Slobodan Janković

CLINICAL PHARMACOLOGY

Kragujevac, 2023.

Clinical pharmacology

The author:
prof. Dr. Slobodan Janković
full professor of pharmacology with toxicology and clinical pharmacy, Faculty of Medical Sciences, University of Kragujevac

Reviewers:

Publisher:
Faculty of Medical Sciences in Kragujevac

Proofreader:
Nera Janković, Romanist philologist

Technical Editor:
Slobodan Janković

Front page:
Slobodan Janković

The press:
InterPrint , Kragujevac

Circulation:
500

ISBN:
???

CIP - Cataloging in the publication of the National Library of Serbia, Belgrade

By the decision of the Commission for publishing activities of the Teaching and Scientific Council of the Faculty of Medicine in Kragujevac, number of year, this book is printed as a textbook for basic teaching in clinical pharmacology.

THE CONTENT

GENERAL PART

CLINICAL PHARMACOLOGY IN THE HEALTH CARE SYSTEM

Clinical pharmacology is a relatively new discipline, founded at the beginning of the second half of the twentieth century. The American pharmacologist Harry Gold was the first to recognize the need for a new type of specialist in medicine, saying the following: "...a special type of specialist is needed, who are not only familiar with the techniques and basics of laboratory pharmacology, but also with clinical medicine...". Clinical pharmacologists are the experts of such a profile, who should use their detailed knowledge of the mechanisms of drug action, their effect in real clinical conditions and pharmacokinetics in solving patients' problems in real life.

However, from the very beginning, clinical pharmacology developed in different directions in different parts of the world. It was generally more research-oriented than health care. In the United States, where it first originated, clinical pharmacology never reached patients: analyzes conducted at the end of the twentieth century showed that of the approximately 800 clinical pharmacologists in that country, the vast majority worked in universities, the pharmaceutical industry, or government agencies. regulatory bodies. The main area of their work is the process of drug development, not the use of drugs in the treatment of specific patients. On the other hand, in European countries, clinical pharmacologists focused on both research and work in health care. However, the involvement of clinical pharmacologists in health care does not go smoothly: there is a lot of misunderstanding of their place and intertwining of competences in the treatment of patients with other specialties.

In Serbia, clinical pharmacology exists as an officially recognized health specialization lasting 4 years, which can be enrolled by general practitioners after completing an internship and passing a professional exam. There is also a narrower specialization in clinical pharmacology - pharmacotherapy lasting 12 months, which can be enrolled by specialists in clinical pharmacology, surgery, internal medicine, and anesthesiology and some other branches of medicine. Upon completion of health specialization or narrower specialization, doctors receive the title of clinical pharmacologist, and can devote themselves in practice to the activities for which they were educated. Based on legislation in the Republic of Serbia, every hospital with more than 400 beds should have at least one clinical pharmacologist, who will work in a special organizational unit of the hospital - the Clinical Pharmacology Service. From such a service, clinical pharmacologists work throughout the hospital, trying to improve the handling

of drugs and quality of medication therapy for all types of patients. Here are some of the activities performed by clinical pharmacologists in hospitals: (1) at the request of doctors of other specialties, they correct and adapt the drug therapy of patients to their needs; (2) on the request of a general practitioner, they correct and adjust the medication therapy of outpatients; (3) carry out therapeutic monitoring of drugs (antiepileptics, antidepressants, antibiotics, etc.); (4) prepare hospital formulary - list of medicines to be procured and used in the hospital; (5) control the rationality of prescribing drugs, particularly - antibiotics and high-priced drugs; (6) create good practice guidelines for the application of certain types of drugs; (7) detect, register and take measures to prevent adverse effects of drugs; (8) designs and conducts clinical drug trials; (9) lead or participate in the work of Hospital Ethics Committees that evaluate the justification of conducting clinical drug trials, and (10) propose and ensure the implementation of the adopted drug use policy in the hospital. Therefore, there is a lot of work for clinical pharmacologists in hospitals, and for now their number in Serbia is significantly less than necessary for the optimal implementation of the mentioned activities.

Unfortunately, clinical pharmacologists have not yet found their place in outpatient health care, so the legislation in Serbia does not provide for a clinical pharmacologist to work in the outpatient Health Center. At least part of the activities that clinical pharmacologists carry out in hospitals could also be carried out in outpatient health care, which would significantly contribute to a more rational use of drugs among outpatients .

In some developed countries (and in some places also in Serbia), part of the work of a clinical pharmacologist is taken over by pharmacists who have completed specialization in the field of clinical pharmacy. Such a practice is a consequence of the relatively small number of clinical pharmacologists in health care, and the great need for specialists with good knowledge of drugs, who master the skills of safe administration of drugs. In fact, clinical pharmacologists and clinical pharmacists are in the same job, and their cooperation in practice further improves the quality of health care. However, only clinical pharmacologists know how to examine a patient and determine whether the use of previously prescribed drugs is justified or not, as well as whether there are indications for the use of non-prescribed drugs. More and more, the treatment of patients requires a multidisciplinary approach, so that in the future, cooperation between experts of different specialties will increase. Let's just remember the growing number of old people in our population, whose capacity to eliminate drugs is significantly reduced; complete treatment of such patients can only be performed by a complete team of health professionals, hopefully led by a clinical pharmacologist.

In the previous decade (2010-2020), a new concept of the organization of work in health institutions appeared, the goal of which is the correct and rational application of medicines. The concept first started with antibiotics, and was named "antimicrobial stewardship", which then expanded to include other medicines, and received the name "medicines stewardship". The point of medicines stewardship is the cooperation of doctors of various specialties, including clinical pharmacologists, on the treatment of individual patients who

are particularly complex in terms of the therapy they need, as well as on the creation and implementation of a specific drug administration policy in a health institution or region. Medicines stewardship has various forms, i.e., specific ways of organizing, which are adapted to the conditions on the ground. It is natural for clinical pharmacologists to coordinate the work of expert teams within the framework of drug management, given their competences, but this is not a rule for now, since the situation is different from institution to institution.

KNOWLEDGE NEEDED BY THE CLINICAL PHARMACOLOGY TO RESPOND TO THE DEMANDS OF PRACTICE

Considering the complexity of the problems that a clinical pharmacologist has to solve in practice, he/she needs tomaster a large number of scientific disciplines. First of all, it is necessary to have a good knowledge of the principles by which drugs act on the human body (pharmacodynamics), and then pharmacokinetics, i.e., how drugs are absorbed, distributed, metabolized and excreted. After that, it is necessary to know clinical medicine, at least to the extent that general practitioners who have clinical experience know it, so that the therapy could be placed in the context of the patient's illness and condition. Knowledge of pharmacovigilance (the science of side effects of drugs) is also needed, in order to be able to interpret the side effects that occur during therapy, then knowledge of pharmacoeconomics (the science of the cost-effectiveness of drugs, i.e., the balance of costs and effects of therapy). Clinical pharmacologist must also understand principles of evidence-based medicine (to be able to assess how effective and safe a drug really is) and preclinical and clinical research methodologies (to be able to assess whether the results of published studies can be trusted, and to create a clinical study protocol - experimental or observational - when asked to do so).

Several other disciplines require from a clinical pharmacologist to become familiar with them. Knowledge of pharmacogenetics is needed to understand how changes in genetic material affect drug action and pharmacokinetics. Knowledge of toxicology is also of great importance, because in practice it often happens that drugs are overdosed, so toxic effects arise that need to be recognized. A clinical pharmacologist should also know the legislation that regulate testing, registration, procurement, administration and other aspects related to the drugs, so that he/she can properly assess whether a certain procedure is a violation of the regulation or not. Pharmacoinformatics is another area whose knowledge is necessary - how to get credible information about drugs and diseases, about the most rational choice of therapy in a certain clinical condition, i.e., how to find and interpret good practice guidelines, systematic reviews, meta-analyses and clinical studies. Finally, a solid

knowledge of statistics is also necessary, as it allows the results of clinical research to be properly interpreted.

The mentioned list of disciplines may seem too long, and the knowledge that needs to be mastered too extensive; it is true that clinical pharmacologists face a very difficult task, and it takes time to overcome and fulfill it. Only continuous learning and improvement in these disciplines, which does not stop until the end of working life, can lead to good quality of clinical pharmacologist's practice and good results, i.e., as many cured patients as possible, and as few unwanted and toxic effects of drugs as possible. If the Latin proverb " Ars longa, vita brevis " ("Knowledge is vast and life is short") could be applied to some discipline, then it is certainly clinical pharmacology.

SCIENCE OF ADVERSE EFFECTS OF MEDICINES

Anything unfavorable that occurs during the administration of the drug (e.g. nausea, disruption of laboratory results, injury, rash, a new illness, or anything else bad for the patient), is called an adverse event, which **may or may not be** in related to the drug. Only if we prove a cause-and-effect relationship between the drug and the adverse event can we say that it is actually an **adverse effect of the drug**. The scientific discipline that deals with the diagnosis and interpretation of adverse drug effects is called pharmacovigilance.

An adverse drug reaction (ADR) is an organism's response to a drug that is harmful and unintended, and which occurs at doses normally used for prophylaxis, diagnosis or treatment of a disease, or changes in some physiological function. In addition to the aforementioned, adverse effects include: unfavorable interactions between drugs, the absence of a therapeutic effect of the drug, and adverse changes that follow the discontinuation of the drug to which the body previously reacted favorably.

There is no drug that does not have side effects; there are only drugs with more or less severe side effects, depending on their ability to react with different tissues and organs. That is why side effects should always be considered when drugs are administered; then we will be able to predict and thus avoid some unwanted effects. In this sense, it is useful to know the early signs of adverse effects; for example, if after the application of lamotrigine, an antiepileptic of the second generation, red spots appear on the lower extremities that are of a regular circular shape, with lighter and darker bands (so that they resemble the drawing of a target), the use of the drug should be stopped immediately, which will prevent the progression of this rash (called erythema multiforme) into the bullous form, with more severe consequences (the bullous form is called Steven-Johnson syndrome).

Adverse effects of drugs are a great burden on the health system. Studies have shown that about 6 percent of all hospital admissions are due to adverse drug reactions. As many as 10 to 20 percent of hospital patients experience at

least some unwanted effect of the drug while staying in the hospital. The main cause of such a high frequency of side effects is the simultaneous administration of a large number of drugs to the same patient. However, there is a great possibility that side effects can be avoided, if you think about them: about 50 percent are preventable.

All side effects can be classified into three large groups:

- A - ADR that can be predicted based on the mechanism of action of the drug (e.g., dry mouth when using tricyclic antidepressants, due to their antimuscarinic effect);
- B – bizarre ADR which are unpredictable, rare, do not depend on the dose, and are usually serious (e.g., agranulocytosis with beta-lactam antibiotics);
- C – ADR that imitate diseases (e.g., a syndrome similar to the - systemic lupus erythematosus when using procainamide or hydralazine).

The frequency of side effects of a drug varies: some occur more often than others. In order to have an orientation, how likely it is that an unwanted effect of a certain drug will appear, they can be classified ***by frequency*** into:

- very common: occur in more than 10 percent of patients;
- common: occur in 1-10 percent of patients;
- they are not common: they occur in 0.1 - 1 percent of patients;
- rare: occur in 0.01 percent - 0.1 percent of patients, and
- very rare side effects: occur in less than 0.01 percent of patients.

Knowing the frequency of adverse effects of specific drugs can be of great use in practice, when a patient takes a large number of drugs and then experiences an adverse event. If that adverse event can be caused by several drugs from those that the patient is taking, one should first suspect the drug among them that causes such an adverse effect with the highest frequency (simply, the highest frequency means the highest probability that that particular drug is the cause of the adverse event).

Of the unwanted effects in practice, we are most concerned about the so-called ***serious*** side effects. Serious side effects lead to some of the following consequences :

- death
- hospitalization
- extension of hospitalization
- disability
- danger to life
- malignant disease or
- congenital anomalies.

For each drug that we give to a patient, we need to know the seriousness of the side effects that it can cause, to warn the patient about them and to familiarize him with the ways to prevent them (for example, patients who take sulfonamides should drink plenty of fluids, in order to prevent crystallization of sulfonamides in kidney tubules and their damage), as well as with mandatory monitoring of laboratory and other parameters that can timely indicate the beginning of an adverse event (e.g., when a patient takes the second-generation antipsychotic clozapine, it is mandatory to check the number of neutrophils in the blood every 7 days during the first 18 weeks of therapy, and then once a month, in order to prevent the occurrence of agranulocytosis) .

As already mentioned, when we notice an adverse event in a patient who is taking a drug, we are not immediately sure that it was that drug that caused the observed event. That's why we initially call such phenomena "unwanted events", and we can call them "side effects" only when we determine the cause-and-effect relationship between the drug and the phenomenon. When determining *the cause-and- effect relationship,* we pay particular attention to the following elements:

1. The time interval from the administration of the drug to the occurrence of ADR? If the event occurred during the use of the drug, or soon after it was stopped, it is more likely a consequence of the use of the drug than any other factor .
2. Dechallenge - What happens after stopping the drug? If the adverse event recedes after stopping its use, it is probably an adverse effect.
3. Rechallenge - What happens after re-administration of the drug? If, after - repeated application of the drug, we observe an adverse event again, there is a very high probability that it was caused by it.
4. Are there alternative causes of ADR? If there is no other explanation for the occurrence of an adverse event, the drug remains the most likely cause.
5. Has such an adverse effect been described before? The experiences of others with the use of a drug followed by an adverse event are always useful for determining causality.
6. Is there a laboratory confirmation? For example, an increase of aminotranspherases in the blood of a patient who had nausea and vomiting during the administration of the drug significantly suggests that chemical hepatitis has occurred).
7. Is there a suitable biological explanation for the occurrence of the adverse - effect of the drug, i.e., can we guess the mechanism of side effects?

It is the duty of both pharmacists and doctors to report any observed adverse reactions to our National Center for Adverse Drug Effects at the Agency for Medicines and Medical Devices of Serbia, on a separate form that can be downloaded from the Agency's website. Therefore, only the suspicion that it is an unwanted effect is enough to fill out and send the report. For new drugs, all side effects are reported within the first 5 years from the moment they are registered in Serbia. For drugs that have been on the market for more than 5 years, only serious side effects and previously unknown side effects are reported. The National Center is obliged to provide an assessment of the cause-and-effect

relationship between the adverse event and the drug, with the help of its experts, to anyone who reports an adverse event and seeks an explanation.

From now on, patients also have the opportunity to report suspected adverse drug effects to the Agency for Medicines, via a special form on the agency's website. Unfortunately, this rarely happens for now, because there is a lack of education of the general public about side effects, the procedure and the importance of reporting suspected side effects.

Regular reporting of all observed adverse events is important for the overall safety of drug administration in the country. It makes possible to detect dangerous drugs, which cause many serious side effects, and to quickly ban their further use. Unfortunately, pharmacists and doctors rarely report adverse drug reactions, and it is estimated that the number of reported cases is only 1-10 percent of the actual number. In Serbia, that number is even lower - only a few hundred reports per year. Why side effects of drugs are underreported is still unclear, but the following reasons are assumed:

- the belief that only safe drugs are on the market ;
- fear that the patient who has noticed an unwanted effect will sue the doctor;
- avoiding to communicate after the report with the persons in charge of pharmacovigilance in the pharmaceutical company whose drug it is (they usually ask for additional data from the doctor who reported the adverse event in order to establish causality);
- a feeling of guilt, because the drug caused the patient discomfort;
- desire to publicize side effects;
- not knowing how to report;
- reluctance to report mere suspicion, and
- disinterest.

There are several research methods available for the study of adverse drug reactions: stimulated reporting, active methods (monitoring of each case of drug prescribing, sentinel studies, registries), observational studies (cross-sectional studies, case/control studies, cohort studies) and experimental clinical studies. **Stimulated reporting** means that the manufacturer of the drug financially stimulates the doctors who prescribe his drug to report every case of an adverse effect that they observe in their patients; when a sufficient number of reports are collected, the manufacturer processes them statistically and graphically, which enables a better assessment of the safety of that drug. **The monitoring of each case of drug prescription** consists of the organization of a monitoring system for each patient who takes a certain drug, whereby the doctors who prescribed the drug are obliged to inform the monitoring organizer in detail about each such patient; the monitoring organizer then processes the written reports, and determines the type of adverse effects and their incidence. **Sentinel studies** involve the registration and analysis of all patients who had an abnormal laboratory or other type of test result; by noticing certain regularities, a lot can

be concluded about the unwanted effects of certain drugs. For some diseases, there are **patient registries** at the national level; in those registers you can also find data on observed side effects of drugs, which can be processed and presented to the professional public. **Cross-sectional studies** include a certain group of patients in one act (no patient follow-up) and record the occurrence of adverse drug effects in patients who are exposed to a drug, as well as in patients who are not exposed to that drug; by determining the difference in the frequency of side effects between the group of exposed and the group of unexposed patients, the connection between the drug and the side effect can be revealed. In contrast to them, **cohort studies** follow a certain group of patients over time and record the occurrence of adverse drug effects in patients who are exposed to a drug, as well as in patients who are not exposed to that drug. In **"case/control" studies,** the researcher first finds patients who have experienced a certain adverse event, and then finds similar control patients who have not experienced such an event; then, in both groups of patients, the extent to which they were exposed to the suspected drug is investigated, and based on that comparison, a conclusion is drawn about the relationship between the adverse event and the drug. Finally, **experimental clinical studies, i.e., randomized, controlled, double-blind studies** may also reveal the existence of adverse effects of a particular drug; unfortunately, considering the relatively small number of patients who can be included in such studies (a few thousand at most), only frequent and very frequent side effects of drugs can be detected.

In summary, only a few of these methods are suitable for clinical pharmacologists, who have limited research time and resources. According to experience so far, the most feasible are sentinel studies and observational studies. The common characteristics of these studies are a relatively small number of patients (less than 200), a focus on adverse effects that appear quickly after exposure to the drug, a non-interventional design, and low costs. If the design of such studies is done adequately, and if they are conducted carefully and according to the protocol, the results will be interesting and useful for practical application. Such studies are a useful addition to much more expensive experimental clinical studies, and to extensive surveillance systems for the occurrence of adverse drug reactions.

The side effects of medicines must always be considered, especially for people who are old and have several diseases at the same time. In medicine, the term "elderly" refers to people older than 65 years, and today it is very common for old people to take a large number of medicines at the same time. If one patient takes 5 or more drugs at the same time, this phenomenon is called "**polypharmacy**" (the obsolete name is "polypragmasy"). Polypharmacy can be both justified and unjustified, so it is always advisable to review the necessity of administering drugs prescribed to an elderly person. Even if it is justified, polypharmacy is a risk factor both for the occurrence of serious side effects and for the occurrence of undesirable drug interactions that have clinical significance. Therefore, the following principle should be respected whenever possible: **the patient should be prescribed the smallest number of drugs that can cure or heal all his health disorders** .

INTERACTIONS BETWEEN MEDICINES

As soon as two or more drugs are found in the body at the same time, there is a probability that they will affect each other by changing their pharmacokinetics or pharmacodynamics. The influence that one drug has on another is called an interaction, which can be pharmacodynamic or pharmacokinetic. **Pharmacodynamic interactions** mean that the drugs change the effect of each other, usually by affecting the same receptor (for example, a beta blocker will interfere with the action of a beta agonist), or by acting on the same tissue in the same or opposite way (for example, pilocarpine leads to constriction of the pupil causing contraction of pupil sphincter muscle - musculus sphincter pupillae - via muscarinic receptors, while phenylephrine leads to dilation of the pupil, causing contraction of the muscle that expands - musculus dilatator pupillae – via adrenergic alpha receptors). If the result of the pharmacodynamic interaction is an enhancement of the effect of one or both drugs, we speak of **agonism**, and if the result is a weakening of the effect of one or both drugs, we speak of **antagonism**. Both agonism and antagonism can be **pharmacological**, if they are the result of the effect of drugs on the same receptor, or **physiological**, if the drugs act on the same tissue, but through different receptors. Pharmacokinetic interactions imply the influence of drugs on each other at the level of absorption, distribution, metabolism or excretion. The most significant pharmacokinetic interactions take place at the level of drug metabolism, namely in liver cells, on cytochromes, where some drugs can induce the formation and activity of cytochromes, while others inhibit them. Induction of cytochromes will result in acceleration of the elimination of drugs that are metabolized by them, and inhibition will slow it down.

In addition to cytochromes, interactions can occur on other enzymes that metabolize drugs, or on membrane transporters by means of which drugs either enter cells or are expelled from them. The largest superfamily of membrane transporters is the so-called ABC superfamily, so named because it binds to itself adenosine triphosphate (ATP) from which they draw energy to transfer drugs across the membrane. This superfamily includes **glycoprotein P** (also called multidrug resistance protein [MRP-1] or ATP- binding cassette B1 [ABCB1]), **a breast cancer resistance protein** (BRCP or other name ATP-binding cassette G2, ABCG2), **protein**

responsible for drug resistance (MDR-1 or other name ATP- binding cassette C1) and many others. Medicines can compete for the same transporter and thus interfere with each other's exit or entry into cells, or in some other way stimulate or inhibit the functioning of membrane transporters. Some drugs are known to act as inhibitors (e.g., oral antidiabetics from the sulfonylurea group glyburide) or stimulators of certain membrane transporters (e.g., pantoprazole), which classifies them as drugs with significant potential for interactions with other drugs.

BASIC PHARMACOKINETIC PARAMETERS

The basic pharmacokinetic parameters that can be used to describe the movement of the drug through the human body are **the volume of distribution, drug clearance and elimination constant**. The volume of distribution refers to the extent to which the drug penetrates the tissues and cells, while the clearance of the drug and the elimination constant express the same thing in different ways: the rate at which the drug is eliminated from the body. There is a mathematical connection between these three parameters, so that any one of them can be calculated at any moment if the other two are known. The mathematical relationship is:

$$K_e = \frac{Cl}{Vd}$$

where Ke = elimination constant, Cl = drug clearance, and Vd = volume of drug distribution.

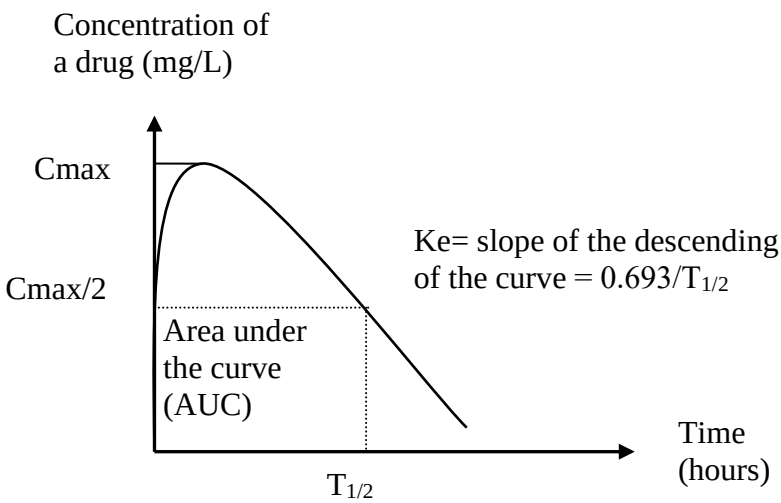
The volume of distribution *(V_d)* is a virtual quantity that is calculated as a quotient between the dose in which the drug was administered *(D)* and its concentration in the blood *(C_p)* :

$$V_d = \frac{D}{C_p}$$

The volume of distribution represents the volume in which the drug would be distributed under the condition that the concentration of the drug is the same in all parts of that volume, i.e., equal to the concentration of the drug in the blood. Although virtual, this size can tell us a lot about the behavior of the drug in the body. If V_d is about 5 L, it can be assumed that the drug was distributed only in the intravascular space and could not leave the blood vessels (e.g., plasma-expander dextran 70). If V_d *is* about 15 L, it can be assumed that the drug was distributed within the extracellular fluid (because there is about 15 L of it), that it is not liposoluble and that it does not penetrate inside the cells or into the central nervous system. If the volume of distribution is around 40 L, the drug has penetrated into all cells of the body (V_d is equal to the volume of total water

in the body), and if V_d is greater than 40 L (sometimes several hundred liters), it means that the drug is somewhere deposited in the organs (most of the dose of the drug is in the depot, the concentration of the drug in the blood is low, so the ratio D/C_p is high).

Mathematical quantities that tell us about the speed of drug elimination from the body are **clearance (Cl), elimination constant (K_e) and half-life ($T_{1/2}$).** All three quantities can be calculated from the curve that describes the serum drug concentration in time (see figure) after oral administration.



Drug concentration in the blood after a single oral dose.

Drug clearance represents the amount of blood plasma that is cleared from the drug in a unit of time. The total clearance of the drug includes all routes of elimination and can be expressed as the sum of renal, hepatic, pulmonary and other clearances. It is calculated as the ratio of the total amount of the drug that is eliminated in a unit of time and the concentration of the drug in the plasma. In practice, *the total* clearance of the drug is determined from the curve of serum drug concentration/time (see the picture above), as a ratio of the drug dose and the area under the curve (AUC). If we would like to calculate only *renal* clearance of the drug, then the total amount of drug that was excreted through the kidneys in the same period of time would be divided by the area under the curve. ***Half-life ($T_{1/2}$)*** is the time during which half of the administered amount of the drug is eliminated from the body. In practice, the half-elimination time is determined from the "serum drug concentration/time" graph (see figure), by reading the time required for the drug concentration to decrease to half on the descending part of the curve. It is clear that the slope of the descending part of the curve actually determines the rate of elimination: the higher the slope, the faster the

elimination, and vice versa. The slope is mathematically expressed as the tangens of the angle at which the descending part of the curve is tilted in relation to the x-axis, and is also called the drug elimination constant (K_e). There is a simple mathematical relationship between the elimination constant (slope of the curve) and the half-life: $T_{1/2} = 0.693/K_e$.

From the mathematical relationship of distribution volume, drug clearance and elimination constant, it can be seen that the elimination of drugs that penetrate into tissues and cells (i.e., whose distribution volume is large) is slow, and vice versa. This can be logically explained by the fact that with a large volume of distribution, the concentration of the drug in the blood is low; as the rate of elimination depends on the level of drug concentration in the blood (the higher the concentration of the drug, the faster the elimination, and vice versa), drugs with a large volume of distribution will be eliminated slowly. Examples of drugs with a large volume of distribution and slow elimination are psychotropic drugs (antidepressants, antipsychotics, sedatives, hypnotics), which due to their high liposolubility (otherwise they could not penetrate the blood-brain barrier) penetrate into tissues and cells and have low concentration in the blood. Due to the slow elimination, drugs from the mentioned groups are administered in only one daily dose. Antibiotics (e.g.. aminoglycosides, penicillins, cephalosporins, etc.), which penetrate poorly into cells, have a high concentration in the blood and are quickly eliminated, give us the opposite example (small volume of distribution and rapid elimination), which results in the need to administer them frequently, every 6 or 8 hours.

Steady state

When it comes to drugs with linear elimination kinetics (i.e., drugs whose elimination mechanisms cannot be saturated at the usual dosage, so the rate of elimination increases with the concentration of the drug in the blood), after repeated administration of the same dose, the equilibrium state is established, in which **the amount of drug that is eliminated between two doses of the drug is equal to that dose**. After the first dose in the dosing interval, only part of the dose is eliminated, so that the next dose significantly increases the concentration of the drug in the blood. An increased concentration of the drug in the blood leads to an acceleration of elimination, so that in the second dose interval a greater part of the dose is eliminated than in the first. The third dose of the drug further increases the concentration of the drug in the blood, so in the third dose interval an even larger part of the dose is eliminated. After 4-5 dosing intervals (provided that they are approximately equal to the elimination half-life of the drug), an equilibrium state is established. Then the concentration of the drug in the blood is maintained at a constant level, oscillating around a certain value. In practice, our goal is to administer the drug to the patient at regular intervals (dose intervals) to reach an equilibrium state in which the concentration of the drug in the blood will be sufficiently high to manifest the

therapeutic effect of the drug, and yet not too high, so as not to manifest toxic effects of the drug.

The steady-state can be reached faster than 4-5 half-lifes, if we apply as the first ***loading*** dose of the drug, which is several times higher than the usual single dose (maintenance dose). We do this, for example, when we administer a loading dose of antibiotics, where our goal is to reach blood concentrations that are effective against the cause of infection as soon as possible. Loading doses are **not adjusted** to possible disorders of liver or kidney function in patients, because with their one-time administration we will certainly not exceed the target concentrations in the blood that we expect in a steady state.

For successful therapy, it is very important that the patient takes his medicine regularly , i.e., not to miss a single dose. If this happens, the steady state is disturbed and the concentration of the drug in the blood drops. It is necessary to pass several dosing intervals to re-establish the original equilibrium state with the desired concentration of the drug in the blood. Also, any change in drug dose or dose interval disturbs the existing equilibrium state, and will result in a new equilibrium state after the next 4-5 dose intervals.

INDIVIDUAL DRUG DOSING

Although it is common knowledge that dose of a drug should be individualized (that is adjusted according to physiological and pathophysiological status the patient to whom the medicine is prescribed), in practice that is difficult to achieve, in the first palce due to complexity of the task. Individualization of doses should first be based on the precise estimate of functional condition of vital organs of the patient, and then on our knowledge about how functional status of an organ affects on the key pharmacokinetic parameters of drugs (clearance, volume distribution, binding for proteins in plasma and biological availability). The issue of individualizing drug dosing is increasingly attempted to be solved using pharmacokinetic calculators based on the information technology, and recently using artificial intelligence, however only with lilmited success.

In spite of numerous publications in which are elaborated principles of individualizing doses of medicines, our knowledge of relationship between functional status of the patient in terms of absorption, distribution, metabolism and elimination is for majority of drugs surprisingly limited. Only a handful of drugs, mostly with narrow therapeutic window, which are object of therapeutic monitoring (i.e., measurement of serum concentrations) have validated pharmacokinetic calculators. There is a need for very busy clinicians to learn how to individualize doses of limited number of medicines they use almost every day in the frame of their own specialties; however, a prerequisite for that is familiarity with principles of individualizing doses of drugs in the most common clinical states which affect their pharmacokinetics.

HOW DO WE KNOW IF THE DOSE NEEDS TO BE ADJUSTED AND HOW MUCH?

Although there are many sophisticated pharmacokinetic methods and ready-made calculators for dose adjustment of a number of drugs, the simplest one is based on target average steady-state plasma concentration of a drug and non-compartmental pharmacokinetic model. The steady-state of certain drug in pharmacokinetic sense is achieved usually after 4-5 dose intervals, when amount of the drug eliminated during the dose interval equals its maintenance dose. During the steady-state fluctuations of the drug plasma concentration are at their minimum for that drug, which is what we want to achieve, since the drug effects also will not fluctuate much in such situation (there is correlation between plasma concentration of a drug and its effect). Since from previous studies we know what is on average optimal target plasma concentration of the drug that will produce wanted effect, we should adjust the drug dose with an aim to reach that target concentration during the steady-state. With non-compartmental pharmacokinetic model we neglect complex equilibria between numerous body compartments and look to the human body as a whole, simplifying mathematical relations between key parameters that describe absorption, distribution and elimination of a drug. Therefore, the dosage regimen could be easily calculated using the equation that relates dose to steady-state target concentration, total drug clearance, volume of distribution and bioavailability :

$$MD = \frac{(C_{ss} \times CL \times \tau)}{F} = \frac{(C_{ss} \times k_e \times V_d \times \tau)}{F}$$

where MD is maintenance dose, Css is the steady-state plasma drug concentration, CL is total drug clearance, τ is dosing interval, ke is the elimination rate constant, and Vd is the volume of distribution. Calculation of loading dose should be made according to the formula:

$$LD = \frac{(C_{ss} \times V_d)}{F}$$

Recommended MD and LD for a drug we can find in its official Summary of product characteristics (SmPC) or prescribing information, so what to do in situations when dosage adjustment is necessary?

Since Css and τ we could consider as fixed parameters (Css is drug concentration in plasma within the therapeutic range that was proved in previous studies as effective, so we do not want to change it, while τ should be fixed in order to enable univariate adjustment of drug dose), MD we could adjust based on expected changes of CL and F, and LD should be adjusted based on changes of Vd and F. Therefore, relative increase or decrease of CL, Vd and F in regard to normal values in healthy persons will cause relative (percentual)

increase or decrease of MD and LD in regard to recommended doses in the SmPC.

Although a myriad of factors can affect a drug's CL, Vd and F, what matters are the most frequent conditions with clinically significant influence on these parameters. In the following table some of the important conditions and quantification of their influence on CL, Vd and F of drugs in general are shown, based on literature review.

Table. The influence of various pathological conditions on the pharmacokinetic parameters of drugs.

Condition of the patient	**Total drug clearance change (CL)**	**Volume of distribution (V) change**	**Oral bioavailability (F) change**	**Approximate correction of formulas for maintenance and loading dose that should keep steady-state plasma concentration within the therapeutic range**
Acutely decompensated or severe chronic heart failure	Decreased if either renal or hepatic drug clearance is flow-dependent (i.e., intrinsic clearance is not capacity-limited)	Increased due to edema if Vd<20L in healthy persons	Probably decreased only in BCS (8) Class 4 drugs (low water soluble and low permeable drugs)	- Percentage of CL decrease equal to percentage of EF decrease. - Vd increased for absolute increase in body weight, approximating kilograms to liters - No firm recommendation for changing F
Hepatic failure (Child-Pugh B or C)	Decreased of drugs with moderate (0.3 – 0.7) to high (>0.7) hepatic extraction ratio, and with low (<0.3) extraction ratio if also moderately or low	Increased in highly protein-bound drugs (fu<0.1) and in water-soluble drugs	Increased if moderate (0.3 – 0.7) to high (>0.7) hepatic extraction ratio	- F approximately doubled - Vd increased for ascites volume in hydrosoluble drugs - No firm recommendations for extent of CL decrease or Vd increase in

	protein bound (fu>0.1)			higly protein bound drugs
Renal failure (stages 3-5, i.e. creatinine clearance < 60 ml/min)	- Decreased renal clearance proportionally to decreased creatinine clearance - Decreased non-renal clearance	Increased for water-soluble drugs with low to moderate Vd (<0.7 L/kg) and in highly albumin bound drugs	Decreased bioavailability	- Decrease renal drug clearance for the same percent for which creatinine clearance is decreased
Hypoalbuminemia	- Increase of total drug clearance of highly albumin-bound drugs	- Increase of Vd of highly albumin-bound drugs	- No change	- CL and Vd almost doubled
Sepsis	- Increase in CL of renally eliminated hydrophyllic drugs, if renal function is not compromised	- Increase of Vd of hydrophyllic drugs	- no reports with clear findings	- increase Vd and CL for about 50% each, if renal function is not compromised

EF – ejection fraction (normal values 74 +/- 9% for women and 63 +/- 7% for men) (14); CL – total drug clearance; BCS - Biopharmaceutics Classification System, which divides drugs to 4 classes (1 – high water solubility and high permeability; 2 - low water solubility and high permeability; 3 - high water solubility and low permeability; 4 - low water solubility and low permeability); fu – fraction of unbound drug in plasma; Vd – volume of distribution.

Therefore, as an example, if a hypothetical drug X, BCS class 2, which is liposoluble, 80% bioavailable after oral administration, with volume of distribution about 100L, highly bound to plasma proteins (>90%) and with high liver extraction ratio (0.8), should be given orally to a male patient with decompensated severe heart failure (EF = 38%), having also hypoalbuminemia (20 g/L) and chronic renal failure (creatinine clearance 45 ml/min), we should adjust the drug dose through the following steps:

1. First we need to quantify effects of the conditions on CL, Vd and F (see Equation 1); from the Table 1 we can see that due to heart failure CL of the drug is decreased according to the following equation::

$$Percent\ decrease\ of\ CL\ =\ 100\% - \frac{EF\ in\ the\ patient}{Average\ EF\ in\ healthy\ person}$$

by about 100% - 38%/63% = 100% - 60% = 40%, and further decrease of non-renal clearance could be expected due to renal failure, but the extent remains unknown. On the other hand, hypoalbuminemia will increase CL (almost double it), so we may suppose that this increase will offset the decrease due to heart and kidney failure. Certain decrease of F could be expected due to renal failure (but we do not know the extent), while Vd should be doubled due to hypoalbuminemia and renal failure.

2. Second, we should estimate effect of changes in CL, Vd and F on MD. The MD is affected only by CL and F (see Equation 1); since CL probably will not change overall, and F will decrease, we should increase the MD, but how much? Since the extent of decrease of bioavailability is unknown, let us be conservative and suppose reduction of only 10%: in the denominator of the MD equation now will be 0.9 x F instead of F, which means that MD should be increased by 11% (10/9 = 1.11 = 1 + 0.11).

3. Third, we should estimate effect of changes in CL, Vd and F on LD. The LD is affected only by Vd and F (see Equation 2); since Vd is doubled, we can say that it is increased by 100%, but there is also decrease of bioavailability by 10%. Therefore in the LD equation we should multiply the numerator with 2 and denominator with 0.9, which means that the LD should be increased by 122% (2 x 10/9 = 2 x 1.11 = 2.22 = 1 + 1.22).

As one can see from this example, a drug dose individualization will depend both on characteristics of the drug and conditions of the patient; although full precision could not be reached, even rough dose adjustments according to the abovementioned principles may help with achieving target steady-state plasma concentrations, and therefore wanted effect on tissues.

THERAPEUTIC MONITORING OF DRUGS

Therapeutic drug monitoring is the process of measuring drug concentrations in the patient's blood, and based on the measured concentrations, adjusting the dose of those drugs in order to achieve the optimal therapeutic effect and reduce the possibility of toxicity. Therefore, it is an auxiliary procedure by which we can achieve the optimal dosage of a drug, without waiting for it to be shown that the dose was not sufficient because it did not cause the expected effect, or that it was too large because it caused toxic effects .

Therapeutic monitoring is not carried out for all drugs, but only for those that meet the following conditions:

1. there is a correlation between the concentration of the drug in the blood and the effect;
2. the therapeutic effect of the drug is not easily measurable;
3. the drug has a narrow therapeutic range (i.e., the difference between the minimum therapeutic and the minimum toxic dose is small);
4. there is great variability between individual patients in terms of drug concentrations achieved in the blood after administration of the same dose;
5. the ratio of the concentration of the drug in the blood during the day and the minimum concentration that has a therapeutic effect is necessary to know in order to predict whether the therapy will be successful in life-threatening situations, e.g., when antibiotics are used to treat sepsis; and
6. there is a methodology available to measure drug concentration in the blood.

For example, we do not conduct therapeutic monitoring with antihypertensives, although there is a correlation between the concentration of the drug in the blood and the effect; the reason for this is simple: antihypertensives have an easily measurable effect (arterial blood pressure), so we do not need to measure their concentration in the blood. We do not carry out therapeutic monitoring for vitamins either, because due to the large therapeutic range, it does not matter if the concentration in the blood is higher or lower, as long as it is in a very wide therapeutic range.

Medicines that meet all the above conditions, and for which **it is mandatory to carry out** therapeutic monitoring, are: antiepileptic drugs, antidepressants, immunosuppressants (cyclosporine, tacrolimus), antibiotics with a narrow therapeutic range (aminoglycosides, vancomycin), reserve antibiotics used in hospitals for the treatment of severe systemic bacterial infections (meropenem, imipenem, piperacillin with tazobactam), cefepime, ceftazidime, etc.) theophylline, cardiotonics, new oral anticoagulants (rivaroxaban , apixaban , dabigatran) and some antiarrhythmics .

Drug concentrations are most often measured in the patient's serum, although it is also possible to measure them in plasma. Although the total concentration of the drug in the serum is usually measured, whenever possible both the total concentration and the concentration of the free drug, which is not bound to plasma proteins, should be measured. The free drug is actually the active part of the drug in the serum, which can diffuse into the tissues and act on the receptors, so the concentration of the free drug is actually in the best correlation with the therapeutic effect. From the patient, up to 5 milliliters of blood is taken from the cubital vein, which is left in an ordinary test tube for spontaneous coagulation, and then the serum is separated by centrifugation.

When do we take a blood sample from a patient for therapeutic monitoring? The basic condition is that the patient must be in a state of equilibrium, because then the concentration of the drug in the blood is relatively stable. This practically means that we can take a blood sample for therapeutic monitoring only after a time that is five times longer than the half-life of the drug being measured has passed. For example, if the half-life of valproic acid is at most 20 hours, we must wait until 5 x 20 hours = 100 hours have passed since the patient started taking the drug, before taking a blood sample. Within the dose interval, a blood sample can be taken at any time, but it is recommended that it should be taken immediately **before the next dose** of the drug.

It should be remembered that any change in the dosage of the drug disturbs the equilibrium state, and that it is necessary to pass **another** five half-lives to establish **a new** equilibrium state. Therefore, if the patient forgets to take a dose of the drug, or if the doctor raises or lowers the dose, the balance is disrupted, and a new one needs to be established before we can take a blood sample from the patient to measure the concentration of the drug.

The drug concentration in the patient's serum can be measured using three types of methods. **The first type are immunological methods**, which are based on measuring the reaction of a drug with an antibody specially prepared to bind to that drug. The antibody is labeled in some way (e.g., with a fluorescent dye, so these are immunofluorescence methods, or with a radioactive element, so these are radioimmunological methods), so that the binding of the drug to the antibody creates a certain signal that can be detected; the more drug there is in the serum, the more drug-antibody complexes will be created, so the signal will be stronger. Immunological methods are relatively easy to perform, because no special preparation of the patient's serum sample is required. It is enough to just mix a drop of the patient's serum with the reagent, and the result can already be read. The downside of immunological methods is that they measure only the drug and not its metabolites; to measure each of the metabolites of a drug, it would be necessary to carry out a special procedure, with the use of special reagents, which is rarely available to doctors.

The second type are chromatographic methods, which are based on the fact that substances of different molecular weight and charge diffuse at different speeds through some inert substrate. A drop of a previously treated sample of the patient's serum is placed at one end of a tube containing a specific inert gel (these tubes are called columns), and at the other end, the so-called “detector” registers the appearance of each substance from the serum sample. For the entire time of measurement, some inert substance, which we call "carrier", also flows through the column, because it facilitates the movement of the drugs that we want to measure through the column. Medicines with lower molecular weight and lower charge will move faster through the column, so we will register them earlier than drugs with higher molecular weight and higher charge. If in the previous procedure we determine after how long the standard of the drug we are measuring can be detected, during the actual measurement we can be sure that the substance that appeared at the end of the column after the same period of time as the standard represents the drug we want to measure. If

there is more of the drug in the serum (i.e., if its concentration is higher), the signal obtained during detection will be stronger. Depending on whether the "carrier" is liquid or gas, chromatography is divided into liquid and gas. Thanks to technological innovations, liquid chromatography today has a high efficiency in measurement, so it is called " high-performance liquid chromatography " (HPLC). The advantages of chromatographic methods are high precision and the possibility of measuring both the drug and its metabolites at the same time. The disadvantages are the complicated preparation of the serum sample (which requires a specially trained person) and the relatively high cost of the measurement.

In the last decade, great progress was made in chromatographic methods with the introduction of liquid chromatography with double mass detection (**LC-MS/MS**). This type of chromatography does not require extensive preparation of the serum sample, and it can simultaneously measure a large number of drugs and metabolites in the sample, without using special standards, but only by comparing the spectra obtained by mass detection with the content of huge databases of spectra obtained by earlier measurements. In mass detectors, the drug molecule is broken into several fragments, which then deviate at different speeds in the magnetic field, depending on their mass, creating a characteristic spectrum for each measured drug. It is expected that in the future this method will be further improved and simplified for routine application in clinical practice, which actually means that therapeutic monitoring will be used significantly more often and for a much larger number of drugs.

The third type are biological methods, in which the effect of the drug on microorganisms is used as a signal for measurement. They are primarily used to measure the concentration of antibiotics. Using the fact that a precisely defined concentration of the antibiotic standard leads to a precisely measurable degree of inhibition of the growth of microorganisms, by comparing the degree of inhibition caused by the patient's serum sample with the degree of inhibition caused by the standard, we can estimate with great certainty the concentration of antibiotics in the patient's serum.

The advantages of biological methods are the simplicity of execution and low cost of measurements, while the disadvantages are insufficient precision and the impossibility of application when it is necessary to measure the concentrations of two or more antibiotics that the patient receives at the same time.

Whichever measurement method we use, we apply the obtained results in practice in the same way. We look at a few elements: the effect of the drug on the patient, whether the concentration is in the therapeutic range (if it is known), whether the ratio of the measured concentrations of the drug in the dose interval and the minimum effective concentration (according to the literature) of the drug is large enough to guarantee the achievement of a therapeutic response, and whether the drug concentration is below or above the minimum toxic concentration. If the drug has a satisfactory effect, the concentration of the drug is in the therapeutic range or the ratio between the measured concentrations and the minimum effective concentration is favorable, we do not change the dosage

regimen; if the concentration of the drug is above the minimum toxic concentration, we reduce the dose of the drug, and if the concentration of the drug is below the therapeutic range, we increase the dose of the drug. From the moment when we change the dose of the drug, we wait for more than 5 half-lives of the drug to pass, then we repeat the measurement of the concentration of the drug for additional dose adjustment. The individualization of drug dose regimen is guided by what we see in the following picture:

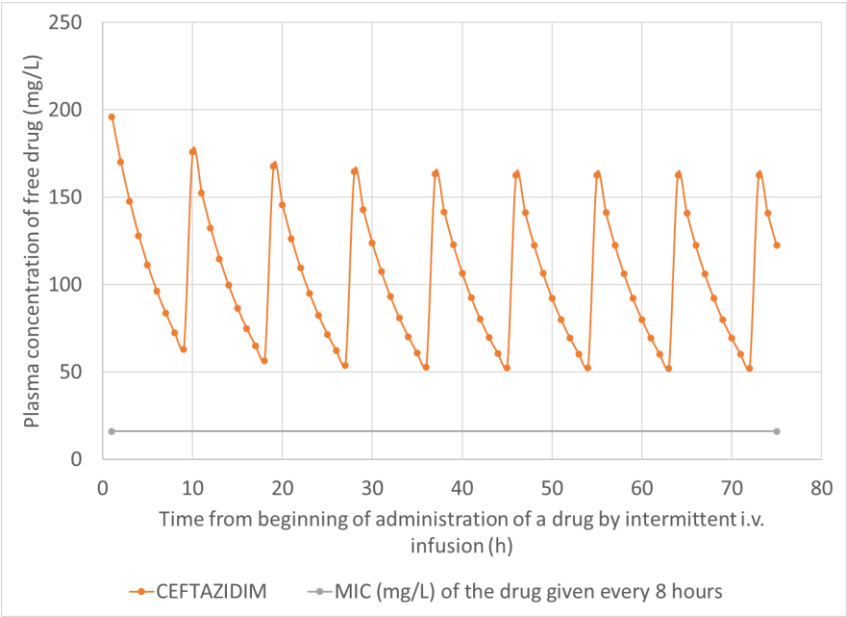


Figure. The concentration of free ceftazidime in the blood plasma of a patient who receives 1 gram of this drug every 8 hours, in the form of an intermittent infusion. The patient is in a state of equilibrium. The horizontal line on the graph represents the minimum inhibitory concentration of ceftazidime, i.e., the minimum concentration that still has a therapeutic effect. As the measured concentrations of ceftazidime are significantly above the minimum inhibitory concentration in the entire dose interval, it can be expected that the antibiotic will exert its full therapeutic effect, and the dose adjustment is not necessary.

It should not be forgotten that drugs can cause unwanted effects when their serum concentration is in the desired therapeutic range. These are usually side effects of type B and C, which are not related to the basic mechanism of action of the drug. Adverse effects should be clearly distinguished from toxic effects, which occur when drugs are administered in doses higher than recommended, or when drug concentrations in serum (or plasma) rise above the minimum toxic concentration, for example due to impaired elimination of the drug in patients with kidney failure.

GENETIC VARIATIONS AND MEDICINES

During evolution, spontaneous mutations of many genes occur, including those encoding enzymes or functional proteins important for the action or metabolism of drugs. Since mutated genes are inherited, people with mutations of certain genes that they carry in their genome appear over time in different ethnic groups. The result of a gene mutation can be the coding of a protein that has a reduced or increased function compared to the protein coded by the non-mutated gene in the rest of the population. This practically means that people with gene mutations that lead to reduced function of a protein through which the drug's effect takes place (e.g., receptor) will have a weaker clinical response to that drug. Conversely, mutations that lead to increased function of a protein will lead to increased sensitivity to that drug in the person carrying the mutation. If it concerns genes that affect enzymes that metabolize drugs (e.g., cytochromes), reduced or increased activity of such enzymes as a result of gene mutation will result in slowed or accelerated metabolism and elimination of the drug. It would be useful to know if our patient has any gene mutation relevant to the effect of the drug we want to prescribe, because then we could immediately adjust the dose of the drug (increase or decrease it) at the beginning of therapy, or perhaps choose another drug. For now, tests that provide such information are available only for some drugs, but thanks to the rapid development of technology, the day is approaching when we will have such information available for most drugs that are in widespread use.

There is also a mathematical rule that describes the frequency of a certain mutation in the population, known as **the Hardy- Weinberg law**. If we have only two possible alleles in the population ("normal" allele and mutated allele), and if we denote the probability of the appearance of the "normal" allele by "p" and the mutated one by "q" (where $p + q = 1$) , then the following formula applies: $p^2 + 2pq + q^2 = 1$. We can calculate the probability from this formula of persons homozygous for the "normal" allele (p^2), the probability of heterozygote (2pq) and probability of homozygous for the mutated allele (q^2). The frequency of such homozygotes and heterozygotes in a certain population is obtained when we multiply the calculated probabilities by the total number of members of that population.

GENETIC POLYMORPHISM AND DRUG METABOLISM

Drug metabolism depends on the amount of active enzyme in human tissues, primarily in the liver. Due to constant changes in genetic material, there are usually differences in the amount and activity of drug-metabolizing enzymes in the human population. Thus, one can find people who are quickly metabolizing a drug, but also people who metabolize it slowly (because the enzyme responsible for metabolism is less active due to a change in the gene that codes for it). In fact, individual differences in drug metabolism are very common,

but only a small percentage of these differences have clinical significance, i.e., can affect the concentration of the drug in the blood to such an extent that it is necessary to correct the dose of the drug, i.e., decrease it or increase it. The following are examples of clinically significant and genetically determined differences in the drug metabolism that require correction of the dose.

Succinylcholine - a number of people have a genetically determined defect in the structure of pseudocholinesterase, so they metabolize succinylcholine much slower. In such persons, the recovery from succinylcholine-induced neuromuscular paralysis is considerably delayed.

About 50% of the population has genetically determined slow **acetylation** of drugs. In such persons, it is necessary to reduce the dose of isoniazid and ensure sufficient application of vitamin B_6 . If the dose is not reduced, isoniazid will cause peripheral neuropathy. In addition to isoniazid, vasodilator hydralazine and antiarrhythmic procainamide are metabolized by acetylation; in people who are slow acetylators, their effect after usual doses can be significantly higher than in "normal" people, and the risk of drug-induced lupus is increased, too. If we determine by testing that a person has slow acetylation, the doses of hydralazine and procainamide should be reduced, which will avoid an overemphasized therapeutic effect and the appearance of an unwanted effect (lupus).

Gene for isoform of cytochrome **CYP2D6** is located on chromosome 22 in humans. About 3-10% of people inherited (in autosomal recessive manner) some defective allele for the isoform of cytochrome CYP2D6 (there are more mutants in Europeans). With alleles that lead to reduced activity of this enzyme (CYP 2D6*3, CYP 2D6 *4 and CYP 2D6*5), the metabolism of many drugs is weakened (beta blockers [metoprolol, propranolol, timolol], antidepressants - [clomipramine, fluoxetine, fluvoxamine, imipramine, amitriptyline, desipramine, mianserin, nortriptyline, paroxetine] , antipsychotics [clozapine, risperidone, haloperidol, thioridazine, aripiprazole], antiarrhythmics [encainide, flecainide, mexiletine, propafenone] , selegiline, codeine, tramadol, dextromethorphan, debrisoquin, etc.). In such persons, very high concentrations of these drugs in the blood can be expected, due to slow elimination. In order to avoid the occurrence of toxic reactions, people with mutations in the gene encoding CYP2D6 (and therefore with reduced CYP2D6 function) should reduce the doses of these drugs. On the other hand, in some Europeans, and even a third of Ethiopians and Saudi Arabians, the gene for CYP2D6 is present in as many as 13 copies, so they metabolize certain drugs 2-3 times faster than other people (e.g.. they should be given 2-3 times the higher dose of nortriptyline to achieve a therapeutic effect). People with increased cytochrome 2D6 activity must also use opioids tramadol and codeine with caution; the active metabolites of these drugs are created much faster and in larger quantities, so unwanted effects can occur, primarily respiratory depression.

Isoform of cytochrome **CYP2C9** may also have reduced activity in some people, due to genetically determined changes in the composition of amino acids. In these people, the metabolism of drugs, which normally takes place through this isoform (ibuprofen, flurbiprofen, phenytoin, tolbutamide, meloxicam,

piroxicam, erdafitinib, varfarin) is slowed. Clinically, the slow metabolism of warfarin is particularly significant, so people with a mutation of the gene for CYP2C9, which leads to the synthesis of a less active enzyme, require a significant reduction in the dose of this drug; otherwise, bleeding occurs. The mutation of another gene is also important for the effect of warfarin: it is the gene for the enzyme "vitamin K epoxide reductase subunit complex 1" (**VKORC1**) , which reduces vitamin K and turns it into its active form. In the case of a mutation that disrupts this gene, thereby reducing the function of VKORC1, the dose of warfarin must also be reduced, otherwise bleeding will occur.

Mutations in the gene for **cytochrome 2C19** can also lead to reduced activity of that cytochrome, and thus to a slower metabolism of some drugs, so it is necessary to reduce their doses so that they do not accumulate in the body. Medicines whose doses need to be reduced if there is a cytochrome 2C19 gene mutation are antiepileptics brivaracetam and clobazam, an antidepressant citalopram, and the proton pump blocker pantoprazole. On the other hand, for the normal activity of clopidogrel, it is necessary for it to be converted into an active metabolite by cytochrome 2C19 ; when a person has a mutation in the gene for this cytochrome, which then codes for a defective cytochrome 2C19, clopidogrel will not be converted into an active metabolite sufficiently, so that its effect is lost.

Cytoplasmic enzyme found in almost all cells of the human body, **thiopurine S-methyltransferase**, is of special clinical importance. This enzyme performs methylation of mercaptopurine, a drug derived from the pro - drug azathioprin, a widely used immunosuppressant. Thanks to the methylation, mercaptopurine normally loses its toxicity and is eliminated from the body. However, one in 300 Europeans is homozygous for mutated alleles of this gene that encode an inactive enzyme (the most common mutated allele is designated as TPMT*3A), and about 11% are heterozygotes, in which enzyme activity is weakened. In these patients (homozygotes are the most at risk), the use of azathioprine in usual doses leads to the accumulation of mercaptopurine and severe damage to the bone marrow; therefore, it is necessary to apply a far smaller dose than usual. Today, there is a commercially available test that can be used to check whether a patient is a carrier of mutated alleles, ie. whether it is necessary to correct the dose of azathioprine, or not.

Cytostatic agents 5-fluorouracil and its precursor capecitabine are metabolized by the enzyme **dihydropyrimidine dehydrogenase**; when the gene encoding this enzyme is mutated (on one or both alleles), the activity of the enzyme is reduced, so 5-fluorouracil and capecitabine accumulate in the body and damage the bone marrow. In people who have a mutation in the dihydropyrimidine gene dehydrogenase, the use of 5-fluorouracil and capecitabine is contraindicated.

Cytostatic **irinotecan** (used for the treatment of large bowel tumors, small cells lung tumors and some other solid tumors) is converted into an active metabolite SN-38 in the body, which inhibits topoisomerase 1. If the enzyme **uridine-diphosphate glucuronosyl transferase 1A1 (UGT1A1)** which

performs conjugation of SN-38 (thus enabling its elimination) is with reduced activity due to the mutation of the gene that encodes it (the UGT1A1*28 mutation), the active metabolite accumulates and causes damage to the bone marrow (severe neutropenia). In patients who have such a mutation, it is necessary to significantly reduce the dose of irinotecan .

Sometimes the mutation of genes encoding membrane transporters is important for the application of drugs. In people with a mutation in **the SLCO1B1 gene**, which reduces the activity of organic anion transport polypeptide 1B1 on the hepatocyte membrane (OATP1B1), less simvastatin can enter the hepatocytes than usual. Due to such a disorder, simvastatin accumulates in the blood and striated muscles, often causing myopathy and even rhabdomyolysis. Although other statins use the same transporter, people with this SLCO1B1 gene mutation have the highest risk of myopathy if they use simvastatin; the risk is the lowest if rosuvastatin or pravastatin are used in therapy.

GENETIC POLYMORPHISM IN THE EFFECT OF MEDICINES

Mutations that lead to the creation of inactive or hyperactive functional proteins through which the action of the drug takes place are also common, but to date only some have proven clinical significance. Thus, it is known that mutations that lead to the change of amino acids at positions 16, 27 and 164 **of the beta 2 receptor** lead to increased acute reactivity of this receptor to beta agonists, as well as a tendency towards its rapid desensitization. People who have one of these mutations will respond well acutely to beta agonists in an asthmatic attack, but this reaction will be short-lived.

Another, this time positive, example where mutations lead to changes in effector proteins is **the epidermal growth factor receptor (EGFR)**. It was noted that a small number of patients with non-microcellular lung cancer responds well to a tyrosine kinase inhibitor gefitinib. The reason for this is most likely a change in the intracellular part of this receptor, so that **gefitinib** binds to it more easily and blocks it more successfully.

In about 20% of patients with breast cancer, **the epidermal growth factor receptor 2 (HER2)** is expressed (i.e., present on the membrane of tumor cells) to a greater extent than usual. In such persons, monotherapy with **trastuzumab**, a blocker of HER2 receptor, is not effective enough in the treatment of tumors, so trastuzimab must be combined with chemotherapy or other blockers are used instead, which can overcome the increased number of HER2 receptors (e.g., pertuzumab or trastuzumab-emtansine).

In order to use the drug **cetuximab**, it is first necessary to prove by pharmacogenetic testing that the epidermal growth factor receptor **(EGFR) is present in a sufficient amount on the tumor cells**, i.e, that there are no gene mutations for this receptor in tumor cells that prevent its synthesis or make

it inactive. Cetuximab normally binds to EGFR, blocks that receptor, and thus prevents the growth of colon cancer and squamous cell tumors of head and neck.

Dasatinib is an inhibitor of kinases (enzymes that phosphorylate proteins) that participate in the control of tumor cell growth, the most important of which are **the BCR-ABL kinase**, then the SRC family of kinases, c-KIT kinase, ephrin (EPH) receptor kinase , and platelet growth factor receptor kinase (PDGFβ). Before starting the treatment of chronic myeloid leukemia or acute lymphoblastic leukemia with dasatinib, it is necessary to prove that the malignant cells contain the abnormal BCR-ABL1 gene, which arises within the abnormal Philadelphia chromosome (translocation 9;22) and encodes the synthesis of BCR-ABL kinase.

Pharmacogenetic testing is also recommended for people who need to start carbamazepine therapy and are of Asian origin. If a person from Asia has a mutated allele **HLA-B*1502, he or she is at an increased risk of** experiencing Stevens-Johnson syndrome during carbamazepine therapy, so it is best not to take that drug at all.

From numerous studies in the field of pharmacogenetics that are ongoing, new discoveries of clinically significant mutations of genes encoding effector proteins are expected.

TYPES OF PHARMACOECONOMIC STUDIES

Pharmacoeconomics is the science that studies how people and society decide to use limited resources (which could have been used for something else) to purchase drugs and medical devices and how they are distributed among - people and social groups in order to gain maximum in quantity and quality of life. Therefore, the funds allocated for health care are limited in every society; pharmacoeconomics helps us to choose the best drugs and medical devices that achieve the greatest possible effect at the lowest price. The focus of pharmacoeconomics is determining the ratio of treatment effects to costs for each drug that could be used in a society, and then financing those drugs for which this ratio is beneficial, i.e, cost-effective. In order to determine the exact ratio of costs and effects, we use several types of studies in pharmacoeconomics.

Cost minimization analysis (CMA) is the simplest type of pharmacoeconomic studies. It is used when the outcome of two alternative therapies for the SAME disease is exactly the SAME, so their prices are the only what should be compared. For example, we know from numerous clinical studies that ibuprofen and diclofenac have exactly the SAME effect on the treatment of tension headache (SAME disease). To find out which is more cost-effective, we only need to compare the average costs incurred when using ibuprofen and diclofenac for the treatment of headaches per patient; the drug whose costs are lower will be more cost-effective.

Analysis of the relationship between costs and clinical effect (Cost/Effectiveness Analysis - CEA) is applied in situations when the

outcome of two alternative treatments is measured with the SAME "natural" UNITS (e.g., the number of prevented strokes), and costs are measured in money. For example, let's say that antiplatelet drug A, when used for 5 years, prevents the occurrence of ischemic stroke in 70% of patients who take it, and that antiplatelet drug B, after administration for the same period of time, prevents the occurrence of ischemic stroke in 80% of patients. Let the price of five-year therapy per patient for drug A is 10,000 dinars, and for drug B 100,000 dinars. What is the cost per stroke averted for both drugs? If 100 patients take drug A, therapy for all of them costs 100 x 10,000 = 1,000,000 dinars; since a stroke was prevented in 70 patients out of 100, per stroke prevented the administration of drug A costs: 1,000,000 dinars / 70 strokes prevented = 14,285.71 dinars. If 100 patients take drug B, therapy for all of them costs 100 x 100,000 = 10,000,000 dinars; since a stroke was prevented in 80 patients out of 100, per stroke prevented the administration of drug B costs: 10,000,000 dinars / 80 strokes prevented = 125,000 dinars. Therefore, drug A is more cost-effective, because the costs per stroke prevented are many times lower than when using drug B. However, drug B is still more effective than drug A: for every 100 patients, 10 more strokes will be prevented with drug B than with drug A. Is it justified to pay more because of this difference in efficiency?

The answer to the previous question can be given by the so-called **incremental cost-effectiveness ratio (ICER)**, i.e., a value that tells us how much money we have to pay to prevent one more stroke with drug B. The incremental cost-effectiveness ratio is calculated as the quotient of the difference in costs and the difference in the effects of the two drugs ([T1 – T2] / [E1 – E2]). In our example, it would be: (10,000,000 – 1,000,000) / (80 – 70) = 9,000,000 / 10 = 900,000 dinars. Therefore, in order to avoid one stroke more with drug B, we need to pay about 900,000 dinars. Is it a lot or a little? Is it justified to pay more in this situation? The answer to this question gives us the preventable outcome; if we know that treating a person with a stroke cost far more than 900,000 dinars (taking into account all costs: hospital treatment, home treatment, care, rehabilitation, loss of work ability, etc.), then it is justified to pay more and finance drug B.

Cost / Utility Analysis (CUA) compares the quality of life provided by two different treatments (often for different diseases), with their costs expressed in money. With the help of more or less well-designed questionnaires, it is possible to obtain from the patient her/his assessment of the quality of her/his own life, and to quantify this assessment on a scale from 0 to 1 (where 0 is loss of life, and 1 is maximum, i.e., full quality of life). If we now put the quality of life in the context of the duration of life, we get a useful unit for quantitatively comparing the cost-effectiveness of drugs from different groups. For example, if the quality of life assessed by the patient as 0.6 (or 60%) is multiplied by 4 years (how long that patient lived after treatment), we will get 0.6 x 4 = 2.4 years of life with full quality. This means that the effect of the treatment under investigation is 100% quality of life for 2.4 years, or using the terminology of pharmacoeconomics, 2.4 quality-adjusted life years (2.4 QALY). QALY = Quality Adjusted Life Years = Years of life adjusted for quality.

Cost-utility, i.e., the pharmacoeconomic justification of drugs can now be compared through treatment costs per quality-adjusted life year. For example, if drug A leads to 3 QALYs, with costs of 6,000 dinars, and drug B leads to 2 QALYs, with costs of 4,000 dinars, it can be concluded that both drugs are equally cost-effective, because the treatment in both cases costs RSD 2,000 per 1 QALY (6,000 dinars / 3 QALY = 4,000 dinars / 2 QALY).

Cost-Benefit Analysis (CBA) compares the effects of two different treatments expressed in financial gains with the costs of those treatments, also expressed in money. Therefore, there is money both in the denominator and in the numerator. For example, if drug A brings 5,000,000 dinars per cured patient (because the patient will be able to live and work independently for the next 5 years), and drug B brings 10,000,000 dinars (because the patient will be able to live and work independently for the next 10 years), this can be compared to the costs: let's say that the cost of applying drug A per cured patient is 1,000,000 dinars, and drug B is 4,000,000 dinars. Therefore, the cost/benefit ratio for drug A is 5,000,000 / 1,000,000 = 5 dinars of benefit for every dinar invested, and for drug B 10,000,000 / 4,000,000 = 2.5 dinars of benefit for every dinar invested. It is clear that drug A is more cost/beneficial. The problem with this type of analysis lies in the fact that it is very difficult to accurately estimate the profit that is achieved by curing, because we come to the key question : how much money is a human life worth? Since no one has answered that question with certainty to date, cost/benefit analyzes are rarely done.

All the mentioned types of pharmacoeconomic studies can be carried out on real patients, through the monitoring of treatment outcomes and incurred costs, provided that the drugs under investigation have already received marketing authorization. Then we actually conduct observational studies of the type of case series, cross-sectional studies, cohort studies or case-control studies; we collect data from patients' medical records, retrospectively or prospectively. However, if the drug we are interested in has not yet received marketing authorization, this approach to research is not possible, because neither the costs nor the results of the treatment have yet occurred. In such a case, we conduct pharmacoeconomic studies by creating **mathematical models** that actually predict what will happen in the future, when the drug receives marketing authorization, using the previous knowledge we have about the effects and possible costs. Mathematical models, which we call pharmacoeconomic models, actually describe the course of the disease, accounting for the acquired time of the patient in full health and the costs incurred during therapy.

TYPES OF COSTS IN PHARMACOECONOMICS

Before listing the types of costs that we consider in pharmacoeconomics, we need to define the term cost. **Cost** includes the total value of all resources used in the production of a good or service . Cost is not the same as the price of a good or service. **The price** is the sum of cost and profit. As an example, we can take the service of intravenous administration of the antibiotic ceftriaxone. The

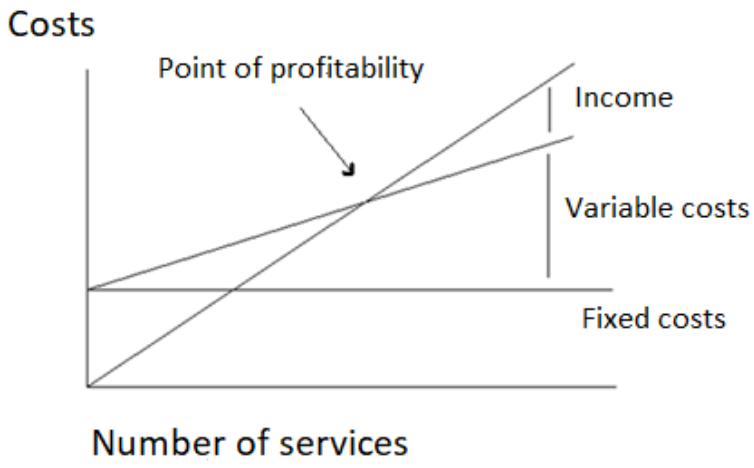
costs of this service include: the value of the lio bottle of ceftriaxone of 1 g the value of the work of the nurse who administers the intravenous injection , the value of the used syringe and two needles and the value of a piece of cotton wool and alcohol that is used to wipe the skin. Let's say **the costs** of intravenous administration of 1 g ceftriaxone is 400 dinars in total. If now the hospital where this intravenous injection is administered ***to these costs adds its profit***, i.e., earnings of 100 dinars, it will determine **the price** of the intravenous injection of 1 g ceftriaxone to be 500 dinars.

We can classify the costs into groups on several grounds. First, according to who pays the costs, we can classify them as direct, indirect and "intangible". **Direct costs** are those paid by the health insurance fund, and are divided into ***medical*** and ***non-medical***. Direct medical costs include the costs of drugs, medical interventions, medical services and hospitalizations. Direct non-medical costs refer to the costs of transporting patients to and from a health facility, the costs of salary compensation paid by the Health Insurance Fund for absence from work ("sickness") for more than 30 days, the costs of a patient's funeral, the costs of "other assistance" paid by the Fund to bed-ridden persons for a long period of time and the like. There are several ways health insurance funds calculate and pay costs. One way is the one currently used in Serbia, where the health insurance fund has its own tariff book for medical services, medicines and medical devices. So, the fund determined how much, say, a doctor's examination, administration of an intramuscular injection, appendectomy, drug simvastatin, artificial hip, etc., is worthy. When the health organization performs, for example today, five appendectomies and administers 10 intramuscular injections, it sends an invoice to the health insurance fund for the services rendered and the material used, on the basis of which the fund makes a payment, i.e., transfers the appropriate amount of money to the account of that health institution. The second method, which is increasingly used in our country, is the so-called DRG system (Diagnosis Related Groups system), where the fund recognizes the total cost for a specific diagnosis that is "treated" in a health facility. For example, the fund admits that the treatment of one patient with appendicitis, which includes diagnosis, preoperative preparation, appendectomy and post- operative treatment, is worth 20,000 dinars, and it will pay that much to the health institution for each such patient, regardless of whether the patient spent less or more medicines, whether he stayed longer or shorter in the hospital, etc. **Indirect costs** are those paid by the patient himself/herself or society (for example, loss of working days, loss of productivity, loss of earnings that the patient previously had, compensation of wages paid to the patient during absence from work due to illness in the first 30 days, transportation costs that the patient himself pays, the costs of adapting the infrastructure in the patient's home to the patient's needs, the costs of care that the patient pays to medical technicians, physiotherapists, etc.). Sometimes indirect costs are significantly higher than direct costs, and they should always be taken into account when making pharmacoeconomic analyses. **Intangible costs** consist of pain, fear, anxiety of the patient, other forms of suffering that the patient goes through, etc. This type of cost is extremely important, because

it disrupts the patient's normal life and his ability to work. However, to date, no reliable way to determine the exact value of these costs expressed in money has been established. How much is 6 hours of renal colic pain? And how many months of worry, nightmares because of suspected malignant disease? Because these questions are not yet answered, intangible costs are often overlooked in pharmacoeconomic studies.

Another classification of costs is carried out on the basis of their variability. **Fixed costs** are costs that do not change with changes in the nature of services or products in a shorter period of time (typically 1 year). This group of costs includes equipment maintenance costs, space rental costs, heating costs of the health facility, costs for the physical security of the health facility, electricity costs, salaries of health workers, and the like. **Variable costs** are costs that change with changes in the volume of services. For example, costs due to the use of medicines (the more patients there are, the more medicines will be consumed), medical equipment, food (the more patients there are, the more food will be consumed), water (the more patients there will be, the more water will be consumed), etc.

A special type of costs are opportunity **costs**, which arise due to the lost benefit if one therapy is chosen instead of another. For example, let's say that in the treatment of hypertension we have to choose between the use of beta-blockers and alpha- blockers. Both types of drugs are approximately similar in effectiveness in the treatment of hypertension, but alpha-blockers, in addition to their antihypertensive effect, can facilitate urination in prostate hypertrophy. If we choose a beta-blocker for our patient, we will lose the possibility to act on prostate hypertrophy, i.e., we will have to apply some additional medicine for that, which creates new costs. Therefore, to the costs of using beta- blockers, we should add the costs of treating prostate hypertrophy, due to the lost opportunity we had with alpha-blockers.



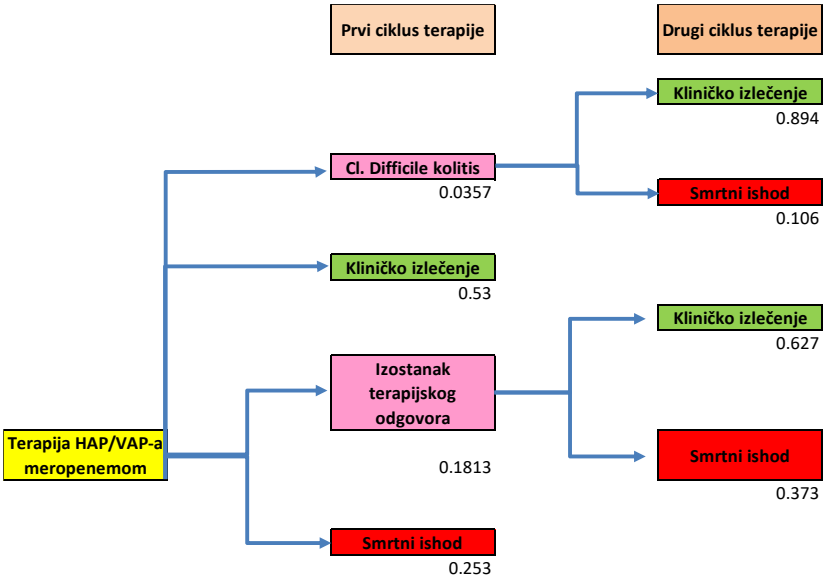
Finally, in pharmacoeconomics there is also the concept **of marginal - costs**. Break-even analysis is a technique used in microeconomics that studies how very small changes in individual variables (costs) affect other variables or the system as a whole. Marginal costs represent the change in total costs if one more or one less service is produced. The break-even point is the number of health services at which revenue covers all fixed and variable costs. If the number of services increases even by one, a profit appears (because marginal costs are lower than the increase in revenue), which increases with a further increase in the number of services. Conversely, reducing the number of services leads to unprofitability, i.e. revenues become less than expenses, that is, from the sum of variable and fixed costs (see figure). The goal in the management of health institutions is to achieve the number of services above the break-even point.

MODELING IN PHARMACOECONOMICS

As already mentioned, pharmacoeconomic models are created when the drug has not yet reached a market, so it is necessary to predict its effects and costs in regular clinical use. There are several types of pharmacoeconomic models, but four are most commonly used in practice: the decision tree, Markov model, partitioned survival model and the discrete event simulation model. Each of these models is used for a certain type of disease, because it can best describe it.

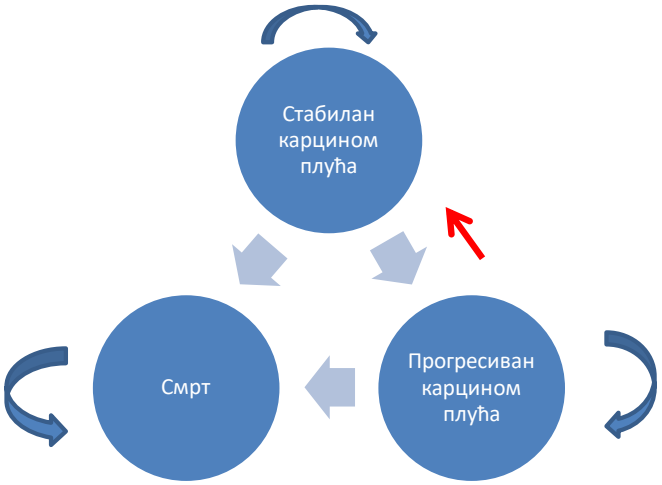
The "decision tree" type model is applied for drugs used in the treatment of acute diseases, the duration of which is limited, i.e., the final outcome occurs within a few months at most. For example, a "decision tree" type model is an appropriate choice for describing the treatment of acute infectious diseases, such as pneumonia, peritonitis, sepsis, etc. In this model, after the administration of a new drug, all possible outcomes (e.g., cure, death, recurrence of infection, adverse effect of the drug) are listed, and then the probability of each outcome is determined. Each outcome is then assigned a life expectancy adjusted for its quality and costs. Multiplying the probabilities of the outcome by the quality-adjusted life expectancy and cost-adjusted life expectancy, and then summing, yields the total quality-adjusted life expectancy and total cost per patient if the new drug of interest is used. The same can be calculated for the old drug, which has already been in use for a long time, and then the gains in life adjusted for quality and costs can be compared for the new and for the old drug, i.e., it can be assessed whether the new drug has a more favorable ratio of costs and effects from old or not.

Figure. Schematic representation of a decision tree model for the treatment of hospital-acquired pneumonia with meropenem. The numbers below the treatment outcomes represent the probabilities of those outcomes.



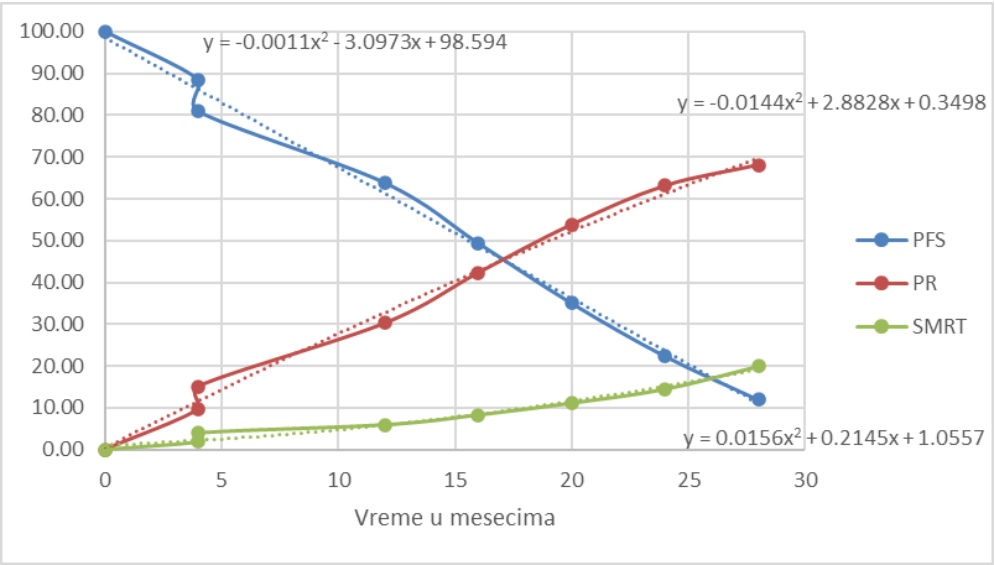
The Markov model is applied to drugs that are used to treat chronic diseases that last for years or decades, where the patient can be in different states, moving from one to another with variable dynamics. The duration of these states is predetermined, and is called a cycle. Since the total duration of the disease being modeled, which is called the time horizon, is defined, it is divided by the duration of one cycle, which gives the total number of observed cycles. Then, we first calculate the probabilities that the patient moves from one state to another (or stays in the same state) for each of the observed cycles, until the time horizon is over. These probabilities are called transition probabilities. Starting from the first cycle and using the transition probabilities, we calculate the probabilities that the patient will be in each of the states, in all cycles. If we now associate the quality of life and corresponding costs to each of the states in which the patient may find himself, using the previously calculated probabilities we can arrive at the total quality-adjusted life gained and the total costs per patient, both when the new drug is used and when the drug is used which is earlier on the market and is already financed by the Health Insurance Fund. By comparing the ratio of costs and effects with the new and old medicine, we come to the conclusion which of the two therapeutic alternatives is more cost/effective.

Figure. Markov model scheme for lung cancer. The arrows in the picture represent the possibilities of moving from one state to another, or staying in the same state.



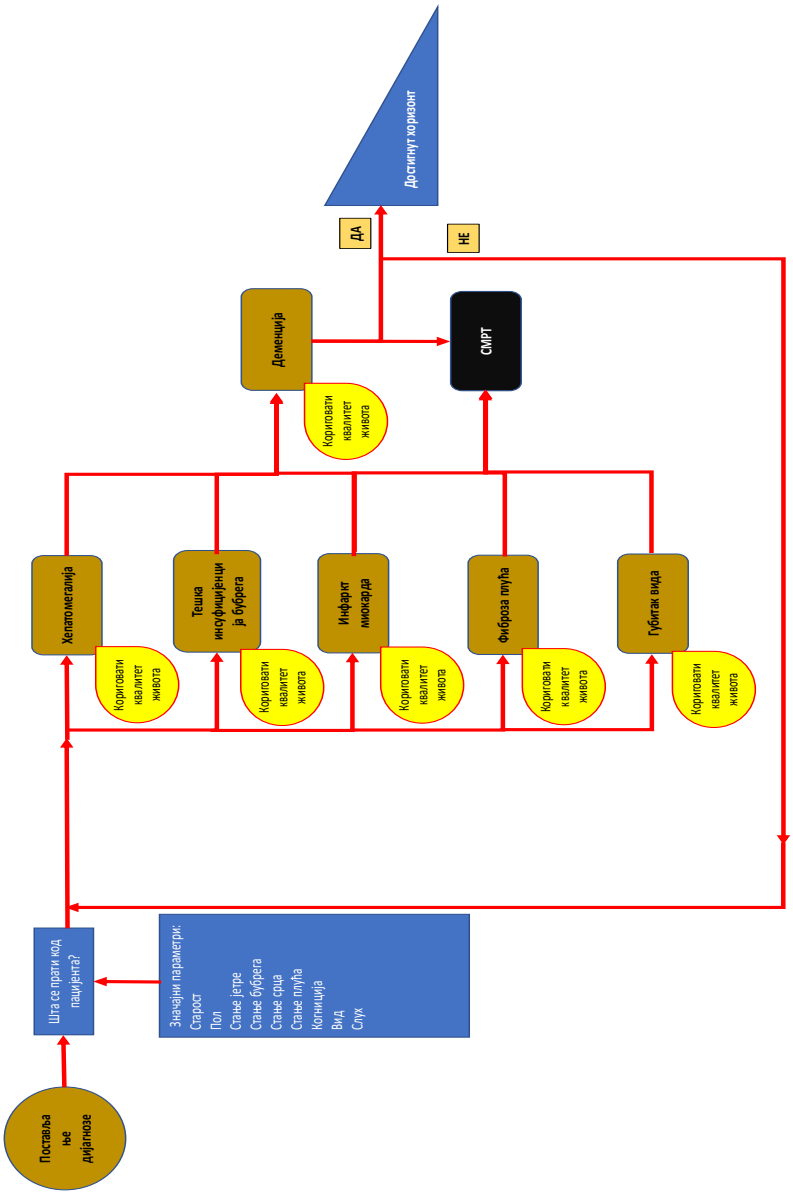
The partitioned survival model is used first for drugs for malignant tumors, and then for drugs used for chronic diseases with high mortality, where Kaplan-Meier survival curves are used to monitor the effects. Here too, the conditions in which the patient can be found, the time horizon and the length of the cycle are defined in a similar way as in the Markov model. However, instead of first determining the transition probabilities and then calculating the probabilities of each state in each cycle, here state probabilities per cycle are calculated by comparing the area under the curves denoting progression-free survival, progression itself, and death. In each cycle of the model, the sum of the areas under all curves can be calculated; the probability that in a certain cycle of the model the patient will be in one of the possible states is obtained by dividing the area under the curve in that state by the sum of the areas under all curves. Furthermore, the procedure is the same as for the Markov model - each condition is associated with the corresponding quality of life and costs, and then, according to the probabilities, the total gained life adjusted for quality and total costs per patient are recalculated for the entire time horizon, for new and old drugs separately.

Figure. Schematic representation of a partitioned survival model for a hypothetical solid tumor. Legend: PFS – survival without tumor progression; PR – tumor progression; DEATH - fatal outcome of treatment.



Illnesses that last a long time, and their complications appear only after several years as isolated events that may or may not have permanent consequences, are best described by **the discrete event simulation model**. Events are actually changes in the patient's health condition, which trigger activities that create costs and affect the quality of life. The time horizon of the model is divided into steps that last the same (the most common step duration is one month), and which are replaced one after the other by means of the so-called simulation clock. When a certain number of steps are taken that corresponds to the time since the onset of the disease when an event is most likely to occur (for example, an epileptic seizure, stroke, visual impairment, etc.), the model registers that event and attributes the effect on quality of life and costs to the patient that the event carries. At the end of the time horizon, all costs and the length of the patient's life adjusted for quality are added up, both with the new drug and with the old drug with which the new one is compared. A schematic representation of one example of a discrete event simulation model (for a fictitious disease) can be seen in the following figure.

Figure. Scheme of the discrete event simulation model.



In all models that describe chronic diseases that last for several years or decades, it is necessary to take into account the fact that with the passage of

time the value is lost, i.e., that the cost or period of life realized in the future is worth less than if it were realized now, primarily because of the uncertainty that it will actually be realized. Therefore, in pharmacoeconomic models, costs or gains in life expectancy that occur after the first year of therapy must be reduced, i.e., discounted at a certain rate. We call this rate the "discount rate", and we usually take it to be equal to the reference interest rate of the national bank of the country for which the analysis is made (most often these are values between 3 and 6%).

When the construction of the model is made as described in the previous text, we only have the so-called " **base case** ", i.e., we get the result of the comparison of the new and the old drug, which consists of a single figure without taking into account possible variability, i.e., without confidence limits. In order for the results of the model to be as close as possible to the reality, we introduce uncertainty into them, i.e., variability that can be expected in the real world. There are two types of uncertainty in pharmacoeconomic models: type one and type two uncertainty. **The uncertainty of the first type** comes from the so-called residual variability between patients, which exists even when they are similar in everything (gender, age, severity of the disease). Uncertainty of the first type is introduced into the models by means of Monte Carlo simulation, by which, based on random numbers, virtual patients in each cycle are classified into one of the possible states, following previously determined probabilities of those states. For example, if there are three possible states in each cycle, and if their previously calculated probabilities are 0.6 for the first state, 0.3 for the second state, and 0.1 for the third state, the Monte Carlo simulation will draw a random number between 0 and 1. If that random a number between 0 and 0.6, the patient will be classified in the first state, if it is between 0.6 and 0.9 in the second state, and if it is between 0.9 and 1 in the third state. When we use 1000 virtual patients in the simulation, the values of their costs and length of life adjusted for quality will be distributed according to a normal distribution, from which we can calculate the mean and variance, ie. confidence limits.

Uncertainty of the second type comes from the unreliability of the input parameters to the models, such as the estimated costs of the model states, the estimation of the quality of life in certain states or the estimation of the transition probabilities. We introduce uncertainty of the second type into the models by using inverse probability distributions of individual values instead of one value of the input parameter. With the introduced uncertainty of the first and second type, the results of the model will contain the necessary variability, i.e., it can be estimated how much the obtained values can be trusted.

SENSITIVITY ANALYSIS IN PHARMACOECONOMICS

When a pharmacoeconomic study is completed, it makes certain conclusions about the cost-effectiveness of the target drug, i.e., about the

relationship between its costs and the positive effects that can be expected. However, no matter how methodologically well such a study was conducted, its results cannot be **absolutely** accurate, i.e., they depend a lot on the conditions that prevailed in the study itself, on the selection of patients, on the current price of the drug on the market, on the current price of health services, etc. In a word, the results of pharmacoeconomic studies depend on the input values of the parameters we take into account. In order to know to what extent we can rely on the results of a pharmacoeconomic study, it is necessary to vary the input values of the parameters, and to monitor whether these variations are reflected in the results. For example, it should be investigated what will happen to the results, if we reduce the price of the drug by 50%, and what will happen to the results, if we increase the price of the drug by 50%. If it turns out that the mentioned reduction or increase in the price of the drug does not significantly change the results of the pharmacoeconomic study, then we can rely on them, and say that they are reliable enough, i.e., solid, when it comes to the price of the drug. Then we need to check how changes in the values of other parameters affect the results of the same study, until we have examined them all. The procedure for examining the magnitude of changes in the results of a pharmacoeconomic study when changing the values of the input parameters is called SENSITIVITY ANALYSIS .

In practice, sensitivity analysis is a mathematical manipulation of the values of the initial parameters and gaining insight into possible changes of the results that these manipulations cause. Most often, in the sensitivity analysis, the values of the effect of the drug, the frequency of adverse effects of that drug, the costs of the used drugs and health services, the frequency and costs of hospitalization, the discount rate and the costs of diagnostic procedures are changed. *The range* in which the value of the parameters are changed is determined by the upper and lower limits. Most often, the range is from +50% to -50% of the value of the parameter used in the study, but it can be different, and formed on the basis of previous clinical research, on the basis of a review of the literature or on the basis of the opinion of those who make decisions. The results of the study are recalculated, using different values the variables within the prespecified range. The results may remain the same, but it can be shown that one drug is more favorable in some conditions, and another drug in others. If possible, one should determine the point at which one drug becomes more favorable than the other, and evaluate the probability of occurrence and the so-called **"breaking"** points. Sometimes we have a statistical distribution of possible input values of the variable; then you should use the 95% confidence interval around the mean value to define the range of variation in the value of the variable.

There are **four** basic types of sensitivity analysis: simple, threshold, extreme value analysis, and probabilistic sensitivity analysis. ***A simple*** sensitivity analysis is most often used. With it, the value of one or more variables changes in the most likely range. A simple sensitivity analysis can be *one-way* (the value of one variable is changed in order to evaluate its effect on the results) or *multi-way* (the values of several variables are changed at the same time and their effect on the results is monitored). A simple sensitivity analysis is also

called a "**scenario analysis**" if the changes in the input variables are connected in some logical whole (e.g., the scenario analysis would be if we wanted to examine how the conclusions of the pharmacoeconomic analysis will change if the following changes in the input parameters occur at the same time: the price of the new drug decreases by 20%, the price of the old drug increases by 5%, the probability of a favorable outcome with the new drug increases by 3%, and the discount rate decreases from 5.5% to 2.5%.

Threshold analysis is actually a modification of one-way sensitivity analysis. In it, the value of one variable changes until the alternative drug becomes equal in outcome to the favorable drug. To find the point where the choice of a more favorable treatment is changed is called breakeven analysis. Threshold analysis can only be performed on parameters that have continuous values. ***Extreme value analysis*** involves using extreme values of variables in a reasonable range. The upper and lower values indicate the best and the worst case scenarios (however, what is the best and what is the worst case scenario depends on the variable that varies). Extreme value analysis is a good method, provided that the range of possible values of the input variables is well known. ***Probabilistic sensitivity analysis*** requires first determining the range of values of a parameter and the type of distribution of specific values of that parameter. Then, the Monte Carlo method of simulating real conditions is used, by randomly assigning parameter values from a determined distribution to a large number of hypothetical patients, and for each the outcome value is calculated. When the outcome values for all hypothetical patients are obtained, then mean outcome values with confidence limits are determined. In probabilistic sensitivity analysis, all input parameters in the pharmacoeconomic model are usually varied simultaneously. The advantage of probabilistic analysis is that it can focus on what is unknown about the parameters; it is especially important for those who make decisions about the financing of this or that drug. Probabilistic analysis is mathematically very demanding, so it can only be done with the help of software.

ANALYSIS OF THE IMPACT ON THE HEALTH INSURANCE FUND BUDGET

Analysis of the impact on the budget is an assessment of the financial consequences for the payer of health services and medicines (most often they are health insurance funds) that will cause the introduction of a new medicine to the list of medicines that the payer already finances. The analysis of the impact on the budget is carried out in several steps: (1) creating a calculator (model) in a spreadsheet, (2) finding input data and (3) creating a report based on the results of the calculator. Before starting the analysis, the perspective from which to work must be determined, because it determines the costs that can have an impact on

the budget: in principle, only the costs recognized by the one who pays for health services, materials and medicines are taken into account. The creation of the calculator is then first based on the assessment of the size of the population of patients who are eligible to use of a new drug, already approved by the Agency for Medicines. We calculate the size of the so-called **target population** as follows: total population * (prevalence or incidence of the disease being treated) = population of patients * percentage of patients diagnosed and treated = target population. Once the target population is calculated, the following input parameters to the budget impact calculator are added: (a) all existing treatment modalities used and financed by the health care payer (insurance fund), (b) everything used in therapy within each treatment modality (medicines + health services + medical supplies), (c) official unit prices of medicines and services. Using these input parameters, the calculator determines treatment costs per patient for each modality by multiplying the utilization of the drug or service within that modality by the unit prices. When data on the market share of all treatment modalities are then entered into the calculator, the conditions are created to calculate for the entire target population how much treatment costs for a certain period of time (most often calculated for a year), as well as to allocate the costs to each treatment modality for part of the target population that uses it. The time horizon for which the impact on the budget is calculated is usually 5 years, so for each year after the possible introduction of a new drug on the List of drugs financed by the Health Insurance Fund (the first, second, third, fourth and fifth), the costs incurred by the new and old treatment modalities should be calculated separately.

When constructing a calculator for calculating the impact on the budget, it is necessary to validate it, i.e., check whether it can be trusted. First, the mathematical calculations are validated (the check should be done by an independent expert for creating spreadsheet models), and then the concept itself (validation of the concept is done by independent medical experts for the disease that is the subject of therapy with a new drug).

Like the models that deal with the relationship between costs and drug effects, the budget impact model requires a sensitivity analysis of the conclusions. Sensitivity analysis is carried out in the form of **scenario analysis**. The scenario is defined by a certain combination of input parameters in the model (e.g., a reduction in the price of a new drug by 5% + an increase in market share by 1% + a reduction in the number of patients who can receive the new drug). Usually, several most likely scenarios are created, and the possible impact on the budget should be calculated for each.

POTENTIALLY INAPPROPRIATE PRESCRIBING OF DRUGS

No matter how hard doctors at all levels of health care try to prescribe optimal therapy for their patients, errors in prescribing drugs are encountered relatively often. These mistakes mostly have no consequences, but sometimes they can lead to serious damage to health and even death of the patient. Let us recall only the cases of Steven-Johnson syndrome in patients with epilepsy who were prescribed high doses of lamotrogine from the beginning . That is why it is important to focus efforts on detecting errors in the prescription of drugs as early as possible, starting from the moment of prescription, regardless of the fact that the consequences have not yet occurred. In research on prescribing errors, we talk about ***potentially inappropriate prescribing*** whenever we observe such an occurrence, whether we conduct the study retrospectively or prospectively, and regardless of whether the consequences have already occurred or not.

In order to determine that the prescription of a drug is potentially inappropriate, it is necessary to be guided by certain criteria. There are explicit and implicit criteria for determining potentially inappropriate drug prescribing. **Explicit criteria** are applied directly, and do not require interpretation by the person applying them. The most frequently used explicit criteria are Beers , Start and Stop. **The Beers criterion** is named after the Canadian doctor Beers, who in the 1990s compiled a list of drugs that should never be prescribed to people over 65 years of age. For example, that list includes benzodiazepines, which cause paradoxical excitation in the elderly instead of sedation. The recommendation from Beers' list is that benzodiazepines should only be prescribed for people over the age of 65 if there is no alternative therapy: for epilepsy, for behavior disorder during the sleep phase with rapid eye movement, for the treatment of withdrawal syndrome in benzodiazepine or alcohol addiction, for periprocedural anesthesia and for severe generalized anxiety disorder. Bierce's list is periodically supplemented even after the death of its creator, under the auspices of the American Geriatrics Society.

The Start and Stop criteria were developed and published in 2008 by the Irish geriatrics specialist O'Mahony (**STOPP/START**). There are 65 stop criteria and 22 start criteria, and they are all classified into subgroups according to organic systems. The Stop criteria actually list drugs that **should not be used** in old patients (over 65 years old), similar to the Beers list, while the Start criteria warn of drugs that are not prescribed for the elderly, and **should be prescribed**. For example, one of the Stop criteria is that non-steroidal anti-inflammatory drugs should not be prescribed to elderly people if they have heart failure, because they can make it worse. An example of the Start criteria is the advice that old patients taking long-term corticosteroid therapy should be prescribed one of the bisphosphonates, in order to reduce the risk of osteoporotic fractures. For the Start and Stop criteria, it has been shown in clinical studies that, if regularly applied in practice, they can reduce the frequency of adverse drug reactions and the total costs of treating elderly people.

Implicit criteria are based on the assessment of the doctor, who takes into account the overall condition and situation of the patient, and then considers whether the prescribed drugs correspond to the needs. The most well-known and accepted implicit criteria are found in the Medication Appropriateness Index (MAI), which has 10 questions that the doctor should answer. Those ten questions refer to whether the medicine was given for the right indication, in the right dose, in the right way and for long enough; also, the prescriber should assess whether there is a clinically significant adverse interaction with other drugs or with another disease that the patient has, as well as whether there is a cheaper alternative for the drug he/she is prescribing. The answers to these 10 questions are scored, so if the sum of the points is greater than 3, it can be said that the drug was inappropriately prescribed, and that correction of the therapy is required.

Criteria for detecting inappropriate prescribing are only somewhat useful in clinical practice; often, prescribing errors are associated with a wrong diagnosis or with a wrong interpretation of the severity of the patient's illness, as well as with the complex interaction of comorbidities and changes in the pharmacokinetics of the drug due to disorders in the body (e.g., in sepsis, clearance first increases and then decreases of hydrosoluble drugs, in patients on hemodialysis, the elimination of drugs depends on the residual diuresis, types of dialyzer membrane, duration of dialysis, etc.). Complete insight into potentially inappropriate prescribing is obtained only within the **clinical review procedure of therapy** ("**clinical audit**"). Clinical audit is a procedure that takes place in several stages: (1) first, the director of the health institution forms a committee that will conduct the audit: the committee should have 3-5 members, at least one of whom should be a clinical pharmacologist, and the rest should be doctors of various specialties dealing with the branches of medicine in which the therapy will be reviewed (e.g., if antibiotic therapy is being reviewed, then an infectious disease specialist and a clinical microbiologist are preferred members); (2) the commission for clinical review of therapy decides which type of therapy will be controlled, in which department and which criteria will be important for assessing whether the therapy is adequately prescribed; (3) in the third phase, the commission for clinical review of therapy announces its visit to the head of the department where the review is planned and informs him/her of the goals of the visit and the criteria for assessing the adequacy of therapy; (4) the fourth stage is the arrival of the Commission at the announced time, a random selection of a certain number of medical histories of patients who are currently undergoing treatment and then a detailed review of those histories in the presence of ward doctors, analysis of therapy according to previously adopted criteria, discussion, drawing conclusions and drawing up minutes that contains all relevant information and audit conclusions; (5) one copy of the report is then handed over to the head of the department where the control is carried out, and the Commission schedules a return visit to the department in about 7 days, when the therapy audit report will be discussed at the professional collegium (attended by all the doctors of that department); (6) the commission comes again in 7 days, as scheduled, and at the expert collegium presents to the

doctors of the controlled department details from the minutes, conclusions and proposals for corrections of prescribing in the future, and then opens a free discussion in which everyone should participate; (7) at the end of the discussion, the Commission formulates definitive conclusions of the revision of therapy and proposals for prescription corrections on which everyone agrees - both the members of the Commission and the doctors of the controlled department; (8) definitive conclusions are written down and forwarded to the head of the department and the director of the health institution, who are further obliged to control the implementation of prescription corrections in practice.

The process of clinical review of therapy has proven to be an extremely effective tool in practice, with long-term positive effects, because corrections of inappropriate prescribing are carried out far more effectively when prescribing doctors understand where they are wrong, and when it is pointed out to them without judgment or violation of their personal integrity.

INCOMPATIBILITY OF DRUGS

Drug incompatibility is the phenomenon that two or more drugs in the same solution "cannot tolerate each other", i.e., they bind to each other, changing chemically, losing activity or becoming toxic. Incompatibility occurs more often when drugs are mixed in the same syringe, than in the same infusion solution, because in a smaller volume, changes in the pH value and drug concentration are significantly greater. The frequency of drug incompatibility in clinical practice worldwide ranges between 10 and 15% of all parenteral drug administrations.

The acidity or alkalinity of the drugs themselves have proven to be key factors in the occurrence of incompatibility. Medicines that are weak bases (that tend to attract protons, i.e., hydrogen ions) are more ionized (and therefore more soluble) in an environment with a low pH value, so they are prepared for parenteral administration in ampoules or vials to which hydrogen chloride has been added or sulfuric acid instead (for example: amiodarone hydrochloride, adrenaline acid tartrate). On the other hand, drugs that are weak acids (e.g., benzylpenicillin, phenytoin) are more ionized and soluble in an environment with a high pH value . If such drugs are diluted, e.g., in the physiological solution for infusion, the pH value will move towards neutrality, as a result of which the drugs created will become less soluble, and precipitation will occur, i.e., turbidity of the solution will be visible. Therefore, for example, phenytoin should never be diluted in intravenous infusion solutions before administration.

Divalent ions of calcium and magnesium easily bind to various chemical substances, creating insoluble salts, which precipitate and cloud the solution. That's why you should never mix medicines that are calcium or magnesium salts with solutions that contain bicarbonates, phosphates, sulfates

or tartrates. Because they contain calcium, Ringer's and Hartmann 's solutions should never be used to dilute drugs; it is a well-known phenomenon that ceftriaxone diluted in Ringer's or Hartmann 's solution immediately precipitates as ceftriaxone-calcium, leading to cloudiness of the solution.

For the primary dissolution of medicines in the bottle in which they are packaged it is best to use sterile water or disolvers prepared by the manufacturers; the dilution of already dissolved medicine before administration in the form of intravenous infusion should, in principle, be carried out with the simplest isotonic solution: a 5% glucose solution or a simple physiological solution (0.9% sodium chloride). With the simplest solutions there is the least chance that the drug will chemically bind to the ingredients of the solution and lose its activity or precipitate in the infusion bottle or set, without reaching the patient's blood. Therefore, drugs **should never be added** to complex physiological solutions (Ringer's and Hartmann's), to sodium bicarbonate solution, to colloidal solutions (dextran, hydroxyethyl starch, gelatin, albumin), to blood preparations, ***or to biological preparations containing*** macromolecules (most often proteins). Macromolecules are unstable, and can easily be denatured due to changes in pH or osmolarity.

Also, there are drugs that are ***very liposoluble, and therefore not - soluble in water***. They are usually prepared in bottles in which they are dissolved in the organic solvents propylene glycol and ethanol. If we dilute such an ampoule in an infusion bottle with physiological solution or 5% glucose, the drug cannot be dissolved in water, so its precipitation and cloudiness of the solution will occur. Such drugs are: clonazepam, diazepam, digoxin, phytomenadione and amiodarone.

Consequences of drug incompatibility can be blockage of the central venous catheter, embolization, loss of drug effectiveness or systemic inflammatory reaction.

Examples of compatibility and incompatibility of some commonly used drugs:

1. **Dexamethasone sodium phosphate** is compatible with ranitidine and metoclopramide, but not compatible with midazolam and promethazine;
2. **Midazolam** is incompatible with hydrocortisone;
3. **Diazepam** is not compatible with any other drugs;
4. **Pantoprazole is a very alkaline substance that is incompatible with many drugs, and incompatibility with** vancomycin is especially common in practice;
5. **Furosemide** is not compatible with chlorpromazine, metoclopramide , midazolam, morphine and promethazine;
6. **Vancomycin and piperacillin-tazobactam** are incompatible in the same solution;
7. **Lidocaine is** compatible with metoclopramide, but not with ampicillin;

8. **Metoclopramide** is compatible with chlorpromazine, dexamethasone, fentanyl, lidocaine, morphine, midazolam and promethazine, but not compatible with ampicillin and furosemide;
9. **Morphine sulfate** is compatible (but only if administered within 15 minutes of mixing) with atropine, bupivacaine, fentanyl, ketamine and metocopramide, but not compatible with aminophylline, furosemide and phenytoin;
10. **Tramadol** it is not compatible with diazepam and midazolam.

The occurrence of incompatibility can be **partly prevented** if central venous catheters with multiple lumens are used, so only drugs are administered through one lumen, and parenteral nutrition through the other. Other prevention methods are: using a special venous access for drugs, and a special one for parenteral nutrition, changing the dosage regimen so that incompatible drugs are not administered at the same time, reducing the number of drugs in therapy or temporarily stopping the use of a drug with a high potential for incompatibility reactions, and switching from parenteral to oral therapy. It is also useful for each department to create cross-tabs with color markings for compatibility or incompatibility of the drugs that are most commonly administered parenterally in that department, and then display such tables in a visible place.

There are several electronic databases in the world on incompatibilities between drugs, drugs and solvents, and drugs and the walls of the bottles or vials in which they are contained or dissolved. One of the most comprehensive databases is called "**stabilis**", and it can be accessed for free at the link https://stabilis.org/ . This database currently contains data on 853 substances based on 2740 references, and is continuously updated.

FUNDAMENTALS OF STATISTICS FOR CLINICAL PHARMACOLOGISTS

Statistics is a science that deals with determining the probability of certain phenomena in the population, i.e. on a large number of observation units. First of all, it is necessary to describe the phenomena in the population, which is done by measures of central tendency, which tell about what is the most common value of a certain phenomenon (e.g. mean value or median), and measures of variability of change in the population, which tell about how many values occur which observed in the population are scattered around measures of central tendency (e.g., standard deviation or

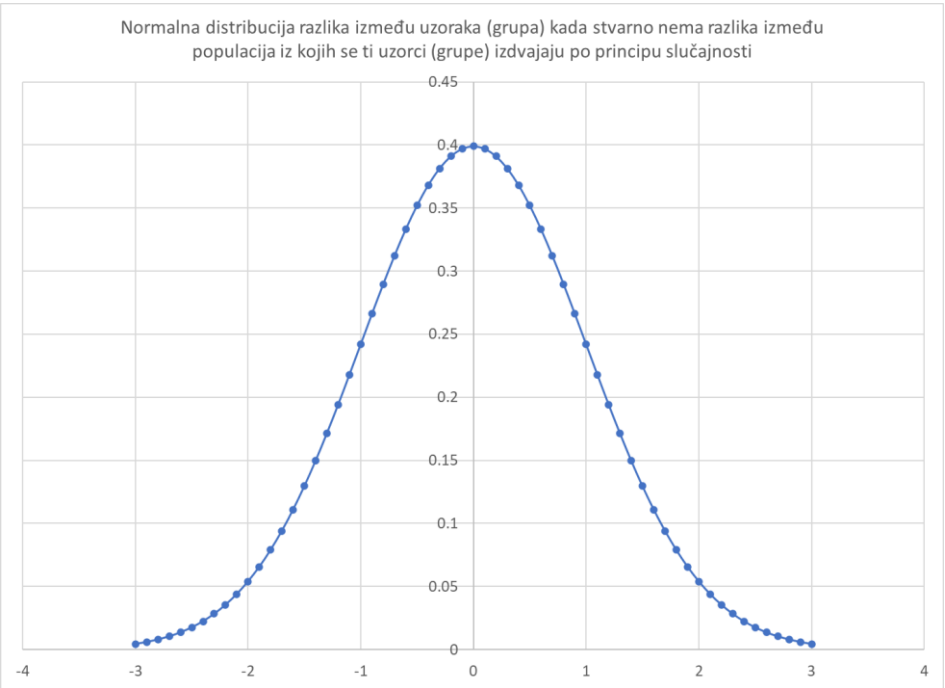
range, i.e., the difference between the minimum and maximum values). When the occurrence is of a categorical nature, i.e., has only certain values (e.g., treatment outcome, can only be "patient cured" or "patient not cured"), then it is described by frequency, i.e.. by the number of patients who have one or another value of a categorical phenomenon, or by the percentage representation of a certain value. After describing the phenomena, it is usually necessary to determine whether there are differences between groups of patients who receive one or another drug, or which of the patient's characteristics (including the drug) affects a certain treatment outcome. In the first case, we use tests that compare two or more groups with each other by outcome, and in the second, so-called multivariate analyses, which connect a larger number of patient characteristics with the outcome of treatment.

TESTS FOR COMPARISON OF TWO GROUPS: STUDENT'S T-TEST, MANN-WHITNEY U-TEST AND CHI-SQUARE TEST

When we statistically compare two groups in clinical or experimental research, we are actually checking whether the so-called null hypothesis, i.e., is it true that there is NO significant difference between the populations from which the groups were sampled in our study. If there really is no significant difference between the populations, and the groups we have extracted from the populations have very large numbers of members (e.g., patients), then the differences observed in a large number of studies between samples taken from those populations will be normally distributed around zero as the mean. The normal distribution of the frequency (or in other words the probability) of the differences between the samples is shown in the following graphic, where on the x-axis there is zero as the mean value and the number of standard deviations of those differences around zero (this number is also called the Z-value), and on the y-axis frequency (or probability). The standard deviation of this distribution is called the standard error of the difference between the means, and is calculated by the formula:

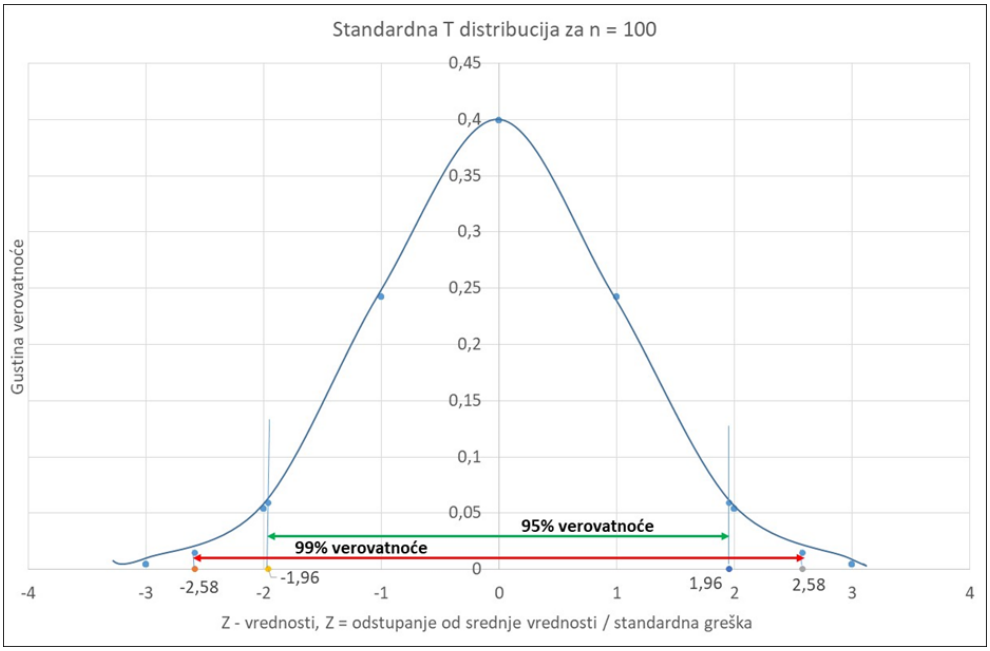
$$SE_{diff} = \sqrt{\frac{\sigma_1^2}{n_1 - 1} + \frac{\sigma_2^2}{n_2 - 1}}$$

where n1 is the number of patients in the first group, n2 is the number of patients in the second group, σ1 is the standard deviation in the first group, and σ2 is the standard deviation in the second group.



If we sum the frequencies (i.e., the probabilities), we will see that between -1 and 1 standard errors of the difference lies 68% of all differences between groups extracted from populations, between -2 and 2 standard errors is 95% of the differences, and between -3 and 3 standard errors errors as much as 99% of all differences. Thus, if we find a difference between -2 and 2 standard errors in one of our studies, this will mean that the probability of the null hypothesis (i.e., that there is no significant difference between the populations) is somewhere between 5% and 100%. Also, if the difference is between -3 and 3 standard errors, then the probability of the null hypothesis is somewhere between 1% and 100%. Conversely, if we want to reject the null hypothesis, i.e., to determine that a difference between populations really exists, then the difference between the groups selected in our study should be less than or greater than two standard errors (then the probability of the null hypothesis is less than 5%), or less than or greater than 3 standard errors (then the probability of the null hypothesis is less than 1%).

The number of members (e.g., patients) of each of the groups we observe significantly affects the distribution of differences between groups; only if the number is very large does the distribution approach normal. In other cases, that distribution is somewhat different, and is called the T-distribution, where 95% of all differences are not between -2 and 2 standard errors, but - 1.96 and 1.96 standard errors. Similarly, with the T-distribution, 99% of all group differences lie between -2.58 and 2.58 standard errors, as shown in the following figure:



To test the significance of the difference between two groups when it comes to some continuous variable (e.g., cholesterol level), the Student's T-test can be used, provided that the values of that variable in each of the groups are normally distributed (because only then will the differences be distributed according to the T-distribution around zero). Thus, the Student's T-test calculation first determines the standard error of the DIFFERENCE between groups, and then whether the difference observed in the study is within or outside the -1.96 to 1.96 or -2.58 to 2.58 standard errors of the difference. If the difference is outside the range of -1.96 to 1.96 standard errors of the difference, then we can reject the null hypothesis, i.e., to say that the probability (denoted by "p") that there is no difference between groups is less than or equal to 0.05 (or 5%). If the difference is outside the range of -2.58 to 2.58 standard errors of the difference, then we can also

reject the null hypothesis, i.e., say that the probability that there is no difference between groups is less than or equal to 0.01 (or 1%). Otherwise, the difference between the groups will not be significant.

If the values of a continuous variable that we are comparing between groups (e.g., cholesterol level) are not normally distributed in each of the groups, then we cannot use the Student's t-test to determine the significance of the difference. In such a situation, we use the so-called a non-parametric test Man Whitney's U test. The essence of this test consists in ranking patients according to the values of a continuous variable (e.g., serum cholesterol) and then summing the ranks for each group separately. The sum of ranks for the first group is then subtracted from the sum $n_1 n_2 + n_1 (n_1 +1)/2$, and for the second group from the sum $n_1 n_2 + n_2 (n_2 +1)/2$ (n_1 and n_2 are the numbers of patients in the first and second groups), in order to obtain the so-called " U " values, U1 and U2. Finally, we look at where the obtained smaller U value is according to special tables that actually compare whether there is a significant difference in distribution frequencies of ranks in the populations belonging to the first and second groups. If the difference of the distributions is significant, the test value will also confirm that there is a significant difference between the groups.

The chi-square test serves us to determine whether there is a difference between the two groups in the representation of the value of a categorical variable. For example, if in a group of 100 patients treated with drug A, 70 of them were cured, and 30 of them died, and in another group of 200 patients treated with drug B, 160 were cured, and 40 died, is the difference between those groups significant, i.e., is drug B really significantly better than drug A? We answer this question with the Chi-square test, which actually compares these observed values of the categorical variable (which in this case is the outcome of the treatment with two possible values - survived or did not survive) with the expected values of the same variable that would be in case there was no difference between the groups. The expected values in this example would be obtained by calculating the percentage of observed values for patients of both groups, and then applying those percentages to each group separately: out of 300 patients, 230 were cured and 70 died, which is 77% versus 23%; this means that if there is no difference between the groups, it would be expected that 100*0.77 = 77 patients would be cured in the first group treated with drug A, and 154 patients in the second group treated with drug B. Then the probability that there is an observed difference between the observed and expected values within a special Chi-squared distribution of the differences obtained by chance after a large number of repeated studies, when there would be no real difference in the effectiveness of drugs A and B, is sought.

If the probability of an observed difference in an example study is less than 5% (that is, 0.05 if the probability is expressed on a scale from 0 to 1), then it can be concluded that the probability of the null hypothesis (that there really is no difference) is small, i.e., that it can be rejected and concluded that the difference in the effectiveness of drug A and drug B is statistically significant. When intending to use the Chi-square test, one should keep in mind that it has one limitation - it cannot be applied if at least one outcome value in any group is less than 5, i.e., if only 5 or fewer patients have such an outcome.

All three mentioned tests (Student's T-test, Mann-Whitney U test and Chi-square test) are found in all statistical software that are widely available today, which means that their application to collected data is very simple; however, it is important to know under what conditions each of these tests can be applied. In short, the Student's T-test and the Mann-Whitney U test can be applied to the comparison of the values of a continuous variable between two groups, with the Student's T-test subject to the mandatory condition that the data are normally distributed in both groups (the normality of the distribution is checked by Kolmogorov - Smirnov test). The Chi-square test is applied if the values of a categorical variable are compared between two groups, provided that none of the values is represented in less than 6 patients.

MULTIVARIATE STATISTICAL ANALYSIS

Research in clinical medicine can be experimental and observational. We call experimental research controlled clinical studies, where we have the opportunity to examine the effect of one independent variable on the dependent variable, and to control the influence of all other, confounding variables (which may indirectly affect the dependent variable) by making the experimental group (which is exposed to the independent variable)) and the control group (not exposed to the independent variable) to equalize with respect to confounding variables. For example, if we want to examine the effect of a drug on the blood pressure of patients, we will form an experimental group that will be exposed to that drug, and a control group that will not be exposed to the drug, but we will select patients so that both groups are similar in age, similar in gender, similar in the presence of chronic diseases, similar in the prevalence of smokers, etc. In processing the results of experimental research, we can then use simple statistical tests to compare two groups with respect to the dependent variable (e.g., Student's

T-test or Mann-Whitney U-test, depending on whether the data are normally distributed or not).

In observational studies, which are conducted much more often because they are cheaper and more feasible, we are not in a position to equate the group exposed to the independent variable and the group not exposed by confounding variables, because we cannot choose which patient will be exposed to the independent variable and which will not. Therefore, in processing the results of observational studies, we must take into account the influence of both independent and confounding variables on the dependent variable (outcome), i.e., we have to use the so-called multivariate statistical analyzes that will examine the simultaneous influence of all the mentioned variables on the outcome, adjusting the influence of each variable for the influence of the others, and evaluate which of the examined variables have a statistically significant influence and which ones do not. Of the multivariate analyzes in research practice, two are most often used: multiple linear regression, if the dependent variable (i.e., the outcome) is a continuous quantity (e.g., arterial blood pressure), and binary logistic regression, if the dependent variable is of a categorical nature (e.g., the patient survived or died).

MULTIPLE LINEAR REGRESSION

Multiple linear regression consists of the construction of a complex linear equation in which on one side of the equal sign is the absolute value of the dependent variable (i.e., the outcome), e.g., of systolic arterial pressure, and on the other are additions, of which only one is a constant, and all others are the product of an independent or confounding variable and their coefficients. If we take for example one of our studies, where we examine the effect of drug A on systolic blood pressure, where the confounding variables are patient age, gender, and the presence or absence of heart failure, the multiple linear regression equation would look like this:

$$y = C + x_1 * B_1 + x_2 * B_2 + x_3 * B_3 + x_4 * B_4 + e$$

where : y – systolic blood pressure , C – constant , x_1 – presence or absence of drug A, B_1 – coefficient that determines the magnitude of the drug's effect on systolic blood pressure , x_2 – the age of the patient , B_2 – the determining coefficient the size of the impact age on blood pressure , x_3 – sex of the patient , B_3 – coefficient that determines the size of the impact male and

female gender on systolic blood pressure , x_4 – presence or absence of heart failure , B_4 – coefficient that determines the size of the impact heart failure on systolic blood pressure , and e - error in relation to the actual, observed value of dependent variable.

The equation of multiple linear regression is often called "model". Statistical analysis consists of minimizing differences between predicted and observed values of dependent variable, using method the smallest squares, until the model (i.e.,equation) is reached which is the best description of influence of independent and confusing variables on the dependent. From that ultimate model we can first estimate if each of the independent and confusing variables has significant influence on the dependent (i.e., on outcome), and then on the basis of size of the coefficients B of variables with significant influence we can determine degree that influence.

Whether multiple linear regression could be used for interpretation of results of some observational study, depends on certain assumptions that must be met. The assumptions for use of multiple linear regression are:

1. normal distribution of " residuals " , i.e., the differences between values of dependent variable predicted by the model and actual, observed values.
2. dependent variable must be linear function of parameters of the multiple linear regression. This condition is checked by graphic display of standardized "residuals" as function of values of dependent variables calculated by the model (in coordinate system where on the x – axis is dependent variable, and on the y- axis size standardized " residuals"). The relation between standardized "residuals" and dependent variable on the graphics should be linear.
3. absence of collinearity, i.e., of interdependence of two confusing variables or independent and some of the confusing variables. This assumption is checked by calculation of variation inflation factor (VIF) which should be less than 10.
4. absence of heteroscedasticity, i.e., of occurrence that "residuals" have trend to increase or reduce with change of values of dependent variable. This assumption is checked by graphic display of standardized "residuals" in function of values of dependent variables calculated by the model (in coordinate system where on the x – axis is dependent variable, and on the y- axis the size of the "residuals").

Equation (model) of multiple linear regression could be easeily determined by some statistical program, but is important to correctly

interpret the obtained model. First of all, one should estimate if obtained model has statistical significance, i.e., if at all we can interprete influence of independent and confusing variables (they are often called "predictors") on dependent variable. Assessment of statistical significance of multiple linear regression equation is conducted in two ways. First, using one-way analysis of variance (ANOVA) we determine if the variability of observed values of dependent variable from the average value obtained by the model is significantly larger from the variability of observed values of dependent variables from the calculated values for every individual patient. If the difference of these variabilities is big enough, the test is considered significant, and the model can be further interpreted. The second test of significance of multiple regression equation is calculation of coefficient of determination, i.e., the square of correlation coefficient between predictor and dependent variables (r^2). Coefficient of determination tells us which share of variability of dependent variable is explained by the multiple regression equation, on a scale from 0 to 100%. Depending on the size of this coefficient we can have confidence in the results of the multiple linear regression, i.e., if it is higher, the results are more reliable.

If the equation of multiple linear regression is statistically significant and has solid coefficient of determination, then we can deal with a question which predictor(s) has significant influence on the dependent variable, and what is the extent of that influence. Statistical programs usually give values of coefficients B for every predictor (independent and confounding variables), together with their 95% confidence intervals, as well as the probability ("p") that that predictor is not significant . If the probability "p" of a predictor is below 0.05, this means that it has significant influence on the dependent variable, and the coefficient B tells how big is that influence. On example, if heart failure significantly affects the systolic blood pressure, and its coefficient B = - 5.3, this means that if the patient has heart failure, his/her systolic blood pressure will be 5.3 mmHg lower than it would be if he/she did not have heart failure. Or, if age significantly affects the systolic blood pressure, and the coefficient for age is B = 0.4, this means that with each year of age systolic blood pressure is increasing for 0.4 mmHg.

Sometimes it is not easy to make significant model of multiple linear regression, if there is large number of predictors. It is important that the study sample is of sufficient size, because each predictor requires at least 10 patients in the sample.

BINARY LOGISTIC REGRESSION

Binary logistic regression is used for multivariate analysis if the dependent variable is categorical, and has only two possible values (e.g., patient is cured or not), whereas independent and confusing variables can be both categorical and continuous. The statistical procedure determines one equation, which at one side has natural logarithm of odds that one of the two values of dependent variable is present (e.g., if out of 100 patients 80 is cured, then the chance for healing, i.e., odds is 80/20=4), and at the other side sum of additions which are products of predictors and their coefficients. Coefficients are natural logarithms of odds ratios that dependent variable has value marked with 1 (e.g., the patient is cured) if the value of predictor changes from one into the other category (if categorical variable) or for one unit of measurement (if continuous variable). On example, if we would like to examine influence of antibiotic B on healing of pneumonia, and as confusing variables we have age of a patient, gender and presence or absence of chronic obstructive syndrome (COPD), we should apply logistic regression. Here is how it looks binary logistic regression equation:

$$y = b_0 + x_1 * b_1 + x_2 * b_2 + x_3 * b_3 + x_4 * b_4$$

where : y is the natural logarithm of the odds of one of the values of the dependent variable , $\ln \frac{p}{1-p}$, b_0 – natural logarithm of the odds (“ odds ”) if there is no predictor influence , x_1 – presence or absence of drug B in therapy , b_1 – natural logarithm of the odds ratio that the patient will be cured if he receives drug B, x_2 – the patient's age , b_2 – the natural logarithm of the odds ratio that the patient will be cured if the age increases by one year , x_3 – gender of the patient (marked with 1 – male , and 0 – female), b_3 – natural logarithm of the odds ratio that the patient will be cured if male, x_4 – presence or absence of COPD, b_4 – natural logarithm of the odds ratio that the patient will be cured if having COPD.

Since the density probability of individual values of dependent variable are distributed according to the Bernoulli's function, which is special form of binomial distribution, and equation of logistic regression is canonical form of Bernoulli's distribution, coefficients of logistic regression are directly calculated from the Bernoulli's distribution. Statistical programs perform that a job for us, giving us results that need interpretation.

In order to use logistic regression, it has to satisfy a number of assumptions :

1. dependent variable must to be categorical, and binary, meaning that it has only two possible values (in our example, cured or not cured);
2. all observations, i.e., measurements of variables have to to be independent from each other; in the other words, it is not allowed to use repeated measurements on the the same patient;
3. predictor which are mutually correlated should not be used simultaneously, i.e., there should not be collinearity. Existence of collinearity is checked by calculation of variation inflation factor (VIF), which for none of the variables should be above10.
4. among the observed data there should not be outliers, i.e., the patients with extreme values of variables. Extreme cases are discovered by calculation of Cook's distance (it shows how much assessment of parameters of logistic regression is changed after removal of the extreme case). If the Cook's distance for a patient is larger then the ratio 4 / number of patients, then such patient is considered extreme by chance, and should be eliminated in order to find optimal model of binary logistic regression.
5. there should be linear relation between any of the predictors and natural logarithm of odds for one from the two values of dependent variable. Existence of this linear relation is checked by the Box-Tidwell transformation of predictors, which consists of multiplication of predictor value with its natural logarithm. Then transformed predictors are together with untransformed introduced into the model of logistic regression, and if transformed predictors do not significantly affect the dependent variable, then assumption of linearity is satisfied.
6. number of patients should be sufficient: at least 10 patient per one predictor.

When model of binary logistic regression is built, there are automatic options, like "delete backward" (after introduction of all variables, one by one is eliminated, following how the elimination affects the model) or "forward conditional" (gradual introduction of one by one variable, if each introduction improves the model). After the model is built, it should be interpreted.

First of all the Omnibus test coefficients should be interpreted. The Omnibus test examines whether introduction of predictors into the model significantly improves its quality in relation to the basal model which has only one constant (b_0). If the Omnibus test shows that probability of zero hypothesis (that introduction of parameters does not improves the model) is below 0.05, this means that model with parameters can be further interpreted, i.e., it has required quality.

Then values of Cox and Snell R^2, and Nagelkerke R^2 should be interpreted. Both values tells us which of variability of the dependent variable is explained by the model of logistic regression. As much as these values are close to 1, the model is better, because explains larger part of variability of the dependent variable. However, the borderline value od coefficienta R^2 are not determined, below which a model would be considered inadequate, so the interpretation is only relative.

Hosmer - Lemeshow test checks if the obtained model is appropriate for the observed data. If probability of zero hypothesis of this test is above 0.05, model is sufficiently good description of the observed data, i.e., the predicted values are not significantly different from the observed values.

The most important a part of results of the binary logistic regression model is assessment of influence of individual predictors on the dependent variable. The significance of coefficient "b" for each predictor is assessed. The program usually displays coefficients "b", but also theirs antilogarithms, marked with "exp (b)", which are odds ratios that one of the values of dependent variable would happen (in our example patient cure) when the predictor has its observed value. On example, if the exp (b) for aadministration of an antibiotic B is 2.5, that means that person who receive antibiotic B has 2.5 times greater chances to be cured than the person who does not receive antibiotic B. In order for value exp (b) to be significant, its "p" value (probability of zero hypotheses, that the predictor does not have importance) must to be below 0.05, and the confidence interval chould not capture value 1 (e.g., odds ratio of 2.5 is acceptable is if its confidence interval is 1.2 – 4.6, but it is not acceptable if its confidence interval is 0.8 – 4.6.

Finally, after construction of the model logistic regression with satisfactory characteristics and interpretation of influence individual predictors on the dependent variable, we should test whether some predictors act synergistically or not. A new model should be tried where combination of two predictors is inserted: if the influence of combination on the dependent variable is more extensive from the influence of every individual predictor (i.e., exp(b) of combination is bigger if the exp(b) of the predictors were > 1, and smaller if the exp (b) of the predictora were < 1), we may conclude that synergism exists, i.e., the combination od predictors more significantly affects the dependent variable from the simple sum of that two predictors. If we find synergism, then we should also try to explain its biological basis, that is, the mechanism.

SPECIAL SECTION

The special part of clinical pharmacology refers to the treatment of certain diseases and conditions. This book will provide details on the treatment of only those diseases and conditions for which a good knowledge of the pharmacodynamics and pharmacokinetics of prescribed drugs, their mutual interactions and serious side effects is important for the outcome. There are two types of therapeutic areas in which the expertise of a clinical pharmacologist is of crucial importance for the outcome: diseases and conditions with high mortality in case of inadequate drug therapy (e.g. sepsis), and situations when it is necessary to apply drugs with a narrow therapeutic range (e.g. antiepileptics, antiarrhythmics, anticoagulants, etc.). In the first case, it is crucial to choose the drug well, and in the second, to dose accurately and avoid numerous factors that can lead to side effects, toxicity or unfavorable interactions with other drugs, food or associated diseases.

TREATMENT OF ATRIAL ARRHYTHMIAS

Atrial arrhythmias include sinus tachycardia and bradycardia, atrial extrasystoles, atrial tachycardia, atrial flutter and fibrillation. Pre-ventricular extrasystoles usually do not have hemodynamic consequences, so it is not necessary to specifically suppress them. All patients in whom it is intended to attempt to interrupt the cardiac arrhythmias with drugs should be given oxygen, a peripheral venous catheter should be inserted, and continuous ECG monitoring should be connected.

In the case of ***paroxysmal supraventricular tachycardia*** a physician should try first Valsalva maneuver or carotid sinus massage for 10 seconds (just below the angle of the mandible), and then if these maneuvres fail, adenosine or verapamil (or diltiazem) should be administered. **Adenosine** is a safer option, and should be administered intravenously, as a bolus injection of 6 mg, which can be repeated after about thirty seconds. An injection of adenosine of 6 mg is administered quickly intravenously, within 3 seconds, and then the venous cannula and the vein are "cleaned " with 20 ml of physiological solution. If this is not enough to stop the tachycardia, then another 12 mg of adenosine should be given. Adenosine leads to temporary high-grade A-V block, which can be very uncomfortable for patients who receive it, but there are usually no permanent and serious consequences. Sometimes adenosine can cause transient sinus tachycardia or block. Some patients get a feeling of discomfort in the chest

and redness of the head and neck, but this has no consequences. Adenosine *should not be used* if the patient has Wolff- Parkinson - White syndrome and atrial fibrillation, because the refractory period of the accessory pathway is shortened, which leads to the rapid conduction of impulses into the ventricles and the occurrence of dangerous ventricular tachycardia. **Verapamil** and diltiazem are calcium channel blockers that can effectively terminate supraventricular tachycardia. Verapamil is administered as a slow intravenous injection from 2 to 5 mg; the injection can be repeated after 30 minutes, if there is no interruption of the tachycardia. Diltiazem is administered orally, 30 mg every 8 hours. Verapamil is less safe than adenosine, because sometimes (especially in children) it can lead to cardiac arrest or severe hypotension. Recently, a new short-acting drug has been used with success instead of verapamil and diltiazem - the calcium channel blocker **etripamil** in the form of a nasal spray. If the paroxysmal supraventricular tachycardia does not respond to all mentioned methods, and the patient is hemodynamically unstable, direct cardioversion is applied.

When the episodes of paroxysmal supraventricular tachycardia repeat frequently, **prophylaxis** with beta blockers or long-acting calcium channel blockers can be applied. In cases that do not respond well to prophylaxis, catheter ablation of aberrant pathways for conducting depolarization impulses is performed.

Sinus bradycardia is the appearance of a regular heart rhythm with a frequency of less than 60 beats per minute. If the patient does not have symptoms, treatment is not necessary. If there is hemodynamic instability, then appropriate measures should be taken. First, drugs (if the patient received them) that have a negative chronotropic effect (e.g. beta-blockers, calcium channel blockers, cardiotonics, muscarinic drugs) should be removed. **Atropine sulfate** should then be applied intravenously: first a dose of 0.6 mg, then 0.5 mg every 5 minutes, up to a maximum of 3 mg. If bradycardia cannot be resolved with atropine, noradrenaline or dopamine can be applied in a continuous infusion, and a permanent solution is installation of a pacemaker.

In patients with ***stable flutter or fibrillation of the atria***, it is enough just to carry out prophylaxis of thrombosis in the atria and control the frequency of the ventricles. Whether it is necessary to use anticoagulants in stable atrial fibrillation in patients without severe mitral stenosis or without a mechanical valve is evaluated using the CHA2DS2 score: if the value is greater than zero in men and one in women, lifelong administration of oral anticoagulants is most often recommended, provided that the patient does not have a high risk of bleeding at the same time, which is evaluated by the HAS-BLED score (if this score is 3 or more, the risk of serious bleeding is 5.9% or more annually, so anticoagulants should be avoided). Thrombosis prophylaxis is carried out using new oral anticoagulants (rivaroxaban, apixaban, edoxaban or dabigatran) or vitamin K antagonists (most often warfarin or acenocoumarol), which are dosed based on the target value of the INR (2 - 3). The frequency of ventricular contractions is regulated by controlling the conduction of impulses through the A-V node: the drugs of first choice for this indication are selective beta 1 blockers

and calcium channel blockers, and the drug of second choice is a cardiotonic digoxin. The dose of metoprolol for this indication is 50 mg every 12 hours, orally, the dose of diltiazem 30 mg every 8 hours, orally, and the dose of digoxin 0.25 mg every 6 hours, orally, for 24 hours, then 0.25 mg per day (after 5 days of administration of the drug, make a break of 2 days).

If atrial fibrillation or flutter occurred ***suddenly***, in persons younger than 65 years, or if the patient's condition is hemodynamically unstable, then ***cardioversion*** can be performed, i.e., returning to sinus rhythm. Cardioversion can be done using a defibrillator or using **amiodarone**. Instead of amiodarone, it is possible to use antiarrhythmics from group Ic (flecainide or propafenone), but only in patients without structural disease of the heart chambers, because flecainide can cause ventricular arrhythmia and ventricular fibrillation.

TREATMENT OF VENTRICULAR ARRHYTHMIAS

Ventricular extrasystoles can occur in people with a healthy myocardium, but also in people with some type of myocardiopathy. By themselves, ventricular extrasystoles do not require treatment with antiarrhythmics; however, if the patient has myocardiopathy, frequent symptoms and reduced ejection fraction due to extrasystoles, a beta blocker or a calcium channel blocker with an effect on the heart (verapamil or diltiazem) can be used. An alternative to the use of antiarrhythmics for the treatment of symptomatic ventricular extrasystoles is catheter ablation of arrhythmogenic focus or of aberrant conduction path.

On the other hand, ***ventricular tachycardia*** must always be treated, because it can easily turn into fibrillation and lead to cardiac arrest. Since it has been shown in clinical studies that antiarrhythmics, although they can reduce symptoms, do not improve survival, ventricular tachycardias are treated first by implantation of cardioverter-defibrillator or catheter ablation procedure. Antiarrhythmics are adjunctive therapy; in the first line, beta- blockers are used, and in the second, the beta- blocker is combined with amiodarone.

If the patient with ventricular tachycardia is hemodynamically unstable (severely hypotensive), it is necessary **to stop the tachycardia** as soon as possible. First of all, the patient should be sedated, a beta blocker should be applied and the previous cardiac therapy should be optimized (e.g., if the patient also has myocardial insufficiency or coronary disease); if such an approach does not lead to cessation of ventricular tachycardia, amiodarone is added to the therapy parenterally or ajmaline. Patients who are refractory to the mentioned therapy should be put under general anesthesia and acute catheter ablation should be performed, with or without hemodynamic support using an aortic balloon pump.

A special type of ventricular tachycardia is **torsade** ("torsades des pointes"), which has polymorphic QRS complexes with a prolonged QT interval. This arrhythmia usually occurs as a consequence of the toxic effect of drugs on the myocardium or in electrolyte disorders. Torsade can be stopped by administering magnesium sulfate intravenously. In adults, 1 - 2 g of magnesium sulfate (8 mM Mg^{2+}) intravenously over 15 minutes is given. This dose can be repeated once more after 30 minutes, if there was no positive response to the therapy. When $MgSO_4$ is used as an intravenous injection, the concentration must not exceed 20%, and the injection must last at least 10 minutes. If administered as an intravenous infusion, the concentration must not exceed 100 mg/ml, and the infusion should last 2-4 hours. Whether the drug is given intravenously by injection or infusion, the rate of drug administration must not exceed 150 mg/min.

After acute correction of ventricular tachycardia, the question ***of prevention of new attacks remains***. If, in addition to tachycardia, the patient's contractile function of the myocardium is reduced (ejection fraction of the left ventricle is less than 40%), then it is best to permanently implant the patient **cardioverter-defibrillator**, because studies have shown that it reduces mortality. If the contractile function of the myocardium is good, then the real solution for the patient is chronic administration **of selective beta1 blockers**, which reduce the mortality of such patients. In patients in whom tachycardia occasionally occurs despite the use of beta blockers, **amiodarone** can be used with success, as it controls symptoms well, but does not reduce mortality.

TREATMENT OF RHYTHM DISORDERS AFTER MYOCARDIAL INFARCTION

After a myocardial infarction, almost 90% of patients have some rhythm disorder. The most common disorders are **ventricular extrasystoles and ventricular tachycardia**. Neither ventricular extrasystoles, if there are less than 10 of them per hour, nor sinus tachycardia require medication; it is enough only to correct possible electrolyte disorders or metabolic disorders, and the patient will always benefit from oxygen therapy and achieving an adequate fluid balance. If the number of extrasystoles is greater than 10 per minute, and if at least one episode of ventricular tachycardia occurs, regardless of duration, antiarrhythmics should be included. It is possible to apply a beta blocker, and in more severe cases amiodarone should be used.

Ventricular tachycardia occurs after a myocardial infarction (this happens in about half of patients, and mostly in the first 24 hours) and if it lasts longer than 30 seconds, antiarrhythmics should be used, because the risk of transitioning to ventricular fibrillation is high. The drug of choice in this - situation is **lidocaine** intravenously, in an initial bolus injection of 1 mg/kg,

after which we administer an infusion at a rate of 1-4 mg/min. In about 5-10% of patients, ventricular tachycardia will turn into ventricular fibrillation. Then we must perform defibrillation immediately, and after apply amiodarone, a bolus injection of 300 mg. Recently, in patients with recurrent ventricular tachycardia after myocardial infarction cardioverter-defibrillator is implanted, which led to a significant reduction in mortality.

In about 15% of patients after a myocardial infarction, the so-called **accelerated idioventricular rhythm appears (the leader of the heart rhythm is somewhere in the ventricles),** but the heart rate is similar to normal (from 60 to 150 per minute), so the patient does not have hemodynamic disorders. This type of arrhythmia usually passes spontaneously, and does not require the use of drugs.

In some cases will appear atrial fibrillation (especially in large anterior wall infarctions) or paroxysmal atrial tachycardia. In the case **of atrial fibrillation, a beta- blocker or calcium channel blocker** should be used, in order to reduce the frequency of the ventricles. If it was **paroxysmal atrial tachycardia**, it is interrupted by rapid (within 3 seconds) intravenous injection of 6-12 mg **of adenosine**. Instead of adenosine, verapamil or propranolol can be used with less success .

In about 40% of patients with infarction of the diaphragmatic wall of the left ventricle, occurs **sinus bradycardia**. It is treated only if the patient has symptoms, with atropine sulfate, 0.5 mg intravenously.

If atrio-ventricular block of the first or second degree with Weckenbach periodics occur (Mobic 1 type - the PQ-interval is gradually lengthened from cycle to cycle, until the absence from the ECG), the patient should be treated only if he/she has symptoms. The drug of choice is intravenous injection of atropine sulfate. Mobic type 2 AV block, or third degree AV block require the use of a pacemaker.

TREATMENT OF SINUS BRADYCARDIA WITH DRUGS

Bradycardia is defined as a heart rate of less than 50 beats per minute when the patient is at rest. Apart from the slowed rhythm, the ECG findings in these patients appear normal. Symptoms occur only in some patients. The patient may feel dizzy, and have chest pain, shortness of breath, and sometimes syncope (loss of consciousness).

At sinus bradycardia drugs are applied only if the patient has symptoms. The drug of choice for the treatment of bradycardia is **atropine sulfate**. Atropine sulfate is administered intravenously or through an endotracheal tube (if it is not possible to provide a venous route), in a dose of 0.5 to 1 mg in adults. If the bradycardia does not disappear after the first dose, two more doses of 1 mg can be administered at 3 to 5 minutes, up to **a total of 3 mg (0.04 mg/kg)**. In children, a single dose of atropine sulfate is **0.02 mg/kg**.

Isoprenaline, a beta receptor agonist, was used in the treatment of bradycardia, but this practice was abandoned due to the proarrhythmogenic effect of this drug. If the patient does not respond to the atropin, a temporary pacemaker is applied.

TREATMENT OF VENTRICULAR TACHYCARDIA "TORSADE DES POINTES"

Ventricular tachycardia "Torsade de pointes", or colloquially " torsade" is a type of polymorphic ventricular tachycardia in which the amplitudes and shapes of the irregular QRS complexes gradually change and oscillate around the isoelectric point. Torsada usually occurs in people with a prolonged QT interval of more than 460 milliseconds; it can also it stops spontaneously, but sometimes turns into ventricular fibrillation.

Since the QT-interval is prolonged in torsade, the use of antiarrhythmics that prolong this interval for the treatment of torsade is contraindicated, because they can accelerate the transition to fibrillation. This actually means that **the use of group IA antiarrhythmics** (quinidine, procainamide, disopyramide) is **contraindicated** in patients with torsade.

If it does not stop spontaneously, the torsade can be stopped with medication. First of all, electrolyte disturbances that contribute to the occurrence of torsades should be corrected: hypokalemia and hypomagnesemia. The drug of choice for terminating torsade is **magnesium sulfate**, administered intravenously as bolus injection in a dose of 2 grams. If the torsade does not stop after the first injection, the same dose can be repeated after 5-15 minutes. The patient should then be given a continuous infusion of magnesium sulfate at a dose of 3-20 mg/min, and maintained for 7-48 hours, until the QT-interval is shortened below 500 milliseconds.

In some patients with an acquired long QT-interval, torsades stops due to bradycardia, which contributes to an additional prolongation of the QT-interval. Such patients can be helped by the administration of a beta-agonist isoprenaline (initial intravenous dose 0.02 - 0.06 mg), which will speed up the heartbeat and shorten the QT-interval, thus leading to the termination of torsade. This is not the case in patients with a congenitally long QT-interval: for them, the administration of isoprenaline would only worsen the condition, so the opposite therapy is used - a short-acting beta-blocker esmolol (initial intravenous dose of 0.5 mg/kg for one minute, followed by an intravenous infusion of 0.05 mg/kg/min during the next 4 minutes).

In the case that drugs cannot stop the torsade, **a temporary transvenous pacemaker is** used with success, which at a frequency of about 100/min shortens the QT-interval enough to stop the torsade.

Torsade can be **prevented** in various ways in patients with congenital and acquired long QT-interval. In patients with a congenital long QT-interval who do

not have bradycardia, the drugs of choice for torsade prevention are **beta-blockers (most often** propranolol is still used). In other patients with congenital long QT-interval and bradycardia or in patients with acquired long QT-interval administration of drugs for prevention torsade is not effective. With frequent life-threatening torsade attacks, such patients should be implanted with a permanent pacemaker or cardioverter-defibrillator.

ADVERSE EFFECTS AND INTERACTIONS ANTIARRHYTHMICS

Antiarrhythmic drugs are drugs with a narrow therapeutic range, which means that the range between the minimum effective dose and the minimum toxic dose is very small. On the other hand, since they act on the heart rhythm, strengthening or weakening of their effect due to variations in blood concentrations or the interference of other drugs in the mechanism of their action can have serious consequences for the patient in terms of hemodynamic instability, or even cardiac arrest. For these reasons, doctors should be well aware of the interactions and side effects of antiarrhythmic drugs , so that they can avoid them, or at least notice them in time and undertake the correction of the therapeutic regimen.

Quinidine increases the concentration of digoxin in the serum, so the dose of digoxin must be reduced to avoid its toxic effects. Quinidine should not be given together with antiarrhythmics amiodarone or flecainide, the antibiotic moxifloxacin, as well as with antipsychotics pimozide, because the risk of new ventricular arrhythmias increases. Quinidine inhibits the isoform of cytochrome CYP2D6, so if it is administered simultaneously with propranolol, it increases its plasma concentration, which requires a 50% reduction in the dose of propranolol. On the other hand, the antifungal drug itraconazole is a strong inhibitor of CYP3A4, so it slows down metabolism quinidine to such an extent that tissue exposure to that drug increases more than twice; and here the solution is to reduce the dose, this time of quinidine, by 50%.

Procainamide should not be given together with amiodarone because the risk of new ventricular arrhythmias increases; also, if procainamide is combined with other antiarrhythmics (including beta- blockers), its depressant effect on the myocardium is strengthened. You should avoid using procainamide at the same time with the quinolone antibiotics moxifloxacin and levofloxacin (they inhibit the tubular secretion of procainamide and increase its concentration in the blood), with tricyclic antidepressants, with antipsychotics (amisulpiride, pimozide, sertindole), with 5-HT_3 blockers or with antimuscarinic drugs, because the risk of new ventricular arrhythmias increases .

Disopyramide is not used together with amiodarone because the risk of new ventricular arrhythmias increases; also, if disopyramide is combined with

other antiarrhythmics (including beta-blockers), its depressant effect on the myocardium is enhanced. Simultaneous use of disopyramide with quinolone antibiotics moxifloxacin and levofloxacin should be avoided, with tricyclic antidepressants, and with antipsychotics (amisulpiride, pimozide, sertindole), because the risk of new ventricular arrhythmias increases. Administration simultaneously with antimuscarinic drugs (antihistamines of the first generation, tricyclic antidepressants) is also not recommended, because the anticholinergic side effect of disopyramide increases. Cytochrome inhibitors in the liver, macrolide antibiotics and imidazole antifungal drugs increase the concentration of disopyramide in plasma.

The effect of lidocaine antagonizes hypokalemia caused by duretics of loop of Henle and thiazides diuretics. Lidocaine should not be administered together with other antiarrhythmic drugs (including beta-blockers), as myocardial depression increases. Antidepressant fluvoxamine and antiarrhythmic amiodarone inhibits the cytochromes on which lidocaine is metabolized in the liver, thus increasing its concentration in the blood and its effect on the myocardium. The simultaneous use of lidocaine with the antibiotics quinupristin and dalfopristin, with antipsychotics, with tricyclics, antidepressants or with 5-HT_3 blockers should be avoided because the risk of new ventricular arrhythmias increases.

Mexiletine is metabolized via CYP2D6 and CYP1A2 isoenzymes, so its elimination can be slowed down by inhibitors of these cytochromes, and in particular by a selective uptake blocker serotonin fluvoxamine. Mexiletine may also increase the plasma concentration of theophylline and caffeine.

Fluoxetine, duloxetine and paroxetine (antidepressants) and amiodarone increase the plasma concentration of flecainide and propafenone because they inhibit cytochrome CYP2D6. Flecainide or propafenone should not be administered together with beta-blockers or calcium channel blockers, as myocardial depression increases. Antipsychotics and 5- HT_3 blockers used together with propafenone increase the risk of new ventricular arrhythmias.

Alpha blockers enhance the hypotensive effect of beta blockers. Combining beta-blockers with other antiarrhythmics should be avoided, as myocardial depression or provocation of ventricular arrhythmias may occur. It is especially harmful to combine beta-blockers and calcium channel blockers, because severe bradycardia and hypotension occur. Beta-blockers can mask signs of hypoglycemia in patients receiving antidiabetic medications. Inhibition of cytochrome CYP2D6 by antidepressants fluoxetine, duloxetine and paroxetine increases the concentration of beta blockers in the blood and enhances their hemodynamic effects (bradycardia and hypotension).

Verapamile, co-trimoxazole, hydrochlorothiazide, triamterene and ketoconazole increase the concentration of dofetilide in plasma by about 50% (because they inhibit the tubular secretion of dofetilide), so new arrhythmias may occur with simultaneous use.

Amiodarone should not be combined with other antiarrhythmic drugs, except in exceptional situations, because there is an increase in the depressant

effect on the myocardium or the emergence of new arrhythmias. Amiodarone and dronedarone are inhibitors of cytochromes CYP3A4 and CYP2C9, as well as efflux pumps of glycoprotein P, so they increase the blood concentration, and thus the effect, of warfarin, statins, cyclosporine and digoxin. When amiodarone is used simultaneously with macrolide antibiotics, co-trimoxazole, antipsychotics, antidepressants or quinolones , the risk of new arrhythmias increases. Amiodarone inhibits the metabolism of oral anticoagulants.

Verapamile and diltiazem are inhibitors of cytochrome CYP3A4, so they increase the blood concentration of statins if they are used simultaneously. On the other hand, cytochrome CYP3A4 inducers, rifampicin, St. John's wort, phenobarbital and carbamazepine can accelerate the metabolism of verapamile, and reduce its concentration in the blood, and thus its effect.

All drugs that are strong inhibitors of cytochrome CYP3A4 lead to a slowing down of the elimination and accumulation in the body of the antianginal drugs ranolazine and ivabradine. Antiarrhythmic drugs such as amiodarone, dronedarone, verapamil and diltiazem, belong to the group of strong cytochrome CYP3A4 inhibitors.

TREATMENT OF PREHYPERTENSION AND FIRST-DEGREE HYPERTENSION

Hypertension based on the level of blood pressure measured in the doctor's office, it is divided **into** 3 categories: **prehypertension or high-normal** pressure (systolic pressure 130 to 139 mm of mercury, diastolic 85 to 89 mm of mercury), **stage 1** (systolic pressure 140 up to 159 mm of mercury, diastolic 90 to 99 mm of mercury) and **stage 2** (systolic pressure > 160 mm of mercury, diastolic > 100 mm of mercury). Although essential hypertension is by far the most common clinical form, before we start treating the patient, we should conduct a package of diagnostic tests that can reveal the specific causes of hypertension, if any. Discovery of the cause of hypertension enables causal treatment (for example, if hypertension is caused by polycythemia, treatment focuses on reducing polycythemia, which will also lead to normalization of blood pressure). The basic package of diagnostic tests that should be performed in every patient who is diagnosed with hypertension includes: measurement of serum sodium, potassium, glycemia, creatinine, cholesterol and triglycerides, blood count, urine sediment examination, ultrasound examination of the heart, renal arteries and carotid arteries, and fundus examination. If all these tests give negative results, hypertension can be marked as essential and treatment can be started. In the treatment of prehypertension and hypertension of the first degree, we use lifestyle changes and medications.

Lifestyle change includes the following measures: (1) stop smoking; (2) reduce salt intake to less than 4 grams per day, which means choosing food

without added salt, avoiding industrial soups, cured meat products, salty grits and not adding salt to food (reducing salt reduces systolic pressure by about 5 mm of mercury); (3) switch to a diet of vegetables, fruits, lean meats, fish, olive oil, and low-fat dairy products; (4) reduce or completely eliminate alcohol intake (systolic pressure decreases by about 4 mm of mercury); (5) introduce mandatory moderate physical activity of 30 minutes every day, but not through lifting loads (systolic pressure decreases by about 7, and diastolic by about 5 mm of mercury column); (6) reduce the waist circumference to less than 94 cm for men, and less than 80 cm for women, reduce the body mass index below 25 kg/m^2 (reducing body weight by 10 kg reduces systolic pressure by 6-10 mm of mercury column). The patient should carry out these non-pharmacological measures for several months, and only then can it be decided whether taking antihypertensive drugs is necessary.

Any of the following antihypertensive drugs is used to treat prehypertension and first degree hypertension: diuretics, beta- blockers, angiotensin-converting enzyme inhibitors and calcium channel blockers. Centrally acting antihypertensives, alpha-blockers, aldosterone receptor blockers (spironolactone, eplerenone, ezaxerenone and finerenone) and direct vasodilators are used mainly for the treatment of hypertension of the second degree.

Thiazides diuretics have good absorption from the digestive tract and long-term effect are satifactory. They are especially useful in renal diseases of moderate severity. Initially, they reduce the vascular volume, but this is soon compensated by the effect of angiotensine, so a direct vasodilatory effect takes place. They are effective in smaller doses than those used to treat edema. Thiazide diuretics are the drugs of first choice for most patients.

Diuretics of Henle's loop have a short-term and too intense effect, so they are not suitable for the treatment of hypertension of the first degree or prehypertension. When using these drugs, electrolyte disorders in the body (hypokalemia, hyponatremia) are significantly more pronounced than when using small doses of thiazide diuretics, so correction is often necessary. There is reason to apply them only if the patient has advanced kidney failure, because then thiazides diuretics act weaker.

Beta-blockers have a hypotensive effect only in people with high blood pressure. At first, they reduce the cardiac output, but later the effect is based on the reduction of renine secretion. They raise serum triglycerides and lower HDL, which is not in their favor. In addition, they can lead to hyperglycemia, sedation, impotence, depression and bronchoconstriction (the latter only in a person with asthma or chronic obstructive pulmonary disease). Given that they are successfully used in the treatment of heart failure with a reduced ejection fraction, it is convenient to use them in patients who have both hypertension and heart failure; however, in such patients, the dosage of beta- lockers must be very gradual at first, starting with the smallest doses, until the minimum dose is reached that helps both of the mentioned conditions, and does not lead to worsening of heart failure due to the negative inotropic effect. On the other hand, beta blockers **should not any** longer be used in patients who have heart failure

with preserved ejection fraction, because they not only do not help, but can also worsen the patient's condition.

Out of ***the calcium channel blockers,*** for the treatment of prehypertension is and hypertension of the first degree, dihydropyridines (nifedipine and amlodipine), which cause vasodilation, are mostly used. Verapamile and diltiazem both reduce cardiac output and lead to vasodilatation, which is not convenient for people with heart failure, because decompensation and AV block may occur after the use of these drugs. A recent analysis of databases with tens of thousands of patients indicated that the use of verapamil or diltiazem in patients with heart failure and preserved ejection fraction was associated with a higher risk of death (hazard ratio 1.21 compared to the use of beta- blockers).

Angiotensin-converting enzyme inhibitors (ACE inhibitors) have a unique advantage over other antihypertensive drugs because they slow down the loss of kidney function in patients with chronic kidney disease. However, they should be used carefully in patients with reduced intravascular volume and narrowing of the renal arteries, as they may provoke the onset of acute renal insufficiency. These drugs are especially indicated for diabetics with high blood pressure, because they slow down the development of nephropathy. A number of patients who use these drugs develop a persistent dry cough, which interferes with a person's normal functioning. In these cases, the patient can be prescribed angiotensin receptor blockers, which have the same beneficial effects as ACE - inhibitors, and do not cause a dry cough. Since some other side effects are less common when angiotensin receptor blockers are used (angioedema, pancreatitis and gastrointestinal bleeding), the prevailing opinion is that the first line of treatment for essential hypertension should start with blockers of angiotensin receptor, and not with ACE - inhibitors. In recent years, a combination of angiotensin receptor blocker **valsartan** and neprilysin inhibitor **succubitril** has been introduced into therapy (neprilysin is an endopeptidase that normally breaks down vasoactive peptides bradykinine, adrenomedullin and natriuretics peptides). The ratio of valsartan and succubitril molecules in this fixed combination is 1:1 thanks to the production process in which co-crystallization occurs. The fixed combination of valsartan and succubitril is often abbreviated ARNi in the literature; it is recommended as the first drug in patients with hypertension and chronic heart failure in whom ejection fraction is **reduced**.

The treatment of prehypertension and hypertension of the first degree is started with ***one drug***. Effectiveness of thiazides, ACE-inhibitors, blockers angiotensin receptors, beta blockers and blockers of calcium channels is quite similar, so we decide on a group of drugs based on associated diseases and conditions that the patient may have. The following table shows the optimal choice of antihypertensive drugs according to existing comorbidities .

Table . Antihypertensives recommended in patients with hypertension and some of the comorbidities.

Comorbidity	Recommended antihypertensives

Coronary disease	ACE inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers
Chronic heart failure with reduced ejection fraction	Valsartan/sacubitril , ACE inhibitors, angiotensin receptor blockers, beta blockers, diuretics
Stroke prevention	ACE inhibitors, angiotensin receptor blockers, diuretics, calcium channel blockers
Type 2 diabetes	ACE inhibitors, angiotensin receptor blockers diuretics, calcium channel blockers
Chronic kidney failure	ACE inhibitors, angiotensin receptor blockers , diuretics , calcium channel blockers

If one drug does not control hypertension, new drugs should be added - "**step by step**". This means that we combine drugs with different mechanisms of action, and slowly titrate the doses (starting from the lowest), preferably not going beyond the submaximal dose, in order to minimize side effects.

Elderly people respond better to diuretics and dihydropyridine calcium channel blockers, than to other groups of antihypertensive drugs. They should avoid beta blockers due to their tendency to cause heart failure and AV block in the heart, as well as ACE inhibitors, because they are less effective in that age group.

In pregnancy and lactation, the use of ACE – inhibitors, angiotensin receptor blockers and combination of valsartan sacubitril is ***contraindicated***, because these drugs disturb the growth and development of tissues, which means that they are teratogenic and slow down the development of the fetus. Also, beta blockers can only be used in the first half of pregnancy; if their use were to continue until the end of pregnancy, premature birth may occur, children are born small for their gestational age, and the risk of death in the perinatal period is increased. During pregnancy, nifedipine, methyldopa and hydralazine can be freely used for the treatment of hypertension.

TREATMENT OF SECOND-DEGREE HYPERTENSION AND HYPERTENSION RESISTANT TO THERAPY

When the patient has hypertension of the second degree, the treatment should be started **immediately with *the combination antihypertensive drugs***, because monotherapy is not effective. Antihypertensives from all groups

that are used in the first line of treatment can be combined with each other, but you should never combine drugs from the same group, because this does not increase the beneficial effect (for example, combining two ACE inhibitors does not achieve anything, except perhaps a higher frequency side effects). The target value of blood pressure in most patients should be slightly below 140/85 mm of mercury column, and in diabetics, renal insufficiency or significant cardiovascular disease around 130/80 mm of mercury column.

If the combination of two antihypertensives fails to lower the pressure to the target level, in the next step a combination of **three drugs should be given**, again combining drugs from different groups. If even this combination of three drugs in the maximum permitted doses fails to control hypertension, so that the blood pressure is above 140/90 mmHg, then we are talking about **resistant** hypertension. Resistant hypertension is successfully treated by adding to the existing therapy a drug from the aldosterone receptor blocker group (one of the following drugs: spironolactone, eplerenone, ezaxerenone or finerenone). All of the above-mentioned aldosterone receptor blockers are equivalent in efficacy, and all cause hyperkalemia, but spironolactone has additional side effects that other drugs do not: it can cause impotence or gynecomastia because it blocks the effect of 5-alpha reductase, the enzyme that converts testosterone into its active form, dihydro-testosterone. For the most resistant forms of hypertension, one of the following is added as a fifth drug: antihypertensive with central action (alpha-methyldopa or clonidine) or some drug from the group of direct vasodilators (e.g., hydralazine). Since about 50% of patients with resistant hypertension have some specific cause of hypertension, after the normalization of blood pressure, intensive measures should be taken to discover the cause with additional diagnostic procedures, and then remove it with causal therapy.

In particular, it should be noted that the use of thiazides diuretics increases the tendency to develop or worsen type 2 diabetes, so these drugs should be avoided (if possible) in patients at risk for developing or worsening diabetes. Also, the use of beta-blockers in patients with type 2 diabetes should be cautious, because they can mask the signs of hypoglycemia and thus lead to damage to the central nervous system due to delayed correction. Explicit contraindications for the use of beta blockers in the treatment of hypertension are the presence of symptomatic bradycardia, AV block of the 2nd or 3rd degree, severe form of bronchial asthma and severe form of occlusive disease of peripheral arteries (including Raynaud's syndrome).

TREATMENT OF HYPERTENSIVE CRISIS

A hypertensive crisis means a sudden increase in blood pressure above 180/120 mm of mercury. Hypertensive crisis is divided into hypertensive emergency and hypertensive urgency. **Hypertensive urgency includes only**

an increase in blood pressure, while there are no signs and symptoms of organ damage. In **a hypertensive emergency,** in addition to an increase in blood pressure, organ damage occurs which is clearly manifested. Hypertensive urgency occurs relatively often: about 1-2% of all patients with hypertension have a hypertensive urgency at least once in their life.

A sudden jump in pressure mechanically damages the endothelium of arteries and arterioles, leading to the activation of the coagulation cascade and deposition of fibrin on the inner surface of blood vessels. Due to the deposition of fibrin, it is more difficult for the oxygen to penetrate the media and adventitia, causing necrosis in the wall of the artery and the formation of thrombosis, which ultimately leads to ischemia of vital organs.

Clinical manifestations of organ damage, which is characteristics of hypertensive emergency, are:

- damage to the central nervous system: nausea, vomiting, confusion, dizziness, signs of intracranial bleeding;
- eye damage: papilledema, retinal hemorrhage, retinal exudates, vision loss, blurred vision;
- damage to the heart and blood vessels: angina pectoris, cardiogenic shock, decompensation in heart failure, aortic dissection;
- kidney damage: proteinuria, hematuria, increase of nitrogenous substances in the blood, acute kidney failure.

All of the above-mentioned manifestations never occur in the same patient, but usually different combinations. The mortality rate of a hypertensive emergency is about 4%, regardless of the treatment method.

In patients with a hypertensive urgency, the elevated blood pressure should be gradually normalized during 24 hours, by administering drugs orally. A sudden decrease in blood pressure in these patients can be harmful, as hypoperfusion of vital organs can occur, followed by the onset of infarction. Treatment of hypertensive urgency can be carried out on an outpatient basis or at the patient's home.

In patients with a hypertensive emergency, the therapy should be carried out exclusively in the hospital, in intensive care with constant monitoring of the patient's vital functions. Blood pressure should be lowered by administering drugs intravenously, adjusting the rate of infusion according to the patient's response. In the first hour, the pressure should not be lowered by more than 25%; in the next 6 hours, the pressure should drop no lower than 160/110 mm mercury column. The pressure should then be normalized by using oral preparations in the next 24 hours.

For the treatment of hypertensive urgency, some of the oral preparations can be used, such as **ACE-inhibitors** or **calcium channel blockers**. If nifedipine is used, only a slow-release tablet should be given, because the use of a regular tablet can lead to a more rapid lowering of blood pressure. A dose of 20 mg nifedipine is given orally; it is preferable that the patient is already under the influence of beta-blockers, in order to avoid reflex tachycardia. It is also useful in these patients to administer a single dose of long-acting orally benzodiazepine

(e.g., diazepam 5-10 mg), because it has been shown that reducing the patient's anxiety contributes to better acute regulation of blood pressure.

For the treatment of hypertensive emergencies, the drugs of first choice are combined alpha and beta blocker labetalol or nicardipine. However, since these drugs are not registered in Serbia, an alpha 1 blocker **urapidil** can be used instead, first in the form of slow intravenous injection of 10-50 mg, after which the infusion continues at a rate of 9 mg/h on average, until blood pressure stabilizes and signs of organ damage disappear. While the patient is still receiving urapidil, chronic antihypertensive therapy can be corrected, so that its dose is gradually reduced, as other antihypertensive drugs begin to control pressure. Ampoules of urapidil contain propylene glycol as a solvent (one ampoule of 25 mg urapidil has 500 mg propylene glycol), which in larger quantities (over 50 mg/kg/day) can cause kidney or liver damage in patients who already have reduced function of these organs. Instead of urapidil, **nitroglycerin** can be given in infusion, 5-10 μg/min. The dose should be increased by 5 μg/min every 5 minutes until the desired blood pressure reduction is achieved; the maximum dose is 100 μg/min. The problems when using nitroglycerin are tachyphylaxis and severe headaches.

ADVERSE EFFECTS OF ANTIHYPERTENSIVES

Antihypertensives are a chemically diverse group of compounds, which can be classified into certain subgroups. The frequency of side effects varies from group to group of antihypertensive drugs; in a cross-sectional study conducted in a single center in Nigeria of 514 patients receiving antihypertensive drugs , the following adverse effects were observed: (1) 6.9% of patients receiving calcium channel blockers experienced urinary frequency, headache, and dizziness; (2) of patients treated with ACE-inhibitors, 8.6% developed dizziness, dry cough, or abdominal pain; (3) diuretics caused excessive urination, dizziness, headache, weakness or insomnia in 9.5% of patients; (4) in 3.4% of patients on beta blocker therapy, dry mouth, dizziness and foot cramps were observed; (5) central antihypertensives caused dizziness, weakness or headache in 12.6% of patients. Considering the small number of patients in this study, only mild side effects were observed that occur often or very often, and are an extension of the pharmacological effect of the drugs. Serious side effects, which occur rarely or very rarely, cannot be observed in such studies, but only by searching databases with spontaneous reports of side effects. These serious and rare side effects are listed in the following text for each group of antihypertensive drugs.

Beta blockers

Unwanted effects of non-selective beta-blockers represent the prolongation of their pharmacological effect, i.e. the consequence of unwanted

blockade of beta-receptors in various tissues. Due to blockade of β_2 receptors in the bronchi, beta blockers can lead to bronchoconstriction in asthmatics, and due to the blockade of $\beta 1$ receptors in the heart, worsening of heart failure and conduction block (worsening of heart failure occurs especially often if patients are immediately given a full dose of beta-blocker). The worsening of diabetes after the use of beta-blockers is due to a reduction of release of insulin as a result of blockade of β_2 receptors on pancreatic endocrine cells. In patients with atherosclerosis, it worsens blood flow through the extremities when they take beta blockers (due to blocking of β_2 receptors that normally cause the arteries in the extremities to dilate). Also, beta-blockers interfere with the compensatory autonomic and metabolic reaction to hypoglycemia, which can mask the clinical picture and enable more severe damage to the nervous system. Due to penetration into the central nervous system and additional blocking effect on channels for Na +, propranolol and metoprolol can cause nightmares, lethargy, depression and feeling tired. Impotence can also be a problem.

Hyperkalemia is another possible side effect of beta blockers, because they prevent the effect of catecholamines on the entry of potassium into cells. The mentioned side effects can only be partially overcome by the use of selective β_1 antagonists (atenolol, metoprolol, betaxolol, bisoprolol and nebivolol) or by the use of β-blockers that have a certain stimulatory activity on β-receptors (so-called partial agonists : oxprenolol, pindolol, etc.).

Beta blockers must be **gradually introduced into the therapy and phased out of the therapy**. Abrupt introduction of a full dose of beta-blocker can provoke decompensation of heart failure, and abrupt discontinuation of administration can cause worsening of coronary disease. If the therapy with beta-blockers is suddenly stopped, the heart suddenly becomes hypersensitive to the action of the sympathetic nervous system (because in the meantime there has been an increase in the number of β_1 receptors, the so- called upregulation of the receptors), so increased oxygen consumption and anginal attacks can occur, or even a heart attack. That's why long-term use of β-blockers requires their *gradual* discontinuation, by reducing doses over a period of several weeks.

Direct vasodilators

Minoxidil, hydralazine, diazoxide and calcium channels blockers act directly on arteries and arterioles; nitroprusside - sodium acts on both arteries and veins. Vasodilators are used only together with diuretics, because if they are used alone, they lead to fluid retention due to reduced blood flow through the kidneys. It is preferable to apply a beta- blocker at the same time, which would prevent the occurrence of reflex tachycardia; due to strong vasodilatation, baroreceptor activity decreases, so application of only vasodilators is followed by tachycardia.

In addition to reflex tachycardia, minoxidil causes nasal congestion and headache. It also enhances hair growth, which in women can result with

hirsutism. Thrombocytopenia can be a problem in some patients, and pericardial effusion sometimes occurs.

Hydralazine is metabolized in the liver, first by hydroxylation, then by glucuronidation and acetylation. Most of the drug goes through the process of acetylation, which takes place not only in the liver but also in the mucous membrane of the small intestine. There are people who have altered genes that regulate the acetylation process, so the amount of the enzyme that performs acetylation is small. In such persons (so-called "slow acetylators") hydralazine is eliminated much more slowly, so its effect is prolonged and enhanced. Other side effects of hydralazine include headache, facial flushing, peripheral neuritis, anxiety with agitation, nasal congestion, and reflex tachycardia. If used for a long time, a number of patients experience a condition similar to systemic lupus erythematodes, and even bone marrow and liver damage.

A special problem with the use of sodium nitroprusside is the accumulation of cyanide and thiocyanate, which are created by the decomposition of this drug. Cyanides lead to metabolic acidosis, dyspnea, headache and loss of consciousness. Thiocyanates can cause delirium. In order for this not to happen, the infusion rate should not exceed 10 μg/kg/min .

In addition to reflex tachycardia and fluid retention, diazoxide can cause hyperglycemia, especially in people with diabetes.

Inhibitors of angiotensin-converting enzyme and angiotensin 2 receptor blockers (indirect vasodilators)

Blockers of angiotensin-converting enzyme (ACE inhibitors: captopril, enalapril, monopril, perindopril, ramipril, lisinopril, etc.) have a lot of side effects due to the very mechanism by which they act. Due to the blockade of convertase, the breakdown of bradykinin is hindered, so **angioedema** can occur in a number of patients, both immediately after taking these drugs, and later, after a longer latent period of several months. Also, it is necessary to gradually introduce these drugs into therapy, starting with the smallest dose; sudden administration of the full dose may lead to severe **hypotension** followed by syncope, and even to acute renal insufficiency, especially in persons in whom the flow through the renal arteries is otherwise reduced due to atherosclerosis. Therefore, an ultrasound examination of the renal arteries should be performed before the start of therapy, and the level of creatinine and urea in the serum should be controlled during the first two weeks after the introduction of one of the ACE - inhibitors; if there is a sudden increase in the level of nitrogen substances in the serum, further therapy with this group of drugs should be stopped.

Due to impaired breakdown of bradykinin, this substance accumulates in the mucous membrane of the respiratory tract, leading to its swelling. Patients feel it as a stimulus that makes them have a persistent **dry cough**. A number of patients are unable to tolerate a dry cough, so they must be given angiotensin

receptor blockers instead (losartan, valsartan, telmisartan, etc.), which have the same antihypertensive effect without this unpleasant side effect.

ACE-inhibitors cause **an increase in the level of potassium** in the serum due to reduced secretion of aldosterone; therefore, they are not combined with potassium-sparing diuretics, but it is very convenient to use them together with thiazide diuretics, which tend to lower potassium levels.

Blockers of angiotensin-converting enzyme should also not be administered during pregnancy: after administration in the first trimester, they act teratogenically, and in the later stages fetotoxic.

Captopril, as an older drug, has additional side effects: it causes neutropenia, metallic taste, edema and worsens asthma. Enalapril, ramipril, cilazapril, quinapril, fosinopril and other newer preparations do not have these pronounced toxic effect on the bone marrow.

Angiotensin receptor blockers generally have the same side effects as ACE-inhibitors, except that they do not cause a dry cough.

Alpha blockers

Although much less often than non-selective α- blockers, prazosin, terazo sin, doxazosin, tamsulosin and other alpha1-selective blockers can lead to reflex tachycardia due to a decrease in the activation of baroreceptors in the aortic arch and carotid sinus. In addition, these drugs prevent ejaculation (or cause retrograde ejaculation) and can lead to fluid retention due to reduced blood flow through the kidneys. They are used to treat moderate hypertension, usually in combination with drugs that work by a different mechanism. To the patient who is prescribed prazosin, the doctor must explain that he should first start with a small dose (e.g., 1 mg) that he/she should take immediately before going to bed; if he/she does not do so, strong hypotension may occur after the first dose (because the body has not yet adjusted), and even syncope (loss of consciousness due to a sudden decrease in blood flow through the brain).

Due to the blockade of alpha1-receptors on the internal sphincter of the urethra, frequent urination may occur in patients using alpha-blockers. Congestion of the nasal mucosa and psychological problems (depression, anxiety, drowsiness) also sometimes accompany the use of alpha-blockers.

A particularly unwanted effect of alpha 1 blockers was observed when a large number of old men on chronic therapy with alpha 1 blockers due to prostate hypertrophy were subjected to cataract surgery by the phacoemulsification procedure. It is **a floppy iris syndrome,** which consists of the tendency of the iris to prolapse through the incisions on the cornea, flaccidity of the stroma of the iris so that the entire iris waves and progressive intraoperative miosis. Because of the floppy iris syndrome, cataract surgery is difficult, so patients have a higher risk of some of the complications of the surgery (e.g., rupture of the anterior or posterior capsule of the lens, injury to the iris, cystoid edema of macule, etc.). Intraoperative floppy iris syndrome can be avoided by discontinuing alpha 1 blockers 7 days before cataract surgery.

Antihypertensives with central effect

Alpha-methyldopa and clonidine lead to water and sodium retention after prolonged use; therefore, in principle, they are not used alone, but in combination with diuretics.

If administered intravenously, clonidine can cause a short-term spike in blood pressure due to direct stimulation of peripheral alpha- receptors. With oral administration, such an effect does not occur. Sometimes clonidine can lead to bradycardia and AV block. Alpha-methyldopa and clonidine cause sedation and drowsiness, dry mouth, nasal congestion, orthostatic hypotension, depression and impotence. In addition, alpha-methyldopa sometimes causes hemolytic anemia, thrombocytopenia or leukopenia. Clonidine sometimes causes constipation, nausea, and even angioedema. The use of clonidine must not be stopped suddenly, because there may be a sudden worsening of hypertension, which is called "rebound" hypertension (patients should be specially warned about this fact!).

Diuretics

Diuretics of Henle's loop cause hypokalemia, transient hearing loss (especially if administered too rapidly intravenously), hyperuricemia (increase in uric acid levels), and hyperglycemia. Only etacrinic acid (whose molecule has no similarity with other diuretics from this group and sulfonamides) does not cause hyperglycemia. Thiazide diuretics also cause hyperuricemia, hypokalemia, and hyperglycemia.

Adverse effects of potassium-sparing diuretics (spironolactone, eplerenone, finerenone, triamterene, amiloride) are hyperkalemia, metabolic acidosis (because inhibition of reabsorption of Na^+ reduces excretion of K^+ and H^+) and neurological disorders (paresthesias, depression). Spironolactone also blocks androgen receptors, so it can cause gynecomastia and impotence in men, and menstrual cycle irregularities in women.

Osmotic diuretic mannitol remains in the extracellular space and expands it. The result of the expansion of the extracellular space can be pulmonary edema, which is the most serious complication of mannitol administration. Also, due to excessive withdrawal of water from the central nervous system, confusion, visual disturbances, lethargy, convulsions, and even coma may occur. Sometimes mannitol causes the so-called osmotic nephrosis, i.e,. acute renal failure. Finally, after administration of larger doses of mannitol, hyponatremia (due to withdrawal of intracellular water into the extracellular space) or hypernatremia (due to excessive diuresis and water loss) may occur.

Calcium channels blockers

Calcium channels blockers are antihypertensives that are generally well tolerated. Mild side effects in the form of headache, facial redness, constipation and leg swelling at the level of the malleolus rarely occur. Verapamil may cause constipation in elderly patients. In principle, calcium channels blockers should not be given together with blockers of β-adrenergic receptors. Since both drugs slow conduction through the A-V node in the heart, their simultaneous administration (especially if at least one of them is given parenterally) can lead to complete A-V block). Also, calcium channels blockers that act on the myocardium (verapamil and diltiazem) should not be given to people with heart failure because they can worsen it due to the weakening of the strength of heart contraction. Overdosing of calcium channel blockers results in hypotension, bradycardia and/or A-V block.

When it comes to nifedipine, one should avoid the use of larger doses than 20 mg at once, because sudden vasodilatation, drop in blood pressure and reflex tachycardia occur; if the patient already has coronary disease, an attack of angina pectoris and even a myocardial infarction may occur. Some studies have shown that nifedipine can worsen heart failure.

Specific side effect of dihydropyridine calcium channel blockers (nifedipine, amlodipine, nicardipine), discovered only after their long-term widespread use, is gingival hypertrophy. This side effect can be particularly problematic in patients who wear dentures, which will no longer fit well on the tissue and cause pressure sores and pain.

CLINICALLY SIGNIFICANT INTERACTIONS OF ANTIHYPERTENSIVES

As with other drugs, interactions involving antihypertensives can be divided into pharmacokinetic and pharmacodynamic. Pharmacokinetic interactions can occur at the level of absorption, distribution, metabolism and excretion.

When it comes to interactions at the level of absorption, the most important one is between methyldopa and oral iron preparations, considering that both drugs are often taken during pregnancy (methyldopa is safe from the aspect of teratogenicity and fetotoxicity, while iron is often prescribed to treat anemia in pregnancy) . Iron binds to methyldopa, forms an insoluble compound and thus interferes with the absorption of methyldopa, up to 50%.

Metabolism of antihypertensive drugs takes place through several cytochromes. Beta blockers are mostly metabolized through cytochrome **CYP2D6**, so drugs that inhibit this cytochrome (inducers are currently unknown) lead to an increase in the concentration of beta blockers in the blood and increase their effect: amiodarone, antidepressants paroxetine and

fluoxetine, the antifungal drug terbinafine. Angiotensin receptor inhibitors irbesartan and losartan, as well as a diuretic torsemide, are metabolized on cytochrome **CYP2C9**; their blood concentration and effect will be increased by inhibitors of that cytochrome (amiodarone, fluconazole, metronidazole, co-trimoxazole), and reduced by inducers (phenobarbital, carbamazepine, rifampicin, phenytoin). All calcium channel blockers (verapamil, diltiazem, nifedipine, felodipine, amlodipine) are metabolized by cytochrome **CYP3A4**; however, verapamil and diltiazem are simultaneously strong inhibitors of that cytochrome. Although inducers (phenobarbital, carbamazepine, rifampicin, phenytoin and St. John's wort) and inhibitors (clarithromycin, erythromycin, ketoconazole, itraconazole, voriconazole) of cytochrome CYP3A4 can decrease or increase the concentration of calcium channel blockers in the blood and their effect, this has no major clinical significance. Cytochrome inhibition of CYP3A4 has much more serious consequences under the influence of diltiazem or verapamil on drugs from other pharmacotherapeutic groups that are used simultaneously. For example, diltiazem and verapamil can **increase the blood concentration of simvastatin**, atorvastatin and fluvastatin; since the effect on simvastatin is the greatest, its dose must be reduced. It is similar with an oral anticoagulant **rivaroxaban and colchicine**, a drug to stop gout attacks; if patients take verapamil or diltiazem at the same time, the doses of these two drugs must be reduced, or bleeding or toxic effects of colchicine will occur.

At the excretion level , the interaction between **lithium** on the one hand, and diuretics, ACE-inhibitors, angiotensin receptor blockers and aldosterone receptor blockers on the other is particularly important. All the mentioned antihypertensives reduce the reabsorption of sodium, as a result of which the reabsorption of lithium is increased, its concentration in the blood and the frequency of side effects increase compensatory. Therefore, it is best not to administer lithium and antihypertensives from the mentioned groups at the same time.

Glycoprotein P is a protein pump that ejects drug molecules from the cell, hinders their absorption in the digestive tract, prevents their passage through the blood-brain barrier and prevents reabsorption in the kidneys from primary urine. **Verapamil** is a strong inhibitor of glycoprotein P, so it can significantly increase the blood concentration of the oral anticoagulant dabigatran and cardiotonic digoxin. As both dabigatran and digoxin are drugs with a narrow therapeutic range, an increase in their blood concentration above the therapeutic range will cause toxic effects.

Spironolactone and digoxin are relatively often combined in the treatment of heart failure, so it should be known that spironolactone increases the concentration of digoxin in the plasma, and that signs of digoxin toxicity (depression of the ST-segment, and bigeminy) can be expected. The exact mechanism of this pharmacokinetic interaction has not yet been determined.

Within **the pharmacodynamic interactions**, diuretics may enhance the hypotensive effect of ACE inhibitors and angiotensin receptor blockers, so one should never initially introduce an ACE inhibitor or angiotensin receptor blocker into the therapy as a combined preparation with a diuretic. Diuretics

enhance the hypotensive effect of both alpha-blockers and beta-blockers, so although their use should be avoided when introducing alpha-blockers into the therapy (because, as with ACE-inhibitors, the hypotensive effect is greatest at the beginning of therapy), later it is possible to combine them.

When potassium-sparing diuretics and ACE inhibitors or angiotensin receptor blockers are given together, the risk of hyperkalemia increases, so these combinations are considered contraindicated.

Nonsteroidal anti-inflammatory drugs (NSAIDs) block the diuretic effect of thiazides; on the other hand, the nephrotoxic effect of NSAIDs is enhanced in the presence of diuretics. Also, NSAIDs increase the risk of hyperkalemia when given together with potassium-sparing diuretics.

Hypokalemia caused by diuretics increases the proarrhythmogenic effect of antiarrhythmics (disopyramide, flecainide, amiodarone, lidocaine, sotalol, digoxin), so monitoring and eventual correction of serum potassium levels are necessary conditions for the safe simultaneous use of antiarrhythmics and diuretics.

Beta blockers enhance the hypotensive effect of ACE inhibitors, alcohol, and alpha blockers. Their enhanced negative inotropic effect can also be expected when they are given together with antiarrhythmics. Also, the risk of bradycardia, conduction block and heart failure is increased when beta blockers are given together with amiodarone.

When given together with nifedipine, beta blockers have a higher risk of causing hypotension and heart failure; when given together with verapamil or diltiazem, beta blockers have a higher risk of causing AV block, hypotension or heart failure.

If beta blockers are given together with adrenaline, noradrenaline or dobutamine, severe hypertension with bradycardia can occur, because due to the blockade of beta-2 receptors in the arteries of the extremities, there is no vasodilator part of the catecholamine effect.

The risk of ventricular arrhythmias is increased when sotalol is given together with amiodarone, disopyramide or procainamide. Sotalol should be avoided at the same time with tricyclics antidepressants or typical antipsychotics, because the risk of ventricular arrhythmias increases.

Among the other significant interactions of beta-blockers, it should be mentioned that propranolol increases the risk of toxic effects of lidocaine (hypotension, arrhythmias, convulsions), and that the concentration of metoprolol in the plasma increases with antidepressants citalopram, escitalopram and paroxetin.

Calcium channel blockers also interact significantly with other drugs. When verapamil or diltiazem is administered with antiarrhythmics, the risk of bradycardia, AV block, myocardial depression and asystole is increased.

Antipsychotics phenothiazines enhance the hypotensive effect of beta blockers. Hypokalemia caused by diuretics enhances the proarrhythmogenic effect of antipsychotics

Other antihypertensive agents may potentiate each other's hypotensive effect, and this is the most common interaction to be expected. Other types of interactions are rarely encountered, or have no clinical significance.

PREVENTION OF STROKE AND MYOCARDIAL INFARCTION

Prevention of ischemic stroke (or transient ischemic attacks - TIA) and myocardial infarction can be primary (in persons who have never had a stroke/TIA or myocardial infarction before, but have significant risk factors) or secondary (in persons who have undergone a stroke stroke or myocardial infarction).

Primary prevention of cerebral stroke/TIA

In the primary prevention of ischemic stroke, non-pharmacological measures must first be used: changing the way of eating and introducing regular physical activity. Then the risk factors for stroke should be treated - hypertension, diabetes mellitus and hyperlipidemia. Aspirin in antiplatelet doses (75-100 milligrams per day) in middle-aged and elderly people without cardiovascular diseases was examined in the studies. It has been shown that aspirin relatively reduces the risk of stroke by about 19%, but also increases the risk of serious bleeding by a similar percentage. Due to such results, there are no clear recommendations whether primary prevention with aspirin is justified or not in people without cardiovascular diseases.

The situation is much clearer in people with atrial fibrillation, where the prophylactic administration of oral anticoagulants significantly reduces the risk of ischemic stroke (relative risk reduction by 60-80%), so it is recommended in all guidelines. New oral anticoagulants (dabigatran , rivaroxaban , apixaban) are somewhat more effective in this indication than warfarin, and less often lead to bleeding in the brain as an unwanted effect.

In addition, there is no justification for the prophylactic administration of small doses of acetylsalicylic acid in people with stenosis of carotid arteries, because the risk of ischemic stroke is not significantly reduced.

Risk factors for cerebral hemorrhage include hypertension, use of antiplatelet drugs, small vessel disease, and advanced age. In the primary prevention of bleeding in the brain, the most important thing is to treat hypertension, because the normalization of blood pressure leads to a relative reduction of the risk by about 60%.

Secondary prevention of cerebral stroke/TIA

If the previous stroke was caused by a venous embolus, patients should receive **oral anticoagulants** prophylactically. If the previous stroke was caused by thrombosis, then antiplatelet drugs should be used as secondary prevention. In the first 2-3 weeks, the patient should take clopidogrel and aspirin, and then a combination of **acetylsalicylic acid and dipiridamol** (in the form of **delayed**-release tablets). If the cause of the stroke was an embolism, but the origin of the embolus is unknown, then aspirin only is used for prevention of secondary stroke.

Primary prevention of myocardial infarction

In the primary prevention of myocardial infarction, it is first of all necessary to influence the patient to stop smoking, to reduce body weight so that the body mass index is below 25 kg/m^2 and the waist circumference is less than 102 cm in men and 88 cm in women, to walk at least 3 km in half an hour a day, and to eat food rich in vegetable fibers, antioxidants , and poor in simple sugars and saturated fatty acids. Then, on the basis of the Framingham scales, the patient's ten-year risk of coronary disease should be determined, because the use of drugs in primary prevention depends on the level of risk. **Statins** are used in primary prevention only in people aged 45-70 years with at least one risk factor (hyperlipidemia, smoking, diabetes or hypertension), whose ten-year risk of cardiovascular disease exceeds 10%. When it comes to the application **of acetylsalicylic acid,** recently new clinical studies have shown that the beneficial effect of aspirin in the primary prevention of myocardial infarction is associated with a significant increase in the risk of bleeding; therefore, aspirin is no longer recommended for primary prevention.

Arterial blood pressure should be normalized if it is elevated, using ACE - inhibitors that reduce the risk of myocardial infarction, especially if the patient has reduced renal function and proteinuria. If the patient has diabetes, it should be regulated.

Secondary prevention of myocardial infarction

Secondary prevention of myocardial infarction includes non-pharmacological and pharmacological measures. Non-**pharmacological measures** whose effectiveness has been proven include : smoking cessation, normalization of body weight with an appropriate diet, well-ballanced physical activity and regular annual flu vaccination. Pharmacological measures include: (1) **anti-aggregation therapy**: daily intake of 100 mg of acetylsalicylic acid until the end of life, or clopidogrel, prasugrel or ticagrelor if the patient does not

tolerate aspirin; if a patient after myocardial infarction had percutaneous coronary intervention with stent implantation, it is recommended to take a combination of P2Y12 inhibitors (clopidogrel, prasugrel, or ticagrelor) and aspirin in the first 12 months, and then only aspirin or P2Y12 inhibitors for life (if the patient has a high risk of bleeding, then the duration of dual antiplatelet therapy is reduced to 6 months) ; (2) taking one of **the ACE - inhibitors** (for ramipril and perindopril there are controlled studies that have proven a reduction in the frequency of re-infarction of myocardium by 20%); (3) taking one of **the beta-blockers**, if there are no contraindications: uncontrolled bronchial asthma, bradycardia below 60/min, AV block of 2nd or 3rd degree, decompensated heart failure or systolic pressure below 100 mm Hg; (4) if the LDL lipoprotein level is higher than 3.37 mM/L with a suitable diet, patients should take **some of the statins**, in order to achieve a target value of less than 2.59 mM/L ; this serum LDL level was associated with a significant reduction in the frequency of re-infarction. With the help of ACE -inhibitors and beta-blockers , arterial **blood pressure** should be **normalized** , as this additionally contributes to reducing the frequency of recurrent myocardial infarction.

TREATMENT OF STROKE

A stroke is a sudden onset of a neurological deficit that lasts longer than 24 hours. It occurs most often in people over 70 years old, and in 80% of patients it is caused by brain ischemia, and in 20% by intracerebrovascular bleeding. Ischemia can be the result of thrombosis, embolism or hypoperfusion, and bleeding occurs as a result of hypertension or poor blood coagulability (due to illness or medication).

To a patient who has experienced a stroke we should first ensure the patency of the airways and give oxygen. If there is hypoglycemia, it should be corrected immediately by administering 25-50 ml of 50% glucose intravenously (after this solution is infused, the infusion of physiological solution should be maintained for some time through the same venous catheter, in order to prevent vein thrombosis that can be caused by a hypertonic glucose solution). Arterial blood pressure should not be lowered too much, because hypoperfusion can worsen ischemia. It is necessary to leave a urinary catheter if the patient cannot urinate.

An emergency computed tomography should be performed, in order to determine whether the stroke was caused by ischemia or bleeding. Ideally , an emergency CT should be performed within the first 25 minutes of admission, and interpreted within the next 20 minutes, in order to immediately administer **intravenous thrombolytic therapy**, if it is ischemia and if the following conditions are met: the symptoms appeared less than three hours ago, the patient has not had a head injury, stroke or myocardial infarction in the last 3 months, the patient has not had a stroke in the last 21 days, there is no gastrointestinal or urinary tract bleeding, in the last 14 days there was no major surgery, and in the last 7 days there was not an arterial puncture in a place where

compresion cannot be performed, the patient had no previous intracranial bleeding, no low-molecular-weight heparins were applied in the last 24 hours, no new oral anticoagulants have been used in the last 48 hours, aPTT and INR are normal, less than 1.7, there is no hypoglycemia or hypertension and the number of platelets is greater than 100,000/mm^3. Alteplase (recombinant tissue plasminogen activator) 0.9 mg/kg in one dose is given, while streptokinase is no longer used. The risk of bleeding in the brain after the use of alteplase is about 6%. Tenecteplase can be used instead of alteplase, with somewhat better results. Anticoagulant and antiplatelet therapy are not given in the first 24 hours after the administration of thrombolytics. Before the administration of thrombolytics, it is necessary to control blood pressure using antihypertensives (e.g., nicardipine intravenously) to be lower than 80/105 mm Hg , as this reduces the risk of bleeding as a complication of thrombolysis.

In patients who cannot receive intravenous thrombolysis, if 6 hours have not passed since the first symptoms, it is possible to apply a thrombolytic intra-arterially or perform mechanical thrombectomy by endovascular approach, but only in specialized centers with trained doctors.

Application of anticoagulants (heparin and low molecular weight heparin) does not affect the outcome of ischemic stroke, so they **should not be used**.

The use of aspirin in the first 24 to 48 hours after ischemic brain infarction is indicated, because there is a modest reduction in mortality and morbidity in such patients. A daily dose of 325 mg is recommended. If the patient has a high risk of transient ischemic attacks or recurrent stroke, clopidogrel or ticagrelor can be used in addition to aspirin during the first 21 days .

Vasodilators such as pentoxifylline should not be given after ischemic stroke because they do not affect mortality and morbidity. The same is true for a large group of " neuroprotective " drugs, the effectiveness of which has also not been proven.

If the cause of the stroke is **intracerebral bleeding** (which is established on an emergency CT scan), then the following measures should be applied: (1) normalization of arterial blood pressure so that the systolic pressure is around 140 mm of mercury; (2) if the bleeding occurred due to the use of oral anticoagulants vitamin K antagonist (warfarin, acenocoumarol) , apply freshly frozen plasma (20 ml/kg of body weight) or prothrombin complex concentrate and vitamin K 10 mg intravenously; (3) if the bleeding occurred due to the previous administration of anti-aggregation drugs, there is no effective means to help the patient, except supportive therapy; (4) if the bleeding is caused by the use of dabigatran, the antidote **idarucizumab** can be used , and if the bleeding is caused by apixaban or rivaroxaban , the antidote is **andexanet alfa;** (5) of the surgical interventions, it is certain for now that only ventriculo-peritoneal shunt should be performed in the event of hydrocephalus and that large hematomas should be evacuated from the posterior fossa; (6) glycemia should be reduced if it exceeds 10 mM/L and body temperature should be normalized, and the patient should be well hydrated; (7) mechanical prophylaxis of deep vein thrombosis should be carried out; (8) if epileptic seizures occur, they should be suppressed with antiepileptic drugs .

TREATMENT OF ABSENCE

Typical absence is characterized by a sudden and short-term loss of consciousness, with the interruption of the activity that the person started before the attack. The loss of consciousness usually lasts up to 20 seconds, after which consciousness returns and the person resumes the activity he/she started. Loss of consciousness is usually accompanied by small twitches of the corner of the mouth or eyelids, drooping of the head on the chest, loosening of the hand grip, sometimes pallor, sweating, movements of licking the lips or swallowing. In EEG, during attacks, pathognomonic "spike-wave" complexes are registered that occur with a frequency of 3-4 Hertz. Absence occurs most often in childhood.

Absence can be prevented by monotherapy with antiepileptic drugs ethosuccimide or valproic acid. These two drugs are equally effective, and prevent attacks in about 80% of patients. When using these drugs, the dose should be gradually increased until the attacks are fully controlled, but monotherapy should not be abandoned until it is shown that even the maximum approved doses do not control the attacks.

If the patient does not respond well to one of these two drugs, he/she should be given the other. Finally, if the patient does not respond well to any of these drugs, a combination can be tried.

In patients who do not respond to the combination of ethosuccimide and valproic acid, an attempt should be made to give the full therapeutic dose of valproic acid and add a small dose of lamotrigine (most often 25 or 50 mg). It has been shown that more than 50% of patients resistant to the use of only ethosuximide or valproate, or to the use of a combination of these two drugs, can control seizures with a combination of valproate and lamotrigine.

In patients who are resistant to the combination of valproate and lamotrigine, acetazolamide or some benzodiazepine can be added, for example clonazepam. However, the success of such combinations is not great.

Carbamazepine, vigabatrin and tiagabine are contraindicated in patients with absence, because they can worsen the patient's condition. Phenobarbital, phenytoin and gabapentin are not effective in the treatment of absence, so they should not be used for that indication.

Atypical absence usually occurs as part of Lennox-Gastaut syndrome, and is distinguished from typical by longer duration, only partial loss of consciousness and more pronounced jerks or automatic movements. Clonazepam, valproate or felbamate are usually used to treat atypical absence.

TREATMENT OF GENERALIZED FORMS OF EPILEPSY

By the generalized form of epilepsy we mean only **primarily** generalized seizures, which begin in the thalamus or other subcortical structures, affect both

hemispheres of the cortex, and are always accompanied by loss of consciousness and bilateral symptoms. Generalized forms of epilepsy can be: tonic, atonic, clonic-tonic, clonic, myoclonic and absence. Since the treatment of absences has already been discussed in a separate chapter, here we will talk about the treatment of other generalized forms of epilepsy.

For the prevention (control) of ***tonic-clonic seizures and myocolonic seizures,*** the drug of first ***choice is valproate***, due to the multiple mechanisms through which it acts and the best results in clinical studies. Apart from valproate, lamotrigine, levetiracetam or topiramate can be used for tonic-clonic attacks (as monotherapy or additional therapy), but they are less effective than valproate; that's why we apply them only when patients cannot tolerate valproate for some reason. Perampanel or zonisamide are used only as additional therapy in these two types of epilepsy.

Phenytoin and phenobarbital can also be used for generalized tonic - clonic seizures, but they have many side effects. Newer antiepileptic drugs (lamotrigine, topiramate, zonisamide and levetiracetam) have the same effectiveness as these two old drugs, but less side effects. For resistant forms of tonic-clonic attacks, the very effective drug felbamate can be used . However, due to severe side effects (liver and bone marrow damage), felbamate is rarely used today.

Since among the mentioned drugs there are inducers of liver enzymes (carbamazepine, phenobarbital and phenytoin), one should be careful when a woman taking one of these drugs also takes oral contraceptives. Because of the induction, sex hormones are eliminated faster, and the protection of oral contraceptives is lost. A woman who has this form of epilepsy and is taking oral contraceptives along with some of the listed liver enzyme inducers should be informed about this.

Tonic and atonic seizures can be most effectively prevented by using valproate (alone or in combination with a benzodiazepine), and if it is not effective, clonazepam or vigabatrin can be used (this last drug carries a high risk of irreversible defects in the visual field). Phenytoin, phenobarbital and carbamazepine are not effective.

TREATMENT OF FOCAL ONSET SEIZURES

Focal onset seizures are characterized by the onset of seizures in a limited area (focus) of only one hemisphere. They can be **simple**, when consciousness is not lost, and **complex**, when there is a disturbance of consciousness.

In a number of pediatric patients, simple partial epilepsies are benign in nature and pass spontaneously. Then it is not necessary to include antiepileptic therapy. If, on the other hand, seizures are very frequent or are of such a nature that they interfere with the normal functioning of a person, it is necessary to introduce antiepileptic therapy.

When it comes to the choice of antiepileptic drugs for the prevention *of simple partial* seizures, there is agreement in the professional literature that none of the existing antiepileptic drugs **can be considered a drug of choice**. Namely, a large number of antiepileptics (except succinimide) have shown relatively similar effectiveness in the prevention of simple partial seizures, so the choice should be made based on the profile of the side effects of individual antiepileptics and the characteristics of the patient. However, if simple partial attacks are secondarily generalized, i.e., if it is about tonic- clonic seizures that have a clearly defined focal onset, one of the following antiepileptic drugs is used as monotherapy in the first line: carbamazepine, oxcarbazepine, phenytoin, topiramate, lamotrigine or levetiracetam. In the second line, as monotherapy or supplementary therapy, valproate, eslicarbazepine, pregabalin, gabapentin, lacosamide, zonisamide or cenobamate are used. Finally, clobazam, vigabatrin, tiagabine or felbamate are used as monotherapy or supplementary therapy for the treatment of secondary generalized tonic-clonic seizures.

In patients who experience the first attack **of complex focal onset seizures,** antiepileptic drugs should not be introduced immediately. First, a precise diagnosis of the type of epilepsy is made, the etiology and localization of the epileptic focus are determined, and antiepileptic drugs are introduced only if another seizure occurs. In the treatment of complex partial epilepsies, all antiepileptics can be used, with the exception of ethosuccimide. The drug should be chosen based on the profile of its side effects and the patient's characteristics, so that the least harm is done. In principle, complex focal onset seizures can be successfully prevented with only one drug (monotherapy).

STATUS EPILEPTICUS

Status epilepticus is a condition in which we have two or more consecutive epileptic seizures without full recovery of consciousness in between, or one seizure that lasts longer than 30 minutes. This, the so-called "***first time point***", means that the application of therapy is necessary; if the status is still not terminated, the "***second time point*** " is reached later, after 60 minutes, when long-term harmful consequences for the patient begin. The "second time point" is when more aggressive therapy must be instituted to terminate the status. Depending on the type of attack, status epilepticus can be convulsive or nonconvulsive. The incidence of status epilepticus is 10-60 cases per 100,000 person-years. It occurs most often in the first year of life and in people over 60 years old. The most common causes of status epilepticus in adults are stroke, hypoxia, metabolic disorders and alcohol poisoning or alcohol withdrawal syndrome. Mortality in this condition is 22% in adults, and about 3% in children.

Status epilepticus leads to serious disruption of the homeostasis of the body, which is manifested by lactic acidosis, hypoglycemia, hypoxia , elevated temperature, rhabdomyolysis and myoglobinuria.

First of all, the patient's airway should be secured, and oxygen should be administered. By means of crystalloid infusion blood pressure should be maintained with isotonic solutions. Apply immediately afterwards 50 ml of 50% glucose intravenously, together with 250 mg thiamine (vit. B_1). Antiepileptics should be administered as soon as possible. The drugs of first choice are **diazepam, midazolam or lorazepam**. Diazepam is administered intravenously, and if we cannot secure venous access, then rectally, as a microenema (there is a special preparation). The dose of diazepam is (0.15–2 mg/kg , maximum 10 mg. Although diazepam is slowly metabolized in the liver, due to its rapid distribution and decreasing concentration in the blood, its effect wears off after about half an hour, so it may happen that interrupted status epilepticus occurs again.

Lorazepam is less liposoluble than diazepam, so the distribution of the drug is less pronounced, and thus the effect lasts longer (6-12 hours). The dose is 0.1 mg/kg of lorazepam i.v. (maximum 4 mg).

Midazolam can also be used to terminate status epilepticus. The initial intravenous dose is 0.2 mg/kg. The drug can be given intramuscularly (10 mg) or buccally in a situation where the venous route cannot be provided.

If benzodiazepines did not stop status epilepticus, second-line therapy is applied. Phenytoin can be given intravenously in a dose of 15-20 mg/kg , at a rate of 20-50 mg per minute. Phenytoin is incompatible with glucose solutions and other drugs, so it should be administered through a separate intravenous line. If extravasation occurs, the hand distal to the application site becomes blue-purple and then edematous ("blue-purple glove" syndrome). Phenytoin can cause arrhythmias and hypotension in people over 40 years of age (due to the solvent propylene glycol). Instead of phenytoin its pro-drug **fosphenytoin** is given today, which is soluble in water, so it does not mix with propylene glycol . The initial dose of fosphenytoin is 15-20 mg/kg , and it is given rapidly up to 150 mg/min. An alternative to fosphenytoin in the second-line treatment of status epilepticus are **levetiracetam** (60 mg/kg) and **valproate** (40 mg/kg), if there are preparations available on the market for intravenous administration.

If fosphenytoin, levetiracetam or valproate are not effective, status epilepticus may respond well to **phenobarbital**. Dose of fenobarbital is 10-20 mg/kg intravenously, at a rate of up to 100 mg/min. Phenobarbital, like phenytoin, is dissolved in 60-80% propylene glycol which can cause myocardial depression or kidney failure. Phenobarbital can also cause respiratory depression and hypotension.

When even second-line therapy does not stop the status epilepticus , then we are talking about **a refractory status**. Refractory status epilepticus is treated by introducing the patient into **general intravenous anesthesia** with the use of rocuronium as a neuromuscular blocker for the introduction itself. The best results are achieved using midazolam or ketamine . If the refractory status continues even after 24 hours from the introduction of the patient into anesthesia, such a condition is called **super-refractory status** epilepticus .

ADVERSE EFFECTS OF ANTIEPILEPTICS

Antiepileptics are drugs that are used for a long time, usually to prevent epileptic attacks or to stabilize mood. Due to long-term use and their mechanism of action (they interfere with the functioning of neurotransmitters and ultimately affect the functioning of ion channels in the membranes of neurons, changing the level of their activity), these drugs disrupt many physiological functions, leading to a large number of side effects. Such side effects, which represent an extension of the pharmacological effect of the drug (and are designated in the literature as "A" type of side effects) are the most common, and are found in all antiepileptic drugs. Type "B" (idiosyncratic side effects) and type "C" (side effects that imitate diseases) side effects occur much less often, and not with all antiepileptic drugs.

Carbamazepine and oxcarbazepine have similar side effects of type "A", only they are less pronounced with oxcarbazepine. In addition to gastrointestinal complaints, diplopia, blurred vision, dizziness, drowsiness, confusion, ataxia, dyskinesias, hyponatremia (due to increased effects of antidiuretic hormone) and, in the elderly, slowing of heart rate. carbamazepine can cause generalized erythema, Stevens-Johnson syndrome, leukopenia and aplastic anemia, and from "C" side effects osteoporosis. Only carbamazepine induces synthesis of CYP3A4 in the liver, so it accelerates the elimination of drugs that are metabolized by the same isoenzyme. This is especially important for oral contraceptives, warfarin and ciclosporin, whose concentration in the blood (and thus the effect) decreases significantly if they are used together with carbamazepine.

Side effects **of phenytoin** are also numerous, and significantly more frequent at higher doses. Tremor, nystagmus, blurred vision, ataxia, confusion, gastrointestinal complaints ("A" type) may occur, as well as gingival hypertrophy, coarse facial features, acne, and in women hirsutism. Like carbamazepine, it induces the metabolism of other drugs and vitamins. Due to the increase in their decomposition, there is a lack of folic acid and vitamin D, so megaloblastic anemia, cerebellar atrophy and osteomalacia may occur ("C" type of adverse drug reactions). Also, the metabolism of warfarin and ciclosporin is accelerated.

Undesirable effects of **valproic acid** and its salts include gastrointestinal complaints, rarely pancreatitis, weight gain due to appetite stimulation, transient alopecia and growth of curly hair, polycystic ovary syndrome, thrombocytopenia, tremor, ataxia and confusion. At the first time of therapy, valproic acid can cause severe chemical hepatitis (this is especially common in children under 3 years old). Therefore, during the introduction of valproic acid into the therapy, liver function must be frequently monitored (primarily the level of transaminases in the serum).

Carbamazepine, phenytoin and especially valproate have **a teratogenic effect, as they increase the risk of** neural tube defects by several percents in children of pregnant women who used them during the first trimester. In order to prevent this side effect, pregnant women who are forced to use any of these three antiepileptic drugs in the first 5 months of pregnancy also take 5-10 milligrams of folic acid per day.

Some of the side effects **of lamotrigine** are similar to the side effects of carbamazepine: rash, drowsiness, diplopia, ataxia, headache, tremors. However, lamotrigine has one specific side effect : it causes *a flu-like syndrome*, most likely due to its effect on prostaglandin synthesis. In addition, if lamotrigine is administered initially in a full dose in a drug-naïve patient, the risk of developing Stevens-Johnson syndrome increases significantly; therefore, the golden rule is to introduce lamotrigine into the therapy gradually, first with small doses that are gradually increased.

Similar to carbamazepine and phenytoin**, phenobarbital** can cause - sedation, fatigue and confusion. In old people, the appearance of paradoxical excitement is possible, and in children, hyperactivity. It leads to folic acid deficiency, because it accelerates its metabolism in the liver. Due to disruption of vitamin D metabolism, it leads to osteoporosis, and the occurrence of connective tissue diseases such as shoulder-hand syndrome, Peyronie's disease and plantar fibromatosis. Similar to phenytoin and carbamazepine, it often leads to skin rashe. Phenobarbital accelerates the metabolism of many drugs, which leads to the loss of their therapeutic effect (e.g., cyclosporine, warfarin, oral contraceptives). It causes psychological and physical dependence.

Ethosuccimide has very few side effects (nausea and anorexia). **Vigabatrin** in addition to the usual adverse effects of type "A" (drowsiness, dizziness, ataxia), also has a serious adverse effect on the retina: it leads to defects in the visual field. That is why its use today is limited only to those patients who do not respond to other antiepileptic therapy. **Gabapentine** can cause drowsiness, ataxia, fatigue, diplopia, nystagmus and tremor. In some people, it also leads to weight gain.

Topiramate is relatively well tolerated; most of the side effects occur in the first 4 weeks: sleepiness, fatigue, difficulty in the movements, confusion. After prolonged use, the appearance of kidney stones has been observed in some patients. It reduces sweating, so in the summer it can lead to hyperthermia. It can also cause acute glaucoma. **Tiagabine** sometimes causes tremors, loss of concentration, aggressiveness and lethargy. **Leveritacetam** can cause drowsiness, depression, aggressiveness, very rarely psychotic reactions; from side effects of type "B" it rarely causes thrombocytopenia.

The most common side effects **of benzodiazepines** are drowsiness, poor motor coordination, confusion and memory loss. Hallucinations, blurred vision, paradoxical excitation and gastrointestinal complaints occur less frequently. *Tolerance* develops to benzodiazepines, and patients become psychologically and physically *dependent* after long-term use of these drugs. If you suddenly stop taking benzodiazepines, a withdrawal syndrome occurs, which consists of the

following symptoms: insomnia, anxiety, tremors, muscle weakness, nausea, hyperalgesia and convulsions (they occur rarely).

In practice, it is very important not to forget that benzodiazepines have an additive depressant effect on the CNS with many other drugs: alcohol , other sedatives, antipsychotics, antihistamines, antiepileptics, opioids and antidepressants .

Of the newer antiepileptics , **stiripentol** and **zonisamide**, apart from side effects of type "A" that are common to all antiepileptics (drowsiness, ataxia, dizziness, irritability), lead to a loss of body weight in patients. Stiripentol still causes neutropenia, and zonisamide oligohidrosis, hyperthermia and nephrolithiasis (similar to topiramate). For **eslicarbazepine** , in addition to side effects of type "A", no serious side effects arising from other mechanisms were recorded. As previously mentioned, **felbamate** is now extremely rarely used because of the severe hepatitis and aplastic anemia it can sometimes cause.

CLINICALLY SIGNIFICANT INTERACTIONS OF ANTIEPILEPTIC DRUGS

Since antiepileptic drugs are sometimes combined, there is a possibility of interactions between them. Carbamazepine, phenobarbital and phenytoin are strong **inducers** of microsomal enzymes of the liver, so that they reduce the concentration in the blood of antiepileptic drugs that are administered together with them (for example, lamotrigine). On the other hand, valproate **inhibits** the metabolism of phenobarbital and lamotrigine (which leads to an increase in their concentration in the blood), and phenytoin displaces it from the connection with plasma proteins, leading to an increase in the concentration of the free fraction of the drug in the blood (and thus to an increase in the effect of phenytoin).

Antiepileptics are often combined with other drugs, due to their long-term use and frequent comorbidities in these patients. Due to the frequent combination with other drugs, conditions are created for the emergence of interactions. Clinically, the following interactions are the most significant:

1. Antidepressants and antipsychotics antagonize the effect of antiepileptics, so they can reduce the threshold for the onset of convulsions in a person who is already taking antiepileptics;
2. Phenobarbital accelerates metabolism and reduces the effect of tricyclic antidepressants, aripiprazole, clozapine, calcium channel blockers, chloramphenicol, cyclosporine, tacrolimus, coumarin derivatives, corticosteroids, estrogens, gestagens, eplerenone, protease inhibitors, theophylline, telithromycin;
3. Carbamazepine accelerates metabolism and reduces the effect of tricyclics antidepressants, aripiprazole, imatinib, simvastatin, estrogen, gestagens, eplerenone, and telitromycin; on the other hand, diltiazem,

verapamil, tricyclic antidepressants and nefazodone increase the concentration of carbamazepine in serum;
4. Metabolism of carbamazepine is inhibited and its plasma concentration is increased by clarithromycin, erythromycin, cimetidine, fluoxetine, fluvoxamine, and isoniazid;
5. The metabolism of ethosuccimide is inhibited by isoniazid, and accelerated by phenytoin ;
6. Estrogens and rifampicin reduce the concentration of lamotrigine in the blood;
7. Carbamazepine and oxcarbazepine reduce the effectiveness of clopidogrel;
8. Oxcarbazepine reduces the blood concentration of estrogen, gestagen and imatinib;
9. The metabolism of phenytoin is inhibited and its concentration in the blood increases by amiodarone, chloramphenicol, cimetidine, fluconazole, fluoxetine, fluvoxamine, sertraline, isoniazid, topiramate, trimethoprim and miconazole.
10. Phenytoin accelerates metabolism and reduces the effect of tricyclic antidepressants, aripiprazole, cyclosporine , corticosteroids, estrogens, gestagens , coumarins, eplerenone, imatinib and telithromycin;
11. Topiramate accelerates the metabolism of estrogen and gestagens;
12. The concentration of valproate in plasma is reduced by carbapenems (meropenem and imipenem);
13. Cimetidine inhibits valproate metabolism;
14. When valproate is used together with olanzapine, the risk of side effects, including neutropenia, increases;
15. Brivaracetam, one of the newer antiepileptic drugs, interacts relatively little with other drugs - phenytoin, carbamazepine, phenobarbital and rifampicin accelerate its metabolism and reduce the area under the curve of brivaracetam concentration in plasma by 19-45%.
16. Carbamazepine, phenytoin and phenobarbital accelerate the metabolism of perampanel.

TREATMENT OF SCHIZOPHRENIA

The first step in the treatment of schizophrenia should be to confirm the diagnosis and rule out psychoses caused by organic diseases, drugs or abuse of various chemical substances. Then the patient should be given an antipsychotic orally, in a dose of 300 to 1000 mg of chlorpromazine equivalent per day (that is, whichever antipsychotic to choose, the dose should be of similar effectiveness to the mentioned doses of chlorpromazine). Today, therapy is usually started with some of the second-generation antipsychotics, due to the less pronounced extrapyramidal side effects and the absence of unwanted anticholinergic, antiadrenergic, and proarrhythmic effects. The antipsychotic should be given

initially in the lowest dose, which is then gradually increased until the patient's optimal response. The antipsychotic is given for 4-6 weeks, after which the effect should be assessed. If the condition of the patient's pain is good, the therapy continues, and if the drug has not achieved the desired effect or has unwanted effects that the patient cannot tolerate, the doctor should prescribe another antipsychotic.

The use of a combination of antipsychotics is not recommended, unless the disease does not respond to monotherapy. If the patient does not take medication regularly, one should switch from oral therapy to the use of antipsychotics in the form of long-acting depot preparations. Today, depot preparations of haloperidol and risperidone are mostly used.

If the patient is taking any of the atypical antipsychotics, biochemical parameters from the serum (glycemia, lipids, glycosylated hemoglobin) should be monitored periodically, in order to detect metabolic disorders in time.

If the patient has not responded satisfactorily to at least two antipsychotics given for 4-6 weeks each, he/she should be prescribed clozapine. When clozapine is prescribed, the blood count should be checked every week for the first 18 weeks, and then once a month. Clozapine, as the most effective antipsychotic, is also prescribed in cases where the patient, despite therapy with other drugs, shows a strong tendency to commit suicide or is still aggressive towards the environment.

In case the patient does not respond favorably to any antipsychotic, or is in catatonia or severe depression, electroconvulsive therapy can be applied.

In the case that depression develops in a stable patient on antipsychotic therapy, it should be treated with antidepressants .

Extrapyramidal side effects are successfully treated with anticholinergic drugs, by reducing the dose of antipsychotics or by switching to an antipsychotic with less pronounced extrapyramidal effects . This is especially true if the patient develops an acute dystonic reaction after the administration of the first doses of antipsychotics. If the patient develops akathisia during treatment with antipsychotics, he/she can be helped by one of the following procedures: reducing the dose of antipsychotics, switching to another antipsychotic, using benzodiazepines or using beta blockers. For the treatment of tardive dyskinesias today there are reversible inhibitors of vesicular monoamine transporter 2 (VMAT2): **tetrabenazine, deutetrabenazine and valbenazine**. These drugs lead to a decrease in the amount of dopamine, serotonin and noradrenaline in the vesicles of nerve endings, as a result of which they affect transmission; have been shown to be effective in reducing involuntary movements in tardive dyskinesia, but also in Huntington's chorea .

During the pregnancy of a person with schizophrenia, antipsychotics should be used , because the risk of complications of untreated schizophrenia for the mother and the fetus is greater than the possible teratogenic or fetotoxic effects of these drugs.

TREATMENT OF ACUTE PSYCHOSIS

Acute psychosis is a mental condition in which the patient suddenly loses the sense of reality, and has symptoms such as crazy ideas, hallucinations, illusions, mood disorders and bizarre behaviors. Patients are sometimes very anxious and agitated, and sometimes not. The non-pharmacological measures should first be tried, i.e., to make an attempt to persuade the patient to cooperate by calm talk and demeanor. If that fails, drug therapy is used.

The drugs of first choice for acute psychosis are **risperidone** (2 mg) and **olanzapine** (10 mg), orally. The drug of second choice is haloperidol (2-5 mg), also orally. If it is not possible to give the patient drugs orally, then olanzapine **should** be administered 10 mg intramuscularly or **haloperidol** 5 – 10 mg intramuscularly or intravenously (caution). The antihistamine **promethazine** can be successfully combined with haloperidol (25 mg orally or in the form of a deep intramuscular injection), which has a sedative effect and somewhat suppresses the extrapyramidal effects of haloperidol. If olanzapine is used, benzodiazepines ***must not*** be given additionally, because excessive sedation and cardiorespiratory depression will occur. **Lorazepam** 1-2 mg orally or intramuscularly can be added to other antipsychotics, if the antipsychotic alone does not calm the patient.

If, along with acute psychosis, the patient has symptoms of mania, lithium is added to the antipsychotic as a mood stabilizer. On the other hand, if the patient is extremely depressed, an antidepressant can be added to the antipsychotic, or in severe cases electroconvulsive therapy can be applied.

TREATMENT OF DELIRIUM

Delirium or acute confused state is actually a syndrome that consists of the following symptoms: loss of orientation in time, space and towards persons, disruption of the thought process and perception disruption. Delirium typically has an acute onset and a course with alternating improvements and worsening. The patient may be hyperactive or hypoactive during the delirium. Delirium occurs extremely often in elderly patients who are hospitalized, because it represents a great psycho-physical stress for them (almost every third person over the age of 65 who is hospitalized experiences delirium). If delirium is not treated on time or is treated inadequately, permanent consequences in terms of cognitive impairment may remain.

When we establish the existence of delirium, we should first try to talk to the patient in order to calm him down. At the same time, we should look for the cause of delirium and try to eliminate it, e.g., medicine as a cause, dehydration as a cause, infection as a cause, pain as a cause, etc.). If the patient does not agree

to the interview and the elimination of the cause does not lead to the calming of the delirium, drugs that can calm the patient must be administered. The drugs of choice for this indication are **risperidone** (2 mg), **olanzapine** (5-10 mg) or **haloperidol** (2-5 mg, second choice) orally . If it is not **possible** to give drugs orally, **olanzapine** (10 mg) or **haloperidol** are administered intramuscularly. Benzodiazepines should not be used, as they lead to cardiorespiratory depression in interaction with olanzapine, and also in old people, they can cause paradoxical excitation. Treatment with antipsychotics should be continued for at least 7 days, during which time the delirium should resolve.

ADVERSE EFFECTS OF ANTIPSYCHOTICS

Antipsychotics are drugs with a lot of side effects, because they act through multiple receptors; their application is always a compromise between the desired effect and the damage caused by unwanted effects.

Because of its indiscriminateness antipsychotics block receptors in other dopaminergic pathways besides the meso-limbic and meso-cortical ones. This is the reason for the appearance of their most common side effects: a syndrome similar to Parkinson's disease (akinesia , rigidity and tremors), acute dystonia (curving of the neck, head, face, oculomotor crises, trismus), akathisia (the patient has the feeling that he must constantly move, which are followed by attacks of hypermotility) and tardive dyskinesias (appearance of choreiform movements, tics or dystonia after several months of therapy, which decrease after rest) due to blockade of the nigro-striatal pathway; milk secretion (galactorrhoea), amenorrhea, gynecomastia, loss of libido in men, and increased libido in women, all due to blockage of the tubero-infundibular pathway and increased secretion of prolactin (often occurs with typical antipsychotics, then risperidone and sometimes olanzapine and ziprasidone). Extrapyramidal side effects (Parkinsonism, tardive dyskinesia, akathisia and dystonia) especially occur with typical antipsychotics that bind tightly to dopamine receptors, such as haloperidol. Parkinsonism-like syndrome and acute dystonia are treated with the use of anticholinergics (e.g., benztropine), and akathisia by reducing the dose of antipsychotics or adding a small dose of propranolol. Late dyskinesia was previously suppressed by gradually transferring the patient to another antipsychotic, usually an atypical one. However, for the treatment of late dyskinesias, there are also reversible inhibitors of vesicular monoamine transporter 2 (VMAT2): **tetrabenazine, deutetrabenazine and valbenazine**. These drugs lead to a decrease in the amount of dopamine, serotonin and noradrenaline in the vesicles of nerve endings, as a result of which they affect transmission; have been shown to be effective in reducing involuntary movements in tardive dyskinesia , but also in Huntington's chorea.

Recently, it has been understood that hyperprolactinemia is associated with osteoporosis, so psychotic patients who have pronounced

hyperprolactinemia and osteoporosis should be switched to a new atypical antipsychotic aripiprazole (because it does not raise prolactin levels).

Antipsychotics also block muscarinic receptors, so they often exhibit unwanted anticholinergic effects: constipation, difficulty urinating, dry mouth, difficulty sweating, accommodation disorder. These effects are particularly pronounced with the phenothiazine group of typical antipsychotics and with atypical antipsychotics clozapine. In larger doses, olanzapine and quetiapine also have anticholinergic effects .

To some extent, typical antipsychotics block also α- adrenergic receptors leading to postural hypotension and impossibility of ejaculation. Antipsychotics also set the hypothalamic thermostat to a lower value, resulting in hypothermia.

All anti psychotics potentially cause heart rhythm disorders (especially thioridazine , which causes prolongation of the QT-interval, and ziprasidone), have a sedative effect (phenothiazines and clozapine the most, followed by quetiapine and olanzapine), cause postural hypotension (phenothiazines and clozapine the most, followed by risperidone and quetiapine), disorders in the sexual sphere, have a proconvulsant effect (especially phenothiazines and clozapine) and in a small number of patients cause hepatitis followed by icterus.

A rare but very serious side effect of antipsychotics is the so-called neuroleptic malignant syndrome. It is characterized by muscular rigor, an increase in body temperature and hypotension with a tendency to progress into a shock state. It is treated primarily by stopping the use of antipsychotics, a drug that prevents the release of calcium from the sarcoplasmic reticulum (dantrolene), bromocriptine and non-specific measures to combat acidosis and shock. If the patient is agitated, he/she should be calmed down by the use of benzodiazepines.

Due to the blockade of H_1 histaminergic receptors, many antipsychotics (especially phenothiazines) cause sedation, so this is the reason that total daily dose of the drug is taken once in the evening, before going to bed.

Antipsychotics cause photosensitisation, and can be deposited in the cornea, lens and retina (thioridazine can also cause retinopathy).

Clozapine it has a special tendency to cause neutropenia (especially in elderly women), so it is necessary to monitor the number of leukocytes in the peripheral blood during therapy with this drug. Another side effect specific to clozapine is sialorrhea, which occurs in about 90% of patients on this drug. Sialorrhea is caused by the cholinergic effect of clozapine, i.e., by stimulating muscarinic receptors. If sialorrhea is less pronounced, it can be treated with local application of ipratropium or atropine preparations (sublingually or in the form of inhalation); in severe cases, anticholinergics must be administered systemically, e.g., trihexyphenidyl, biperiden or benztropine. Finally, in some patients in the first few months of therapy, clozapine can cause **myocarditis**, which, if not treated, leads to heart failure. Myocarditis is manifested by chest pain, dyspnea, fatigue, swelling of the legs, palpitations, orthopnea and often elevated temperature. When using clozapine, one should be careful in the first few months, and in case of suspicion of myocarditis, urgently perform ECG and

myocardial enzymes in the serum; if a diagnosis of myocarditis is made, clozapine must be stopped immediately. Myocarditis usually resolves after discontinuation of cozapine .

Some of the atypical antipsychotics cause obesity and metabolic disorder in terms of type 2 diabetes mellitus; clozapine and olanzapine cause the metabolic disorder the most frequently . Aripiprazole and ziprasidone have the least tendency to cause obesity and type 2 diabetes.

CLINICALLY SIGNIFICANT INTERACTIONS OF ANTIPSYCHOTICS

Because they are administered for a long time, metabolized by cytochromes in the liver, and act through multiple receptors, antipsychotics have a high tendency to interact with other drugs. In addition, in practice, they are often combined with other psychotropic drugs (with antidepressants, mood stabilizers and benzodiazepines), sometimes unjustifiably, which further increases the likelihood of undesirable interactions. The clinically most important interactions of antipsychotics are as follows:

1. Macrolide antibiotics and fluoroquinolones inhibit the metabolism of many antipsychotics and thus increase their concentration in the blood; also, due to the blockage of potassium channels in the heart, these antibiotics, together with antipsychotics, can prolong the QTc interval and lead to ventricular arrhythmias or even fibrillation. The use of macrolide antibiotics and fluoroquinolones is not recommended in patients on antipsychotic therapy.
2. Out of the drugs for the treatment of tuberculosis, rifampicin accelerates the metabolism of antipsychotics, and isoniazid inhibits it: this leads to a decrease or an increase in the concentration of antipsychotics in the blood, and thus to a change in their effect.
3. The use of azole antifungals in patients on antipsychotic therapy is also associated with the possibility of adverse interactions. Ketoconazole, itraconazole and posaconazole are strong inhibitors of cytochrome 3A4, so they significantly increase the concentration of antipsychotics in the blood. Fluconazole and voriconazole inhibit cytochromes significantly less, but therefore prolong the QTc interval and increase the risk of ventricular arrhythmias if given together with antipsychotics.
4. Antiviral drugs also significantly interact with antipsychotics. Protease inhibitor ritonavir inhibits cytochromes 3A4 and 2D6, and induces cytochrome 1A2; due to this effect, this drug increases the concentration in the blood of most antipsychotics , except for clozapine and olanzapine, whose concentration decreases in the blood because they are metabolized via cytochrome 1A2. Another protease inhibitor indinavir also induces cytochrome 1A2, so the consequence of its application is the

acceleration of the metabolism of clozapine and olanzapine. Non-nucleoside reverse transcriptase inhibitors (efavirenz, nevirapine, etravirine) are inducers of cytochrome 3A4 and prolong the QTc interval, while nucleoside inhibitors of reverse transcriptase (nelfinavir, saquinavir, atazanavir) inhibit cytochrome 3A4 and prolong the QTc interval. Also, drugs for the treatment of hepatitis C virus infection (boceprevir, simeprevir, combination paritaprevir/ombitasvir/ritonavir/ dasabuvir, and combination elbasvir/grazoprevir) inhibit cytochrome 3A4 and thus increase the blood concentration of many antipsychotics .

5. Antipsychotics enhance the hypotensive effect of general anesthetics ;
6. Antipsychotics increase the risk of cardiac arrhythmias if they are used together with antiarrhythmics that prolong the QTc - interval or with methadone;
7. Beta blockers interacting with antipsychotics can lead to bradycardia, ventricular arrhythmias or hypotension; atorvastatin and simvastatin when administered together with risperidone, quetiapine or haloperidol in a number of patients lead to myopathy.
8. Antipsychotics increase the concentration of tricyclics antidepressants in the blood.
9. Antipsychotics reduce the anticonvulsant effect of antiepileptics; valproate lowers the blood level of olanzapine, while risperidone increases the blood level of valproate. Olanzapine together with valproate increases the risk of neutropenia and other side effects of valproate.
10. Metabolism of aripiprazole is inhibited by fluoxetine, paroxetine, itraconazole, and ketoconazole, and accelerated by rifampicin, carbamazepine, phenobarbital, phenytoin, and St. John's wort.
11. The risk of ventricular arrhythmias increases if amisulpride is given together with amiodarone, disopyramide, methadone, sotalol and diuretics that cause hypokalemia.
12. The metabolism of clozapine is accelerated by carbamazepine, and slowed down by fluoxetine, erythromycin, fluvoxamine, paroxetine, protease inhibitors, sertraline or venlafaxine.
13. Risk of agranulocytosis increases if clozapine is used together with chloramphenicol, penicillamine, sulfonamides or cytostatics.
14. When olanzapine and benzodiazepines are administered parenterally at the same time, hypotension, bradycardia and respiratory depression may occur.
15. Amiodarone, disopyramide, parenterally applied erythromycin, haloperidol and sotalol increase the proarrhythmogenic effect of sulpiride;
16. Amiodarone, disopyramide, moxifloxacin and sotalol increase the proarrhythmogenic effect of phenothiazine;
17. Propranolol increases the concentration of chlorpromazine in the blood;
18. Amiodarone, disopyramide, moxifloxacin, sulpiride and sotalol increase the proarrhythmogenic effect of haloperidol;

19. Fluoxetine inhibits, and rifampicin accelerates, the metabolism of haloperidol.

PREVENTION OF DEEP VENOUS THROMBOSIS

Deep vein thrombosis often occurs as a result of a patient's long stay in the hospital, especially if there are several factors that increase the tendency for blood to clot. Therefore, when a patient is admitted to the hospital, it is first necessary to determine ***to which*** deep vein thrombosis risk group he/she belongs. When we determine the degree of risk, we choose the method of prevention of thrombosis accordingly.

There are three groups of patients according to the degree of risk:

1. Low-risk patients (minor operations in mobile patients under 40 years of age, non-surgical patients who are mobile) - it is not necessary to give deep vein thrombosis prophylaxis, but only to insist that the patient starts to get out of bed as soon as possible after the intervention;
2. Patients with moderate risk (minor surgery in people between 40 and 60 years old who have no risk factors, minor surgery in people with risk factors, major surgery in people under 40 without risk factors, non-surgical patients who cannot get out of bed) – elastic socks with gradual compression + non-fractionated heparin or low molecular weight heparin or fondaparinux or rivaroxaban or dabigatran;
3. High-risk patients (major surgery in those over 40 with risk factors, hip or knee replacement, hip fracture fixation, major trauma, spinal cord injury, elective neurosurgery, surgery for malignant tumors, thrombophilia or surgery in people who have already had thrombosis) - elastic socks with gradual compression + low-molecular heparin, or fondaparinux, or rivaroxaban, or dabigatran, or warfarin.

Risk factors for the occurrence of deep vein thrombosis are: age over 60 years, smoking, therapy with selective modulators of estrogen receptors (tamoxifen, raloxifene), heart failure, immobilization, indwelling venous catheters, limb injury, myeloproliferative diseases, limb injury, obesity, nephrotic syndrome, oral contraception, replacement of sex hormones in menopause, pregnancy and midwifery, surgery in the last 3 months, trauma, previous venous thrombosis and hypercoagulable conditions (antiphospholipid syndrome, antithrombin deficiency, heparin-induced thrombocytopenia, factor V mutation Leiden, protein S or C deficiency, hyperhomocysteinemia, paroxysmal nocturnal hemoglobinuria).

Prophylactic dose of unfractionated of heparin is 5000 IU subcutaneously for 8 or 12 hours, and of low molecular weight heparin 20-100 IJ/kg subcutaneously daily. Warfarin is given until an INR of 2.0 to 3.0 is reached. The dose of fondaparinux is 2.5 mg subcutaneous daily, the dose of dabigatran 150 mg every 12 hours orally, and the dose of rivaroxaban 10 mg orally once daily.

The duration of prophylaxis is between 10 and 35 days, depending on the degree of risk.

A small percentage of people (up to 5%) have thrombophilia, i.e., due to mutations of genes encoding certain coagulation or anticoagulant factors, the function of such factors is disturbed, leading to an increased tendency to venous thrombosis. The most common are mutations of factors encoding factor 5 (Leiden mutation), prothrombin (G 20210A mutation), and mutations that cause protein C , S , or antithrombin 3 deficiency. Although people carrying these mutations have a greater tendency to thrombosis, the risk is not so high that it would justify continuous thromboprophylaxis if they had no previous complaints. However, if a person with the mutation develops a thrombosis, the risk of recurrence is more than 10 times higher than in people with thrombosis but without the mutations. In such a situation, it is worth determining which mutation it is, and based on that and other risk factors, it is necessary to assess how long thromboprophylaxis will be applied, often for life.

TREATMENT OF DEEP VENOUS THROMBOSIS

Deep vein thrombosis occurs in about 7.1 per 10,000 inhabitants per year. Since a thrombus in a deep vein can spread to larger veins and parts of the thrombus can break off and reach the pulmonary artery with the blood stream, blocking it (called a pulmonary embolism), it is necessary to treat deep vein thrombosis **immediately** after diagnosis with anticoagulants.

Deep vein thrombosis therapy **should be started with some of the low molecular weight heparins,** and not with unfractionated heparin, because with low molecular weight heparins the mortality is lower, and bleeding as a complication occurs less often. The advantage of low molecular weight heparins also lies in the fact that ***they can be used for the treatment of deep vein thrombosis in ambulatory conditions***, i.e., at patient's house. Thanks to more favorable pharmacokinetics of low molecular weight than that of unfractionated heparin, low molecular weight heparin therapy provides stable concentrations of the drug in the blood, i.e., it rarely happens that the concentration of the drug reaches toxic values, or is lower than the threshold concentration.

Simultaneously with the application of low molecular weight heparin, the patient should take an oral anticoagulant from the group of vitamin K antagonists (e.g., warfarin or acenocoumarol). When the value of the INR increases to 1.5 to 2.5, further application of low-molecular-weight heparin is stopped, and the oral anticoagulant is further administered for 3-6 months if it is a first thrombosis, and 12 months if it is a repeated thrombosis.

For certain low molecular weight heparins, such as dalteparin, it have been shown that they may be used to treat deep vein thrombosis alone, without oral anticoagulants, for 6 months. The effects of such application are almost the same as with the combined application of low molecular weight heparin and oral

anticoagulants. For now, this type of application is reserved for patients who, in addition to thrombosis, have a malignant disease, or who cannot tolerate oral anticoagulants for some reason.

Instead of warfarin, after 7 days of application of low molecular weight heparin therapy can be continued with a direct thrombin inhibitor, **dabigatran** etexilate, or factor Xa inhibitor, **edoxaban**. There is also the possibility to treat deep vein thrombosis from the beginning, without prior application of low-molecular heparin, with direct factor Xa inhibitors, **rivaroxaban** or **apixaban**. When using new oral anticoagulants (dabigatran, edoxaban, apixaban rivaroxaban) it is not necessary to monitor the INR level. However, there is one important limitation to the use of dabigatran, edoxaban and rivaroxaban : they must not be given to patients whose clearance creatinine is less than 30 ml/min.

In pregnancy other anticoagulants are not used because of the teratogenic effect, but only low molecular weight heparins.

Since the risk of post-thrombotic syndrome (chronic vein obstruction due to thrombus organization and narrowing of the vein) is very high, one month after the first thrombosis the patient should start wearing elastic stockings with gradual compression. Socks should be worn regularly for at least 11 months.

TREATMENT OF PULMONARY EMBOLISM

Pulmonary embolism is an emergency condition in which a sudden blockage of the pulmonary artery (most often by a thrombus, in more than 70% of patients) leads to a sudden load on the right ventricle, and in more severe cases to acute insufficiency of the right ventricle. This condition can be life-threatening (acute mortality is about 10%), but if appropriate treatment is undertaken immediately, the prognosis for most patients is good.

The method of treating pulmonary embolism depends on the size of the embolus, that is, on the degree of cardiorespiratory function disorder. If the patient is **hemodynamically stable** and not in respiratory danger, pulmonary embolism can be treated conservatively, only with anticoagulants. If the size of the embolus is so large that the patient is not hemodynamically stable, therapy is undertaken that can lead to at least partial removal of the embolus.

Infusion of dobutamine, dopamine (if cardiac index is reduced and arterial pressure is normal), noradrenaline (if arterial pressure is lowered) or adrenaline (if there are signs of shock) can be used to restore **flow.** In order to facilitate the flow of blood through the pulmonary artery, it is recommended to inhale nitrogen monoxide or an aerosol of prostaglandin E1, prostacyclin. The infusion of the phosphodiesterase 5 inhibitor, sildenafil, as well as blockers of endothelin receptors, bonsetan, can have a favorable vasodilatory effect on the pulmonary artery. On top of that, the patient should be given oxygen through nasal catheters.

A mandatory part of therapy for establishing flow through the pulmonary artery in **severe** pulmonary embolism followed by shock is the administration

of thrombolytics: streptokinase, urokinase or alteplase. All thrombolytics are administered intravenously, in the form of an infusion of various duration. Streptokinase is given as a loading dose of 250,000 IU over 30 minutes followed by 100,000 IU/hour for 12-24 hours, or 1,500,000 IU is given as a single infusion over 2 hours. Recombinant tissue activator of plasminogen (alteplase) is given intravenously in a single dose of 100 mg, over 2 hours. Heparin must not be given simultaneously with urokinase and streptokinase, but it can be administered together with alteplase. Due to less immunogenicity and slightly higher efficiency, alteplase is used in the first line today, while streptokinase and urokinase are increasingly becoming obsolete drugs. The effectiveness of thrombolytics in establishing the flow through the pulmonary artery is great; in 92% of patients, the clinical picture and ultrasonographic findings improve. Thrombolytic therapy has the greatest effect if it is applied in the first 48 hours, but it makes sense to give it up to 14 days after the occurrence of a pulmonary embolism. An alternative to thrombolytic therapy is suction embolectomy through an intravascular catheter placed up to the pulmonary artery.

Thrombolytics are **not used in milder forms of pulmonary embolism**, without acute right ventricular failure. The reason for this is the high frequency of serious bleeding when using thrombolytics (13%), where intracranial bleeding is especially dangerous (occurring in about 1.8% of patients).

Embolectomy or percutaneous catheter embolectomy /fragmentation can be performed in cardiac surgery centers. Such treatment methods in recent clinical studies show similar or better results than thrombolytic therapy.

Anticoagulants must be used in all patients with pulmonary embolism. For the first 5 days, unfractionated heparin (or low molecular weight) is applied together with warfarin or acenocoumarol; since after 5 days the effect of oral anticoagulants is established and the INR is between 2 and 3, further administration of heparin is stopped. Oral anticoagulants are then administered for another 6 months. Instead of vitamin K antagonists, direct oral anticoagulants can also be administered: dabigatran and edoxaban are started after 7 days of initial therapy with low molecular weight with heparin, while rivaroxaban and apixaban can be given from the beginning. Low molecular weight heparins, dabigatran, rivaroxaban and edoxaban are not used in people with moderate and severe renal insufficiency, as well as in people who have a high risk of bleeding.

The duration of anticoagulant therapy after a pulmonary embolism depends on whether the pulmonary embolism was **provoked or not** (provoked means that there was a clear reason for the occurrence of the pulmonary embolism, e.g., surgical intervention after which the patient was bedridden for a long time or similar). If pulmonary embolism was provoked, and it occurred for the first time, anticoagulant therapy ***can be stopped after 6 months***. If the pulmonary embolism is unprovoked, or if it occurs for the second time, the patient must take anticoagulant therapy ***for life*** .

All patients with pulmonary embolism should wear elastic stockings with graduated compression for at least one year.

In addition to bleeding, a very serious side effect of unfractionated heparin and low molecular weight of heparin (rarely) is thrombocytopenia, which occurs from the 5th to the 14th day after the start of the administration of these drugs. The number of thrombocytes drops to less than 100,000/mm^3, but the main problem with this condition is the increased frequency of thrombosis at the ends of the extremities, which is accompanied by gangrene of the fingertips. This thrombocytopenia with thrombosis is treated with the use of direct thrombin inhibitors: lepirudin or argatroban.

TREATMENT OF DISSEMINATED INTRAVASCULAR COAGULATION

The name disseminated intravascular coagulation (DIC) comes from blood clotting in small blood vessels, which has two serious consequences : (1) due to weaker blood perfusion, ischemia and damage to vital organs, and (2) due to the consumption of coagulation factors and platelets, the patient begins to bleed diffusely throughout the body. The causes of DIC can be sepsis, complications of pregnancy and childbirth, severe trauma, major operations, malignant tumors, snakebite and others. DIC can be an acute or chronic condition, when it is more difficult to diagnose.

When diagnosis of DIC is made, two things should be done: **find out the cause** and **compensate for the coagulation disorder itself**. The patient should first compensate for the lost circulatory volume with infusions of crystalloid and colloid solutions. Then, if the patient continues to bleed, especially after the start of heparin administration, it is necessary to replace erythrocytes and coagulation factors. Transfusion ***of washed erythrocytes and fresh frozen plasma*** is used: for every 4-6 units of washed erythrocytes, two units of fresh frozen plasma, which is rich in coagulation factors, are given. The patient should also be given ***platelet preparations*** , if their number falls below 20 x 10^9/L, or if the bleeding does not stop after the previous therapy.

Simultaneously with the replacement of coagulation factors and platelets, ***heparin*** should be given to patients with DIC ***intravenously***. If the heparin is effective, the patient's condition will improve after 4-6 hours. Heparin should not be used in case of bleeding in the brain, open wounds, imminent surgery or severe thrombocytopenia.

Usually, DIC can be stopped by causative therapy, replacement of coagulation factors and blood cells, and administration of heparin. If the patient does not stop bleeding despite all of the above, one of the fibrinolysis inhibitors - ***epsilon- aminocaproic acid or tranexamic acid - is administered***. Tranexamic acid is safer preparation, because it less often causes fibrin deposition in capillaries and ischemia of vital organs, followed by hyperkalemia, hypotension, and ventricular arrhythmias.

In Japan, the use of thrombomodulin (a receptor for thrombin that inactivates it) and antithrombin has been approved for the treatment of

disseminated intravascular coagulation, but the results compared to heparin are not impressive - the number of patients who need to be treated to avoid one death is about 20. In Serbia, antithrombin 3 is registered for human use, but there is no approved indication within the framework of disseminated intravascular coagulation.

SUPPRESSION OF PATHOLOGICAL FIBRINOLYSIS

Fibrinolysis is one of the essential mechanisms that maintain the patency of blood vessels, i.e., prevents their clogging with thrombi. After activation, plasminogen turns into plasmin, which breaks down the created fibrin. However, in certain situations, fibrinolysis is either dangerous or not desirable, as it can break down much-needed thrombi that have just stopped bleeding. Thus, the indications for the suppression of fibrinolysis , i.e., for the use of antifibrinolytic drugs are: overdose of fibrinolytic therapy, excessive fibrinolysis after prostatectomy or bladder surgery, tooth extraction in a person with hemophilia, traumatic bleeding in the eye, bleeding after heart surgery and placental abruption. Antifibrinolytic drugs should never be used for thromboembolism and hematuria, and in patients with DIC, the application must be very careful, in order not to intensify the occlusion of small blood vessels.

The most used antifibrinolytics in medical practice are tranexamic acid and epsilon- aminocaproic acid. **Tranexamic acid** can be administered orally (1-1.5 g 2-3 times a day) and intravenously (0.5 to 1 g three times a day in the form of a slow intravenous injection), while **epsilon-aminocaproic acid** is applied initially in a dose of 5 g (orally or intravenously), and then 1 g every hour orally or intravenously. When antifibrinolytics are given intravenously, it must be done slowly, so as not to cause hypotension.

Adverse effects of tranexamic acid are thromboembolism, convulsions, hypotension and disturbances in color vision. Adverse effects of epsilon-aminocaproic acid are nausea, hyperkalemia, suffusions on the conjunctiva, headache, myopathy and rash.

FIBRINOLYTIC THERAPY OF MYOCARDIAL AND BRAIN INFARCTION

Myocardial infarction

When a myocardial infarction occurs with elevation of the ST-segment or with the appearance of a completely new left bundle branch block, the only

causal drug therapy is the use of fibrinolytics. However, today fibrinolytics are used only if it is not possible to perform percutaneous coronary intervention with insertion of a stent, which is considered a more effective and safer therapy. Fibrinolytics lead to the conversion of plasminogen to plasmin, an enzyme that breaks down intravascular fibrin, and thus the thrombus that blocked the coronary artery. Most authors and guidelines for the treatment of myocardial infarction with ST-elevation or new left bundle branch block agree that fibrinolytics should be administered as soon as possible after diagnosis, even before the patient is admitted to the hospital. The best results are achieved if thrombolytics are administered within the first 30 minutes.

Streptokinase was applied intravenously, 1.5 million units, dissolved in 50 ml of 5% glucose, as an infusion lasting 60 minutes. Considering that patients often become sensitized to streptokinase after the first administration, the rule was that the next thrombolytic administration should not use streptokinase, but human recombinant plasminogen activator (e.g., alteplase), in order to avoid possible allergic reactions. Today, streptokinase is no longer used in practice, because safer thrombolytics are available that are easier to apply.

Alteplase is another fibrinolytic that can be used in ST-elevation myocardial infarction. Vials of 50 or 100 mg are diluted with water for injections to a concentration of 1 mg/ml. A bolus is then administered intravenously as injection of 15 mg, followed by a dose of 0.75 mg/kg alteplase as an intravenous infusion over 30 minutes. When the previous infusion has expired, another 0.5 mg/kg is given over the next 60 minutes.

Recently, fibrinolytic that have been used a lot is **tenecteplase**. The dose of tenecteplase is 30-50 mg intravenously as bolus injection that should last only 5 seconds. Before administration, the vial of 50 mg is dissolved with 10 ml of water for injections. **Reteplase** is also administered simply: 10 units are administered intravenously over 2 minutes, then the same dose again after 30 minutes.

There is an upper time limit for the use of fibrinolytics: 12 hours from the onset of symptoms and signs of ischemia. Also, there are absolute contraindications for the use of fibrinolytic therapy: previous intra cerebral hemorrhage, known intracranial structural vascular lesion, malignant intracranial tumor, active bleeding, suspected aortic dissection, and significant head injury with the possibility of intracerebral hemorrhage.

Simultaneously with the use of fibrinolytics, aspirin and heparin, or one of the low molecular weight heparins, should be used. In particular, the combination of tenecteplase and enoxaparin was extensively tested, which proved to be effective and sufficiently safe. If the patient previously received heparin and experienced heparin - induced thrombocytopenia, bivalirudin (direct thrombin inhibitor should be used together with streptokinase or some other thrombolytic; low molecular weight heparins can also cause thrombocytopenia.

Aspirin is given in a single daily oral dose of 160 to 325 mg (in the form of a chewable tablet). Unfractionated heparin is given intravenously bolus dose of 60 IU/kg , then as an infusion of 12 IU/kg/h , so that a PTT is extended between

1.5 and 2 times. Enoxaparin is given as an intravenous bolus of 30 mg in people younger than 75 years, and then continued subcutaneously in a dose of 1 mg/kg, every 12 hours.

Brain infarction

Out of all cases of brain infarction, about 87% are caused by ischemia due to thrombosis or embolism. When it comes to ischemic brain infarction, the use of thrombolytics is indicated. **Streptokinase** is **not used for thrombolysis any more,** because it causes intracranial bleeding in a high percentage of patients. Alteplase or tenecteplase can be used.

Alteplase is applied only if **less than 3 hours** have passed since the onset of ischemic stroke, and if the infarction is neither too small nor too large (on the scale of the National Health Institute of S.A.D., the score must be between 4 and 22). The use of tenecteplase is not yet standardized. The main adverse effect of alteplase administration is intracranial bleeding (in about 2.2% of patients).

Alteplase is administered as an intravenous infusion, at a dose of 0.9 mg/kg, over 60 minutes. About 10% of the dose at the beginning of the infusion is administered as a bolus.

Absolute contraindications for the use of fibrinolytics in ischemic brain infarction are: intracranial bleeding present or in the patrient's history, suspicion of subarachnoid bleeding, existence of an arterio-venous malformation in the brain, systolic pressure higher than 185 mm of mercury, diastolic pressure higher than 110 mm of mercury, platelet count less than 100 x 10^9/L, INR greater than 1.7, acute trauma, acute internal bleeding, head injury or stroke in the previous 3 months, epileptic seizure with postictal neurological deficit and puncture of an artery in a place that cannot be pressed in the last 7 days.

In the case of ischemic brain infarction, when fibrinolytics are used, neither anticoagulants, nor antiplatelet drugs should be given concomintantly, because the risk of intracranial bleeding increases too much.

PREVENTION OF INTRAVASCULAR STENT THROMBOSIS

Thrombosis of an intravascular (most often intracoronary) stent occurs relatively rarely, in about 1.9% of patients. The largest number of thromboses occur in the first 2 days after stent implantation. When stent thrombosis occurs, patient mortality is about 20% in a six-month period.

The risk of thrombosis is most influenced by the speed of **stent placement**: if it is faster (i.e. it is done under higher blood pressure), the risk of stent thrombosis is lower, and vice versa.

Clinical trials have shown that anticoagulation drugs are less effective than antiaggregatory drugs in the prevention of stent thrombosis. Standard prevention today involves the use of **acetylsalicylic acid and one of the blockers of P_2Y_{12} adenosine diphosphate receptors at the same time (the so-called "dual antiplatelet therapy")**. Initially, only clopidogrel was used as a P_2Y_{12} receptor blocker, but when it was found that about 40% of people have reduced cytochrome activity, which creates an active metabolite from clopidogrel (which is actually a pro -drug), which means that the full antiplatelet effect is missing, instead of clopidogrel ticagrelor or prasugrel are used.

Dual antiplatelet therapy is applied for one year if the stent was implanted due to acute coronary syndrome, and for six months if it was implanted due to stable angina pectoris.

Modern stents are designed to release drugs that prevent proliferation of endothelial cells, thus preventing blockage of stent due to intimal hyperplasia . Most often, stents that release sirolimus or paclitaxel are used. These stents are good at preventing blockage endothelial cells, but some studies indicate that they increase the frequency of stent thrombosis, especially the so-called late blockages. For now, these stents remain in use, with mandatory use of anti-aggregation drugs.

ADVERSE EFFECTS ANTICOAGULANT DRUGS

Adverse effects of oral anticoagulant drugs - vitamin K antagonists (warfarin, acenocoumarol, phenindione) are relatively common, and include bleeding in the digestive tract and CNS, thrombosis of subcutaneous veins with necrosis of fatty tissue (in the breast and gluteal area , due to decreased plasma protein C activity) and, rarely, liver damage. Thrombosis of subcutaneous veins occurs at the very beginning of therapy (in the first 2-3 days), while the anticoagulant effect has not yet been established. Rarely, diarrhea, alopecia, necrosis of the small intestine and livid toes occur. Phenindione can sometimes turn urine pink or orange. Due to the constant possibility of causing bleeding, oral anticoagulants are contraindicated in all conditions where there is an increased possibility of bleeding with serious consequences: if there is peptic ulcer, in case of malignant hypertension, bacterial endocarditis, thrombocytopenia and similar conditions.

Warfarin, acenocoumarol and phenindione have a teratogenic effect if used in the first three months of pregnancy, and in the second two trimesters they often cause bleeding in the organs and tissues of the fetus. That is why these drugs are never given during pregnancy. Anticoagulant effect in pregnancy is achieved by the use of low-molecular-weight heparin.

If bleeding occurs due to the use of oral anticoagulant drugs - vitamin K antagonists, their use should be stopped and 5 mg of vitamin K_1 should be given slowly intravenously, together with coagulation factor concentrate or freshly frozen plasma.

A newer oral anticoagulant **dabigatran** can also cause bleeding as an adverse effect, similar in frequency to vitamin K antagonists. In addition, dabigatran causes gastrointestinal complaints and alopecia. If it causes bleeding, the effect of dabigatran can be interrupted ***by idarucizumab***, a humanized Fab antibody fragment that binds to dabigatran and its metabolites, thus preventing their effects on thrombin .

Rivaroxaban, also a more recent oral anticoagulant, causes bleeding and nausea as an adverse effect. In addition, it can rarely cause hypotension, tachycardia, thrombocytopenia, alopecia and pain in the extremities .

Apixaban, the third direct oral anticoagulant in use in our country, has only bleeding as a significant side effect. Other side effects that have been reported occur very rarely, so the question remains whether they are really caused by apixaban or not. Bleeding caused by rivaroxaban or apixaban can be stopped with **andexanet alfa** (recombinant inactivated factor Xa that directly binds to rivaroxaban or apixaban, thus preventing their effect on active factor Xa) or a concentrate of four coagulation factors (II, VII, IX and X) .

The most common side effects of **heparin** are bleeding and thrombocytopenia . Thrombocytopenia occurs in about 5-30% of patients, and can be "early" and "delayed". "Early" thrombocytopenia occurs immediately after the administration of heparin, and is transient in nature. "Delayed" thrombocytopenia occurs 4-10 days after the start of drug administration, and is a consequence of the formation of antibodies to the complex of heparin and platelet factor 4. Delayed thrombocytopenia is also called "heparin-induced thrombocytopenia", and implies a drop in the number of platelets by 50 % (or below 150 x 10^9/L). The main problem for the patient in this condition is not the reduced number of platelets, but the paradoxical propensity for thrombosis and the formation of thrombus in the arteries of the extremities, which often results in gangrene of the fingers or the entire limb. Low molecular weight heparins can also cause thrombocytopenia, but they do so far less often than unfractionated heparin. Low molecular weight heparin that the most rarely causes thrombocytopenia is fondaparinux. Heparin - induced thrombocytopenia is treated with the use of direct thrombin inhibitors: argatroban, lepirudin or bivalirudin.

In addition to the two already mentioned side effects, heparin can cause fever, alopecia, osteoporosis, bone pain, skin necrosis and hypoaldosteronism with hyperkalemia. As well as oral anticoagulants, heparin should not be given in conditions where there is a tendency to bleeding with severe consequences.

Both unfractionated and low molecular weight heparins can cause reduced secretion of aldosterone, which ultimately leads to hyperkalemia.

SIDE EFFECTS OF ANTIAGGREGATORY DRUGS

Acetylsalicylic acid, as the oldest drug from this group, has many known side effects: serious gastrointestinal bleeding, exacerbation of bronchial asthma and irritation of the gastrointestinal tract. If used in the second half of pregnancy, it can cause bleeding in the uterus and delay the onset of labor. Mothers who are breastfeeding should avoid aspirin, as it is found in milk and can cause Reye's syndrome in children. During and immediately after the surgical intervention, the use of aspirin should be stopped, until safe hemostasis is established.

Ticlopidine in addition to bleeding (frequency about 5%), may cause serious side effects: nausea and diarrhea in 20% of patients, neutropenia in 1% of patients, and hyperlipidemia in 1-10% of patients.

Adverse effects **of dipyridamole** are: confusion, abdominal pain, hypotension with tachycardia, headache, allergic reactions and increased frequency of bleeding during and after surgical interventions.

The most common side effects of **clopidogrel and prasugrel** are gastrointestinal complaints and bleeding. Clopidogrel rarely causes leukopenia, thrombocytopenia and paresthesias, and rarely dizziness, pancreatitis, vasculitis and allergic manifestations. Patients on prasugrel therapy may complain of headaches and increased blood pressure. Very rarely, clopidogrel and prasugrel can cause thrombotic events thrombocytopenic purpura.

Ticagrelor causes bleeding, bradyarrhythmias, dyspnea or sleep apnea as side effects, and very rarely thrombotic thrombocytopenic purpura.

Eptifibatide has bleeding and thrombocytopenia as side effects. **Tirofiban** causes bleeding, bradycardia, anemia and thrombocytopenia.

ADVERSE EFFECTS OF FIBRINOLYTICS

The most common side effects after administration of fibrinolytics are nausea and vomiting. The most serious side effect when using fibrinolytics is bleeding (at the site of drug administration, in the digestive tract or the CNS). It can be suppressed by the use of coagulation factors, inhibition of the conversion of plasminogen into plasmin by tranexamic acid or direct inhibition of plasmin by aprotinin.

When fibrinolytics are used to treat myocardial infarction after reperfusion, arrhythmias may occur. In the treatment of brain infarction and pulmonary embolism, brain or lung edema may occur after reperfusion.

Sometimes, in patients receiving fibrinolytics hipotension occurs, which can be suppressed by slowing down the infusion of the drug and elevating the patient's legs.

All thrombolytics can rarely cause allergic reactions of the first type, especially streptokinase. In order to prevent the occurrence of an allergic

reaction in a situation where the patient has previously received streptokinase, one of the less immunogenic drugs, such as alteplase or tenecteplase, should be chosen during the next administration of thrombolytic therapy .

Very rarely, administration of streptokinase can cause Guillain-Barré syndrome.

CLINICALLY SIGNIFICANT INTERACTIONS OF ORAL ANTICOAGULANS

Oral anticoagulants are drugs that are known to have a large number of interactions, and that the consequences of their interactions can be very severe (bleeding or thrombosis). That is why it is NECESSARY that physicians for every patient who is on chronic anticoagulant therapy check the possibility of interactions when introducing a new drug into the therapy using the available interaction "checkers" (Lexicomp, Micromedex, Medscape, Epocrates), and then adjust the therapy. Below are just a few of the many interactions with potentially serious consequences.

The effect of oral anticoagulants in terms of bleeding tendency is enhanced by all non-steroidal anti-inflammatory drugs, especially diclofenac and ketorolac .

The most important oral anticoagulant, **warfarin**, is actually a mixture of equal amounts of "S" and "R" isomers . The "S" isomer is about 5 times more active than the "R" isomer. These isomers are metabolized by different cytochromes , so they interact with different drugs. Metabolism of the "R" isomer is inhibited by the following drugs: cimetidine and omeprazole. The metabolism of the "S" isomer is inhibited by sulfinpyrazone, metronidazole and the combination of trimethoprim-sulfamethoxazole. Amiodarone is a drug that stands out because it inhibits the metabolism of both "S" and "R" isomers. All the mentioned drugs increase the effect of warfarin due to the inhibition of metabolism.

On the other hand, drugs that accelerate the metabolism of warfarin, carbamazepine, phenytoin, barbiturates and rifampicin weaken the anticoagulant effect of warfarin. Vitamin K directly antagonizes the action of warfarin and acenocoumarol.

The effect of both **warfarin and acenocoumarol** is enhanced by aspirin (due to its anti-aggregatory effect), clopidogrel, prasugrel, ticagrelor, dipyridamole, anabolic steroids, azithromycin, cephalosporins, chloramphenicol, ciprofloxacin, erythromycin, fibrates, fluconazole, fluorouracil, norfloxacin, ofloxacin, tamoxifen, thyroid hormones and tramadol.

Metabolism **of phenindione is** inhibited by amiodarone, thus enhancing its anticoagulant effect. Anticoagulant effect of phenindione is also enhanced by aspirin and other antiplatelet drugs, anabolic steroids, fibrates, non-steroidal anti-inflammatory drugs, tetracyclines and thyroid hormones. On the other

hand, the anticoagulant effect of phenindione is reduced by estrogens, progestagens and vitamin K.

The new oral anticoagulants also interact a lot with potentially serious consequences. Rivaroxaban and apixaban are metabolized via cytochromes, so they also interact with drugs that inhibit or induce cytochromes; in addition, both drugs use the P-glycoprotein pump, so they interact with drugs that bind to that pump. On the other hand, dabigatran is not metabolized via cytochromes, but uses the P-glycoprotein pump. The situation is further complicated by the fact that all three drugs (rivaroxaban, apixaban and dabigatran) are difficult to excrete in case of kidney or liver insufficiency, and their use is contraindicated if there is severe liver insufficiency or if the clearance of creatinine is below 25 ml/min.

The anticoagulant effect **of rivaroxaban and apixaban** is enhanced by ketoconazole, itraconazole, posaconazole, voriconazole and ritonavir, due to inhibition of their metabolism on cytochromes.

Dabigatran concentration in plasma is increased by dronedarone, ketoconazole, itraconazole, voriconazole, cyclosporin and verapamil due to inhibition of binding to the P - glycoprotein pump.

Nonsteroidal anti-inflammatory drugs increase the risk of bleeding in patients receiving new oral anticoagulants.

CLINICALLY SIGNIFICANT INTERACTIONS OF HEPARIN

Both unfractionated and low molecular weight heparins enter into similar interactions with other drugs. **Enhancement of the anticoagulant effect of heparin** occurs if other anticoagulants or antiplatelet drugs, non-steroidal anti-inflammatory drugs, thrombolytics, cytostatics (because they lead to thrombocytopenia), dextran 40, or ethacrynic acid are used at the same time. Some antibiotics, such as piperacillin with tazobactam, enhance the anticoagulant effect of low-molecular-weight heparin. **Weakening of the anti-coagulant effect of heparin** occurs if anti-histamines, digoxin, tetracycline, vitamin D or glyceryl trinitrate are given in infusion at the same time. It should be borne in mind that ***in case of renal insufficiency, the excretion of low molecular weight heparin is greatly reduced***, so it is necessary to decrease doses; in such patients, the consequences of possible interactions of low molecular weight heparins with other drugs can be particularly difficult.

Since heparins reduce the secretion of aldosterone in the adrenal gland, the elimination of potassium ions in the kidneys decreases, so patients tend to have an increase in serum potassium. If heparins are given together with aliskiren (blocker of renin), ACE-inhibitors, potassium-sparing diuretics, potassium-containing supplements or angiotensin receptor blockers, this may cause **hyperkalemia**.

CLINICALLY SIGNIFICANT INTERACTIONS OF ANTIAGGREGATORY DRUGS

Thienopyridines (clopidogrel, prasugrel and ticlopidine) are actually pro-drugs, which are converted in the liver into active forms, under the action of cytochrome oxidase CYP2C19 and CYP3A4. Medicines that inhibit these cytochromes will reduce the synthesis of active forms of thienopyridine, and thus their antiplatelet effect. Omeprazole can inhibit cytochrome CYP2C19 and thus theoretically reduce the antiplatelet effect of these drugs, but published data on the clinical significance of this interaction are controversial. Dihydropyridine-type calcium channel blockers inhibit cytochrome c activity CYP3A4 in the liver, which can lead to a reduced effect of thienopyridine, but this has not been clearly demonstrated in clinical studies and clinical practice. Apart from these two groups of drugs, theoretically, other CYP2C19 inhibitors could slow down the formation of active metabolites and thus reduce the antiplatelet effect: ketoconazole, fluconazole, voriconazole, etravirine, fluoxetine, fluvoxamine, etc.).

There are several studies with conflicting results that have addressed the question of whether the simultaneous use of serotonin reuptake blockers (which have an antiplatelet effect to some extent) and classic antiplatelet drugs increases the risk of bleeding. The answer to that question is not yet definitive, but such interactions cannot be ruled out for now.

It is similar with atorvastatin, which inhibits cytochrome CYP3A4 in the liver, but does not reduce the effectiveness of clopidogrel and other thienopyridines.

None of the anti-aggregatory drugs affect the metabolism of warfarin, so there are no pharmacokinetic interactions. However, all anticoagulation drugs when given together with warfarin increase the risk of nonfatal and fatal bleeding, due to the cumulative effect on hemostasis in general.

Ibuprofen binds to the same site as aspirin on the cyclooxygenase in platelets, thereby **weakening the** antiplatelet effect of aspirin. The clinical significance of this interaction is still unclear, but it is recommended to avoid the simultaneous use of these two drugs. If aspirin and ibuprofen must still be administered to the same patient, it is recommended that ibuprofen be administered either 30 minutes after the oral dose of aspirin or at least 8 hours before the administration of aspirin.

Simultaneous long-term use of anti-aggregatory drugs and non-steroidal anti-inflammatory drugs can increase the risk of gastrointestinal bleeding, so such a situation should be avoided. In the event that simultaneous administration is necessary, the patient should also be given a blocker of

histamine H_2 receptors (ranitidine or famotidine), because then the risk of gastrointestinal bleeding decreases.

Another important interaction between **morphine and blockers of P_2Y_{12}** adenosine diphosphate **receptors** (clopidogrel, ticagrelor, prasugrel) has recently been discovered. Morphine, which is normally given in the case of myocardial infarction, reduces the bioavailability of these antiplatelet drugs and to some extent their activity, so that the antiplatelet effect weakens, and patients are at a higher risk of re-infarction. The possibility of using fentanyl instead of morphine is being considered, as there is some evidence that the interaction with fentanyl is weaker, but a definitive conclusion has not yet been reached.

TREATMENT OF OVERDOSE OF ORAL ANTICOAGULANTS AND HEPARIN

Overdose of oral anticoagulants

If the INR increases above 5, in most patients it is sufficient to stop the further administration of oral anticoagulants and give **1-2.5 mg of vitamin K** 1 orally or parenterally; if there is no bleeding, this is usually enough to normalize the INR within a day or two. The INR should be measured every 6 to 12 hours, and as soon as it falls below 5, oral anticoagulans should be reintroduced at a reduced dose.

If the INR is greater than 9, further use of oral anticoagulants should be stopped and **5 mg of vitamin K1 should be given,** orally, subcutaneously or intravenously. Intravenous administration should be avoided because of a possible anaphylactoid reaction. The INR should be measured every 6 to 12 hours, and as soon as it falls below 5, the oral anticoagulant should be reintroduced at a reduced dose.

If the overdose of warfarin is pronounced, it may happen that after two days the effect of the administered vitamin K_1 wears out; then the same dose of vitamin K_1 should be repeated .

In the event that the increased INR is accompanied by **bleeding**, the patient should immediately be given coagulation factors, cryoprecipitate or fresh frozen plasma, because only these preparations can stop the bleeding without delay. It takes a day or two for vitamin K to work.

Overdose of heparin

If unfractionated or low molecular weight heparins are overdosed, bleeding occurs. In such situation a drug that neutralizes heparin should be used : protamine sulfate. Every 100 units of unfractionated or submolecular heparin are neutralized by 1 mg of protamine sulfate. Protamin sulfate (1% solution) should be administered by slow intravenous injections (lasting at least 10 minutes each), in a maximum dose of up to 50 mg. Protamin sulfate can cause hypotension and a severe anaphylactoid reaction, so when using it, you should keep an anti – shock therapy ready.

PREVENTION AND TREATMENT OF KIDNEY TRANSPLANT REJECTION

Both prevention and treatment of kidney transplant rejection are done with the help of immunosuppressive drugs. The use of immunosuppressive drugs after kidney transplantation can be divided into 3 phases:

1. **Induction therapy** - involves the intensive use of immunosuppressants in the first few days or weeks after transplantation. In this phase***, antibodies against lymphocytes are*** used (antithymocyte globulin, thymoglobulin or OKT3 - monoclonal IgG antibody of mouse origin against the CD3 complex on the lymphocyte membrane) or monoclonal antibodies ***against the receptor for interleukin 2,*** basiliximab and daclizumab. Antibodies against lymphocytes are more effective, so they are used in patients with a high risk of transplant rejection; however, since they reduce the number of lymphocytes, they lead to serious side effects such as lymphoproliferative diseases, cytomegalovirus infections and other infections. Basiliximab and daclizumab are used in patients who have a moderate or low risk of transplant rejection; these drugs are well tolerated, because they do not reduce the number of lymphocytes.
2. **Maintenance immunosuppression** - classic maintenance immunosuppression is triple therapy: **calcineurin inhibitor (cyclosporine or tacrolimus) + antimetabolite (azathioprine - or mycophenolate mofetil) + prednisolone.** More recently, after the appearance of sirolimus, the application of maintenance immunosuppression that will not have a calcineurin inhibitor or in which prednisolone is gradually discontinued is being tried, but the right place for such protocols remains to be determined. *When choosing between ciclosporin and tacrolimus*, it should be borne in mind that tacrolimus is more effective than cyclosporin (acute transplant rejection occurs less

often), and that it causes hypertension and *hyperlipidemia* less often. On the other hand, cyclosporin should be given to patients who have a high risk of developing diabetes mellitus after transplantation, because this risk with cyclosporin is much lower than with tacrolimus. *When choosing between azathioprine and mycophenolate mofetil*, this second drug should be used, because it is less toxic and more effective than azathioprine.

3. **Transplant rejection treatment** - if, despite the prophylactic use of immunosuppressants, an acute reaction of transplant rejection occurs, then the so-called "rescue" therapy must be applied. Acute graft rejection can be **hyperacute** (immediately after vascularization of transplant and up to 1 hour after), **accelerated acute rejection** (from 24 hours to 7 days after transplantation) and **"ordinary" acute rejection** (in the first 6 months after transplantation). While hyperacute rejection cannot be treated, and always ends in graft loss, in accelerated acute rejection therapy makes sense.

   The therapy to be applied in acute transplant rejection depends on the type of rejection. There are three types: **T-lymphocyte rejection, B- lymphocyte rejection and mixed rejection**. What type of rejection is involved can only be said on the basis of a biopsy of the graft and a histological examination. If it is a question of T-lymphocytic rejection, only high doses of corticosteroids are applied in milder cases (milder histological picture), and in more severe cases, antithymocyte immunoglobulin together with corticosteroids. When rejection is of the B-lymphocytic type and occurs within a year of transplantation, plasmapheresis is performed, high doses of corticosteroids are administered, and intravenous immunoglobulins; also, the doses of immunosuppressants from maintenance therapy are increased. Rejection of transplants B-lymphocytic type, which occurs after one year of transplantation, is treated with corticosteroids and intravenous immunoglobulin alone, without plasmapheresis. Mixed rejection is treated with a combination of the above therapeutic approaches.

PREVENTION AND TREATMENT OF REJECTION OF LIVER TRANSPLANT

Unlike kidney transplantation, after liver transplantation, **induction immunosuppressive therapy is not routinely applied, but only in about 20% of patients**. The reason for this approach is the greater resistance of the liver to the activation of the immune system. If induction therapy is still applied, daclizumab and basiliximab are used (monoclonal antibodies against

the receptor for interleukin 2), or antithymocyte immunoglobulin, or alemtuzumab (anti CD25 monoclonal antibody) .

Immunosuppression **is** most often based on the application of a combination of **calcineurin inhibitors (cyclosporine or tacrolimus) and corticosteroids**. An antimetabolite (preferably mycophenolate mofetil) can be added to that combination, or the mammalian target of rapamycin (mTOR) inhibitor (sirolimus), which allows the dose of calcineurin inhibitors or corticosteroids to be reduced, thereby reducing the risk of side effects of these drugs. Calcineurin inhibitors are nephrotoxic and neurotoxic, corticosteroids cause osteoporosis, Cushing's syndrome and diabetes, antimetabolites lead to cytopenia, and sirolimus leads to cytopenia, hyperlipidemia, impaired wound healing and thrombosis of the hepatic artery.

The transplant rejection - if despite the prophylactic use of immunosuppressive drugs, an acute rejection of the liver transplant occurs, then the so-called "rescue" therapy must be applied. Acute graft rejection can be **hyperacute** (immediately after vascularization of the transplant and up to 1 hour after), **accelerated acute rejection** (from 24 hours to 7 days after transplantation) and **"ordinary" acute rejection** (most often after 7 to 14 days). While hyperacute rejection cannot be treated, and always ends in graft loss, in accelerated and "ordinary" acute rejection, treatment can be effective. Similar to kidney transplant rejection, therapy depends on the type of rejection, which can be threefold: **T-cell early rejection (up to 6 months after transplantation), T-cell late rejection (after 6 months after transplantation), B-cell and chronic**. The type and severity of rejection is assessed by fine needle biopsy of the liver. Early T-cell rejection is treated if mild with moderate-dose corticosteroids, and if moderate or severe with high-dose corticosteroids and antithymocyte immunoglobulin is added if there is no response to corticosteroids. Late T-cell rejection is treated with a combination of corticosteroids and antithymocytes immunoglobulin. If B-cell rejection is acute (appears in the first few weeks after transplantation), it is treated with plasmapheresis, intravenous immunoglobulins and rituximab bortezomib or eculizumab. If B-cell rejection is chronic, it is treated with bortezomib. Finally, for chronic transplant rejection, the patient should increase the doses of immunosuppressive drugs to the maximum, or take other immunosuppressive drugs from those he/she was taking until the rejection happened, until the rejection stops. After the cessation of the rejection process, the doses of immunosuppressants can be gradually reduced.

PREVENTION AND TREATMENT OF REJECTION OF HEART TRANSPLANT

Similar to kidney, prevention and treatment of heart transplant rejection is achieved with the help of immunosuppressive drugs through 3 phases:

1. **Induction therapy** - involves the intensive use of immunosuppressants 7 to 14 days after transplantation. In this phase**,** ***antibodies against lymphocytes*** are used (antithymocyte globulin, thymoglobulin or OKT3 - monoclonal IgG antibody of mouse origin against the CD 3 complex on the lymphocyte membrane) or monoclonal antibodies ***against the receptor for interleukin 2 ,*** basiliximab and daclizumab. Antibodies against lymphocytes are more effective, so they are used in patients with a high risk of transplant rejection; however, since they reduce the number of lymphocytes, they lead to serious side effects such as lymphoproliferative diseases, cytomegalovirus and other infections. Basiliximab and daclizumab are used in patients who have a moderate or low risk of transplant rejection; these drugs are well tolerated, because they do not reduce the number of lymphocytes and do not lead to a greater tendency to infections.
2. **Maintenance immunosuppression** - as after bone marrow transplantation, classic maintenance immunosuppression is triple therapy: **calcineurin inhibitor (cyclosporine or tacrolimus) + antimetabolite (azathioprine or mycophenolate mofetil) + prednisolone.** After a year or two, prednisolone can be completely discontinued with a gradual dose reduction, so that the patient is left with only two drugs. In patients who develop vasculopathy in a transplanted heart and have kidney failure, sirolimus is introduced into the therapy, which allows for a reduction in the dose of calcineurin inhibitors.
3. **Transplant rejection** - if, despite the prophylactic use of immunosuppressants, an acute heart transplant rejection reaction occurs, then so-called "rescue" therapy must be applied. It depends on the severity of rejection, which is assessed on the basis of the histological image of the biopsied myocardium, and on the hemodynamic status of the patient. If the histological picture is mild and there are no hemodynamic changes, acute rejection does not need to be treated separately, but the patient can continue with maintenance immunosuppression. If the histological picture is mild, but there is hemodynamic disfunction, high doses of corticosteroids are used. When the histological picture is moderate or severe, and there are no hemodynamic changes, therapy also consists of high doses of corticosteroids. Finally, in the case of a moderate or severe histological picture and the presence of hemodynamic disfunction of the organism, a combination of corticosteroids and antithymocyte immunoglobulin is given.

IMMUNOSUPPRESSIVE THERAPY OF CONNECTIVE TISSUE DISEASES AND BIOLOGICAL THERAPY OF RHEUMATOID ARTHRITIS

Connective tissue diseases include rheumatoid arthritis, systemic lupus erythematosus, scleroderma, polymyositis/dermatomyositis and mixed connective tissue disease. At the root of all these diseases is an autoimmune process, which damages healthy tissue and leads to symptoms and signs of the disease. That is why **immunosuppressive drugs** are used in the treatment of all connective tissue diseases.

Immunosuppressive therapy can be **"classic"**, when small molecule drugs are used that inhibit the autoimmune process with insufficient specificity, or " **biological"** , when antibodies or other protein preparations are used that act very specifically, binding to only one receptor or another functional protein, so that the autoimmune process is inhibited in a precisely defined part. "Classic" immunosuppressive therapy has significantly more side effects than "biological" due to its insufficiently specific effect.

As part of "classic" immunosuppressive therapy, corticosteroids are used for all diseases, which have a fast and strong immunosuppressive and anti-inflammatory effect, so that patients quickly feel improvement. However, due to numerous side effects, corticosteroids are used as short as possible, and are replaced by other immunosuppressants: methotrexate in rheumatoid arthritis, cyclophosphamide or mycophenolate mofetil in lupus, cyclophosphamide in scleroderma, and methototrexate, azathioprine or mycophenolate mofetil in polymyositis/dermatomyositis.

"Biologic" immunosuppressive therapy is most commonly used in rheumatoid arthritis, usually in combination with methotrexate. **Medicines** are used **that inhibit tumor necrosis factor alpha**, a cytokine that normally activates lymphocytes and polymorphonuclear cells and leads to the creation of other pro-inflammatory cytokines and increased inflammation. Tumor necrosis factor alpha is inhibited **by etarncept** (soluble receptor for tumor necrosis factor alpha), **infliximab** (chimeric monoclonal antibody against **tumor** necrosis factor alpha) and **adalimumab** (recombinant monoclonal antibody that binds to tumor necrosis factor alpha). These drugs are administered subcutaneously or intravenously, with an interval of one to several weeks. They are usually well tolerated by patients (with minor irritation at the application site), but increase the risk of opportunistic infections (e.g., tuberculosis) and demyelinating neurological diseases. Therefore, before introducing these drugs, it is necessary to rule out the existence of latent tuberculosis. It is still not clear whether these drugs also increase the risk of malignant diseases. Infliximab has another specific side effect - it can worsen the condition of patients with heart failure and increase the risk of death in such patients.

Abatacept is a recombinant protein consisting of the Fc fragment of a human IgG antibody and the extracellular part of a cytotoxic T-lymphocyte-

associated protein 4 (CTLA4); it can also be used in the treatment of rheumatoid arthritis. Abatacept binds simultaneously to CD80 and CD86 molecules on the lymphocyte membrane (co-stimulation).

Rituximab is a humanized murine monoclonal antibody that binds to the CD20 antigen on B-lymphocytes, leading to the death of those cells and a reduction in the immune response.

In the last decade antibodies against the interleukin 6 receptor were used, too: **tocilizumab and sarilumab**. Their side effects are similar to side effects of tumor necrosis factor alpha inhibitors. These drugs are administered parenterally, with an interval of one or more weeks.

"Biological" therapy leads to improvement in about 60% of patients with rheumatoid arthritis. So far, these drugs have been used for the longest time in the same patient for two years; clinical studies examining the efficacy and safety of longer-term use are ongoing.

ADVERSE EFFECTS OF IMMUNOSUPPRESSANTS

Due to the suppression of the immune response and insufficiently specific mechanism of action, drugs from this group have significant side effects. Due to the fact that they suppress the immune response, the frequency of infections and malignant diseases increases with all drugs from this group.

Cyclophosphamide binds its active group (chloro-ethyl-amine) to ***nucleic*** bases in DNA and leads to errors during replication. Adverse effects are a consequence of its basic pharmacological effect: neutropenia, thrombocytopenia, alopecia, hemorrhagic cystitis. ***Azathioprine***, as ***a*** precursor of mercaptopurine, also interferes with normal DNA synthesis. Mercaptopurine, as a false nucleotide, is incorporated into the DNA of rapidly dividing cells so that errors and cell death occur during replication. Mercaptopurine also damages blood lines, leads to anemia, leukopenia and thrombocytopenia, and can damage the liver. The main side effects of azathioprine are suppression bone marrow, gastrointestinal complaints, increased susceptibility to infections and carcinogenicity.

Methotrexate is an analogue folic acid that blocks dihydrofolate - reductase, reduces the synthesis of tetrahydrofolic acid and interferes with the functioning of the enzyme whose cofactor is methyl-tetrahydrofolic acid. The most important enzyme from this group is thymidylate synthetase, the block of which prevents the creation of thymidylate, one of the four nucleotides necessary for DNA synthesis. Methotrexate leads to anemia, leukopenia and thrombocytopenia.

Mycophenolate mofetil is a newer cytotoxic immunosuppressant that inhibits the synthesis of guanosine. It is used to prevent rejection of kidney, liver and heart transplants in the first 6 months after surgery, often together with cyclosporine and corticosteroids. It is currently more effective than all other

immunosuppressants for this indication. It leads to bone marrow damage and increases the incidence of skin and lymphatic tissue cancer.

As can be seen, when cytostatics are applied as immunosuppressants, a one-week control of the patient's blood count is necessary. If there is a sudden drop in the number of leukocytes or platelets, discontinuation of therapy is indicated.

Cyclosporine, a lipid-soluble peptide antibiotic (cyclic peptide with 11 amino acids), blocks the differentiation of T-lymphocytes in the early stages of an immune response. It binds to the cytoplasmic protein, cytophilin C; that complex inhibits the enzyme calcineurin phosphatase, which leads to a decrease in the synthesis and release of many cytokines, such as interleukins 2, 3 and 4, interferon alpha and tumor necrosis factor. Cyclophosphamide has a pronounced *nephrotoxic effect, so urine and* serum creatinine levels must be controlled during therapy. In addition, it causes hyperglycemia, hyperlipidemia, hirsutism, neuropathy and mild hepatitis. In the same group of antibiotics there is also a newer drug, ***tacrolimus.*** The mechanism of action and side effects are similar to that of ciclosporin.

Sirolimus is structurally similar to tacrolimus, but works by a different mechanism. It inhibits cytoplasmic serine-threonine kinase (a molecule to which rapamycin binds), thereby preventing the proliferation of T-lymphocytes. It is used only in combination with cyclosporine, for the prevention of acute rejection of the transplanted kidney. Sirolimus leads to cytopenia, hyperlipidemia, impaired wound healing and thrombosis of the hepatic artery.

Antilymphocyte and antithymocyte globulins **are** used to prevent graft rejection, especially if corticosteroids have failed. As T-lymphocytes are mainly found in the blood, antilymphocyte globulin primarily suppresses cellular immunity. Adverse effects of these preparations are anaphylactic reaction, serum sickness and the occurrence of histiocytic lymphoma at the site of multiple injections of globulin.

Muromonab - CD 3 (OKT3) is a monoclonal antibody obtained from the blood of mice, which binds to the CD3 antigen on T lymphocytes. The consequence of the binding of muromonab to the CD3 antigen is inhibition of the activation of T lymphocytes, so that they lose their function. The drug is used to prevent rejection of kidney, liver or heart transplants, as well as to reduce the number of T lymphocytes in the bone marrow of the donor (before transplantation). Adverse effects include pulmonary edema, fever, vomiting, and anaphylactic reaction.

Adverse effects of **baziliximab and daclizumab**, monoclonal antibodies that bind to the receptor for interleukin 2, which are used in induction therapy for the prophylaxis of kidney or heart transplant rejection, are: anaphylactoid reactions, onset of diabetes, hepatotoxicity, opportunistic infections and lymphoproliferative diseases.

CLINICALLY SIGNIFICANT INTERACTIONS OF IMMUNOSUPPRESSANTS

Due to the fact that immunosuppressants are almost always used in combination, there are clinically significant interactions between these drugs , which can lead to serious clinical consequences. In order to avoid undesirable consequences, it is necessary to know these interactions, and to periodically monitor the serum concentration of an immunosuppressant, with appropriate dose adjustment.

Cyclosporine (unlike tacrolimus) inhibits enterohepatic recirculation of **mycophenolic acid** (which is formed from the pro-drug mycophenolate mofetil) due to the inhibition of the MRP2 transporter in the bile ducts and intestinal epithelium. As a result of this inhibition, the serum level of mycophenolic acid decreases by as much as 50%. To preserve the immunosuppressive effect of mycophenolate mofetil in patients receiving cyclosporine at the same time, it is necessary to double the daily dose from one to two grams of mycophenolate mofetil. Tacrolimus , which belongs to the group of calcineurin inhibitors like cyclosporine, does not affect the blood level of mycophenolic acid, so it is easier to combine it with mycophenolate mofetil in practice.

Cyclosporine is metabolized via cytochrome CYP3A4 in the liver, and simultaneously inhibits that enzyme. Since sirolimus is metabolized by the same isoenzyme, the simultaneous use **of cyclosporine and sirolimus** leads to an increase in serum concentrations of both drugs. The consequence of this interaction can be the manifestation of toxic effects of cyclosporine on the kidney.

Due to metabolism via CYP3A4, cyclosporine interacts with other drugs that can inhibit or induce the activity of this enzyme. Thus, the known inhibitors of CYP3A4 activity, macrolides, imidazoles, chloramphenicol, grapefruit juice and protease inhibitors will lead to an increase in the concentration of cyclosporine in the serum, and the known inducers of CYP3A4 carbamazepine, phenobarbital and rifampicin lead to a decrease in the serum concentration of cyclosporine.

On the other hand, due to the pronounced nephrotoxic side effect of cyclosporine, its simultaneous use with other nephrotoxic drugs (e.g., aminoglycosides, vancomycin, amphotericin B, non-steroidal anti-inflammatory drugs, etc.) increases the risk of damage to this organ.

It has been observed that discontinuation of **corticosteroids** in patients who have been receiving corticosteroids and tacrolimus for several months leads to an increase in **tacrolimus serum concentrations** by 10 to 35%. It is believed that this is due to the cessation of the stimulatory effect of corticosteroids on the activity of CYP3A4, by which tacrolimus is metabolized, and on P-glycoprotein, which expels tacrolimus from the intestinal epithelium, but there is not enough evidence to confirm this assumption.

All immunosuppressants interact with live vaccines, allowing the overgrowth of microorganisms from the vaccine that cause severe systemic infection of the organism. Also, when administered together with other types of vaccines, which do not contain living organisms, immunosuppressants prevent the development of specific immunity. That is why the use of immunosuppressants with vaccines is **contraindicated**. The simultaneous application of several immunosuppressants has an additive effect on the immune system and leads to its severe suppression, which results in the uncontrolled development of infections with pathogens that are not normally very virulent, so we call them opportunistic microorganisms.

APPLICATION OF ANTIBIOTICS TO IMMUNOSUPPRESSED PATIENTS

Patients with transplanted organ and immunosuppressive therapy

Before solid organ transplantation, all possible foci of future systemic infection (e.g., urinary infection, dental infections, etc.) should be cured in the patient. The patient should also be vaccinated against pneumococcus, influenza, varicella and hepatitis B. During the transplant surgery itself, routine antibiotic prophylaxis is applied, as with other major surgical interventions.

After the transplantation, in patients who are at risk of fungal infections (for example, if they were colonized with Aspergillus or Candida before the transplant, or if they had any fungal infection previously), prophylaxis with an antifungal drug is applied. Invasive fungal infections can occur in organ transplant patients with a frequency of up to 56%. The use of prophylaxis in patients at risk reduces the rate of fungal infections to only 10%. For prophylactic purposes, **fluconazole** is most often given, although amphotericin B is also an option.

When it comes to the prophylaxis of bacterial infections with antibiotics, the use of the combination **sulfamethoxazole-trimethoprim** for 6 months is justified, which prevents infection of the urinary tract, and infection with nocardia, listeria, toxoplasma or pneumocystis. Prophylactic use of vancomycin, quinolones or other antibiotics does not reduce the frequency of bacterial infections, but increases the frequency of patients with vancomycin-resistant enterococci infection. Nystatin drops or oral clotrimazole gel should also be added to prevent fungal infections.

Acyclovir or **valacyclovir** should be administered for at least one month in persons who are herpesvirus-seropositive. **Valgancyclovir** or gancyclovir is given prophylactically in persons who receive higher doses of immunosuppressants, or there is seropositivity for cytomegalovirus in their or

the donor's blood. Vaccination of patients against influenza, hepatitis B and varicella-zoster virus is also recommended before the transplantation. The use of live vaccines is contraindicated.

If an infection does occur in transplanted patients, it is usually caused by multiresistant strains, so treatment should be started immediately with a combination of antibiotics that is also active against multiresistant Pseudomonas and methicillin-resistant Staphylococcus (carbipenem or extended spectrum semi-synthetic penicillin together with a glycopeptide).

Patients with malignant disease and on chemotherapy

It is not necessary to apply prophylaxis of bacterial or fungal infections in patients with solid tumors in whom the episode of neutropenia is expected to last less than 7 days after administration of a course of chemotherapy. Prophylaxis of viral infection is carried out in these patients only if they have previously had episodes of herpesvirus infection. However, in patients with malignant tumors of blood cells, antibiotic prophylaxis is indicated when severe neutropenia occurs (absolute neutrophil count below 0.5×10^9/L). In prophylaxis, fluoroquinolones are most often used.

When an infection occurs in patients receiving chemotherapy, treatment with antimicrobial drugs should be started as soon as possible, and the antimicrobial drug should be chosen that will be effective against the most likely causative agent. Antimicrobial drugs with the strongest effect should be applied immediately, i.e., with the greatest probability that they will be effective, and exclusively by parenteral means.

Patients with febrile neutropenia

If in a patient who received chemotherapy, the number of leukocytes falls below 1.5×10^9/L, and he/she gets an elevated body temperature (oral temperature above 38.3 °C), the probability that he has an established bacterial or fungal infection is over 50%. We call such a condition febrile neutropenia, and it is considered a medical emergency. Then strong broad-spectrum antibiotics (carbapenems or semi-synthetic penicillins of extended spectrum together with glycopeptide) should be applied immediately, until the causative agent is isolated and its sensitivity tested, when the therapy can be targeted towards the isolate. The probability of a fungal infection can be estimated by measuring the presence of mannan and galactomannan in the patient's serum (these are molecules from the cell wall of fungi, mannan from Candida and galactomannan from Aspergillus), so in case of a positive result, antifungal therapy is added.

Patients receiving inhibitors of tumor necrosis factor alpha

Patients with rheumatoid arthritis who receive etanercept, infliximab or adalimumab are at particular risk of developing ***tuberculosis***. Therefore,

before using these drugs, it should be checked whether the patient may have latent tuberculosis, and if so, antituberculosis drugs should be included immediately. In addition to tuberculosis, these patients may also develop fungal infections.

USE OF CORTICOSTEROIDS IN THE TREATMENT OF MALIGNANT BLOOD TUMORS

Corticosteroids are used as part of the ***acute lymphocytic leukemia treatment protocol***. In the phase **of induction** according to the so-called "Linker" protocol 60 mg/m² of prednisone is applied daily, orally, divided into three doses, during the first 28 days of treatment. If malignant cells are detected on the bone marrow biopsy on the 28th day of treatment, prednisone is given in the same dose from the 29th to the 42nd day. In the **consolidation phase, 60** mg/kg/day of prednisone is administered for 14 days, orally, divided into three doses. In **maintenance** terapy corticosteroids are **not used**. In some other protocols for the treatment of acute lymphocytic leukemia, dexamethasone is - used instead of prednisone.

Corticosteroids are also used in the treatment ***of chronic lymphocytic leukemia***. Then they are applied as part of combined therapy, per cycle, usually in the first 5 days of the cycle. Cycles of cytostatic therapy are usually repeated after 21 to 28 days. Prednisone is most often used, in a daily dose of 30 to 100 mg/m². Sometimes prednisone can be used as the only drug, in a dose of 20-30 mg/m² per day, in the first three weeks of the monthly cycle.

In the treatment ***of Hodgkin's lymphoma,*** corticosteroids are used as part of the MOPP protocol (cyclophosphamide, vincristine, procarbazine and prednisone). The dose of prednisone is 40 mg/m² per day, orally, from the 1st to the 14th day of the monthly chemotherapy cycle. If bleomycin is used in any of the other protocols for the treatment of Hodgkin's lymphoma, hydrocortisone, 100 mg should be given before its administration, intravenously in a single dose.

When it comes to the treatment ***of non-Hodgkin's lymphomas***, prednisone or dexamethasone are indispensable members of many therapeutic protocols. Prednisone is given orally, in a dose of 50 to 100 mg/m² per day, in the first 5 days of monthly therapeutic cycles.

Prednisone is also an integral part of therapeutic protocols for ***multiple myeloma***. It is usually administered in a daily dose of 60 mg/m² , orally, every 5 days of monthly therapeutic cycles. In some protocols, dexamethasone (40 mg/m²/day) is used instead of prednisone. Recently, new, more effective drugs are used in the treatment of multiple myeloma, so corticosteroids are used in new protocols in smaller doses than those mentioned.

USE OF CORTICOSTEROIDS IN THE TREATMENT OF AUTOIMMUNE DISEASES AND THEIR SIDE EFFECTS

Corticosteroids are used systemically in the treatment of many autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus and polymyositis, and in osteoarthritis and bursitis they are applied intra-articularly and peri-articularly. They are very effective in controlling the symptoms and signs of inflammation, but they do not affect the progression of the disease itself. They are usually applied at the beginning of treatment, with the aim of calming the sympt, or during exacerbations. Corticosteroids actually give time to other drugs, which can stop the progression of the disease, to have their effect.

Due to the large number of serious side effects, corticosteroids are chronically administered in the smallest effective doses, orally. Prednisone or its active metabolite prednisolone are most often used for chronic administration. In periods of exacerbation, corticosteroids are administered for several days in high doses, parenterally (e.g., methylprednisolone, 1 gram per day). Triamcinolon hydrochloride or methylprednisolone acetate are administered intra-articularly. Intra-articular injections of corticosterids should not be applied more than 4 times a year, because joint cartilage may be damaged. When giving intra-articular injection, it is necessary to strictly observe the principles of asepsis and antisepsis, because the possible introduction of an infection would have disastrous consequences.

After binding to their intracellular receptor, corticosteroids control gene expression. The expression of lipocortin increases, which reduces the synthesis of phospholipase A_2 and the migration of leukocytes. Lipocortin also reduces the synthesis of prostaglandins and leukotrienes.

Cortisol (hydrocortisone) in the blood is mostly bound to alpha$_2$-globulin (90%), and the rest is partly bound to albumin and partly free. Only free cortisol is active, while the bound part acts as a cortisol depot, which is in balance with free cortisol. The half-elimination time of cortisol is 60-90 minutes; most of the cortisol is reduced in the liver to tetrahydrocortisol and tetrahydrocortisone, then conjugated and excreted in the urine. Prednisolone is completely absorbed after oral administration. Although the half- life is about 3 hours, prednisolone can be administered once a day because the effects last more than 24 hours.

Adverse effects of corticosteroids are directly dependent on the daily dose and duration of administration. Whenever possible, the daily dose of prednisolone should be reduced to 5-7.5 mg per day (it is best to apply it in one morning dose, because then the secretion of cortisol is the highest), which is equivalent to the daily physiological secretion of cortisol in the suprarenal gland. Also, the duration of administration should be as short as possible, but not at the expense of controlling the disease for which the corticosteroid is used.

Corticosteroids can cause peptic ulcer, especially if the patient simultaneously takes non-steroidal anti-inflammatory drugs. Also, when used for more than a few months, osteoporosis occurs; osteoporosis can be prevented

if the patient takes bisphosphonates and vitamin D at the same time. Corticosteroids also cause skin atrophy, psychotic manifestations, hypertension and cataracts, increasing the risk of fungal, viral and mycobacterial infections. In addition to these side effects, corticosteroids also cause: myopathy, diabetes, glaucoma and psychiatric disorders (agitation, insomnia, psychosis, hypomania, irritability, anxiety, unstable mood).

After a few weeks of therapy, the adrenal gland will be suppressed, so that Addison's crisis (hyponatremia, hyperkalemia, hypotension) may occur in the event of a sudden interruption of administration. The use of corticosteroids should be stopped very gradually, over several months. Even a few years after the gradual cessation of corticosteroid administration, the patient may fall into Addison's crisis, if there are stressful conditions (surgery, severe infection, trauma); this kind of complication can be prevented by applying an additional dose of corticosteroids , before or at the moment when such a condition occurs.

USE OF CORTICOSTEROIDS IN THE TREATMENT OF EDEMA AND THEIR ADVERSE EFFECTS

Corticosteroids have been used for decades with success in the treatment of edema that occurs around brain tumors. The mechanism of action of corticosteroids consists in inhibition of phospholipase A_2 (which normally leads to the release of arachidonic acid), stabilization of lysosome membranes, improvement of peritumor microcirculation and reducing the expression of vascular endothelial growth factor, which otherwise increases capillary permeability.

Dexamethasone is most commonly used to reduce edema around brain tumors, in a dose of 4 to 16 **mg** per day. The full effect is achieved after 1-3 days. Dexamethasone, unlike other corticosteroids, does not have a mineralocorticoid effect, which is not a favorable circumstance, because it could theoretically lead to hyponatremia, which favors the development of brain edema. That is why some researchers believe that it is better to use prednisone instead of dexamethasone.

Corticosteroid equivalent doses are: dexamethasone 0.75 mg = cortisol (hydrocortisone) 20 mg = prednisone 5 mg = methylprednisolone 4 mg

Adverse effects of corticosteroids are: myopathy (proximal muscle weakness), hypertension, Cushingoid face, disorder of glucose metabolism, skin atrophy, appearance of acne on the skin, increased tendency to the occurrence of acute tonsillitis, cataracts, slowed growth in children and increased acid secretion in the stomach. In order to prevent the formation of stomach ulcers, it is recommended to use along with corticosteroids H_2 blockers or proton pump

inhibitors in patients who simultaneously receive non-steroidal anti-inflammatory drugs, or antiaggregatory drugs, or anticoagulant drugs. H_2 blockers or proton pump or inhibitors should be also given perioperatively, then to people over 65 years of age, and to people with a history of gastritis or ulcers .

In about 18% of patients who receive 12 mg or more of dexamethasone, psychiatric disorders may occur: acute psychosis, mania or depression. Also, the use of corticosteroids to treat brain tumors has been associated with an increased risk of Pneumocystis pneumonia.

If the brain tumor is successfully operated on, corticosteroids should be discontinued after the patient's recovery. They must be withdrawn gradually, by reducing the dose by 25% every 8 days. If corticosteroids are stopped abruptly, two complications occur: (1) "withdrawal syndrome " and (2) acute adrenal insufficiency. "**Abstinence syndrome**" consists of arthralgia, myalgia, headache, lethargy and subfebrility. **Acute adrenal insufficiency** consists of hypotension that can only be treated with vasoconstrictors, followed by weakness, skin pigmentation and weight loss.

Triamcinolone acetonide can be administered as an intravitreal injection to treat macular edema after surgery or in diabetes. Usually, 1 mg of this medicine is administered. Possible complications of this method of administration include increased intraocular pressure, cataracts and infectious endophthalmitis.

Corticosteroids are successfully used to treat **angioedema, edema of larynx and edema of other tissues**. In those situations, high doses of corticosteroids should be given parenterally (e.g., 40-80 mg methylprednisolone) without fear of side effects, because the therapy will last short, less than 7 days.

CLINICALLY SIGNIFICANT INTERACTIONS OF CORTICOSTEROIDS

Since all corticosteroids have some mineralocorticoid effect, they lead to sodium retention and potassium loss. Due to this loss of potassium, if other drugs that lead to potassium loss (e.g., diuretics, beta-2 agonists) are used at the same time, **hypokalemia may occur**. Hypokalemia is a significant risk factor for a heart arrhythmia, so if the patient simultaneously takes a drug that has a proarrhythmogenic effect (e.g., digoxin, thioridazine, tricyclic antidepressants antiarrhythmics, etc.), the occurrence of **arrhythmias** is very possible. Dexamethasone and triamcinolone interact less frequently than other corticosteroids.

Macrolide antibiotics inhibit the metabolism of corticosteroids by cytochrome oxidase in the liver, leading to an increase in the concentration of corticosteroids in the serum. This kind of interaction has been shown in practice for erythromycin and clarithromycin on the one hand, and for methylprednozolone on the other.

Viral protease inhibitors inhibit the metabolism of corticosteroids by cytochrome oxidase in the liver, leading to an increase in serum corticosteroid concentrations. This kind of interaction has been demonstrated in practice for ritonavir on the one hand, and for prednisone on the other.

Dexamethasone increases the hepatotoxicity of high doses of methotrexate; the mechanism of this interaction is unknown.

If corticosteroids are used together with non-steroidal anti- inflammatory drugs, the risk of **peptic ulcer and gastrointestinal bleeding is increased** (non-steroidal anti-inflammatory drugs interfere with the synthesis of prostaglandins, which reduces blood supply to the gastric mucosa, and corticosteroids increase acid secretion).

Drugs that induce the synthesis and activity of cytochrome oxidases (phenobarbital, phenytoin, carbamazepine, rifampicin, rifabutin) lead to accelerated elimination of corticosteroids (dexamethasone, methylprednisolone, prednisolone and prednisone), and thus to a decrease in their clinical effect.

Corticosteroids reduce the concentration of lithium in the blood, and increase the effect of warfarin and other vitamin K antagonists. Some antiviral drugs reduce the effect of corticosteroids (nevirapine, efavirenz), and some increase it (ritonavir, indinavir, atazanavir).

Finally, corticosteroids (in high, immunosuppressive doses, e.g., more than 40 mg of prednisolone per day) **should never be used simultaneously with live vaccines**, because severe generalized infections can occur. A gap of at least 3 months should be made between the administration of corticosteroids and vaccination with a live vaccine.

TREATMENT OF ADDISON'S CRISIS

Addison's crisis usually occurs due to **bleeding in the adrenal gland** (Watterhaus -Friedrichson syndrome in meningococcal sepsis or anticoagulant overdose), after sudden **discontinuation of** long-term use of corticosteroids, or as an acute exacerbation of chronic insufficiency due to **surgical intervention or sepsis**.

Patients during Addison's crisis feel weakness, hyperpigmentation occurs if the insufficiency persists, weight loss, sometimes abdominal pain, diarrhea, and syncope.

Treatment primarily involves fluid replacement and correction of hypoglycemia, hyponatremia, hyperkalemia, and hypercalcemia. The main drug in the treatment of Addison's crisis is **hydrocortisone, which is administered in a dose of 100 mg intravenously, every 6 hours**. Due to the strengthening of the mineralocorticoid effect, the patient should also be given **fludrocortisone, 0.1 mg per day, orally**.

Of course, work must be done to eliminate the cause of the Addison's crisis.

SUBSTITUTION OF HORMONES IN MENOPAUSE

Substitution of sex hormones in menopause is carried out in women who have pronounced symptoms (waves of feeling hot and cold, irritability, depression, vegetative instability). Hormone substitution has beneficial consequences (the risks of developing osteoporosis and colon cancer decrease), but also side effects (increasing the risk of developing breast cancer, endometrial cancer, ovary and stroke).

Most practice guidelines agree that sex hormone substitution in previously healthy women for a total duration of up to 10 years has more positive than negative medical consequences. The requirements for substitution of sex hormones in menopause are the age under 60, and less than 10 years elapsed since the cessation of menstrual cycles. Sex hormone substitution should not be done in women who have already had breast, endometrial or ovarian cancer, who have already had venous thrombosis, myocardial infarction or stroke, as well as in those who have not regulated their hypertension or have liver disease.

Substitution of sex hormones begins after the cessation of normal menstrual cycles. If a woman's uterus is surgically removed, only estrogen is substituted, i.e., such a person takes preparations containing some of the synthetic estrogens. In women with preserved internal sex organs, preparations containing both estrogen analogues and progesterone analogues are used; it is necessary to use a combination, because progestogens reduce the risk of cancer of the endometrium, which estrogens themselves increase. When only estrogen can be used, transdermal preparations are more favorable, because they contain a lower total dose of estrogen, and successfully control menopausal symptoms. That is why transdermal preparations are used in women who have had their uterus removed and have diabetes, hypertriglyceridemia, obesity, increased risk of thrombosis, migraine or liver disease.

Preparations for hormone substitution in menopause can be such that they provide **cyclical** or **continuous** administration of hormones. With cyclic preparations, during the first 15 days (cyclic preparations at the monthly level) or the first 3 weeks (cyclic preparations at the three-month level), the tablets contain only estrogen analogues, and for the next 14 days until the end of the cycle, the tablets contain only analogues of progesterone. Continuous preparations contain both an estrogen analogue and an analogue of progesterone in each tablet, so female patients who take these preparations do not have menstrual bleeding at all. Preparations for hormone substitution can be applied in the form of vaginal cream, tablets, vaginal tablets, transdermally or in the form of implants.

After 5-10 years of use, preparations for the substitution of hormones during the menopause are gradually discontinued, in order to prevent the reappearance of menopause symptoms. Women are also recommended to use vaginal creams without hormones to prevent vaginal dryness, and to use bisphosphonates or denosumab to prevent osteoporosis.

HORMONAL THERAPY OF STERILITY IN BOTH SEXES

A polypeptide of 10 amino acids that is secreted in the hypothalamus through the portal system reaches the pituitary gland and there leads to the release of gonadotropic hormones, follicle-stimulating (FSH) and luteinizing - (LH). This polypeptide is called **gonadotropin-releasing hormone (GRH).** GRH is used to induce ovulation in people suffering from infertility. In order to achieve this effect, it is necessary to administer GRH in the form of an intravenous infusion, pulsed (a small dose of GRH is injected every hour for several days), because only then does the secretion of FSH and LH increase. The dose of GRH is 5 micrograms per pulse intravenously or 5-25 micrograms per pulse subcutaneously. The effect of this drug is monitored by measuring LH excretion in urine and by ultrasound examinations of the ovaries.

FSH and LH can be obtained in larger quantities from the urine of women in postmenopause (the preparation is called human menopausal gonadotropin **HMG** or **urofollitropin**. A synthetic FSH hormone called **follitropin** is used today with the same success. **Human chorionic gonadotropin** can be used instead of LH (hormone of the corpus luteum and placenta, which is found in large quantities in the urine of pregnant women, hHG), which has very similar effects. Both preparations are used sequentially to induce ovulation in patients suffering from sterility and to stimulate spermatogenesis in men.

Human menopausal gonadotropin contains 75 IU FSH and 75 IU LH per milliliter. It is used to induce ovulation primarily in patients with primary amenorrhea due to hypopituitarism, or in secondary amenorrhea that has not responded to the use of other ovulation inducers. The use of gonadotropins leads to a lot of side effects: ectopic pregnancy (about 8%), multiple pregnancy (about 30%), spontaneous abortion (about 20%), rupture and torsion of the ovary, and ovarian hyperstimulation syndrome (up to 30%). Hyperstimulation syndrome ovary is characterized by enlargement of the ovary, accumulation of fluid in the interstitial space and peritoneal cavity (ascites and the like), hemoconcentration, hyponatremia and hyperkalemia. If the patient is not treated on time, hyperstimulation syndrome can be complicated by acute renal failure and thrombosis. Hyperstimulation syndrome is treated with the infusion of an isotonic saline solution, the infusion of a 25% albumin solution and the use of prophylactic doses of heparin.

Dose of human menopausal gonadotropin is initially 75IJ daily, subcutaneously. After 7 days, based on the measurement of estradiol in the serum and the size of the follicles on the ultrasound, the dose is adjusted until the follicle size is 18 mm in diameter. Ovulation is then induced with an intramuscular injection of 10,000 IJ of human chorionic gonadotropin.

Clomiphene is a drug that blocks estrogen receptors in the pituitary gland and hypothalamus, interfering with the negative feedback loop of estrogen on the release of gonadotropins. As a result of the effect of clomiphene, the secretion of gonadotropins increases, and thus enables the occurrence of ovulation. The dose of clomiphene is 50 mg orally, from the 3rd day of the

menstrual cycle, for the next 5 days. The occurrence of ovulation is monitored by measuring the excretion of LH in the urine; when the amount of secreted LH increases suddenly, ovulation usually occurs after a day or two. Clomiphene is most commonly used to induce ovulation in polycystic ovary syndrome patients. Other selective modulators of estrogene receptors have similar efficacy to clomiphene, e.g., tamoxifen and raloxifene.

Adverse effects of clomiphene are thickening of cervical mucus (due to which sometimes conception may not occur even though ovulation has occurred), hot flashes, vaginal dryness, and ovarial hyperstimulation syndrome.

Metformin, an oral antidiabetic drug that increases the sensitivity of peripheral tissues to the action of insulin, is also used to stimulate ovulation, although this indication is not officially approved. The results of clinical studies are equivocal - some studies have demonstrated a positive effect and some have not. Only the future will tell if metformin will continue to be used for these purposes.

When it comes to infertility **in men**, first of all, it should be determined whether the production of gonadotropin and testosterone is within normal limits. If not, then **clomiphene or human menopausal gonadotropin** can be used. Clomiphene increases the release of gonadotropin from the pituitary gland, and human menopause gonadotropin leads to improvement of spermatogenesis and increase of testosterone production. If the patient's - gonadotropin production is normal and there is oligospermia or azoospermia, then the in vitro fertilization procedure is started.

ADVERSE EFFECTS OF THERAPY WITH SEX HORMONES

The side effects of estrogens are numerous, and mostly represent an extension of their pharmacological effect. The frequency of thrombosis has increased, especially in women over 35 years of age who smoke, which increases the risk of stroke and myocardial infarction. Hypertension occurs due to sodium retention. The sensitivity of the breasts is increased, confusion may arise, the risk of cancer is higher endometrium and breast. Nausea, vomiting and bloating sometimes accompany the use of these drugs. Estrogens can lead to premature closure of the epiphyseal plates in prepubertal females, and short stature. The risk of migraine is also increased. Hypertriglyceridemia can be observed in the blood of patients receiving estrogen for a long time. In the event that only estrogens without progestagens are applied, the endometrium hypertrophies and after some time, despite the presence of estrogen, it peels off, causing - massive menorrhagia. Hyperpigmentation can occur on the skin and hair loss follows. Less known side effects of estrogens are: worsening of epilepsy, worsening of asthma, irritability, galactorrhea, hypocalcemia, pancreatitis, vulvovaginal candidiasis and growth of uterine fibroids.

Progesterone should not be used during pregnancy because it increases the frequency of hypospadias in male newborns! In non-pregnant women, progesterone can cause depression and edema. Derivatives of 19-nortestosterone have significant androgenic side effects: they can cause hirsutism (increased male pattern baldness), acne, skin pigmentation, and a decrease in HDL lipoprotein levels in the plasma. Due to retention of sodium in the renal tubules caused by progestogens, patients often have hypertension. Long - term use reduces bone density, and ovulation slows down. In addition to the listed side effects, progestogens also cause the following: irregular vaginal bleeding, hyperkalemia and increased frequency of follicular ovarian cysts.

When estrogens and progestogens are given together as part of contraceptive preparations, the following side effects have been recorded: increase in blood coagulation factors (thereby increasing the tendency to arterial and venous thrombosis), increase in blood lipids, migraine headaches, hypertension, enlargement of uterine fibroids, fibrocystic breast disease, occurrence of telangiectasia, carcinogenic effect on the cervix uterus and breast, depression, increased appetite, acne, hirsutism, jaundice, reduced level of HDL lipoproteins in the blood, cervicitis and fluid retention. Within **the increased risk of thromboembolism,** myocardial infarction**,** stroke, deep vein thrombosis and pulmonary embolism may occur, especially in older women, smokers, women who have previously had thrombosis and women who have some of the genetic disorders which lead to increased blood coagulability (e.g., antiphospholipid syndrome) .

Adverse effects **of androgens** are: masculinization of the woman, cholestatic jaundice, acne on the the skin and retention of sodium. Paradoxically, excessive doses in men cause feminization (gynecomastia, reduction of testicles, infertility), due to inhibition of the pituitary gland and conversion to estrogens. High doses also cause hostility and aggression. They can also cause cholestatic jaundice, increased liver enzymes, and rarely liver adenomas or hepatocellular cancer.

CLINICALLY SIGNIFICANT INTERACTIONS OF ORAL CONTRACEPTIVES

Interactions between oral contraceptives and other drugs can be two-fold: drugs can reduce the effectiveness of oral contraceptives, or oral contraceptives can interfere with the metabolism of other drugs. Medicines that reduce the effectiveness of oral **contraceptives** due to the acceleration of the metabolism of estrogen and gestagen in the liver are **carbamazepine, phenytoin, phenobarbital, topiramate, oxcarbazepine, ritonavir, griseofulvin and rifampicin.** The mentioned drugs induce the synthesis of additional

amounts of cytochrome 3A4 isoform od P 450, as a result of which the metabolism of oral contraceptives accelerates. St. John's wort extract works similarly.

Broad spectrum antibiotics also reduce the **effectiveness** of oral contraceptives, but the mechanism of this undesirable effect is not yet known with certainty, except for rifampicin, which accelerates their metabolism. So far, only tetracyclines and penicillins have been shown to reduce the plasma concentration of ethinylestradiol.

On the other hand, **vitamin C and paracetamol** compete with ethinyl estradiol for sulfation enzymes, thereby increasing the concentration of ethinyl estradiol in plasma. Oral contraceptives also increase the concentration **of cyclosporine** in plasma, and decrease the concentration of **lamotrigine**.

ANTIESTROGENS IN THE TREATMENT OF TUMORS

There are two types of intracellular estrogen receptors: **alpha and beta**. When estrogens bind to alpha receptors, it is a strong signal for cell proliferation, while activation of beta receptors leads to inhibition of cell proliferation.

Only alpha estrogen receptors are functional in breast tumor cells , so the growth of breast tumors containing these receptors can be stopped using alpha estrogen receptor blockers. A drug from the group of **selective modulators of estrogen receptors**, tamoxifen blocks alpha estrogen receptors in breast tumor cells, and stops tumor growth. Also, a drug from the group of **selective destroyers of estrogenic receptor**, **fulvestrant**, has been successfully used to treat breast tumors that contain alpha estrogen receptors. The problem in the clinical application of these two drugs is the rapid development of tumor resistance.

Selective modulators of estrogen receptors, **tamoxifen and raloxifene**, block alpha estrogen receptors in breast tissue, and act as agonists of these receptors in bones, liver and blood vessels. In the endometrium, these drugs act both agonistically and antagonistically. Tamoxifen and raloxifene are used to treat and prevent breast tumors. Due to its agonistic action in the liver, blood vessels and endometrium, tamoxifen has a greater tendency to thrombosis and an increased risk of cancer of endometrium as side effects. Unlike tamoxifen, raloxifene does not increase the risk of cancer of the endometrium, but increases the tendency for the occurrence of venous thromboses. On the other hand, tamoxifen reduces the risk of myocardial infarction, and lowers serum cholesterol levels.

Aromatase is an enzyme found in adipose tissue, muscle, liver and mammary gland; this enzyme converts androgen androstenedione into estriol, which is the main source of estrogen in menopausal women. Medicines that inhibit aromatase can be used as adjunctive therapy for breast cancer in postmenopausal women (provided the cancer contains estrogen receptors).

Until recently, aminoglutethimide, a drug that simultaneously blocks the synthesis of steroid hormones in the adrenal cortex, was used for these purposes. Today, there are selective aromatase inhibitors that have few side effects and are effective. Some of these drugs are **letrozole, anastrozole and exemestane**.

Recently, **inhibitors of cyclin-dependent kinase 4 and 6 (CDK 4/6 inhibitors)** have been combined with aromatase inhibitors. Cyclin D1 and CDK 4/6 are parts of the signaling pathway that, in breast cells with estrogen receptors, lead to the progression of the cell cycle from G1 to S phase, that is, to proliferation. This group of drugs includes **palbociclib, ribociclib and abemaciclib**. Unwanted effects of these drugs are a higher frequency of infections, depression of blood lines (anemia, leukopenia, thrombocytopenia), interstitial lung disease (pneumonitis), peripheral neuropathy and thromboembolism.

Destroyers of estrogen receptors are used as **second-line** drugs in the treatment of breast tumors containing alpha estrogen receptors. When a metastatic breast tumor becomes resistant to tamoxifen, raloxifene or aromatase inhibitors, **fulvestrant is used**. **Fulvestrant** binds to alpha estrogen receptors and includes them in proteosome, where they are quickly destroyed. Fulvestrant does not have the slightest agonistic effect on estrogen receptors, so it does not cause a greater tendency to thrombosis and does not lead to an increase in the risk of cancer of endometrium.

In women who are in premenopause, in addition to the endocrine therapy and chemotherapy mentioned above, it is necessary to suppress the function of the ovaries. In the past, this was done by surgical oophorectomy (removal of the ovaries), and today **leuprolide**, an analog of gonadotropin-releasing hormone is used, which prevents the release of FSH and LH from the pituitary gland.

HORMONAL THERAPY OF PROSTATIC CANCER

The essence of hormonal therapy for prostate cancer lies in reducing the effect of androgens on cancer cells, which normally divide much faster under the influence of androgens. When the effect of androgens decreases, tumor cells enter the process of apoptosis.

Reducing the effect of androgens cannot cure the prostate tumor, but it slows the progression of the disease, increases the quality of life and prolongs survival. It usually takes 18 to 30 months from the introduction of drugs that reduce the effect of androgens, until the tumor progresses again.

In the past, reducing the effect of androgens on prostate cancer was achieved by surgical castration, and today, instead of surgery, analogues of gonadotropin-releasing factor are used, **goserelin or leuprorelin**. Due to the reduction in the number of receptors for the releasing factor, these drugs inhibit the release of follicle-stimulating and luteinizing hormone from the pituitary gland, which reduces the production of testosterone in the Leydig cells and spermatogenesis. However, at the very beginning of the use of these drugs, there

is a transient increase in the level of testosterone, so it is necessary for the patient **to receive an androgen receptor blocker at the same time** (preferably 7 days before the first injection of goserelin or leuprorelin, and 14 days after the injection), in order to prevent worsening of disease symptoms.

Goserelin and leuprorelin are made in the form of depot preparations, which are applied once a month or once every three months. There is a possibility that instead of agonists of gonadotropine releasing factor an antagonist is used, **degarelix or relugolix**, which do not cause initial increase in the release of testosterone. These drugs lead to improvement of symptoms in 85% of patients, which lasts about 1-1.5 years.

Clinical studies have shown that simultaneous long-term use of blockers of androgen receptors (**flutamide or bicalutamide**) together with analogues of gonadotropin-releasing factor is no more effective than the use of analogues of gonadotropin releasing factor alone. That is why the use of flutamide and bicalutamide is currently limited to only twenty days when the first dose of the analog of gonadotropin releasing factor is applied.

It is considered that hormone therapy of locally advanced or metastatic prostate cancer should be started early, before symptoms appear, because survival is prolonged.

Adverse effects of hormone therapy for prostate cancer include decreased libido, hot flashes, weight gain, depression, osteoporosis, and memory loss.

When a patient with prostate cancer stops responding to therapy with analogues of gonadotropin releasing factor, then we are talking about prostate **cancer resistant to castration**. In such a situation, the so-called **second line** hormone therapy is used. First, newer blockers of androgen receptors are given, **enzalutamide and apalutamide**. When using enzalutamide, the occurrence of epileptic seizures was observed, while the use of apalutamide was accompanied by a higher frequency of falls and fractures. If there is no favorable response to enzalutamide or apalutamide, **abiraterone** is used, a drug that blocks the enzyme 17 alpha-hydroxylase/C17,20-lyase (CYP17) necessary for androgen synthesis, which is found in the tissue of the adrenal gland, testicles and prostate. Abiraterone in combination with **prednisone** is used to treat metastatic castration-resistant prostate cancer. Adverse effects of abiraterone are fluid retention, hypertension and hypokalemia.

The penultimate line of treatment for castration-resistant prostate cancer is the use of **olaparib**, a drug that inhibits the enzyme poly ADP-ribose polymerase (PARP inhibitor). PARP is an enzyme that participates in DNA transcription, in the repair of damaged DNA and in the regulation of the cell cycle. Olaparib is only effective in prostate cancer that has **a BRCA1 or 2** gene mutation. BRCA (abbreviation of "BReast CAncer") 1 and 2 are genes that create proteins whose function is to correct DNA damage, so people with mutations in these genes have an increased tendency to develop malignant tumors.

If the patient does not respond to olaparib, the estrogen **stilbestrol** can be given, which, although sometimes effective, has many side effects: thromboembolism, fluid retention and gastrointestinal disorders.

TREATMENT OF MYOCARDIAL INFARCTION IN OUTPATIENTS

Myocardial infarction is divided into infarction with ST-elevation and without ST-elevation on the ECG, at admission. A heart attack usually occurs at rest, usually early in the morning. Symptoms of a myocardial infarction are: sudden chest pain that does not go away with nitroglycerin, cold sweat, weakness and fear, restlessness, difficulty breathing, cough, syncope... However, even a third of patients with a heart attack do not feel any pain. In 50% of patients, death occurs before arriving at the hospital. Among the signs of myocardial infarction, the most common are bradycardia or tachycardia, hypertension or hypotension, and low fever, which usually starts after 12h and lasts for several days.

Biochemical markers of myocardial infarction in blood are creatine kinase (CK-MB), and troponin I and troponin T. These enzymes become positive at the earliest 4-6 hours after the heart attack, and they are almost always elevated after 8-12 hours. Troponins remain elevated for a long time, even 5-7 days.

Characteristic changes occur in ECG , which go through the following phases: pointed and high T-waves, ST-segment elevation, appearance of Q-waves and finally inversion of T-waves.

All patients with myocardial infarction should be prescribed **aspirin** - orally in a dose of 325 mg, **preferably** in the form of a chewable tablet. Patients allergic to aspirin can take clopidogrel 300 mg at once, if percutaneous coronary intervention is planned, or only 75 mg otherwise. Also, all patients should be given **oxygen** through a mask (2-4 L/min). The use of nitroglycerin under the tongue should be avoided if we are sure that a myocardial infarction has already occurred, because there are many contraindications, which are difficult to check in the field: increased intracranial pressure, circulatory shock, marked hypotension, dehydration of the patient followed by hypovolemia, cardiac tamponade, aortic stenosis, mitral stenosis, cardiomyopathy. In the case of the mentioned conditions, nitroglycerin will reduce blood flow to the heart and worsen the symptoms. With the use of morphine for pain control, which was previously proposed, one should also be very careful, because it has been shown to depress respiration, reduce myocardial contractility, dilate veins and reduce the effect of clopidogrel, so some studies have demonstrated a higher mortality in patients with myocardial infarction who received morphine.

After the aforementioned therapy in the field, the patient should be transported as soon as possible in a supine position to the nearest cardiology center where revascularization can be attempted by means of percutaneous coronary intervention with stent placement or by thrombolytics.

Finally, it is important to mention that **antiarrhythmics are not used prophylactically**, and that **calcium channel blockers are not used in myocardial infarction**, because they increase mortality.

TREATMENT OF STATUS ASTHMATICUS

Status asthmaticus is a medical emergency in which the symptoms of an asthmatic attack **do not subside** after the application of maximum doses of initial bronchodilator therapy.

Salbutamol (beta-2 agonist) should be administered using a nebulizer , in a dose of 10 to 15 mg/h. If you don't have a nebulizer, you can use a pump with a measured dose together with the spacer; the dose is 4 pump activations every 15 minutes to half an hour.

Instead of salbutamol, its R isomer, **levalbuterol,** can be used, which causes arrhythmias and tremors less frequently, and has the same bronchodilator effect as the racemate.

If the attack does not stop with the use of beta-2 selective agonists, the patient should be given subcutaneously 0.3 to 0.5 milligrams of adrenaline.

Ipratropium bromide, a muscarinic receptors blocker, can be used as additional therapy, through a nebulizer. The dose of ipratropium is 250 to 500 micrograms every 6-8 hours. Children respond better to ipratropium bromide than adults.

Although its effectiveness has not been proven, **magnesium sulfate** in a dose of 1 to 2.5 grams intravenously can be given to stop asthmatic status.

Saturation of arterial blood with oxygen should be monitored with a pulse oximeter. If it falls below 92%, **oxygen should also be applied**, through a nasal cannula or a mask.

However, the most important therapy for status asthmaticus is the administration of corticosteroids. **Prednisone** is usually given in a dose of 1-2 mg/kg/day, orally. The effect of corticosteroids is more significant after 4-6 hours. Methylprednisolone can be used intravenously instead of oral prednisone, 1 mg/kg/dose every 6 hours. When corticosteroids are administered, glycemia should be controlled and corrected with insulin. If hypokalemia occurs, **potassium should be supplemented**, or muscle weakness occurs, which further complicates breathing.

A very important part of the therapy is good hydration of the patient, using saline solution intravenously .

The use of antibiotics is not indicated in the treatment of status asthmaticus.

In case the aforementioned therapy does not help the patient and does not stop the asthma attack within 24 hours, **theophylline can also be used**. Theophylline is usually given intravenously as aminophylline, but it can also be given orally. Since aminophylline can cause tachycardia, arrhythmias and convulsions, it is necessary to measure its concentration in the serum, and based

on it, the drug is dosed (so that the serum concentration is maintained between 10 and 15 micrograms per milliliter). Ciprofloxacin, digoxin and warfarin interfere with the metabolism of theophylline and increase its concentration in the serum, and phenytoin and smoking accelerate the metabolism of theophylline and decrease its concentration in the serum. The usual loading dose of aminophylline is 5-6 mg/kg intravenously, and the maintenance dose is 0.5-0.9 mg/kg/hour.

TREATMENT OF ANAPHYLACTIC REACTION

Anaphylaxis is a severe systemic allergic reaction with a potentially fatal outcome. It begins suddenly, lasts no longer than 38 hours, affects one or more organ systems and creates one or more symptoms and signs: angioedema, stridor, dyspnea, hives, itching, vomiting or shock .

An anaphylactic reaction occurs due to the immune-induced release of mediators from mast cells and/or basophils, after exposure to an antigen to which the person was previously sensitized. Antigens are most often from insect venom, drugs, latex, from peanuts, almonds, pistachios, fish, eggs, milk and wheat.

Anaphylactoid reactions are clinically indistinguishable from anaphylactic reactions, but the IgE antibody-antigen reaction does not play a role in their occurrence, i.e., it is not an immunological reaction. Anaphylactoid reactions can occur after the use of non- steroidal anti-inflammatory drugs, opioids or contrast agents in radiology.

Symptoms of an anaphylactic reaction usually appear after a few minutes of exposure to the allergen, but sometimes there is a latent period of one hour. About 80 percent of anaphylactic reactions end in one phase, but in the remaining 20 percent there is ***a two-phase course***, i.e., the symptoms calm down after the application of the therapy, and then after (on average) around 10 hours (the range ranges from 1 to 38 hours), the symptoms reappear. In a third of patients, the second phase is more difficult than the first.

Table 1. Symptoms and signs of anaphylactic reaction

Organ system	**A symptom or sign**
Nervous system	fainting, dizziness, rarely convulsions
Upper respiratory tract	sneezing, hoarseness, stridor, edema of larynx, cough
Eye	itching, tearing, redness
Lower respiratory tract	dyspnea, bronchospasm, tachypnea, cyanosis
Cardiovascular system	tachycardia, hypotension, arrhythmias, cardiac arrest, myocardial infarction
Skin	redness, itching, hives, angioedema
Gastrointestinal system	nausea, vomiting, diarrhea, abdominal pain

Treatment

The first drug to be administered when an anaphylactic reaction occurs is adrenaline, 0.3 - 0.5 mg ***intramuscularly*** (0.3 - 0.5 ml of the dilution 1:1000). Subcutaneous application should be avoided, because absorption of the drug from the application site is unpredictable. Intravenous administration should be reserved only for severe anaphylactic shock, because such a route of administration is associated with a high risk of arrhythmias. If adrenaline is administered intravenously, it must first be diluted in a ratio of 1:10,000.

The dose of adrenaline for children is 0.01 mg/kg, up to a maximum of 0.3 mg. Doses of adrenaline both in adults and in children can be repeated *every 10 minutes*, until the signs and symptoms of anaphylaxis disappear, or the adverse effects of the drug (palpitations, tremors, fear) occur.

Also, it is necessary to ensure the patency of the airways in patients, and apply oxygen. After adrenaline, the patient should be given blockers of histamine H_1 and H_2 receptors, chlorpyramine 20 mg and famotidine 20 mg, intravenously. The combination of H_1 and H_2 antihistamines is more effective than the use of H_1 antihistamines alone. If the patient has bronchospasm, it is useful to use salbutamol (a beta-two receptor agonist) in the form of inhalation.

All patients with anaphylaxis should also be given corticosteroids (e.g., methylprednisolone 125 mg , intravenously, or 50 mg prednisone orally). They can prevent the occurrence of the second phase of anaphylactic reaction. If the patients are extremely hypotensive, they should be given intravenously 500 ml of physiological solution.

If a patient with an anaphylactic reaction is on chronic therapy with beta-blockers or angiotensin-converting enzyme inhibitors, he will not respond well to adrenaline. **Glucagon** should then be **applied** 1 mg (subcutaneously or intravenously, if a preparation for intravenous administration is available), which does not act through beta-receptors, but has a chronotropic, inotropic and vasoactive effect, and causes the release of catecholamines from nerve endings.

When the patient's condition improves, continue the treatment with antihistamines and corticosteroids for another four days. After the anaphylaxis has subsided completely, it is necessary to determine which antigen the patient is allergic to, in order to be able to avoid it in the future. This can be done by allergic skin tests and determining the presence of specific IgE antibodies in the blood.

Any patient who once experienced anaphylaxis should always have **an auto-injector of adrenaline with him/her** (special device for self-administration of adrenaline, which resemble a pen) and be trained to self-administer it as soon as a new anaphylactic reaction occurs. In some countries, patients wear necklaces with a pendant, on which it is written that they are allergic to a certain antigen. In this way, doctors can effectively help them in the event that anaphylaxis occurs again.

TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA

Community-acquired pneumonia is caused in 85% of cases by Pneumococcus, Haemophilus influenza and Moraxella cataralis (so-called typical pathogens), and in 15% by chlamydia, mycoplasma or legionella (so-called atypical pathogens).

When treating community-acquired pneumonia, antibiotics should be used that are effective against both typical and atypical pathogens. This can be achieved by monotherapy, or by using two antibiotics. Monotherapy is used in milder forms of pneumonia that do not require hospitalization, and dual therapy in patients with a more severe form of pneumonia that requires hospitalization.

Monotherapy for community-acquired pneumonia means treating the patient with one drug from the following antibiotic groups: **tetracyclines, macrolides and respiratory fluoroquinolones** (levofloxacin and moxifloxacin)**.** Nevertheless, macrolides should be avoided in monotherapy, because it has been shown that there is a natural resistance of 25% of Pneumococcal strains to macrolides. **Combined therapy** usually consists of **ceftriaxone plus tetracycline, azithromycin or a respiratory quinolone**. Treatment of community-acquired pneumonia with antibiotics should last about 7 days. In the case of severe community-acquired pneumonia, antibiotics should initially be administered parenterally, and when the patient's condition improves, switch to the oral route of administration should be attempted. In the case of mild pneumonia, it is possible to administer antibiotics orally from the beginning.

If quinolones are used for the treatment of pneumonia, **the simultaneous use of proton pump inhibitors or H2 blockers should be avoided, because epidemiological studies have** shown that the percentage of pneumonia recurrence increases after the treatment is stopped.

TREATMENT OF OTITIS MEDIA IN CHILDREN

The most common agents causing acute otitis media are *Streptococcus pneumoniae (40-50%), Haemophilus influenzae (30-40%)* and *Moraxella catarrhalis (10-15%).*

About half of all causative agents secrete beta-lactamases, which means that they are resistant to some of the beta-lactam antibiotics.

In about 70% of children, acute otitis media passes spontaneously after 7-14 days, so antibiotics are not indicated for **all** children with this disease. Antibiotics must be given to children with acute otitis media who are younger

than 6 months, to children between 6 months and two years old if the diagnosis of otitis media is completely certain, and to children older than 2 years if they have a severe form of acute otitis media (temperature higher than 39°C and severe pain in the ear). However, if antibiotics are not used, it is necessary **to observe the child carefully and strictly**, in order not to miss the deterioration and emergence of complications.

The antibiotic of first choice for the treatment of acute otitis media is **amoxicillin, 80-90 mg/kg/day,** divided into two oral doses, for 10 days. It is always applied, unless the child has already received antibiotics in the last month, if purulent conjunctivitis accompanies otitis, in children who normally take amoxicillin for prophylactic purposes and in children allergic to penicillin. In such situations, azithromycin, clarithromycin or clindamycin can be used. The optimal duration of antibiotic administration for otitis media is 10 days.

If the initial therapy does not improve after 72 hours, then it is a so-called persistent acute otitis media. Then you should stop using amoxicillin and apply **amoxicillin with clavulanic acid** (90 mg/kgday, orally**,** divided into two doses), or azithromycin, 20 mg/kg/day for three days. In children who are vomiting, ceftriaxone can be used parenterally, for three days. If there is no improvement even after the second-line therapy, **clindamycin and tympanocentesis should be applied** as the third-line therapy.

If an effusion in the middle ear persists after acute otitis media, such a condition should only be monitored. The use of nasal decongestants and corticosteroids does not significantly affect the outcome of this condition. If the effusion does not go away and there is significant hearing loss, then a tympanostomy should be placed.

In children who develop chronic otitis media with perforation of the tympanic membrane, local antibiotic administration has a greater effect than systemic administration. The best effect is achieved by local application **of ofloxacin drops with hydrocortisone,** 3 drops twice a day, or **drops with ofloxacin only.** Aminoglycosides and polymyxins should be avoided due to possible damage to the auditory and vestibular nerves. Antibiotics are administered systemically only if there is no response to local therapy, or if septic complications occur.

TREATMENT OF FEBRILE CONVULSIONS

Febrile convulsions occur in otherwise neurologically healthy children aged between 6 months and 5 years, who have developed a high body temperature, most often due to some viral infection. Febrile convulsions can be divided into **simple** (last less than 15 minutes, do not have a focal onset, and do not recur in the first 24 hours after onset) and **complex** (have a focal onset or character, last longer than 15 minutes, with or without pauses, and recur in the first 24 hours from the onset).

Benzodiazepines are used to stop febrile convulsions, but only if the convulsions last longer than 5 minutes. Diazepam, midazolam or lorazepam can be used. However, there is the most experience with **diazepam**, which is administered rectally in the form of a microenema (0.5 mg per kilogram, maximum 20 mg per dose) in children **older than 2 years**. If the first dose of diazepam does not stop the convulsions , a second dose is given after 10 minutes.

Instead of diazepam, **midazolam** can be used buccally or intranasally, in a dose of 0.25-0.5 mg/kg , maximum 10 mg. Midazolam can be given to children **older than 3 months** .

If intravenous administration of drugs is possible (e.g., in a hospital), **lorazepam** is administered, 0.05 - 0.1 mg/kg, as a slow intravenous injection for 5 minutes, which can be repeated every 10 minutes up to a total of 3 doses if the attack does not stop.

If benzodiazepines cannot stop febrile convulsions, **fosphenytoin is** administered, 15-20 mg (phenytoin equivalents)/kg, i.v. injection for 15 - 30 minutes. In refractory cases, phenobarbital, levetiracetam or valproate can be used.

Apart from the administration of medicines, care should be taken to keep the child's airway open; immediately after the cessation of convulsions, apply oxygen through a mask or nasal catheter. If apnea occurs after the administration of benzodiazepines, endotracheal intubation should be performed and artificial ventilation started if necessary.

TREATMENT OF UNCOMPLICATED URINARY TRACT INFECTION

Uncomplicated urinary tract infections most often occur in sexually active women. The most common cause of these infections is *Escherichia coli* (about 90% of cases), followed by *Staphylococcus saprophyticus*.

Symptomatic uncomplicated urinary tract infection is treated with antibiotics. **Co- trimoxazole** (sulfamethoxazole with trimethoprim) is used as the empirical therapy of the first choice for three days, in a dose of 800/160 mg twice a day, but only if the patient lives in an area where the resistance *of Escherichia coli* to this antibiotic is below 20%. Instead of cotrimoxazole, **ciprofloxacin** 250 mg twice a day, orally, or **fosfomycin**, 3 grams orally in a single dose can be used. Beta-lactam antibiotics should not be used in the treatment of these infections, because they are not effective enough. Compared to co-trimoxazole and ciprofloxacin, fosfomycin has an advantage when used in pregnant women, because it carries a very low risk of congenital anomalies.

When using ciprofloxacin and other fluoroquinolones, it should be remembered that they can weaken the tendons of large muscles; the patient - should be warned to avoid greater physical activity while taking

fluoroquinolones, otherwise tendon rupture may occur. In addition to this unwanted effect, fluoroquinolones have a proarrhythmogenic and proconvulsant effects, so it is not convenient to use them in people with diseases of the heart or central nervous system.

OPIOID ANALGESICS IN THE TREATMENT OF SEVERE PAIN

In the treatment of severe pain, **morphine** is most often used **orally**; if it has to be used parenterally, the dose should be about 1/3 of the oral dose, because then the liver is bypassed, where morphine is rapidly metabolized. Hydromorphone or oxycodone can be used orally instead of morphine.

If the patient cannot swallow, if he/she does not comply with oral therapy or if he/she has side effects of morphine, he/she should be prescribed a transdermal preparation of fentanyl or buprenorphine.

Methadone can also be used to treat severe pain, but there are large differences between patients in terms of duration of action and half-life time.

When opioids are administered parenterally, the subcutaneous or intravenous route should be chosen, because intramuscular injections are painful and offer no advantage. Parenterally opioids are given in a situation where the patient requires urgent pain relief.

In principle, we give fixed doses of opioids at fixed intervals in order to prevent emergence of pain. If it happens that the patient feels pain in spite of the fixed doses (the so-called "breakthrough pain"), he/she should be given the additional dose of opioids, the so-called "breakthrough dose", which is usually about 10 to 15% of the daily opioid dose. If we are forced to give more than 4 breakthrough doses during the day, then the fixed doses of opioids should be increased. For "breakthrough doses " it is best to use opioids with a short half-elimination time and a quick onset of action.

Opioid analgesics can be combined with non-steroidal anti-inflammatory drugs, antidepressants or biphosphonates (for pain due to bone metastases).

Initial doses of opioids, which are equivalent to each other, for treatment of severe pain are:

- 30 mg of morphine sulfate orally,
- 10 mg of morphine sulfate parenterally,
- 20 mg oxycodone orally,
- 25 mg hydrocodone orally,
- 8 mg hydromorphone orally,
- 10 mg oxymorphone orally,
- 120 mg tramadol orally,
- 12 micrograms/hour of fentanyl transdermally.

Morphine should be avoided in people with hypotension, shock or bronchospasm, because it releases histamine from mast cells more than other opioids. In patients with liver or kidney failure, hydromorphone and fentanyl are better choices than other opioids .

In addition to the known side effects of opioids (respiratory depression, constipation, nausea, vomiting, urine retention, psychomotor weakness), there is also a neuroexcitatory effect, which is reflected in the appearance **of myoclonus**. If this side effect is not recognized in time, hyperalgesia, delirium and epileptic attack may occur. The neuroexcitatory side effect is managed by reducing the opioid dose or changing the opioid (the so-called "rotation" of opioids).

ANTIBIOTIC PROPHYLAXIS

We can use antibiotics both for the treatment of already existing infections and for their prophylaxis. The prophylactic use of antibiotics has been questionable for a long time, but most clinical trials have proven its justification in precisely defined indications. The basic idea in the prophylactic administration of antibiotics is to reach the bactericidal concentration of antibiotics in the patient's blood at the moment when the penetration of bacteria into the tissues is expected. Exposed to such a high concentration of antibiotics, the relatively few bacteria that have penetrated the tissues will not be able to survive there.

The most important indications for the prophylactic use of antibiotics are:

1. **Preoperative administration**
   a. Antibiotics should not be used prophylactically in all surgical procedures, but only in specific situations. When it comes to the so-called " **clean**" surgical interventions, in which there is neither infection at the operative site, nor is any of the hollow organs opened during the operation, antibiotic prophylaxis is only required if any type of foreign material is implanted during the operation (e.g., artificial heart valves, pacemaker, blood graft, artificial hip and the like). When one of the hollow organs is opened during a surgical intervention, such an operation is called " **clean-contaminated**", and then the prophylactic administration of antibiotics is mandatory. Finally, if the surgical intervention is carried out due to an existing infection, antibiotics are immediately applied therapeutically, so we are not talking about prophylactic application.
   b. The antibiotic should be administered one hour before the start of the operation, and then the therapeutic concentration in the blood should be maintained during the operation and during the first 24

hours. The parenteral route of administration is practically the only one that can be considered.

c. One of the examples of the prophylactic use of antibiotics is that during operations on the head and neck with the opening of the oral cavity, pharynx, esophagus or trachea (operations in maxillofacial - and ear-nose-throat surgery). In patients who are exposed to such an intervention, vancomycin 1 gram should be administered intravenously 2 hours before the start of the operation or clindamycin 600 mg i.v. 30 minutes before the start of anesthesia, and then another 300 mg i.v. after 12 hours from the start of anesthesia.

2. Administration of antibiotics in one intravenous dose 1 hour before a percutaneous intervention (coronary or cerebrovascular).
3. Long-term use of a depot preparation of benzatin-benzylpenicillin in children who have suffered an attack of rheumatic fever in order to prevent the recurrence of attacks due to the colonization of the pharynx by streptococci.
4. Administration of penicillin or erythromycin before tooth extraction or dental calculus cleaning in persons who have had rheumatic endocarditis (to prevent bacteria from the mouth from settling on previously damaged valves).
5. Long-term use of depot preparations of benzatin-benzylpenicillin in children whose spleen was removed due to traumatic rupture (because they have a high risk of pneumococcal infections).
6. Prophylactic use of isoniazid in unvaccinated persons living in a household with a tuberculosis patient.
7. Prophylactic administration of rifampicin to all members of a closed collective (e.g., a company of soldiers) if one of them falls ill with meningococcal meningitis.
8. Prophylactic use of fluoroquinolones in patients with severe neutropenia (neutrophil count below 0.5 x 10^9/L).

Apart from these indications, the prophylactic administration of antibiotics is also justified in patients with malnutrition (if exposed to an intervention that can lead to bacteremia, e.g., procedures in dentistry), a defect in the immune system (in situations where there is a risk of introducing an infection due to some medical procedure), or in patients under steroid, chemotherapy or radiotherapy, if they lead to neutropenia.

Table. Antibiotics that are recommended for prophylaxis of infection in certain surgical interventions:

TYPE OF SURGICAL INTERVENTION	**PROPHYLAXIS**
Cardiovascular surgery: Reconstruction of the abdominal aorta Lower extremity surgery involving incisions of femoral area and	Cefazolin 1 g i.v. as a single dose or 1 g /8 hours for 1-2 days OR

implantations of a graft or other foreign body Amputation of the lower limb due to ischemia Heart surgery Installation of permanent pacemakers	cefuroxime 1.5 g i.v. as a single dose or 1.5 g /12 hours, a total of 4 doses OR vancomycin 1 g i.v. as a single dose
Gastroduodenal operations	Cefazolin 1 g i.v. as a single dose or 1 g /8 hours for 2 - 3 days OR cefuroxime 1.5 g i.v. as a single dose or 1.5 g /12 hours, a total of 4 doses
Biliary operations, including laparoscopic cholecystectomy in high-risk patients	
Colorectal surgery Elective surgery	The day before surgery, the patient should drink 4 liters of polyethylene glycol solution within 2 hours. About 1 hour before surgery, 1 g of ertapenem is applied intravenously
Colorectal surgery, including appendectomy Emergency surgery	1 g of ertapenem intravenously
Abdominal hollow organ rupture	1 g of ertapenem intravenously
Head and neck surgery that involves opening the mucous membrane of the oral cavity or pharynx	Cefazolin 2 g i.v. as a single dose OR clindamycin 600-900 mg i.v. as a single dose + gentamicin 1.5 mg / kg i.v. as a single dose
Neurosurgical operations, clean, without installing implants	Cefazolin 1 g i.v. as a single dose OR vancomycin 1 g i.v. as a single dose
Neurosurgical operations, clean, contaminated (through the sinuses or nasopharynx)	Cefuroxime 1.5 g i.v. + metronidazole 0.5 g i.v.
Neurosurgical operations, installation of a CSF shunt	Vancomycin 10 mg into the cerebral ventricles + gentamicin 3 mg into the cerebral ventricles
Hysterectomy, vaginal or abdominal	Cefazolin 2 g i.v. as a single dose 30 minutes before surgery OR cefuroxime 1.5 g i.v. 30 minutes before surgery
Cesarean section during active labor or premature rupture of membranes	Cefazolin 1 g i.v. as the only dose as soon as the umbilical cord is clamped
Abortion in the second trimester	Cefazolin 1 g i.v. as a single dose
Implkantation of a hip joint prosthesis, fusion of spinal vertebrae	Cefazolin 1 g i.v. as a single dose or 1 g /8 hours for 1-2 days OR

	cefuroxime 1.5 g i.v. as the only dose or another 750 mg /8 hours, a total of 3 doses OR vancomycin 1 g i.v. as a single dose
Implantation of prostheses of other joints	Cefazolin 1 g i.v. as a single dose OR cefuroxime 1.5 g i.v. as the only dose or another 750 mg /8 hours, a total of 3 doses OR vancomycin 1 g i.v. as a single dose
Open reposition of a closed fracture with internal fixation	Ceftriaxone 2 g i.v. or i.m. as a single dose
Catheter placement for peritoneal dialysis	Vancomycin 1 g as a single dose 12 hours before surgery
Urological operations - prophylaxis is used only if the patient has bacteriuria	Cefazolin 1 g i.v. at 8 hours, 3 doses, and then oral co-trimoxazole for 10 days
Prostate biopsy, transrectally	Ciprofloxacin 500 mg orally 12 hours before biopsy and 500 mg orally 12 hours after biopsy
Mastectomy	Cefazolin 1 g i.v. as a single dose
A wound caused by trauma	Cefazolin 1 g / 8 hours i.v. during 5 days

DRUGS IN PREGNANCY AND LACTATION

The real specificity of women concerning medication is with regard to drug therapy during pregnancy and lactation. The placenta does not represent a significant barrier to the passage of drugs; practically, it can be considered that every drug that the mother takes reaches the bloodstream of the fetus, so only those that do **not harm the fetus can be considered safe drugs for use during pregnancy.** During the first two weeks after fertilization (14 - 30 days from the first day of the last menstrual period), the drugs either lead to death and elimination for the fetus or (if the embryo survives) they do not leave any effects on the fetus. This means that the accidental administration of a teratogenic drug (a drug that causes congenital malformations) in the first two weeks after conception is not an indication for artificial termination of pregnancy. In the next 10 weeks of pregnancy (first trimester), a number of drugs (known as teratogens) can cause disturbances in the development of the fetus that are manifested at birth by malformations (so-called congenital malformations). That is why these 10 weeks are the riskiest period in the development of the fetus. In the second two trimesters of pregnancy, some drugs can have a toxic effect on fetal tissues and lead to minor (microscopic and

functional) damage, usually to the CNS and the eye (because their development takes place throughout pregnancy). Because of all that has been said, every doctor should know which drugs are allowed and which should not be used nduring pregnancy, and if he/she is not sure, he should consult the appropriate literature or a specialist in clinical pharmacology. There are numerous guides for the use of drugs during pregnancy, one of which is also available on the website of the Ministry of Health of our country.

When it comes to lactation, the problem is somewhat different. A certain number of drugs that are very polar barely penetrate into milk, so they can be administered to the mother during lactation without consequences for the infant. It is considered that such drugs are those in which less than 1% of the dose of the drug reaches the infant via milk, which is therapeutic for an infant of that age. However, most drugs pass into milk to a significant extent; many liposoluble drugs in milk reach the same concentration as in plasma (e.g., antidepressants) or even concentrate in it. Given that the pH of milk is around 6.5, those drugs that are weak bases will also be concentrated in it. The concentration of the drug that is achieved in milk depends primarily on the dose taken by the mother, on the concentration of the drug that is achieved in the mother's blood, its liposolubility, binding to plasma proteins (high binding means weaker excretion in milk) and the existence of an active secretion mechanism.

Drugs with high affinity for the milk protein lactalbumin can also be concentrated in milk, as well as medicines that act as chelating agents, i.e., bind calcium from milk (e.g., tetracycline antibiotics).

When the mother is taking a medicine, she should skip the first feeding after the next dose of the medicine, because that's when the largest amount of medicine is in the milk. Medicines that are soluble in fats will be more present in the milk, if the feeding is in the morning and if the feeding lasts longer, because then the fat content in the milk is higher.

When prescribing drugs to mothers who are breastfeeding, it is necessary to consult specific literature on whether breastfeeding with that drug is safe or not, or to consult a specialist in clinical pharmacology. There are numerous guides for the use of drugs during lactation, one of which is also available on the website of the Ministry of Health of our country.

TREATMENT OF BACTERIAL ENDOCARDITIS

Bacterial endocarditis is one of the most serious infectious diseases because it is very difficult to eliminate the bacteria that settle on the heart valves. Although the heart valves are located in the middle of the blood stream, so at first glance antibiotics would easily reach the microorganisms on them, in reality this is not the case. The bacteria "stick" to the damaged or uneven surface of the heart valve with their adhesive molecules, and then fibrin fibers are attached to

them, resulting in a formation firmly attached to the valve called "vegetation". It is difficult for antibiotics to penetrate the vegetation from the blood, which is a problem in treatment. Another problem is the fact that vegetation that is compact cannot be penetrated by polymorphonuclear cells or other defense cells to complete the job of destroying bacteria that the antibiotic started. This means that the antibiotic must have a bactericidal effect, i.e., destroy **ALL** bacteria in the vegetation. To deal with these problems, doctors in the practice of treating bacterial endocarditis use only antibiotics with **bactericidal action** (for example, bacteriostatics tetracyclines and macrolides cannot be applied), in **large doses** to achieve a sufficient concentration in the vegetation and for a long enough time, which means at least **6 weeks** of therapy.

To cure bacterial endocarditis, the isolation of the causative agent from the blood is of key importance. Immediately after the diagnosis, several blood samples should be taken (from several different veins, at several points in time) and sent to the microbiological laboratory. After isolating the causative agent and testing its sensitivity to antibiotics, **TARGETED** therapy is undertaken, always **with a combination of** two antibiotics to which the isolated bacteria is sensitive. The most common causative agents of bacterial endocarditis are Streptococcus viridans, Enterococcus, Coagulase-positive staphylococcus or Coagulase-negative staphylococcus. Specifically in people who have abused addictive substances (e.g., heroin) and injected them intravenously, endocarditis usually occurs on the valves of the right side of the heart, and is caused mostly by gram-negative enterobacteria.

However, since the patient with bacterial endocarditis is in difficult condition, **immediately** after the diagnosis and taking blood samples for blood culture, antibiotics must be applied empirically, based on previous experiences, although the exact causative agent is not yet known to us. We usually start therapy with a combination of the glycopeptide antibiotic **vancomycin** and a carbapenem **meropenem**, because vancomycin has an excellent effect on gram-positive pathogens (streptococci, enterococcus and staphylococci), and meropenem on gram-negative bacteria, but it also has a significant effect on gram-positive pathogens. As soon as the microbiological laboratory receives information about the causative agent and its sensitivity to antibiotics, targeted antibiotic therapy is started, and empiric therapy is stopped.

TREATMENT OF ANEMIA

Anemia is the name for a condition in which the concentration of hemoglobin in the blood is lowered below normal values. As long as the hemoglobin concentration is above 70 g/L, the patient's life is not threatened, and there is time to find the cause and adequately treat the anemia. When the hemoglobin concentration is below this value, immediate intervention must be done by transfusion of erythromass or whole blood.

There are three major groups of causes of anemia: (1) blood loss; (2) ineffective erythropoiesis in the bone marrow; and (3) hemolysis, i.e., excessive

breakdown of erythrocytes. When the cause is blood loss, it most likely occurs in the gastrointestinal tract (tumors, peptic ulcer, anticoagulant therapy) or urinary tract (e.g., bladder tumor); in women, the second most common cause of blood loss is bleeding from the uterus (e.g., with uterine myoma). Eliminating the cause of bleeding leads to its cessation, and then gradually to the withdrawal of anemia.

Ineffective erythropoiesis can have a number of causes: lack of iron in the diet, lack of vitamin B_{12} and/or folic acid, lack of vitamin B_6 and copper, lack of erythropoietin in renal failure, lead poisoning, alcohol poisoning, administration of drugs that suppress erythropoiesis (chloramphenicol, linezolid, cycloserine), myelophthisic anemia (due to bone marrow infiltration by pathological tissue, for example tumors), myelodysplasia, aplastic anemia as a consequence of the toxic effect of drugs (e.g., carbamazepine, metamizole). In this type of anemia, treatment can be achieved by supplementing the missing substance. Iron deficiency can be compensated by using iron preparations, which are mostly intended for oral use (**ferrous sulfate, ferrous gluconate, ferrous fumarate**). Oral iron supplementation has been associated with gastric irritation, causing patients to experience nausea and loss of appetite. Also, oral supplementation lasts a long time, because iron has a very low bioavailability - only about 10%. Because of these problems, oral iron supplementation sometimes fails, so parenteral iron preparations must be used. The advantage of parenteral preparations is that the entire amount of iron that is missing can be applied once or with several applications. Among the parenteral iron preparations available today are **iron dextran** (problematic due to frequent allergic reactions), **iron gluconate** (must be given in a large number of doses), **iron sucrose** (must be given in a large number of doses) and **ferumoxytol** (currently the most favorable preparation, because all the necessary iron is given in just two doses, and allergic reactions are rare).

The lack of **vitamin B_{12}** is compensated by the use of cyanocobalamin or hydroxycobalamin in the form of intramuscular or subcutaneous injections, and the lack of **folate** acid using an oral preparation of folic acid in a dose of 5 milligrams per day. The lack of erythropoietin is compensated by the use of recombinant preparations **erythropoietin.** There are several erythropoietin preparations on the market (erythropoietin alpha, beta, omega), which have the same sequence of amino acids as endogenous erythropoietin, but differ from each other in the degree of glycosylation. There is generally no essential difference in the effectiveness and safety of these erythropoietins, which are administered intravenously. The most important thing when using erythropoietin is to avoid a too rapid rise in the number of erythrocytes and hemoglobin levels; a rapid increase in hematocrit leads to a sudden increase in blood density, which can result in cerebral artery thrombosis and strokes, or coronary artery thrombosis.

Excessive hemolysis can be caused by a defect in the erythrocytes themselves (congenital spherocytosis, congenital stomatocytosis, glucose-6-phosphate dehydrogenase deficiency, hemoglobinopathy) or by the effect of external factors on erythrocytes (malaria, Epstein -Barr virus infection,

paroxysmal cold hemoglobinuria, thrombotic thrombocytopenic purpura, hemolytic anemia of warm antibodies, hypersplenism). External factors can be treated if they are of an immunological nature with the use **of intravenous drugs immunoglobulin** or **rituximab** (antibody against CD_{20} antigen on B lymphocytes) or **plasmapheresis**.

TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS

Treatment of systemic lupus depends on the severity of the disease. **Mild to moderate Lupus** (only the appearance of skin rash, fever, arthritis, pleuritis and pericarditis) is treated with the use of non-steroidal anti-inflammatory drugs and **hydroxychloroquine** (unless the patient has glucose-6-phosphate dehydrogenase deficiency, when hydroxychloroquine is contraindicated). The daily dose of hydroxychloroquine is 5 mg/kg, orally. Hydroxychloroquine slows the course of the disease and reduces mortality. With prolonged use, it can cause toxic maculopathy, so it is necessary to check with an ophthalmologist.

If hydroxychloroquine fails to control the course of the disease, it can be added to the immunosuppressants mentioned earlier: methotrexate, azathioprine or mycophenolate mofetil. If even these immunosuppressants do not work, mild to moderate Lupus can be treated with the monoclonal antibody **belimumab**, which inhibits the B lymphocyte stimulator, an endogenous factor that enables the survival of B lymphocytes. Due to the effect of belimumab, the survival of lymphocytes decreases, and thus their number and the intensity of the autoimmune process. Belimumab greatly increases the risk of infections, and severe allergic reactions may occur. A number of patients may develop severe depression with suicidal ideation.

Heavy form of Lupus is treated with corticosteroids in combination with classical immunosuppressants (mycophenolate mofetil, azathioprine, cyclophosphamide) and belimumab. A new drug in the treatment of severe Lupus is **voclosporin**, which is used as an additional immunosuppressive therapy. Voclosporin is a cyclosporine derivative, which acts as a calcineurin inhibitor, reducing the production of proinflammatory cytokines. Unlike ciclosporin, voclosporin is eliminated from the body faster, so its side effects are significantly smaller than those of ciclosporin, and it is especially less toxic to the kidneys. In the most severe forms of Lupus, another monoclonal antibody, **anifrolumab, is used .** Anifrolumab blocks the receptor for interferon 1. This drug also has side effects typical of immunosuppressants: increased frequency of infections, higher risk of malignant diseases and allergic reactions.

RATIONAL USE OF ANTIBIOTICS AND ANTIBIOTICS STEWARDSHIP

The rational prescribing of antibiotics implies their use in a way that achieves the maximum beneficial effect in patients with infections, with minimal side effects, undesirable interactions and the induction of bacterial resistance. This actually means that for each established bacterial infection, an antibiotic should be chosen that can cure it, without harming the patient and his environment. In order for the use of antibiotics to be rational, certain principles must be followed. The most important principles to be respected are:

1. Apply antibiotics in treatment only if the diagnosis of bacterial infection has been established. In practice, this principle is often not respected, so unfortunately many doctors apply antibiotics only on the basis of elevated values of laboratory parameters of systemic inflammation. These parameters (increased number of leukocytes, C-reactive protein - CRP, procalcitonin) are not specific enough for infection, so they are often increased in conditions where there is no bacterial infection, e.g., in case of deep vein thrombosis or rheumatic diseases. In such a situation, the patient receives an antibiotic that he does not really need, with all its side effects and increased treatment costs. That is why the sarcastic expression used by some clinical pharmacologists that in practice antibiotics are used to treat everything, including " CRP - itis", is not surprising.
2. Before applying antibiotics, it is mandatory to take a tissue or body fluid sample and send it to a microbiological laboratory in order to isolate the causative agent and determine its sensitivity to antibiotics; this allows us to treat the patient with "targeted" therapy, i.e., giving an antibiotic to which the causative agent is certainly sensitive.
3. Immediately after taking the samples for the microbiological laboratory, apply an antibiotic empirically, based on the knowledge of the most likely causes of infection in a certain location. Empiric therapy should not be delayed, because every hour during the infection that passes without adequate antibiotic therapy reduces the patient's chances of recovery.
4. If the isolated bacteria is sensitive to several antibiotics, you should always choose the one with the narrowest spectrum of action, because such a drug will cause the so-called postantibiotic diarrhea, and diarrhea due to Clostridium difficile overgrowth (so-called pseudomembranous colitis).
5. The prescribed antibiotic must penetrate sufficiently into the tissue where the infection is located, otherwise it will not be able to exert its effect. For example, tetracyclines, tigecycline, macrolide antibiotics, clindamycin and aminoglycosides cannot be used to treat infections of the central nervous system or the eye, because as water-soluble substances they minimally penetrate the hematoencephalic barrier.

6. In patients who have certain diseases (comorbidities), the use of antibiotics that worsen these diseases should be avoided. For example, if the patient has severe renal insufficiency, the use of aminoglycosides is contraindicated, because they can worsen the renal insufficiency and lead to anuria.
7. Before prescribing antibiotics, all potential **interactions** with drugs that the patient is already receiving should be checked, and corrective measures should be taken, if they are recommended in the Summaries of the characteristics of the drug. For example, if meropenem is prescribed to a patient with epilepsy who is otherwise on valproate therapy, it is known that meropenem can lower the concentration of valproate by about 40%, and lead to convulsions; in order to prevent convulsions, the dose of valproate should be increased by about 50%.
8. In the case of severe infections that threaten the patient's life, we always use a combination of two or three antibiotics in order to achieve a synergistic effect (at least additive) and prevent the emergence of resistant strains.
9. There are two types of antibiotics in terms of the dynamics of their action on bacteria: antibiotics in which the killing of bacteria is proportional to the time in which the concentration of the antibiotic in the tissue is above the minimum inhibitory concentration (so-called **time-dependent killing**) and antibiotics in which the killing of bacteria is proportional to the concentration of antibiotic in the tissue (so-called **concentration-dependent killing**). Time-dependent antibiotics include all beta lactams, while concentration-dependent antibiotics include aminoglycosides. Most of the other antibiotics depend on both parameters: fluoroquinolones, glycopeptides, tetracyclines, etc. These dependencies can be quantified by determining the limit values of the so-called pharmacokinetic-pharmacodynamic parameters. Parameter T>Mic indicates the percentage of time within 24 hours in which the antibiotic concentration is above the minimum inhibitory concentration, and its threshold value for cephalosporins that must be exceeded to cure the patient is 60%. The Cmax/Mic parameter indicates the ratio of the maximum achieved concentration of the antibiotic in the serum to the minimum inhibitory concentration, and its threshold value for fluoroquinolones that should be exceeded in order to cure the patient is 10. With antibiotics whose effect depends on both time and concentration, it is more appropriate to use the third parameter (index) - AUC/Mic - which represents the ratio of the area under the curve of drug concentration in serum, in time, and the minimum inhibitory concentration. For example, in order for fluoroquinolone ciprofloxacin to work well, AUC/Mic index greater than 125 should be achieved. The practical consequence of these principles is that the daily dose of beta-lactams should be divided into as many individual doses as possible, and that the daily dose of aminoglycosides should be administered once in most cases.

10. The duration of antibiotic administration should be optimal, neither too long, nor too short. When treating infections in localizations where antibiotics have a hard time penetrating to the tissues and reaching the causative agent, therapy should last a long time, and vice versa (e.g., brain abscess is treated for 21 days, osteomyelitis for 6-8 weeks, tuberculosis for 6 months, neuroborreliosis for 21 days, but uncomplicated urinary infection only 3-5 days, intra-abdominal infections 5-7 days, pneumonia 5-7 days).
11. The loading dose of antibiotics should not be reduced in case of severe kidney or liver insufficiency, but the maintenance dose should be adjusted to the function of these two organs. Recommendations for adjusting the dose of antibiotics to the current liver or kidney function can be found in the official summaries of product characteristics.

Antibiotic management in the hospital is popularly called "antimicrobial stewardship". There are several specific forms of antibiotic stewardship, and they differ from hospital to hospital due to the specifics of each. In short, the institution must first have an **expert body** that will deal with antibiotic management. This professional body should consist of a clinical pharmacologist, a pharmacist, and several doctors of other specialties who often prescribe antibiotics (e.g., infectious disease specialists). The task of the professional body is to adopt the so-called "**Antibiotic Policy**", which will determine the way of using antibiotics, which must be respected by all doctors of the institution. The Antibiotic Policy primarily lists the antibiotics that will be procured for the hospital and for each of them the exact indications for which they are approved. Also, the Policy has principles of empirical application of antibiotics and the choice of antibiotics for prophylaxis in surgery. After adopting the Antibiotic Policy, the expert body controls its implementation through regular clinical audits.

In addition to the Antibiotic Policy, antibiotic management also includes organizing **a consilium for prescribing antibiotics** to complex patients who are in a serious condition and have a lot of comorbidities. Such patients are mostly found in the central intensive care units of hospitals, so a separate consilia should be formed for each of the intensive care units. Mandatory members of these consilia are an infectious disease specialist, a clinical microbiologist and a clinical pharmacologist. Through team consideration of all aspects of antibiotic application, the consilium can make far better decisions than individual specialists. In addition to teamwork, real-time consultation of clinical databases on diseases, diagnostics and therapy, which are based on the principles of evidence-based medicine, is very important. Such a database is the " UpToDate " database (www.wolterskluwer.com/en/solutions/uptodate) also available on mobile devices, which almost instantly provides a precise answer to most of the dilemmas faced by antibiotic prescribers. In addition to this base, The Sanford Guide to Antibiotics is extremely useful, available in both print and electronic form.

Another important element of antibiotic management in the hospital is **the systematic monitoring** of antibiotic consumption by departments and diagnoses, and statistical analysis of microbiological isolates, also by departments and diagnoses. The consumption of antibiotics must be expressed in the number of defined daily doses per 100 patient days, and the descriptive analysis of microbiological isolates through the incidence rate (number of isolates per 1000 bed days per year) and resistance rate (number of resistant isolates per 1000 bed days per year). Monitoring antibiotic consumption trends and the incidence of infection or resistance makes it possible to spot places in the hospital where antibiotics are irrationally prescribed, on the basis of which corrective measures are planned and implemented, first of all additional staff education.

DRUG DOSAGE IN HEMODIALYSIS PATIENTS

In hemodialysis, the movement of the drug between the blood and the dialysis fluid (ultrafiltrate) is carried out according to the principle **of DIFFUSION**, i.e., movement from a place of higher (blood plasma) to a place of lower (ultrafiltrate) concentration. The clearance of the drug is proportional to the speed of movement (flow) of the dialysate.

In **hemofiltration**, due to increased hydrostatic blood pressure, the ultrafiltrate produced in the dialyzer is removed without retrograde movement back into the blood. Drug molecules are removed by the process **of CONVECTION**. Drug clearance during hemofiltration is proportional to the speed of ultrafiltration.

In intermittent ("ordinary") hemodialysis, the membranes allow the free passage of drugs whose molecular weight is below 500 daltons. With continuous hemodialysis and hemofiltration, the membranes are more permeable, so even drugs with a molecular weight of up to 30,000 daltons can pass through. The Gibbs-Donnan effect is also important for the passage of drugs through the dialyzer membrane: drugs that are anions pass through the membrane more easily than drugs that are cations (e.g., aminoglycosides, levofloxacin). The mentioned effect is due to retention of albumin (which are anions) on the blood side of the dialysis membrane.

The loading dose does **not change** in patients who are on hemodialysis or hemofiltration compared to the loading dose in people with healthy kidneys. The loading dose does not depend on kidney function, since its purpose is to quickly achieve the therapeutic concentration of the drug in the serum. Therefore, the size of the loading dose depends on the volume of distribution of the drug and the desired therapeutic concentration, and none of these parameters were changed in patients with impaired kidney function. We calculate the loading dose according to the formula: target concentration * volume of distribution / bioavailability. Therefore, by multiplying the target

concentration in milligrams per liter by the volume of distribution in liters, we get the dose of the drug that should be increased if the bioavailability is less than unity (that is, 100%), so it is divided by the bioavailability, because dividing by a decimal number increases the amount.

The parameter that describes the degree to which the drug from the blood passes through the hemodialysis membrane into the ultrafiltrate is called the sieving coefficient. **Sieving coefficien** is the ratio of the concentration of the drug in the ultrafiltrate to the concentration of the drug in the blood plasma. The sieving coefficient is actually almost exactly equal to the fraction of free drug in the plasma, because only the drug that is not bound to proteins can pass through the hemodialysis membrane. We use the sieving coefficient to calculate the amount of drug eliminated by one hemodialysis. The sieving coefficient should be multiplied by the concentration of the drug in the plasma in the equilibrium state and the volume of the ultrafiltrate, because the product of the sieving coefficient and the concentration of the drug in the plasma actually represents the concentration of the drug in the ultrafiltrate. When the concentration of the drug in the ultrafiltrate is multiplied by its volume, it is clear that the amount of the drug that was eliminated together with the ultrafiltrate is obtained.

The parameter that describes the degree to which the drug from the blood passes through the hemofiltration membrane into the ultrafiltrate is called the saturation coefficient. **The saturation coefficient** is the ratio of the concentration of the drug in the effluent (the volume of liquid that is removed during hemofiltration) and the concentration of the drug in the blood plasma. The saturation coefficient is specific for each drug that can be found in the blood of a person undergoing hemoperfusion, and it depends primarily on the molecular weight of the drug. The saturation coefficient is used to calculate the amount of drug eliminated by one hemofiltration. The concentration of the drug in the plasma in the equilibrium state and the volume of the effluent should be multiplied by the saturation coefficient, because the product of the saturation coefficient and the concentration of the drug in the plasma actually represents the concentration of the drug in the effluent. When the concentration of the drug in the effluent is multiplied by its volume, the amount of the drug that is eliminated together with the effluent is obtained .

Since we calculate the amount of drug that is eliminated with one hemodialysis or one hemofiltration, in order to maintain the desired concentration of the drug in the blood plasma, that calculated amount of the drug is actually **the maintenance dose** that should be administered in the period between two hemodialysis or hemoperfusion, immediately after the completion of one episode of hemodialysis or hemoperfusion. If the drug is eliminated to a significant extent also extrarenally, the amount of drug that is thus eliminated between two hemodialysis or hemofiltration should be calculated and added to the already calculated maintenance dose based on only hemodialysis or only hemoperfusion.

LITERATURE

1. Janković SM. Clinical pharmacology in health care service. Vojnosanit Pregl 2005; 62(10): 757-61.
2. Janković SM, Ninković V. Monitoring of serum concentrations of antibiotics by microbiological method : a one-year experience . Med Pregl 1998; 51 : 333-42.
3. Atkinson AJ, Abernethy DR, Daniels CE, Dedrick RL, Markey SP. Principles of Clinical Pharmacology. 2 nd ed., Academic Press, Amsterdam, 2007.
4. Janković SM. Basics of clinical pharmacy. 1st ed., Faculty of Medicine , Kragujevac, 2010.
5. Malek M. Decision analysis and quality control . The Pharmaceutical Journal 1997 ; 258: 99-102.
6. Walley T, Haycox A. Pharmacoeconomics : basic concepts and terminology . Br J Clin Pharmacol 1997; 43: 343-8.
7. Malek M. Pharmacoeconomics : introduction . The Pharmaceutical Journal 1996 ; 256: 759-62.
8. Malek M. Pharmacoeconomics : measuring quality of life impacts . The Pharmaceutical Journal 1997; 258: 22-4.
9. Haycox A, WalleyT . Pharmacoeconomics : evaluating the evaluators . Br J Clin Pharmacol 1997; 43: 451-6.
10. Murney P. To mix or not to mix - compatibilities of parenterally friend soluti ons . Austr Pescr 2008; 31: 98-101.
11. Cruickshank J. Initial management of cardiac arrhythmias . Aust Fam Physician 2008; 37: 516-20.
12. Anugwom C, Sulangi S, Dachs R. Adenosine vs. _ calcium channel blockers for supraventricular tachycardia . Am Fam Physician 2007; 75: 1653-4.
13. Hall MC, Todd DM. Modern management of arrhythmias . Postgrad Med J 2006; 82(964): 117-25.
14. Holdgate A, Foo A. Adenosine vs intravenous calcium channel antago nists for the treatment of supraventricular tachycardia in adults . Cochrane Database Syst Rev 2006; (4): CD005154.
15. Kistler PM, Obeyesekere MN. Pharmacological management of tachycardia . Aust Fam Physician 2007; 36: 500-5.
16. Hebbar K, Hueston WJ. Management of common arrhythmias : Part II. Ventricular arrhythmias and arrhythmias in special populations . Am Fam Physician 2002; 65: 2491-6.
17. Livingston MW, Overton DT. Sinus bradycardia . eMedicine Specialties 2010. Available at : http://emedicine.medscape.com/article/760220-overview , visited on 20.3.2011.

18. Tzivoni D, Banai S, Schuger C, Benhorin J, Keren A, Gottlieb S, Stern S. Treatment of torsades de points with magnesium sulfates . Circulation 1988; 77: 392-397.
19. Jatin D. Torsade de points . Medscape References , available at : http://emedicine.medscape.com/article/1950863 . The last access website 19.6.2011.
20. Huang N. Lifestyle management of hypertension . Aust Prescr 2008; 31: 150-3.
21. Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, Se ver PS, Thom SMcG . British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary . BMJ 2004; 328; 634-640.
22. Rinka JR. Management of hypertensive crisis . US Pharm 2009; 34(5): HS-8-HS-12.
23. Janković SM, Stefanović SM. Delayed angioedema during therapy with angi otensin-converting enzymes inhibitors. Vojnosanit Pregl 2011; 68(4): 372-6.
24. Kral M, Herzig R, Sanak D, Skoloudik D, Vlachova I, Bartkova A, Hlustik P, Kovacik M, Kanovsky P. Oral antiplatelet therapy in professions prevention. Minireview. Biomed Pope Med Fac Univ Palacky Olomouc Czech Repub 2010; 154(3): 203-10.
25. Hall SL, Lorenz T. Secondary prevention of coronary artery disease. Am Fam Physician 2010; 81(3): 289-96.
26. Medical Services Commission . Cardiovascular disease-primary prevent - him . Victoria (BC): British Columbia Medical Services Commission ; 2008 Mar 15. 18 p.
27. Adams HP Jr , del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, Grubb RL, Higashida RT, Jauch EC, Kidwell C, Lyden PD, Morgenstern LB, Qureshi AI, Rosenwasser RH, Scott PA, Wijdicks EF; American Heart association _ American Stroke Association Stroke Council ; Clinical Cardiology Council ; Cardiovascular Radiology and Intervention Council ; Atherosclerotic Peripheral Vascular Disease and Quality of Emperor Outco mes in Research Interdisciplinary Working Groups . Guidelines for the early management of adults with ischemic strokes : a guideline from the American Heart Association / American Stroke Association Stroke Council , Clinical _ Cardiology Council , Cardiovascular Radiology and Intervention _ Council , and the Atherosclerotic Peripheral Vascular Disease and Quality of Empress Outcomes in Research Interdisciplinary Working Groups : the American Academy of Neurology affirms the value of this guidelines as an educational tool for neurologists . Stroke 2007; 38(5): 1655-711.
28. Elliott J, Smith M. The acute management of intracerebral hemorrhage : a clinical review . Anesth Analg 2010; 110(5): 1419-27.
29. Panayiotopoulos CP. Typical absence seizures and their treatment . Arch Dis Child 1999; 81: 351-5.

30. Walker M. Status epilepticus : an records based guide . BMJ 2005; 331(7518): 673-7.
31. Janković SM, Prostran M, Todorović Z. Pharmacology and toxicology , 2nd ed ., Faculty of Medicine, Kragujevac, 2007.
32. Janković SM. Handbook of pharmacology and toxicology, 6th edition, Faculty of Medicine, Kragujevac, 2021.
33. Janković SM. A Critique of Pharmacokinetics Calculators for Friend Dosing Individualization. Eur J Drug Metab Pharmacokinetics. 2020;45(2):157-162.
34. Janković SM. Personalization of friend dose thematic issue : introduction article . Expert Opin Friend Metab Toxicol. 2021;17(12):1363-1367.
35. Antanasković A, Janković SM. Guidance for interactions between antiseizures medications. Expert Opin Friend Metab Toxicol . 2023;19(5):239-242.
36. Kanner AM. Lamotrigine-induced Rash : Can We Stop Worrying ? Epilepsy Curr 2005; 5: 190–191.
37. British National Forms . No 62, September 2011. BMJ Group and Pharmaceutical Press , available at : http://bnf.org/bnf/ , last the road as remembered on 18.9.2011.
38. Verma S, Chan LL, Chee KS, Chen H, Chin SA, Chong SA, Chua W, Fones C, Fung D, Khoo CL, Kwek SK, Ling J, Poh P, Sim K, Tan BL, Tan C, Tan CH , Tan LL, Tay WK; MOH Clinical Practice Guidelines Workgroup he Schizophrenia . Ministry of Health clinical practice guidelines : schizop - hrenia . Singapore Med J 2011; 52: 521-5.
39. Keks N, Blashki G. The acutely psychotic patient -- assessment and initial management. Aust Fam Physician 2006; 35: 90-4.
40. Delirium : diagnosis , prevention and management. NICE clinical guidance 103. July 2010. Available at : http://www.nice.org.uk/nicemedia/live/13060/49913/49913.pdf , last _ the road visited on 18.9.2011.
41. Muench J, Hamer AM. Adverse effects of antipsychotic medications . Am Fam Physician 2010; 81: 617-22.
42. Bang SM, Jang MJ, Oh D, Kim YK, Kim IH, Yoon SS, Yoon HJ, Kim CS, Park S; Korean Society of Thrombosis and Hemostasis . Korean guidelines for the prevention of venous thromboembolism . J Korean Med Science 2010; 25: 1553-9.
43. Emadi A, Streiff M. Diagnosis and management of venous thromboembo lism : an update a decade into the new millennium . Arch Iran Med 2011; 14: 341-51.
44. Snow V, Qaseem A, Barry P, Hornbake ER, Rodnick JE, Tobolic T, Ireland B , Segal JB, Bass EB, Weiss KB, Green L, Owens DK; American Col lege of Physicians ; American Academy of Family Physicians Panel he Deep Venous Thrombosis / Pulmonary Embolism . Management of venous thromboembolism : a clinical practice guidelines from the American Colle

ge of Physicians and the American Academy of Family Physicians . Ann Intern Med 2007; 146: 204-10.

45. Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galiè N, Pruszczyk P, Bengel F, Brady AJ, Ferreira D, Janssens U, Klepetko W, Mayer E, Remy-Jardin M, Bassand JP; ESC Committee for Practice Guidelines (CPG). Guidelines he the diagnosis and management of acute pulmonary embo lism : the Task Forces for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J 2008; 29: 2276-315.
46. Gobel BH. Disseminated Intravascular Coagulation in Cancer : Providing Quality Empress . Topics in Advanced Practice Nursing eJournal 2002; 2(4) © 2002 Medscape .
47. Rivera-Bow WL. Thrombolytic therapy in emergency medicine . Medscape References © 2011 WebMD , LLC. Available at : http://emedicine.medscape.com/article/811234-overview , accessed according to the latter road 9.10.2011.
48. McKenna B. Coronary Stent Thrombosis Post-percutaneous Interventions : Preventing _ Complications , Optimizing Outcomes . HCP Live publica tions , available at : http://www.hcplive.com/publications/Resident-and-Staff/2006/2006-01/2006-01_08 , accessed the last road 9.10.2011.
49. British National Forms No 62, September 2011, Copyright © BMJ Group and Pharmaceutical Press 2011.
50. Hirsh J, Dalen J, Anderson DR, Poller L, Bussey H, Ansell J, Deykin D. Oral anticoagulants : mechanism of action , clinical effectiveness , and opti mal therapeutic ranges . Chest 2001; 119(1 Suppl): 8S-21S.
51. Kalyanasundaram A, Lincoff AM. Managing Adverse Effects and Comrade - Comrade Interactions of Antiplatelet Agents . Nat Rev Cardiol 2011; 8(10): 1-9.
52. Gallus AS, Baker RI, Chong BH, Ockelford PA, Street AM on on behalf of the Australasian Society of Thrombosis and Haemostasis . Consensus guideli nes for warfarin therapy , Recommendations from the Australasian Society of Thrombosis and Haemostasis . *MJA* 2000; 172: 600-605.
53. Lerma EV, Burns JS, Nissenson AR. Current Diagnosis & Treatment . Nephrology & Hypertension . 1 st edition , The McGraw-Hill Companies , Inc. , 2009.
54. Manzarbeitia C. Liver Transplantation . Medscape References © 2011 WebMD , LLC. Available at : http://emedicine.medscape.com/article/431783-overview , accessed according to the latter road 22.10.2011.
55. Lindenfeld J, Miller GG, Shakar SF, Zolty R, Lowes BD, Wolfel EE, Mestro ni L, Page RL 2nd, Kobashigawa J. Drug therapy in the heart Tran Splant recipient : part I: cardiac rejection and immunosuppressive drugs . Circulation 2004; 110(24): 3734-40.

56. Kuypers DR. Influence of interactions between immunosuppressive drugs he therapeutic friend monitoring . Ann Transplant 2008; 13(3): 11-8.
57. Baillie GM, Chavin KD, Periyasamy B, Baliga P. Pharmacologic Strategies for Prophylaxis and Treatment of Liver Transplant Recipients . Medscape Transplantation © 2003 Medscape , LLC. Available at : http://www.medscape.org/viewarticle/458012 , accessed the last road 22.10.2011.
58. Mainous AG, Pomeroy C. Management of antimicrobials in infectious disea ses.Impact of antibiotic resistance . 2 nd edition , Humana Press , 2010.
59. Carruthers SG, Hoffman BB, Melmon KL, Nierenberg DW. Melmon and Morrelli's Clinical Pharmacology , 4th Edition , McGraw-Hill , 2000.
60. Evert CA Kaal and Charles J. Vecht . The management of brain edema in brain tumors . Current Opinion in Oncology 2004; 16: 593–600.
61. Baxter K. Stockley's Drugs Interactions Pocket Companion 2009. 1 st edit on , Pharmaceutical Press , London-Chicago , 2009.
62. Klauer KM. Adrenal Crisis in Emergency Medicines . Medscape Transplantation © 2003 Medscape , LLC . Available at : http://emedicine.medscape.com/article/765753-overview , accessed according to the latter time 13.11.2011.
63. Puscheck EE. Infertility . Medscape References © 2011 WebMD , LLC. Alas _ at : http://emedicine.medscape.com/article/274143-overview#a1 , accessed the last road 26.12.2011.
64. Back DJ, Orme ML. Pharmacokinetics friend interactions with oral contra ceptives . Clin Pharmacokinet 1990; 18: 472-84.
65. Shanle EK, Xu W. Selectively targeting estrogen receptors for cancer treatment . _ Adv Friend Deliv Rev 2010; 62: 1265-76.
66. Horwich A. Systemic treatment for prostate cancer . Ann Oncol 2006; 17 Suppl 10: x211-3.
67. Saadeh CK. Status Asthmaticus . Medscape References , updated March 29, 2011, available at: http://emedicine.medscape.com/article/302238-overview#a1 , last visited site November 21, 2011.
68. Cunha BA. Community-Acquired Pneumonia . Medscape References , upda ted October 11, 2011, available at: http://emedicine.medscape.com/article/234240-overview#a30 , last - visited site 21.11.2011.
69. Ramakrishnan K, Sparks RA, Berryhill WE. Diagnosis and treatment of go tis media . Am Fam Physician 2007; 76(11): 1650-8.
70. Esau R, ed . 2006/2007 British Columbia's Children's Hospital Pediatrician Friend Ranges Guidelines . 5 th edition . Vancouver : Department of Pharmacy Children's and Women's Health Centers of British Columbia . in 2006
71. Mehnert-Kay S. Diagnosis and management of uncomplicated urinary tract infections . Am Fam Physician 2005; 72: 451-456.

72. Maison O, Tardy S, Cabelguenne D , Parat S , Ducastelle S , Piriou V , Lepape A, Lalande L. _ Friend incompatibilities in intravenous therapy : evaluation and proposal of prevention tools in intensive Emperor and hematology units . European Journal of Clinical Pharmacology 2019; 75(2):179-187.
73. Mahtani AU, Nair DG. Supraventricular Tachycardia . Med Clin North Am . 2019;103(5):863-879.
74. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr , Ellinor PT , Ezekowitz MD, Field ME, Furie KL, Heidenreich PA, Murray KT, Shea JB, Tracy CM, Yancy CW. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation : A Report of the American College of Cardiology / American Heart Association Task Forces he Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons . Circulation . 2019;140(2):e125-e151.
75. Marcus GM. Evaluation and Management of Premature Ventricular Complexes . Circulation . 2020;141(17):1404-1418.
76. Tang PT, Do DH, Li A, Boyle NG. Team Management of the Ventricular Tachycardia Patient . Arrhythm Electrophysiol Rev. _ 2018;7(4):238-246.
77. Deneke T, Nentwich K, Ene E et al . Acute management of ventricular tachycardia . Herzschr Electrophys 2020 ; 31 : 26–32.
78. Frampton J, Ortengren AR, Zeitler EP. Arrhythmias After Acute Myocardial Infarction . Yale J Biol Honey . 2023;96(1):83-94.
79. Sidhu S, Marine JE. Evaluating and managing bradycardia . Trends Cardiovasc Honey . 2020;30(5):265-272.
80. Saridas A , D uyan M , G unlu S. _ Current approaches that torsades de points . HEALTH & SCIENCE , 2021-III, 119.
81. Mar PL, Horbal P, Chung MK, Dukes JW, Ezekowitz M, Lakkireddy D, Lip GYH, Miletello M, Noseworthy PA, Reiffel JA, Tisdale JE, Olshansky B, Gopinathannair R; from the American Heart Association Electrocardiography and Arrhythmias Committee of the Council of Clinical Cardiology . Friend Interactions Affecting Antiarrhythmic Friend Ears . Circ Arrhythm Electrophysiol . 2022;15(5):e007955.
82. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, Ramirez A, Schlaich M, Stergiou GS, Tomaszewski M, Wainford RD, Williams B, Schutte AE. 2020 International Society of Hypertension Global Hypertension Practice Guidelines . Hypertension . 2020;75(6):1334-1357.
83. Meyer M, Wetmore JB, Weinhandl ED, Roetker NS. Association of Nondihydropyridines Calcium Channel Blockers Versus β- Adrenergic Receptor Blockers With Risk of Heart Failure Hospitalization . Am J Cardiol . 2023;197:68-74.
84. Palau P, Seller J, Domínguez E, Sastre C, Ramón JM, de La Espriella R, Santas E, Miñana G, Bodí V, Sanchis J, Valle A, Chorro FJ, Llácer P, Bayés-

Genís A, Núñez J. Effect of β- Blocker Withdrawal he Functional Capacity in Heart Failure and Preserved Ejection Fraction . J Am Coll Cardiol . 2021;78(21):2042-2056.

85. Chen R, Suchard MA, Krumholz HM, Schuemie MJ, Shea S, Duke J, Pratt N, Reich CG, Madigan D, You SC, Ryan PB, Hripcsak G. Comparative First-Line Effectiveness and Safety of ACE (Angiotensin-Converting Enzyme) Inhibitors and Angiotensin Receptor Blockers : A Multinational Cohort Study . Hypertension . 2021;78(3):591-603.
86. Usuda D, Higashikawa T, Hotchi Y, Usami K, Shimozawa S, Tokunaga S , Osugi I, Katou R, Ito S, Yoshizawa T, Asako S, Mishima K, Kondo A, Mizuno K, Takami H, Komatsu T, Oba J , Nomura T, Sugita M. Angiotensin receptor blocker Neprilysin inhibitors . World J Cardiol . 2021;13(8):325-339.
87. Lauder L, Mahfoud F, Azizi M, Bhatt DL, Ewen S, Kario K, Parati G, Rossignol P, Schlaich MP, Teo KK, Townsend RR, Tsioufis C, Weber MA, Weber T, Böhm M. Hypertension management in patients with cardiovascular comorbidities . Eur Heart J. 2023;44(23):2066-2077.
88. Meidahl Petersen K, Jimenez-Solem E, Andersen JT, et al al β-Blocker treatment during pregnancy and adverse pregnancy outcomes : a nationwide population-based cohort studyBMJ Open 2012;2:e001185.
89. Janković SM, Stojković S, Petrović M, Kostić T, Zdravković M, Radovanović S, Cvjetan R, Ratković N, Rihor B, Spiroski D, Stanković A, Anđelković B, Gocić Petrović R. Results of the trycort : Cohort study of add-on antihypertensives for treatment of resistant hypertension . Medicine (Baltimore). 2023;102(22):e33941.
90. Rossi GP, Rossitto G, Maifredini C, Barchitta A, Bettella A, Latella R, Ruzza L, Sabini B, Seccia TM. Management of hypertensive emergencies : a practical approach . Blood Press . 2021;30(4):208-219.
91. Olowofela AO, Isah AO. And profiles of adverse effects of antihypertensive medicines in a tertiary Emperor clinic in Nigeria . Ann Afr Honey . 2017;16(3):114-119.
92. Christou CD, Tsinopoulos I, Ziakas N, Tzamalis A. Intraoperative Floppy Iris Syndrome : Updated Perspectives . Clin Ophthalmol . 2020;14:463-471.
93. McComb MN, Chao JY, Ng TMH. Direct Vasodilators and Sympatholytic Agents . Journal of Cardiovascular Pharmacology and Therapeutics . 2016;21(1):3-19.
94. Fravel MA, Ernst M. Drug Interactions with Antihypertensives . Curr Hypertension Rep . 2021;23(3):14.
95. Jost L, Roila F. Management of cancer pain : ESMO Clinical Practice Guide lines . Annals of Oncology 2010; 21 (Supplement 5): v257–v260 .
96. Diener H, Hankey G, et al. Primary and Secondary Prevention of Ischemic Stroke and Cerebral Hemorrhage. J Am Coll Cardiol . 2020, 75 (15) 1804–1818.

97. Patrono, C., Baigent, C. Role of aspirin in primary prevention of cardiovascular disease. Nat Rev Cardiol 2019 ; 16 : 675–686.
98. US Preventive Services Task Force. Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: Preventive Medication. August 23, 2022. Available at: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/statin-use-in-adults-preventive-medication
99. TUKA, Vladimir; HOLUB, Josef; BĚLOHLÁVEK, Jan. Secondary Prevention after Myocardial Infarction: What to Do and Where to Do It. Reviews in Cardiovascular Medicine, 2022, 23.6: 210.
100. Powers WJ, Rabinstein AA, Ackerson T, et al . Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2019 ; 50 (12):3331–3332.
101. Migdady I, Rosenthal ES, Cock HR. Management of status epilepticus: a narrative review. Anesthesia. 2022;77 Suppl 1:78-91.
102. PERUCCA, Piero; GILLIAM, Frank G. Adverse effects of antiepileptic drugs. The lancet neurology, 2012, 11.9: 792-802.
103. BAILIE, George R., et al. Med facts pocket guide of Drug Interactions. in 2021
104. Moseley BD, Chanteux H, Nicolas JM, Laloyaux C, Gidal B, Stockis A. A review of the drug-drug interactions of the antiepileptic drug brivaracetam. Epilepsy Res. 2020;163:106327.
105. Keepers GA, Fochtmann LJ, Anzia JM, Benjamin S, Lyness JM, Mojtabai R, Servis M, Walaszek A, Buckley P, Lenzenweger MF, Young AS, Degenhardt A, Hong SH; (Systematic Review). The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia. Am J Psychiatry. 2020;177(9):868-872.
106. Zareifopoulos N, Panayiotakopoulos G. Treatment Options for Acute Agitation in Psychiatric Patients: Theoretical and Empirical Evidence. Cureus. 2019;11(11):e6152.
107. Stroup TS, Gray N. Management of common adverse effects of antipsychotic medications. World Psychiatry. 2018;17(3):341-356.
108. Spina E, Barbieri MA, Cicala G, de Leon J. Clinically Relevant Interactions between Atypical Antipsychotics and Anti-Infective Agents. Pharmaceuticals. 2020; 13(12):439.
109. Siwek M, Woroń J, Gorostowicz A, Wordliczek J. Adverse effects of interactions between antipsychotics and medications used in the treatment of cardiovascular disorders. Pharmacol Rep. 2020;72(2):350-359.
110. Aburamadan HAR, Sridhar SB, Tadross TM. Assessment of potential drug interactions among psychiatric inpatients receiving antipsychotic

therapy of a secondary care hospital, United Arab Emirates. J Adv Pharm Technol Res. 2021;12(1):45-51.
111. Guntupalli SR, Spinosa D, Wethington S, Eskander R, Khorana AA. Prevention of venous thromboembolism in patients with cancer. BMJ. 2023;381:e072715.
112. Iba T, Helms J, Connors JM, Levy JH. The pathophysiology, diagnosis, and management of sepsis-associated disseminated intravascular coagulation. J Intensive Care. 2023;11(1):24.
113. Gelbenegger G, Jilma B. Clinical pharmacology of antiplatelet drugs. Expert Rev Clin Pharmacol. 2022;15(10):1177-1197.
114. Kubica J. Opioids and oral P2Y12 receptor inhibitors: A drug-drug interaction. Cardiol J. 2022;29(5):727-729.
115. Harrington CR, Yang GY, Levitsky J. Advances in Rejection Management: Prevention and Treatment. Clin Liver Dis. 2021;25(1):53-72.
116. Hodgens A, Sharman T. Corticosteroids. [Updated 2023 May 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554612/
117. Pinkerton JV. Hormone Therapy for Postmenopausal Women. N Engl J Med. 2020;382(5):446-455.
118. Lindheim SR, Glenn TL, Smith MC, Gagneux P. Ovulation Induction for the General Gynecologist. J Obstet Gynaecol India. 2018;68(4):242-252.
119. Delgado BJ, Lopez-Ojeda W. Estrogen. [Updated 2022 June 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538260/
120. Edwards M, Can AS. Progestin. [Updated 2023 Mar 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK563211/
121. Merck Manuals Professional Edition [Internet]. [cited 2023 Aug 13]. Febrile Seizures - Pediatrics. Available from: https://www.merckmanuals.com/professional/pediatrics/neurologic-disorders-in-children/febrile-seizures?query=febrile%20convulsions%20treatment
122. Bhatnagar M, Pruskowski J. Opioid Equivalency. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Aug 13]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK535402/
123. ezar R, Lichtenauer M, Haar M, Hödl G, Kern JM, Zhou Z, Wuppinger T, Kraus J, Strohmer B, Hoppe UC, Wernly B. Infective endocarditis - A review of current therapy and future challenges. Hellenic J Cardiol. 2021;62(3):190-200.
124. Janković SM. The Handbook of Pharmacology and Toxicology. 6th edition, Faculty of Medical Sciences, Kragujevac, Serbia, 2021.