or weakening the molecular and other mechanisms of disease development. It is used to treat most non-microbial diseases. Most pharmacotherapeutic agents are classified as pathogenetic drugs. For example, cardiac glycosides can eliminate weakness of the heart muscle, but they are not able to eliminate heart valve defects, which cause the development of heart failure (HF). The anti-inflammatory effect of acetylsalicylic acid is due to a decrease in the synthesis of prostaglandins, which cause the development of swelling and redness of tissues, as well as pain during inflammation.
The means of pathogenetic therapy include a fairly large group of drugs with substitutive action (enzyme preparations, hydrochloric acid, hormonal and vitamin preparations, various mineral preparations) that compensate for the lack of endogenous substances.
Replacement therapy, without affecting the causes of the disease, can ensure the normal existence of the body. For example, insulin preparations for diabetes do not eliminate the cause of the changes (absence or insufficient formation of insulin), but provided they are constantly introduced into the body throughout life, they ensure normal carbohydrate metabolism.
Symptomatic therapy is aimed at eliminating or reducing individual symptoms of the disease (for example, using painkillers for headaches, using laxatives for constipation or astringents for diarrhea).
Medicines that eliminate individual signs of the disease are called symptomatic drugs. Their therapeutic effect is based only on the weakening of any symptom of the disease, while the main mechanism of its development is preserved. That is why the medicinal value of symptomatic medications, although undoubted, is not so significant.
Preventive therapy is carried out to prevent the disease (vaccines, serums, antivirals, antiseptics, disinfectants).

The PT strategy consists of eliminating or weakening the causes and mechanisms of disease development, as well as stimulating natural protective mechanisms of compensation and recovery. The fastest and most complete recovery is achieved with the simultaneous use of drugs that eliminate the cause of the disease and suppress the mechanisms of its development (pathogenesis), and drugs that stimulate the body’s defense mechanisms, so the doctor sometimes justifiably strives to simultaneously prescribe several drugs.

The effectiveness of PT increases when it is prescribed in combination with a certain regimen of rest or activity, an appropriate diet, and suitable physiotherapeutic procedures. In addition, it can complement surgical treatment methods.

PHARMACOKINETICS

FC studies the characteristics of drug entry into the body depending on the route of administration, absorption and bioavailability, association with blood plasma proteins, as well as the distribution and elimination of drugs and their metabolites from the body. In other words, PK makes it possible to assess the dynamics of the presence of a drug and its metabolites in the body (Fig. 2) and answers the question: "What does the body do with the drug?" For CP, studies of pharmacological processes in healthy and sick patients are important.

Knowledge of the FC of drugs provides the opportunity to carry out individual selection of drug therapy for a particular patient, based on the condition of the affected organs and systems affected by the pathological process.

PK data make it possible to determine the dose, the optimal route of administration, the regimen of use of the drug and the duration of treatment.

Regular monitoring of the content of drugs in biological media (drug monitoring) allows timely making the necessary adjustments to the treatment regimen.

The study of FC is of particular importance in cases of ineffective treatment or poor tolerability of drugs.

Pharmacokinetic studies are necessary when conducting PT in patients with liver and kidney diseases, as well as when prescribing combination drug treatment.

It is impossible to do without pharmacokinetic studies when developing new drugs and their dosage forms, as well as during experimental and clinical trials of new drugs.

Features of the introduction of drugs into the body

Drugs can be introduced into the body in various ways: through the gastrointestinal tract (through the mouth, into the rectum), skin, injection (into a muscle, vein, etc.), inhalation, etc. The route of administration largely determines the possibility of the drug reaching the site of action; The effectiveness and safety of the drug depends on it.

Traditionally, enteral and parenteral routes of drug administration into the body are distinguished.

Enteral route of administration

In this case, the drugs are administered through the gastrointestinal tract. This route is very convenient, since the patient can administer it independently, without the help of medical personnel. It is relatively safe (there is no risk of infection and development of local complications, for example, the formation of infiltrates, pain). With the enteral route of administration, drugs can have not only a resorptive, but also a local effect (for example, in the intestines). The latter is typical for some sulfonamides and anthelmintics (piperazine adipate, pyrantel).

Enteral administration can be done in different ways.

Ingestion (orally - per os). Using this method of administration, medications are prescribed to provide a resorptive effect or create high concentrations of pharmacologically active components in their composition in the gastrointestinal tract. In the first case, the drug should be well absorbed in the stomach or intestines, but in the second, on the contrary, poorly.

Among the disadvantages of oral administration, one should highlight the relatively slow development of the therapeutic effect, a fairly large difference in the speed and completeness of absorption, the

impossibility of using drugs that irritate the gastrointestinal tract in case of vomiting and unconsciousness of the patient.
Oral administration is used to administer various dosage forms: solutions, gels, suspensions, powders, tablets, capsules, dragees and pills. The irritating effect of some drugs is eliminated by coating the tablets with films that ensure absorption of the drug in a certain environment. To prolong the effect, tablets with multilayer shells are used. It should be remembered that some capsules and tablets, when taken in a lying position, can linger in the esophagus and cause ulcerative damage to its walls. This is especially true for older people whose gastrointestinal motility is impaired. In this case, it is recommended to drink the drug with plenty of water.
For oral administration, there are special dosage forms that provide gradual slow release of the active substance at a constant rate for a long time and a prolonged therapeutic effect. Retard dosage forms in the absence of a dividing strip cannot be crushed, since this will result in the loss of the properties of the drug. Using various retardation technologies, four long-acting dosage forms have been created.

For example, nitroglycerin (to relieve angina attacks), nifedipine (for hypertensive crisis) or buprenorphine (anesthetic) are prescribed sublingually. The drugs are usually kept under the tongue until completely absorbed. If this method is used frequently, irritation of the oral mucosa may occur.
The buccal route is considered a type of taking drugs by mouth. This is how drugs produced in the form of polymer films (nitroglycerin or trinitrolong♠) are used. The latter are “glued” to the gum or cheek. Their melting under the influence of saliva creates conditions for the gradual release of a pharmacologically active substance (for example, nitroglycerin in Trinitrolong *), its absorption and the creation of therapeutic concentrations in the systemic bloodstream for a certain time.
Rectal method (introduction into the rectum). Many drugs are well absorbed from the surface of the rectal mucosa, which has a dense network of blood and lymphatic vessels. Bypassing the liver, through the hemorrhoidal veins in the lower rectum they enter the systemic circulation.

The rectal route of administration avoids the irritating effect of drugs on the stomach and small intestine. It is also acceptable if it is impossible to take the drug orally. Drugs are prescribed rectally in the form of suppositories or in the form of liquids using enemas. At the same time, they have both a local and resorptive effect.

Parenteral route of administration
The parenteral route is the introduction of drugs into the body, bypassing the gastrointestinal tract.
The following types of parenteral administration of drugs are distinguished.
Intravenous administration ensures a rapid onset of the therapeutic effect, allowing you to immediately stop the development

Methods for intravenous administration of injection solutions

Bolus administration (from the Greek bolos - lump) - rapid intravenous administration of the drug over 3-6 minutes. The dose of the administered drug is indicated in milligrams of the drug or in milliliters of a solution of a certain concentration.
Infusion administration (usually intravenous, but sometimes intra-arterial or intracoronary) is carried out at a certain speed, and the dose is calculated quantitatively (for example, ml / min, mcg / min, mcg / [kg × min]) or less accurately (in the form of the number of drops of solution , administered in 1 min). For more accurate continuous infusion, it is preferable, and in some cases, strictly necessary (for

example, intravenous administration of sodium nitroprusside), to use special dispensing syringes, systems for infusion of micro quantities of the drug, special connecting tubes to prevent the loss of drugs in the system due to its adsorption on the walls of the tubes (for example, when administering nitroglycerin).

Combined intravenous administration allows you to quickly achieve a constant therapeutic concentration of the drug in the blood. For example, a bolus is administered intravenously and a maintenance intravenous infusion or regular intramuscular administration of the same drug (for example, lidocaine) is immediately started at certain intervals.

When performing intravenous administration, you should make sure that the needle is in the vein: penetration of the drug into the perivenous space can lead to irritation or tissue necrosis. Some drugs, especially with long-term use, have an irritating effect on the walls of the veins, which may be accompanied by the development of thrombophlebitis and venous thrombosis. When administered intravenously, there is a risk of infection with hepatitis B, C and HIV viruses.

Depending on the clinical situation and the characteristics of the drug's PK, medicinal substances are injected into the vein at different rates. For example, if you need to quickly create a therapeutic concentration of a drug in the blood that is subject to intensive metabolism or binding to proteins, use rapid (bolus) administration (verapamil, lidocaine, etc.). If there is a danger of overdose with rapid administration and there is a high risk of developing undesirable and toxic effects (cardiac glycosides, procainamide), the drug is administered slowly and in dilution (with isotonic solutions of dextrose or sodium chloride). To create and maintain therapeutic concentrations in the blood for a certain time (several hours), drip administration of drugs is used using blood transfusion systems (aminophylline, glucocorticoids, etc.).

Intramuscular administration is one of the most common methods of parenteral administration of drugs, providing a rapid onset of effect (within 10-30 minutes). Depot preparations, oil solutions and some drugs that have a moderate local and irritant effect are administered intramuscularly. It is not advisable to administer more than 10 ml of the drug at a time and perform injections near nerve fibers. Intramuscular administration is accompanied by local pain; Abscesses often develop at the injection site. Penetration of a needle into a blood vessel is dangerous.

Subcutaneous administration. Compared to intramuscular injection, with this method the therapeutic effect develops more slowly, but lasts longer. It is not advisable to use it in a state of shock, when, due to insufficiency of peripheral circulation, drug absorption is minimal.

Recently, the method of subcutaneous implantation of certain drugs has become very common, providing a long-term therapeutic effect (disulfiram - for the treatment of alcoholism, naltrexone - for the treatment of drug addiction, some other drugs).

Inhalation administration is a method of using drugs produced in the form of aerosols (salbutamol and other β2-adrenergic agonists) and powders (cromoglycic acid). In addition, volatile (anesthesia ether, chloroform) or gaseous (cyclopropane) anesthetics are used by inhalation. This route of administration provides both local β2-adrenergic agonists and systemic (anesthetic) effects. Do not administer drugs with irritating properties by inhalation. It must be remembered that as a result of inhalation, the drug immediately enters through the pulmonary veins into the left chambers of the heart, which creates conditions for the development of a cardiotoxic effect.

Inhalation administration of drugs allows for accelerated absorption and ensures selectivity of action on the respiratory system.

Achieving a particular result depends on the degree of penetration of the drug into the bronchial tree (bronchi, bronchioles, alveoli). When administered by inhalation, absorption will increase if the particles of the drug penetrate into its most distal parts, i.e. into the alveoli, where absorption occurs

through thin walls and over a larger area. For example, nitroglycerin, when administered by inhalation, enters directly into the systemic circulation (as opposed to the enteral route of administration).
To achieve a selective effect of a drug on the respiratory system, for example in the treatment of asthma, it is necessary to distribute the bulk of the drug in the bronchi of medium and small caliber. The likelihood of systemic effects depends on the amount of the substance entering the general bloodstream.

Nebulizers are devices that operate by passing a powerful jet of air or oxygen under pressure through a drug solution, or by ultrasonic vibration of the latter. In both cases, a fine aerosol suspension of drug particles is formed, and the patient inhales it through a mouthpiece or face mask. The dose of the drug is delivered over 10-15 minutes while the patient is breathing normally. Nebulizers provide the maximum therapeutic effect with the best ratio of local and systemic effects. The drug reaches the respiratory tract as much as possible, no additional effort is required to inhale. It is possible to administer drugs to children from the first days of life and to patients with varying degrees of disease severity. In addition, nebulizers can be used both in hospitals and at home.
Irritating drugs should not be administered by inhalation. When using gaseous substances, stopping inhalation leads to a rapid cessation of their effect.
Local application is the application of drugs to the surface of the skin or mucous membranes to obtain effects at the site of application. When applied to the mucous membranes of the nose, eyes and skin (for example, patches containing nitroglycerin), the active components of many drugs are absorbed and have a systemic effect. In this case, the effects can be desirable (prevention of angina attacks using nitroglycerin patches) and undesirable (side effects of glucocorticoids administered by inhalation).

Other routes of administration. Sometimes, for a direct effect on the central nervous system, drugs are injected into the subarachnoid space. This is how spinal anesthesia is performed and antibacterial drugs are administered for meningitis. To transfer drugs from the surface of the skin to deep tissues, the method of electro- or phonophoresis is used.

Information for health care professionals.

• For any method of drug administration, medical personnel are obliged to inform the patient about:
- name and purpose of the drug;
- possible side effects;
- timing and signs of the onset of the effect of the drug used;
- method of drug use.
• Before giving medication to the patient:
- read the appointment sheet carefully;
- make sure that the patient in front of you is the one whose name is indicated on the appointment sheet;
- check the name of the drug, its dose, method of administration, and whether the label on the package corresponds to the doctor's prescription.
• Be especially careful when prescribing to patients with the same last names and (or) receiving the same drugs.
• Never give drugs to a patient without packaging.
• The patient has the right to know the name, purpose and dose of the drug.
• He needs to be told what to take the medicine with.

• The patient should be informed about the peculiarities of the interaction of the drug taken with food. Chewing tablets and other hard drugs changes the effect of the drug.

Any drug purchased at a pharmacy is accompanied by special instructions for use. Meanwhile, compliance (non-compliance) with the rules of administration can have a large and sometimes decisive impact on the effect of the drug. For example, when ingested, food, gastric juice, digestive enzymes and bile, which are released during digestion, can interact with the drug and change its properties. That is why the connection between taking the medicine and eating is important: on an empty stomach, during or after a meal.

4 hours after or 30 minutes before the next meal (on an empty stomach), the stomach is empty, the amount of digestive juice in it is minimal (a few tablespoons). Gastric juice (a product secreted by the stomach glands during digestion) at this time contains little hydrochloric acid. As breakfast, lunch or dinner approaches, the amount of gastric juice and hydrochloric acid in it increases, and with the first portions of food their secretion becomes especially abundant. As food enters the stomach, the acidity of gastric juice decreases as a result of neutralization by food (especially when consuming eggs or milk). Within 1-2 hours after eating, it increases again, since by this time the stomach is empty of food, and the secretion of juice still continues. Particularly pronounced secondary acidity is found after eating fatty fried meat or black bread. In addition, when eating fatty foods, its exit from the stomach is delayed and sometimes pancreatic juice produced by the pancreas is refluxed from the intestines into the stomach (reflux).

Food mixed with gastric juice passes into the initial section of the small intestine - the duodenum. Bile produced by the liver and pancreatic juice secreted by the pancreas also begin to flow there. Due to the content of a large number of digestive enzymes in pancreatic juice and biologically active substances in bile, the active process of food digestion begins. Unlike pancreatic juice, bile is secreted constantly (including between meals). Its excess amount enters the gallbladder, where a reserve is created for the needs of the body.

If there are no instructions in the instructions or doctor’s prescriptions, it is better to take the drug on an empty stomach (30 minutes before meals), since interaction with food and digestive juices can disrupt the absorption mechanism or lead to a change in the properties of the drug.

Take on an empty stomach:

• all tinctures, infusions, decoctions and similar preparations made from plant materials, since they contain active substances, some of which, under the influence of hydrochloric acid of the stomach, can be digested and converted into inactive forms; in addition, in the presence of food, the absorption of individual components of such drugs may be impaired and, as a result, an insufficient or distorted effect may occur;

• all calcium preparations (for example, calcium chloride) that have a pronounced irritant effect; calcium, binding to fatty and other acids, forms insoluble compounds; to avoid irritating effects, it is better to drink such drugs with milk, jelly or rice water;

• drugs that are absorbed with food, but for some reason have an adverse effect on digestion or relax smooth muscles (for example, drotaverine - a drug that eliminates or weakens spasms of smooth muscles);

• tetracycline (you cannot take it and other tetracycline antibiotics with milk, as the drugs bind to calcium).

Take all multivitamin preparations during meals or immediately after them. After eating, it is better to take drugs that irritate the gastric mucosa (indomethacin, acetylsalicylic acid, hormonal agents, metronidazole, reserpine, etc.).
A special group consists of drugs that must act directly on the stomach or the digestive process. Thus, drugs that reduce the acidity of gastric juice (antacids), as well as drugs that weaken the irritating effect of food on a sore stomach and prevent excessive secretion of gastric juice, are usually taken 30 minutes before meals. 10-15 minutes before meals, it is recommended to take drugs that stimulate the secretion of digestive glands (bitterness) and choleretic drugs.
Gastric juice substitutes are taken with food, and bile substitutes (for example, allochol♠) are taken at the end or immediately after meals. Medicines that contain digestive enzymes and help digest food (for example, pancreatin) are usually taken before, during or immediately after meals. Acid suppressants (such as cimetidine) should be taken immediately or shortly after meals, otherwise they block digestion at a very early stage.
Not only the presence of food masses in the stomach and intestines affects the absorption of drugs. The composition of food can also change this process. For example, when eating foods rich in fat, the concentration of vitamin A in the blood increases (the speed and completeness of its absorption in the intestines increases). Milk enhances the absorption of vitamin D, the excess of which is dangerous, first of all, for the central nervous system. With a predominantly protein diet or consumption of pickled, sour and salty foods, the absorption of the anti-tuberculosis drug isoniazid worsens, and with a protein-free diet, on the contrary, it improves.

Patient Information
In addition to the technique of administration (administration), it is necessary to clarify whether the patient knows:
• the purpose of taking the prescribed drug;
• expected effect and possible side effects;
• what to do if side effects occur;
• method and time of administration;
• what to take with drugs;
• the need to exclude any foods from the diet during treatment;
• the need to avoid alcohol;
• expected duration of treatment;
• consequences of non-compliance with the treatment regimen;
• about the impact of the use of other drugs in addition to the existing regimen (especially important when the patient is independently taking drugs that were not prescribed to him).
If the patient does not have all the necessary information, this may lead to non-compliance with the drug intake (administration) regimen. Patients suffering from chronic diseases often forget about the need for constant use of one or more drugs.

Biotransformation (metabolism) of drugs

Biotransformation is a complex of physicochemical and biochemical transformations of drugs, during which polar water-soluble substances (metabolites) are formed that can be eliminated from the body

There are two main types of drug transformation:
• metabolic transformation;

• conjugation.
Metabolic transformation is the transformation of substances as a result of oxidation, reduction, hydrolysis.
Conjugation is a bisynthetic process that involves the addition of a number of chemical groups or molecules of endogenous compounds to a drug or its metabolites.
Drug metabolism includes a complex of chemical transformations in the body that prepare for the elimination of the drug and is carried out in two directions:
• decrease in solubility of drugs in lipids;
• decrease in the biological activity of the drug.

Metabolism of drugs can occur in all tissues and fluids of the body. The most pronounced processes of destruction of substances occur in the cavities and mucous membranes of the stomach and intestines.
The main places and methods of metabolism of medicinal and toxic substances in the body
The liver is the main organ in which drug metabolism occurs. In addition, certain substances may undergo biotransformation in the kidneys (for example, imipenem), blood plasma and other tissues (for example, in the intestinal wall).
Excretion of drugs
Excretion is the removal of drugs from the body.
Drugs are excreted from the body after partial or complete conversion into water-soluble metabolites; Some drugs are excreted unchanged. The most common route of drug excretion is in the urine. Other ways of eliminating drugs are through bile, exhaled air, saliva, sweat, milk, tears and feces.
The elimination of substances largely depends on the process of their reabsorption (reabsorption) in the renal tubules.
Drugs are reabsorbed primarily by simple diffusion.
Renal excretion depends on the amount of renal clearance, the concentration of the drug in the blood, and the degree of its protein binding.
Excretion of drugs through the intestines. Two types of drugs are excreted through the intestines.
• Lipid-insoluble or ionized at intestinal pH molecules that are not absorbed through the intestinal mucosa and are excreted unchanged or, before excretion, form complexes with bile present in the intestinal lumen (for example, anion exchange resins colesteramine, colestipol).
• Non-ionized molecules (eg digoxin), polar substances with a molecular weight greater than 300 (eg hormones, antidepressants, erythromycin), soluble in water. Many drugs and their metabolites, entering the gastrointestinal tract with bile, are then reabsorbed and later excreted in the urine, which leads to a longer maintenance of their concentration in the blood. The drug can enter the gallbladder with bile and remain there.
Excretion with saliva. Drugs excreted in saliva enter the oral cavity and are usually swallowed, like drugs taken orally. Saliva is a mixture of secretions from the parotid, submandibular, sublingual and other glands, slightly different in protein composition.
In some cases, there is a correlation between the concentrations of the drug not bound to protein in the blood and saliva. With rapid intravenous administration of procainamide, its content in saliva is initially higher than in plasma, and then gradually changes. The concentration of the drug in saliva does not usually reflect that in the blood plasma.
Pulmonary excretion is not limited to volatile anesthetics, but in other cases (for example, cardiovascular drugs) its significance is small.
Excretion into breast milk. Medicinal substances contained in the blood plasma of a nursing mother can be excreted in small quantities into milk and have undesirable effects on the infant. Breast milk is

more acidic than blood plasma. Drugs with base properties are more ionized and accumulate in it, as well as drugs with good solubility in lipids. The amount of drug bound to breast milk proteins is usually half that bound to plasma proteins. It must be taken into account that a newborn is sometimes supplemented with cow's milk, which may contain antibiotics (benzylpenicillin, etc.), which can cause allergic reactions in the child.

The following cardiovascular drugs are contraindicated for a nursing mother: the indirect anticoagulant phenindione, the antiarrhythmic drug amiodarone, acetylsalicylic acid (with long-term use), the β-blocker sotalol (most other β-blockers are safe), diuretics (some suppress lactation) and glucocorticoids (for example, when taking prednisolone at a dose of 10 mg/day or more, the development of adrenal insufficiency is possible, but replacement therapy is safe).

Factors that quantitatively and qualitatively change the effect of drugs

• Physiological factors:

- age - children are often more sensitive to changes in water, electrolyte metabolism and acid-base balance caused by drugs; elderly patients may react unusually due to impaired distribution, inactivation and elimination of the drug due to age-related anatomical and physiological changes in the body, as well as due to concomitant diseases;
- gender - women (especially during pregnancy) may be more sensitive to drugs;
- chronesthesia - cyclical changes in the sensitivity of the body's biological systems to drugs (circadian changes - within a day; circatrigent - within a month; circannual - within a year);

• Features of individual Physiokinetics of drugs.

• The time of drug administration depends on the intake and nature of food, the influence of environmental factors.

• Genetic factors affecting the bioavailability and effectiveness of drugs.

• Drug interactions when taking multiple drugs.

• Associated pathological changes in organs (liver, kidneys, gastrointestinal tract).

• The patient's sensitivity to drugs.

• Patient's adherence to treatment.

Illustrative material: electronic slides

Literature: Appendix 1

Security questions (feedback):

• What are drugs and medicinal substances?

• Principles of drug classification.

• Main types of drug treatment.

• What is the importance of FC in the treatment of diseases of internal organs?

• What determines the route of drug administration?

• What is absorption? Types of absorption.

• List the factors affecting drug absorption.

• Paths of distribution of drugs in the body.

• List the main routes of excretion, give examples.

• List the main pharmacokinetic parameters.

LECTURE No. 2: CLINICAL PHARMACOLOGY OF TREATMENTS FOR PRNNEUMONIA
Target: To familiarize students with the means of treating various types of pneumonia.

PHARMACOTHERAPY OF COMMUNITY-ACQUIRED PNEUMONIA

Community-acquired pneumonia (CAP) is understood as pneumonia acquired outside a hospital or that developed during the first 48 hours of hospitalization in a medical institution. The incidence of community-acquired pneumonia is 10-12% and increases significantly in elderly patients. Mortality ranges from 1-3% in young and middle age to 15-20% in old and senile age. The etiology and drugs of choice for the treatment of community-acquired pneumonia are presented in Table. 6.1.

Considering the difficulties of microbiological diagnosis of pneumonia, which include the absence of sputum, difficulties in identifying intracellular pathogens, the presence of initial colonization of the respiratory tract, the possibility of taking an antibacterial agent until the pathogen is identified, the duration of obtaining microbiological results, there is a need for empirical antibacterial therapy.

To date, there is no convincing data that would allow us to speak about the obvious superiority of one class of antibiotics over another. In this regard, the implementation of the following rules of antimicrobial chemotherapy of CAP is of particular importance (Strachunsky L. S., 2005):

- the most active drugs and those with the best bioavailability in the group should be used (for example, amoxicillin, amoxicillin/

Table 6.1. Etiology and drugs of choice for the treatment of community-acquired pneumonia

Возбудитель	Особенность		Частота выявления, %	Препараты выбора
Пневмококк (*Streptococcus pneumoniae*)	Наиболее частый возбудитель среди всех возрастных групп, в том числе в организованных коллективах; первое место по летальности		30–50	Для чувствительных штаммов: бензилпенициллин, аминопенициллины
				Для пенициллинрезистентных штаммов (PRP): бензилпенициллин, аминопенициллины, цефалоспорины III–IV поколения, карбапенемы, ванкомицин
Микоплазма (*Mycoplasma pneumoniae*)	Часто в тесно взаимодействующем коллективе (школьники, военнослужащие; пожилые люди, проживающие в домах престарелых)	До 35 лет	20–50	Макролиды, респираторные фторхинолоны, доксициклин
		После 35 лет	1–9	
		После 60 лет	1–3	
Гемофильная палочка (*Haemophilus influenzae*)	При ХОБЛ, хроническом бронхите, курении; у пациентов, проживающих в домах престарелых		3–10	Для чувствительных штаммов: аминопенициллины
				Для резистентных штаммов: защищенные аминопенициллины, цефалоспорины II–III поколения
Легионелла (*Legionella pneumophila*)	При контакте с кондиционерами, увлажнителями воздуха, системами охлаждения воды; обычно тяжелое течение (второе место по летальности)		2–10	Макролиды, респираторные фторхинолоны

End of table 6.1

Хламидии (*Chlamydophila pneumoniae*)	Часто в тесно взаимодействующем коллективе (школьники, военнослужащие; пожилые люди, проживающие в домах престарелых); как правило, нетяжелое течение	5–15	Макролиды, респираторные фторхинолоны, доксициклин
Кишечная палочка (*Escherichia coli*), клебсиеллы (*Klebsiella pneumoniae*)	При наличии сопутствующих заболеваний (сахарный диабет, хроническая сердечная, почечная и печеночная недостаточность), алкоголизм	3–10	Для чувствительных штаммов: цефалоспорины III поколения
			Для резистентных штаммов: цефалоспорины IV, защищенные аминопенициллины, монобактамы, карбапенемы, аминогликозиды, фторхинолоны
Стафилококк (*Staph. aureus*)	После гриппа, в пожилом возрасте, при декомпенсированном сахарном диабете, при наркоманиях и гемодиализе	3–10	Для чувствительных штаммов: аминопенициллины
			Для резистентных штаммов, продуцирующих β-лактамазы: оксациллин, защищенные аминопенициллины, цефалоспорины I–II поколения, оксазолидиноны, стрептограмины
			Для метициллинрезистентных штаммов (MRSA): ванкомицин, фузидиевая кислота, оксазолидиноны, стрептограмины
Моракселла (*Moraxella catarrhalis*)	При хроническом бронхите, ХОБЛ, обструкции бронхиальных путей, в пожилом возрасте	1–3	Для чувствительных штаммов: аминопенициллины
			Для резистентных штаммов: защищенные аминопенициллины, цефалоспорины II–III поколения

clavulanate; clarithromycin, azithromycin; levofloxacin, moxifloxacin);

- antibiotics must be used in high doses (for example, amoxicillin 3 g/day);
- for severe CAP - a combination of β-lactam and macrolide or monotherapy with a “respiratory” fluoroquinolone.

A similar approach to the choice of antibiotic in the treatment of CAP is enshrined, in particular, in the consensus recommendations of the Russian Respiratory Society, the Interregional Association for

Clinical Microbiology and Antimicrobial Chemotherapy (IACMAC) and the Alliance of Clinical Chemotherapists and Microbiologists (Table 6.2).

Table 6.2. Empirical treatment of community-acquired pneumonia in outpatients (Chuchalin A. G. et al., 2003, modified by Sinopalnikova A. I., 2005)

Характер заболевания	Возбудители	Лечение	
		препараты выбора	альтернативные препараты
Нетяжелые пневмонии у больных до 60 лет без сопутствующих заболеваний	*Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydophila pneumoniae*	Амоксициллин внутрь или макролиды внутрь (кларитромицин, рокситромицин, азитромицин, спирамицин). Макролиды являются препаратами выбора при подозрении на «атипичную» этиологию пневмонии *(Chlamydia pneumonia, Mycoplasma pneumoniae)*	«Респираторные» фторхинолоны (моксифлоксацин, левофлоксацин, гемифлоксацин) внутрь
Пневмонии у больных старше 60 лет и/или с сопутствующими заболеваниями	*Streptococcus pneumoniae, Haemophilus influenzae,* род *Enterobacteriacea, Legionella pneumophila, Chlamydophila pneumoniae, Staphylococcus aureus*	Защищенные аминопенициллины (амоксициллин/клавуланат, амоксициклин/сульбактам) внутрь	«Респираторные» фторхинолоны (моксифлоксацин, левофлоксацин, гемифлоксацин) внутрь

Doxycycline is used only when pneumonia caused by Mycoplasma pneumoniae or Chlamydophila pneumoniae is suspected. For CAP caused by pneumococcus, use of this antibiotic
irrational, given the fairly high level of pathogen resistance to the drug (in the Russian Federation more than 30%).

In all cases, preference should be given to oral administration of antibiotics, and parenteral dosage forms are resorted to only if it is impossible for the patient to take the drug orally. After 3-5 days, the effectiveness of the antibiotic therapy is assessed, and if it is adequate, treatment is continued for up to 7-10 days (for atypical pneumonia - 14 days). At the same time, the X-ray picture cannot be a full-fledged criterion for extending the duration of therapy.

Indications for hospitalization for CAP are determined based on criteria for the severity of the patient's condition in accordance with the risk class of disease outcome (Table 6.3) or according to the CRB-65 scale.

Criteria for assessing the risk of an unfavorable outcome of CAP (PORT, Fine MJ et al., 1999)

Критерий	Баллы
Мужчины	Возраст в годах
Женщины	Возраст в годах –10
Постоянное проживание в домах престарелых	+10
Сопутствующие заболевания	
Онкологические заболевания	+30
Патология печени	+20
Застойная сердечная недостаточность	+10
Цереброваскулярные заболевания	+10
Заболевания почек	+10
Данные физикального обследования	
Нарушения психики	+20
Дыхание >30 в 1 мин	+20
Систолическое АД <90 мм рт. ст.	+20
Температура тела < 35 °С или >40 °С	+15
Частота пульса >125 уд./мин	+10
Лабораторные данные	
pH <7,35	+30
Азот мочевины >7 ммоль/л или креатинин >176,7 мкмоль/л	+20
Натрий <130 мэкв/л	+20
Глюкоза >13,9 ммоль/л	+10
Гематокрит <30%	+10

Ending

Критерий	Баллы
PO_2 <60 мм рт. ст. (насыщение O_2 <89%) при дыхании комнатным воздухом	+10
Плевральный выпот	+10

Table 6.3.CAP outcome risk classes (Fine MJ et al., 1997)

Класс риска	Баллы	Летальность, %	Место лечения
I	0	0,1	Амбулаторно
II	≤70	0,6	Амбулаторно
III	71–90	2,8	Стационар
IV	91–130	8,2	Стационар
V	>130	29,2	Стационар

In addition, indications for hospitalization of patients with community-acquired pneumonia may be:
1. Old age (over 65 years old).
2. The impossibility of adequate care and fulfillment of all medical prescriptions in an outpatient setting.
3. Preference of the patient or his family.
4. The presence of at least one criterion for a serious condition (see above).
5. Concomitant diseases (see above) and conditions:

- alcoholism;
- immunodeficiency;
- leukopenia;
- hyperleukocytosis;
- aspiration;
- septic shock;
- destruction of lung tissue.

6. Unsatisfactory or special social conditions. It should be taken into account that when deciding on hospitalization
of the patient, in addition to the medical aspect (severity of pneumonia, exacerbation/decompensation of concomitant diseases, etc.), a number of social factors should be taken into account, for example, the impossibility or complexity of caring for the patient (at home, when in organized groups, etc. .).
Currently, in the treatment of CAP in hospitalized patients, the feasibility of possibly earlier parenteral administration of antibiotics has been proven (in the first 4-8 hours from the moment
hospitalization). Initial oral use of antibacterial drugs is allowed only in the presence of mild pneumonia (Table 6.4).

Table 6.4. Empirical treatment of community-acquired pneumonia in hospitalized patients (Chuchalin A. G. et al., 2003, modified by A. I. Sinopalnikova, 2005)

Характер заболевания	Возбудители	Лечение	
		препараты выбора	альтернативные препараты
Нетяжелая пневмония (независимо от возраста)	*Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydophila pneumoniae, Staphylococcus aureus,* род *Enterobacteriacea*	Бензилпенициллин (внутривенно, внутримышечно). Ампициллин (внутривенно, внутримышечно). Амоксициллин/клавуланат (внутривенно). Цефотаксим (внутривенно, внутримышечно). Цефтриаксон (внутривенно, внутримышечно)	«Респираторные» фторхинолоны (моксифлоксацин, левофлоксацин). (внутривенно) Азитромицин (внутривенно)
Тяжелая пневмония (независимо от возраста)	*Streptococcus pneumoniae, Legionella pneumophila,* род *Enterobacteriacea, Staphylococcus aureus*	Амоксициллин/клавуланат (внутривенно) + макролид (внутривенно) Цефотаксим + макролид (внутривенно) Цефтриаксон + макролид (внутривенно) Цефепим внутривенно + макролид (внутривенно)	«Респираторные» фторхинолоны (моксифлоксацин, левофлоксацин) (внутривенно) «Ранние» фторхинолоны [ципрофлоксацин (внутривенно), офлоксацин (внутривенно)] + + цефалоспорины III поколения (внутривенно)

If in severe pneumonia in hospitalized patients with CAP there is a suspicion that the disease is caused by Pseudomonas aeruginosa, the drugs of choice are ceftazidime, cefepime, cefoperazone/sulbactam, ticarcillin/clavulanate, piperacillin/ta-

Zobactam, carbapenems (meropenem, imipenem). These drugs can be used in monotherapy or in combination with aminoglycosides of the generation.
In the presence of destruction of lung tissue, often caused by Staphylococcus aureus and Klebsiella with the addition of anaerobes, metronidazole or clindamycin may be added.
If aspiration is suspected, amoxicillin/clavulanate, cefoperazone/sulbactam, ticarcillin/clavulanate, piperacillin/tazobactam, and carbapenems should be prescribed.
After 3-4 days of antibacterial therapy (sometimes longer) when a clinical effect is achieved (1 - reduction in the severity of intoxication; 2 - reduction in cough, volume of expectorated sputum, shortness of breath; 3 - normal body temperature with two consecutive measurements with an 8-hour interval; 4 - normal number of leukocytes in the peripheral blood; 5 - absence of gastrointestinal absorption disorders), the issue of transferring the patient to oral antibiotics (“stepped therapy”) can be considered. Step therapy (initial administration of the drug parenterally, followed by transition to the enteral route of administration) provides the following advantages:
- increasing the patient’s adherence to treatment;
- reducing the cost of antibacterial therapy;
- reducing the risk of post-injection and nosocomial infections;
- reducing the length of stay of the patient in the hospital;
- improving the quality of life;
- facilitating the working conditions of medical personnel. The total duration of treatment with antibacterial therapy in hospitalized patients with CAP is, as a rule, 7-10 days, and in patients with severe CAP - 10 days. If clinical and/or epidemiological data indicate a mycoplasma or chlamydial infection, the duration of treatment should be 14 days. For CAP caused by Staphylococcus aureus or bacteria of the genus Enterobacteriacea, the duration of antibiotic therapy is 14-21 days, and for Legionella etiology - 21 days.
Sometimes the timing of antibacterial therapy must be determined individually, for example, in the case of a protracted course of the disease or complicated pneumonia (destruction, abscess formation, empyema).
Possible reasons for the protracted (progressive) course of pneumonia during antibacterial therapy:
• Inadequate antibacterial therapy.
• Local airway obstruction (cancer, adenoma, mucoid obstruction).
• Cystic fibrosis.
• Bronchiectasis.
• Immunity disorders.
• Formation of a lung abscess.
• Recurrent aspiration (achalasia, esophageal cancer).
• Activation of tuberculosis infection.
To decide whether to complete antibiotic therapy for pneumonia, the following criteria are used:
• Normal body temperature for at least 2-3 days.
• No intoxication.
• Hemodynamic stability and absence of respiratory failure.
• No purulent sputum.
• Absence of negative radiographic dynamics.
• The number of leukocytes in peripheral blood is less than 10 × 109/l, neutrophils <80%, juvenile forms <6%.

The persistence of certain clinical, laboratory and/or radiological signs of the disease is not an indication for continued antibacterial therapy or its modification. As a rule, these symptoms resolve on their own or under the influence of symptomatic therapy.

Clinical and laboratory signs that are not an indication for continuing antibacterial therapy or replacing the antibiotic (Chuchalin A. G. et al., 2004)

Клинические и лабораторные признаки	Примечание
Стойкий субфебрилитет (температура тела 37,0–37,5 °С)	При отсутствии других признаков бактериальной инфекции может быть проявлением неинфекционного воспаления, постинфекционной астении (вегетативной дисфункции), медикаментозной лихорадки
Сохранение остаточных изменений на рентгенограмме (инфильтрация, усиление рисунка)	Могут сохраняться в течение 1–2 месяцев после перенесенной внебольничной пневмонии
Сухой кашель	Может сохраняться в течение 1–2 месяцев после перенесенной внебольничной пневмонии, особенно у курильщиков и пациентов с ХОБЛ

End of the table

Клинические и лабораторные признаки	Примечание
Сохранение сухих хрипов при аускультации	Сухие хрипы могут сохраняться в течение 3–4 недель и более после перенесенной внебольничной пневмонии и отражать естественное течение заболевания (локальный пневмосклероз на месте фокуса воспаления)
Увеличение СОЭ	Неспецифический показатель, не является признаком бактериальной инфекции
Сохраняющаяся слабость, потливость	Проявления постинфекционной астении

The resistance of microorganisms to the antibiotics used is of great importance for the effectiveness of antibacterial therapy. According to the results of the multicenter Russian study PeGAS-I, β-lactam antibiotics retain high activity in vitro against the studied population of Streptococcus pneumoniae: insensitivity (frequency of moderately resistant and resistant strains) to amoxicillin and amoxicillin/clavulanate is 0.5%, to cefotaxime and cefepime - 2%, to benzylpenicillin - 9%. Resistance to macrolides (erythromycin, azithromycin, clarithromycin, etc.) ranges from 2 to 6%. No resistance to the “respiratory” fluoroquinolone levofloxacin was detected. The highest percentage of insensitive strains (27 and 33%, respectively) was observed for tetracycline and co-trimoxazole. Some generalized information on the resistance of pneumonia pathogens is given in Table. 6.5 and 6.6.

Table 6.5. Resistance of pneumonia pathogens

Резистентный штамм	Частота выявления, %	Группа антибиотиков	Механизм резистентности
Streptococcus pneumoniae пенициллинрезистентный (PRP)	10	β-лактамы, ассоциированная резистентность к макролидам, тетрациклинам, ко-тримоксазолам и др.	Нарушение функции пенициллинсвязывающих белков

End of table. 6.5

Резистентный штамм	Частота выявления, %	Группа антибиотиков	Механизм резистентности
Streptococcus pneumoniae эритромицинрезистентный	2–12	Эритромицин	Не связан с выработкой β-лактамаз
Haemophilus influenzae	20	β-лактамы (пенициллины, цефалоспорины I)	Выработка β-лактамаз
	4,7	Аминопенициллины	
	50	Эритромицин	Не связан с выработкой β-лактамаз
	5	Тетрациклины	
	29,8	Ко-тримоксазолы	
Moraxella catarrhalis	До 75%	β-лактамы	Выработка β-лактамаз
	До 8%	Ампициллин, эритромицин	Не связан с выработкой β-лактамаз
Staphylococcus aureus	До 75%	Пенициллины	Выработка β-лактамаз
	До 10%	Метициллин, макролиды	Не связан с выработкой β-лактамаз, нарушение функции пенициллинсвязывающих белков
Klebsiella pneumoniae	99%	Аминопенициллины	Выработка β-лактамаз
	До 5%	Цефалоспорины	

Table 6.6. Levels of resistance of Streptococcus pneumoniae to benzylpenicillin and drugs of choice

Чувствительность	МПК, мкг/мл	Препараты
Чувствительные	0,06	Бензилпенициллин или аминопенициллины
Промежуточная резистентность	0,1–1	Высокие дозы бензилпенициллина (или аминопенициллинов) или цефотаксим (или цефтриаксон)

End of table. 6.6

Чувствительность	МПК, мкг/мл	Препараты
Высокая резистентность	>2	Цефалоспорины (IV поколение), карбапенемы, респираторные фторхинолоны, ванкомицин

Note:MIC - minimum inhibitory concentration.

6.2. PHARMACOTHERAPY OF HOSPITALIZED PNEUMONIA

Hospital (nosocomial, nosocomial) pneumonia (HP) is a bronchopulmonary infection that developed 48 hours after hospitalization, provided that during the first two days there were no clinical or radiological signs of pneumonia.

Clinical classes of hospital-acquired pneumonia

Hospital pneumonia that developed in a general hospital department:

• Early - up to 5 days of hospitalization.

• Late - after 5 days of hospitalization.

Hospital-acquired pneumonia that developed in the intensive care unit and is associated with mechanical ventilation (ventilator-associated pneumonia, VAP):

• Early VAP: ≤ 4 days after mechanical ventilation.

• Late VAP: >4 days after mechanical ventilation

Taking into account the characteristics of the profile of the medical department and risk factors, GPs can be divided as follows:

1. Pneumonia that developed in patients in a general ward without risk factors or early VAP that developed in the ICU.

Pathogens: Streptococcus pneumoniae, genus Enterobacteriacea, Haemophilus influenzae, less commonly Pseudomonas aeruginosa, Staphylococcus aureus (mainly methicillin-sensitive, MSSA).

2. Pneumonia that developed in patients in the general ward in the presence of risk factors or late VAP that developed in the intensive care unit and intensive care unit.

Pathogens: genus Enterobacteriacea, Pseudomonas aeruginosa, Acinetobacter sp., less commonly Staphylococcus aureus (mostly methicillin-resistant, MRSA).

Hospital-acquired pneumonia differs from community-acquired pneumonia primarily in that it is caused by gram-negative microorganisms.

mi (Pseudomonas aeruginosa and Haemophilus influenzae, genus Enterobacteriacea), as well as Staphylococcus aureus (Table 6.7). In almost 50% of cases, several microorganisms are detected at once.

Table 6.7. Etiology of hospital pneumonia

Возбудитель	Частота выявления, %	Предрасполагающие факторы
Pseudomonas aeruginosa	25–35	Длительная госпитализация, продолжительная ИВЛ, лечение глюкокортикоидами, предшествующая антибактериальная терапия, бронхоэктазы
Энтеробактерии (прежде всего *Klebsiella pneumoniae* и *Enterobacter sp.*)	25–35	Алкоголизм, мужской пол, пожилой возраст
Staphylococcus aureus (MSSA и MRSA)	15–35	Сахарный диабет, кома, черепно-мозговая травма, почечная недостаточность, длительная госпитализация, предшествующая антибактериальная терапия, «внутривенные» наркоманы, грипп
Анаэробы (в ассоциациях)	10–30	Аспирация, недавние торакоабдоминальные операции
Haemophilus influenzae	10–20	Хронические обструктивные заболевания легких, госпитализация менее 1 недели
Streptococcus pneumoniae (особенно PRP)	10–20	Госпитализация менее 1 недели, предшествующая госпитализация, предшествующая терапия β-лактамами

Note:PRP - penicillin-resistant Streptococcus pneumoniae; MSSA - methicillin sensitive Staphylococcus aureus; MRSA - methicillin-resistant Staphylococcus aureus.

Hospital-acquired pneumonia is more severe than community-acquired pneumonia and is more often fatal. Mortality with HP reaches 30%, and with infection with Pseudomonas aeruginosa - up to 70%.

Risk factors for the development of hospital-acquired pneumonia are:

- elderly age;
- chronic obstructive pulmonary disease;
- severe concomitant diseases;
- disturbances of consciousness;
- aspiration;
- endotracheal intubation.

In addition, the incidence of hospital-acquired pneumonia may increase with the prescription of sedatives and hypnotics (increased risk of aspiration), the use of glucocorticoids (formation of immunosuppression), and the use of H2-histamine blockers and antacids (increased microbial colonization of the stomach).

Recommendations for empirical treatment of hospital-acquired pneumonia are presented in Table. 6.8.

Table 6.8. Empirical treatment of hospital-acquired pneumonia

Вид пневмонии	Препараты выбора	Альтернативные препараты
Пневмонии, развившиеся у пациентов в отделении общего профиля без факторов риска или ранние ВАП, развившиеся в отделении интенсивной терапии и реанимации	Амоксициллин/клавуланат (внутривенно). Сультамициллин (внутривенно, внутримышечно). Цефотаксим (внутривенно, внутримышечно). Цефтриаксон (внутривенно, внутримышечно). Цефуроксим (внутривенно, внутримышечно)	Моксифлоксацин (внутривенно). Левофлоксацин (внутривенно). Цефепим (внутривенно) + Амикацин (внутривенно). Цефепим (внутривенно) + Гентамицин (внутривенно)
Пневмонии, развившиеся у пациентов в отделении общего профиля при наличии факторов риска или поздние ВАП, развившиеся в отделении интенсивной терапии и реанимации*	Имипенем (внутривенно). Цефтазидим (внутривенно). Цефоперазон (внутривенно). Цефепим (внутривенно). Меропенем (внутривенно) + Амикацин (внутривенно) ± Ванкомицин (внутривенно)	Азтреонам (внутривенно, внутримышечно). Моксифлоксацин (внутривенно). Левофлоксацин (внутривенно). Пиперацил-лин/тазобактам (внутривенно) + Амикацин (или гентамицин (внутривенно). Тикациллин/клавуланат (внутривенно) + Амикацин (или гентамицин) (внутривенно)

Note:* - high risk of infection with multidrug-resistant pathogens.

It should be taken into account that recommendations for empirical treatment of HP are largely conditional, and such treatment should be based on local data on the etiological structure of hospital infections and the frequency of spread of antibiotic-resistant strains in hospital departments.

TreatmentGP should begin with intravenous antibiotics, but if there is a good response, some patients can be switched to oral antibiotics (primarily this applies to linezolid and fluoroquinolones, the oral forms of which are bioequivalent to intravenous solutions).

One of the factors that optimizes antibacterial therapy for HP is the prescription of antibiotics, taking into account their pharmacokinetic/pharmacodynamic characteristics (in particular, the dependence of the bactericidal effect of drugs on concentration or exposure time) (Table 6.9).

Table 6.9. Distribution of antibiotics by pharmacodynamic parameters (Craig W., 1998)

Фармакодина-мика	Важнейшие ФД/ФК параметры	Антибиотики	Цель режима дозирования
Зависимый от концентрации бактерицид-ный эффект	Cmax/МПК ПФК/МПК	Аминоглико-зиды Фторхинолоны Тетрациклины* Азитромицин Ванкомицин	Достижение макси-мальной пиковой концентрации пре-парата в сыворотке крови (очаге инфек-ции)
Зависимый от времени экспозиции бактерицид-ный эффект	t >МПК	Пенициллины Цефалоспорины Монобактамы Карбапенемы Макролиды Линкозамиды	Максимальное со-хранение препарата в сыворотке крови и очаге инфекции в концентрациях, пре-вышающих МПК

Note:* - bacteriostatic effect; FC - pharmacokinetic; PD - pharmacodynamic.

Thus, β-lactams are characterized by a time-dependent bactericidal effect, i.e., the greatest death of microorganisms is observed if the source of infection is maintained for as long as possible.

The antibiotic concentration exceeds the MIC90 by 4 times. Consequently, when using drugs of this group in patients with HP (especially those in the ICU), their long-term intravenous infusion is more preferable. An exception may be carbapenems, for which an intermittent dosage regimen is possible due to the presence of a post-antibiotic effect and instability in solutions at room temperature during the day.

In contrast to β-lactams, aminoglycosides and fluoroquinolones have a concentration-dependent bactericidal effect, and therefore, maximum eradication of microorganisms is observed at drug concentrations exceeding the MIC by 10 times (for fluoroquinolones) or 10-12 times (for aminoglycosides). Thus, the optimal regimen for aminoglycoside therapy is to administer the entire daily dose once intravenously as a short infusion, which, along with good bioavailability, creates antibiotic concentrations that maximally exceed the MIC at the site of infection. If the patient receives combination therapy with aminoglycosides, then if there is a good response, they can be discontinued after 5-7 days.

Fluoroquinolones can also be administered once a day, however, given their ability to cause undesirable reactions from the nervous system in very high concentrations, the daily dose of drugs can be divided into two administrations.

With adequately selected antibiotic therapy, the condition of patients with HP usually improves 48-72 hours after the start of treatment, therefore, the antimicrobial therapy regimen should be changed no earlier than this period, except in cases where the deterioration of the condition progresses or this is dictated by the results of bacteriological examination.

The traditional duration of treatment for HP is 14-21 days, but if the disappearance of clinical signs of the disease occurs earlier than this period, then the duration of therapy can be reduced to 7 days (except for cases of infection caused by Pseudomonas aeruginosa). Longer antibiotic therapy against the background of resolved infection (14 days or more) can lead to colonization by new microorganisms (primarily Pseudomonas aeruginosa and Enterobacteriaceae) and relapse of pneumonia.

If empirical antibiotic therapy is adequately selected, clinical signs of infection disappear.

Illustrative material: electronic slides

Literature: Appendix 1

Security questions (feedback):

LECTURE No. 3: COVID-19 ASSOCIATED PNEUMONIA

Purpose: To familiarize students with pharmacotherapy for covid-19 associated pneumonia.

Drug treatment:

Management of patients with mild COVID-19.

For mild severity:

- body temperature is normal/subfebrile/febrile;
- no shortness of breath, respiratory rate <20 per minute, SpO2 at rest >95%;
- there are no changes on the X-ray / CT scan of the lungs (if present, the picture does not coincide with the clinic);
- background diseases (DM, hypertension, ischemic heart disease, CKD, etc.) are absent or compensated;
- Heart rate 60-80 beats. per minute (must be correlated with body temperature);
- in the hemogram the content of leukocytes, neutrophils, lymphocytes, platelets is within the reference values.

When a patient has a mild degree of COVID-19, it is recommended to adhere to the following provisions:

1) If the body temperature is above 38°C, fever relief is carried out using physical cooling methods or NSAIDs:

- Paracetamol 500 mg (no more than 2 g per day)

or

- Ibuprofen 200-400 mg (no more than 1200 mg) [20, 21].

To stop the inflammatory process:

Ibuprofen 200-400 mg 3 times a day (no more than 1200 mg) for 5 days. When used together with ACT and ASA, assess the risk of bleeding [75-77, 89].

2) Patients with COVID-19 with a diagnosis of cardiovascular diseases established using invasive and non-invasive methods are prescribed acetylsalicylic acid (ASA) at a dose of up to 100 mg per day (or continue taking it if patients were previously prescribed) to prevent recurrent ischemic events:

- previous ACS (myocardial infarction or unstable angina);
- stable angina pectoris;
- coronary revascularization (PCI, CABG, etc. with arterial revascularization);
- previous stroke and transient ischemic attack;
- aortic aneurysm and atherosclerosis of peripheral arteries;
- in the presence of peripheral artery stenosis >50% according to imaging methods, including ultrasound examination of the arteries;
- DM with target organ damage (microalbuminuria) or with the presence of major risk factors: smoking, hyperlipidemia;
- stage 3 hypertension;
- type 1 diabetes (>20 years);
- severe renal failure with eGFR <30 ml/min/1.73 m2;
- familial hyperlipidemia with CVD of atherosclerotic nature and other major risk factors.

In addition, ASA may be recommended for primary prevention in patients with a SCORE risk >10% and in patients with colorectal cancer. If there are contraindications to the administration of ASA, clopidogrel 75 mg per day can be prescribed [22].

3) Prevention of venous thrombosis in mild forms is not indicated.

4) Patients taking DOACs for indications (persistent atrial fibrillation, deep vein thrombosis, venous sinus thrombosis, etc.) are recommended to continue taking them under medical supervision. In this case, tolerability, adherence, liver function, kidney function and bleeding risk should be regularly assessed using the IMPROVE scale.

5) The routine combination of ASA or clopidogrel with anticoagulants is not recommended for COVID-19, with the exception of patients with ACS and atrial fibrillation who underwent PCI with stenting.

6) Persons with chronic diseases, including persons over 60 years of age, during the unfavorable epidemiological situation regarding COVID-19, are under the dynamic supervision of primary health care specialists (Appendix 7).

Persons with mild illness are removed from medical observation and isolation after 10 days from the onset of symptoms plus at least 3 days without symptoms (e.g., elevated body temperature, respiratory symptoms) (PCR testing and CT/X-ray diagnostics are not required).

*For example:*the patient was symptomatic for the first two days, in which case isolation and discontinuation of contact and drip prophylaxis measures can be discontinued after 10 days + 3 days without symptoms = 13 days [42].

With increasing clinical symptoms of the disease, any deterioration in well-being and indicators of measuring body temperature, pulse rate, respiration, blood pressure, saturation must be notified to the local doctor, who, after assessing the severity of the condition, determines further management and, according to indications, refers to an infectious diseases hospital.

Management of patients with moderate forms of the disease (prior to hospitalization according to indications).

With moderate severity, patients experience:

- increase in body temperature to subfebrile/febrile levels;
- shortness of breath during exertion, respiratory rate - 20-22 per minute, SpO2 at rest 94-95%;
- on Rg/CT of the lungs (if available) - signs of viral lung damage with CT conclusion 1-2 - the volume of lung damage is up to 50%;
- there are underlying diseases (DM, hypertension, ischemic heart disease, CKD, etc.), but without signs of decompensation or exacerbation;
- Heart rate 80-100 beats. per minute (must be correlated with body temperature);
- the hemogram shows slight lymphopenia (more than 15%).

When a patient is diagnosed with moderate severity of COVID-19, it is recommended to adhere to the following provisions:

1) If the body temperature is above 38°C, fever relief is carried out using physical cooling methods or NSAIDs:

- Paracetamol 500 mg (no more than 2 g per day)

or

- Ibuprofen 200-400 mg (no more than 1200 mg) [20, 21].

To stop the inflammatory process:

- Ibuprofen 200-400 mg 3 times a day (no more than 1200 mg) for 5 days.

When used together with ACT and ASA, assess the risk of bleeding [75-77, 89].

2) Routine prophylaxis of venous thromboembolism in the absence of a risk of venous thrombosis is not carried out.

3) In the presence of concomitant diseases (oncological diseases in the active stage, previous deep vein thrombosis and pulmonary embolism, thrombophilia, recent myocardial infarction, ischemic stroke and major surgical interventions, elderly age ≥70 years, CHF), the risk of venous

thromboembolism should be determined using the PADUA scale or using the IMPROVE risk assessment model, then assess the risk of bleeding according to the IMPROVE score.

Venous thromboembolic risk score in hospitalized non-surgical Padua patients

Risk factor	Point	
Active malignancy (metastasis and/or chemotherapy/radiotherapy <6 months ago)		
History of DVT/PE (excluding superficial vein thrombosis)		
Limited mobility (bed rest with toilet access) ≥3 days		
Known thrombophilia (antithrombin, protein C or S defects, factor V Leiden, G20210A prothrombin mutation, antiphospholipid syndrome)		
Trauma and/or surgery ≤1 month ago		
Age ≥70 years		
Cardiac and/or respiratory failure		
Myocardial infarction or ischemic stroke		
Acute infection and/or rheumatological disease		
Obesity (BMI >30 kg/m2)		
Continued use of hormone replacement therapy or oral contraceptives		

Note:*with a score ≥4, the risk of venous thromboembolic complications is considered high and their prevention with anticoagulants is indicated.*

IMPROVE Risk Assessment Model

Risk factors	Points
History of VTE	
Thrombophilia	
N/C paralysis at present	
Cancer now	
Immobilization for at least 7 days	
Admission to ICU or cardiac intensive care unit	
Age >60 years	

0-1-low risk = no need for prophylaxis.
2 or more = high risk requires prevention.

IMPROVE bleeding risk assessment model

	Points
Active gastric and duodenal ulcers	
Bleeding <3 months before hospitalization* (LC, II, note NOAC)	
Platelets <50000** (approx. ASA and P2Y12)	
Age >85 years	

Liver failure with PT level >1.5 ULN	
Severe renal failure with eGFR<30 ml/min	
Hospitalization in the ICU	
Presence of a central catheter	
Having a rheumatic or autoimmune disease	
Cancer active	
Age: 40-84 years	
Men	
eGFR 30-59 ml/min	
High risk ≥7 points, low risk <7 points.	

4) Patients who took DOACs before hospitalization and a prophylactic dose of LMWH in the hospital have a low incidence of PE [23]. DOACs are more convenient for use in outpatient practice in patients with COVID-19 compared to the use of vitamin K antagonists (VKAs) [24].

5) DOACs should be prescribed after assessing the risk of thrombosis according to the PADUA scale, a general blood test (hemoglobin, platelet values) and, if indicated, D-dimer, creatinine, estimated creatinine rate (eGFR) or creatinine clearance (CC), bilirubin level, liver enzymes and bleeding risk assessment (IMPROVE scale). If an eGFR result is available, this eGFR indicator should be divided by 10, the resulting figure will indicate how many months (3-6 months) the examination should be repeated. If the patient fits within these time periods, it is possible to conduct biochemical tests a little later and allow the use of DOACs. In such cases, the primary care doctor may limit himself to the results of the CBC, D-dimer and, if indicated, perform liver test analysis (ALT, AST, bilirubin).

Recommended treatment regimens for DOACs at the minimum dose for persons without concomitant (comorbid) diseases:

- Apixaban* 2.5 mg 2 times a day for 10 days,

or

- Dabigatran etexilate * 110 mg x 2 times a day for 10 days

or

- Rivaroxaban* 10 mg 1 time per day for 10 days.

After 10 days, you should monitor your general clinical condition, the level of D-dimer, platelets, creatinine, ALT, AST, and bilirubin.

Note:*in patients with a decrease in eGFR to 15 ml/min, no dose adjustment of Apixaban is required;*

- in patients with eGFR <15 ml/min, the use of Apixaban is not recommended; The combined use of Apixaban and rifampicin, St. John's wort, carbamazepine phenobarbital, ketoconazole, clarithromycin and erythromycin is not recommended;

- use dabigatran etexilate with caution in conditions that increase the risk of bleeding: age 75 years and older; eGFR <30 ml/min, in patients at high risk of MI. The combined use of Dabigatran and St. John's wort, verapamil, amiodarone, carbamazepine, phenobarbital and ketoconazole significantly increases the level of Dabigatran in the blood and is therefore not recommended.

- Rivaroxaban should be avoided in patients with severe renal impairment (eGFR <30 ml/min).

- the combined use of Rivaroxaban and ritonavir, rifampicin, St. John's wort, carbamazepine, phenobarbital, clarithromycin and erythromycin is not advisable; - the use of oral factor Xa inhibitors is preferable to the use of an oral factor IIa inhibitor [29].

6) ASA in a dose of 75-100 mg should be prescribed:

- patients for secondary prevention of CVD in the absence of a risk of thrombosis according to the PADUA scale and the reference level of D-dimer; as well as for primary prevention in patients with colorectal cancer and with a SCORE level ≥10% (if there are contraindications to the use of ASA, clopidogrel 75 mg is prescribed) under medical supervision [22].

7) In the presence of a high risk of thrombosis and a low level of bleeding, patients are recommended to undergo drug prophylaxis of venous thrombosis with careful monitoring of the patient's condition and re-assessment of the risk of thrombosis. If the patient's condition worsens, the further route is determined by the primary care physician.

8) Patients with concomitant (comorbid) diseases who take DOACs according to indications (persistent atrial fibrillation, history of deep vein thrombosis, etc.) continue to take them at the dose recommended for the underlying disease [25-28].

9) Persons with chronic diseases, including persons over 60 years of age during the unfavorable epidemiological situation regarding COVID-19 are under the dynamic supervision of primary health care specialists (Appendix 7).

Note:*Before use, you must read the instructions for each drug in detail, especially the drug interactions section. The indicated doses of DOACs for the prevention of VTE in patients with COVID-19 are based on the consensus opinion of the experts who are responsible for drawing up this protocol after careful analysis of the results of RCTs. There are currently no RCT results on the use of DOACs in patients with C0VID-19. As new data become available, changes in the dosage and duration of ACT in patients with C0VID-19 are possible. [22, 25, 26].*

Persons with moderate severity of the disease are removed from medical observation and isolation after at least 10 days from the development of symptoms plus at least 3 days without symptoms (see examples above) (PCR testing is not required, CT/X-ray diagnostics if indicated) [42].

A summary table of comprehensive medical care at the outpatient level is presented in the Algorithm for the management of patients with CVI COVID-19 at all levels of medical care (section 5).

3.3. Surgical intervention: No.

3.4 Further management:

After discharge from the hospital, medical observation of convalescents who have suffered a moderate or severe disease continues at home under the supervision of a primary care doctor. The observation period is determined individually depending on the general condition of the convalescent.

Upon early discharge from hospital:

*Example 1.*If the patient has had symptoms for 14 days, then isolation is stopped - 14 days (symptoms were present) + 3 days (no symptoms) = 17 days.

*Example 2:*the patient had symptoms for 30 days (fever and profuse cough with sputum) - 30 days (symptoms) + 3 days (no symptoms) = 33 days [42].

According to indications, psychological and respiratory rehabilitation is carried out on an outpatient basis or treatment/rehabilitation in a specialized hospital [30-32]. (Appendix 6,8,9).

According to indications, prevention of thromboembolic complications is carried out:

- patients who have had a severe or critical illness of COVID-19, as well as with risk factors for the development of VTE (hypodynamic, on bed rest, with a BMI> 30, with a history of VTE, active cancer) are recommended to undergo thromboprophylaxis with parenteral anticoagulants LMWH (nadroparin and enoxaparin), fondaparinux (if platelet count <100,000, with intolerance to LMWH), UFH (in the absence of LMWH or contraindications to LMWH) after discharge for 10-14 days [33, 34].

After 10 days from the start of taking LMWH or UFH, in patients who have had severe or critical COVID-19 disease, but with persistent high levels of D-dimer (above 2 ULN), it is advisable to switch to DOACs (apixaban, rivaroxaban) in prophylactic doses for a period up to 30 days (there is no evidence base for the use of DOACs for COVID-19, so a council decision and informed consent of the patient is necessary, given the large area of lung damage and the high risks of VTE in this category of patients) [33, 35];

In case of exacerbation of concomitant chronic non-infectious diseases, with the development of post-Covid conditions, the primary health care doctor refers the convalescent person for consultation to a specialized specialist. Management and treatment are carried out in accordance with the clinical protocol for diagnosis and treatment of concomitant diseases.

3.5 Treatment effectiveness indicators:

- normalization of temperature for more than 3 days without taking antipyretic drugs;
- regression of intoxication symptoms (weakness, headaches, myalgia);
- regression of respiratory symptoms (sore throat, cough).

4. Indications for hospitalization, indicating the type of hospitalization:

4.1 Indications for planned hospitalization: No.

4.2 Indications for emergency hospitalization:

- moderate severity of the disease in a patient with risk factors for severe disease;
- severe disease;
- extremely severe/critical severity (ARDS, sepsis, septic shock);

And

- fever of 38°C or higher for 5 days, resistant to antipyretic drugs;
- respiratory rate >24 per minute;
- shortness of breath of an increasing nature, during normal household activities, conversation;
- decrease in SpO2 <93%;
- persons with risk factors (age over 60 years, diabetes, hypertension, etc.) with moderate severity (NPV 20-24 per 1 min., SpO2 93-95%, CT 1-2 if available);
- KT3-KT4.

At the level of ambulance and hospital emergency room, it is recommended to carry out triage according to the Algorithm of the Interdepartmental Comprehensive Triage Tool (Appendix 3).

5. Treatment tactics at the hospital level[11, 16, 20, 21, 35, 36, 39, 40, 43-63, 66-78, 81-90]:

5.1 Non-drug treatment:

- Semi-bed mode (depending on the severity of the disease, it is desirable to change the position of the body in bed, walking around the ward under the control of the patient's condition (RR, heart rate, SpO2)).
- In case of lung damage, it is recommended to use a prone position of the patient's body on his stomach to improve oxygenation of the lungs with a gradual increase in time (1 hour 4 times a day, maximum up to 12-16 hours, night sleep) under the control of the patient's condition (RR, heart rate, SpO2), diaphragmatic breathing (according to how you feel).
- A diet balanced in the content of proteins, fats, carbohydrates, microelements, taking into account concomitant pathologies.
- Early rehabilitation of patients is carried out in accordance withAppendix 8.

5.2 Drug treatment:

Currently, etiotropic experimental drugs are used in clinical trials; the main principle in the management of patients diagnosed with COVID-19 remains optimal pathogenetic treatment depending

on the nature of clinical symptoms, severity of the disease, presence/absence of pneumonia (X-ray and CT/signs), type and degree of complications, concomitant diseases.

Etiotropic (experimental) therapy* - conditional recommendation[66-74].

- in hospitalized patients with risk factors for severe COVID-19, receiving oxygen (insufflation, high-flow oxygen therapy, NIV) and not receiving mechanical ventilation, as early as possible from the onset of the disease.

- Remdesivir*200 mg IV on day 1, then 100 mg IV daily for a total of 5-10 days.

Note:

Contraindications for use:

- signs of multiple organ failure;
- coagulopathy;
- liver failure;
- decrease in GFR less than 30 ml/min by 1.73 m2;
- chronic heart failure with reduced ejection fraction;
- mechanical ventilation for 48 hours or more;
- ECMO;
- known hypersensitivity to the drug or its components;
- increase in transamines more than 5 norms.

Note:

* prescribed to the patient only upon signing informed consent personally or by his legal representative as part of participation in a clinical trial;

*Taking into account possible side effects, the attending physician should conduct clinical and laboratory monitoring for ET, if detected, cancel ET and submit a yellow card to the National Center for Medical Examination;

* in later stages of the disease, effectiveness decreases.

Pathogenetic therapy.

When the body temperature is above 38°C, fever relief is carried out using physical cooling methods or NSAIDs:

- Paracetamol 500 mg (no more than 2 g per day)

or

- Ibuprofen 200 - 400 mg (no more than 1200 mg) [20, 21].

To stop the inflammatory process, use NSAIDs:

- Ibuprofen 200-400 mg x 3 times a day for 5 days (according to the drug instructions) [75-77, 89].

When used together with ACT and ASA, assess the risk of bleeding. [75-77, 89].

Patients with mild to moderate severity of the disease (high fever, sweating, loose stools) are strongly recommended to drink plenty of fluids in the form of enteral fluid replacement for the purpose of detoxification, correction of hemoconcentration and hydration of the mucous membranes. (Annex 1).

Intensive therapy for severe cases(Appendix 1, 2).

If there are indications, infusion therapy is carried out under the control of diuresis (not lower than 0.5 ml/kg/h), saturation, assessment of edema, hematocrit (>35%). It is necessary to manage patients in zero or negative fluid balance.

Respiratory support (prevention and control of hypoxia)(Appendix 1, 2)

If SpO2 decreases to less than 93%, it is recommended to start oxygen therapy using a mask or nasal cannulas with an oxygen flow of 5-10 liters per minute until SpO2 reaches >95%. The combination of oxygen therapy (standard or high-flow) with the patient lying on his stomach in a

prone position for at least 12-16 hours a day leads to improved oxygenation. Early initiation of respiratory support reduces the risk of developing cerebral hypoxia.

Non-invasive ventilation and high-flow nasal oxygenation (HFNO):

Indications:

- constantly growing oxygen demand (for example, O2 flow from 5 l/min to 15 l/min) with SpO2 86-93%;
- tachypnea 22-28 per minute. (without the participation of auxiliary muscles), which is not eliminated after a decrease in body temperature, accompanied by an increase in the O2 flow rate, regardless of the SpO2 level;
- subjective feeling of lack of air;
- PaO2 <60 mmHg, or PaO2/FiO2 100-300 mmHg;
- PaCO2 >45 mmHg;
- SpO2 86-93% without signs of respiratory muscle fatigue.

Aerosol-generating procedures, which include NIV and HFNO, must be carried out in special boxes with negative atmospheric pressure (Melzer boxes) with an air exchange of at least 12 volumes/hour and with the presence of hepafilters in the recirculation system that trap viruses in the air.

NB!!!When using NIV and HFNO in conditions that do not meet the requirements described above, it is necessary to be aware of the high risk of aerosol formation, which can lead to infection of ICU staff and the spread of the infectious agent in the ICU room. If these interventions are carried out outside of single-occupancy ICU rooms with inadequate ventilation systems, then to protect against airborne transmission of infection, it is advisable to group patients eligible for these treatments in designated areas with adequate ventilation, into which staff can only enter while wearing appropriate PPE.

Absolute contraindications (as indications for invasive ventilation):

- lack of full cooperation with the patient (severe encephalopathy, lack of consciousness);
- anomalies and deformations of the facial skeleton that prevent the application of a mask.
- Moderate to severe ARDS.

*Description of the method:*Non-invasive mask ventilation (NIV), as a rule, is carried out in trigger auxiliary modes, most of which are implemented on many modern ventilators.

CPAP and/or PS can provide higher mean airway pressure and thus better opening of collapsed alveoli (recruitment).

CPAP does not lead to an increase in tidal volume, which results in more gentle ventilation of the lungs. CPAP or positive end expiratory pressure (PEEP) in the range of 5-15 mbar (cm H2O). When using CPAP/PS mode, the PS range is from 8 to 20 mbar (cm H2O).

If FiO2 >60% and SpO2 <92%, consider increasing expiratory pressure (PS) levels.

When stopping NIV (meals, rest), it is recommended to connect HFNC using a flow to maintain SpO2 from 88% to 94%. Lower flow rates, below 30 L/min, may have lower aerosol output. To minimize flow, titrate fraction of inspired oxygen (FiO2) to maximum support before increasing flow above 30 L/min.

Tracheal intubation is indicated when non-invasive ventilation is ineffective, accompanied by:

- persistence or increase in hypoxemia (preservation of SpO2 <90% with clinical signs of respiratory failure, the need to increase the O2 flow rate with HFNO or increase FiO2 by 30% or more during the day with the mask method of NIV);
- lack of full cooperation with the patient (severe encephalopathy, lack of consciousness);

- decompensated metabolic acidosis or respiratory alkalosis;
- no increase in the PaO2/FiO2 index;
- high work of breathing (desynchronization with the respirator, participation of auxiliary respiratory muscles, “failures” during inhalation triggering on the pressure-time curve).

Invasive ventilation:

Before making a decision to intubate a patient, a detailed assessment of the patient's clinical condition (general systemic status of the patient, presence of complications, progression of the disease) is very important.

NB!!! The intubation is performed by the most experienced doctor on the team.

Indications for transferring a patient to invasive ventilation:

1. SpO2 ≤90%, accompanied by hypercapnia pO2 >50 mmHg and/or clinical signs of respiratory failure during NIV.
2. Severe signs of respiratory failure: increased work of breathing against the background of SpO2 ≤90%, accompanied by:
- the patient breathes through the mouth, dilation of the nasal nostrils, diaphoresis;
- tachypnea ≥30 per minute;
- participation in the act of breathing of auxiliary muscles, retraction of the intercostal spaces, yielding places of the chest, regardless of the respiratory rate.
3. Impaired consciousness: agitation, drowsiness, lethargy (as manifestations of hypoxic encephalopathy).
4. Initially low oxygenation index. Oxygenation index ≤200 mm Hg. Art. (with PEEP ≥5 cm H2O, or without NIV).
5. The presence of initial or development during NIV of decompensated metabolic acidosis or respiratory alkalosis against the background of clinical manifestations of respiratory failure

It is recommended to assess the severity of patients using the NEWS scale [16, 44]. When performing NIV (CPAP), the patient's condition should be assessed. If CPAP is ineffective within 30-60 minutes from the start of therapy (continued hypoxia - SpO2 <90%, signs of deterioration of gas exchange, significant participation of the respiratory muscles in the act of breathing), with a progressive deterioration in the patient’s oxygenation, or if the patient does not tolerate the CPAP device, consider tracheal intubation and transfer to mechanical ventilation. CPAP should not delay intubation in a patient with indications for intubation and mechanical ventilation.

NIV guidelines do not recommend its use in hypoxemic respiratory failure (except for cardiogenic pulmonary edema, postoperative respiratory failure, and early use of NIV in immunosuppressed patients) or in pandemic viral diseases (based on available studies of SARS and pandemic influenza). Risks include delayed intubation, large tidal volumes, and traumatic transpulmonary pressures. Limited data suggest a high failure rate of NIV in patients with other viral infections such as MERS CoV.

Anticoagulant therapy (ACT) for - prevention of thromboembolic complications.

For all hospitalized patients with COVID-19, depending on the presence of a risk of thromboembolic complications and the severity of the disease (see section 3.2 of the PADUA scale - risk of venous thromboembolism / IMPROVE risk assessment model, IMPROVE scale - risk of bleeding, a prophylactic dose of drugs is recommended.

Intermediate doseselected for patients with a BMI >30, a history of VTE, the presence of active cancer and an increased D-dimer level >4 times.

Fondaparinuxis the drug of choice for thrombocytopenia (with a decrease in platelets <100,000x109/l);

ACT for prevention in severe and critical patients

Drug name	Doses	Note
Nadroparin calcium injection solution in syringes - 0.3 ml 2850 ME anti Xa: 0.4 ml / 3800 IU anti-Xa: 0.6 ml / 5700 IU anti-Xa	**Prophylactic dose** s/c 0.3-0.4 ml 1 time per day. **Intermediate dose** 0.4 ml 2 times a day.	Should not be used in patients with eGFR <30 ml/min. Contraindicated in case of bleeding.
Enoxaparin solution for injections in syringes 4000 anti-Xa IU/0.4 ml, 6000 anti-Xa IU/0.6 ml,	**Prophylactic dose s.c.** 0.4 ml 1 time per day. **Intermediate dose** 0.4 ml 2 times a day s.c.	Should not be used in patients with eGFR <30 ml/min. Contraindicated in case of bleeding.
Fondaparinux solution for injections in syringes of 0.25 mg is the drug of choice for thrombocytopenia	**Prophylactic dose s.c.** 2.5 mg 1 time per day.	Should not be used in patients with eGFR <25-30 ml/min. **Prescribed when platelets decrease <100,000x109/l**
Heparin 1 ml - 5000 IU	**Prophylactic dose** Subcutaneously 5000 IU 3 times a day.	Bioavailability by SC is up to 30% Drug of choice for eGFR <30 ml min.

In the case of diagnosis of DVT and PE, the patient should be transferred to a therapeutic dose of unfractionated heparin, LMWH, fondaparinux (according to the instructions, see the clinical protocol for diagnosis and treatment “Pulmonary embolism”).

For patients in the ICU with VTE with unstable hemodynamics, it is preferable to use UFH under weight-controlled aPTT.

In patients with severe severity but relatively stable hemodynamics, LMWH can be continued. In case of hemodynamic instability or deterioration of renal function (when creatinine clearance level is below 30 ml/min), transfer to UFH).

Diagnosis and treatment of VTE in patients with COVTO-19.

- Any changes in the clinical status of patients with COVID-19 should be regularly monitored. If there are symptoms of VTE, it is necessary to urgently assess the likelihood of VTE.

- In case of suspected development of acute cerebrovascular accident, medical care is provided to patients in accordance withAppendix 5.

- In patients with COVID-19 with suspected VTE, if the study is not possible due to lack of clinic capacity, parenteral treatment with LMWH should be started as first line in the absence of contraindications.

- In critically ill patients with COVID-19 in the presence of signs of high-risk pulmonary embolism in combination with hypotension or deterioration of hemodynamics in combination with echocardiography data confirming pulmonary embolism and overload of the right heart, rescue thrombolytic therapy is recommended according to the clinical protocol for diagnosis and treatment “Pulmonary embolism” "[43].

- In critically ill COVID-19 patients with refractory circulatory collapse or cardiac arrest, ECMO combined with surgical embolectomy or catheter-directed therapy may be considered.

NB!The use of thrombolytic therapy (TLT) in COVID-19 patients with high-risk PE (alteplase, urokinase) and in ARDS without confirmation of PE (mainly urokinase) is not contraindicated.

Glucocorticosteroids (GCS).

GCS are not recommended for routine use in patients with mild to moderate severity of the disease in an outpatient setting, since the effectiveness and safety of GCS in mild to moderate severity have not been proven; the appointment of GCS requires mandatory monitoring of laboratory parameters (CRP, GOST, ferritin, blood glucose, coagulogram).

GCS are recommended only in hospital settingsfor the purpose of treating hyperactive immunoinflammatory syndrome in patients with severe disease, a marked increase in inflammatory markers and the need for oxygen therapy or respiratory support [11, 45, 52]. Before starting GCS therapy, the following studies must be carried out: CRP, procalcitonin, blood sugar, D-dimer, coagulogram, and, if possible, ferritin, LDH, interleukin-6. The duration of the GCS course, the choice of the initial dose and the rate of reduction are carried out under the control of the above laboratory parameters and depend on the clinical situation. The anti-inflammatory effect is recommended to be assessed by daily CRP testing [11, 45, 46, 52].

Systemic corticosteroids can be administered either orally or intravenously. It should be noted that although the bioavailability of dexamethasone is very high (i.e., similar concentrations are achieved in plasma after oral and intravenous administration), in severe and critical cases, clinicians may consider administering systemic corticosteroids intravenously rather than orally if there is concern. for intestinal dysfunction. Dexamethasone once daily may improve adherence. A 6 mg dose of dexamethasone is equivalent (in terms of glucocorticoid effect) to 40 mg prednisolone, 32 mg methylprednisolone (eg, 8 mg every 6 hours or 16 mg every 12 hours).

Dexamethasone has shown the greatest effectiveness in preventing mortality and reducing the frequency of transfer to mechanical ventilation in patients with severe COVID-19 [47-52]. Systemic corticosteroids should not be discontinued in patients with non-severe COVID-19 who are already receiving systemic corticosteroids for other reasons (eg, patients with chronic obstructive pulmonary disease do not need to discontinue systemic oral corticosteroids or other chronic autoimmune diseases). If patients with non-severe COVID-19 worsen clinically (ie, increased respiratory rate, signs of respiratory distress, or hypoxemia), they should receive systemic corticosteroids.

GCS therapy regimens

GKS	**Basic scheme [39, 40]**
Dexamethasone	6 mg orally/intravenously once a day for 7-10 days.
Methylprednisolone	32 mg PO/IV, given in 2–3 divided doses (eg, 8 mg every 6 hours or 16 mg every 12 hours), 7–10 days.
Prednisolone	40 mg per day orally in 1-2 divided doses, 7-10 days.

The use of glucocorticosteroids should be carried out in combination with anticoagulant therapy. According to indications, antibacterial therapy, histamine H2 receptor blockers, and proton pump inhibitors are recommended [11].

NB!!!Depending on the clinical situation and indications, the dose, frequency and duration of GCS may change based on the decision of the medical council.

Anti-inflammatory therapy (combat immunoinflammatory syndrome and cytokine storm).

In severe cases of COVID-19, cytokine release syndrome (cytokine storm) develops, which poses a threat of the onset and progression of ARDS, multiple organ failure and death. Therefore, it is extremely important to diagnose cytokine storm in the early stages of its development.

Early laboratory signs of cytokine storm are:

- increase in IL-6 level more than 5-6 ULN;
- increased serum ferritin level >600 ng/ml;
- decrease in leukocyte content ≤3.0x109/l;
- decrease in the absolute number of lymphocytes ≤1.0x109/l, the relative content of lymphocytes ≤10%;
- decrease in platelet count ≤180x109/l,
- a rapid decrease in the content of platelets and/or leukocytes, lymphocytes (within 24 hours) by more than two times against the background of continued high inflammatory activity;
- increased ACT activity;
- decrease in blood fibrinogen ≤3.6 mg/l.

Clinical signs:

- high fever over 38°C for 5 days, resistant to antipyretic drugs or a sharp increase in temperature to febrile levels;
- rapid worsening of respiratory failure, sharp decrease in SpO2 saturation <90%;
- development of ARDS;
- rapid progression of the process in the lungs with a lesion volume of more than 50%.

Drug based on monoclonal antibodies - conditional recommendation[81-90].

Tocilizumab* (inhibits IL-6 receptors)indicated for adult patients in need of oxygen, with clinical signs of a systemic inflammatory process, with rapid worsening of respiratory failure: clinical signs of acute respiratory distress syndrome, “cytokine storm” syndrome after determining interleukin-6 levels (more than 5-6 norms).

Prescribed in conjunction with dexamethasone, except in cases where there are contraindications to the use of corticosteroids in the patient.

Concentrate for preparing a solution for infusion in a single dose of no more than 400 mg intravenously by slow drip (over at least 1 hour), if the clinical effect is insufficient, repeat the administration after 12 hours.

Suggested dose of tocilizumab based on body weight:

Patient weight	**Dose of the drug - course**
>90 kg	800 mg
>65 and ≤90 kg	600 mg
>40 and ≤65 kg	400 mg
≤40kg	8 mg/kg

Note:

** is prescribed to the patient only upon signing informed consent personally or by his legal representative as part of participation in a clinical trial.*

** taking into account possible side effects, the attending physician should conduct clinical and laboratory monitoring for a possible side effect of tocilizumab, and if detected, discontinue the drug and submit a yellow card to the National Center for Drug Control.*

** Patients who are at risk of developing sepsis and activation of chronic infectious diseases (viral hepatitis B, C, herpes virus infections, HIV infection, tuberculosis, etc.) should not start treatment with tocilizumab. If serious infections develop, tocilizumab therapy should be discontinued. Use with caution in patients with a history of recurrent infectious diseases, as well as with concomitant diseases that predispose to the development of infections (for example, diverticulitis, diabetes mellitus, intestinal ulcers), with concomitant immunosuppressive therapy, with liver failure, with a decrease in the absolute number of neutrophils < 2.0x09/l, with a decrease in platelets <100,000x109/l, with an increase in transaminase levels above 3-5 ULN.*

Convalescent immune plasma* is a potential treatment for coronavirus disease (COVID-19)indicated for COVID-19 patients in the early pulmonary period of the disease in the absence of the risk of venous thromboembolism [53-61].

Use of fresh frozen immune plasma anti-COVID-19 virus inactivated:

1. Immune plasma can be used in the treatment of patients with laboratory confirmed COVID-19 (PCR and/or ELISA/CLLA) and (or) pneumonia presumably associated with COVID-19, verified by any available instrumental method.

2. The decision to use immune plasma is made by a medical council in the event of a progressive course of COVID-19 with one or more of the following signs:

- hospitalization for fever (axillary temperature >36.7°C or oral temperature >38.0°C) and respiratory rate >24 breaths/min or cough;
- shortened breathing (dyspnea);
- blood oxygen saturation <93% when breathing air;
- ratio of partial pressure of oxygen of arterial blood to the fraction of inspiratory oxygen <300;
- rapid development of pulmonary infiltrate >50% within 24-48 hours;
- need for oxygen therapy;
- reduction in the level of lymphocytes in peripheral blood up to 15%.

Contraindications.

Immune plasma should not be used:

- as a “therapy of despair” in patients with subtotal (more than 75%) or total lung damage who are on mechanical ventilation for more than 72 hours;
- in patients with bacterial sepsis and multiple organ failure;
- when the disease began more than 10-12 days ago;
- with volume overload and pulmonary edema until the condition stabilizes;
- if there is a history of indications of transfusion intolerance.

The Council reserves the right to use additional criteria for prescribing or refusing the use of immune plasma.

3. The dosage of immune plasma is determined individually, taking into account possible complications associated with circulatory overload. The recommended dosage is 1 dose (200-300 ml) on the first day, 1 dose (200-300 ml) on the second day of immune plasma therapy (after 12-24 hours).

Notes:

** Treatment regimens that include immune plasma are prescribed to the patient only after signing informed consent (Appendix 4) personally or his legal representative as part of participation in a clinical trial. Taking into account a possible side effect, the attending physician should conduct clinical and laboratory monitoring, and if detected, discontinue the plasma and submit a yellow card to the National Center for Drug Control. [62].*

Intensive therapy for the development of DN and ARDS (Appendix 1, 2).

Antibacterial therapy for COVID-19.

The viral etiology of lung damage in COVID-19 is not an indication for initial empirical antibiotic therapy. The use of ABT is indicated in case of secondary bacterial pneumonia (appearance of purulent sputum, increase in procalcitonin, CRP), with exacerbation of chronic foci of infection, while taking corticosteroids, the addition of bacterial complications of any localization, during invasive measures, venous catheterization, mechanical ventilation, ECMO, etc. (empirically/and/or taking into account the sensitivity of the isolated strain).

Treatment of comorbid diseases, conditions and complications are carried out in accordance with clinical protocols for diagnosis and treatment for these diseases, conditions and complications (Appendix 7). An algorithm for dynamic monitoring of patients with chronic diseases, including people 60 years of age and older, during an unfavorable epidemiological situation regarding COVID-19.

ACE inhibitors and angiotensin II receptor blockers: Patients with concomitant cardiovascular disease (or other indications) due to COVID-19 who were previously prescribed ACEIs and ARBs are strongly recommended to continue taking these drugs [63].

Statins: Patients with COVID-19 who are prescribed statin therapy for the treatment or prevention of cardiovascular disease should continue taking these drugs [63].

NSAIDs:patients with COVID-19 who are taking NSAIDs to treat a concomitant disease should continue previously prescribed therapy [63].

Inhaled corticosteroids: Patients with COPD, asthma, allergic rhinitis are advised to continue prescribed inhaled corticosteroids. The use of nebulizer therapy, if necessary, should be carried out in a separate room with negative pressure [63].

Algorithm for managing patients with coronavirus infection COVID-19 at all levels of medical care

Periods Therapeutic measures	**Initial (flu-like) days 1-7**	**Height**		**Convalescence**
		Early pulmonary period 8-14 days	**Late pulmonary period 15-28 days**	
Stages of medical care	**mild severity Outpatient level**	**moderate severity Outpatient/inpatient level**	**severe, extremely/severe severity (rehabilitation) Inpatient level/ICU**	**Outpatient**
General recommendations	- A regimen according to the patient's condition (changing body position in bed, walking around the ward). - Drink plenty of fluids depending on the patient's condition and concomitant diseases (preferably warm or hot).			General mode Psychological rehabilitation
NSAIDs	Paracetamol 500 mg (no more than 2 g per day) for antipyretic purposes. Ibuprofen 200-400 mg (no more than 1200 mg) for 5 days to relieve the inflammatory process.			Respiratory rehabilitation
Prevention of hypoventilation of the lower basal parts of the lungs	not shown	Position the patient's body on his stomach for at least 1 hour - 4 rubles. per day (if tolerated), diaphragmatic breathing (according to how you feel).		

Respiratory support	not shown	Oxygen therapy according to indications (saturation less than 93%)	Oxygen therapy. NIV, IVL, ECMO - according to indications	According to indications, prevention of thromboembolic complications is carried out (see CP)
Anticoagulants	not shown	If there is a high risk of thrombosis and a low level of bleeding, patients are recommended to undergo drug prophylaxis of venous thrombosis with careful monitoring of the patient's condition and re-assessment of the risk of thrombosis. Anticoagulants should be prescribed after assessing a complete blood count (hemoglobin, platelets), D-dimer, if indicated - creatinine (eGFR or CK estimates), bilirubin, liver enzymes and bleeding risk assessment (IMPROVE scale).	**If there is a high risk of thrombosis, LMWH or heparin in prophylactic doses.** **Intermediate dose** selected for patients with a BMI >30, a history of VTE, the presence of active cancer and an increased D-dimer level >4 times. **Nadroparin calcium** **Prophylactic dose**s/c 0.3-0.4 ml 1 time per day Intermediate dose 0.4 ml 2 times per day s/c, **Enoxaparin** **Prophylactic dose**s/c 0.4 ml once a day Intermediate dose 0.4 ml 2 times a day subcutaneously,	
		At the outpatient level, DOACs are recommended in prophylactic doses: - Apixaban 2.5 mg*2 times a day *or* - Dabigatran 110 mg x 2 times *or* - Rivaroxaban 10 mg per day	**Fondaparinux**(with a decrease in platelets <100,000x109/l) Prophylactic dose s.c. 2.5 mg 1 time per day **Heparin-** Subcutaneously 5000 IU 3 times a day (if eGFR decreases <30 ml min)	
			NB! ACT (LMWH or heparin) in therapeutic doses only with proven signs of thrombosis (see CP).	
Antiplatelet agents	To prevent recurrent ischemic events, patients with COVID-19 are prescribed acetylsalicylic acid (ASA) at a dose of up to 100 mg per day, and ASA is also indicated for secondary prevention of cardiovascular events.			

	ASA may be recommended for primary prevention in patients with SCORE risk ≥10% and in patients with colorectal cancer. If there are contraindications to the administration of ASA, clopidogrel 75 mg per day can be prescribed.			
Corticosteroids not shown		Not recommended for routine use in patients with moderate forms of the disease in outpatient settings.	**Dexamethasone**6 mg orally/intravenously once a day for 7-10 days *or* **Methylprednisolone** 32 mg PO/IV, given in 2–3 divided doses (eg, 8 mg every 6 hours or 16 mg every 12 hours), 7–10 days *or* **Prednisolone**- 40 mg per day orally, in 1-2 divided doses, 7-10 days	
Etiotropic therapy not shown		Not indicated at the outpatient level, at the inpatient level strictly according to indications. **Remdesivir 200 mg IV on day 1, then 100 mg IV daily for a total of 5-10 days.** - in hospitalized patients with risk factors for severe COVID-19, receiving oxygen (insufflation, high-flow oxygen therapy, NIV) and not receiving mechanical ventilation, as early as possible from the onset of the disease		
Tocilizumab not shown		not indicated on an outpatient basis, at the stationary level strictly according to indications	With the progression of the immunoinflammatory syndrome with the development of a “cytokine storm”, strictly according to indications (see CP). Depending on the patient's body weight >90 kg - 800 mg; >65 and ≤90 kg - 600 mg; > 40 and ≤65 kg - 400 mg; ≤40 kg 8 mg/kg	
Convalescent immune plasma not shown		not indicated on an outpatient basis at the hospital level according to indications	Convalescent immune plasma is indicated for COVID-19 patients in the absence of a risk of venous thromboembolism - The recommended dosage is 1 dose (200 ml) on the first day, 1 dose (200 ml) on	

			the second day of immune plasma therapy (after 24 hours).	
Antibacterial therapy	Not recommended	Not recommended	In case of secondary bacterial infection, as indicated.	
Therapy concomitant diseases (DM, COPD, CSD)	Continuation of basic therapy for concomitant diseases.			

Note:*Currently, no RCTs have been completed on the use of DOACs in patients with COVID-19. As new data become available, changes in the dosage and duration of ACT in patients with COVID-19 are possible. The DOAC doses indicated in the table for the prevention of VTE in patients with COVID-19 are based on expert consensus, after careful analysis of the results of RCTs.*

Indications for transfer of adults to the ICU:

(One of the criteria is sufficient):

Indications for transfer of adults to the ICU are carried out after examination by a resuscitator (one syndrome from the criteria is sufficient).

- Respiratory failure, desaturation (less than 85-90%) with adequate oxygen therapy (2-4 l/min through nasal cannulas in the Pron position), respiratory rate more than 30 per minute.

- Disturbances of consciousness of any origin(hypoxic, vascular, hepatic or renal (uremic) encephalopathy).

- Circulatory disorders.

- hypotension (SBP less than 90 mmHg) or hypertension (SBP above 190 mmHg during primary crisis);

- new complex, threatened heart rhythm disturbances (ventricular extrasystole, ventricular tachycardia, ventricular fibrillation) and conduction disturbances such as 2nd degree AV block, accompanied by attacks of syncope (Morgagni-Adams-Stokes syndrome (MES))

Acute liver failure with clinical and laboratory manifestations:

- impairment of consciousness: hepatic encephalopathy grade 2-3;
- hypoproteinemia (protein below 45 g/l);
- hypocoagulation (PTI less than 70%; MHO more than 1.5; APTT more than 45 seconds in the absence of heparin therapy with clinical manifestations of hemorrhagic syndrome);
- increase in bilirubin level above normal by more than 20 µmol/l per day for 2 days.

- Acute renal failure:

- creatinine is more than 2 times higher than normal with oliguria (500 or less ml/day) with adequate hydration;
- tendency to hypoglycemia (blood sugar less than 3.0 mmol/l with clinical manifestations).

- Coagulopathy:

- blood clotting time is less than 3 minutes during heparin therapy or more than 15 minutes in the absence of heparin therapy;
- increasing petechial or hemorrhagic rash, the appearance of hematomas;
- increasing thrombocytopenia (platelet count <100 thousand/µl or their decrease by 50% of the highest value within 3 days).

Diagnosis and treatment of emergency conditions for COVID-19 and ECMO are presented inAnnexes 1 and 2.

List of essential medicines: No.

List of additional medicines:

Pharmacotherapeutic group	**International nonproprietary name of the drug**	**Mode of application**	**Level of evidence**
NSAIDs. Other analgesics-antipyretics. Anilides.	Paracetamol, tablets 200 mg, 500 mg; solution for infusion 1%; 10 mg/ml	Adults: Tablets: 500 mg every 4-6 hours as needed. The interval between doses is at least 4 hours. The maximum daily dose of paracetamol should not exceed 4 g. Solution for infusion: Maximum daily dose ≤10 kg - 30 mg/kg >10 kg to ≤33 kg - 60 mg/kg not more than 2 g >33 kg to ≤50 kg - 60 mg/kg not more than 3 g >50 kg - 100 ml - 3 g	**WITH**
NSAIDs. Propionic acid derivatives	Ibuprofen film-coated tablets 200 mg, 400 mg. Suspension 100 mg/5 ml; 200 mg/5 ml. Solution for intravenous administration 400 mg/4 ml; 800 mg/8 ml	Adults, elderly in tablets of 200 mg 3-4 times a day; in tablets of 400 mg 2-3 times a day. The daily dose is 1200 mg (do not take more than 6 tablets of 200 mg) (or 3 tablets of 400 mg) within 24 hours. Solution for intravenous administration: after administering 400 mg of the drug, you can take another 400 mg every 4-6 hours or 100-200 mg every 4 hours. The duration of intravenous administration should be at least 30 minutes.	**WITH**
Experimental drugs with an antiviral mechanism of action	Remdesivir	200 mg IV on day 1, then 100 mg IV daily for 5-10 days.	**WITH**
A drug based on monoclonal antibodies that	Tocilizumab.	Concentrate for preparing a solution for infusion 400 mg	

inhibits IL-6 receptors.		intravenously by slow drip (over at least 1 hour), if the effect is insufficient, repeat the administration after 12 hours.	
Regulators of water-electrolyte balance and acid-base balance	Sodium chloride 0.9% solution, 100 ml, 200 ml, 250 ml, 400 ml, 500 ml 5% glucose solution	Starting infusion of 0.9% sodium chloride solution at a rate of 10-20 ml/kg over 30 minutes IV (under hemodynamic control). IV drip	WITH
Alpha adrenergic agonist Dopamine receptor agonist Beta-1 adrenergic agonist	Norepinephrine Dopamine Dobutamine 1 bottle	Norepinephrine solution 0.05-0.3 mcg/kg/min - administration only if central access is available; in the absence of norepinephrine or central access, dopamine 4% 5-10-15 mcg/kg/min and/or dobutamine 5-10 mcg/kg/min is administered	WITH
Diuretic	Furosemide 1% 2 ml (20 mg)	The initial dose is 1 mg/kg	WITH
Regulators of water-electrolyte balance and acid-base balance	Sodium bicarbonate solution 4%	Solution 100 ml, 200 ml, 400 ml	WITH
Glucocorticosteroids	Prednisolone 30 mg	Solution 1 ml - 30 mg	
Glucocorticosteroids	Prednisolone 5 mg	5 mg tablet	
Glucocorticosteroids	Dexamethasone 4 mg/ml	solution for IM, IV injections	WITH
Glucocorticosteroids	Methylprednisolone IV	250 mg per vial	
Glucocorticosteroids	Methylprednisolone, 4 mg	4 mg, tablets	
Direct anticoagulant	Heparin 1 ml 5000 IU 5 ml	Only in the hospital. Subcutaneously 5000 IU/day, with continuous intravenous infusion 1000-2000 IU/h	WITH
Low molecular weight heparin	Nadroparin calcium injection solution in pre-filled syringes, 2850 IU anti-Xa/0.3 ml, 3800 IU anti-Xa/0.4 ml, 5700 IU anti-Xa/0.6 ml,	Only in the hospital. Adults - for the prevention of VTE, 0.3-0.6 ml subcutaneously once a day. For the treatment of DVT and PE at the rate of 0.1 ml per kg of body weight n/r if the patient's weight is 60 kg then 0.6 2 times a day and so on.	WITH

	Enoxaparin injection solution in syringes 4000 anti-Xa IU/0.4 ml, 6000 anti-Xa IU/0.6 ml, 8000 anti-Xa IU/0.8 ml	Adults - Subcutaneously 0.2-0.4 ml 1 time per day for the prevention of VTE For the treatment of DVT and PE at a dose of 1 mg/kg body weight 2 times a day.	
	Fondaparinux solution for subcutaneous and intravenous administration; 0.5 ml of the drug in a pre-filled glass syringe.	Only in the hospital. Do not use intramuscularly! For adults, for the prevention of TE, 2.5 mg 1 time per day as a subcutaneous injection. For the treatment of DVT and PE for patients weighing less than 50 kg - 5 mg; for patients weighing 50-100 kg - 7.5 mg; for patients weighing more than 100 kg - 10 mg. Patients with CC less than 30 ml/min should not be prescribed.	
Oral anticoagulants	Apixaban Tablets 2.5; 5 mg	2.5 mg x 2 times a day	
	Dabigatran etexilate 110 mg x 2 times	110 mg x 2 times	
	Rivaroxaban Tab., coated film coated 10 mg	10 mg x 1 time per day	
Antiplatelet agents	acetylsalicylic acid 75/100	75 x mg 1 time / 100 mg x 1 time	
	clopidogrel 75 mg	75 x mg 1 time	

Illustrative material: electronic slides
Literature: Appendix 1
Security questions (feedback):

LECTURE No. 4: Acute coronary syndrome with ST segment elevation.
Acute coronary syndrome without ST segment elevation.

Purpose: To familiarize the student with pharmacotherapy for coronary syndrome.

Drug therapy of acute coronary syndrome without ST segment elevation Drug treatment of patients with ACS without ST segment elevation includes the complex use of nitrates, β-blockers, Ca2+ channel blockers, antiplatelet drugs (acetylsalicylic acid, clopidogrel, platelet IIb/IIIa receptor blockers) , antithrombin drugs (fractionated and unfractionated heparins) and statins.

Nitrates. At the initial stage of treatment of patients with ACS without ST segment elevation, nitrates are administered as a continuous intravenous infusion through JIC dispensers at a starting dose of 5 mg/h, followed by its adjustment depending on the blood pressure and the clinical condition of the patient. The duration of intravenous infusion of nitrates most often does not exceed 48 hours (this is usually enough to stabilize the condition), after which they switch to the oral or transdermal route of administration of nitrates.

β-Adrenergic blockers. There is no direct evidence of the beneficial effect of β-blockers on the clinical outcome in patients with non-ST segment elevation ACS, however, given the antianginal and anti-ischemic effect of β-blockers, their pharmacological action causes a slowdown in heart rate, a decrease in myocardial oxygen demand, and a decrease in the risk of fatal ventricular arrhythmias, the high effectiveness of their use in patients with myocardial infarction with Q-wave, we can talk about the advisability of their use in patients with ACS without ST-segment elevation. Calcium channel blockers. The use of short- and long-acting dihydropyridines (nifedipine, amlodipine) in patients with acute coronary syndrome without ST-segment elevation who are not receiving beta-blockers is contraindicated. The efficacy and safety of two non-dihydropyridine calcium channel blockers, verapamil and diltiazem, have never been evaluated in placebo-controlled clinical trials in patients with non-ST-segment elevation ACS. It is likely that verapamil, like diltiazem, can be used in patients when there are absolute contraindications to the use of β-blockers. However, the most suitable niche for the clinical use of diltiazem is Prinzmetal's variant vasospastic angina. Antiplatelet drugs. Acetylsalicylic acid remains one of the first choice drugs in the treatment of patients with non-ST segment elevation ACS. Acetylsalicylic acid in an initial dose of 160–320 mg (the first dose should preferably be chewed) should be prescribed as early as possible to patients with undoubted ACS without ST-segment elevation or suspected of it, followed by continuous administration at a dose of 100 mg/day. (preferably in enteric form) indefinitely. Thienopyridines (clopidogrel and ticlopidine), by blocking platelet P2Y12 receptors, irreversibly suppress ADP-induced platelet aggregation. Compared with ticlopidine, clopidogrel is better tolerated, less likely to cause side effects from the gastrointestinal tract, leukopenia and thrombocytopenia, has a more pronounced antiplatelet effect and can be used in a loading dose.

According to current recommendations, clopidogrel should be prescribed as early as possible to patients hospitalized with non-ST segment elevation ACS in the following cases:

-if patients experience hypersensitivity to acetylsalicylic acid or intolerance to it due to gastrointestinal side effects;

-using a loading dose together with acetylsalicylic acid, if percutaneous coronary interventions are not planned, followed by 1 to 9 months;

-using a loading dose together with acetylsalicylic acid if percutaneous coronary interventions are planned, followed by 1 to 9 months if there is no risk of serious hemorrhagic complications.

Blockers of platelet Pb/Sha receptors(abciximab, eptifibatide and tirofiban) are the most powerful antiplatelet drugs. Clinical studies have irrefutably proven the high effectiveness of platelet IIb/IIIa receptor blockers when performing percutaneous coronary interventions in patients with non-ST segment elevation ACS. At the same time, Diagnosis and Treatment of Acute Coronary Syndrome 11 As part of complex drug therapy in patients with ACS without ST-segment elevation, in whom percutaneous coronary interventions are not planned, only eptifibatide and tirofiban (but not abciximab) can be used, although they should be administered It is only appropriate for high-risk patients.

Antithrombin drugs(unfractionated heparin, low molecular weight fractionated heparins, factor Xa inhibitors) are one of the key in the treatment of patients with non-ST segment elevation ACS.

*Unfractionated heparin.*When using UFH in the complex treatment of patients with non-ST segment elevation ACS, UFH should be administered for at least 48–72 hours only intravenously as a continuous infusion through JIC dispensers under regular monitoring of the APTT (target APTT is 1.5–2 times higher than the initial value). In addition to the need for constant intravenous infusion, UFH has other relative disadvantages: the occurrence of thrombocytopenia, the development of the "rebound" phenomenon at the end of drug administration, pronounced variability in the degree of binding to plasma proteins, which makes the angicoagulant effect of UFH difficult to predict, increases the likelihood of bleeding and requires frequent laboratory monitoring . Low molecular weight heparins. LMWHs, compared to UFH, have a lesser effect on thrombin formation and block factor Xa to a greater extent. Important advantages of LMWH: the possibility of subcutaneous administration 2 times a day (this achieves predictable and sufficient anticoagulation), no need for laboratory monitoring and a less frequent development of thrombocytopenia. Clinical trials have shown that neither dalteparin nor nadroparin have significant clinical advantages over UFH, except for ease of use, and enoxaparin is more effective than UFH.

Factor Xa inhibitors(fondaparinux sodium). Unlike LMWH, fondaparinux sodium exclusively blocks factor Xa, which is much more beneficial and effective in terms of suppressing the coagulation cascade. In the treatment of patients with non-ST segment elevation ACS, fondaparinux is as effective as enoxaparin; the total incidence of bleeding with its use is significantly lower.

Selection of initial treatment tactics for acute coronary syndrome with ST segment elevation

The main goal in the treatment of patients with ST-segment elevation ACS is the fastest (in the first 12 hours after the onset of the clinical picture of the disease), complete and stable restoration of blood flow (reperfusion) through the occluded coronary artery. There are two ways to restore coronary blood flow in patients with ST-segment elevation ACS - reperfusion with thrombolytic drugs (streptokinase, tissue plasminogen activator) or with primary percutaneous coronary interventions (balloon angioplasty and coronary artery stenting). In this case, the concept of "primary percutaneous coronary intervention" refers to balloon angioplasty or stenting of an infarct-related coronary artery, performed within the first 12 hours after the onset of the clinical picture of myocardial infarction without the previous use of thrombolytic or other drugs that can dissolve blood clots. According to the 2005 European Guidelines for Percutaneous Coronary Interventions, it is believed that primary percutaneous coronary interventions are the method of choice for treating patients with ST-segment elevation acute coronary syndrome hospitalized in the first 12 hours of the disease. However, the vast majority of patients with acute coronary syndrome with ST segment elevation throughout the world, including in Russia, receive thrombolytic drugs as reperfusion therapy. Each of these tactics has its own advantages and disadvantages. The advantages of thrombolytic therapy include the simplicity of its implementation, relatively low cost, and the possibility of performing it both at the prehospital stage (a

significant reduction of the time before the start of reperfusion therapy by at least 30 minutes) and in any hospital. The disadvantages include low efficiency (from 50 to 80% depending on the type of thrombolytic drug and the time elapsed from the onset of the disease), the development of early (5–10% of patients) and late (30% of patients) repeated occlusions of the coronary arteries, the likelihood of severe complications, including hemorrhagic stroke in 0.4–0.7% of patients. The advantages of primary percutaneous coronary interventions include more effective restoration of the patency of the coronary arteries (95–98%), a low incidence of early and late repeated occlusions of the coronary arteries, more complete preservation of myocardial contractile function, and a lower incidence of strokes, including hemorrhagic ones. All this translates into good long-term clinical results. Disadvantages of primary percutaneous coronary interventions: organizational difficulties, loss of time at the preoperative stage, high cost.

Drug therapy for acute coronary syndrome with ST segment elevation

Main goals:

-pain relief;

-rapid restoration of blood flow through the occluded coronary artery (thrombolytic therapy or primary percutaneous coronary intervention);

-limitation of the necrosis zone (restoration of coronary blood flow, β-blockers, nitrates);

-prevention of recurrent coronary artery thrombosis (antiplatelet and antithrombin drugs);

-treatment of complications of myocardial infarction.

Narcotic analgesics (morphine, trimeperidine, fentanyl) are usually used to relieve pain. The most effective is a 1% solution of morphine, which is administered intravenously slowly after dilution in 20 ml of isotonic sodium chloride solution. Any narcotic analgesic should be used with caution, keeping in mind their ability to depress the respiratory center and lower blood pressure. Systemic thrombolysis. It is fundamentally important that systemic thrombolysis is advisable only in the first 6 hours after the onset of clinical signs of ACS. At a later stage, systemic thrombolysis is not indicated, since its effectiveness is extremely low and it does not have a significant effect on in-hospital and long-term mortality rates. Currently, the most widely used drugs are streptokinase (the most commonly used drug in the world) and tissue plasminogen activators, which include alteplase (t-PA), reteplase (rt-PA) and tenecteplase (nt-PA).

Indications for systemic thrombolysis:

-the presence of a typical clinical picture of ACS in combination with ECG changes in the form of ST segment elevation of more than 1.0 mm in two adjacent standard limb leads or ST segment elevation of more than 2.0 mm in two or more adjacent chest leads;

-first identified complete blockade of the left bundle branch in combination with a typical clinical picture. Signs of effective thrombolysis:

-a decrease in the S-T interval by 50% or more compared with the severity of the initial rise 90 minutes after the end of the thrombolytic administration;

-the appearance of reperfusion arrhythmias (frequent ventricular extrasystole, slow ventricular tachycardia, VF occurs extremely rarely). It should be noted that thrombolytic therapy, which is formally effective based on indirect evidence, does not always lead to the restoration of coronary blood flow, according to coronary angiography. The reperfusion efficiency of streptokinase is about 50%, alteplase, reteplase and tenecteplase - 75–85%. Compared with streptokinase (first-generation thrombolytic), alteplase and reteplase (second-generation thrombolytics), which require intravenous drip administration over a certain period of time, the convenience of using tenecteplase (third-generation thrombolytic) lies in the possibility of its bolus intravenous administration. This is extremely convenient when performing prehospital thrombolysis in an emergency medical team.

Absolute contraindications:
-a history of hemorrhagic stroke or stroke of unknown origin;-ischemic stroke within the last 6 months;
-the presence of vascular pathology of the brain (arteriovenous malformation);
-the presence of a malignant brain tumor or metastases;
Diagnosis and treatment of acute coronary syndrome
-recent trauma, including traumatic brain injury, abdominal surgery within the last 3 weeks;
-gastrointestinal bleeding within the last month;
-known diseases accompanied by bleeding;
-suspicion of dissection of the aortic wall.
Relative contraindications:
-transient ischemic attack within the last 6 months;
-therapy with indirect anticoagulants;
-pregnancy and 1st week after birth;
-puncture of vessels that cannot be compressed (for example, the subclavian vein);
-resuscitation measures accompanied by chest trauma;
-uncontrolled hypertension (systolic blood pressure > 180 mm Hg);
-peptic ulcer of the stomach and duodenum in the acute phase;
-advanced liver diseases;
-infective endocarditis.
It must be emphasized that if previously age over 75 years was also considered a contraindication to thrombolytic therapy, this restriction has now been lifted.
*Streptokinase*administered intravenously in a dose of 1.5 units, dissolved in 100 ml of 0.9% isotonic sodium chloride solution or 5% dextrose for 30–60 minutes. Previously, in order to reduce the likelihood of allergic reactions, it is advisable to administer 60–90 mg of prednisolone intravenously.
*Alteplase*administered in a total dose of 100 mg as follows: initially, 15 mg of the drug is administered intravenously as a bolus, then over the next 30 minutes, intravenous drip administration of alteplase is started at the rate of 0.75 mg/kg, in the next 60 minutes it is continued at the rate of 0.5 mg/kg.
*Reteplase*administered intravenously in the form of two bolus injections at a dose of 10 units each with a 30-minute interval between injections.
*Tenecteplase*administered intravenously as a single bolus injection in a dose calculated depending on the patient's body weight: with a weight of 60–70 kg, 35 mg of the drug is administered, 70–80 kg – 40 mg, 80–90 kg – 45 mg, more than 90 kg – 50 mg. To enhance the thrombolytic effect and prevent recurrent coronary artery thrombosis (with effective thrombolysis), antiplatelet drugs (acetylsalicylic acid, clopidogrel) and antithrombin drugs (UFH, LMWH, factor Xa inhibitors) are used. Acetylsalicylic acid should be prescribed as early as possible to all patients with ST-segment elevation ACS (in the absence of absolute contraindications), and the first dose should be chewed. Thienopyridines (clopidogrel). Adding a combination of acetylsalicylic acid and clopidogrel to thrombolytic therapy is even more effective. Blockers of IIb/IIIa platelet receptors, according to current information, are not indicated for use in combination with thrombolytic drugs in order to enhance the reperfusion effect of the latter.
Antithrombin drugs. The advisability of using UFH in the treatment of patients with acute coronary syndrome with ST segment elevation depends on whether systemic thrombolysis was performed, and if so, what thrombolytic was used. If systemic thrombolysis is not performed for any reason, it is advisable to start intravenous UFH and continue the infusion over the next 24–72 hours. If systemic thrombolysis was performed using streptokinase, then subsequent use of UFH is not necessary,

although it is possible (the GUSTO study showed that the administration of UFH after systemic thrombolysis with streptokinase did not affect the patency of the infarct-related coronary artery). If tissue plasminogen activator (alteplase, reteplase, tenecteplase) was used as a thrombolytic drug, then after its administration it is advisable to start an intravenous infusion of UFH and continue it for 24–48 hours. This allows for more stable patency of the infarct-related coronary artery. The route of administration of UFH is of fundamental importance: it should be prescribed exclusively as a continuous intravenous infusion through dosing devices under APTT monitoring. The target APTT value is 1.5–2 times greater than the initial value. To do this, UFH is initially administered intravenously as a bolus of 60 U/kg (but not more than 4,000 U), followed by intravenous infusion at a dose of 12 U/kg/h, not exceeding 1,000 U/h, at regular intervals (after 3, 6, 12 and 24 hours after the start of the infusion) by monitoring the aPTT with appropriate adjustment of the dose of UFH. In some cases (in people under 75 years of age and in the absence of signs of renal failure), enoxaparin (initially an intravenous bolus of 30 mg, then at 15-minute intervals in the form of subcutaneous injections at a dose of 1 mg/kg every 12 hours) can serve as an alternative to UFH.

Nitrates. Routine use of nitrates at the initial stage of treatment of patients with ACS with ST segment elevation is inappropriate.

β-Adrenergic blockers. Early routine intravenous use of β-blockers in patients with ST-segment elevation ACS is not indicated. Taking β-blockers orally at the initial stage of treatment of patients with ST-segment elevation ACS is safer and, in the absence of contraindications, can be recommended for all patients, regardless of whether they were treated with thrombolytic therapy or percutaneous coronary intervention. Contraindications: clinical signs of acute left ventricular failure (congestive moist rales in the lower lungs), arterial hypotension (systolic blood pressure < 90 mm Hg), bradycardia (< 60 beats), AV block (PR interval more than 0.24 s), the presence of severe broncho-obstructive syndrome.

Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. In the absence of contraindications, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers should be prescribed to all patients with ST-segment elevation ACS on the first day of the disease, but they are especially indicated for high-risk patients. Slow calcium channel blockers. The results of clinical studies do not allow us to recommend calcium channel blockers (both short-acting and slow-release dihydropyridines) as routine therapy for patients with ST-segment elevation ACS. Magnesium preparations and a glucose-insulin potassium mixture do not affect the prognosis and course of ACS with ST segment elevation, therefore their routine use is not indicated. Lidocaine. Current recommendations do not recommend prophylactic administration of lidocaine to patients with ST-segment elevation ACS.

Illustrative material: electronic slides

Literature: Appendix 1

Security questions (feedback):

LECTURE No. 5: CLINICAL PHARMACOLOGY OF ARTERIAL HYPERTENSION

PURPOSE: To familiarize the student with pharmacotherapy for arterial hypertension

Arterial hypertension (AH) is a disease that has a genetic predisposition and is characterized by a persistent increase in systolic (>140 mm Hg) and diastolic (>90 mm Hg) blood pressure (BP). It is estimated that more than 1 billion people worldwide have hypertension, and approximately 7.1 million deaths per year are associated with this pathology. Taking into account the above facts, optimal antihypertensive therapy should not only reduce blood pressure, but also prevent complications associated with hypertension [1]. Hypertension can be effectively treated with a variety of medications, including angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin II AT1 receptor blockers (ARBs), calcium antagonists (CAs), diuretics, alpha blockers, and beta blockers (BABs). Blood pressure changes throughout the day, therefore, the risk of many cardiovascular complications also varies at different hours, so antihypertensive drugs that minimize diurnal fluctuations in blood pressure are most effective in controlling blood pressure and potentially provide the best protection for the cardiovascular system [2, 3] .

Classification of blood pressure levels and definition of arterial hypertension:

Optimal blood pressure is < 120/80 mm Hg. Art. Normal blood pressure – < 130/85 mm Hg. Art. Increased normal blood pressure – 130–139/85–90 mm Hg. Art. Stage 1 hypertension: systolic blood pressure (SBP) – 140–159 mm Hg. Art., diastolic blood pressure (DBP) – 90–99 mm Hg. Art. Stage 2 hypertension: SBP – 160–179 mm Hg. Art., DBP – 100–109 mm Hg. Art. 3rd degree hypertension: SBP – 180 mm Hg. Art. and higher, DBP – 110 mm Hg. Art. and higher. Isolated systolic hypertension: SBP – above 140 mm Hg. Art., DBP – below 90 mm Hg. Art.

Non-drug therapy

If the 1st degree of hypertension is detected, it is recommended to control blood pressure and begin non-drug therapy, which includes: psychological relief - normalization of central nervous system function (prevention of stress), formation of a daily routine (constant time of getting up and going to bed), adherence to a work and rest schedule with getting enough sleep at night. Irregular working hours, night shifts and seven days off should be avoided. It is necessary to quit smoking and limit the consumption of alcoholic beverages - no more than 30 ml of pure ethanol per day for men (corresponding to 50–60 ml of vodka, 200–250 ml of dry wine, 500–600 ml of beer) and 20 ml for women. Physical exercises aimed at training endurance (general developmental exercises, breathing exercises, exercise equipment, swimming, walking, running) lead to a noticeable hypotensive effect. It is best to exercise for 30-40 minutes every day, gradually increasing the load from light to moderate. A good method of self-monitoring is to measure your pulse during exercise. Its frequency should not exceed the age limit, which is determined by the formula: 180 minus age in years. The nutrition of patients with hypertension should be rational - the calorie content of food should be reduced in order to control weight (limit sweet, fatty and flour foods), consumption of animal fats (whole milk, butter, sour cream, sausage, cheeses, lard). Fats can be consumed per day no more than 50–60 g, and 2/3 of them should be fats of vegetable origin. It is necessary to limit the consumption of foods containing large amounts of easily digestible carbohydrates (sugar, honey, products made from butter and yeast

dough, chocolate, semolina, rice cereals). The food should contain a sufficient amount of proteins (low-fat fish, poultry, low-fat dairy products). It is recommended to avoid foods that stimulate the nervous system (coffee, tea, carbonated drinks containing caffeine, hot spices and strong alcoholic drinks). It is necessary to limit the consumption of table salt to 5 g/day, while it should be taken into account that many products (cheeses, smoked meats and pickles, sausages, canned food, mayonnaise, chips) contain a lot of salt. It is necessary to replace the salt with herbs, garlic or salt with a low sodium content. It is advisable to eat foods rich in potassium and magnesium, such as prunes, apricots, pumpkin, cabbage, bananas, rose hips, dark bread with bran, dark chocolate, oatmeal, buckwheat, millet porridge, beets, carrots, salad. If, despite non-drug therapy, blood pressure remains elevated (>140/90 mm Hg) or there are risk factors for the development of cardiovascular complications, hypertension, drug treatment should be prescribed immediately. Among the risk factors that affect the prognosis in patients with hypertension and necessitate early use of antihypertensive therapy, the following can be identified: smoking, high blood cholesterol, diabetes, older age (men over 55 years old; women over 65 years old), male gender ,

Principles for choosing drug therapy for hypertension

Optimal treatment of hypertension implies a gradual decrease in blood pressure and stable maintenance of blood pressure at the target level, patient compliance, regression of target organ damage, increased life expectancy and improved quality of life. Target blood pressure is the blood pressure level at which the minimum risk of cardiovascular morbidity and mortality is recorded (Table 1).

Таблица 1. Целевые уровни артериального давления

Группа пациентов	Целевое АД, мм рт. ст.
Общая популяция пациентов с АГ	<140/90
АГ + СД, протеинурия < 1 г/сут	<130/85
АГ + СД, протеинурия > 1 г/сут	<125/75
АГ + ХПН	<125/75
Пациенты старше 60 лет	<150/90

For patients who do not have specific indications, the main classes of antihypertensive drugs will be ACE inhibitors or ARBs, dihydropyridine CB. The presence of concomitant diseases dictates the use of specific antihypertensive drugs, since these drugs have positive effects independent of lowering blood pressure. For example, after the ALLHAT trial, alpha blockers continue to be used for the treatment of hypertension in patients with benign prostatic hyperplasia, although they were not recommended for the continuous treatment of hypertension itself [4]. Classification of antihypertensive drugs: 1. Diuretics: a) loop; b) thiazide and thiazide-like; c) potassium-sparing; d) carbonic anhydrase inhibitors. 2. Adrenergic receptor antagonists: a) alpha blockers; b) beta-blockers; c) alpha and beta adrenergic blockers. 3. Adrenergic receptor agonists: a) alpha2-agonists. 4. Calcium channel blockers. 5. ACE inhibitors. 6. Angiotensin-2 receptor blockers. 7. Aldosterone antagonists. 8. Vasodilators. 9. Centrally acting adrenergics or stimulators of alpha receptors in the brain. 10. Direct renin inhibitors. It is advisable to select an antihypertensive drug according to a specific algorithm consisting of 4 stages. The use of such an algorithm should help the doctor achieve maximum effectiveness and at the same time minimize the risk of side effects of the pharmacotherapy.
*First stage*the choice of an antihypertensive drug is pathogenetic, i.e. the choice of a drug will depend on the cause of the increase in blood pressure. The physician should try in each specific case to

determine which hemodynamic factor contributes to the increase in blood pressure (Table 2).

Таблица 2. Распределение гипотензивных препаратов в соответствии с их влиянием на причины артериальной гипертонии

Повышенный сердечный выброс	Повышенное периферическое сопротивление	Повышенный ОЦК
БАБ Агонисты I_1-рецепторов Недигидропиридиновые АК	Ингибиторы АПФ БРА Дигидропиридиновые АК Агонисты I_1-рецепторов Симпатолитики БАБ с вазодилатирующим действием Альфа-блокаторы	Диуретики

For example, in patients with increased cardiac output (with the “hyperkinetic” version of hypertension in hyperthyroidism or in the early stages of hypertension in young people), it is advisable to prescribe drugs that reduce cardiac output (blockers, centrally acting drugs, non-dihydropyridine AKs). In elderly patients with a long history of hypertension, the most common cause of hypertension is increased peripheral resistance. Initially, it is caused by transient increases in peripheral arterial vascular resistance in response to increased blood pressure; over time, hypertrophy of the middle muscular layer of arterioles and increased vascular resistance develop. This category of patients is indicated for the prescription of drugs that reduce total peripheral vascular resistance, such as ACE inhibitors, ARBs, dihydropyridine AKs, centrally acting drugs (I1 receptor agonists: rilmenidine, moxonidine, etc.), sympatholytics, beta-blockers with a vasodilating effect (carvedilol , nebivolol, etc.), long-acting alpha blockers (doxazosin, terazosin, etc.). In patients with obesity and edema of the lower extremities, we can talk about the presence of a pathogenetic mechanism caused by an increased volume of circulating blood (CBV) with the formation of volume-dependent hypertension; thus, it is preferable to prescribe diuretics for this category of patients. It should also be remembered that mixed hemodynamic options are possible; in such cases, combinations of antihypertensive drugs are prescribed [2, 4].

*At the second stage of selection*When using an antihypertensive drug, it is necessary to assess the presence of target organ damage in the patient: this could be the brain and its vessels, the heart (hypertrophy or dilatation of the left atrium and ventricle, coronary angiosclerosis with obvious or hidden myocardial ischemia), kidneys (microalbuminuria, hyperazotemia). In accordance with the identified target organ, it is necessary to prescribe an antihypertensive drug with appropriate organoprotective properties (cardio-, cerebro- or nephroprotective). ACE inhibitors, ARBs, beta blockers, AKs have proven cardioprotective properties, and calcium antagonists have cerebroprotective properties. Nephroprotective properties in hypertension, especially with a combination of hypertension and diabetes, have been proven for ACE inhibitors, ARBs, and AA (Table 3).

Таблица 3. Распределение гипотензивных препаратов в соответствии с их органопротекторными свойствами

Кардиопротекторные ЛП	Церебропротекторные ЛП	Нефропротекторные ЛП
Ингибиторы АПФ БРА ББ АК Агонисты I_1-рецепторов	АК	Ингибиторы АПФ БРА АК

Having compared the antihypertensive drugs from Tables 2 and 3, it is necessary to leave in the final list only those drugs that were present in both lists at the same time. The third stage of choosing the optimal drug for the treatment of hypertension is devoted to assessing the safety of the treatment. To solve this problem, it is necessary to evaluate the medical history (indications of intolerance or unsatisfactory tolerability of certain drugs). Next, you should analyze the presence of concomitant diseases in this patient, identifying contraindications to taking certain medications. For example, if you have a history of bronchial asthma, drugs from the beta blocker group are contraindicated. These same drugs, with the exception of beta blockers that have vasodilating properties, are contraindicated in patients with stenosing atherosclerosis of the arteries of the lower extremities with intermittent claudication. BBs are also contraindicated in cases of atrioventricular block above 1st degree / bradycardia less than 50/min. Alpha blockers are contraindicated in case of concomitant angina pectoris, as they can cause an increase in anginal attacks. Sympatholytics are contraindicated in persons with peptic ulcer disease. OCs are contraindicated in patients with gastroesophageal reflux disease (GERD) because they cause relaxation of the lower esophageal sphincter and thereby may exacerbate GERD symptoms. Verapamil may aggravate constipation and is therefore contraindicated in this category of patients. Diuretics can increase the level of uric acid in the blood, so hyperuricemia and gout are contraindications for them. A number of antihypertensive drugs can have a negative impact on the course and outcome of pregnancy. Therefore, a limited range of antihypertensive drugs is prescribed for her: methyldopa, labetolol, nifedipine, hydralazine. Thus, after the third stage of selection, drugs that are effective and safe for patients with hypertension will remain on the list. The fourth and final stage of choosing an antihypertensive drug is the stage of selecting individual pharmacotherapy. When deciding which pharmacotherapy is indicated for a given patient (mono- or combined), one should proceed from the degree of increase in blood pressure and the duration of hypertension. In cases of mild hypertension, not corrected by non-drug treatment methods, and moderate hypertension, monotherapy is possible in some cases. However, when treating hypertension, there is a rule: combinations of antihypertensive drugs with different mechanisms of action are preferable to high-dose monotherapy. Firstly, in combination, the effect is achieved by influencing different parts of the pathogenesis of hypertension, and secondly, with the right combination, the side effects of the drug are mutually neutralized. For example, “escape” of the hypotensive effect due to activation of the sympathoadrenal system (SAS) manifests itself when taking arteriolar vasodilators by increasing cardiac output; when taking all antihypertensive drugs, except diuretics, due to sodium and water retention in the body; when taking diuretics - due to the activation of the body's neurohormonal systems, in particular the renin-angiotensin-aldosterone system (RAAS) [2, 3]. For maintenance antihypertensive therapy, long-acting drugs with a long half-life are indicated. Another important advantage of drugs with a long duration of action is the possibility of taking them 1–2 times a day,

which helps to increase patient adherence to treatment. In this regard, the ARB candesartan (Giposart, Akrikhin company) is of interest, as it has the longest half-life of all drugs in this group (more than 24 hours), which makes it possible to achieve blood pressure control also in the morning. In addition, candesartan has advantages over other drugs in cases of combination of hypertension with CHF, diabetes, nephropathy, and left ventricular myocardial hypertrophy. To date, the results of 14 placebo-controlled studies with candesartan in 3377 patients with hypertension are available. Daily doses of the drug ranged from 2 to 32 mg with a follow-up period of 4 to 12 weeks. The initial DBP level ranged from 95 to 114 mmHg. Art. Within this dosage range, 2350 patients received active candesartan therapy and 1027 patients received placebo. All studies showed a significant hypotensive effect of candesartan, which was dose-dependent. The absence of a “first dose effect” was demonstrated, i.e., when taking the first dose of candesartan, there was no sharp decrease in blood pressure. As with other antihypertensive drugs, the hypotensive effect of candesartan increased during the first 2 weeks. and by the end of this period it was already clearly expressed. Similar to other antihypertensive drugs, the maximum effect was observed at the end of the 1st month. therapy, while the hypotensive effect of candesartan did not depend on the age and gender of the patients. Of particular note is the good tolerability of candesartan even at a daily dose of 32 mg. As for the stability of the hypotensive effect, in studies lasting up to 1 year, there was no “escape” of the hypotensive effect of candesartan [5–10]. The safety of candesartan was assessed in studies that included more than 3600 patients, including more than 3200 patients with hypertension. In 600 of these patients, the safety of the drug was studied for at least 6 months, in more than 200 patients - for at least 1 year. In general, treatment with candesartan was well tolerated, and the overall incidence of side effects with it was similar to that of placebo. The rate of drug discontinuation due to side effects in all studies in patients with hypertension (total 7510) was 3.3% (108 of 3260) of patients receiving candesartan as monotherapy and 3.5% (39 of 1106) of patients receiving placebo . In placebo-controlled studies, discontinuation of therapy due to adverse clinical events occurred in 2.4% (57 of 2350) of patients receiving candesartan and in 3.4% (35 of 1027) of patients receiving placebo. The most common reasons for discontinuation of candesartan therapy were headache (0.6%) and dizziness (0.3%). Side effects, observed in placebo-controlled clinical trials in at least 1% of patients treated with candesartan (at a higher incidence (n=2350) than placebo (n=1027)): back pain (3% vs 2%) , dizziness (4% vs. 3%), upper respiratory tract infections (6% vs. 4%), pharyngitis (2% vs. 1%). Side effects that were observed in less than 1% of patients receiving candesartan in placebo-controlled clinical trials, but occurred at approximately the same frequency as in the placebo group: fatigue, peripheral edema, chest pain, headaches, cough, sinusitis, nausea, abdominal pain, diarrhea, vomiting, joint pain, albuminuria [7–10]. According to controlled studies, practically no clinically significant changes in the value of standard laboratory parameters associated with taking candesartan were observed. Thus, extremely rarely, a slight increase in the level of urea and creatinine in the blood serum was observed. Hyperuricemia was rare: 19 (0.6%) of 3260 patients receiving candesartan and 5 (0.5%) of 1106 patients receiving placebo. Minor decreases in hemoglobin and hematocrit levels (mean decreases of approximately 0.2 g/L and 0.5 volume percent, respectively) occurred extremely rarely in patients receiving candesartan as monotherapy, and were of virtually no clinical significance. The development of anemia, leukopenia, thrombocytopenia with subsequent withdrawal was observed in only 1 patient among participants in all clinical trials of the drug. A slight increase in serum potassium levels (average 0.1 mmol/L) was noted in patients receiving candesartan monotherapy, but this was rarely of clinical significance. In 1 patient with congestive heart failure, severe hyperkalemia was observed (serum potassium = 7.5 mmol/l), requiring discontinuation of the drug, but this patient was also receiving spironolactone. Increased levels of liver enzymes were detected in 5 patients, bilirubin – in 2 patients [7–10]. In case

of long-term hypertension with high levels, therapy should be started with a combination of antihypertensive drugs. If combination therapy is ineffective, they switch to prescribing drugs that are part of the combination used in full dose or add a 3rd drug in a low dosage. If this therapy does not lead to achieving target blood pressure levels, then a combination of 2-3 drugs is prescribed in usual effective doses. The question still remains open as to which patients can be prescribed combination therapy at the first stage of treatment. To make a decision on how to treat a patient with hypertension who has come for an appointment for the first time or repeatedly, we suggest that doctors use the algorithm presented in Figure 1. pharyngitis (2% vs. 1%). Side effects that were observed in less than 1% of patients receiving candesartan in placebo-controlled clinical trials, but occurred at approximately the same frequency as in the placebo group: fatigue, peripheral edema, chest pain, headaches, cough, sinusitis, nausea, abdominal pain, diarrhea, vomiting, joint pain, albuminuria [7–10]. According to controlled studies, practically no clinically significant changes in the value of standard laboratory parameters associated with taking candesartan were observed. Thus, extremely rarely, a slight increase in the level of urea and creatinine in the blood serum was observed. Hyperuricemia was rare: 19 (0.6%) of 3260 patients receiving candesartan and 5 (0.5%) of 1106 patients receiving placebo. Minor decreases in hemoglobin and hematocrit levels (mean decreases of approximately 0.2 g/L and 0.5 volume percent, respectively) occurred extremely rarely in patients receiving candesartan as monotherapy, and were of virtually no clinical significance. The development of anemia, leukopenia, thrombocytopenia with subsequent withdrawal was observed in only 1 patient among participants in all clinical trials of the drug. A slight increase in serum potassium levels (average 0.1 mmol/L) was noted in patients receiving candesartan monotherapy, but this was rarely of clinical significance. In 1 patient with congestive heart failure, severe hyperkalemia was observed (serum potassium = 7.5 mmol/l), requiring discontinuation of the drug, but this patient was also receiving spironolactone. Increased levels of liver enzymes were detected in 5 patients, bilirubin – in 2 patients [7–10]. In case of long-term hypertension with high levels, therapy should be started with a combination of antihypertensive drugs. If combination therapy is ineffective, they switch to prescribing drugs that are part of the combination used in full dose or add a 3rd drug in a low dosage. If this therapy does not lead to achieving target blood pressure levels, then a combination of 2-3 drugs is prescribed in usual effective doses. The question still remains open as to which patients can be prescribed combination therapy at the first stage of treatment. To make a decision on how to treat a patient with hypertension who has come for an appointment for the first time or repeatedly, we suggest that doctors use the algorithm presented in Figure 1. pharyngitis (2% vs. 1%). Side effects that were observed in less than 1% of patients receiving candesartan in placebo-controlled clinical trials, but occurred at approximately the same frequency as in the placebo group: fatigue, peripheral edema, chest pain, headaches, cough, sinusitis, nausea, abdominal pain, diarrhea, vomiting, joint pain, albuminuria [7–10]. According to controlled studies, practically no clinically significant changes in the value of standard laboratory parameters associated with taking candesartan were observed. Thus, extremely rarely, a slight increase in the level of urea and creatinine in the blood serum was observed. Hyperuricemia was rare: 19 (0.6%) of 3260 patients receiving candesartan and 5 (0.5%) of 1106 patients receiving placebo. Minor decreases in hemoglobin and hematocrit levels (mean decreases of approximately 0.2 g/L and 0.5 volume percent, respectively) occurred extremely rarely in patients receiving candesartan as monotherapy, and were of virtually no clinical significance. The development of anemia, leukopenia, thrombocytopenia with subsequent withdrawal was observed in only 1 patient among participants in all clinical trials of the drug. A slight increase in serum potassium levels (average 0.1 mmol/L) was noted in patients receiving candesartan monotherapy, but this was rarely of clinical significance. In 1 patient with congestive heart failure, severe hyperkalemia was observed

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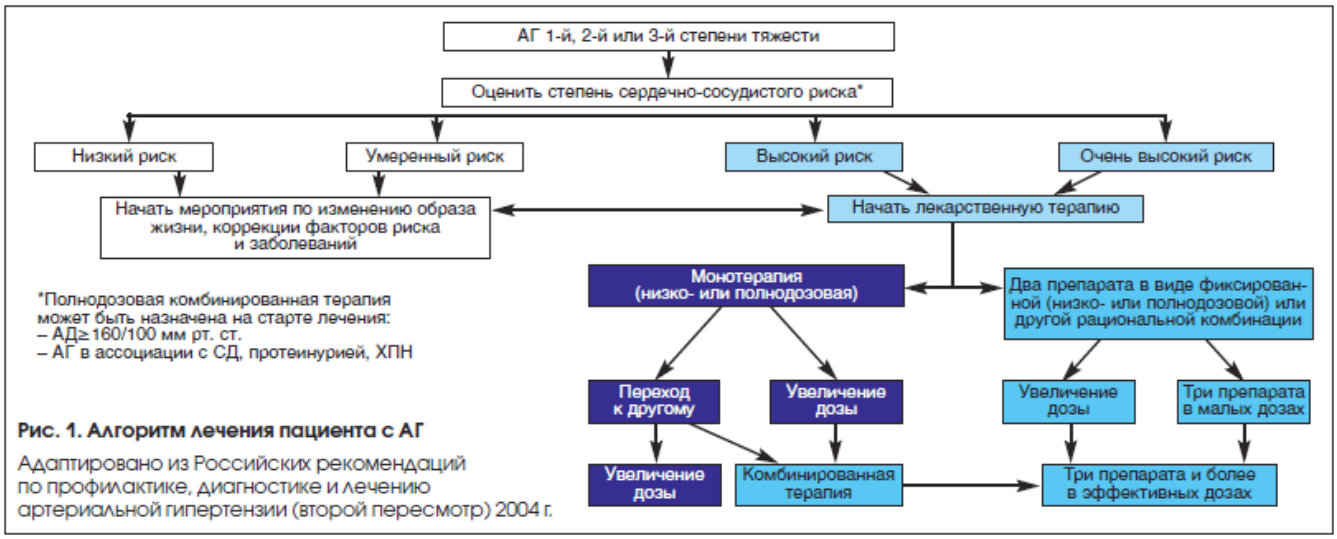

Рис. 1. Алгоритм лечения пациента с АГ

Адаптировано из Российских рекомендаций по профилактике, диагностике и лечению артериальной гипертензии (второй пересмотр) 2004 г.

In this case, rational and irrational combinations of antihypertensive drugs are distinguished (Fig. 2).

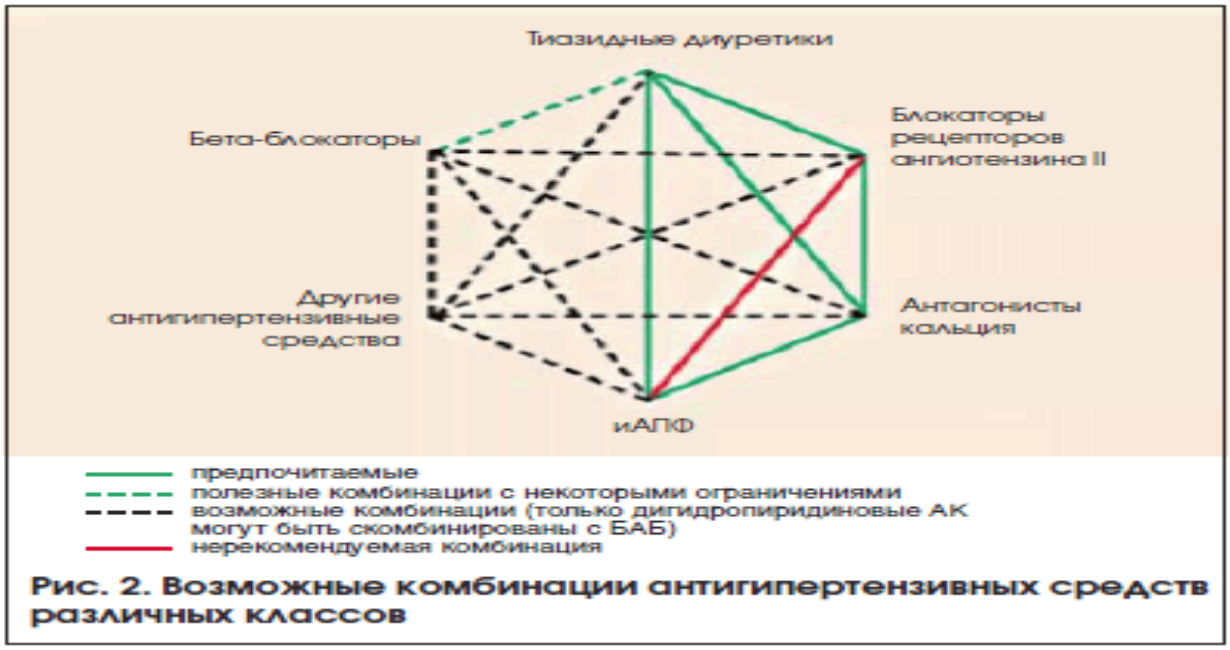

Рис. 2. Возможные комбинации антигипертензивных средств различных классов

Rational combination therapy must meet a number of mandatory conditions: safety and effectiveness of the components; the contribution of each of them to the expected result; different but complementary mechanisms of action; higher efficiency compared to that of monotherapy with each component; balance of components in terms of bioavailability and duration of action; strengthening organoprotective properties; impact on the mechanisms of blood pressure increase; reduction in the number of adverse events and improved tolerability. Table 4 shows the undesirable consequences of using antihypertensive drugs and the possibility of eliminating them by adding a second drug.

Таблица 4. Нежелательные явления гипотензивных средств и возможности их устранения

Препарат А	Нежелательные эффекты препарата А	Корригирующий препарат
Дигидропиридиновые АК	Активация САС, сердцебиение	ББ
	Периферические отеки	Ингибитор АПФ, БРА
Диуретик	Гипокалиемия, гипомагниемия, инсулинорезистентность, активация РААС	Ингибитор АПФ, БРА
	Дислипидемия	Альфа-блокатор
ББ	Задержка натрия, снижение сердечного выброса и почечного кровотока	Диуретик
	Периферический вазоспазм	АК
Альфа-блокатор	Вазодилатация, гипотония первой дозы, постуральная гипотония	ББ

Combination therapy does not always mean an increase in the hypotensive effect and can lead to an

increase in adverse events (Table 5).

Таблица 5. Неблагоприятные последствия комбинированного применения гипотензивных препаратов

Препарат А	Препарат Б	Неблагоприятные эффекты, усиливаемые препаратом Б
Диуретик	Вазодилататоры	Гипокалиемия
	БАБ	Гипергликемия, дислипидемия
АК (недигидропиридиновый)	БАБ	Атриовентрикулярная блокада, брадикардия
АК (дигидропиридиновый)	Альфа-блокатор	Гипотония
Альфа-блокатор	Диуретик	Гипотония первой дозы, постуральная гипотония
Ингибитор АПФ	Диуретик	Уменьшение скорости клубочковой фильтрации
	Калийсберегающий диуретик	Гиперкалиемия
	Альфа-блокатор	Гипотония
Гидралазин	АК (дигидропиридиновый)	Сердцебиение, ишемия миокарда

Conclusion

The algorithm for choosing a drug for the treatment of hypertension is aimed at maintaining target blood pressure levels, achieving a protective effect on all target organs, preventing complications and improving the prognosis of life of patients with hypertension. For a long time, ARB drugs were considered by doctors as reserve drugs, prescribed only in case of poor tolerability of ACE inhibitors. There were two other important barriers to wider use of ARBs in clinical practice: the smaller evidence base for ARBs compared with that of ACE inhibitors, and the higher cost of treatment for ARBs compared with ACE inhibitors. The article presents an algorithm for choosing the optimal antihypertensive drug, and also provides the evidence base for the effectiveness and safety of the drug candesartan (Giposart, Akrikhin company). Candesartan has a good dose-dependent antihypertensive effect in all categories of patients with hypertension and can be recommended for wider clinical use.

Illustrative material: electronic slides
Literature: Appendix 1

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