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Evaluation of the effectiveness of using biodegradable implants based on magnesium oxide compared to titanium alternatives
Experimental study

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Abstract. The issues of improving surgical implants used in treating patients with traumatological and orthopedic profiles continue to remain relevant. The development of a material not inferior in its elastic-strength properties to metal and that does not require further removal remains a reason for studying new samples that are inert during resorption. The purpose of this study was to experimentally explore and compare the bone tissue reaction to the introduction of titanium and magnesium oxide implants, as well as to study the state of magnesium oxide structures at different times after implantation. The material for the study was an implant based on magnesium oxide manufactured by the «MAGNEZIX» company. We operated on 30 rabbits based on the experimental laboratory of the Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry. The main group consisted of 10 rabbits, which were injected with a biodegradable screw made of a material based on magnesium oxide. The control group included 10 rabbits, which were injected with a titanium screw. In addition, another group of rabbits was studied. It included 10 young subjects who were injected with an implant based on magnesium oxide into the growth zone. Subjects were removed from the experiment one at a time at various stages. Then X-ray and histological assessment of the paraimplant zone were performed. As a result, the experiment showed that biomaterials based on magnesium oxide are bioinert, do not cause an inflammation reaction or osteolysis of the surrounding tissue, do not lead to the release of gas and the formation of a pathological cavity. During the introduction of magnesium-containing implants to young subjects, no pathological changes in bone tissue, deformities or stunting in the growth of the studied individuals were detected. Based on the obtained experimental data gathered for 6 months, it should be concluded that the material based on magnesium oxide is very promising and suitable for use in traumatology and orthopedics.

Keywords: osteosynthesis, screw, magnesium, biodegradable, implant.

Introduction. Modern traumatology and orthopedics are focused primarily on the surgical treatment of injuries and diseases of the skeleton with the use of various fixators and devices for osteosynthesis. Throughout many years of the development of these sections, various materials have been used for the manufacture of fixing structures. Nowadays, preference is given to metal, ceramic and polymer materials [4]. The most widely used structures are based on a titanium alloy. Their advantages include strength and biocompatibility. Nevertheless, such disadvantages as radiopacity and the need for further extraction in many situations create serious problems for clinicians [1, 3, 4, 10, 11]. That determined the search for new materials. The most budding among them are the biodegradable materials that can be resorbed in biological tissues [3, 4]. It allows avoiding repeated operations and in many cases it is a fundamental requirement for choosing a fixative. One example is intra-articular arthroscopic operations and periarticular interventions in children in the area of growth zones.

At present, here are many different biodegradable materials: polyglycolides, lactides, polyurethanes based on polycaprolactone and polyethylene oxide, magnesium oxide [1, 4, 11]. From this list, magnesium oxide is the most preferable. Resorbable implantable products made on its basis have good biocompatibility and high strength. As part of the resorption, they turn into endogenous tissue, which additionally stimulates bone growth [5, 9, 10, 11, 13]. Magnesium oxide-based structures are already used in clinical practice, but there is a certain shortage of studies devoted to the research of the reaction of bone tissue to their implantation. This is determined the relevance and the necessity of this study.

Aim of the research. To study and compare the reaction of bone tissue to the introduction of titanium and magnesium oxide implants in the course of an experiment, as well as to investigate the state of magnesium oxide structures at different time constraints after implantation.

Material and methods. From April to October 2019, experiments on rabbits (chinchillas) were conducted on the basis of the experimental laboratory FSBI of the N.N. Burdenko MMCH of the Ministry of Defense of the Russian Federation. 30 individuals were operated on, 2 groups were formed from them. The 1st group included 20 adult rabbits aged from 6 to 9 months. Therefore, they were divided into 2 subgroups. Subgroup 1-A (main) consisted of 10 rabbits, which were injected into the proximal femur with a biodegradable implant (BDI) made of a material based on MAGNEZIX magnesium oxide with a diameter of 2.7 mm and a length of 16 mm. Subgroup 1-B (control) included 10 rabbits, which were injected into the same zone using an identical technique

To study and compare the reaction of bone tissue to the introduction of titanium and magnesium oxide implants in the course of an experiment, as well as to investigate the state of magnesium oxide structures at different time constraints after implantation

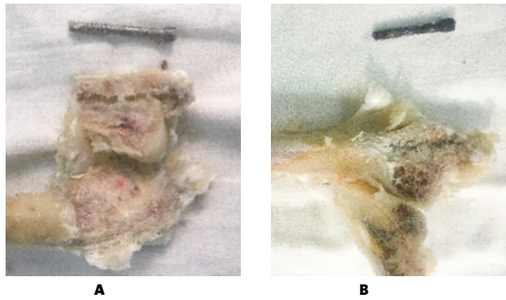
with a titanium compression screw (Herbert type) with a diameter of 2.7 mm and a length of 16 mm.

The animals were removed from the experiment after a week, a month, 2, 3 and 6 months — two individuals for each period. The operated limbs and extracted implants were subjected to macroscopic, X-ray and microscopic examination. After the formation of gross specimens, the remaining parts of the corpse were cremated.

Macroscopic examination was used to study the condition of the bone canal and surrounding tissues in the implantation zone, the appearance and palpation-determined implant properties. Gross specimens were sent for X-ray examination — X-rays were performed in direct and lateral projections. The state of bone tissue, radiological signs of biodegradation of magnesium implants, the absence or presence of a gas cavity around them, the formation of which was noted in some publications, were evaluated [10, 11, 13]. The composition of paraimplant tissues was studied by microscopic examination. Also, after the preliminary removal of the implants, the replacement of the bone canal with endogenous (fibrous/connective) tissue was evaluated.

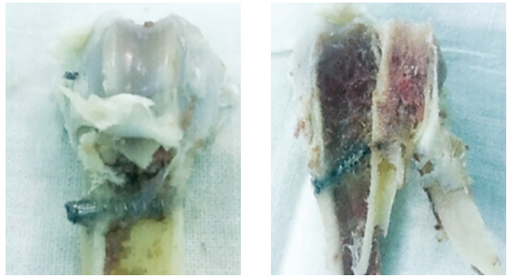
The 2nd group included 10 young rabbits (1–3 months), which were injected with a MAGNEZIX BDI with a diameter of 2.0 mm and a length of 10 mm into the zone of the distal metaepiphysis of the femur (the assumed growth zone) in the transverse direction after preliminary drilling. The animals were removed from the experiment after a week, a month, 2, 3 and 6 months. The same types of research were performed as in the 1st group.

Results and discussion. In the research of gross specimens, a change in the appearance and structure of BDI in subgroup 1-A was noted. A week after the operation, they were easily removed, the originally applied thread was determined on them, they remained



A B

Fig. 1. Gross specimens of operated rabbits in a month: A — a titanium screw; B — a biodegradable implant



A B

Fig. 2. Gross specimens of operated rabbits after 6 months: A — a titanium screw; B — a biodegradable implant.

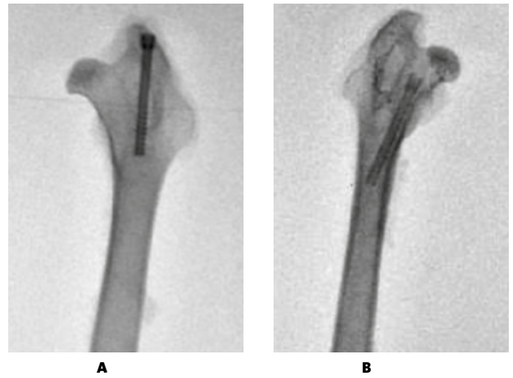
fragile and they broke with considerable effort. After 1–3 months, there were certain difficulties in removing the nails from the bone, associated with their integration into the surrounding bone tissue. Smoothness and indistinctness of the thread were noted, with significant bending efforts, the nails were deformed (Fig. 1). After 6 months, the nails were integrated into the surrounding bone. It was almost impossible to remove the implants, visually the border between the nail and the bone was blurred. The product itself was an oblong formation of gray-blue color, without clear contours, with a tightly elastic consistency (Fig. 2).

Titanium implants in subgroup 1-B retained their previous appearance and mechanical properties, and were also easily removed. In the early stages (from a week to2 months), the canal walls were represented by a spongy bone. During 3–6 months, a compaction area (sclerosis) formed around the titanium implant.

The radiographs in subgroup 1-A showed signs of gradual biodegradation as the observation period increased. During the systematic assessment, a decrease in the intensity of the BDI shadow was noted, especially starting from the 3rd month of the experiment. The intensity of the boundary of the titanium implant did not change during all the stages of the study (Fig. 3 and 4).

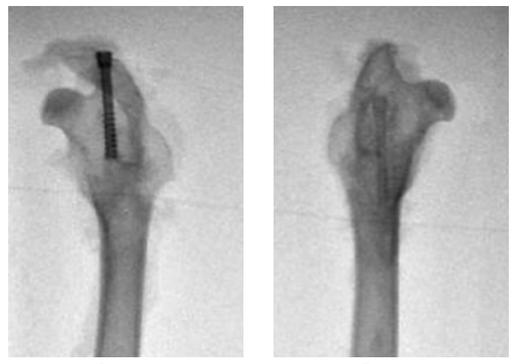
Some authors note the formation of a gas cavity in the implant area and associate it with the release of hydrogen gas and magnesium ions as products of the reaction of interaction between magnesium and the wet (or aqueous) environment [10, 13]. At the same time, by means of physiological metabolic processes, the body manages to either remove the above-mentioned products, or integrate them into the natural metabolic process. In our study, no such phenomenon was found in any case.

Microscopic examination after removal of the implant showed the predominance of vitreous fibrous tissue in its area, which noticeably fills the implant area



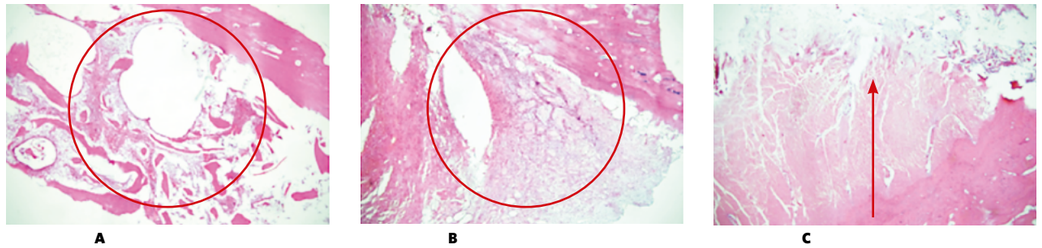
A B

Fig. 3. Radiographs of the femoral bone in 2 months: A — a titanium screw; B — BDI, its clear contours are visible, the lack of reaction of the surrounding tissues



A B

Fig. 4. Radiographs of the femoral bone after 6 months: on the left — a titanium screw; on the right — BDI, its contours are blurred, the borders are difficult to determine, the intensity of the shadow is significantly reduced



A B C

Fig. 5. Microscopic picture in the BDI area (subgroup 1-B): A — after 1 month, the presence of fibrous tissue was noted in the BDI zone; B — after 3 months, there is a predominance of fibrous tissue in the zone of destruction of the magnesium implant; C — after 6 months, there is a replacement of the bone canal with fibrous tissue in the area of the cortical layer of the bone

at the final stages of the experiment (Fig. 5). Fibrous tissue is formed as a result of a natural metabolic process and is a replacement product of the BDI destruction process. When assessing the paraimplant zone, no signs of inflammation and osteolysis zones were found.

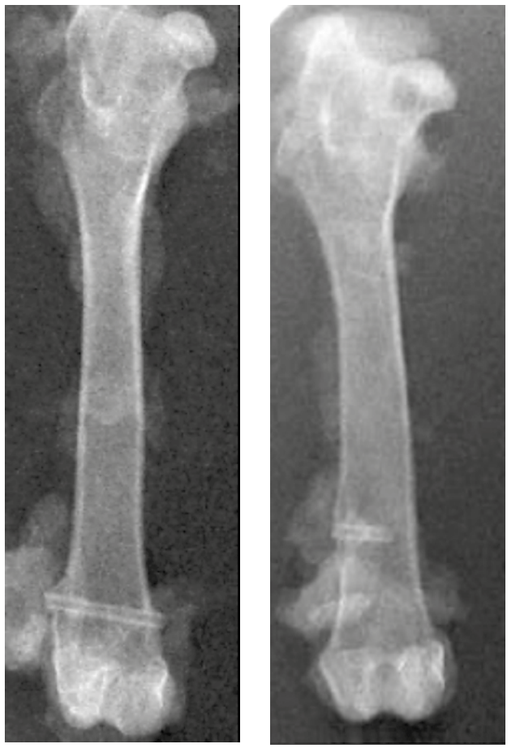
In the 2nd group, macroscopic evaluation of femoral bone preparations and BDI revealed changes similar to those that occurred in 1st group. There was a significant displacement of the implant proximally from the gap of the knee joint, which is associated with the progressive growth of the limb and a corresponding increase in the length of the femoral bone due to the growth zone located distally from the BDI embedded in the femur. Initially, BDI was inserted into the femoral bone at a distance of 5 mm from the gap of the knee joint. On radiographs performed after 2 weeks, they were found at a distance of 7±1 mm, 1 month — at a distance of 8±1 mm, 2 months — at a distance of 9±2 mm, or 3 months — at a distance of 11±2 mm after 6 months — at a distance of 14±3 mm (Fig. 6).

On radiographs, when comparing the length and shape of the femoral bones on both sides, there were no growth delays or deformities associated with damage to the growth zone on the side of the introduction of BDI.

Conclusion. The conducted experiment showed that magnesium oxide-based BDIs are bioinert, do not cause an inflammation reaction or osteolysis of the surrounding tissue, and do not lead to the release of gas and the formation of a cavity.

In the control subgroup, the presence of areas of necrotic tissue was detected during the introduction of titanium screws, while in the BDI zone, the predominance of areas of fibrous tissue with focal hyalinosis was observed.

During the introduction of BDIs to young individuals, no pathological changes in bone tissue, deformities or lags in the growth of the studied femoral preparations were noted.



A B

Fig. 6. Radiographs of the rabbit's femoral bone from the 2nd group: A — the position of the BDI at a distance of 5 mm from the joint gap immediately after surgery; B — a change in the position of the BDI, 6 months after the operation, it is determined at a distance of 14 mm from the joint gap

BDI lysis detected during 6 months of observation and their integration into the surrounding bone is the justification for the preservation of such structures in the implantation zone without extraction.

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Treating diabetic foot syndrome at the General Surgery Clinic of the S.M. Kirov Military Medical Academy

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Abstract. We examined 180 patients with purulent-necrotic complications of diabetic foot syndrome, in whom the proposed diagnostic algorithm was used. Magnetic resonance imaging of the feet, ultrasound Doppler with duplex angioscanning, magnetic resonance and computed angiography of the lower extremities, as well as assessment of transcutaneous oxygen tension were performed. Surgical treatment tactics depended on the form of the diabetic foot syndrome, as well as the severity of the disease. As a local treatment, physical methods were used to accelerate the course of the wound process. The proposed diagnostic algorithm for the diagnosis and selection of surgical treatment for various forms of diabetic foot syndrome has made it possible to reduce the number of "high" amputations and maintain a supporting limb.
Purpose of the study is to improve treatment outcomes for purulent-necrotic complications of diabetic foot syndrome by developing and applying a diagnostic algorithm and differentiated treatment tactics.
The main group consisted of 180 patients with purulent-necrotic complications of diabetic foot syndrome, in whom the developed diagnostic algorithm and differentiated tactics of surgical treatment were used, as well as physical methods of influencing the wound process (ultrasonic cavitation and local ozonation) were used as local treatment.
The control group included 40 patients with purulent-necrotic complications of diabetic foot syndrome, whose treatment involved the use of drugs that improve the rheological properties of blood and tissue microcirculation (rheopolyglucin, trental, actovegin) according to conventional schemes. Local treatment included sanitation and treatment of wound and ulcerative surfaces with antiseptic solutions and ointments, depending on the phase of the wound process. Data analysis in this group was carried out based on a retrospective study of case histories and an assessment of long-term results of treatment by follow-up examinations and telephone interviews. Control group included 25 (63%) men and 15 (37%) women; the average age was 67.3±10.3 years.
The developed unified approaches in diagnosing and treating patients with purulent-necrotic complications of diabetic foot syndrome, who, in complex treatment, underwent staged necrectomy with simultaneous ultrasonic cavitation of purulent wounds and their ozonization, can reliably reduce the number of ulcer recurrences from 28% to 2.7%, "high" amputations by 34%, and the number of re-amputations — 10 times.
The use of minimally invasive surgical technologies for the rehabilitation of deep purulent foci of the foot, in comparison with the classical principles of treatment of purulent wounds, makes it possible to achieve a complete cleansing of wounds, preparation for plastic surgery, and an increase in the number of functional supportable lower limbs by 42.7%. According to the data obtained, it is optimal to perform sanitizing operations after revascularization of at least one artery no earlier than 3–4 days, which makes it possible to increase their efficiency and reduce the number of repeated surgical interventions.
The approach to managing patients with diabetic foot syndrome at all stages of treatment and rehabilitation should be interdisciplinary and include the following specialists: endocrinologist, orthopedist, surgeon, psychologist, trained nursing staff.

Keywords: diabetes mellitus, diabetic foot syndrome, ultrasound cavitation, wound ozonation, biofilms, general surgery.

Introduction. According to the World Health Organization, there are over 194 million people with diabetes in the world, and by 2035 this figure would reach 334 million. Diabetes mellitus (DM) is the main cause of cardiovascular diseases, vision loss, amputation of the lower extremities, and renal failure. Every year, about 3 million people die from the complications from diabetes mellitus, and about 1 million amputations are performed. About 90% of patients have type II diabetes mellitus [1]. The International Diabetes Federation (IDF) has recognized that future incidence rates will begin to outpace the ability of national health systems to cope with this socially significant diagnosis [2]. Every 20 seconds in the world, a patient with diabetes undergoes a lower limb amputation. Up to 70% of all amputations in the world are associated with diabetes mellitus. About 85% of such operations could be prevented with adequate treatment and patient awareness. Complications associated with the lower extremities take up to 15% of healthcare financial resources in developed countries, while in developing countries this figure can reach 40% [3]. In Russia about 2.5 million people suffer from diabetes mellitus, of which over 24 thousand are children and adolescents with type I diabetes [4]. The prevalence of diabetic foot syndrome among patients with diabetes is 4–10% on average.

Diabetic foot syndrome (DFS) is an infection, ulcer and (or) destruction of deep foot tissues associated with neurological disorders and (or) a decrease in the main blood flow in the lower extremities' arteries of varying degrees of severity. With DFS, there are favorable conditions for the development and progression of surgical infection [5]. Purulent-necrotic process development in patients with DFS is 40–70% of indications for all non-traumatic amputations of the lower extremities [6]. Patient mortality after lower limb amputation is as follows: thigh level amputation — 50–85%, lower-leg level amputation — 24–35%, foot level amputation — 6%. 35% of all patients die within 3 years after the amputation, and 75% — within 5 years [7, 8].

Aims of the study. To improve DFS purulent-necrotic complications treatment by developing and applying a diagnostic algorithm and differentiated treatment tactics.

Material and methods. The main group consisted of 180 patients suffering from DFS purulent-necrotic complications, to whom the developed diagnostic algorithm and differentiated tactics of surgical treatment were applied. In addition to this, physical methods of influencing the wound process (ultrasonic cavitation and local ozonation) were used as local treatment.

The control group consisted of 40 patients with DFS purulent-necrotic complications treated by standard drugs improving rheological properties of blood and tissue microcirculation (rheopolyglucin, trental, actovegin).

Topical treatment was carried out by wound and ulcerative surfaces sanitation and treatment with antiseptic solutions and ointments, depending on the phase of the wound process. The control group data analysis was based on case reports as well as long-term treatment results assessment by follow-up examinations and telephone interviews. Among the patients of the control group, there were 25 (63%) men and 15 (37%) women, age 67.3±10.3 years.

There were of 85 (47%) men and 95 (53%) women in the main group. Age distribution: 5% (30–40 years), 19% (40–50 years), 57% (60–7 years), 19% (over 70 years). Patients with type II diabetes predominated (82.3%): 15% (disease duration of less than 5 years), 19% (5–10 years), 21% (10–15 years), 21% (15–20 years), 14% (20–25 years), 10 % (over 25 years).

In 82.5% of cases, patients were hospitalized with decompensated diabetes. In 60% of cases, patients were admitted for urgent indications with a severe degree of intoxication, requiring an urgent decision on the level of the lower extremity amputation. Diabetes mellitus was diagnosed for the first time in 9% of patients.

According to the form of DFS, patients were distributed as follows: ischemic — 74 (41%) patients, neuroischemic — 72 (40%), neuropathic — 34 (19%).

Patients of both groups were comparable in terms of age, gender, and degrees of severity of diabetes mellitus (Table 1). Concomitant somatic diseases were present in all patients.

In the structure of primary operations in patients of the main group, in 90% of cases, surgical interventions were localized within the foot. The number of "high" (above the foot) amputations was performed in 12 (8.5%) patients of the experimental group versus 43% in the control group.

Considering the multidisciplinary approach in the diagnosis and choice of treatment tactics, all patients underwent a complex of general clinical research methods, as well as an assessment of the course of the wound process, detection of neuropathy and (or) the degree of ischemia. The depth, prevalence of destructive changes in the foot and the degree of compensation for diabetes mellitus were studied.

Detachable wound bacteriological examination with sensitivity to antibiotics determination was carried out in all admitted patients. The quantitative and qualitative composition of the microflora of the wounds was investigated during treatment. Biopsy specimens for bacteriological analysis were taken before and immediately after surgical treatment (1st session of ultrasound treatment), as well as on the 7th (2nd session of ultrasound processing) and 12th (3rd session of ultrasound processing) days from the treatment beginning. Smears-prints of wound (ulcerative) surfaces in 54 patients were subjected to cytological examination according to the method of M.P. Pokrovskaya and M.S. Makarov (1942). Qualitative analysis of smears-prints characterized by the determining the phase of the wound (ulcerative) process by the presence of cellular elements, microflora, fibrous structures, and their ratio. Electron microscopes "JEM-100C" and "Hitachi" were used in transmission and scanning modes for electron microscopic examination. Feet X-ray in two projections was performed in 100% of patients, regardless of the form of DFS, to exclude chronic osteomyelitis, pathological fracture and to clarify the stage in Charcot's arthropathy. Ultrasound duplex scanning with color mapping was performed to assess the shape of the Doppler curve, which was used to determine the type of blood flow in the studied vessel.

All patients underwent determination of the partial pressure of oxygen in the tissues upon admission to the hospital to objectify the severity of critical lower limb ischemia.

A re-examination was performed after surgery in 4–5 and 15 days, evaluating the treatment effectiveness. Determination of oxygen tension in the tissues was repeated before closing the wound, objectifying the indications for plastic of the skin defect.

Spiral computed tomography angiography (SCTA) was performed to obtain volumetric images and high quality three-dimensional (3D) vascular reconstructions.

Contrast-enhanced magnetic resonance angiography (MRA) was performed in case of SCTA contraindication. Stenoses were classified according to a five-point scale developed for other vascular areas and adapted for contrast-enhanced MRA of the lower extremities' arteries: I — normal (no stenosis, reduced lumen 0–19%); II — hemodynamically insignificant lesion (stenosis 20–49%); III — hemodynamically significant lesion (stenosis 50–74%); IV — critical stenosis; V — occlusion.

Results and discussion. The development of a standard treatment strategy that could be applied to any variant of purulent-necrotic foot disease is fraught with certain difficulties. At present, the treatment is based on the saving principle, that is, the maximum possible preservation of the supporting function of the foot. Surgical treatment of the wound, supplemented by ultrasonic cavitation and ozonation, reduces the duration of the phases of the wound process by 18±2 days and reduces the number of "high" amputations by 34%, and the number of re-amputations by 10 times.

Considering that in most cases the lumen of the affected arteries had an irregular shape, stenosis was assessed by the ratio of the areas of the lumen of the vessel in the place of maximum narrowing and in the unchanged area using reconstructed images in the axial plane. Even in the presence of multilevel stenoses and occlusions of arteries, contrast enhanced MRA allows assessing the state of the main arteries of the lower extremities from the

Table 1. Characteristics of patients

Characteristics	Group	
	Control	Experimental
Patients	n=180	n=40
Age (years)	63,2±11,8	67,3±10,3
Diabetes mellitus duration (years)	12,3±3,8	13,4±4,2
Glycemia on admission, mmol/l	8,63±1,03	8,92±1,71
History of ulcerative defects	63,6%	100%
History of amputation	59%	90%
DFS forms:		
neuropathic	18,4%	5%
ischemic	41,2%	86%
neuroischemic	40,4%	10%
Surgery before hospitalization	59%	90%

*p>0,05

bifurcation of the aorta to the arteries of the feet, as well as assessing the state of soft tissues and bone structures, and thereby choosing the right tactics for patient treating. If there were contraindications to magnetic resonance imaging (MRI), CT angiography of the lower extremities was performed.

Percutaneous determination of tissue oxygen saturation is highly informative, non-invasive, and allows assessing the degree of soft tissue ischemia. Thus, in patients with diagnosed purulent complications in the postoperative wound, a decrease in oxygen tension around the wound below 25–30 mmHg by the 4th–5th day was noted. In patients with this indicator remained at 35 mmHg and higher, no infectious complications were observed, and no reoperations were required. Oxygenation of tissues below 30–35 mmHg indicates severe ischemia and makes a favorable prognosis of spontaneous healing less likely.

Lesions of bone structures determine the relevance of the examination aimed at verifying osteomyelitis. For this, we performed an MRI scan of the feet, which made it possible to detect changes in bone marrow density at an early stage.

In the neuropathic form with a purulent-necrotic process within the foot, the patient was attempted to perform a radical surgical operation with the simultaneous closure of the postoperative wound. If it was impossible to carry out a one-stage operation and the appearance of repeated necrosis, the patients underwent staged surgical treatments using ultrasonic cavitation and ozonation to prepare the wound for closure. The total duration of treatment was 18±5 days.

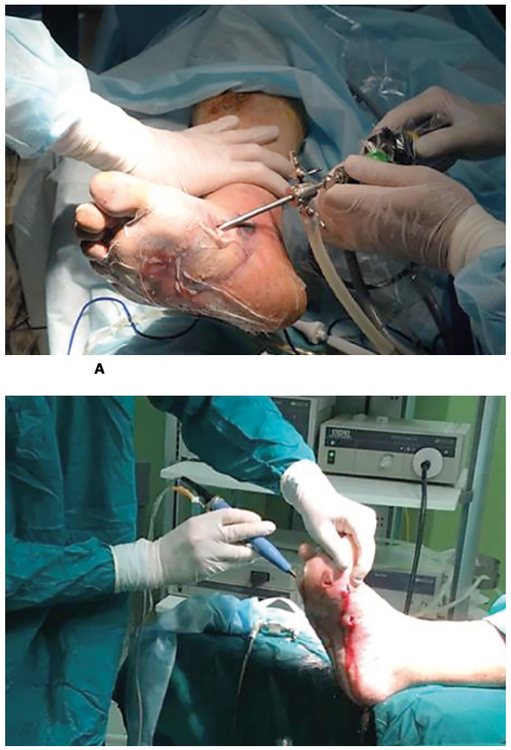
12 (8.5%) patients with wet gangrene of the entire foot and severe intoxication, including sepsis and (or) end-stage chronic renal failure, underwent amputation at the level of the thigh or lower leg for urgent indications, 10 (7%) patients with wet gangrene limited to fingers — amputation of fingers with intraoperative ultrasonic cavitation, 8 (4%) patients — transmetatarsal amputation. After stabilization, vascular reconstruction was performed. Then the patients underwent repeated surgical treatments with ultrasonic cavitation and ozonation until the appearance of granulations. The total duration of treatment was 44±10 days.

Patients with diagnosed ischemic DFS with dry gangrene of the toes or distal part of the foot first underwent revascularizing surgery on the arteries of the lower extremities or therapy with vasaprostan at a dose of 60 ug per day.

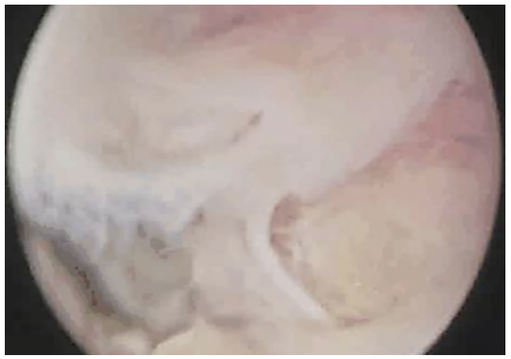
In 18 (47%) patients with hemodynamically significant ischemia of the lower extremities, endovascular recanalization with balloon angioplasty was performed: with stenting of the ilio-femoral segment — in 3 (8%), open surgery — in 14 (37%) femoral-popliteal shunting — in 8 (21%), thromboendarterectomy — in 3 (8%), as well as hybrid interventions with simultaneous open and endovascular stages — in 6 (16%) patients.

With the successful restoration of the main blood flow to the foot through at least one of the arteries of the lower leg, a pronounced rise in the partial pressure of oxygen in the tissues occurs from the 1st to the 3rd day and averages 26 mmHg (when restoring patency along one artery of the lower leg). By the 7th and 15th days, there is no significant increase in partial pressure. The nature and severity of the infection and the severity of reperfusion edema have a significant impact on the measurement of transcutaneous oxygen tension.

The second stage, against the background of compensated ischemia, was the amputation of fingers in 24



A



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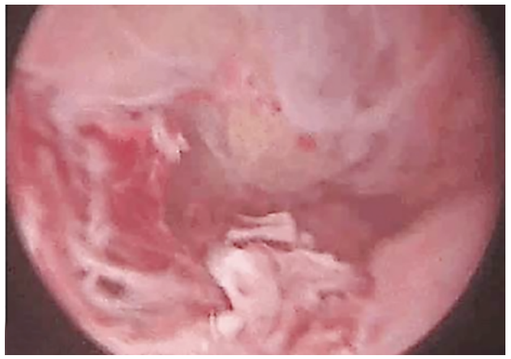
C



D

Fig. 1. Surgical treatment of wounds under the control of endovideoscopic imaging:
A — installation of an arthroscope in the wound channel;
B — soft tissues before surgical treatment;
C — ultrasound treatment of wounds;
D — endovideoscopic imaging after surgical debridement

(19%) patients with one-stage (88%) and staged (12%) closure of a skin defect or transmetatarsal foot amputation, which was performed in 10 (6%) patients. The duration of treatment was 40±7 days.

As part of a clinical study, we analyzed the results of treatment of 10 patients with purulent-necrotic complications of DFS, who were diagnosed with deep phlegmon of the plantar foot surface. The dissection of the purulent focus was performed considering the data of the MRI study on the spread of the infectious process.

In the projection of the maximum accumulation of purulent-necrotic masses, in the identified low-vascular zones, which were determined after performing a number of topographic and anatomical methods for assessing the angioarchitectonics of the foot, a horizontal linear skin incision 1.5 cm long was performed, then counterperture was applied along the contralateral lateral surface in the low-vascular zone. The number of incisions varied from 2 to 4 and depended on the data on the spread of the purulent-necrotic process obtained in the preoperative study, and later — according to the results of endovideoscopic imaging (Fig. 1).

After performing a low-traumatic approach in the low-vascular zone, an arthroscope was installed in a cannula into the wound with a single-stage supply of 0.05% chlorhexidine solution in a flow-washing mode. The cavity was revised, the anatomical structures of the foot were visualized. Particular attention was paid to the presence of streaks and areas of necrotic tissue.

The developed minimally invasive method assumes end-to-end flow-lavage drainage of wounds with perforated PVC drainages. One to two drains were required depending on the severity of the purulent-necrotic process. The diameter (from 0.5 to 0.8 cm) of the drainage tubes also depended on the severity of the purulent-necrotic process.

Flow-flush drainage was carried out by connecting a PVC drainage (system for transfusion of infusion solutions) on one side and supplying a 0.05% solution of chlorhexidine bigluconate in a volume of 800 ml. A container was connected to the opposite end of the drainage to collect the discharge.

The overwhelming majority of diabetic patients with foot purulent-necrotic lesions were found to have polymicrobial complexes. Mixed aerobic-anaerobic microflora was detected the most often. Aerobic gram-positive cocci were leading in the "chronicization" of the infectious process in the wound.

A decrease in microbial contamination was revealed by low-frequency ultrasound. The healing properties of ultrasonography are associated with its antibacterial, anti-inflammatory and antispasmodic effects. Cavitation is considered to be the main mechanism for providing bactericidal action of ultrasonic testing.

It has been established that low-frequency ultrasound mechanically destroys devitalized tissues, disintegrates and inactivates protease macromolecules on the surface of ulcers and purulent wounds, destroys microbial cells, and improves microcirculation through tissue vibration in the affected area. The power used (cavitation frequency was 40–80 kHz) does not have a destructive effect on healthy tissues, selectively removing only pathologically altered ones, which is important for DFS treatment due to the extremely small reserve of own soft tissues.

At present, bacterial biofilms formed on wound sites are of importance in the development of relationships between micro- and macroorganisms in the process of the onset of purulent-inflammatory diseases. The role of bacterial biofilms in the development of such a chronic disease as a DFSpurulent-necrotic complication has not been discussed previously.

Analysis of electron diffraction patterns obtained during tissue biopsy made it possible for the first time to reveal bacterial biofilms - microbial communities containing clusters of bacterial cells attached to the dense surface of the periosteum. The lysosomal accumulations contained in the cytoplasm of cells were revealed, indicating autolysis. After ultrasound, the biofilm is destroyed, the number of lysosomes decreases, which indicates a decrease in autolysis processes. The special role of biofilms is probably associated with the development of a prolonged infectious process, often turning into a chronic disease and causing the recurrence of purulent-necrotic complications. In our opinion, ultrasound treatment is the "gold standard" in the local treatment of purulent-necrotic complications of diabetic foot syndrome.

In 87 patients underwent the foot wound surface ozonation in various modes, the domestically manufactured ozon generator Orion-Si (OP1-M) was used. The effect of ozone is antibacterial, stimulating and oxygenating. Bacteria and viruses die in direct contact with ozone due to oxidative destruction of cell membranes and the breakdown of DNA and RNA, as well as destructive action of peroxidase. Aeration of the affected limb in a plastic insulator was carried out daily with an ozone-oxygen gas mixture with an ozone concentration of 40–80 ug/ml. The concentration and rate of ozone supply in the air mixture changed depending on the phase of inflammation of the wound process.

In the phase of inflammation, an air-ozone mixture with an ozone concentration of 80 ug/ml was used; when granulations appeared in the wound, the concentration of ozone in the mixture decreased to 40 ug/ml. The exposure in both cases was 15 minutes. Covers of different sizes made it possible to treat wounds of different area, depth, and shape.

Despite a 5-fold increase in the total number of operations in the main group, postoperative mortality decreased from 14.3% to 0.8%. The number of repeated "high" amputations has decreased by an order of magnitude. The average duration of inpatient treatment was 26 and 44 days in the main and control groups, respectively.

Surgical interventions for DFSpurulent-necrotic complications inevitably lead to the appearance of wound defects in the tissues of the foot. As a result, diffi-

With the successful restoration of the main blood flow to the foot through at least one of the arteries of the lower leg, a pronounced rise in the partial pressure of oxygen in the tissues occurs from the 1st to the 3rd day and averages 26 mmHg (when restoring patency along one artery of the lower leg). By the 7th and 15th days, there is no significant increase in partial pressure. The nature and severity of the infection and the severity of reperfusion edema have a significant impact on the measurement of transcutaneous oxygen tension

Table 2. Patients with DFS purulent-necrotic complications: immediate and long-term results

Characteristics	Group	
	Experimental	Control
Inpatient treatment period, days (M±m)	26±12	44±15
Wound epithelialization period, months (M±m)	4±1,2	6±1,5
Postoperative death rate, %	0,8%	14,3%*
Remission period (before the next operation), months (M±m)	9±2,1	4±1,2*
Ulcer recurrence rate, %	2,7%	28%*
Re-amputation rate, %	0,6%	8%*
The number of saved stops with the preservation of functionality, %	92,7%	50%*
*p<0,05		

culties arise in the treatment of patients, and the lack of plastic material, which is formed after radical surgical treatment, is especially acute. Of 180 patients, 79 (44%) required the closure of the skin defect with one of the types of plastic surgery. The choice of the method of skin grafting depends on the general condition of the patient, localization, depth and shape of the wound defect. The best results of plastic with a free perforated graft were achieved when it was used to close skin defects on the dorsum and plantar surfaces of the feet. After transmetatarsal amputation, a special original device was used to form the foot stump by early and gradual convergence of the wound edges until the appearance of cicatricial changes in the soft tissues. The gradual stretching of soft tissues in the wound area, especially the skin, prevents the frequently occurring marginal necrosis in the area of interrupted sutures. Infectious complications were noted in 12.7% of patients in the postoperative period. At the same time, partial lysis of the wound graft prevailed after free autodermoplasty, which can be explained by large areas, as well as by the involvement of functional zones (joints). Suppuration of the postoperative wound in patients using the device is explained by the imposition conditions, namely, the absence of a clear boundary between healthy and pathological tissues, pronounced edema. Combined plastics did not lead to any complications, however, insufficient number of patients does not allow making a final conclusion.

We obtained the immediate and long-term results, comparing the indicators in the experimental group of patients treated according to the developed algorithm, and in the control group, where patients received conventional therapy (Table 2).

Distribution of plantar pressure analysis makes it possible to assess the biomechanical consequences of amputations within the foot, as well as to identify changes on the contralateral limb that can lead to secondary purulent-necrotic complications. When analyzing the distribution of plantar pressure in patients who underwent various amputations within the foot, one should pay attention to the fact that the volume and localization of the removed segment of the foot have a significant influence on the formation of ulcers and purulent-necrotic complications.

Studying the quality of patients' life, we found that 80% of patients have difficulties with self-care, about 70% — with movement, as well as in daily activities in general. Pain syndrome of varying severity was present in 90%. However, the physical component prevailed in patients with ischemic DFS.

Taking into account the need to comply with the continuity of the continuation of treatment and rehabilitation of patients at the outpatient stage, we found that the turn to an orthopedist was only 10% of all operated patients. About 9% of patients operated on within the foot used orthopedic insoles to correct foot deformities. Among the patients who underwent "high" amputations, only one patient used a prosthesis.

Thus, developed unified approaches in the diagnosis and treatment of patients with DFS purulent-necrotic complications, who underwent staged necrectomy with simultaneous ultrasonic cavitation of purulent wounds and their ozonization in the complex treatment, make it possible to reliably reduce the number of ulcer recurrences from 28% to 2.7%, "high" amputations — by 34%, and the number of re-amputations — 10 times.

Minimally invasive surgical technologies for the debridement of deep purulent foci of the foot, in comparison with the classical principles of treatment of purulent wounds, makes it possible to achieve a complete cleansing of wounds, prepare them for plastic surgery and increase the number of functional supportable lower limbs by 42.7%. According to the obtained results, it is optimal to perform sanitizing operations after revascularization of at least one artery no earlier than on the 3–4th day, which makes it possible to increase their efficiency and reduce the number of repeated surgical interventions.

Conclusion. Management of patients with DFS at all stages of treatment and rehabilitation should be interdisciplinary and include the following specialists: endocrinologist, orthopedist, surgeon, psychologist, as well as trained nursing staff.

Based on the obtained results, the following conclusions can be drawn:

1. The wound process in DFS is characterized by polyvalent microbial landscape and biofilms localized on the periosteum, which reduce the effectiveness of treatment and lead to a relapse of the destructive process in the foot.
2. Surgical treatment of the wound, supplemented by ultrasonic cavitation and ozonation, reduces the duration of the phases of the wound process by 18±2 days and reduces the number of "high" amputations by 34%, and the number of re-amputations by 10 times.
3. The proposed algorithm for the diagnosis and selection of surgical treatment for various forms of DFS made it possible to reduce the risk of further progression of gangrenous changes in the foot and to preserve a supportable and functional limb.

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Tricuspid regurgitation prevalence in general hospital patients

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Abstract. Tricuspid regurgitation (TR) is a widespread valvular heart disease. Most times life expectancy doesn't depend on trace to mild degrees of TR. Tricuspid valve surgery is probably recommended for patients with moderate to severe TR because of their poor long-term outcomes. It is necessary to study TR in different patients. The aim of this work was to study the incidence of TR in general hospital and to investigate moderate to severe TR incidence rate. We analyzed 50.647 transthoracic echocardiograms (TTE) done in Federal State Governmental Establishment «Burdenko Main Military Clinical Hospital» of Russian Federation Defense Ministry in 2004–2019. The median age of patients was 56 years (age 54.23±17.95 years). We discovered 44.854 cases of TR. Moderate to severe TR was detected in 5.735 (11.3%) patients (age 68.11±14.42 years, M=71 years). In general hospitals TR can be found in 88% of patients. Patients with moderate to severe TR are older patients with progressive TR. Male patient with severe TR is often older than a female patient.

Keywords: echocardiography, tricuspid valve, tricuspid regurgitation, tricuspid valve insufficiency.

Introduction. Even though tricuspid regurgitation (TR) is often detected during echocardiographic examination, until recently it did not attract the attention of cardiologists and cardiac surgeons. One possible explanation is that even severe TR often remains asymptomatic for a long time and the diagnosis is made already at a late stage of right ventricular (RV) failure. Severe tricuspid valve insufficiency often leads to poor prognosis [1–4]. Moderate and pronounced isolated TR leads to significant mortality with a five-year survival rate of 51.7% and a ten-year survival rate of 30.5% [5]. Surgical treatment extends patients life expectancy [6], but only a small number of patients with severe TR undergo surgical treatment since there is often a high surgical risk, especially in elderly patients with RV failure [7]. Therefore, it is important to understand both TR prevalence and the incidence rate of its variants, which affect hemodynamics and worsen the prognosis, both in the general population and in certain groups of patients.

Aim of the study. To assess TR prevalence and the incidence rate of moderate to severe TR in general hospital patients.

Material and methods. We analyzed 50647 transthoracic echocardiograms (TTE): 37.477 (74%) men and 13.170 (26%) women who were examined and treated in Federal State Governmental Establishment «Burdenko Main Military Clinical Hospital» of Russian Federation Defense Ministry in the period from 01.01.2004 to 30.10.2019. The analysis was carried out using TTE Browser database, developed at the center for functional diagnostic research of the hospital. If the patient underwent several TTE, then the first echocardiogram was included in the study. TTE was performed on Vivid 3, Vivid 4, Vivid 5, Vivid E95 (General Electric); Acuson Sequoia 512, Acuson Cypress (Siemens); Artida SSH-880CV (Toshiba).

TTE and the assessment of TR severity were performed in accordance with the recommendations of American Society of Echocardiography, European Society of Cardiology Working Group on Echocardiography, European Association of Echocardiography, European Association of Cardiovascular Imaging, relevant at the time of the study [8–10]. Based on the findings, the patients were divided into groups depending on the TR presence and its severity.

Results and discussion. Analysis of 50,647 patients (age 54.23±17.95 years, M=56 years) revealed that TR of varying severity was found in 44.854 (88.56%) patients (age 55.79±17.47 years, M=57 years). Among 37.477 men (age 53.96±18.29 years, M=55 years), TR was detected in 33,253 (88.73%) cases (age 55.49±17.83 years, M=57 years), while among 13.170 women (age 55.03±16.94 years, M=56 years) it was detected in 11.601 (88.09%) cases (age 56.64±16.38 years, M=58 years).

In 44.912 (88.67%) cases (age 52.47±17.58 years, M=53 years), TR was not detected, or was insignificant and did not affect hemodynamics: 33.373 (89.05%) men (age 52.11±17.87 years, M=53 years) and 11.539 (87.62%) women (age 53.51±16.69 years, M=55 years).

Moderate to severe TR affecting hemodynamics was diagnosed in 5.735 (11.32%) cases (age 68.11±14.42 years, M=71 years). The detection rate in 4,104 men was 10.85% (age 69.03±14.24 years, M=71 years), in 1.631 women it was 12.38% (age 65.83±14, 63 years, M=68 years). The average age of female patients was lower compared to male patients ($p<0.001$).

Patients with moderate to severe TR were older than those who weren't diagnosed with it (or had insignificant TR), for both female and male patients ($p<0.001$).

The findings are consistent with the previous results devoted to TR prevalence investigation. Thus, according to Framingham Heart Study, TR was recorded by TTE in 82% of male and 85.7% of female patients [11]. In 2004, a joint group of US researchers reported TR in 88.5% of patients of Veteran Affairs Palo Alto Health Care System, the majority were men (98%), aged 66.5±12.8 years [12]. Most often, trace or insignificant TR is detected with TTE, which is often found with a structurally normal valve in healthy people [10]. TR without a significant effect on hemodynamics could be considered physiological [13]. Severe TR might be considered as an RV failure. Right atrioventricular valve failure is often functional (secondary) and develops with intact leaflets due to expansion of the fibrous ring or a phenomenon called tethering – restriction of leaflet movement due to remodeling of the right ventricle causing displacement of the papillary muscles, which prevents the leaflets to shift into systole to completely cover the opening of the RV. Functional TR is usually associated with pancreatic enlargement and/or dysfunction, pulmonary hypertension, and atrial fibrillation. Much less often, the valves themselves and other elements of the valve apparatus suffer. In this case, TR is identified as primary (organic) and can be observed in infective endocarditis, carcinoid syndrome, leaflet prolapse in myxomatous degeneration, rheumatism, heart injury, etc.

Previous research shows that moderate to severe TR affects hemodynamics and may be associated with a poor prognosis and increased mortality, regardless of the causes of occurrence [10, 12, 14]. In 2004, J. Nath and colleagues identified moderate and severe TR in 15.6% of the examined patients [12], and in 2020, E. Chorin and colleagues found TR in 12.1% of patients who underwent inpatient examination and treatment in Tel Aviv Medical Center (Israel) [14]. There was an identical prevalence of moderate to severe TR among our patients.

Conclusion. According to TTE, TR prevalence in general hospital exceeds 88%, which is consistent with the general population. Moderate to severe TR occurs in about 11% of cases. Among females, TR is detected

at a younger age and more often compared to males. Patients with moderate and severe TR were older than those who wasn't diagnosed with the disease (or had insignificant TR).

Thus, obtained results may help researchers to plan cardiac surgery aimed at correcting RV dysfunction and increasing patient life expectancy.

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Monocytosis in rational empirical antibacterial therapy in moderate forms of COVID-19

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Abstract. Microbiologically confirmed bacterial co-infection occurs in 1.2%–7% of hospitalized patients with COVID-19. The study of rational approaches to empirical antibacterial therapy (ABT) of SARS-CoV-2 virus-induced pneumonia continues. Glucocorticoid (GCS) therapy, the main method for pathogenetic treatment of moderate forms of COVID-19, can lead to the development of neutrophilic leukocytosis. The criterion for the differential diagnosis of leukocytosis could be determining the quantity of peripheral blood monocytes. Assessing the significance of identifying the monocyte quantity can serve as an additional criterion for assigning empirical ABT in the treatment of pneumonia caused by the new coronavirus infection. The aim of the study was to identify the characteristics of glucocorticoid-induced leukocytosis in patients with moderate COVID-19. The study included 86 patients with a confirmed diagnosis of COVID-19 (ICD codes: U07.1, U07.2) of moderate severity. The patients were divided into 2 groups. The comparison group consisted of 40 patients who were prescribed ABT after the manifestation of leukocytosis on the background of glucocorticoid therapy. The control group included 46 people who were not prescribed ABT after the manifestation of leukocytosis on the background of glucocorticoid therapy and until the end of their stay in the hospital. We compared the parameters of the clinical blood tests (the absolute number of white blood cells, neutrophils and monocytes ($\times10^9$/L)) on days 3, 6 and 9 from the start of GCS therapy. As a result, on the 3rd day, both groups had neutrophilic leukocytosis (>9.0×10^9/L) and absolute monocytosis (>0.8×10^9/L). There was a statistically significant decrease in the absolute number of white blood cells, neutrophils and monocytes by days 6 and 9, compared with day 3 from the start of glucocorticoid therapy. When comparing blood parameters between the groups, there was no statistically significant difference in the number of cells on the 3rd, 6th and 9th day of GCS therapy ($p>0.05$). Glucocorticoid-induced leukocytosis is associated with absolute monocytosis. The administration of ABT in response to the occurrence of leukocytosis in this study did not affect the change in the level of white blood cells. At the same time, a likely factor in reducing these indicators was a decrease in the daily dosage of corticosteroids.

Keywords: SARS-CoV-2, COVID-19, clinical blood test, hematological examination, monocytosis, glucocorticoids, antibacterial therapy.

Introduction. Currently, the issue of management approach to the treatment of bacterial complications of pneumonia caused by the SARS-CoV-2 virus remains unresolved. According to a number of authors, microbiologically confirmed bacterial coinfection occurs in 1.2–7% of hospitalized patients with COVID-19, while empiric antibiotic therapy (ABT) is prescribed in 50–90% of cases [1–3]. The world scientific community continues to research management approaches to empirical ABT pneumonia caused by the SARS-CoV-2 virus. The recommendations of the National Institutes of Health of the US Health Department recognize the lack of research aimed at rationalizing approaches to ABT in COVID-19, while suggesting both a routine approach to prescribing ABT to all patients with moderate to severe hypoxemia, and the selective one where the signs of bacterial coinfection are lobar lesions on the lung X-ray, leukocytosis, increased serum lactate levels, microbiological tests, and the state of shock [4]. On the other hand, domestic clinical guidelines suggest prescribing empiric ABT in the presence of convincing signs of bacterial infection: an increase in the level of procalcitonin >0.5 ng/ml, leukocytosis >12×10^9/L (in the absence of previous use of glucocorticoids (GC)), an increase in the number of band neutrophils more than 10%, the appearance of purulent sputum [5, 6]. GC-therapy, the main method of pathogenetic treatment of moderate forms of COVID-19, can lead to the development of neutrophilic leukocytosis [7], however, the study of the level of procalcitonin in COVID-19 patients shows low sensitivity [8]. In view of the above, it is necessary to develop additional criteria to differentiating bacterial neutrophilic leukocytosis from the GC-induced one. Analyzing the monocyte count in peripheral blood could become such a criterion. The development of macrophage activation syndrome in coronavirus pneumonia patients suggests the increase in the activity of circulating monocytes. At the same time, there is data on the effect of GC on the monocyte count in the peripheral blood [9]. Determining the significance of identifying monocyte count can serve as an additional criterion for the appointment of empirical ABT during the treatment of coronavirus pneumonia.

Aim of the study. To study the nature of glucocorticoid-induced leukocytosis in patients with moderate COVID-19.

Materials and methods. A study which included 86 patients with a confirmed diagnosis of COVID-19 (ICD codes: U07.1, U07.2) was conducted on the basis of a temporary infectious diseases hospital in the Moscow region (Patriot Park), from November 2020 to January 2021. Patient inclusion criteria: moderate course (NEWS score 5–7, percentage of lung damage according to computed tomography data up to 50%, baseline level of C-reactive protein (CRP) on admission from 30 mg/l), age up to 85 years, no taking systemic corticosteroids at the outpatient stage, the day of illness at admission is 8–12, leukocytosis on the 3rd day of therapy with systemic corticosteroids: dexamethasone 20 mg/day or prednisolone 150 mg/day intravenously for 3 days, followed by a gradual decrease in the daily dosage by 4 mg/day or 30 mg/day, respectively, for 4 days.

Patients were divided into 2 groups. Group 1 (comparison) included 40 patients who were prescribed ABT to treat leukocytosis. Group 2 (control) included 46 patients who did not get receive ABT throughout the course of their treatment. Patient exclusion criteria: deterioration in the severity of the disease, which required an increase of the GC dosage or the use of anticytokine therapy; ABT up to the 3rd day from the start of taking corticosteroids; the presence of extrapulmonary sources of bacterial infection. Comparison of indicators of the clinical blood test (absolute count of WBC, neutrophils and monocytes ($\times10^9$/l)) on the 3rd, 6th and 9th days from the start of GC-therapy. Laboratory tests were performed on automatic hematological analyzers ABX Yumizen H 500 (France) with the division of WBC into 5 populations.

Software packages Statistica 12, Microsoft Office Excel 2016, Past 3, IBM SPSS Statistics 26 were used for statistical processing. The numerical values of the analyzed indicators of each group in accordance with the law of normal distribution established using the Shapiro-Wilk W-test were presented as arithmetic mean (M) and standard deviation (σ), otherwise — in the form of median (Me) and interquartile range (Q25; Q75). Intergroup differences of quantitative variables with normal distribution were determined using the Student's t-test after checking the equality of variances (Leuven's test). In case of abnormal distribution of quantitative data,

Currently, the issue of management approach to the treatment of bacterial complications of pneumonia caused by the SARS-CoV-2 virus remains unresolved

Table 1. Patient group characteristics

Parameters	Group 1 (n=40)	Group 2 (n=46)	p
Age, years	61,5±13,6	60,6±11,1	0,77
Sex, male., n/%	17/42,5%	22/47,8%	0,62
Sex, female., n/%	23/57,5%	24/52,2%	
Arterial hypertension, n/%	24/60%	25/54,3%	0,59
Diabetes mellitus, n/%	11/27,5%	15/32,6%	0,61
CRP, mg/l	79,8±31,9	69,5±42,79	0,08

Table 2. Comparison of indicators of the clinical blood test of groups 1 and 2 on the 3rd, 6th and 9th days of GC therapy

Parameters	Me (Q25; Q75) (3rd day)		p	Me (Q25; Q75) (6rd day)		p	Me (Q25; Q75) (9rd day)		p
	Group 1	Group 2		Group 1	Group 2		Group 1	Group 2	
WBC count. ×10⁹/l	12,18 (11,25; 14,29)	11,48 (10,34; 12,33)	0,07	10,14 (8,79; 11,94)	9,12 (8,08; 11,01)	0,09	6,02 (4,58; 8,65)	7,41 (6,11; 8,78)	0,015*
Neutrophil count. ×10⁹/l	9,66 (8,82; 11,90)	9,1 (8,14; 10,09)	0,04*	7,96 (6,07; 8,87)	7,63 (6,54; 9,12)	0,65	5,47 (3,61; 6,72)	5,78 (4,87; 6,23)	0,46
Monocyte count. ×10⁹/l	0,97 (0,86; 1,03)	0,87 (0,81; 1,09)	0,35	0,74 (0,60; 0,81)	0,70 (0,55; 0,81)	0,47	0,60 (0,43; 0,77)	0,67 (0,46; 0,76)	0,52

* p<0,05

differences were determined using the Mann-Whitney U-test, within the group — using the Wilcoxon T-test. To determine the differences between categorical variables (gender, diabetes mellitus, arterial hypertension), the chi-square test (Pearson's test) was used. Multiple intragroup comparisons were performed using the Friedman test. The critical level of significance was p <0.05.

Results and discussion. The observed groups did not differ in age, sex, or comorbidities (table 1).

At the first point of the study (day 3 of GC therapy), both both neutrophilic leukocytosis (>9.0×10⁹/L) and absolute monocytosis (>0.8×10⁹/L) were observed in both groups, as well as the statistically significant decrease in the absolute count of WBC, neutrophils and monocytes by the 6th and 9th days compared to the 3rd day from the start of GC therapy. It should be noted that this decrease in indicators was associated with a decrease in the daily dose of GCs in both groups of patients. On the 3rd day of GC therapy (the 1st point), the daily dose was 20 mg of dexamethasone per day (or 150 mg of prednisolone per day), after which by the 6th day (2 point) the dosage gradually decreased (8 mg of dexamethasone or 60 mg prednisolone) and was completely canceled on the 7th day in all patients (Fig. 1–3) .

When comparing blood parameters between the groups, there was no statistically significant difference in the number of cells on the 3rd, 6th and 9th days of GC therapy. An exception was the identification of a significant difference in the neutrophil count on the 3rd day of taking corticosteroids (9.66 (8.82; 11.90) versus 9.1 (8.14; 10.09) in groups 1 and 2, respectively (p= 0.04) and by the number of leukocytes on the 9th day of GCS intake (6.02 (4.58; 8.65) versus 7.41 (6.11; 8.78) in groups 1 and 2, respectively (p=0.015). However, given the unidirectional nature of changes in these indicators in groups, it can be assumed that these differences do not make a significant contribution to the interpretation of intergroup comparisons in general (table 2).

Some authors provide data on GC therapy in various conditions inducing both monocytopenia. and monocytosis [10]. According to the received data, GC-induced leukocytosis is associated with absolute monocytosis. The appointment of ABT in response to the occurrence of leukocytosis on the 3rd day of GC therapy in this study did not affect the change in the WBC count. At the same time, a decrease in the daily dosage of glucocorticoids was a likely factor in the decrease in these indicators.

Conclusion. Despite the low incidence of bacterial complications in COVID-19, neutrophilic leukocytosis developing during the treatment of coronavirus pneumonia with glucocorticoids requires the development of additional differential diagnostic criteria. A clinical blood test is the most accessible laboratory test in routine clinical practice and requires regular monitoring of the WBC count in patients with COVID-19.

A study which included 86 patients with a confirmed diagnosis of COVID-19 (ICD codes: U07.1, U07.2) was conducted on the basis of a temporary infectious diseases hospital in the Moscow region (Patriot Park), from November 2020 to January 2021. Patients were divided into 2 groups. Group 1 (comparison) included 40 patients who were prescribed ABT to treat leukocytosis. Group 2 (control) included 46 patients who did not get receive ABT throughout the course of their treatment

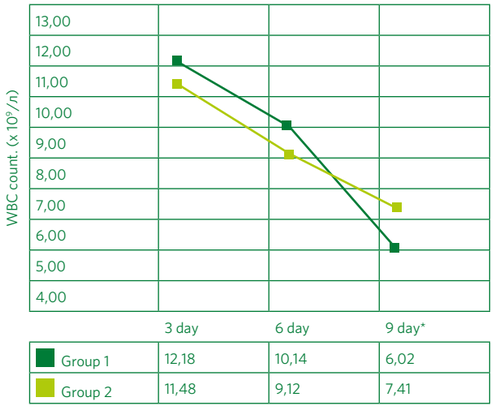

Fig. 1. Dynamics of the WBC count in the observed groups from the moment of leukocytosis manifestation on the 3rd day of GC therapy to the end of the therapy.
*p<0.05. Intergroup differences are statistically significant (Friedman's test: 58.4, p <0.001 and 61.2, p <0.001 for groups 1 and 2, respectively)

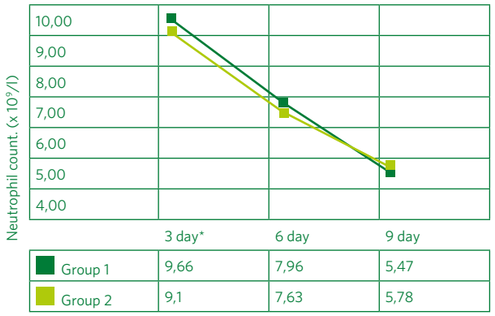

Fig. 2. Dynamics of neutrophil count in the observed groups from the moment of the appearance of leukocytosis on the 3rd day of GC therapy and until the end of the therapy.
*p <0.05. Intergroup differences are statistically significant (Friedman's test: 54.5, p <0.001 and 62.7, p <0.001 for groups 1 and 2, respectively)

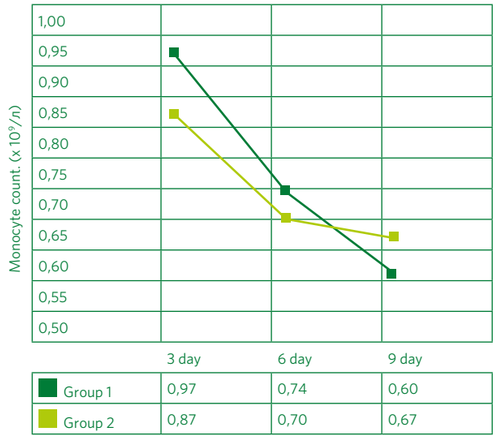

Fig. 3. Dynamics of monocyte count in the observed groups from the moment of the appearance of leukocytosis on the 3rd day of GC therapy and until the end of the therapy.
Intergroup differences are statistically significant (Friedman's test: 51.4, p<0.001 and 32.1, p<0.001 for groups 1 and 2, respectively)

Based on our research, the following conclusions can be drawn:

1. GC therapy is accompanied by a dose-dependent increase in the number of circulating blood monocytes.
2. Neutrophilic leukocytosis with monocytosis during therapy with GC is not an indication for antibiotic therapy.
3. Identification of absolute monocytosis of peripheral blood may indicate the effectiveness of GC therapy which requires further research.
4. Neutrophilic leukocytosis without monocytosis during therapy with corticosteroids may be a consequence of insufficient systemic anti-inflammatory therapy and a sign of bacterial infection overlay.

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Selecting the surgical treatment for patients with diaphragmatic hernia

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Abstract. Hernias of the diaphragm (HAP) are a common pathology that negatively affects the patients' quality of life and in some cases requires high-quality surgical correction. This pathology has a progressive course, which leads to an increase in the severity of clinical manifestations with the age of the patient. At present, behavioral and conservative therapy is the first line of treatment for HAP, while surgical correction is performed only if they are ineffective. This tactic helps to reduce the likelihood of discrediting surgical treatment and increase its effectiveness. The article presents the experience of surgical treatment of HAP on the basis of general surgery clinics of the N.N. Burdenko MMCH of the Ministry of Defense of the Russian Federation.

Keywords: hernias of the diaphragm, treatment.

Introduction. Hernias of the diaphragm (HAP) are one of the most urgent problems of modern surgery and gastroenterology [1]. The incidence rate of HAP in the structure of the pathology of the gastrointestinal tract ranges from 3% to 33%, taking the third place after cholelithiasis, peptic ulcer disease and duodenal ulcer disease [3]. Diaphragmatic hernia has a progressive course, which leads to an increase in the severity of clinical manifestations with the age of the patient [4]. The clinical course of HAP is accompanied by a significant decrease in the patients' quality of life and does not respond to therapeutic treatment. In the etiology of HAP, the leading role is assigned to genetic predisposition and congenital weakness of connective tissue [5, 6]. This pathology is associated with the structural degradation of the phrenicoesophageal ligament connective tissue fibers, weakening of gastric and other ligaments [7, 8]. Predisposing factors: obesity, bad posture, chronic intra-abdominal hypertension (persistent cough, astriction) [9].

Four types of HAP are currently distinguished [10]:

- Type I (axial, sliding) — there is an axial displacement of the gastroesophageal junction, gastric fundus or gastric body into the mediastinum through the expanded diaphragm and, in case of a change in the position of the body, their return to the abdominal cavity;
- Type II (paraesophageal) — the gastroesophageal junction is located in the abdominal cavity, and part of the stomach moves to the mediastinum;
- Type III (mixed) — there are anatomical changes of axial and paraesophageal hernias;
- Type IV — other organs of the abdominal cavity, such as the omentum, small and large intestines, pancreas, hepatic ligaments, are displaced to the mediastinum.

As a rule, half of patients with HAP are either asymptomatic or have a minimal clinical signs, many of which are not strictly specific for this disease, so the most frequently HAP is detected accidentally, during diagnostic examinations for other diseases [11]. Most researchers emphasize that a long period usually passes from the moment of occurrence of any symptoms to visiting a doctor and determining a correct diagnosis. In most times, patients with HAP are observed by a gastroenterologist for reflux esophagitis. Treatment begins with behavioral and conservative therapy: reduction of physical activity, rational food intake, diet, pharmacotherapy with proton pump inhibitors, H2-histamine receptor blockers, prokinetics. The outcome of conservative treatment depends on many factors: the patient's age, the presence of comorbidity, the severity of the pathological process, etc. Therefore, the effectiveness of conservative treatment, according to the literature, is in the range of 23–75% [12].

In the absence of the effectiveness of conservative therapy, surgical treatment is recommended for patients with HAP. The pioneer of surgical correction of HAP is Rudolf Nissen. In 1936, he was the first to propose and perform the fundoplication, which was the gold standard of treatment before the implementation of endoscopic technique. Currently, the most common method of interventional treatment of HAP is laparoscopic posterior Nissen fundoplication with crurorаphy [10, 13]. This method is considered the most adequate way to restore the barrier function of the gastroesophageal junction. Some HAP types are asymptomatic or have minimal clinical manifestations, and are often accidental diagnostic findings, and the vast majority of patients with this pathology are middle-aged and elderly people with assident somatic pathology. Thus, there are characteristic difficulties in determining indications for surgical treatment of HAP [3, 7]. The effectiveness of surgical treatment of HAP, according to various sources, reaches 75%–95% [8].

The indication for the surgical treatment of axial HAP is the ineffectiveness of conservative therapy of gastroesophageal reflux disease (GERD). Surgical interventions for asymptomatic axial hernias are not indicated [9].

The indication for surgical treatment of paraesophageal and mixed HAP is the presence of their clinical manifestations. The development of acute complications (infringement of HAP, obstruction in paraesophageal and mixed HAP) is an indication for emergency surgery.

With type IV HAP, surgical treatment is indicated in the presence of clinical manifestations or detection of small or large intestine guts in the hernial protrusion [7].

Over the past 10 years, the general surgery clinics of the N.N. Burdenko MMCH of the Ministry of Defense of the Russian Federation has accumulated extensive experience in surgical correction of HAP. These results may be of interest to practicing surgeons.

Aims of the study. To determine the effectiveness of surgical treatment of HAP in different categories of patients.

Materials and methods. The total number of treated patients was 216, of which 43 were men and 173 were women. The distribution of patients by age (according to the WHO classification) is shown in Figure 1.

Indications for surgical treatment were ineffectiveness of conservative therapy of HAP (34.5%), recurrent reflux esophagitis (30.4%), the degree of HAP according to additional research methods (52.5%). All patients were operated, 34 patients underwent simultaneous laparoscopic cholecystectomy. Laparoscopic access was used during the operation.

The contents of the hernial sac were represented in 53.4% by the gastric cardia, in 44.1% — by the gastric fundus and body, in 2.5% it contained the entire stomach, the loops of the small or large intestine. In all patients, the correction of HAP was performed with the formation of a circular fundoplication cuff with a size of 3.4±0.4 cm.

Results and discussion. The immediate results of treatment (after 6 months) were evaluated in 97 patients using clinical and instrumental data according to the criteria of H. Wykypiel and co-authors (2005).

It turned out that the immediate excellent and good outcomes of treatment according to clinical data were in 92% of cases, satisfactory and unsatisfactory results — in 5.4 and 2.7% of cases respectively. According to the results

54,4%	Young age
1,8%	Retirement age
7,5%	Old adults
36,1%	Middle-aged adults

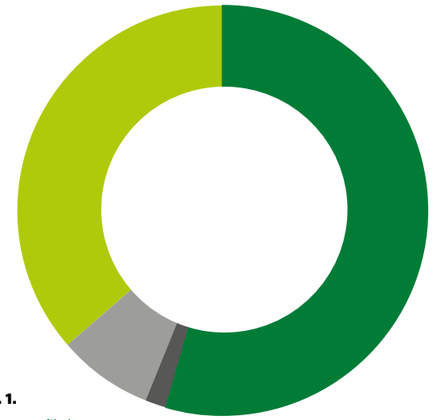
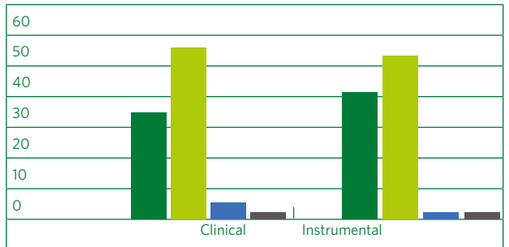
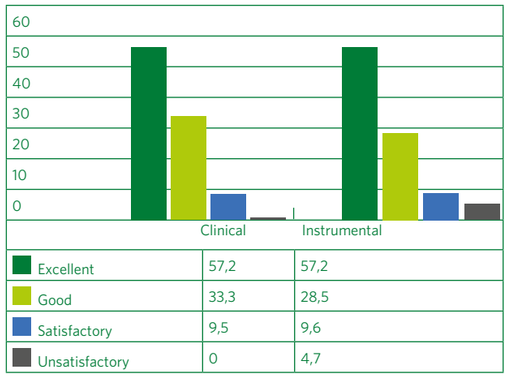


Fig. 1.
Patient profile by age



Excellent	35,1	40,6
Good	56,7	54,0
Satisfactory	5,4	2,7
Unsatisfactory	2,7	2,7

Fig. 2. Short-term results of treatment of patients with a diaphragmatic hernia



Excellent	57,2	57,2
Good	33,3	28,5
Satisfactory	9,5	9,6
Unsatisfactory	0	4,7

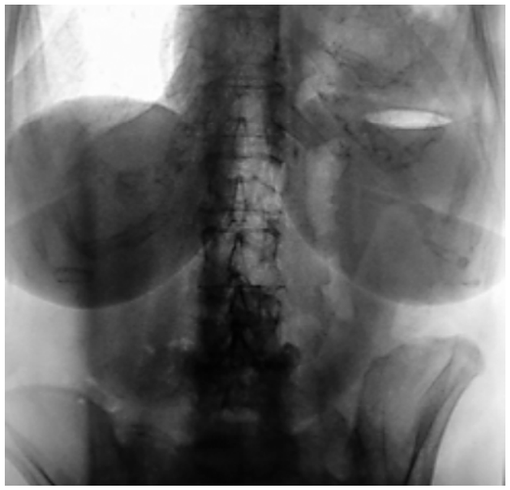
Fig. 3. Long-term treatment results according to clinical and instrumental examination data

of the instrumental survey, excellent and good outcomes were reached in 40.6% and 54% of cases, respectively, satisfactory and unsatisfactory — in 2.7 and 2.7% (Fig. 2).

Long-term outcomes in period of 24 to 36 months were studied in 51 patients using the same criteria. According to clinical data (Fig. 3), excellent and good results were in 57.2% and 33.3% of cases, satisfactory results — in 9.5% of cases.

Intraoperative complications were detected in 8 (3.4%) cases. In 6 cases, right sided pneumothorax was diagnosed, which was associated with damage to the mediastinal leaf of the parietal pleura. In 2 cases, emphysema of the chest, neck, and face was noted. In all cases, intraoperative complications did not affect the performance of the planned extent of operation.

Thus, with an uncomplicated persistent course of reflux-associated esophagitis against the background of



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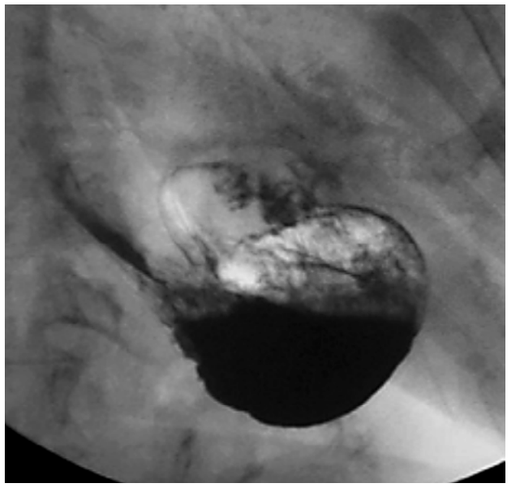

B

Fig. 4. Paraesophageal hernia of the diaphragm (thoracic stomach). Duodenal compression

the presence of HAP after a course of conservative therapy aimed at eliminating inflammation of the esophageal mucosa, laparoscopic hernia removal with antireflux operation is indicated.

In the complicated course of the disease, in our opinion, it is necessary to resort to two-stage endovideosurgical treatment. At the first stage, organic and functionally significant complications should be eliminated with the help of flexible intraluminal endovideoesophagoscopy, at the second stage, according to the indications, the elimination of HAP with antireflux surgery should be

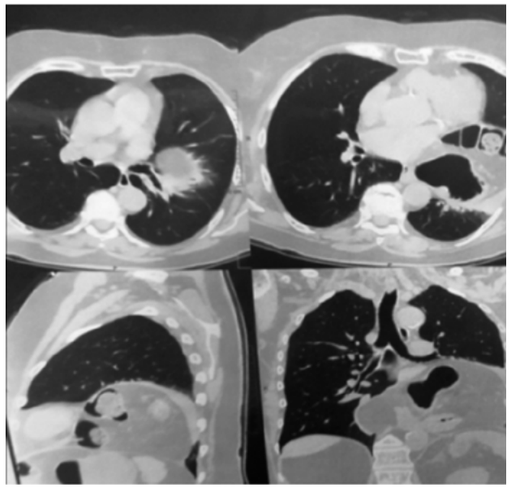

Fig. 5. CT-signs of a giant hernia of the diaphragm

performed by endovideosurgical method. In our opinion, laparoscopic cruroraphia with Nissen–Rosetti fundoplication should be considered the operation of choice.

A clinical case of an unfavorable course of HAP. Patient D., female, 79 years old, was taken by an ambulance team on 02.01.2020 to the emergency department of the MMA with complaints of a feeling of heaviness in the epigastrium, aching, bursting pains radiating to the heart area when eating food, heartburn, belching "rotten" air, nausea, repeated vomiting.

From the patient history it is known that nausea has been bothering the patient for the last three weeks, vomiting appeared suddenly. After taking antispasmodics and self-induced vomiting, the pain subsides. The patient notes a rapid feeling of fullness after taking a small amount of food. Pain attacks occur 1–3 times a day and last about 1–1.5 hours.

Development and course of the disease: epigastric pain has been bothering the patient for 10 years. Since December 2019, the above-described complaints have appeared. In October 2019, she underwent inpatient care in a surgical hospital for anemia. During the examination, grade IV HAP and hypochromic anemia were found. The patient was offered planned surgical treatment of HAP.

Comorbidity: atherosclerosis of the aorta and its branches, hypertension of the 2 degree (arterial hypertension of the 2 degree, the risk of MACE is 4), circulatory inefficiency of the 2A degree, coronary heart disease, chronic gastritis, chronic non-calculous cholecystitis, chronic pancreatitis, adrenal adenoma, pelvic cyst of the left kidney, kidney stone disease, stones and microliths in the kidney, diverticular disease of the descending and sigmoid colon, antelisthesis of the L4 vertebra, incomplete right sacralization of the L5 vertebra, peptic ulcer disease of the duodenum (remission), chronic gastroduodenitis.

On presentation, the patient's condition is of moderate severity. Height — 156 cm, weight — 62 kg. The skin is pale, clean. Breathing is vesicular, there are no crackles. The sound of the lung is percussion. The heart tones are rhythmic, clear. Blood pressure — 110/70 mm Hg, pulse — 64 beats/min. The tongue is moist; the stomach is soft, painless. Volumetric formations in the abdominal cavity are not palpated. Peristalsis is sounded. Blumberg's sign is negative. The symptom of concussion on both sides is negative.

Laboratory data. Detailed blood test: WBC — 14.0×109/L; banded neutrophiles — 6, segmented neutrophils—75; lymphocytes — 10; monocytes — 9; Hb — 113 g/L; ESR — 43 mm/h; anisocytosis+.

The results of biochemical blood test: K+ 3.07; urea 20.0 mmol/L; creatinine — 155 mmol/L.

Urine analysis: qty — 50 ml, color — nebulous, sp gr —1007, SQEP — 9–11 per HPF, WBC — 15–20 per HPF, RBC — 4–6 per HPF, mucus+, oxalates+.

Instrumental research methods. Abdominal ultrasound from 02.01.2020: ultrasound-signs of diffuse liver changes by the type of fibrosis, gallbladder polyps, diffuse changes of the pancreas, kidney stone disease, stones and microliths of both kidneys, gastrostasis. VGDS from 05.01.2020: the cardia is located 34 centimeters from the incisors, a significant deformation of the lumen is determined due to a displaced stomach 3/4 higher than the hiatal opening. There is a large amount of stagnant contents in the lumen (more than 1.0 l) and its absence in the antrum. A two-light feeding probe with a diameter of 12 Fr was installed to the level of the ligament of Treitz. Total paraesophageal hernia. Erythematous gastropathy. Deformity of duodenal bulb. Respiratory function test from 10.01.2020: the function of external respiration is preserved, VC: lower limit of normal. Stomach X-ray: the lower third of the esophagus forms a bend in the chest cavity. The entire stomach, the gas bubble is located in the chest cavity. The stomach is filled with contrast, by a small curvature on the posterolateral wall of the retraction. There is no evacuation of contrast from the stomach (Fig. 4).

CT of thoracic region, abdominal ultrasound from 02.01.2020: giant HAP with the presence of compressive changes in the adjacent lung tissue, fluid in the pericardial cavity, coronarosclerosis, deformation of the gallbladder, increasing the density indices of bile, CT-picture of the lesion of both adrenal glands, cystic formation in the sinus of the left kidney — pelvic cyst, diverticulosis of the descending colon and the sigmoid colon, forming an umbilical hernia, atherosclerosis of the aorta and its branches, antelisthesis of the L4 vertebra, incomplete right sacralization of the L5 vertebra (Fig. 5).

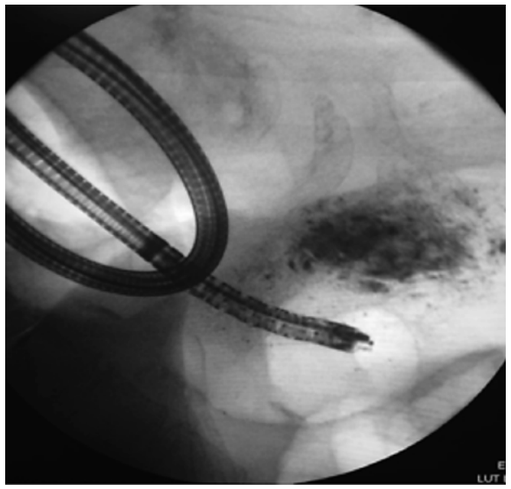

Fig. 6. Installing the probe into the lumen of the duodenum

Within 24 hours in connection with fluid, antispasmodic therapy, there was no significant positive dynamics; vomiting continued up to 8 times a day, accompanied by severe asthenia; pain in the left hypochondrium and epigastric region persisted. Due to the persistent severe vomiting and symptoms of duodenal obstruction, as well as in order to prepare the patient for surgical treatment, a two-light nutrient probe was installed under endoscopic control into the lumen of the stomach and into the duodenal (Fig. 6).

After compensation of water-electrolyte disorders and stabilization of the patient's condition, a planned operation was performed on 11.01.2020: plastic repair of the hernia of the diaphragm, posterior and anterior diaphragmatic surgery, Nissen fundoplication. During the revision, it was found that the stomach is completely displaced into the mediastinum through the esophageal opening of the diaphragm and is fixed there by a scar-adhesive process. The transverse colon and the loop of the small intestine are also located in the hernial sac. The adhesions and cicatricial tissue were dissected with ultrasonic scissors. The transverse colon and stomach are relegated to the abdominal cavity. With the help of an ultrasound dissector, short gastric vessels were crossed, the esophageal arch was mobilized. The lower third of the esophagus is isolated. Esophageal hiatus is expanded to 10 cm (Fig. 7).

The crus diaphragma are sewn behind and in front of the esophagus to the normal physiological size. Interrupted stitches were applied to the bottom of the stomach, the anterior wall of the esophagus with the formation of a muff (Nissen fundoplication) (Fig. 8 and 9).

The introduction of laparoscopic techniques in surgery has reduced the number of early and late postoperative complications in the treatment of HAP. The recommendations of the Society Of American Gastrointestinal and Endoscopic Surgeons (SAGES) on the surgical treatment of GERD show a positive effect of laparoscopic fundoplications in 85–93% of patients whose drug therapy was ineffective [13]. In general, the immediate and long-term outcomes of surgical treatment of HAP demonstrated efficacy results similar to the literature data

Drainage into the subphrenic space on the left and the residual cavity is installed (Fig. 10).

The patient was discharged on the 7th day.

Thus, a certain practical interest of the presented clinical case is considered by us as a rare observation of a diaphragmatic hernia of the IV degree with signs of decompensated duodenal obstruction, with certain difficulties in conducting differential diagnosis, preparing the patient and performing surgery with laparoscopic access.

Conclusion. The occurrence of the diaphragmatic hernia is caused by many factors. The results obtained confirm the literature data that HAP is more often manifested in women, and not in men.

The main clinical manifestations of HAP are considered to be esophageal symptoms caused by the course of non-erosive and erosive reflux esophagitis: heartburn, retrosternal pain, dysphagy, belching and regurgitation. The study confirmed the predominance of esophageal

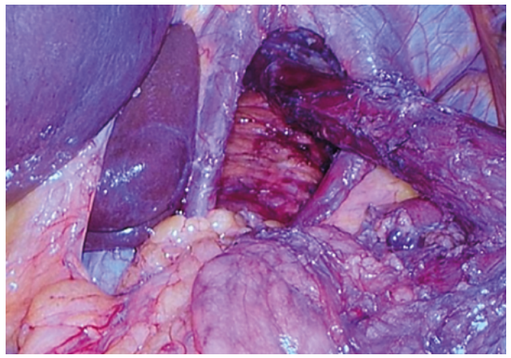

Fig. 7. Mobilized esophagus and crus diaphragma

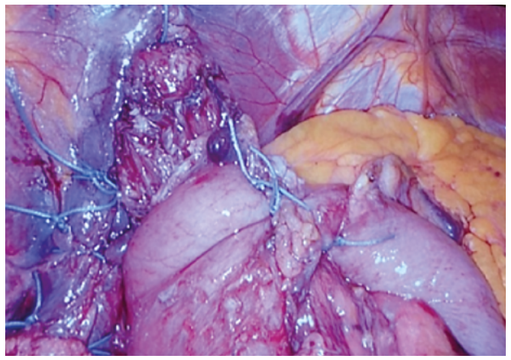

Fig. 9. Nissen fundoplication

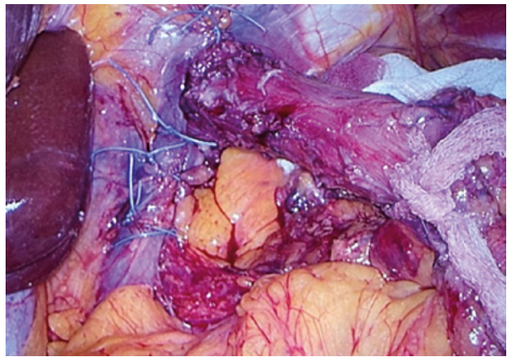

Fig. 8. Front and rear cruroraphia

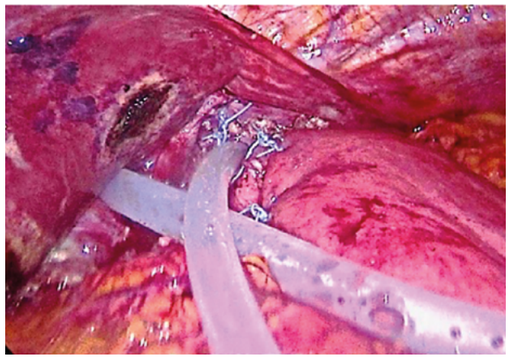

Fig. 10. Drainage of the hernia cavity and subphrenic space

symptoms in patients with HAP that were detected in 95% of patients. Currently existing effective drugs (antacid, antisecretory and prokinetic) for the treatment of GERD, the leading clinical manifestation of HAP, have reduced the number of indications for surgical treatment of this pathology. In our practice, we also align with this strategy, operating on patients when conservative methods of hernia treatment are ineffective.

The introduction of laparoscopic techniques in surgery has reduced the number of early and late postoperative complications in the treatment of HAP. The recommendations of the Society Of American Gastrointestinal and Endoscopic Surgeons (SAGES) on the surgical treatment of GERD show a positive effect of laparoscopic fundoplications in 85–93% of patients whose drug therapy was ineffective [13]. In general, the immediate and long-term outcomes of surgical treatment of HAP demonstrated efficacy results similar to the literature data.

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Early diagnosis of melanoma: current challenge for a modern clinician

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Abstract. Authors assessed the incidence of skin melanoma during outpatient consultations at the Consultation and Diagnostic Center of the Main Military Clinical Hospital named after academician N.N. Burdenko. During the period from 2019 to 2020, the authors diagnosed 68 patients with skin melanoma with stages ranging as follows: in situ — 3 (4.4%) cases, stage IA — 11 (16.2%) cases, IB — 13 (19.1%) cases, IIA — 11 (16.2%) cases, IIB — 6 (8.8%) cases, IIC — 9 (13.2%) cases, IIIA — 3 (4.4%) cases, IIIB — 4 (5.9%) cases, IIIC — 3 (4.4%) cases, IV — 5 (7.4%) cases. The necessity to apply the knowledge about the clinical and dermoscopic features of this malignant disease to diagnose skin melanoma, as well as exceptional prognostic significance of early detection of skin melanoma, were demonstrated.

Keywords: skin melanoma, outpatient appointment with a dermatologist, dermatoscopy.

Introduction. Skin melanoma is a socially significant issue due to its high mortality rate, which is almost 80%, the high metastatic potential of the tumor, and the low efficiency of systemic therapy for inoperable (advanced) forms of the disease [1, 2]. In recent decades, the incidence of skin melanoma has been steadily increasing in most countries, although it differs significantly depending on the geographic region [3]. In the USA it has tripled over the past 30 years [4], in Netherlands the number of cases has doubled over the past 10 years [5], and in Russia the absolute number of newly diagnosed melanoma increased 1.3 times over the period of 2004–2014 [6]. In early localized forms of the disease, the prognosis is favorable if the thickness of the primary tumor does not exceed 1–2 mm [7]. However, the epidemiological situation in Russia is characterized by high frequency of advanced and locally advanced forms of skin melanoma. By the time of the start of adjuvant therapy, the disease is already widespread in approximately 75% of cases [8] and, as a result, there is a higher incidence of disease progression and mortality rates from melanoma compared with the EU, the USA and Australia [9].

A group of risk factors for the development of melanoma has been identified, and some of them are genetically determined changes, while the other factors are associated with environmental exposure [10, 11]. Nevertheless, there is no reliable way to prevent melanoma. The most effective way to reduce mortality from melanoma might be its early detection and adequate timely treatment. Studies conducted in Germany have shown that early detection of skin melanoma reduces mortality rates by almost 50% [12, 13], therefore current research focuses on possible methods of examining high-risk groups, as well as the general population [4].

Skin melanoma is visually localized, therefore, a full clinical examination of a patient by a qualified specialist is the primary and obvious way to detect it. Examination effectiveness is increased by dermatoscopy, which has recently become widespread. The diagnostic capabilities of this informative and non-invasive method are used both for early diagnosis of melanoma and for monitoring pigmented skin lesions. In 2010, dermatoscope was included in the equipment standard for dermatological offices in the Russian Federation. Research has shown that the use of dermatoscopy by trained and experienced physicians can help detect complex cases of melanoma without characteristic features earlier and reduce unnecessary biopsies of benign skin lesions [14, 15].

To date, the main method for melanoma diagnosis remains histological, and it determines the final diagnosis of melanocytic skin tumors [16, 17]. Immunohistochemical analysis is of particular importance, especially in the case of non-pigmented melanoma. Melanoma is always negative in reactions with cytokeratins, EMA, general leukocyte antigen and is always positive in reactions with S100 protein, melanoma-associated antigen (HMB-45) and vimentin. Recently, great importance has been attached to the biopsy of the sentinel lymph node [8].

Aims of the study. To study the possibilities of early diagnosis of skin melanomas, to compare theoretical data with our own research on the early diagnosis of skin melanomas based on clinical and dermatoscopic signs.

Methods and materials. In the period from 2019 to 2020, during outpatient consultations at the Consultation and Diagnostic Center of the Main Military Clinical Hospital named after academician N.N. Burdenko, 68 cases of skin melanoma were diagnosed. Clinicoanamnestic and dermatoscopic methods were the main methods of pigmented neoplasms diagnostics. In case of suspicion of the presence of potentially malignant and malignant skin tumors in the examined patients, morphological diagnostic methods (cytological and histological) were used. A magnifying glass (6x or 7x magnification), side illumination, and a dermatoscope were used to examine the skin lesions. The diagnosis was based on knowledge of the elements of the skin rash and the peculiarities of their color.

Results and discussion. In our practice, the incidence of skin melanoma increased 5.7 times compared to the period of 2006–2007, when skin melanoma was diagnosed only in 12 patients [18]. The analysis of the effectiveness of early diagnosis of skin melanoma in Russia in 2014 revealed that at stage I of the disease, patients with melanoma were identified in 30.2% of cases. Basically, patients with stage II of the disease (44.1%) were identified [6, 19]. 68 patients with melanomas were diagnosed with stages ranging as follows: in situ — in 3 (4.4%) people, stage IA — in 11 (16.2%), IB — in 13 (19.1%), IIA — in 11 (16.2%), IIB — in 6 (8.8%), IIC — in 9 (13.2%), IIIA — in 3 (4.4%), IIIB — in 4 (5.9%), IIIC — in 3 (4.4%), IV — in 5 (7.4%). Special attention should be paid to the fact that out of the above patients, 6 (9.7%) patients were referred after examination by dermatologists at the primary care clinic for another pathology, and skin melanomas were detected in this group during consultation with diagnostic centers' dermatologists. A number of studies have shown that if patients are not specifically referred for skin examination, there is one malignant skin tumor diagnosed for every 47 patients, and one melanoma for every 400 examined patients [4, 20]. In our case, skin melanomas were detected during the examination of 3358 primary patients. Thus, there was 1 case of skin melanoma for 560 examined patients. In all cases skin melanoma did not progress past stage I of the disease (in situ - in 1 person, stage I - in 5 people). Dermatoscopy was used to increase the specificity of the skin melanoma clinical diagnosis. 3- and 7-point dermatoscopic diagnostic algorithms were adopted in our practice [21, 22].

The diagnostic algorithm of the 3-point rating system is recommended as a screening method for less experienced professionals. For a physician who has recently started using this method in his practice, the purpose of dermatoscopy is to decide how to deal with a suspicious lesion. The main task is that no patient leaves the doctor

Skin melanoma is visually localized, therefore, a full clinical examination of a patient by a qualified specialist is the primary and obvious way to detect it

with a missed diagnosis of melanoma. For inexperienced physicians the following checklist was specially developed, which might help not to miss the diagnosis of melanoma:

- dermatoscopic asymmetry of color and structure along one or two perpendicular axes;
- atypical pigment net (pigment net with irregular cells and thick lines);
- blue-white structures (a combination of a blue-white veil and regressing structures, any blue and/or white structures).

Identification of 2 signs (2 points) indicates the risk of melanoma, 3 signs — a very high probability of skin melanoma [23–25].

The 7-point melanoma diagnostic algorithm consists of seven points that help not to miss the diagnosis of melanoma and is used by more experienced professionals. The algorithm criteria include:

- atypical pigment network (2 points);
- white and blue veil (2 points);
- atypical vessels (2 points), often polymorphic vessels, when two or more types of vessels meet, for example, a combination of serpentine and corkscrew vessels; for hypopigmented melanoma, a pink veil is characteristic;
- "smudges" of irregular shape (1 point);
- regression structures (1 point);
- uneven and irregular pigmentation (1 point);
- dots / globules of irregular shape (1 point).

A score of more than "2" is regarded as a suspicion of melanoma [21, 26].

All of the above once again emphasizes the critical importance of a full clinical examination and the use of dermatoscopy in improving the prognosis of survival in melanoma. Currently, there are no state programs for the early diagnosis of skin melanoma in Russia and, as Professor L.V. Demidov said in the interview for Effective Pharmacotherapy, Oncology, Hematology, and Radiology Journal, "... their creation requires significant material costs", and they "should be aimed at solving a variety of problems" [7]. In addition, in the absence of randomized clinical trials that support screening for melanoma, the recommendations of the expert groups vary greatly. For example, the American Academy of Dermatology recommends people at high risk to see a doctor for a skin examination at least once a year, be sure to examine the skin on their own and protect it from excessive sun exposure. Mass screening of other populations is not recommended by the American Academy of Dermatology [4].

In resource-poor settings, being a time-consuming and laborious procedure, a full clinical examination is often difficult. Considering that pigment and pigmented formations, under the mask of which melanoma can be disguised, are found in 90% of the population, the issue of melanomas becomes especially serious, aggravated by the lack of screening programs of the population at the present time [8].

Conclusions. An experienced dermatologist may suspect skin melanoma by clinical and anamnestic signs during outpatient treatment.

Dermatoscopy increases the specificity of differential diagnosis of skin melanoma with other pigmented formations. The main criteria for its differential diagnosis are the following: atypical pigment network, blue-white veil, atypical vessels, “smudges” of irregular shape, regression structures, uneven and irregular pigmentation, points/globules of irregular shape.

Skin melanoma diagnosis can be established at an outpatient appointment with a dermatologist at an early stage of the tumor process.

Dermatoscopy increases the specificity of differential diagnosis of skin melanoma with other pigmented formations. The main criteria for its differential diagnosis are the following: atypical pigment network, blue-white veil, atypical vessels, “smudges” of irregular shape, regression structures, uneven and irregular pigmentation, points/globules of irregular shape

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Severe reactive hyperthrombocytosis secondary to coronavirus infection
Clinical cases

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Abstract. The article presents two cases of the new coronavirus infection COVID-19 with pronounced hyperthrombocytosis, which resolved independently.

Keywords: COVID-19, hyperthrombocytosis.

Introduction. Reactive thrombocytosis (RT) often accompanies various disorders and conditions of the human body and is most common with malignant tumors, including malignant diseases of the blood, hemorrhaging, iron deficiency, and infections [1]. Differential diagnosis is usually made for chronic myeloproliferative diseases (CMPD), mainly for essential thrombocythemia. It is generally accepted that platelet level of more than 1000×10^9/l and higher is characteristic of CMPD and requires molecular and morphological (bone marrow trepanobiopsy) diagnostics. Bone marrow trepanobiopsy is an invasive and unpleasant manipulation that can lead to iatrogenic complications. In the case of the insignificant isolated thrombocytosis, a watch-and-wait approach was adopted, as well as excluding infections (mainly bacterial) and conducting an "oncology search". Hyperthrombocytosis level of more than 1000×10^9/l is usually characterized as a high possibility that the patient has CMPD [2]. In the available literature there is no information about hyperthrombocytosis secondary to coronavirus infection [3, 4].

We present a description of clinical cases of two patients with severe reactive hyperthrombocytosis after the new coronavirus infection, which resolved on its own.

Clinical case №1. Patient A, 22 years old, underwent examination in the traumatology department owing to a compression fracture of the 5th lumbar vertebra. Within 3 weeks, he noted a loss of taste and smell, infrequent subfebrile condition up to 37.3 °C. He did not seek medical treatment. Complete Blood Count (CBC) dated 09.10.2020: increased platelet level — 568×10^9/l; CBC dated 10/29/2020: platelet level is 1260×10^9/l. The level of hemoglobin and WBC is normal; leucogram is without peculiarities. Fluorography of the chest organs from 01.10.2020: no pathology. Abdominal ultrasound dated 29.10.2020: the liver is not enlarged, the spleen is 10×4.8 cm.

On 01.12.2020, the patient was transferred to the hematology department for examination and further treatment. CBC from 02.12.2020: platelets according to Fonio — 375×10^9/l + accumulations. Erythropoietin, folates, vitamin B12, serum iron are within normal limits. Antibodies to COVID-19 from 07.12.2020 were detected: IgM SARS-COV-2 — negative, IgG SARS-COV-2 — 15.320 (normal up to 10.0), throat and nose swab from 02.12.2020 for SARS-COV-2 — negative. The myelogram from 03.12.2020: blasts — 1.8%; hypocellular bone marrow - 27×10^9/l, polymorphic, myeloid lineage is slightly narrowed — 50%, with the predominance of mature forms; the erythroid lineage is narrowed — 11.2%, according to the normoblastic type of hematopoiesis, without megaloblastoid; moderate amount of megakaryocytes — 35.1×106/l, with a moderate platelets release. Alkaline phosphatase of neutrophils is reduced (6 units). Trepanobioptate dated 09.12.2020: with silver impregnation, reticular myelofibrosis was not detected (MF0); the morphological picture corresponds

to the hypocellular bone marrow with hyperplasia of the megakaryocytic lineage, which can be observed in essential thrombocythemia and other conditions leading to hyperplasia of the megakaryocytic lineage. In the blood from 09.12.2020: platelets — 215×10^9/l, WBC — 66.09×10^9/l, RBC — 6.09×10^9/l, hemoglobin — 124 g/l. The patient was discharged with a "Reactive thrombocytosis after suffering a new coronavirus infection COVID-19" diagnosis (confirmed on 07.12.2020 by an increase in the level of SARS-COV-2 IgG antibodies — 15.320).

Clinical case № 2. Patient B, 45 years old, noted severe blood loss during menstruation since September 2020, a gradual increase in weakness. Since 08.03.2021, she suffered a new coronavirus infection caused by the COVID-19 virus, which was confirmed by a PCR test. The patient had a fever up to 38 °C, lung damage up to 25%, antibiotic therapy, Xarelto, was carried out. On 23.03.2021, the patient was hospitalized due to persistent fever. On admission there was a decrease in hemoglobin to 65 g/l, leukocytosis — 21×109/l (neutrophils — 17×109/l), platelets — 2140×109/l. Computed tomography from 23.03 and 28.03.2021 showed lung lesions of less than 25%. Ultrasonic investigation of the abdominal cavity organs: the spleen is of normal size, other internal organs were normal. Examination of the patient by a gynecologist revealed uterine fibroids with a prolapsed myomatous node, as well as uterine bleeding. She was prescribed therapy with intravenous iron preparations, low molecular weight heparins, dexamethasone, and antibiotics. Taking into account uterine bleeding, on 28.03.2021, the patient was transferred to the surgical department. Ultrasound from 28.03.2021: the uterus is 88×73×80 mm, a myomatous node appearing in the cervical canal. In the myometrium, the node was 33 mm, the uterine cavity was up to 41 mm, in the lumen there was a multinode formation — 37 mm. Uterine fibroids was diagnosed. The bleeding has decreased. The patient was examined by a gynecologist: surgical treatment was recommended after normalization of blood counts. On 31.03.2021, the patient was discharged. At home, she noted an increase in weakness, shortness of breath with minimal physical activity, palpitations. The patient was referred to a hematological hospital to clarify the diagnosis and prepare for surgical treatment. On admission, the patient's condition was moderate, hemoglobin — 73 g/l, RBC — 4.5×1012/l, WBC — 6,8×109/l, platelets — 820×109/l, serum iron — 3.5 µmol/l (normal level is 5.8–34.4). Previously detected changes in blood tests (thrombocytosis, neutrophilic leukocytosis) were regarded as reactive changes against the background of coronavirus infection, anemia and inflammation. On 02.04.2021, ultrasonic investigation of the abdominal cavity organs revealed: uterine fibroids, heterogeneous contents in the uterine cavity, destructive changes in the myomatous node in the uterine cavity. In order to relieve the manifestations of anemic syndrome, a transfusion of 1 dose of erythro-suspension was performed and iron supplementation was started, as well as antibacterial therapy was carried out. Manifestations of anemic syndrome during treatment were partially relieved. CBC from 20.04.2021: hemoglobin — 83 g/l, RBC — 4.5×1012/l, WBC — 6.1×109/l, platelets — 284×10^9/l. The patient was examined by a gynecologist: planned surgical treatment was recommended. In early April 2021, the patient was operated on, the uterus was extirpated. CBC did not reveal pathology.

Conclusion. We observed two patients who, given an infection caused by the SARS-COV-2 virus, had a maximum increase in platelets up to 1280×10^9/l and 2140×10^9/l, respectively. Despite the fact that patient B had a reason for thrombocytosis due to blood loss, we have not previously observed thrombocytosis of more than 1000×10^9/l in such patients.

Thus, in patients with a previous coronavirus infection caused by the SARS-COV-2 virus, reactive hyperthrombocytosis with high platelet counts can be detected, which can lead to essential thrombocythemia.

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Practical use of parenteral calcimimetics for severe secondary hyperparathyroidism
A case report

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Abstract. Secondary hyperparathyroidism (SHPT) leads to bone disorders and cardiovascular complications in long-term dialysis patients. SHPT is caused by hyperphosphatemia. Abnormalities of calcium-sensing receptor (CaSR) are associated with the pathogenesis of SHPT. Clinical trials have shown that calcimimetics significantly reduce the risks of parathyroidectomy, bone fracture and cardiovascular hospitalization among long-term dialysis patients with SHPT. Etelcalcetide, a novel calcimimetic compound, acts as a direct CaSR agonist, restores the sensitivity of the CaSR in parathyroid cells, and decreases serum parathyroid hormone without inducing hypercalcemia or hyperphosphatemia. Etelcalcetide's properties allow it to be administered intravenously thrice weekly at the end of a hemodialysis treatment session improving medication adherence.

Keywords: mineral and bone disorders, chronic kidney disease, secondary hyperparathyroidism, PTH, hemodialysis, calcimimetics, etelcalcetide.

Delayed phosphate elimination due to decreased glomerular filtration rate (GFR) and deficiency of the hormonal form of vitamin D are the leading mechanisms of bone mineral disorders in patients with chronic kidney disease (CKD-MBD), which contributes to the development of hypocalcemia, partially associated with this deficiency, as well as hyperphosphatemia [1]. The production of parathyroid hormone also increases, since receptors responsible for it are also located on the surface of the parathyroid glands (PTH), its physiological role is to maintain normal calcium levels by activating osteoclasts and leaching calcium from bone tissue, which is a reservoir of this cation. Over time, an increasing need for parathyroid hormone begins to arise and the so-called renal bone disease develops which is the most noticeable manifestation of secondary hyperparathyroidism (SHPT). Calcitriol production decreases in the earliest stages of CKD, which also provokes an increase in parathyroid hormone. Undoubtedly, this process is of an adaptive nature at the beginning, but over time it acquires the features of maladjustment. The synthesis of the hormonally active form of vitamin D is also inhibited by the action of fibroblast growth factor 23 (FGF-23) [2]. The progressive decrease in GFR leads to hyperphosphatemia, which triggers the activation of a specific bone phosphate sensor responsible for the induction of FGF-23, the most powerful phosphatonin, that is, a factor that inhibits renal phosphorus reabsorption. FGF-23 is a connecting link between the intestine (reduces the absorption of phosphates and calcium), bone and kidneys (causes hyperphosphaturia and inhibition of 1′-hydroxylase) in phosphorus homeostasis. Due to the action of this factor, the concentration of phosphorus and calcium can remain normal for a long time until the first case of the end-stage renal failure (ESRD). Thus, the modern scheme of CKD-MBD pathogenesis is phosphate-centric.

Bone is a living organ that is constantly being renewed. The activity of bone resorption is regulated by parathyroid hormone. With parathyroid hormone deficiency, e.g., after removal of the parathyroid gland or with age-related involution, adynamic bone disease, a form of renal osteodystrophy with a low rate of bone metabolism, may develop. With SHPT, bone renewal occurs very quickly, as a result of which the organic matrix does not have time to be synthesized, on the basis of which the mineralization process takes place. Resorption cavities are filled with connective tissue and fibrous osteitis develops. As a result, a disordered bone structure with impaired mechanical properties is formed, while the "amount" of bone in the volume is usually normal or sometimes increased, and in rare cases osteoporosis is observed. As a result, the strength of the bone decreases due to the failure of the connection between the trabeculae.

The clinical consequences of SHPT are pathological fractures, the surgical management of which is associated with significant difficulties [3], and ectopic calcification (calcification of the heart and blood vessels). Both intimal and media calcific sclerosis lead to thrombosis or rupture of blood vessels in vital organs, significantly increasing the risk of critical cardiovascular complications in patients with chronic renal failure [4]. On the other hand, impaired compliance of the vessel wall leads to hypertrophy of the left ventricular myocardium and the development of heart failure. In 2006, the concept of CKD-MBD was formulated, which includes three groups of factors: laboratory abnormalities, bone disorders, and calcification of the heart and blood vessels, the combination of which significantly worsens the prognosis of dialysis treatment [5].

With a long-term SHPT, the developing parathyroid hyperplasia stimulates progression of the disease, and every third patient with 20 years of dialysis needs parathyroidectomy. Radiography is one of the first methods that made it possible to identify changes in bone structures during the development of the pathological condition. X-ray examination makes it possible to detect such a typical manifestation of SHPT as the formation of cysts, and to visually determine focal destructive changes, but this method allows to assess the decrease in bone density only with a decrease in bone mass by 25–40%, not to mention the possibility of quantitatively assessing the loss of calcium in bones. Currently, X-ray diagnostics is not considered as the main method for diagnosing SHPT, but it can be useful due to the lack of densitometric equipment, CT, and other necessary methods.

One of the simplest and most affordable methods for detecting changes in bone densitometric density is dual-energy X-ray absorptiometry. The advantages of this method are as follows: non-invasiveness, fast obtaining of measurement results, relative safety with minimal health risk, high accuracy and reproducibility of quantitative analysis; the patient does not need to actively participate in the examination [6].

Current clinical guidelines for CKD-MBD treatment include [11]:

- control of bloom calcium levels — consumption with food, therapy with vitamin D or its synthetic analogues of selective action, dialysis fluid with a medium calcium content;
- control of phosphate levels — restriction of consumption with food (primarily refusal of inorganic phosphorus derivatives), use of phosphate binders (containing/not containing calcium), adequate hemodialysis;
- control of the level of parathyroid hormone within target range — calcimimetics and their combination, parathyroidectomy.

In contrast to non-selective vitamin D preparations, calcimimetics suppress the secretion of parathyroid hormone, while simultaneously lowering the level of calcium and sometimes phosphorus. For this group of drugs, resent research provides strong evidence for a decrease in the severity of uremic osteodystrophy and the need for parathyroidectomy, as well as a decrease in the frequency of fractures and cardiovascular complications [7, 8]. Nevertheless, side effects, mainly nausea and vomiting, limit the patient's adherence to treatment and effectiveness of the therapy. In 2016, a second-generation calcimimetic was registered in Russia - etelcalcetide, which is not inferior in effectiveness to cinacalcet and is characterized by better tolerance [9, 10]. The key feature of the drug is the intravenous dosage form. The parenteral route of its administration excludes the factor of patient adherence to treatment.

Clinical case. We present a clinical observation of patient M., born in 1978, with end-stage kidney failure caused by chronic mixed glomerulonephritis. Programmed hemodialysis has been performed since 2016.

In 2017, severe SHPT was diagnosed. Started taking sevelamer (800 mg, 3 times a day).

In 2018, adenomas of the parathyroid gland were identified.

Conclusion of ultrasound examination: in the projection of the parathyroid gland on the right, a rounded hypoechoic formation with clear contours measuring 6×8 mm was identified; in the projection of the parathyroid gland on the left, a heterogeneous hypoechoic formation with clear contours measuring 26×19 mm was identified. Phosphate binder treatment was discontinued by the patient on his own due to dyspeptic symptoms.

In early January 2019, they suffered a closed fracture of the left femoral neck with displacement of fragments and a fracture of the 9th rib on the left. Surgical treatment was performed — total cementless arthroplasty

In contrast to non-selective vitamin D preparations, calcimimetics suppress the secretion of parathyroid hormone, while simultaneously lowering the level of calcium and sometimes phosphorus

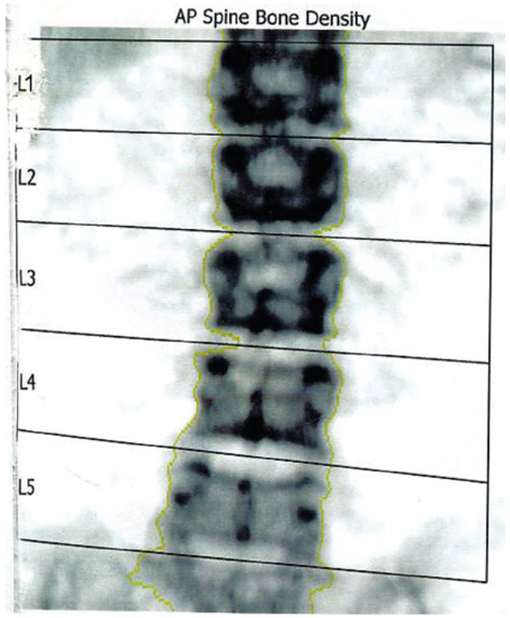

Fig. 1. Densitometric image of the lumbar spine (Lunar Prodigy scanner, GE)

of the left hip joint with the Biomet endoprosthesis. At the end of January, they suffered a closed fracture of the right femur neck with displacement of fragments and a spontaneous fracture of the right clavicle. Surgical treatment was performed — single-pole bipolar cement arthroplasty of the right hip joint with the Zimmer endoprosthesis. X-ray osteodensitometry from 31.01.2019: bone mineral density (BMD) in the proximal right femur was 0.661 g/cm, Z-score — 2.3 SD, which is lower than the expected deviation for this age. BMD in the distal part of the right forearm as a whole was 0.531 g/cm, Z-score — 3.4 SD, which is lower than the expected deviation for this age. Laboratory signs of severe SHPT in the framework of CKD-MBD were revealed: the level of parathyroid hormone was 2820 picogram /ml, hypercalcemia — 2.72 mmol/l, hyperphosphatemia — 2.09 mmol/l. X-ray osteodensitometry from 25.09.2019: BMD in the lumbar spine at the L2–L4 level was 68% of the peak bone mass and 74% of the population norm; Z-score — 2.4 SD, which is consistent with the lower bound of osteopenia. The maximum negative values were found in the L4 vertebra, Z-score — 2.7 SD, which corresponds to osteoporosis with a high risk of fractures (Fig. 1).

The patient refused the repeatedly offered surgical treatment for adenomas of the parathyroid gland. Drug therapy with cinacalcet was started, which was accompanied by dyspeptic symptoms, which forced the patient to interrupt drug therapy. From May 2019, treatment with intravenous calcimimetic etelcalcetide was started at a dose of 5 mg (3 times a week) at the end of each hemodialysis, with a gradual increase in the dose to a maximum of 15 mg (3 times a week). Since July 2019, a decrease in the concentration of parathyroid hormone has been revealed, in August 2019 its level was 1810 picogram/ml, and by 2020 it reached 805 picogram/ml, while the concentration of serum calcium stabilized at 2.47 mmol/l, phosphorus — 1.62 mmol/l. Fractures did not recur, signs of extraosseous calcification were not documented.

Conclusion. Despite the presence of obvious indications for surgical treatment of SHPT, the use of calcimimetics can increase the sensitivity of the parathyroid gland to the regulatory effect of calcium ions, thereby reducing the level of parathyroid hormone and reducing the risk of low-energy fractures. The parenteral route of administration allows to control drug dosage and the effectiveness of the treatment, even in case of low adherence to treatment.

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Potential predictors of the immunotherapy effectiveness

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Abstract. The development of novel predictors of immunotherapy efficacy is a clinically important and rapidly developing area. The currently existing predictors (PD-L1, MSI tumor status) do not always guarantee a positive treatment result. In addition, performing these analyses is characterized by the complexity, high cost, and long execution period. Thus, identifying potential new biomarkers in peripheral blood, which would be more accurate and accessible from a technical and economic point of view, is of great interest and is the object of active research. The article is a literature review of the currently available studies written worldwide on the topic of potential markers of the immunotherapy effectiveness. The most interesting and promising studies with intermediate conclusions are presented. We highlighted a number of clinical studies on the use of various assays and platforms for monitoring peripheral immune status. These studies point to the usefulness of these biomarkers as potential prognostic indicators.

Keywords: immunotherapy, predictors, immunity control points, interleukin-6 (IL-6), interleukin-18 (IL-18), interferon-gamma (IFNγ).

Cancer immunotherapy is one of the most complex and rapidly developing areas of oncology in recent years. This direction studies the essence and features of the formation of antitumoral immune protection, starting from the processes of recognition and identification of tumor antigens to the molecular cellular mechanisms of "escaping" tumor cells from the immune response. Currently, it is known that the interaction between the cells of the immune system and the tumor is a delicate balance between the processes of immune activation and immune suppression, the violation of which in one direction or another suggests the corresponding course of the disease. The interaction of direct participants in the immune response process — tumor cells, their antigens and cells of the host body's immune system, their humoral innate and adaptive factors—occurs in the microenvironment, which is formed as a result of processes occurring between the tumor cell and different types of surrounding cells, such as infiltrating immune, endothelial and stromal cells. The main role in possible interaction of the above elements of the immune response system in the tumor microenvironment is assigned to cellular receptors located on immunocompetent cells, with the direct primary participation of extracellular signaling molecules — chemokines, cytokines, adhesion molecules, growth factors and metabolic regulators.

Since the 2000s, a number of foreign authors have developed the 3E concept, which included three stages of the interaction between the immune system and tumor progression (Fig. 1). Notably, the main components guaranteeing the interaction of the tumor and the immune system were the cell cooperation of transformed tumor cells and a sufficiently large number of immunocompetent cells of the innate and adaptive immune system, providing protection of the body with a set of specialized immune response mechanisms [22]. It was determined that the carcinogenesis process in the human body goes through three phases: elimination, or observation of the immune system for the occurrence of cancer; equilibrium, or cancer persistence; escape, or cancer progression.

It became clear which cells of the immune system are involved in this process. But as it turned out, that the mechanisms of the cellular immune response may be different for different tumors, and this required in the following years to devote considerable time to studying the types of tumors and the features of cellular and intercellular interaction both between immunocompetent cells and between tumor cells and cells of the immune system. The role of signaling molecules in the tumor process is currently being studied. At the same time, it has become clear that the impact on the control points (activation and suppressor) of immunity is a key moment in the therapy of tumors.

The study of the above-described processes and the understanding of the ways of immunoregulation, the mechanisms of escaping from immune surveillance allows us to identify and implement new therapeutic approaches to ensure modern strategies for the treatment of oncological diseases. In fact, over the past few years, immunotherapy has revolutionized the treatment of patients with malignant solid tumors, significantly improving its results. The multiple increase in the number of patients with a widespread tumor process and long-term responses, as well as the achievement of remission of the disease in some of them, strengthened the position of this treatment type in the clinical recommendations of the world's main oncological communities.

At the same time, the existing predictors of the efficiency of immunotherapy with checkpoint inhibitors (PD-L1, MSI-tumor status) do not always correctly predict the result of treatment and are derived from the analysis of only one participant in the immune response system. Furthermore, the complexity, high price and long deadlines for performing these analyses, combined with the above, lead to the fact that the detection of potential new biomarkers that would be more accurate and accessible from a technical and economic point of view, is of great interest and is the object of active research.

We assume that in the antitumor immune response, not only the characteristics of the tumor tissue are important, but also various extracellular signaling molecules described above, as well as populations of innate and adaptive immune cells that are heterogeneous and contain both cells with antitumor activity and regulatory cells that promote tumor progression. A considerable number of clinical studies have demonstrated a significant relationship between the number of certain populations of immunocompetent cells in the tumor microenvironment and peripheral blood with a total life expectancy and the duration of a relapse-free period in patients with malignant neoplasms. Hence, in this review, we have tried to pay attention to the most interesting works devoted to the identification of new predictors of the immunotherapy efficiency in peripheral blood.

Initially, many studies on this topic studied changes in routine blood parameters during immunotherapy, since these markers are often obtained during routine clinical care and they do not require additional costs. For instance, some researchers have studied the role of lactate dehydrogenase (LDH) in patients with non-small cell lung cancer and skin melanoma treated with nivolumab or pembrolizumab, and have shown that elevated LDH levels at baseline correlate with a low level of response to immunotherapy [1, 14].

Some authors claim that high levels of eosinophils and low levels of neutrophils before starting treatment with ipilimumab or pembrolizumab are associated with an improved response to immunotherapy in pa-

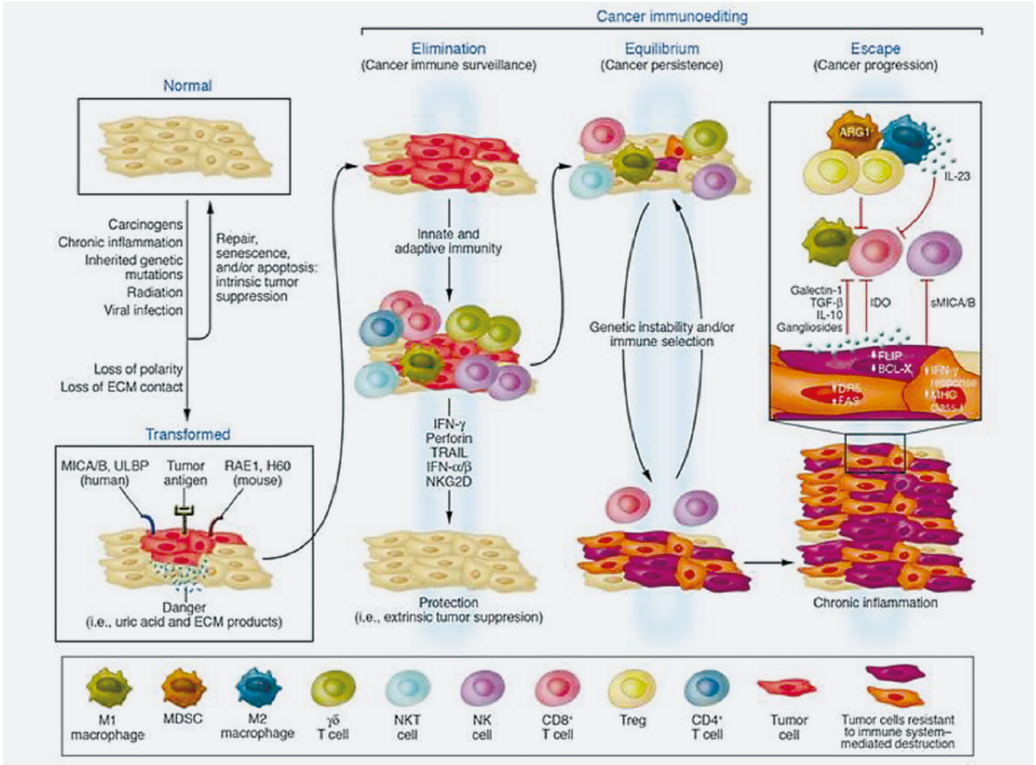

Fig. 1. Three phases in the cancer immunoediting process

tients with melanoma [2, 20]. Then, Nakaya A. and colleagues revealed a relationship between neutrophil to lymphocyte ratio (NLR) and prognosis of patients in a retrospective analysis of 101 patients with small cell lung cancer treated with nivolumab: median progression-free survival (PFS) in patients with NLR<3 before treatment was 3.4 months, whereas in patients with NLR≥3 it was 2.9 months (p=0.484) [10].

The improvement of laboratory immunochemical technologies, the development of flow cytometry and the further search for clinically useful markers led to a quantitative analysis of the composition and functional properties of immunocompetent cells and the role of signaling molecules, primarily cytokines, in peripheral blood in patients receiving immunotherapy. It turned out that in the future, some of the indicators or their ratios may be useful both in diagnosis and monitoring, and as predictors of the response to therapy. In particular, the researchers' attention was attracted by a heterogeneous population of immature myeloid cells, which under pathological conditions (tumor process) acquire immunosuppressive properties — suppressor cells of myeloid origin, or myeloid-derived suppressor cells, MDSC.

Thus, a study of patients with advanced melanoma (n=209) treated with ipilimumab showed that initially low LDH, absolute number of monocytes and MDSC, high values of the absolute number of eosinophils, relative number of lymphocytes correlated with an improvement in overall survival [9]. Retseck J. and colleagues studied the same MDSC and T-regulatory cells in patients with stage III B/C melanoma (n=35) who received ipilimumab after surgery [5, 11, 13]. The study showed similar results: lower baseline levels of T-regulatory cells and MDSCs are associated with higher relapse-free survival.

Tietze J. and the colleagues came to the conclusion that the baseline level of cytotoxic CD45RO+CD8+ T-cells is a promising factor as a biomarker of the effectiveness of treatment with ipilimumab for advanced skin melanoma [19]. In their study, patients (n=30) with normal baseline levels of CD45RO+CD8+ T-cells were significantly more likely to respond to treatment with ipilimumab.

An interesting work was presented by Nonomura Y. and colleagues [12], showing that an early increase in the number of T-helper cells — Th9 subpopulation producing intracellular interleukin-9 (IL-9) during treatment with nivolumab was associated with an improved clinical response in patients with metastatic melanoma.

The presence of a correlation between interleukin levels, their ratios and various conditions in patients with solid tumors indicates a significant role of cytokines in the complex relationship between the tumor and the immune system in this category of patients [15]. It is noteworthy that in the face of the current COVID-19 pandemic, many publications have been devoted to the phenomenon of a cytokine storm, which, by the way, also occurs as part of the immune response to a tumor — this is indicated by the appearance of "ground glass opacity" in the lung tissue, characteristic not only for COVID-19, but also for immune-mediated pneumonitis against the background of checkpoint inhibitor therapy, and an increase in the levels of various kinds of cytokines in the peripheral blood, for example, IL-6. In point of fact, a large number of reports have shown the potential usefulness of a variety of soluble blood factors, such as transforming growth factor beta 1 (TGF-'1), IL-6, IL-8 and IL-10 as predictors of the effectiveness of immunotherapy [7, 8, 16, 18]. Elevated serum levels of interferon gamma (IFNy) and IL-18, as well as reduced levels of IL-6, were associated with a positive effect from the treatment of malignancies of various localizations with an antibody against PD-L1 (MPDL3280A) [6].

Sayapina M. and colleagues [17]in the search for potential markers of the immune system, allowing to judge the efficiency of nivolumab therapy in patients with metastatic renal cell carcinoma (n=20), found that factors with positive effect on progression-free survival, are the initial levels of IL-17A and soluble forms of the receptor PD-1 (sPD-1) in serum, the source exceeds the threshold. Plus, the researchers found that a negative prognostic factor during immunotherapy was an initially increased concentration of TGF-β1 in the blood serum compared to the threshold level (20 ng/ml).

Similar results were obtained by Zhou J. and colleagues when studying changes in the concentration of the soluble PD-1 receptor in the blood of patients with metastatic melanoma during treatment with ipilimumab: high concentrations of sPD-L1 before treatment were associated with rapid progression of the disease. However, an increase in sPD-L1 after 5 months of treatment correlated with partial responses to treatment[21].

Di Noia V. and colleagues in their study [3]analyzed serum amyloid A (SAA) level as a predictor of efficacy in patients with advanced non-small cell lung cancer treated with pembrolizumab. The initial indicator of SAA ≤ the threshold value of 29.9 mg/l was significantly associated with higher RR (53.6 vs. 7.1%; OR 15.95% CI 1.72–130.7; p=0.009), longer PFS (17.4 vs. 2.1 months; p<0.0001) and OS (not achieved compared to 7.2 months; p<0.0001) compared to patients who had higher SAA levels.

A very interesting preliminary data was obtained by a group of researchers led by Simoni Y. [23], which consists in the fact that patients with tumors without EGFR mutations and having a high density of CD8+ T-cells in the tumor microenvironment respond better to treatment with pembrolizumab.

A considerable analysis of 262 patients with metastatic melanoma treated with ipilimumab was performed by Hannani D. and colleagues[4], having established that the initial serum concentrations of soluble CD25+ (sCD25) were an independent indicator of overall survival, and high levels of sCD25 were associated with resistance to therapy. Based on this study, the authors announced the first immunologically significant biomarker predicting resistance to CTLA-4 block (CD152) in patients with melanoma.

Petitprez F. and colleagues, deeply studying soft tissue sarcomas, identified a subgroup of patients with tumors of this localization, especially those rich in B-cells [24]. This group demonstrated improved survival and the best response to pembrolizumab therapy in phase 2 clinical trials.

Conclusion. Thus, given the complexity of the pathogenesis of malignant formations and the not fully clear relationship between different forms of the tumor and the human immune system, it is still impossible to fully predict the response when using immune checkpoint inhibitors. The current immunotherapy effectiveness predictors are insufficient for accurate diagnosis, monitoring and predicting the response to therapy for all patients with solid tumors.

The search for immunotherapy effectiveness predictors is a clinically important and rapidly developing area. The clinical studies highlighted in our review using various analyzes and platforms for monitoring the peripheral composition of the cellular component of the immune system indicate the usefulness of examining checkpoint data on immunocompetent cells as potential prognostic indicators. It is even more difficult to examine the tissues of solid tumors to detect the number and functional activity of localized immunocompetent cells.

The number of publications on this topic continues to increase from year to year. Nevertheless, it is extremely important not only to evaluate the composition and functional properties of cells of the immune system, but to determine the threshold levels for the diagnosis and for methods unification when determining these predictors. In addition, the clinical implementation of laboratory immunological research data based on the analysis of the composition and functional properties of immunocompetent cells and the levels of signaling molecules in peripheral blood will require a large-scale prospective verification.

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