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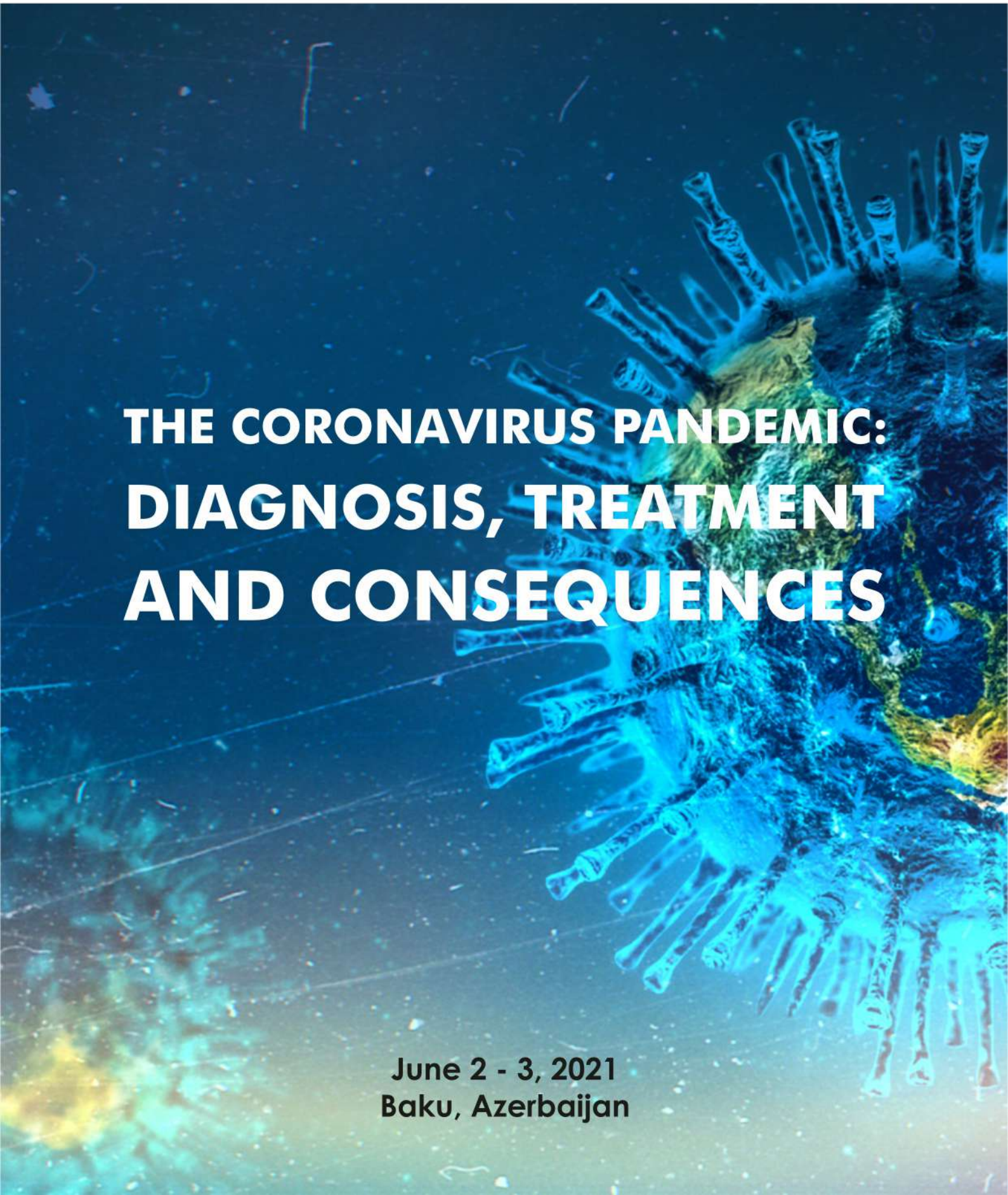

# THE CORONAVIRUS PANDEMIC: DIAGNOSIS, TREATMENT AND CONSEQUENCES

June 2 - 3, 2021
Baku, Azerbaijan

# THE SECOND EURASIAN CONFERENCE

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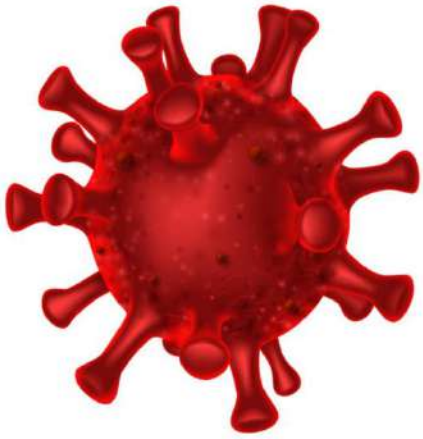

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Prof. Dr. Vugar Aliyev (Editor)

*Proceedings of the Second Eurasian Conference*

# *The Coronavirus Pandemic:*

# *Diagnosis, Treatment and Consequences*

*PANDEMIC-2021 (June 2 – 3, 2021, ROYAL HOTEL, Baku, AZERBAIJAN )*

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The Coronavirus Pandemic: Diagnosis, Treatment and Consequences
June 2 – 3, 2021

*Editor*
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Director of the International Event Organizer Company
AMIR Technical Services LLC

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# About PANDEMIC – 2021

The Second Eurasian Conference “Coronavirus Pandemic: Diagnosis, Treatment and Consequences” will be held on June 2 – 3, 2021, in Baku, AZERBAIJAN.

The relevance of the conference is beyond doubt. The devastating impact of the COVID-19 pandemic has become a truly serious test for the entire global community. The spread of COVID-19 and its mutants has long passed from the category of "the most significant challenge to the resilience of public health systems" into a threat to all spheres of human activity. In the fight against the growing threat, almost all countries of the world have chosen the path of isolation from the outside world.

The main goal of the conference is to spread “know-how” knowledge and technologies in diagnostics, emergency medical care, treatment, vaccination and innovative approaches in the prevention of coronavirus infection.

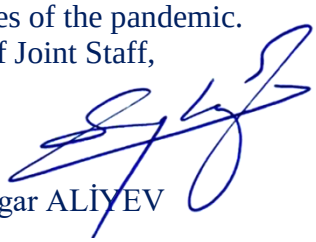
We intend to analyze and summarize the lessons of the COVID-19 pandemic, discuss the effects and "challenges" that it poses for national health systems and government institutions.

The conference program is expected to discuss the optimal strategy for overcoming the pandemic, which is better: natural immunity or vaccination?

We call on all stakeholders to actively participate in the conference, share experience and knowledge, and contribute to the common cause of sustainable development of the Eurasian continent in the face of the risk of the coronavirus pandemic.

It is symbolic that we will meet on the hospitable land of Azerbaijan - a beautiful ancient country at the junction of Europe and Asia, which leaves its mark in the heart of everyone who has been here at least once. A special cultural program has been prepared for the conference participants. We hope that universal vaccination will help defeat the coronavirus and we will gather in Baku and discuss new challenges, innovative solutions and the possible consequences of the pandemic.

On behalf of Joint Staff,



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# EXPERIENCE OF FOLLOW-UP MONITORING OF COVID-19 CONVALESCENTS (LONG COVID SYNDROME)

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**Abstract:** Various clinical scenarios of the course of the post-COVID syndrome in the period of convalescence were studied. The frequency and volume of studies in combined pathology in patients who have undergone COVID-19 are considered. The controlled indicators of the medical state within the framework of follow-up monitoring and the minimum frequency of follow-up visits were clarified.

**Key words:** New coronavirus infection, convalescents, the long COVID syndrome, follow-up monitoring

**Introduction.** In the world as of April 22, 2021, the World Health Organization (WHO) registered 143 184 614 confirmed cases of COVID-19, in 223 states and territories of the world [1], 82 199 239 people recovered [2]. The number of cases in Russia exceeded 4.7 million, more than 4.343,229 million patients recovered [3]. To date, COVID-19 has been recognized as a multi-organ disease with a wide range of manifestations [4, 5], and WHO has obtained factual data on the presence of persistent symptoms in COVID-19 convalescents (fatigue, chronic cough and exercise intolerance, cognitive impairment, arthralgia and decreased quality life [6, 7, 8]) and / or delayed or long-term complications after 12 weeks from the onset of the disease not associated with alternative diagnoses ("post-coronavirus syndrome") [4, 9].

Observational cohort studies [8, 10] showed that in the United States of 1250 patients discharged alive, after 60 days, 32.6% reported persistent symptoms, including 18.9% about the appearance of new or progression of existing ones [10], and in China [8], when examining 1733 patients after 6 months, 76% noted the presence of at least one symptom. That is why, the organization of systematic monitoring of patients who have undergone COVID-19 is of particular importance. The collection and analysis of data related to possible long-term risks in patients who have undergone COVID-19 should help to make a prognosis of the disease and the choice of tactics for their management during the period of convalescence, which emphasizes the relevance of the chosen research topic.

**Purpose**: to determine the changes that occur during the period of convalescence, the immediate and long-term prognosis in patients who have undergone COVID-19, and to form an optimal scientifically grounded system of measures to improve dispensary observation for such patients (including the duration of observation, frequency and examination standards) and optimization of personalized therapy of concomitant diseases, to increase adherence to therapy and reduce the risk of complications and adverse outcomes.

**Characteristics of the study.** A prospective observational study has been conducted on the basis of the Center for Medical Prevention "IIPM - Branch of the IC&G SB RAS" since 2020, in accordance with the National Standards of the Russian Federation GOST-R 52379-2005 "Good Clinical Practice" (ICH E6 GCP), with mandatory observance ethical principles set out in the 1975 Declaration of Helsinki (as amended in 1983) and obtaining informed consent from patients. The study was approved by the Local Ethics Committee (Protocol No. 23, dated May 26, 2020).

*Study design* - sequential enrollment of patients 12-16 weeks after the onset of the first symptoms. Sample capacity: 300 people. - the main group (underwent COVID-19 complicated by pneumonia), comparison group 1 - 300 people who underwent uncomplicated COVID-19, comparison group 2 - 300 people (asymptomatic carriers of COVID-19), 300 people - control group (non-COVID-19 pneumonia convalescents).

*Inclusion criteria*:

1. Signing informed consent to participate in the study.

2. Reconvalescents: COVID-2019 (with code U07.1 or U07.2) over 18 years old or pneumonia (not COVID-2019) over 18 years old.

3. Ability to understand and comply with the requirements of the research protocol.

4. Absence of contraindications to the diagnostic procedures stipulated by the research protocol.

*Criteria for premature exclusion*: Refusal to further participate in the study.

The duration of observation within the framework of the protocol is 18 months, with the possibility of extension based on the results of a preliminary analysis of the data obtained.

Supervised in 2020-2021 (pilot project) there were 141 COVID-2019 convalescents aged 28 to 72 years, with an average age of 53.22 years. The diagnosis of COVID-2019 was considered verified in the presence of a positive laboratory test for SARS-CoV-2 RNA (using nucleic acid amplification methods) or SARS-CoV-2 antigen (using immunochromatographic analysis), regardless of clinical manifestations [11] and / or antibodies of the IgA, IgM and / or IgG class in patients with clinically confirmed infection with COVID-19 [12].

Research methods: The subjective severity of sleep disorder symptoms was determined using the ISI-20, calculated using a questionnaire consisting of 7 items, assessed on a Likert scale from 0 to 4 points [13]. General and / or mental weakness, increased exhaustion, irritability, decreased productivity of mental processes, sleep disorders, physical weakness and other autonomic-somatic disorders were identified using the MFI-20 questionnaire [14], taking into account subscales: general asthenia, decreased activity, decreased motivation , physical asthenia, mental asthenia. The level of anxiety and depression (express screening) was assessed on the basis of answers to 14 questions (with 4 answers) in the hospital. scale of anxiety and depression (HADS) [15], with the sum of points in each part (anxiety and depression) more than 7, an in-depth examination by a psychotherapist was carried out. When conducting an extended neuropsychological examination, tests of "verbal associations", "symbolic-digital coding" [16], drawing of a clock [17], and functional deficit — a questionnaire of functional activity [18] were used to identify cognitive impairments.

The relative cardiovascular risk in convalescents aged 18 to 40, inclusive, was assessed on the SCORE scale, while in the presence of cardiovascular diseases of atherosclerotic genesis, type 2 diabetes mellitus and chronic kidney diseases, the risk level on the SCORE scale was not determined and was assessed as very tall; The absolute cardiovascular risk was determined in subjects over the age of 40.

Exercise tolerance was analyzed using the Borg Scale [19], the dynamics and severity of dyspnea were analyzed using the MRC (shortness of breath) [20], BDI and TDI [21, 22] scales. The quality of life was assessed according to the results of the EQ-5D-3L quality of life questionnaire [23].

On examination, blood pressure (BP) was measured three times with an interval of two minutes on the right arm in a sitting position after a 5-minute rest using an Omron M5-I automatic tonometer with recording the mean of three measurements. We found out whether the patients had a previously elevated blood pressure and information about taking antihypertensive drugs during the last two weeks. Persons with previously diagnosed arterial hypertension (AH), but with normotensiveness during examination (in cases of taking antihypertensive drugs), were also counted as patients with AH. The body weight was measured with an accuracy of 0.1 kg on a VMEN-150-50/100-D-A-«Norm-4» electronic medical scale with a REP-1 stadiometer.

Blood for biochemical and molecular genetic studies was taken by venipuncture using fasting vacutainers after 12 hours of abstinence from food. The content of triglycerides, high-density lipoprotein cholesterol, total cholesterol, blood glucose, alanine aminotransferase, aspartate aminotransferase was determined by enzymatic methods on an automatic biochemical analyzer Kone Lab Prime 30i. Blood centrifugation was performed on a CM-6M Elmi centrifuge. Genomic DNA was isolated from venous blood leukocytes by phenol-chloroform extraction; its quality was assessed using an Agilent 2100 Bioanalyzer capillary electrophoresis system (Agilent Technologies Inc.). DNA is stored in the BioBank IIPM - Branch of the IC&G SB RAS. Molecular genetic research was performed using high-throughput sequencing methods, the interpretation of the data obtained was carried out in accordance with the recommendations of the American College of Medical Genetics and Genomics. The study of the indicators of the hemostasis system was carried out using the hemolysate-aggregation test in the modification according to L.Z. Barkagan, B.F. Arkhipov, V.M. Kuchersky (1980) [24], indicators of leukocyte-platelet aggregation modified by A.A. Gromov, (1986), (principle of Arkhipov B.F., Subach V.I.) [24], fibrinogen, prothrombin index. The electrical and viscoelastic parameters of erythrocytes obtained from the whole venous blood of patients were studied by dielectrophoresis in an inhomogeneous alternating electric field using an electro-optical cell detection system [25].

A comprehensive approach that allows to reliably evaluate information about the presence and nature of long COVID syndrome included a study of respiratory function with a bronchodilation test on a Microlab spirometer, an assessment of the risk of developing nocturnal hypoxia, obstructive or central apnea-syndrome (screening study of nocturnal computed pulse oximetry on a PulseOx 7500 SPO Medical): with an increase in the desaturation index to 5 per hour, a computer night somnography was performed (using a WatchPAT device, Itamar medicai).

Left ventricular function indicators (ejection fraction, end-diastolic and systolic volumes of the left ventricle) were measured by echocardiographic examination using the Vivid ultrasound diagnostic medical System (in the Vivid E95 version).

The structure, wall thickness, location of internal organs (liver, gallbladder, pancreas, kidneys, spleen, kidneys, ureters, adrenal glands) were assessed using a comprehensive study using the Vivid ultrasound diagnostic medical system. The degree of liver fibrosis was determined by indirect elastometry (FibroScan® 502 Echosens).

For the detection of irritable bowel syndrome, bacterial overgrowth syndrome, determination of intestinal transit time, intolerance to malabsorption of fructose, lactose, in real time GastroCheck Gastrolyzer, the levels of hydrogen (H2) and methane (CH4) in exhaled air were measured simultaneously.

Statistical data processing was carried out using Statistica, SPSS software. The data are presented as the median Me and [25; 75] percentiles.

**Results.** In 2020-2021 50 men and 91 women were under dispensary observation. The average age of men was 52.50 [41.75; 65.50] years, women - 52.70 [41.75; 65.00] years ($p > 0.05$).

12-16 weeks after the onset of the first symptoms of COVID-19, when filling out questionnaires and during examinations by specialists (pulmonologist, cardiologist, somnologist, neurologist, endocrinologist, therapist), 86.5% of patients reported having at least one of the symptoms. indicating mental weakness, increased exhaustion, irritability, decreased productivity of mental processes, sleep disorders, decreased physical performance, cognitive and other autonomic-somatic disorders. It was found that one of the most common problems leading to sleep disturbance was restless legs syndrome, which was found in 57.5% of the patients. The presence of comorbid pathology was associated with obstructive sleep apnea syndrome: in case of impaired carbohydrate metabolism, breathing disorders during sleep (mainly moderate or severe) were found in 85% of the observed, with concomitant arterial hypertension and diabetes mellitus - in 25.2% of cases. Of the entire spectrum of pulmonary manifestations, the most common and persistent symptom in COVID-19 convalescents was shortness of breath, both expiratory and mixed, which was noted in more than 40% of patients who had no history of respiratory pathology before the disease.

**Discussion.** The obtained data are similar to the results obtained by A. Carfi et al. (Italy) [6], who reported persistence of symptoms in 87.4% of patients who recovered from acute COVID-19 (with an average follow-up period of 60 days from the onset of the first symptom). Fatigue (53.1%), shortness of breath (43.4%), joint pain (27.3%) and chest pain (21.7%) were most common, with 55% of patients presenting with three or more symptoms [6]. Fatigue, shortness of breath and psychological disorders such as post-traumatic stress disorder, anxiety, depression, and impaired concentration and sleep were reported in more than 30% of study participants in France [26].

**Conclusion.** Clarification of the features of the course of comorbid pathology in COVID-19 convalescents, search for evidence of the risk of long COVID, gaining new knowledge in interdisciplinary collaboration on the management of such patients indicate the relevance of the WHO organization in 2021, a series of consultations aimed at reaching a consensus on the characteristics of this syndrome, its subtypes and agreement on the definition.

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# CURRENT ASPECTS OF HEALTH PROTECTION AND SAFETY OF MEDICAL WORKERS DURING THE COVID-19 PANDEMIC FROM THE POINT OF VIEW OF PROFESSIONAL RISKS

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**Abstract**. The health of medical workers is the basis of a high labor potential, an indicator of the level of culture, the most striking criterion for the effectiveness of public health management. At present, the health protection of medical workers is a national problem. The relevance of the topic is determined by the fact that the study of occupational health risks for doctors creates a new interdisciplinary problem field that has social significance from the point of view of the safety of the Institute of medicine and the health of the nation as a whole.

**Keywords**: health, health workers, pandemic, occupational risk

**Introduction**. In the XXI century, infectious diseases have become a major threat to public health worldwide, affecting both physical and mental health. Emerging as a group of unexplained cases of pneumonia in Wuhan, China, the new coronavirus disease, officially designated COVID-19, was declared a pandemic by the World Health Organization on March 11, 2020. One of the main strategies to combat the virus has become the isolation of people from each other. Health care providers who care for infected patients are at high risk of developing mental health problems and need government support.

A review of the available literature [1-3] demonstrated that most health care professionals were highly stressed and had high risks of adverse mental health outcomes during epidemics and pandemics, including the COVID-19 outbreak. Negative emotions and stress experienced by health care workers who treated infected patients were characterized as trigger events leading to errors and delays in care delivery. The main source of stress for caregivers is their work, especially in crisis situations. Long working hours, a large number of responsibilities, lack of a clear work assignment, insufficient organization, as well as the need to work in danger zones – all these are factors of work stress that medical workers can be exposed to [4,5]. Providing assistance, medical personnel constantly feel responsible for the safety of people and taking care of them.

Medical workers, performing their professional duties, are constantly exposed to the complex influence of unfavorable production factors. The main harmful factors of the production environment are biological, physical, chemical and psychoemotional. They have to work in conditions of air pollution in operating rooms with narcotic gases, in diagnostic rooms with scattered X-rays, in laboratories with constant contact with medicines, contaminated biological material, have contact with infectious patients at the reception. [6,7]. High workload, round-the-clock work with mandatory shifts, the risk of complications in the condition of patients, contact with dying patients, when the doctor does not see the positive results of his efforts to save the patient and often feels his own powerlessness, can be considered as factors that also have a negative impact on the overall psychoemotional health of medical workers [8, 9].

The occupational risk of medical workers can be considered in various aspects: socio-economic, medical and legal.

The socio-economic aspect of the professional risk of medical workers is the need to match the social significance of the tasks assigned to medical workers to the economic support of their activities. The problems associated with the financing of the healthcare industry have become chronic. Public health institutions are currently characterized by insufficient funding, low salaries of medical workers, and working conditions that do not correspond to modern achievements of medical science, while one of the main tasks of the social state is to take care of the health of the country's population**.**

The medical aspect of the professional risk of doctors is the increased danger of their work for their own health, which is due to various factors: unlike other categories of workers, doctors experience both the impact of unfavorable production factors (harmful working conditions), and increased psychological, emotional, physical and intellectual stress, since the object of their activity is the health of the patient.

The medical principle of the professional risk of doctors is the inadmissibility of reducing the professional ability to work. If representatives of other professions can count on a reduction in the rate of production, a reduction in the working day, etc., when their health condition worsens, then the legislation requires medical workers, regardless of their state of working capacity, to implement generally established standards for the diagnosis and treatment of patients. Of course, in this case, the relevant models provided for by the labor legislation can be applied (transfer to another job, creation of special working conditions, etc.). But their effectiveness, in our opinion, is not high enough.

The specificity of the object of medical activity determines the establishment of strict legal liability for professional offenses, which is manifested in the legal aspect of the professional risk of medical workers, which is associated with the peculiarities of the legal assessment of the performance of their professional duties.

Taking the oath of a doctor, a medical worker promises to be always ready to provide medical care to any person.

The main principle, which is reflected in both the legal and deontological norms of the relationship between medical professionals and the patient, is the priority of the rights and interests of the patient. It consists in the fact that the use of certain medical instruments and technologies is aimed at minimizing the risk to the patient, the protection of the doctor in such cases is secondary.

For a medical worker, the result of his activity is characterized by the effectiveness of providing medical care. This attitude determines the existence of such an ethical category as the “self-denial” of medical workers, which is expressed in the willingness of the doctor to sacrifice himself in the name of saving the lives of others.

The legal aspect of the professional risk of medical professionals is that usually the criminal liability of representatives of certain professional groups is established for committing illegal actions, violating certain rules of conduct (for example, violating the rules of traffic safety and operation of railway, air, sea or river transport).

In relation to medical workers, the article's disposition is formulated in such a way that their inaction under any circumstances (except for the presence of valid reasons) it is already a criminal offense.

The presence in the Criminal Code of a special provision providing for liability for failure to provide assistance to the patient, indicates the exceptional importance and value of the object of professional activity of medical workers. The fact that the criminal legislation does not establish such requirements for representatives of other professions allows us to distinguish medical workers from other professional categories. This once again underlines the special social significance of their profession.

In the current socio-economic situation, the occupational risk monitoring system is considered as a fundamental mechanism for the justification, development and selection of the order of implementation of management decisions aimed at optimizing labor and preserving the health and longevity of medical workers. In order to reduce the probability of losing a management decision, it is necessary to collect all available information, both primary and secondary [10, 11].

The quality of medical care, as well as any other complex and complex phenomenon, depends on various factors: the effectiveness of building a health system on the scale of the state, the availability of modern material and technical base of medical institutions, the possibility of using the latest scientific developments in the field of medicine and modern diagnostic equipment, the timely development of standards of medical care.

In the age of technological progress and outbreaks of previously unknown diseases, modern healthcare is characterized by the introduction of high-tech types of medical care, the expansion of the list of diagnostic procedures, new equipment, the computerization of workplaces, and of course medical prevention.

The ability of health systems to rapidly respond to the crisis by mobilizing health workers while maintaining essential, continuous services is both critical and challenging. The main measures include occupational safety and health, decent working conditions, psychological support for health workers, professional training and training for the rapid re-profiling of personnel and the admission of new health workers in accordance with the requirements of the health system [12, 13].

The most important condition for the successful implementation of the constitutional right to protect the health of the entire population is the activity of highly qualified medical personnel. The presence of these aspects illustrates the need for increased protection of this category of employees from occupational risks. To provide high-quality medical care, it is necessary to provide medical workers with favorable working and housing conditions, decent wages and protection from occupational risks. The effectiveness of the health system in protecting the health of the country's population is directly related to the health of the health workers themselves.

The governments of many countries around the world are taking a whole range of measures to reduce the spread of the virus among the population. Governments should consult with social partners on monitoring and regulating the work of temporary workers during a crisis, as appropriate. Governments must ensure that health professionals and novices are properly supervised and organized to ensure that they are all trained and have the relevant skills needed to deal with a pandemic.

Social dialogue is important not only for emergency preparedness, but also for improving the effectiveness of emergency response and coordination. It is necessary for the timely exchange of information and the resolution of issues such as the safety and health of health workers. The local response strategy of prevention and infection control methods is increasingly being used in countries to strengthen the response to COVID-19.

While these measures promise to provide the necessary medical care, they require a careful approach to implementation in practice, so that health workers are provided with the same level of protection as other workers. In addition to ensuring occupational safety and health, it is necessary to create other employment conditions for health workers, including social protection, remuneration, rest periods and working hours.

In addition to the Charter for the Safety of Health Workers, WHO, on the occasion of World Patient Safety Day 2020, also formulated specific goals for health system managers for the coming year in areas such as funding, statistics collection, and improving the safety of health workers [14].

“The COVID-19 pandemic has reminded us of the indispensable role of health workers in alleviating suffering and saving lives,” said WHO Director – General Tedros Adhanom Ghebreyesus. – “No country, hospital or medical institution can ensure the safety of patients if the safety of medical personnel is not ensured. The WHO Charter for the Safety of Health Workers is a step forward in ensuring that medical personnel are provided with safe working conditions, adequate training, decent pay and the respect they rightfully deserve.”

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# EPIDEMIOLOGY OF VIRAL HEPATITIS WITH PARENTERAL TRANSMISSION DURING THE SARS-COV-2 PANDEMIC

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**Abstract.** The article shows the analysis of long-term dynamics of acute viral hepatitis morbidity in the Republic of Kazakhstan and Karaganda region for 2010-2020, lists the main reasons of decrease of HBV morbidity, the average duration of hospitalization, mortality, the causes of HBV patient's infection of other patients, preferential drug provision to certain categories of citizens at the expense of budgets of different levels of funding.

**Key words**: viral hepatitis, morbidity, region, republic.

**Introduction**. Hepatitis B is a potentially life-threatening infectious liver disease caused by the hepatitis B virus (HBV). It is a serious public health problem worldwide. The infection can progress to a chronic form with a high risk of death from cirrhosis and liver cancer [1, 2]. The coronavirus pandemic complicates the fight against hepatitis worldwide. This was stated by the director general of the World Health Organization (WHO), Tedros Adanom Gebreyesus, on July 27, 2020. Hepatitis affects the liver and kills almost 900,000 people every year [3].

To date, there is no conclusive evidence that people living with hepatitis B or hepatitis C are at greater risk of contracting COVID-19 than others. However, they are more likely to develop serious complications if infection with COVID-19 has not been avoided. In particular, a history of hepatitis B or hepatitis C increases the likelihood of severe COVID-19 even if hepatitis has been successfully treated.

The new coronavirus has been found to penetrate the body's cells via angiotensin converting enzyme receptors (ACE-2). Such receptors are most abundant in lung cells, but they are also present in hepatic cells (hepatocytes) and in blood vessel cells of the liver. Thus, it is not excluded that the virus can affect liver cells directly [4].

**The aim of our study** was to assess the epidemiology of viral hepatitis with parenteral transmission during the SARS-COV-2 pandemic.

**Results and discussion**. Analysis of multiyear dynamics of acute viral hepatitis (CVH) morbidity in Kazakhstan and Karaganda region for 2010-2020 is shown in figure 1.

This figure shows uneven multiyear dynamics of acute viral hepatitis morbidity in both the Republic of Kazakhstan and Karaganda region for 2010-2020. In comparative analysis it is marked that level of morbidity in Republic decreased in 13,33 times from 30,67‰ in 2010 to 2,3‰ in 2020. In the region the reduction is more than 8.8 times from 18.52‰ in 2010 to 2.1‰ in 2020. Republican level of incidence of acute viral hepatitis in 2010 is 1.65 times higher than the regional one, but by 2020 almost the same indicators are registered. Every year both in the republic and in the region there is a decrease in the incidence rate. In 2014 and in 2018 insignificant rises of acute viral hepatitis in the country

and in the region were revealed. So in Kazakhstan the morbidity in these years was 5.92‰ and 5.82‰, in the region 6.62‰ and 10.73‰ respectively.

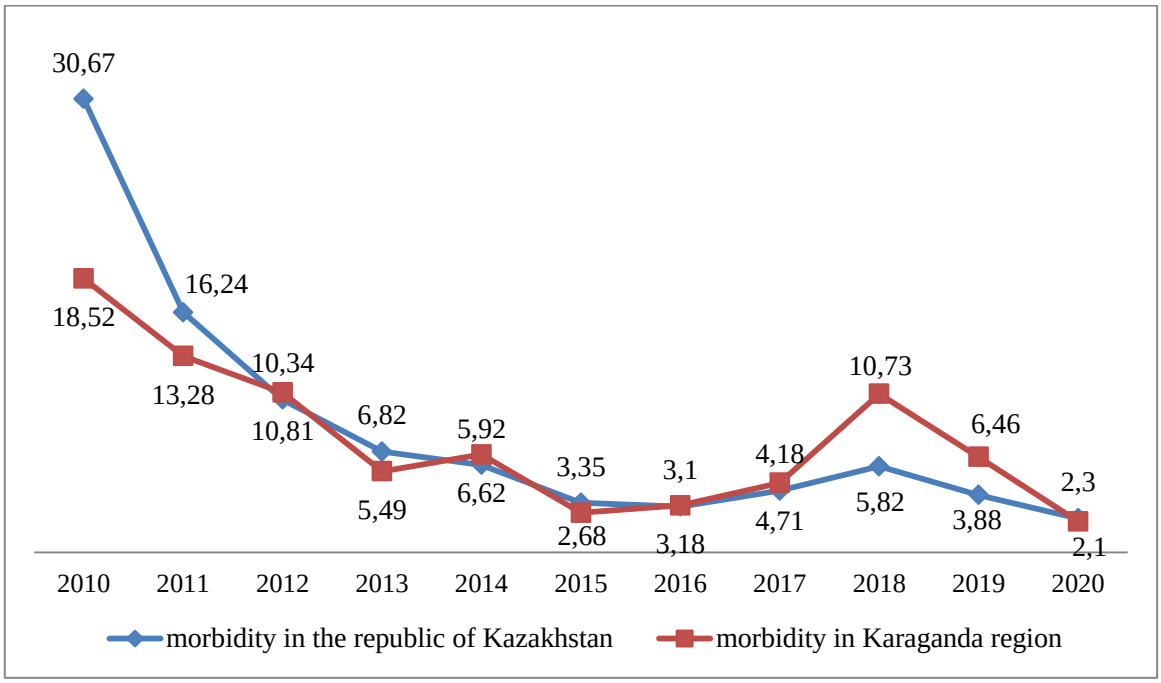


Figure 1. Multiyear dynamics of OIA incidence in Kazakhstan and Karaganda region for 2010-2020. (‰)

The main directions of changes in the intensity of the epidemic process in the long-term dynamics of morbidity of EVD both in the republic and in the oblast reflect its decrease. The epidemic trend of incidence of acute viral hepatitis in the republic was -8.8 and is regarded as a pronounced rate of decline. In the oblast scale the rate is -4.2 and is assessed as moderate to declining. Since 2010 in Kazakhstan and Karaganda region there is a synchronous decrease in the incidence of acute viral hepatitis.

In Kazakhstan, thanks to planned immunization against viral hepatitis B, over the past more than 20 years there has been a steady decline in the incidence of acute viral hepatitis B up to 59.8 times [5].

The decrease in the incidence of acute viral hepatitis is connected with the fact that within the framework of the Global Health Sector Strategy on Viral Hepatitis a number of measures are being prioritized - these are improvement of laboratory diagnosis of viral hepatitis and functioning of National Reference Hepatitis Laboratories, implementation of National External Quality Assessment Program for Viral Hepatitis; improvement of existing screening programs for early detection and treatment; increasing access to antiviral drugs; inclusion of regimens for re-treatment of patients with viral hepatitis in the state provision of free of charge medical care for patients (GOPMP); improvement of organization of infection control in medical institutions; conducting specific prevention of perinatal transmission of viral hepatitis B; strengthening of human resources capacity. Since 2011, hepatocabins and hepatocenters have been created and exist in all regions of the country, and in Kazakhstan preventive screening for detection of viral hepatitis B and C has been conducted for many years among the decreed population groups [5].

At the same time, the growth of newly detected chronic forms of viral hepatitis raises concerns. In Kazakhstan, more than 6 thousand cases of newly detected chronic viral hepatitis are registered annually. Of these, chronic viral hepatitis B accounts for 48%. At the same time the highest morbidity of chronic forms of viral hepatitis, about 87%, is registered in the age

group of 30 to 60 years old [5]. Hepatitis B "viral carrier" level in Kazakhstan and Karaganda region is characterized by significant fluctuations in indicators, which is associated with improvement of clinical and laboratory examination of HBsAg “carriers” and clarification of diagnoses of chronic liver lesion.

In 2019, 719 new cases of acute viral hepatitis and 6483 cases of chronic viral hepatitis were diagnosed in Kazakhstan. The average length of hospital treatment for infectious hepatitis patients increased by 11.7% in 2019 and 12.4% in 2018. Lethality was 0.8% in 2019 and 0.5% in 2018.

In Karaganda region, viral hepatitis B equally afflicted both men 46% and women 54%. Epidemiological anamnesis showed that 22.1% of patients associate their disease in with tooth extraction, 20.1% were infected during transfusion of donor blood, also causes of disease in anamnesis of patients are dental treatment, surgery, least of all people are infected while performing various cosmetic manipulations – 1.6% (Figure 2).

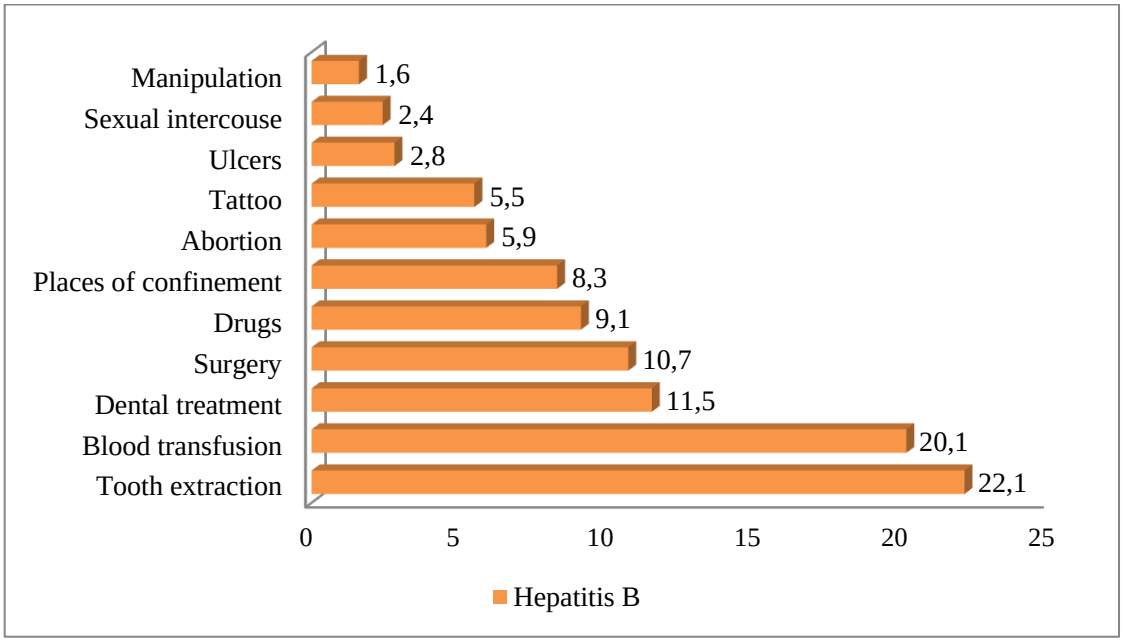


Figure 2. Main Causes of HBV Infection (%)

Analysis of the incidence of SARS-COV-2 among patients registered with HBV found that 1.97% of these patients had had a coronavirus infection with laboratory confirmation of the diagnosis by PCR. The course of the disease in all patients was severe, and it was also found that one patient had a concomitant disease of diabetes mellitus and another had HIV infection.

The state policy in the field of drug supply is an integral part of the policy in the health care system of the republic. One of directions of public health as branch is provision of the population with accessible, qualitative medical aid, and provision with medicines is considered as the component of medical care.

The provision of drugs to certain categories of citizens at the expense of budgets of various levels of financing of preferential drug provision is carried out at the expense of budgets of three levels: federal, regional and municipal budgets.

Drugs under the SGBP with HBV in Karaganda region began to be issued only since the end of 2017, it is the antiviral drug “Tenofovir”. It is noted that since 2017, the provision of drugs within the framework of SGBP is increasing every year. So, if in 2017 only 1.2% of patients received antiviral drugs, in 2020 20.2% of patients received them.

In the republic, since 2016, patients within the framework of SBSMP began to receive therapy for the first time with modern direct antiviral drugs, the effectiveness of which reaches 95-100%. To date, about 14,000 people have been provided with free antiviral therapy [5].

Thus, hepatitis B virus remains a topical problem in our country as well which demands further research and analysis, introduction of new preventive measures aimed at reduction of morbidity, complications and mortality.

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# COVID-19 AND TUBERCULOSIS CO-INFECTION: SIMILARITIES AND DIFFERENCES IN DIAGNOSIS

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**Abstract.** COVID-19 pandemic has represented a serious problem to global healthcare and economy. Presentation of the disease is highly variable. Tuberculosis, one of the top ten causes of mortality has a presentation conspicuously similar to the current SARSCoV-2 infection. The presentation of disease ranges from a mild cough, fever and sore throat to pneumonia, acute respiratory distress syndrome and death. We suggest proper tuberculosis screening, isolation of patient, remote tracking of suspected patients for symptoms during the current pandemic.

**Key words:** Tuberculosis, COVID-19, Co-infection

**Introduction.** The World Health Organization (WHO) estimated in 2019, 10 million tuberculosis (TB) cases with 1.6 million deaths worldwide. Patients with associated comorbidities are usually more vulnerable for a severe disease. As of 15th June 2020, 78 million people have been infected in 216 countries with case fatality rate of 5.52%. India has reported 13.7 million cases with 9520 deaths during the same time Lung is the most frequent TB localization, but any organ can be affected. Since 2020, Coronavirus Disease-2019 (COVID-19) caused by Severe Acute Respiratory Syndrome–CoronaVirus-2 (SARS-CoV-2) spread globally with around 111 million cases reported. There is evidence, that COVID-19 pandemic worsened TB epidemic globally due to TB-services fragmentation and additional pressures on health systems by COVID-19 resulting in weakening of the National TB programs [1].

COVID-19 is characterized by several clinical features ranging from an asymptomatic state to severe forms with immune dysregulation that may lead to immune pathology . As for TB, lung is the most frequent disease localization, and in a minority of patients, it may lead to a rapid respiratory failure and death [2].

Current evidences on TB-COVID-19 coinfection suggest that COVID-19 may occur independently of TB either before, during or after TB disease. However, whether COVID-19 may reactivate or worsen TB disease still needs to be elucidated. The impact of sequelae and the need for further rehabilitation requires further evaluation. The main determinants of mortality for COVID-19 are age and co-morbidities, HIV co-infection and poverty, and all of these have an impact on TB mortality as well. Recently, TB has been associated with higher mortality in COVID-19-patients. Concomitant Mtb-specific and SARS-CoV-2-specific response is not yet fully understood. Recently, it has been reported a similarity of the immune signatures associated with COVID-19 clinical severity and the spectrum of asymptomatic- and symptomatic-TB [3].

Still undescribed are the biological effects of the interaction of the two infections that may recall the concept of ‘cursed duet’ that in the past was used to describe TB and HIV coinfection.

Therefore, in this study we evaluated the impact of SARS-CoV-2 and Mtb concomitant infections on the immune response specific for each pathogen, using a whole-blood-based assay platform. Patients diagnosed with TB can become infected with COVID-19, which in turn might result in deterioration of a patient’s condition. According to the Center for Disease Control and Prevention, TB patients who are at least 65 years old, have respiratory compromise from their TB infection or other medical conditions, including HIV and immunocompromised state, are at greater risk for severe COVID-19 infection [4]. A

study has evaluated the host-expression correlation with SARS-CoV-2 and interaction of 26 proteins of SARS-CoV-2 with 332 human proteins. It was seen that *Mycobacterium tuberculosis* shares most host protein interaction partners (same interactome) as SARSCoV- 2 and is of utmost importance as both infections have high affinity towards lung tissue [5].

Very few studies have determined the mortality in cases of co-infection with COVID-19 and TB. A study was done by Tadolini *et al.* in a cohort of 49 patients. It was seen that 53.0% patients had past history of TB, 28.5% developed COVID-19 first and 18.3% patients were diagnosed with TB and COVID-19 simultaneously. In 38.8% patients, COVID-19 developed during treatment for TB showcasing the potential risk of transmission to care-givers. Lack of/inadequate protective measures in handling patients of TB favoured the nosocomial spread of COVID-19 in two health care workers [6]. Another study done by Chen *et al.* warranted that COVID-19 infection and severity would be likely higher in patients of active and latent TB infection [7]. In a study by Motta *et al*. in Italy, two cohorts of patients co-infected with TB and COVID-19 were analysed. In about 69 patients from two cohorts, 8 patients (11.6%) succumbed to the co-infection.

We agree, it is possible that the diagnosis of COVID-19 was made before TB because of acute onset of symptoms caused by SARS-CoV-2 in addition to the alarm generated by the COVID-19 pandemic, which determined rapid access to radiological examinations and subsequent discovery of underlying TB.

However, apart from the speculation on what disease comes first, it is evident that the co-existence of TB and COVID-19 poses a challenge in differential diagnosis.

Table 1. Similarities and differences between tuberculosis and COVID-19.

| No | Characteristic | Tuberculosis | COVID-19 |
|---|---|---|---|
| **1** | Geographical distribution | Global existence<br>More prevalence in South-East Asia region and African region | More incidence in Americas and Europe |
| **2** | Incidence | 10 million cases (in 2019) | 10 million cases and counting |
| **3** | Agent | *Mycobacterium tuberculosis*<br>Corona virus shares genomic similarities with *Mycobacterium tuberculosis* | Novel Coronavirus (SARS COV-2) |
| **4** | Age group | All age groups and both sexes are at risk<br>Mostly affects adults in productive age group (15-34 years). Older adults and people who have severe underlying<br>People with HIV/AIDS are at higher risk of infection | Older adults and people who have severe underlying. People with HIV/AIDS are at higher risk of infection medical conditions like heart or lung disease or<br>diabetes seem to be at higher risk for developing more serious complications from COVID-19 illness |
| **5** | Incubation period | 6-8 weeks | 2-14 days |
| **6** | Mode of spread | Respiratory droplets produced when an infected person coughs, sneezes, or talks | Virus can also spread from touching a surface or object that has virus on it and then touching their own mouth, nose, or possibly their eyes (less common route) |
| **7** | Clinical features | Cough with sputum and blood at times, weight loss, lever and night sweats, chest pain, weakness | Fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny |

| | | | |
|---|---|---|---|
| | | | nose, nausea or vomiting, diarrhoea |
| **8** | Laboratory features | High erythrocyte sedimentation rate, leukopenia, lymphopenia, high lactate dehydrogenase thrombocytopenia, anemia | Decreased albumin, high C-reactive protein, high aspartate amino transferase, high alanine amino transferase, high creatinine kinase, leukocytosis, high bilirubin, high creatinine |
| **9** | Chest X-ray features | Consolidation, thick walled cavity, cavities with air-fluid levels, clustered and military nodules and pleural effusion | Bilateral lower lobe consolidations, peripheral air space opacities, ground glass opacities, diffuse lung opacities and pleural effusion |
| **10** | Diagnostic tests | Sputum smear microscopy, culture test, TB interferon gammarelease assays, chest X-rays, serological tests, tuberculin skin tests, molecular assays as Genexpert and Truenat | Viral load detection (RT-PCR), serological-antibody tests (IgM and IgG) [TrueNat Beta CoV is used as a screening tool in India |
| **11** | Treatment | Specific treatment guidelines available (isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin, etc.) | Many trials are underway. Hydroxychloroquine and corticosteroids are currently in place |
| **12** | Case fatality | 1.4 million deaths (in 2019) | 0.5 million deaths and counting (case fatality rate is 4.9%) |
| **13** | Health sector expenditure | USD 6.8 billion (in 2019) | Unknown, but would be huge leading to global recession |
| **14** | Social impact - stigma | Yes | |
| **15** | Data sharing platform | Lack of organized data sharing platform | |
| **16** | International surveillance system | Lack of finances | Appropriate surveillance systems in place to track the spread |
| **17** | Knowledge on individual susceptibility | Absent | |
| **18** | Vaccine availability | BCG | Currently not available. Research for new vaccine is ongoing |
| **19** | Rapid policy response | No | Yes |
| **20** | Contact tracing | Helpful in case detection | |
| **21** | Preventive measures | Following respiratory hygiene and cough etiquettes | |

**Conclusions.** This review provides an insight into the neglected paradigm of a long-standing infectious disease, tuberculosis amidst the ongoing COVID-19 pandemic. Though multi-faceted approaches are in place to deal with the pandemic, few other measures taken at this time might enhance to contain COVID-19 and prevent the illeffects of missing potential suspects of Tuberculosis.

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# ASSESSMENT OF THE EFFECT OF QUARANTINE MEASURES ON THE HEALTH STATUS OF THE POPULATION IN THE FIGHT AGAINST COVID-19

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**Abstract.** Comparative assessment of some parameters characterizing the health status of the population before and about a year after quarantine measures. It is concluded, that quarantine measures during a pandemic have a destrimental effect on human health, and some parameters that characterize the state of health change significantly. Decreased physical activity, eating disorders, lifestyle changes, weakening of social relations, restrictions in the socio-cultural sphere have a negative impact on the health of the population and reduce its quality of life. Therefore, it is very important to regularly check the population, especially those with chronic diseases, and monitor their health.

**Key words:** Coronavirus pandemic, risk factors, quarantine, non-communicable diseases, healthy lifestyle.

**Introduction.** In the current pandemic, the health status of the population has changed significantly. Thus, despite the fact that measures to combat COVID-19 play an important role in the prevention of this disease, these measures also have an indirect negative impact on the health of the population. Harmful factors such as social isolation, distance from work, home closures, hypodynamics, eating and violation of daily wok routine, changes in the rhythm of life, stress during the pandemic creates conditions for the emergence and exacerbation of non-epidemic diseases such as arterial hypertension (AH), diabetes (D), hypercholesterolemia (HCL) , hypertriglyceridemia (HTG), excess body weight (EBW), obesity, emotional stress (ES), etc.

As we know, risk factors such as low physical activity, hypercholesterolemia, excess body weight, obesity, stress play an important role in the development of non-communicable diseases (NCDs) both freely and interaction with each other. Restrictions on people's employment, closure of gyms, psychological stress in the family due to the transition of children to online classes, restrictions on group gatherings, social relations, socio-cultural needs exacerbates aggravation, lowers people's quality of life.

**Materials and methodology.** Due to the closure of schools and workplaces due to the pandemic and the impossibility of personal contact with people, we were able to get information about some indicators (body weight, blood pressure, amount of sugar, cholesterol, triglycerides in blood) through mobile communications, as well as the results of medical examinations. Blood pressure was measured with a tonometer, blood sugar was measured with a glucometer, blood cholesterol and triglycerides were measured with an Accutrend Plus, excess body weight and obesity based on the Ketle index, on the ES Reeder scale, and life quality index was calculated using the SF-36 international survey. Statistical evaluation was conducted using the $\chi^2$ criterion.

**Results obtained.** Our observations on the long-tem control group showed once again that the health indicators of the population are deteriorating due to the impact of quarantine measures. Thus, during the observation of the fixation group for long-term control, some parameters of health indicators were checked comparatively with the indicators before the

quarantine measures and about one year after the quarantine measures of the population included in that fixation group and changes were observed in these parameters (Table 1).

Mainly during the mentioned period, AH increased from 25.3±2.2% to 33.5±3.0%; blood sugar range from 17.7±2.2% to 24.2±2.8% (P<0.05); life quality index from 55.7±2.8% to 75.1±2.7% (P< to 0.01); excess body weight from 29.0±2.7% to 37.3±3.3% (P<0.02); obesity from 15.5±2.3% to 25.9±3.0% (P<0.05); HCL ranged from 46.6±3.8% to 63.4±4.2% (P<0.01); HTG from 26.1±3.3% to 38.8±4.4% (P<0.02); ES from 22.2±3.1% to 33.9±4.3% (P<0.05).

Table 1. Indicators of the health status of the fixed population before and 1 year after the start of quarantine due to Covid-19.

| Indicators | Parameters | Before quarantine | | | One year after the start of quarantine | | |
|---|---|---|---|---|---|---|---|
| | | Number of examined people | Detection | | Number of examined people | Detection | |
| | | | Abs. | % | | Abs. | % |
| AH | >140/80 mm Hg | 387 | 98 | 25.3±2.2 | 242 | 81 | 33.5±3,0 |
| Diabetes | >146 mmol/l | 316 | 56 | 17.7±2.2 | 227 | 55 | 24.2±2.8 |
| Life qualit | <70 point | 318 | 177 | 55.7±2.8 | 261 | 196 | 75.1±2.7 |
| EBW | 25-30 kg/m² | 293 | 85 | 29.0±2.7 | 212 | 79 | 37.3±3.3 |
| Obesity | >30 kg/m² | 293 | 57 | 15.5±2.3 | 212 | 55 | 25.9±3.0 |
| HCL | >5.2mmol/l | 176 | 82 | 46.6±3.8 | 121 | 84 | 63.4±4.2 |
| HTG | >2.2 mmol/l | 176 | 46 | 26.1±3.3 | 121 | 46 | 38.8±4.4 |
| ES | >2 point | 176 | 39 | 22.2±3.1 | 121 | 41 | 33.9±4.3 |

**Conclusion.** From the above, it is clear that quarantine measures during a pandemic have a destrimental effect on human health, and some parameters that characterize the state of health change significantly. Decreased physical activity, eating disorders, lifestyle changes, weakening of social relations, restrictions in the socio-cultural sphere have a negative impact on the health of the population and reduce its quality of life. Therefore, it is very important to regularly check the population, especially those with chronic diseases, and monitor their health.

# HEALTH RESORT REHABILITATION OF THE COVID-19 CONVALESCENTS (LONG COVID)

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**Abstract.** The paper substantiates the development necessity of an optimal science-based system of measures to improve rehabilitation (using curative natural and preformed factors) during convalescence in COVID-19 patients, which will increase adherence to therapy and reduce the risk of complications and adverse outcomes. The effectiveness of the resort and spa phase of rehabilitation for patients with long-COVID has been shown as follows: multidisciplinary rehabilitation programmes shall lead to improved functional impairments (they can reduce shortness of breath, fatigue, increase endurance) and improve the quality of life.

**Key words:** New coronavirus infection, convalescents, the long COVID syndrome, medical rehabilitation, natural healing factors, sanatorium-resort rehabilitation.

**Introduction**. In the world, the cumulative number of COVID-19 cases as of April 23, 2021 is more than 146.2 million, recovered - more than 124.3 million [1], in 223 states and territories of the world [2]. In Russia, the number of cases exceeded 4.70 million, more than 4.38 million patients recovered [1]. Currently, COVID-19 is classified as multiple organ diseases with a wide range of manifestations [3, 4], this requires multi-stage rehabilitation using the principle of a multidisciplinary approach and the participation of a multidisciplinary team. The long-term effects of COVID-19 are unknown, but evidence from previous outbreaks of CoV suggests impaired lung and physical function, decreased quality of life, and cognitive and psychological impairment [5]. WHO has obtained evidence on the presence of persistent symptoms in COVID-19 convalescents [6, 7, 8] and / or delayed or long-term complications that persist (or appear) after 12 weeks from the onset of the disease, not associated with alternative diagnoses (long COVID) [ 3, 9].

It is predicted that the burden on institutions involved in medical rehabilitation will persist for 12 months or more (during the transition to the chronic phase) [5]. The greatest opportunities for rehabilitation treatment of patients are at the spa stage of the rehabilitation system. However, there are no scientific studies regarding the effectiveness of the rehabilitation of patients after suffering a coronavirus infection at the spa stage.

**Purpose**: to form an optimal scientifically grounded system of measures to improve sanatorium and resort rehabilitation during the period of convalescence in patients who have undergone COVID-19 (long COVID), which will increase adherence to therapy and reduce the risk of complications and adverse outcomes.

**Study characteristics.** A prospective observational study has been conducted on the basis of the SANATORIUM PARUS-RESORT LLC since 2020 in accordance with the National Standards of the Russian Federation GOST-R 52379-2005 “Good Clinical Practice” (ICH E6 GCP), in compliance with ethical principles, set out in the 1975 Declaration of Helsinki (as amended in 1983) and obtaining informed consent from patients. The study was

approved by the Local Ethics Committee of the IIPM - Branch of the IC&G SB RAS (protocol No. 23 dated May 26, 2020).

*Study design* - sequential enrollment of patients 12-16 weeks after the onset of the first symptoms. Sample capacity: 300 people - the main group (underwent COVID-19 complicated by pneumonia), comparison group 1 - 300 people who underwent uncomplicated COVID-19, comparison group 2 - 300 people (asymptomatic carriers of COVID-19).

*Inclusion criteria*:

1. Signing informed consent to participate in the study.

2. Reconvalescents: COVID-2019 (code U07.1 or U07.2) over 18 years old.

3. Availability of rehabilitation potential on the scale of rehabilitation routing (RRM) 2–3 points;

4. Ability to understand and comply with the requirements of the research protocol.

5. Absence of contraindications to sanatorium-resort rehabilitation [10] medical and diagnostic procedures provided for by the research protocol.

*Criteria for premature exclusion*: Refusal to further participate in the study.

The duration of the spa rehabilitation is from 14 to 21 days.

Sanatorium-resort stage of rehabilitation lasting 14 days in 2020-2021 (pilot project) passed 268 COVID-2019 convalescence patients. The diagnosis of COVID-2019 was considered verified in the presence of a positive laboratory test result for SARS-CoV-2 RNA (using nucleic acid amplification methods) or SARS-CoV-2 antigen (using immunochromatographic analysis), regardless of clinical manifestations [11] and / or antibodies of the IgA, IgM and / or IgG class in patients with clinically confirmed infection with COVID-19 [12].

**Methods of sanatorium rehabilitation and control over its effectiveness.**

The sanatorium stage of rehabilitation provides for the implementation of rehabilitation measures using therapeutic natural factors, preformed physical factors, physiotherapy exercises, and motor regimes. The main tasks of the rehabilitation of COVID-2019 convalescents are restoration (improvement) of impaired functions, mental and social rehabilitation, prevention of complications.

The medical base of SANATORIUM PARUS-RESORT LLC includes, in addition to climatic factors (aerotherapy, photo- or heliotherapy), peloid-balneotherapy (highly mineralized baths with a salt concentration of 300 g/l: sodium-magnesium chloride with a high bromine content; applications with high-sulfide and high-saline mud of Saki Lake) and rehabilitation using preformed methods of treatment: in the balneological department (hydropathic procedures - showers: “Charcot”, ascending, circular), in the physiotherapy department (magnetotherapy including a high-intensity magnet (BTL 6000 Super Inductive System Elite), laser therapy , including a high-intensity laser (BTL-6000 7W -12 W), electrotherapy on the BTL-4820SL PREMIUM device, oxygen therapy, helioxytherapy (inhalation device BreezeLite) electrosleep; aerosol therapy with natural alkaline water, sodium bicarbonate chloride type with a high content of fluorides and boric acid, p with a record content of natural iodine, with a mineralization level of 9-10 g / l “VINCENTKA” (massage - classic manual). In the COVID-19 (long COVID) spa rehabilitation complex for convalescents, nutritional status correction is applied (to maintain muscle strength with the help of sufficient protein and vitamins in the diet), recreational and physiotherapy exercises, psychotherapy.

The priority of a structured comprehensive program of rehabilitation measures for COVID-19 (long COVID) convalescents in a sanatorium was given to methods aimed at restoring the parameters of the respiratory system and exercise tolerance, in an increasing load mode under clinical condition control [13]. The basis of the studied program, which includes a complex of health-improving procedures and provides for an individual approach to each

patient, is pulmonary rehabilitation - the main component of treatment for chronic respiratory diseases. [fourteen]. Under the supervision of a medical and physical culture doctor, classes were conducted, including exercises that develop strength and strength endurance of the leading muscle groups, aerobic interval training, alternating with high-intensity exercises (taking into account the patient's condition and physical capabilities). Respiratory gymnastics included training the respiratory muscles on special simulators that differentially involve the inspiratory and expiratory respiratory muscles in the work (Threshold PEP, PARI O-PEP).

The control over the effectiveness of rehabilitation was carried out on the first and last days of rehabilitation. A point was made for the subjective severity of insomnia symptoms (according to the ISI-20 questionnaire) [15], general and / or mental weakness, increased exhaustion, irritability, productivity of mental processes, sleep disorders, physical weakness and other autonomic-somatic disorders using the MFI questionnaire – 20 [16] taking into account subscales: general asthenia, decreased activity, decreased motivation, physical asthenia, mental asthenia. The level of anxiety and depression (express screening) was assessed on the basis of answers to 14 questions (with 4 answers) in the hospital. scale of anxiety and depression (HADS) [17], with the sum of points in each part (anxiety and depression) more than 7, an in-depth examination by a psychotherapist was carried out. When conducting an extended neuropsychological examination to identify cognitive impairments, we used tests of “verbal associations”, “symbolic-digital coding” [18], drawing a clock [19], and functional deficit — a functional activity questionnaire [20].

Exercise tolerance, disease prognosis and the effectiveness of spa rehabilitation were analyzed according to the dynamics of the Borg Scale [21], the 6-minute walk test [22], dyspnea - MRC [23], BDI and TDI [24, 25]

The quality of life was assessed according to the results of the EQ-5D-3L quality of life questionnaire [26].

A comprehensive approach that allows to reliably evaluate information about the presence, nature of long COVID syndrome and the effectiveness of its sanatorium-resort rehabilitation, included, in addition to the questionnaire, monitoring the function of external respiration (with a bronchodilatory test on a Microlab series spirometer), assessing the risk of developing nocturnal hypoxia, obstructive or central APNEA (screening study of nighttime computerized pulse oximetry using a PulseOx 7500 SPO Medical device), with an increase in the desaturation index to 5 per hour, nighttime computer somnography was performed (using a WatchPAT device, Itamar medicai).

Statistical data processing is carried out using Statistica, SPSS software. Data are presented as the median Me and [25; 75] percentiles.

**Results.** In 2020-2021 at the spa stage of rehabilitation. (pilot project) there were 268 COVID-2019 (long COVID) convalescents, of which 104 were men and 164 were women. The average age of men was 54.50 [43.55; 67.40] years, women - 53.40 [42.75; 67.10] years ($p > 0.05$). The control group included 50 men and 91 women who did not undergo the sanatorium-resort stage of rehabilitation and who were in 2020-2021 at dispensary observation at the Center for Medical Prevention “IIPM - Branch of the IC&G SB RAS”. The average age of men was 52.50 [41.75; 65.50] years, women - 52.70 [41.75; 65.00] years ($p > 0.05$).

12-16 weeks after the onset of the first symptoms of COVID-19 when filling out questionnaires and during examinations by specialists (pulmonologist, cardiologist, somnologist, neurologist, endocrinologist, therapist), 86.5% of patients undergoing dispensary observation and 91.4% of those undergoing the sanatorium-resort stage of rehabilitation reported that they had at least one of the symptoms indicating mental weakness, increased exhaustion, irritability, decreased productivity of mental processes, sleep disorders, decreased physical performance, cognitive and other autonomic-somatic disorders. It was found that in

both groups, one of the common problems leading to sleep disturbance was restless legs syndrome, which was found in more than half of the patients. The presence of a comorbid pathology was associated with obstructive sleep apnea syndrome: in case of impaired carbohydrate metabolism, breathing disorders during sleep (mainly moderate or severe) were found in 85% of patients, with concomitant arterial hypertension and diabetes mellitus - in 25.2% of cases. Of the entire spectrum of pulmonary manifestations, the most common and persistent symptom in COVID-19 convalescents was shortness of breath, both expiratory and mixed, which was noted in more than 40% of patients undergoing dispensary observation and in 63.43% of patients undergoing a sanatorium-resort rehabilitation, who did not have a history of respiratory pathology before the disease. As a result of sanatorium and resort rehabilitation, COVID-19 (long COVID) convalescents showed a decrease in dyspnea on the MRC scales (dyspnea) from 2.98 [2.43; 3.12] to 1.25 [0.64; 1.68] points and TDI to 2.35 [1.78; 2.87] points, a decrease in the overall mean score for asthenia according to the MFI questionnaire –20 from 59.57 [42.98; 67.65] to 38.23 [25.32; 44.14], as well as a decrease in general asthenia from 16.28 [14.33; 18.76] to 10.10 [6.00; 12.14] points and an increase in physical activity from 17.45 [14.78; 19.20] to 9.10 [6.00; 11.23]. In the group of patients undergoing dispensary observation in the period 14-18 weeks after the onset of the first symptoms of COVID-19, there were no significant changes in the MRC (dyspnea) scales, TDI MFI-20 was not detected.

**Discussion.** The obtained data are similar to the results obtained by A. Carfi et al. (Italy) [6], who reported persistence of symptoms in 87.4% of patients who recovered from acute COVID-19 (with an average follow-up period of 60 days from the onset of the first symptom). Fatigue (53.1%), shortness of breath (43.4%), joint pain (27.3%), and chest pain (21.7%) were most common, with 55% of patients experiencing three or more symptoms [6]. Fatigue, shortness of breath, and psychological disorders such as post-traumatic stress disorder, anxiety, depression, and impaired concentration and sleep were reported in more than 30% of study participants in France [27]. There is currently no information on the effectiveness of the spa rehabilitation of COVID-19 convalescents.

**Conclusion.** Considering the number of COVID-19 (long COVID) convalescents, in the world and in the Russian Federation, the existing potential of sanatorium-resort institutions, it seems relevant and promising to use the sanatorium stage of rehabilitation for these patients.

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# MOST EXPRESSED SYMPTOMS IN PATIENTS AFTER NEW CORONAVIRAL COVID-19 INFECTION

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**Abstract**. Since the "Spanish flu" in 1918, there has not been such a large-scale pandemic, causing significant damage to the economy of Russia and other countries, as the new coronavirus infection COVID-19, which began in December 2019. The SARS-CoV-2 virus is highly infectious, can proceed both asymptomatic and in an extremely severe form, especially in the presence of comorbidity. Despite the fact that the clinical picture is associated with respiratory syndrome, other long-term symptoms are increasingly observed. In this study, we tried to find out the most pronounced and long-lasting symptoms in the first 6 months after the new coronavirus infection COVID-19.

**Key words**: COVID-19, SARS-CoV-2, nervous system, neurological complications, coronavirus infection, postcoid complications, neurocytoprotection strategy.

**Introduction**. Coronavirus is a pathogenic agent with leading clinical manifestations in the form of cough, shortness of breath and fever. In addition to respiratory symptoms, the virus, possessing neurotropism, causes disturbances in the activity of the central nervous system of varying severity and duration [1-3]. Neurological disorders were found in approximately 36.4% of patients with COVID-19 [4]. The most frequent are: epileptic seizures -20%; dizziness - 16.8%; mental status - 15%; confusion, headache - 13.1%; "Musculoskeletal syndrome" -10.7%; taste - 5.6%; nausea, vomiting, convulsions, impaired sense of smell - 5.1%. Most often, neurological symptoms were observed in comorbid patients with moderate to severe and severe forms of the disease - 75.7% [5]. These complications are similar to the described cases in other coronavirus epidemics [6, 7]. The mechanism of penetration of the SARS-CoV-2 virus into the central nervous system (CNS) is similar to the SARS virus (Severe acute respiratory syndrome), which appeared in 2002 and MERS (Middle East respiratory syndrome), which appeared in 2015 [8-10].

Studies using transgenic mice have shown that, when administered intranasally, SARS-CoV and MERS enter the central nervous system through the olfactory nerves, and then spread to some specific regions of the brain, including the thalamus and brainstem [11]. There are suggestions that the SARS-CoV-2 virus can similarly enter the brain through the olfactory nerves in the early stages of infection, causing inflammation and demyelination [12]. The high frequency of olfactory and gustatory dysfunctions in COVID-19 once again proves the neurotropic nature of the virus [13].

Other options for the mechanism of damage to the nervous system in the new coronavirus infection COVID-19 are being considered. The permeability of the blood-brain barrier increases with the development of a cytokine storm, creating an opportunity for viruses, immune cells, bacteria and inflammatory agents to penetrate into the structures of the central nervous system. Single studies by genome sequencing have identified SARS-CoV-2

RNA in the cerebrospinal fluid of patients with COVID-19, which indicates the possibility of virus penetration through the blood-brain barrier [8, 14].

Angiotensin converting enzyme 2 (ACE2) is a cardio-cerebral vascular protective factor of many organs, skeletal muscles, and the nervous system. Through the cell membrane in the places where the ACE2 receptors are located, SARS-CoV-2 penetrates into the cell with the help of the S-protein ("spike" glycoprotein). This glycoprotein, located on the processes or corona of the virus, complicates the recognition of the coronavirus itself by the immune system of the body by imitating molecules important for the vital activity of cells, injecting its RNA into it and penetrating into the cells of the respiratory tract, blood vessels, etc. [15, 16].

Preventing the disease, finding an effective treatment for COVID-19 and its complications is an important task for scientific communities, health systems and other departments around the world. In addition to the high contagiousness of the virus, the possibility of a severe course of the disease in some patients, various complications and a long rehabilitation process caused by the new coronavirus infection COVID-19 are becoming a serious problem.

Currently, there is not a sufficient base of clinical and instrumental data, with the help of which we could determine the duration and severity of complications after suffering a new coronavirus infection COVID-19, with which it is necessary to actively work at the stages of rehabilitation [17].

According to NICE 2021, cardiorespiratory consequences (shortness of breath, increased heart rate, chest tightness, chest pain, residual cough, etc.), neurological consequences (neuropathy, increased fatigue, dizziness, headache, etc.), cognitive consequences ( memory impairment, concentration, attention, sleep disturbance, etc.), endocrinological consequences (steroid effect, impaired carbohydrate metabolism), kidney-related consequences (acute kidney damage, progression of chronic kidney disease, proteinuria), musculocutaneous effects (skin rashes, pain in muscles, joints), hematological consequences (increased ferritin, prothrombotic status-thromboembolism in 1 out of 5 patients and 3% of strokes despite taking oral anticoagulants), gastrointestinal consequences (decreased appetite, abdominal pain, nausea, diarrhea, etc. .), psychological consequences (emotional stress, worries about loved ones during hospitalization, restrictions e usual communication, etc.) [18].

**Objective**: To determine the most pronounced and long-lasting symptoms in the first 6 months after the new coronavirus infection COVID-19.

**Materials and methods.** The data for the study was obtained on the basis of an online survey conducted from January 1 to February 1, 2021. Study participants were asked to fill out a questionnaire through the Google Forms Internet platform, which contained 20 specially designed questions. The questionnaire included the sociodemographic data of the respondents, information about the presence of comorbidities, symptoms during and after the new coronavirus infection COVID-19. Respondents were asked to mark any number of symptoms that appeared both during and after COVID-19.

The inclusion criteria were: 1) the presence of consent to the processing of personal data, the fact of which was considered to be the completion of all the proposed survey forms; 2) the presence of a positive PCR test to detect the RNA of the SARS-Cov2 virus; 3) COVID-19 disease no more than 6 months ago.

Exclusion criteria: 1) age of participants <18; 2) the absence of a positive PCR test for the detection of SARS-Cov2 virus RNA; 3) the presence of unfilled sections of the questionnaire.

**Results**. The final register includes 436 records collected during the above period. Data from 52 non-eligible respondents were excluded from the analysis. Thus, statistical analysis was carried out for the survey data of 384 respondents.

***Demographic indicators***

Most of the sample were women - 81.2%. The average age of the respondents reached 39 years (min-28, max-78). The sample included respondents from all federal districts of Russia. Of the entire sample, 78.7% worked, 13.8% studied, 6.4% temporarily did not work (temporary disability certificate, decree, etc.), and 7.2% were pensioners.

***Accompanying illnesses.***

An assessment of the categories of comorbidity showed that 51% of the respondents had up to 2 concomitant diseases, 28% had 3 or more concomitant diseases. The most common diseases were hypertension (58%), obesity (37%), chronic heart failure (26%), ischemic heart disease (26%).

***Severity.***

According to the results of the survey, 55.7% of patients had a mild COVID-19 infection, 39.6% - a moderate one, 4.7% - a severe form of the disease. 81.4% of the respondents were on outpatient treatment, 18.6% on inpatient treatment, of which 8.5% received oxygen therapy, including two patients required invasive mechanical ventilation and one patient required non-invasive mechanical ventilation.

***Characteristics of the most common symptoms after COVID-19.***

48.9% of respondents complained of feeling tired after suffering a new coronavirus infection COVID-19, 43.9% of respondents complained of constant weakness, 22.6% of lethargy, 20.4% of frequent headaches after infection, and 17.8% of dizziness.

**Conclusion**. In this study, we tried to find out the most pronounced and long-lasting symptoms in the first 6 months after the new coronavirus infection COVID-19. Neurological disorders are common consequences. In our opinion, in the absence of serious disorders, an important role in the rehabilitation process of this group of patients will be played by the strategy of neurocytoprotection, which is aimed at preventing and reducing damage to neurons by affecting the cellular mechanisms of neuroregeneration and cerebral reorganization, which leads not only to structural and metabolic, but also to functional recovery. Despite the continued growth in the number of publications on this topic, information on the neurological aspects of the consequences of COVID-19 is incomplete and requires further research.

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# SCHOOL CHILDREN'S SATISFACTION WITH DISTANCE LEARNING DURING THE COVID-19 QUARANTINE PERIOD

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**Abstract.** In the modern primary school, as well as in the whole society, the information activity of a person, carried out on the basis of modern means of computer technology, as well as various means of information interaction and exchange, becomes dominant. More than 80 % of teachers ' respondents consider it necessary to use a computer in the classroom. Free access to Internet resources allows students to independently choose the content of educational information according to their preferences and level of readiness, which ensures the individualization of educational activities. In modern conditions, the role of the student as a consumer of educational information is changing. The student gets an opportunity for independent information activity: search and analysis of information, its processing, production and transmission.

**Keywords:** school, quarantine, stress, psychoemotionality, state.

**Introduction**. Distance learning involves the mandatory use of the Internet as the main means of communication. There are the following forms of distance learning: 1) traditional (part-time): focused only on independent work and does not involve the presence of interaction between the teacher and the student, involving the conduct of installation lectures, and then the continuation of independent work on the issued sets of methodological support; 2) fragmentary use of information and communication technologies. In this case, the student independently works with a set of educational and methodological support, which is partially presented in electronic form. The interaction of the teacher and the student is carried out using various types of communication; 3) electronic, based on receiving educational and methodological support by e-mail and independently studying it; 4) combined. Each type of distance learning differs from the previous one by shifting the center of gravity of the educational process towards its remote component [1, 2].

Most often, a distance learning profile is used-a course for high school students, which is currently methodically analyzed with good recommendations for the successful conduct of distance learning with schoolchildren [3].

The aim of the work was to assess the satisfaction with distance education of secondary school students.

The survey of student satisfaction was conducted for the period March-April 2020, by sending a questionnaire via Google platforms (online).

The online questionnaires included 13 questions that were devoted to the data of the equipment used, the difficulties of completing tasks in subjects, the mode of the day, the contribution of parents in completing homework or downloading answers, the time spent on completing tasks and preparing, as well as compliance with the norms and working time on the computer.

A total of 97 responses were sent online. The age composition was as follows: 53.5 % of the respondents were students aged 10-12 years, 38% were aged 7-9 years; 8.5% were students aged 13-14 years. As can be seen from figure 2, mainly in the survey attended by schoolchildren and adolescents (Figure 1).

More than 97.8% participated in a distance learning format, of which 51.5 per cent responded that this format does not like them, 27.8% and doubt and 20.6 % liked this format of training (Figure 2).

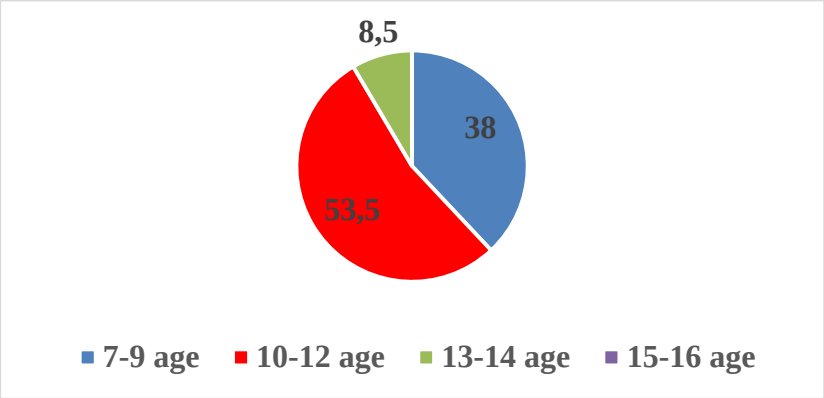


Figure 1. The age composition of students who participated in the survey.

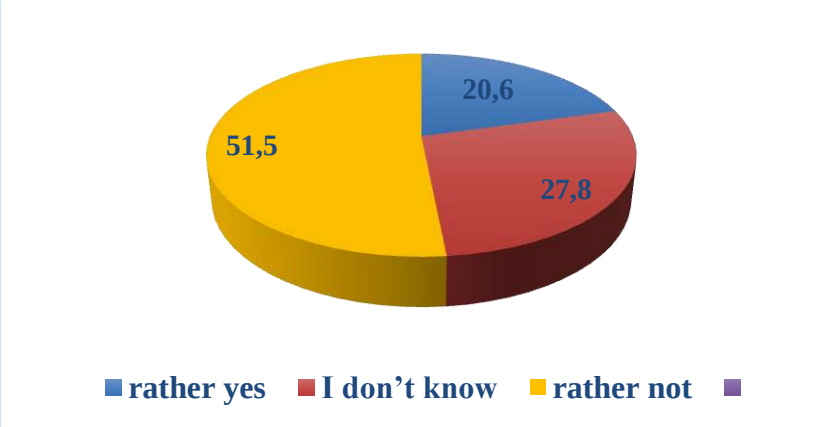


Figure 2. Satisfaction with the distance learning format.

Most distance education took place on the following platforms: 43.3% on whatsapp; 8.2% chat; 8.2% kundelik; 3.1% zoom; 26.8% classroom.

More than 55.7 % noted that the daily routine has changed a lot, 37.1% said that there were few changes and 7.2% said that nothing has changed.

Completing homework with distance learning was a little more difficult for 42.3%, 32% said that it was easy to study, 11.6% said that the training format was not clear, and 5.2% indicated that it was difficult to pass DL.

Very interesting answers were given by schoolchildren to the question of what prevents them from studying at home. As can be seen from Figure 3, most of them are not satisfied with the absence of a teacher (45.4%), then they are hindered by the home environment (20.6%), about 15.5% of students indicated poor communication, 4.1% were hindered by the presence of parents, 3% did not interfere with anything and 1% each indicated the absence of friends and all of the above.

An important point of training is the equipment on which students are engaged. So, the survey showed that more than 69.1% are engaged on a mobile phone or smartphones, 22.7% are engaged on desktop computers, 5.2% are engaged on a tablet, 2.1% work on laptops.

Taking into account the methodological features of conducting the lesson remotely, and the urgency of the transition of full-time education in the Republic of Kazakhstan to remote (in connection with the introduction of the COVID-19 quarantine), we asked the

question "which subject is easier to pass remotely". As can be seen from Figure 5, the answers were different, but 47.4% of students indicated math, 24.7% reading, 8.2% writing, 2.1% computer science, 1% indicated history, and the rest indicated all subjects equally.

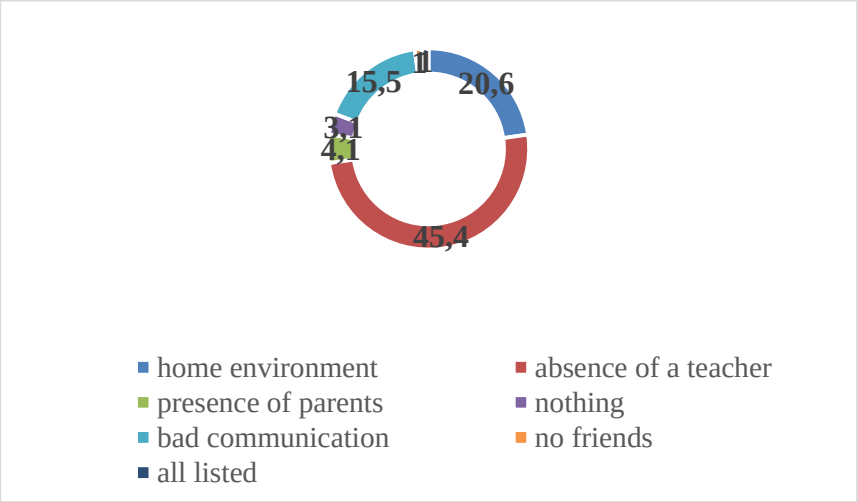


Figure 3. School children's' answers to the problems of learning at home.

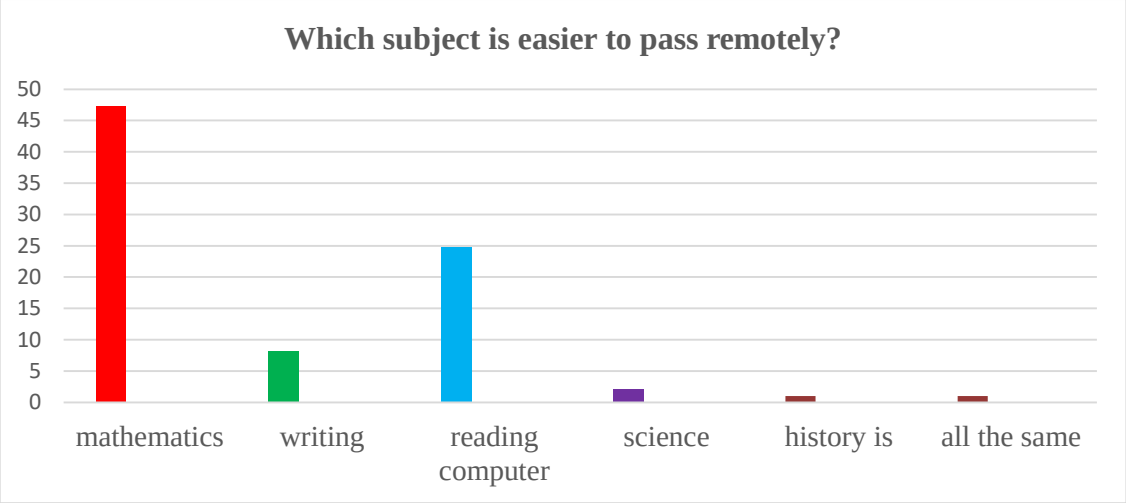


Figure 4. School children's answers to the ease of learning in the subjects.

An important point is to observe the daily routine of the student, including compliance with the hygienic requirements for the organization of the workplace, the organization of warm-up. We asked questions about the time of completing homework, the availability of warm-ups between remote classes. More than 51.5% of students said that the time for completing homework has changed, 41.2% said that it has not changed much and only 7.2% said that it has not changed. Of this number of children, more than 66% perform a warm-up, but 34% do not do it, which is a bad factor that affects the child's earlier fatigue.

An important point of learning is the independence of performing tasks, 40.2% perform tasks with their parents and 59.8% perform independently.

Given that secondary schools were not ready for distance learning, but this format requires development, in connection with the forecast of the situation on COVID-19 for the

fall of 2020, we asked the question whether students need additional classes in a remote format. More than 26.8% said yes and 73.2% said no.

Thus, the survey showed that a larger percentage of schoolchildren are still not satisfied with the DL format, mainly due to the absence of a teacher, the presence of parents during the lesson. An unfavorable factor was the revealed large percentage of students working on the phone or smartphone, which is a sign of non-compliance with the requirements for the organization of the child's workplace, including changing the mode of performing lessons and warming up between classes.

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# EPIDEMIOLOGY OF CORONAVIRUS INFECTION (VIRUS NOT IDENTIFIED) OF A SMALL CITY POPULATION

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**Abstract.** The article shows the analysis of discharge reports of patients who were hospitalized in a small town with a diagnosis of U07.2 “Coronavirus infection” (virus not identified). It was found that 51% of patients were females, 49% were males, 23% of patients were in the age category 60-69 years, 20% were 70-79 years old, 70% lived in the city, 42% were pensioners, 19% concomitant diseases such as pneumonia were recorded, 17% had arterial hypertension, most often the patients had clinical symptoms: fever, general weakness, cough, shortness of breath.

**Key words:** coronavirus infection, virus not identified, morbidity.

From August 1, 2020, in order to ensure maximum transparency of data on cases of COVID-19 and pneumonia, the Ministry of Health of the Republic of Kazakhstan has determined new approaches to accounting information and generating statistical data, and therefore a decision was made to switch to coding and accounting for COVID-19 cases based on new codes of the international classification of diseases.

All laboratory confirmed cases of COVID-19 are combined with cases of pneumonia with a negative PCR test result, but with clinical and epidemiological signs of COVID-19. This need is associated with the similarity of the course of these diseases, the use of common approaches to the tactics of their treatment and will make it possible to make correct predictions of morbidity, adequately plan the necessary resources: medical personnel, beds, medical equipment, medicines, and also ensure transparency of statistics**.** [1].

The aim of our study was to analyze the discharge reports of patients who were hospitalized in a small town with a diagnosis of U07.2 "Coronavirus infection" (the virus was not identified).

In the course of this study, we analyzed the discharge reports of patients who were diagnosed with U07.2 "Coronavirus infection" (virus not identified) at the Central Hospital of Shakhtinsk. The dynamics of the incidence of coronavirus infection (virus not identified) in Shakhtinsk from August to December 2020 is shown in Figure 1.

From August to December 2020, 118 people were registered in Shakhtinsk with a diagnosis of Coronavirus infection (virus not identified), all of them were hospitalized in a hospital.

Figure 1 shows that there is a decrease in the incidence of this infection from 52 people in August to 4 people in November. No cases of coronavirus infection were reported in December (no virus identified). This is possibly due to the fact that the incidence of coronavirus infection (the virus is identified) also gradually declined from August to December 2020.

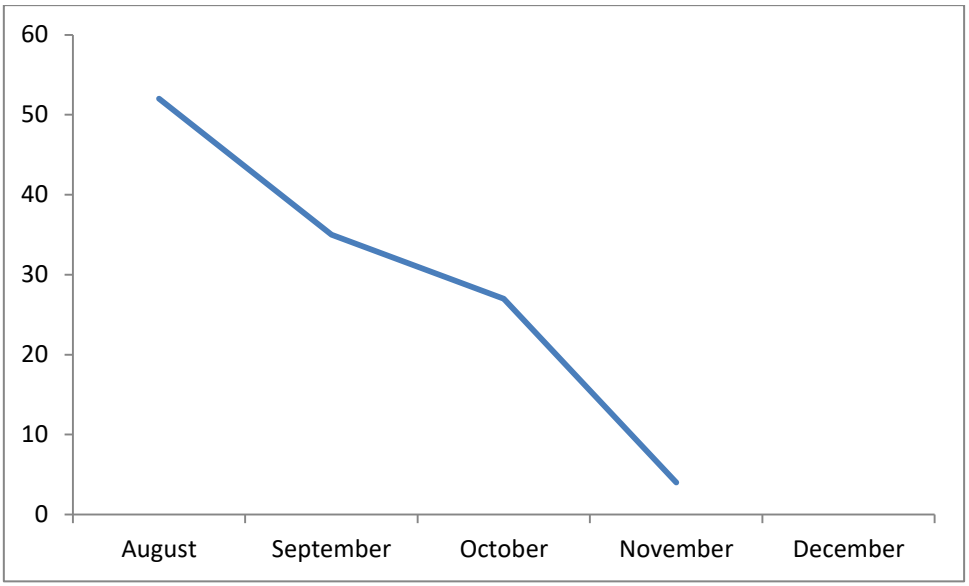


Figure 1. Dynamics of the incidence of coronavirus infection (virus not identified) in Shakhtinsk from August to December 2020

The gender of people diagnosed with coronavirus infection (virus not identified) in Shakhtinsk in 2020 is shown in Figure 2.

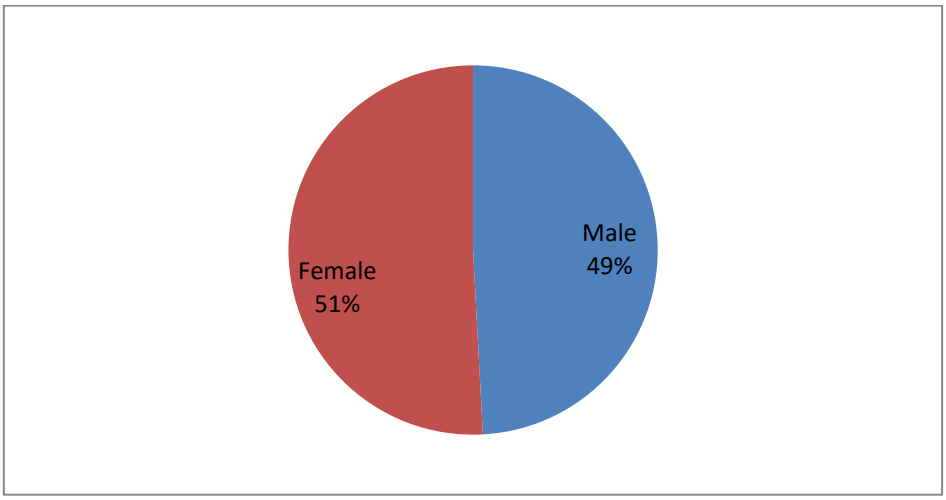


Figure 2. Gender of people diagnosed with coronavirus infection (virus not identified) in Shakhtinsk from August to December 2020

When analyzing discharge reports from the Shakhtinsk Central Hospital, it was revealed that 51% of cases of coronavirus infection (virus not identified) were female and 49% were male.

The age of people diagnosed with coronavirus infection (no virus identified) in Shakhtinsk in 2020 is shown in Figure 3.

The analysis of the age of the patients found that most of the patients were registered in the age ranges from: 60-69 years (23%), 70-79 years (20%), 50-59 years (17%) and 80-89 years (13%). The smallest number of people with this diagnosis is registered in the range of 90-99 years (1%).

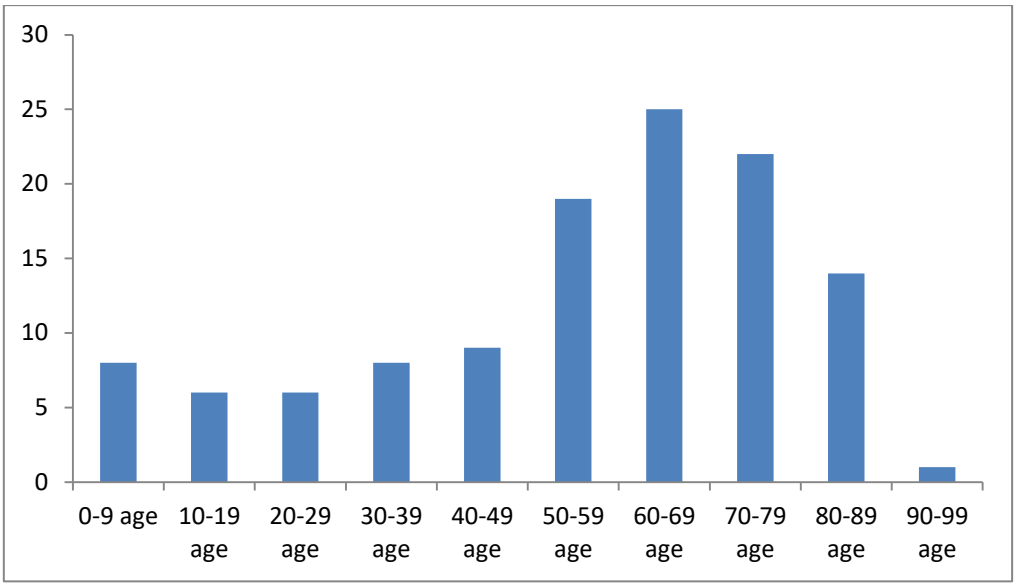


Figure 3. Age of people diagnosed with coronavirus infection (virus not identified) in Shakhtinsk from August to December 2020

The place of residence of patients with coronavirus infection (the virus is not identified) in Shakhtinsk for 2020 is shown in Figure 4.

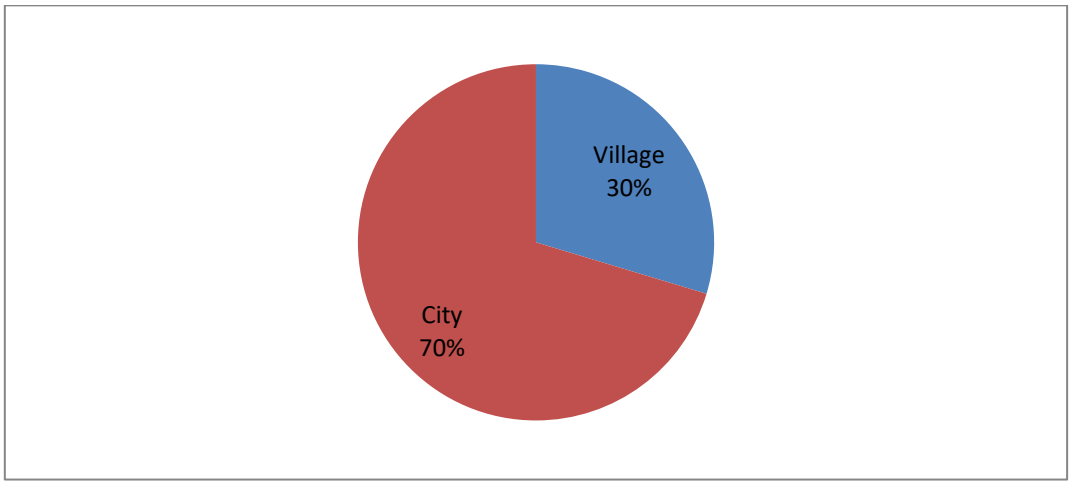


Figure 4. Place of residence of patients with coronavirus infection (virus not identified) in Shakhtinsk from August to December 2020

When analyzing the discharge reports from the Shakhtinsk Central Hospital, it was revealed that 70% of patients with coronavirus infection (the virus has not been identified) live in the city, and the remaining 30% - in the villages.

Concomitant diseases in patients with coronavirus infection (no virus identified) in Shakhtinsk for 2020 are shown in Figure 5.

We found that the most common concomitant disease in coronavirus infection (the virus is not identified) is pneumonia and accounts for 19% in the overall morbidity structure, then arterial hypertension 17%, coronary heart disease 10%, pyelonephritis in 6%, chronic obstructive pulmonary disease and iron deficiency anemia 5% each, diabetes mellitus 4%. 6% of people with this diagnosis did not have a single concomitant disease.

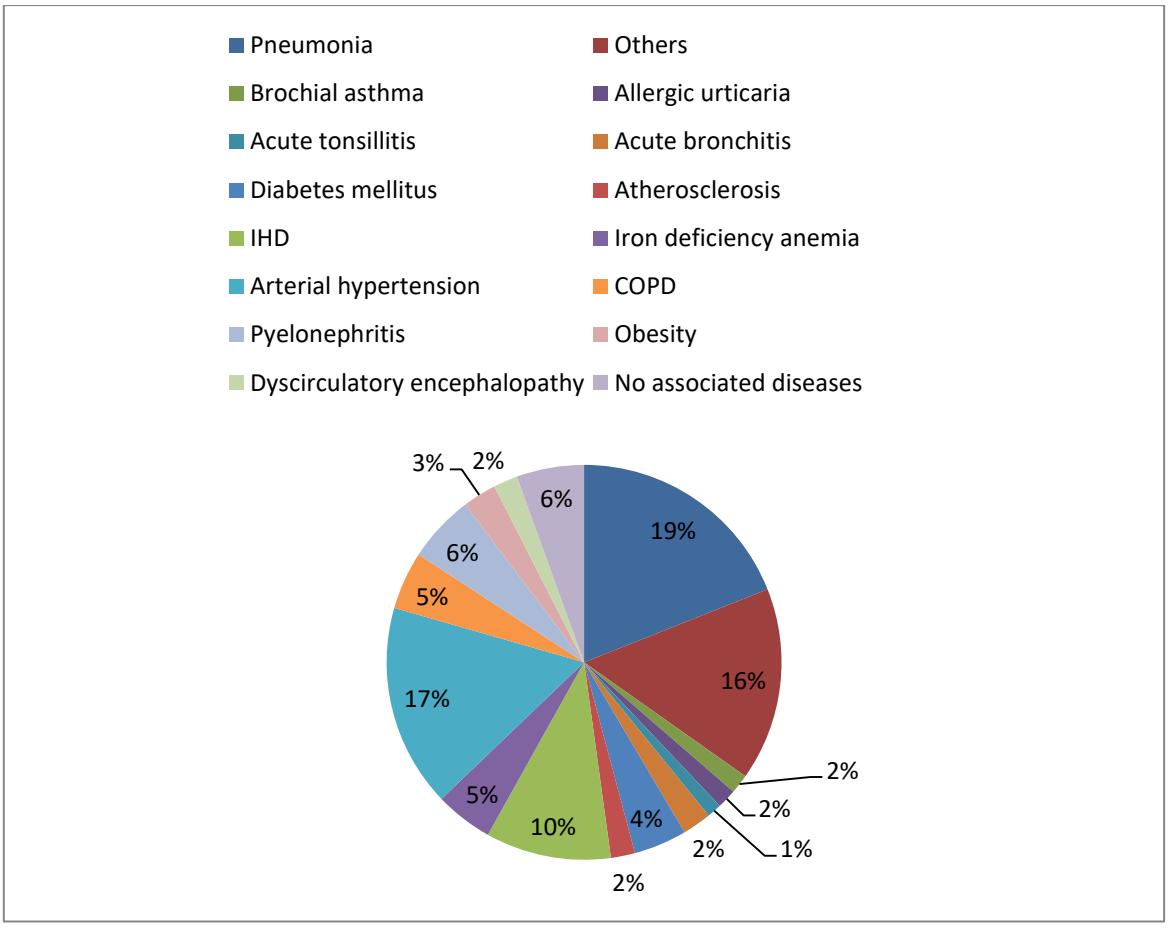


Figure 5. Concomitant diseases of patients with coronavirus infection (virus not identified) in Shakhtinsk from August to December 2020

The occupational composition of patients with coronavirus infection in Shakhtinsk in 2020 is shown in Figure 6.

An analysis of the professional composition of patients with coronavirus infection (the virus has not been identified) in Shakhtinsk revealed that the largest part of the sick are pensioners, 42%. Sick with the status of “housewife / unemployed” make up 15%, then children under 6 years old - 8%, the third group - 6%, miners - 5%, students - 3% and employees of private structures - 3%.

An analysis of clinical symptoms that were recorded in patients with coronavirus infection (the virus was not identified) revealed that in 70% of cases there is an increased body temperature of up to 380C and above, general weakness in 68% of patients, cough - 63%, shortness of breath - 52%, pain in breasts - 32%. Lack of smell and lack of taste were noted in 2.5% and 0.8% of patients, respectively.

We analyzed the drugs that were received by patients with a diagnosis of coronavirus infection (the virus was not identified) and found that 78% of patients were treated with ceftriaxone, 56% were prescribed ambroxol, 22% - zitmak, 20% - dexamethasone and 12% ciprofloxacin.

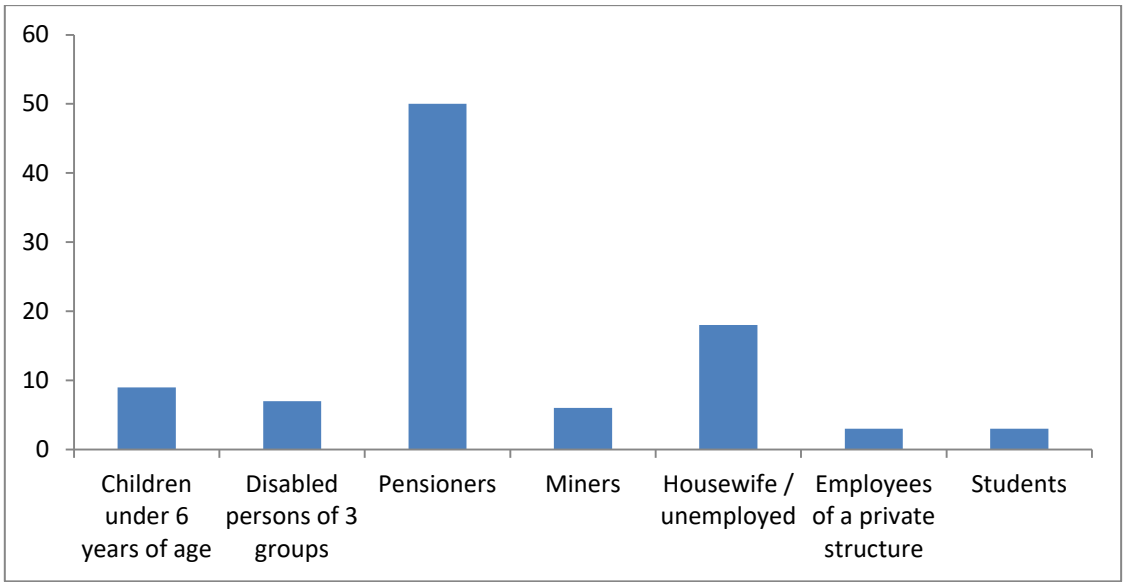


Figure 6. Professional composition of patients with coronavirus infection in Shakhtinsk from August to December 2020

Thus, analyzing the data of the discharge epicrisis of patients with coronavirus infection (the virus is not identified) in Shakhtinsk from August to December 2020, it was established that the greatest epidemiological significance is the persons of the age category from 50 to 89 years old, living in the city, who are pensioners or the same housewives / unemployed, with such concomitant diseases as pneumonia, arterial hypertension, coronary heart disease, pyelonephritis, chronic obstructive pulmonary disease, diabetes mellitus and iron deficiency anemia and with clinical symptoms: fever, general weakness, cough, shortness of breath.

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# EPIDEMIOLOGICAL SITUATION REGARDING NEW TYPE CORONAVIRUS INFECTION (COVID-19) AMONG MEDICAL WORKERS IN MOLDOVA

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**Abstract.** The emergence of the new coronavirus (SARS-CoV-2) has led to a rapid spread of the induced infection (COVID-19) worldwide. The article deals with the diminishing the negative impact on the health system and the national economy, thanks to the up-to-date adjustment of the control and response measures developed in the process of epidemiological surveillance of COVID-19 infection among medical staff. It is proved that ehe share of infection cases among medical workers from the total number of infections is 9.45%, and approximately 39.08% of infections were registered in Chisinau. The majority of cases being registered among nurses (41.8%) and more frequently affecting health workers (71.4%), the ratio between women and men is 4:1.

**Key words**: COVID-19, medical workers, SARS-CoV-2, infection diseases.

**Introduction.** The emergence of the new coronavirus (SARS-CoV-2) has led to a rapid spread of the induced infection (COVID-19) worldwide. On 30 January 2020, the WHO declared COVID-19 a public health emergency of international interest, and on 11 March 2020, the outbreak of COVID-19 was described as a pandemic [5]. As of February 1, 2021, more than 103,989,900 cases and more than 2 million deaths have been reported globally [4]. In the European Union, as of February 1, 35,003,091 cases and 767,235 deaths caused by the SARS-CoV virus have been reported. [2]. The incidence for the last 14 days in the EU was 421 cases per 100,000 population, approximately twice as high as in the Republic of Moldova (200 cases per 100,000 population), where the first COVID-19 case was registered on March 7, 2020 [3], and already on February 1, 2021, a total of 159,804 confirmed COVID-19 cases have already been registered, out of which over 3400 deaths.

**Aim of the study.** Diminishing the negative impact on the health system and the national economy, thanks to the up-to-date adjustment of the control and response measures developed in the process of epidemiological surveillance of COVID-19 infection among medical staff.

**Materials and methods.** Data on incidence, prevalence and mortality of COVID-19 pine were analyzed and evaluated among medical staff, based on the selection of data from the digital information-epidemiological surveillance system of COVID-19 infection with SARS CoV-2 virus.

**Results.** From the beginning of the pandemic in our country until February 1, 2021, 42,124 medical workers were tested to the presence of SARS-CoV-2. Of these medical workers tested positive were 14,709 people, of them 4,358 doctors; nurses 6,147, cleaning staff 1,988, auxiliary staff 2,216. As a percentage of the groups of medical workers mentioned above, the following shares accounted for: doctors - 29.6%, nurses - 41.8%, cleaning staff - 13.5% and auxiliary staff - 15.1%. The share of infection cases among medical workers from the total number of infections is 9.45%. The share of deaths in relation to the total number of infected medical workers is 0.5%.

**Discussions.** The results of this study can be explained by the fact that medical staff both in the world and in the Republic of Moldova is the most exposed social class due to daily

contact with infected or potentially infected people, as well as closer contact between subjects and shorter social distance, granting the medical act as well as the subsequent contacting of the infection in the community. At the same time, an assessment of the situation in medical institutions with a review of the cause of infection of medical workers (insufficiency of personal protective equipment, insufficient training) would have an expected effect in reducing the number of infected medical staff [1].

**Conclusions.** The share of infection cases among medical workers from the total number of infections is 9.45%, and approximately 39.08% of infections were registered in Chisinau. The majority of cases being registered among nurses (41.8%) and more frequently affecting health workers (71.4%), the ratio between women and men is 4:1.

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# FREQUENCY OF COVID-19 DETECTION IN NUR-SULTAN FOR THE PERIOD 2020-2021

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**Abstract**. This article will provide information on the prevalence of coronavirus infection (Covid-19) and the frequency of detection of COVID-19 among the population of Nur-Sultan, Republic of Kazakhstan for the period from September 2020 to March 2021. And also a comparative analysis was carried out to identify coronavirus infection in the Republic of Kazakhstan for the entire period since the beginning of the pandemic.

**Key words**: laboratory, diagnosis, PCR, coronavirus, disease.

**Introduction**. Today, every person on earth, regardless of which country he lives in, is worried about the outbreak and the rapid spread of a new disease - coronavirus infection. The coronavirus infection (COVID-19) pandemic has become worldwide in a short period of time. The number of infected people in Kazakhstan and around the world increases every day [1].

The new decade of the 21st century (2020) started with the emergence of a novel coronavirus known as SARS-CoV-2 that caused an epidemic of coronavirus disease (COVID-19) in Wuhan, China. It is the third highly pathogenic and transmissible coronavirus after severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) emerged in humans [2].

The COVID-19 epidemic ("coronavirus disease 2019") has already gone down in history as an emergency of international importance [3]. We still have to study the specifics of this epidemic, learn lessons, analyze the shortcomings of ensuring the biological safety of the population. One thing is clear: new viruses will appear, this is an integral part of our world. Humanity must learn to confront these threats. Currently, it is known about the circulation among the population of four coronaviruses (HCoV-229E, -OC43, -NL63, -HKU1), which are present year-round in the structure of ARVI, and, as a rule, cause damage to the upper respiratory tract of mild and moderate severity [4].

It is known that coronaviruses were first isolated in 1975, currently they are divided into 4 subfamilies (alpha, beta, delta and gamma) and more than 30 species, the list of which is constantly growing. The reason for the emergence of new coronaviruses that cause severe and rapidly spreading diseases is spontaneous mutations. Therefore, all types of coronaviruses can potentially be dangerous to humans [5].

The diagnosis is established on the basis of data from the epidemiological history, clinical examination and laboratory results. Laboratory diagnosis is specific: detection of SARS-CoV-2 RNA by PCR. The main type of biomaterial for laboratory research is material obtained by taking a swab from the nose, nasopharynx and/or oropharynx, as well as bronchial lavage water obtained by fibrobronchoscopy (bronchoalveolar lavage), sputum, biopsy or autopsy lung material, whole blood, serum, urine [4].

According to WHO recommendations, detection of SARS-CoV-2 RNA in nasopharyngeal samples by real-time polymerase chain reaction (RT-PCR) is a common method for diagnosing COVID - 19 infection. "Molecular diagnostics", including polymerase

chain reaction (PCR) testing, detects the genetic material of the virus and, thus, allows you to determine whether a person is currently infected with the SARS-CoV-2 virus [6].

In our article, we provide an overview of data on the frequency of detection of COVID-19 among the population of Nur-Sultan, Republic of Kazakhstan for the period from September 2020 to March 2021. And also a comparative analysis was carried out to identify coronavirus infection in the Republic of Kazakhstan for the entire period since the beginning of the pandemic (data obtained from open sources of the Ministry of Health of the Republic of Kazakhstan).

In the process of work, a retrospective analysis of PCR diagnostics of the clinical material of the examined persons for the detection of coronavirus (COVID-19) was carried out. The study and sampling of the material was carried out on the basis of the BIO Lab clinical diagnostic laboratory in Nur-Sultan. The research method - polymerase chain reaction, was carried out in an automated way on the equipment DT Prime 5M1. Detection of SARS-CoV-2 RNA in nasopharyngeal samples by real-time polymerase chain reaction (RT-PCR) is the main method for diagnosing COVID-19.

In total, for the period from September 2020 to March 2021, 30,545 people underwent PCR diagnostics in the BIO Lab in Nur-Sultan: in September - 658; in October - 1482, in November - 3745, in December - 4551, in January - 6055, in February - 4507 and in March - 9547 people.

Positive results were obtained in 446 cases, which amounted to 1.46% for the entire study period, negative results were obtained, respectively, in 30,099 applicants, which amounted to 98.54%. The number of positive cases of COVID-19 by month is presented in Table 1.

Table 1. The result of PCR diagnostics for the period of 2020-2021.

| | **Number of investigated** | **Positive** | | **Negative** | |
|---|---|---|---|---|---|
| | | **abs.** | **%** | **abs.** | **%** |
| September, 2020 | 658 | 11 | 2% | 647 | 98% |
| October, 2020 | 1482 | 33 | 2,2 % | 1449 | 97,8% |
| November, 2020 | 3745 | 27 | 0,72 % | 3718 | 99,28% |
| December, 2020 | 4551 | 87 | 1,9 % | 4464 | 98,1 % |
| January, 2021 | 6055 | 74 | 1,2 % | 5981 | 98,8 % |
| February, 2021 | 4507 | 34 | 0,75 % | 4473 | 99,25 % |
| March, 2021 | 9547 | 180 | 1,9 % | 9367 | 98,1 % |
| **Total** | 30545 | **446** | **1,46%** | 30099 | 98,54% |

As can be seen from the table 1. in September, a total of 658 people were examined. Positive results were obtained in 11 people, which amounted to 2% of all surveyed this month. In October, out of 1482 surveyed, 33 people had positive results, this amounted to 2.2%. In November, out of 3745 people who passed the diagnosis, only in 27 cases the result was positive, amounting to 0.72%. In December with positive results were diagnosed in 87 people (1.9%), in January - 74 (1.2%), in February and March - 34 (0.75%) and 180 (1.9%), respectively. The results of the obtained data in percentage terms can be seen in diagram 1.

Based on these data, it is difficult to say for sure whether the incidence of coronavirus (COVID-19) in Nur-Sultan has increased or decreased. Based on the data, it can be seen that the virus circulates among the population due to its regular occurrence.

We would also like to review the data on cases of coronavirus infection in the Republic of Kazakhstan for the period from March 13, 2020 to April 2021, during the pandemic in the Republic of Kazakhstan, the total number of cases was 294,946 people [7]. The number of registered cases in the Republic of Kazakhstan in the context of regions is

increasing daily, thus, for April 19, 2021, the statistics were: Nur-Sultan - 10, Almaty -16, Shymkent - 6, Akmola region - 12, Aktobe region - 4, Almaty region - 38, Atyrau region - 8, East Kazakhstan region - 4, Zhambyl region - 15, in West Kazakhstan, Karaganda, Pavlodar and North Kazakhstan regions - 2 cases each, Kostanay region - 6, Kyzylorda region - 1, Mangistau region - 4 and in Turkestan region the number of new cases was - 3 [8].

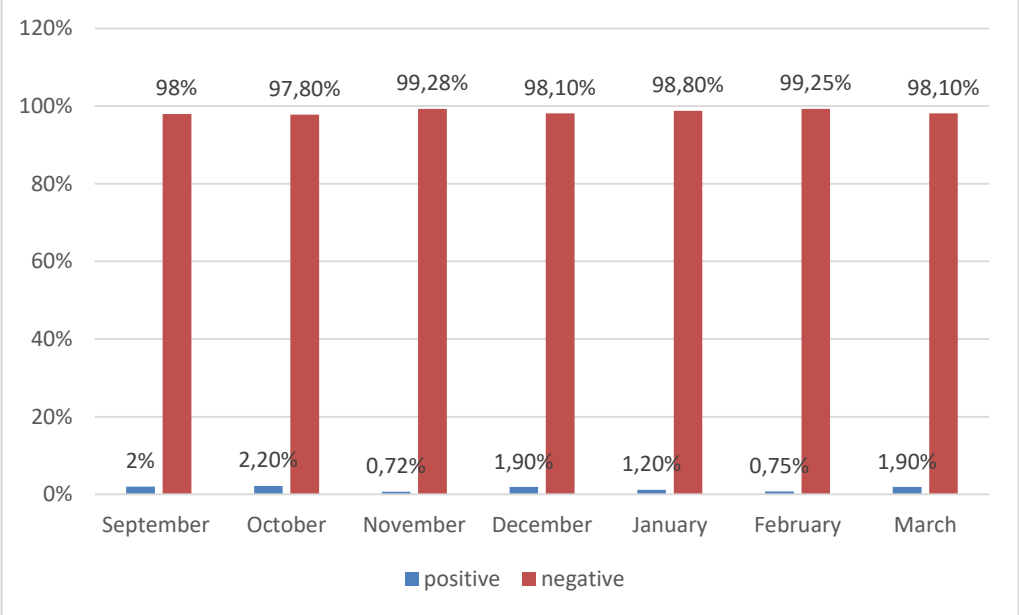


Figure 1. Frequency of detection of COVID-19 based on PCR results

To prevent the spread of coronavirus infection and to develop herd immunity around the world, a campaign to vaccinate the population has begun. In the Republic of Kazakhstan, active work is also underway to organize and pass vaccination by the population. Preparations for the COVID-19 vaccination campaign in the Republic of Kazakhstan have been carried out since 2020. Taking into account the availability of vaccines, at the first stage, vaccination of persons with a high risk of infection with coronavirus infection was implemented; today, as vaccines become available, coverage of the population with vaccination against COVID-19 is expanding [8].

Thus, from the results we have obtained, we can conclude that the current situation dictates to all of us the need to strengthen epidemiological surveillance of coronavirus infection and ensure a through epidemiological analysis of the incidence.

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# ENTOMOLOGICAL PREPARATIONS – A POTENTIAL SOURCE OF ANTIVIRAL PEPTIDES

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**Abstract.** There is currently no specific treatment for Coronavirus disease 2019 (COVID-19), therefore effective measures to find novel molecules with antiviral potential are needed. Some known antiviral drugs interfere with host cell function and result in toxicity. In this context, antimicrobial peptides originate from natural sources could be an interesting alternative. Insects could be exploited as such sources determined by the possibility of obtaining from their extracts various biologically active substrates and products that are formed in the processes of morphogenesis and adaptation to maintain homeostasis. Among the advantages of natural antiviral peptides, we can list, the possibility of high specificity, low toxicity, also some additional effects such as anti-inflammatory, immunomodulatory effect and antioxidant capacity.

**Key words**: antiviral peptides, imupurin, imuheptin.

**Introduction**. The Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) or (COVID-19) was declared a pandemic by the World Health Organization and considered as one of the most life-threatening pandemic viral infections that humanity has witnessed in the past decades. This is affecting the world economy and will later cause severe implications on human welfare. Accordingly, finding an antiviral drug or a vaccine is the only route for the survival of humans against COVID-19 infection. Many substances are under study and to date, no specific antiviral treatment has been confirmed [1].

Viruses remain a major cause of human diseases today, even though scientific advances have led to the production and distribution of vaccines and antiviral drugs. For long times, insects were used as medicine, and today, scientists are studying and trying to rediscover many natural products from insects [2]. The interest in insects was determined by the possibility of obtaining from their extracts various biologically active substrates (lipids, proteins, carbohydrates, enzymes, vitamins, antioxidants, ions etc.) and products that are formed in the processes of morphogenesis and adaptation to maintain homeostasis. The insects in contact with the microbial agent or adverse factor have formed a variety of proteins and peptides with antibacterial, antifungal, antiviral, immunomodulatory, anti-inflammatory, antioxidant, antitumor, hepatoprotective, antithrombotic, antihypertensive and detoxifying activity. Several insect peptides and their synthetic derivatives are currently known with antiviral activity (cecropin A, melitin, melectin, ponericin, spinigerin and synthetic analogues – alloferon, omiganan, iseganan, cecropin + mageinin) [3, 4, 5, 6, 7, 8].

A considerable number of AMP genes have been identified in *Drosophila*, the honey bee *Apis cerana* and the silkworm *Bombyx mori*. Antimicrobial peptides (AMPs) with antiviral activity (antiviral peptides: AVPs) have become a big research interest and already show immense potential to become pharmaceutically available antiviral drugs. The numerous novel molecules with antiviral properties have now been isolated from the moth *Hyalophora cecropia* (cecropin A), from bee (*Apis mellifera*) venom (melittin), from wasp (*Vespula lewisii*) venom (mastoparan), from spider (*Lachesana tarabaeve*) venom (lactarcin), and the hemolymph of blowfly (*Calliphora vicina*) (alloferon 1 and 2). The antimicrobial peptides with antiviral activities against human viruses are still undergoing studies, emphasizing the most promising ones that may become medicines for clinical use [2, 9, 10].

Antimicrobial peptides are biologically active molecules produced by a wide variety of organisms as an essential component of their innate immune response against invading pathogens. AMPs are short sequence peptides polymer ranging from 10 to 100 amino acids, positively charged, amphiphilic. They have been isolated from organisms, belonging to six kingdoms, including humans. The Antimicrobial Peptide Database contains more than 3000 antimicrobial peptides, among which are 189 AMPs with antiviral activities [1, 11].

AMPs provide a wide range of biological functions (see Figure 1A). In addition to antimicrobial, antibacterial, antiviral, antifungal, antiparasitic activity, AMPs may have more specific effects (see Figure 1B) [12].

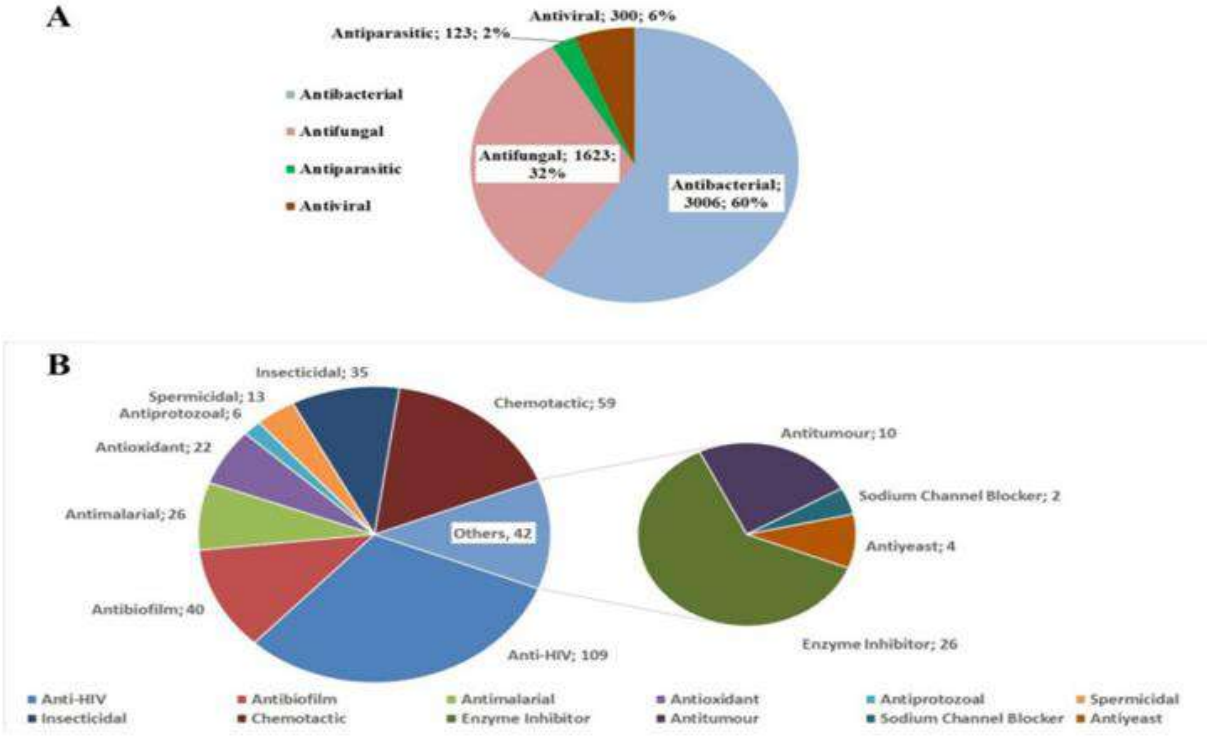


Figure 1. Distribution of AMPs by their biological activity according to dbAMP data: general (A) and special (B).

The study of AVPs has been the focus of numerous research projects in recent years, also their structure and mechanism of action (Fig. 2), these are mostly called virucidal when they act directly by inhibiting the viral particle; or by competing for the protein link site in the host cell membrane, interfering in their interaction and consequent adsorption. They also may influence other stages of the viral cycle and the suppression of viral gene expression is one of them [10].

The antiviral activity of the AMPs was shown against enveloped RNA and DNA viruses, except some non-enveloped viruses. The antiviral activity of AMPs develops due to adsorption on the viral surface or direct effect on the viral envelope. The AMPs positively charged residues enable them to interact electrostatically with negatively charged cell surface molecules such as heparan sulfate. Heparan sulfate consists of glycosaminoglycan molecules that are strongly related to viral attachment. It was proven that AMPs that block heparan sulfate should be able to reduce the viral infection. Also, the AMPs antiviral effect is related to their ability to inhibit the spread of a virus from a cell to another cell across tight junctions (cell-to-cell spread) or inhibit the formation of giant cells (syncytium) [1].

Of particular interest is the potential for the use of peptides that tend to self-assembly. The therapeutic potential of peptide molecules prone to aggregation is truly enormous due to

the diversity of their structure and properties, in particular, the ability to form supra-molecular complexes with other peptides and proteins. It was shown that peptide co-aggregation is necessary for the destruction of bacterial membranes. Kurpe et al. proposed another mechanism of the antimicrobial action of peptides, based on the directed co-aggregation of the amyloidogenic peptide with the target protein and the subsequent dysfunction of this protein. Using programs predicting amyloidogenic regions in a protein molecule, sequences of peptides with a tendency to aggregate with the target protein were selected. Peptides that tend to co-aggregate with viral proteins or prevent the virus from interacting with cell receptors can be used against the spread of coronavirus infection caused by SARS-CoV-2 [12].

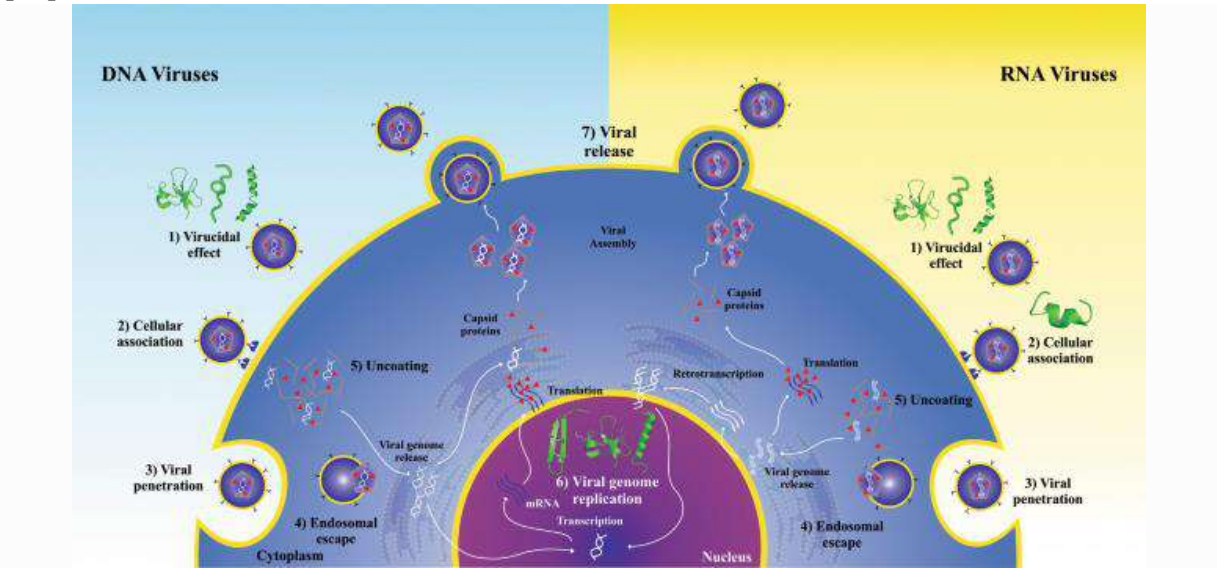


Figure 2. Antiviral peptide inhibition sites on viral replication cycle (Vilas Boas L.C.P.,2019). The antiviral peptides with a described mechanism of action were placed in their inhibition sites as follows: 1, virion inhibition; 2, adsorption; 3, viral penetration; 4, endosomal escape; 5, viral uncoating; 6, viral genome replication and 7, release of mature virions.

The wide variety of AMPs and their functions indicates the complexity of their defense mechanisms. The selectivity of AMPs action is regulated by inducible production and limited localization at the lesion sites or by the nature of the peptide. The selectivity of AMPs can be determined by the physicochemical and structural parameters such as conformation, charge, hydrophobicity, hydrophobic moment, amphipathicity. Despite the great variety of the primary structure, AMPs form typical elements of the secondary and tertiary structure. The important activity of AMP is disrupting the integrity of the cell membrane and cell wall of bacteria. At the moment, five such mechanisms are known: the threshold concentration mechanism, the conformational phase transition mechanism, the keg mechanism, the toroidal pore mechanism and the “carpet” mechanism. Kurpe et al. described a new mechanism based on the direct co-aggregation of amyloidogenic peptide with protein or protein silencing mechanism. Because the SARS-CoV-2 spike protein is critical for penetration into the host cell, it could be an interesting target protein option for the development of antiviral peptides. The identification of regions of a protein molecule prone to aggregation/formation of amyloid fibrils is an important step for the development of AMPs acting on the basis of a co-aggregation mechanism [12].

The most important mechanisms of action of AVPs are as follows: interacting with glycosaminoglycans which act as receptors for viruses, so the peptides can compete with viruses for binding to these receptors; preventing the virus from entering the cell by binding

to the receptors needed for the virus entrance; inhibition of fusion or integration of the virus to the target cell membrane; inhibition of the viral gene expression; inactivation of ribosomes and inhibition of the viral protein chain elongation; induction of inflammatory and immunomodulatory responses that indirectly induce antiviral properties; direct degradation and deformation of the lipid coating of the viruses [13].

In the 2002-2003 years, under the aegis of Mr Victor Ghicavîi, corresponding member of the ASM, collaborations were initiated with Mr Mircea and Veaceslav Ciuhrii in the research of products of entomological origin (entoheptin, imuheptin, imupurin, adenoprosine), obtained from *Lymantria dispar* at different stages of development. The *in vitro* study of antimicrobial properties showed that the investigated substances (entoheptin, imuheptin and imupurin) did not show direct antiviral activity on RNA-dependent virus (poliomyelitis vaccine type 1, type 2, type 3, vesicular stomatitis virus) and DNA-dependent (herpes simplex virus type 1) [4,14]. On the other hand, clinical studies have shown that including drugs of entomological origin in the complex treatment of chronic viral hepatitis has contributed to a faster and more marked improvement of the clinical picture, a significant decrease of transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, a cholestasis improvement, a reduction of lipid peroxidation processes, an amplification of the synthetic function of the liver, a modulation of the parameters of the immune system. The complex treatment with entomological preparations of patients with chronic hepatitis of different genesis has contributed to a faster improvement of asthenia, pain and dyspeptic syndrome, a significant decrease of moderate cytolysis and cholestasis syndrome, lipid peroxidation processes, modulation of immune system parameters with the restoration of cellular immunity [4, 14, 15, 16].

The screening of the anti-inflammatory properties allowed us to find that the drugs of entomological origin (entoheptin, imuheptin, imupurin) do not prevent inflammation but had an anti-inflammatory activity comparable to that of diclofenac. The involution of oedema occurred 24-48 hours after the induction of inflammation. The investigated substances showed anti-inflammatory effect when they were administered 3-5 days before induction of inflammation, while use 1 hour before, caused a slower and less obvious involution, but more important than in the control group. The comparative analysis between the anti-inflammatory potential of entoheptin, imuheptin, imupurin and diclofenac revealed that entoheptin possesses the strongest anti-inflammatory activity, achieving complete healing in 48 hours, followed by diclofenac and imuheptin. Imupurin showed the weakest anti-inflammatory action, but it was more intense than in the group of untreated animals [17]. The study of the influence of entomological drugs on the exudative and proliferative processes of subacute inflammation showed that imuheptin did not significantly influence the evolution of subacute inflammation and imupurin slightly inhibited inflammatory exudates by 1-5% and weight of granulation tissue by 3-8%, but importantly decreased IL-6 level and increase IL-10 level. Imuheptin decreased the levels of the proinflammatory cytokines TNF-alpha, IL-1-beta, IL-6 and the anti-inflammatory IL-10. Imuheptin and imupurin reduced the percentage of immature neutrophils, monocytes and granulocytes, with a non-essential increase in the percentage of lymphocytes, basophils and eosinophils [18].

The inflammatory process, linked with higher production of ROS, induces oxidative stress and reduces cellular antioxidant capacity. The animals with subacute inflammation expressed an imbalance between the pro-oxidant and antioxidant system revealed by increasing the DAM level, total thiol, native thiol, prooxidant-antioxidant balance and decreased the SOD activity. Imuheptin after 7 days of administration decreased the level of DAM and pro-oxidant-antioxidant balance, and increased SOD activity and level of total thiol. Imupurin caused a more pronounced decrease in DAM level and increased SOD activity. Entomological preparations showed antioxidant activity through their components:

unsaturated fatty acids, proteins, peptides and amino acids (serine, arginine, histidine, lysine, methionine, cysteine, etc.); phenolic compounds (flavones, flavonols, flavanones flavanonols, flavanols (catechins), an[1]thocyanins and chalcones, etc.), tannins (proanthocyanidins, etc.), alkaloids, terpenoids; antioxidant enzymes (SOD, CAT, GPx, GST). Several mechanisms can be responsible for antioxidant action of entomological preparations: the presence of hydroxyl groups, which confer the ability to stabilize unpaired electrons; protection of cells against lipid peroxidation; acting as hydrogen donor agents, singlet oxygen and superoxide radicals quencher; activating antioxidant enzymes and metal chelation; free radical scavenging (superoxide anion, hydroxyl radical); changes in the activity of antioxidant enzymes (SOD, CAT, GST, GPx) and the level of endogenous antioxidants (GSH) [19].

The analysis of the obtained results regarding the immunotropic properties reveals that the drugs of entomological origin studied increased the nonspecific host resistance and intensified the phagocytosis of neutrophils and macrophages in a dose-independent manner. The immunotropic effect is determined by the active substance, as well as their quality, the presence of peptides, lipoprotein complexes, polysaccharides and other protein lysates which are responsible for stimulating the immune system and inactivating microbial agents. *In vitro* studies with monoclonal antibodies have shown that imupurin and imuheptin increase the level of T lymphocytes (CD3+) insignificantly and decrease slightly B lymphocytes (CD20+) and increase the percentage of T-helpers (CD4+). Analysis of the immunomodulatory index showed that imuheptin and imupurin possess immunomodulatory action when the functional activity of neutrophils was increased and stimulatory action if the functional activity of neutrophils was decreased. Entoheptin determined stimulatory properties on the functional activity of neutrophils regardless of their initial degree. Imupurin and imuheptin exert an immunomodulatory action on cellular immunity revealed by increased T-helper lymphocytes (CD4), an insignificant increase in cytotoxic lymphocytes (CD8) and the immunomodulation index. The inclusion of imupurin in the complex treatment of patients with human immunodeficiency virus infection contributed to a positive dynamics of T-helper lymphocyte count and viral load, as well as to normalization of ALAT level and reduction of thymol sample. The entomological preparation had a beneficial influence on cellular immunity, possibly by restoring the Th1/Th2 balance, with the manifestation of an indirect antiviral effect by normalizing the profile of cytokines released by T lymphocytes [4, 14, 20, 21, 22].

**Conclusions.** Drugs of entomological origin are considered to be the most promising direction and source of biologically active substances with various properties. The discovery of new antiviral drugs will supplement the existing therapies and will provide a possibility to treat viral diseases that cause serious pandemics. Research in this field should focus on the study of the composition of entomological products, the development of synthetic analogues, the elucidation of pharmacological properties and effectiveness in different pathological conditions. The analysis of insect metamorphosis at different stages of development, the elaboration of methods and techniques for the separation of active compounds, the studies of pharmacokinetics, pharmacogenetics and toxicology will ensure the development of entomotherapy, used in folk medicine, through valuable scientific arguments.

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# DIGITAL MECHANISM OF ONLINE DISTANCE LEARNING TOOLS IN THE EDUCATIONAL PROCESS

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**Abstract**. The situation that arose in connection with the pandemic caused by the COVID-19 virus demanded to revise the content and organization of distance learning for students of the "Astana Medical University".

**Key words**: distance learning (DL) Moodle, digital technologies, Internet resources, Zoom, Microsoft Teams, Learning Apps.org.

**Introduction**. Today, distance learning (DL) technology during a pandemic is relevant in all areas of education. Its relevance is evidenced by a large number of publications devoted to the theoretical aspects of the use of distance learning technology and the mechanisms of its implementation in the educational activities of medical universities [1, 2]. The article is devoted to online tools that a teacher can use in their professional activities not only in the implementation of DL, but also in offline classes and in blended learning technology. There are several hundred online tools, they differ in: the level of complexity; tasks that are solved in the educational process; the presence of ready-made didactic materials; the presence of instructions for working with the tool itself, etc. [1, 2, 3, 4].

**Purpose**: to study the attitude of students of the "Astana Medical University" to the transition to distance learning during a pandemic.

**Materials and methods.** For the organization of distance learning, teachers have compiled a number of online tools - these are electronic courses (interactive, slides, presentations, documents, etc.), electronic tests (Google, Kahoot, Quizizz), electronic content, e-books, videos - and audio content, holding a video conference and viewing their recordings (Zoom, Microsoft Teams, Learning Apps.org, etc.), blogs, forums, polls, feedback forms (homework, questionnaires).

**The main part.** With the help of online tools for students, you can create both online and mixed learning paths using distance learning, in preschool, the teacher's task is to organize the teacher's work online as efficiently and effectively as possible [4]. It can also be noted here that online tools can be used not only in the process of implementing blended learning technology, but also in a traditional lesson. Thus, the study of DL allows you to improve information and communication competence.

Each training system can have different options for interfaces, within which a certain set of tools is implemented. This can be a traditional training portal, a mobile portal, a mobile application (for online and offline learning), non-standard interfaces (for example, chat bots). Today, the department implements distance learning as much as possible in the educational process within the corporate network. However, given the requirements of a modern student for mobility and for the quality of electronic content, a traditional portal is no longer enough to organize effective e-learning. Accordingly, the introduction of mobile portals and applications is really necessary for DO.

We can confidently assert that the digital mechanism of online tools that we use in the educational process is working successfully, allowing us to solve various tasks in the educational process: create content for classes, develop didactic materials and assignments for

assessing students, receive feedback, organize joint activities, etc. e. For the competent use of online tools, it is important to rely on a methodology: an understanding of what electronic content is and how it is developed. Only after this understanding appears, you can proceed to the choice of a development tool.

In order to conveniently navigate online tools, we have prepared content for each discipline for all faculties. Such content allows the student to independently prepare theoretical material, perform practical tasks, SROP, perform test tasks, etc., which allows the teacher to solve educational problems.

So, for example, the main part of the tools - the Online platform that allows you to manage the learning process - the Moodl platform is a service that can be used to support the educational process, this platform allows students to determine how much they understand the topic being studied, it contains many already developed tasks, tests, videos, etc. It is especially important to note that this platform allows you to create different types of tasks using one service, as well as create applications using different templates. Using Google Forms, you can create a quiz, questionnaire, feedback form or test, as it allows you to add questions of different types: open-ended question; with several correct answers; with one correct answer; a question with a picture or video; numeric answer.

One of the services for creating test items with a choice of the correct answer on mobile devices is Kahoot, which allows the teacher to create tests and quizzes that include a wide range of multimedia elements such as videos, images and text. The above services are a digital tool for formative assessment of students.

**Results and discussion.** When choosing a distance learning system, it is important to decide not only on a set of tools and an interface (method of teaching and content presentation), but also on the specifics of the DL implementation process itself.

DL is an e-learning tool for learners that can be independently and effectively used in the educational process to improve the quality of knowledge. The most important result of the massive introduction of DL was that the teachers of the department organized work with students who learned to use e-learning technologies to organize preparation for the lesson.

The main advantage of the e-learning course is the ability to restructure the scheme of work with students in order to increase the effectiveness of training. The introduction and development of distance learning is one of the productive means for solving urgent problems in the whole of the entire developed society.

**Conclusions.**

1. Thus, today students at the department have full access to distance courses in all disciplines.

2. Systematic work with a distance course motivates students to a deeper understanding of the theoretical program material, activates their independent cognitive activity.

3. Students can take an active part in scientific conferences that are held in medical universities in the near and far abroad, publish their scientific research, created on the basis of platforms such as Moodle, Microsoft Teams, which significantly increases the motivation of students to master the Internet resource for effective use in the educational process and the future in their professional activities.

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# ANALYSIS OF THE COURSE OF A NEW CORONAVIRUS INFECTION IN PATIENTS WITH CONCOMITANT DISEASES, INCLUDING VARIOUS LUNG PATHOLOGIES

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**Abstract.** The article deals with analyze the course of a new coronavirus infection in 607 patients with concomitant diseases, including various lung pathologies. As a result of the analysis, it was revealed that 76.4 % of patients with a new coronavirus infection had various comorbidities. In 8.2% of patients, the course of a new coronavirus infection occurred against the background of chronic lung diseases. It was somewhat surprising that patients with initial lung damage as a result of various lung diseases and suffering from a new coronavirus infection did not require any ventilation support, either in the form of non-invasive or invasive ventilation.

**Key words:** SARS-COV-19, comorbidity, lung pathology

**Introduction**. The presence of comorbidity is a risk factor for disease incidence and mortality in patients with COVID-19 [1]. It was found that in the structure of patients with a new coronavirus infection the proportion of patients with concurrent chronic lung diseases ranges from 8 to 19% [2]. According to the world literature, chronic obstructive pulmonary disease was mostly registered in patients who died from COVID-19 [3]. The analysis of 1590 laboratory-confirmed cases of Covid-19 carried out by foreign researchers showed the absence of diagnosed bronchial asthma in patients [4]. The presence of latent or active tuberculosis is suggested to increase the susceptibility to SARS-COV-19 infection, as well as lead to faster development of pneumonia and increase the severity of COVID-19 [5].

**Results**. The average age of the patients was 62 (55; 64) years. There were 46.7% of men and 53.3% of women. 76.4 % of patients had various comorbidities (Table 1). The largest number of patients suffered from diseases of the circulatory system (45.8%), diseases of the endocrine system, eating disorders and metabolic disorders (12.5%), as well as certain infectious and parasitic diseases (4.8%).

In 8.2% of patients, the course of a new coronavirus infection occurred on the background of chronic lung diseases. The structure of concurrent lung diseases in patients with COVID-19 is presented in Table 2.

All patients without comorbidity (143 people) were discharged with recovery. It is worth noting that no deaths were recorded in the groups of patients with diseases of the endocrine system and eating disorders - E00-E90 (76 people), diseases of digestive system - K00-K93 (16 people), diseases of respiratory system - J00-J99 (12 people), blood diseases - D50-D89 (4 people), diseases of nervous system - G00-G99 (3 people), diseases of the skin and subcutaneous tissue - L00-L99 (3 people), mental and behavioral disorders - F00-F99 (2 people), congenital anomalies - Q00-Q99 (2 people), diseases of the eye and adnexa - H00-H59 (1 person).

73.97% of patients required oxygen support. All patients with the disease caused by the human immunodeficiency virus, toxic substances and multiple myeloma required artificial lung ventilation. 75% of patients with cerebrovascular diseases needed non-invasive and invasive lung ventilation. About half of the patients (48.39%) with concurrent coronary heart disease had various options of ventilation support.

Table 1. Distribution of patients with COVID-19 into disease groups according to ICD-10

| ICD-10 code | Disease group (distribution according to ICD-10) | Incidence | Percentage |
|---|---|---|---|
| - | Absence of comorbidity | 143 | 23,6 |
| I00-I99 | Diseases of the circulatory system | 278 | 45,8 |
| E00-E90 | Endocrine, nutritional and metabolic diseases | 76 | 12.5 |
| A00-B99 | Certain infectious and parasitic diseases | 29 | 4,8 |
| C00-D48 | Neoplasms | 17 | 2.8 |
| K00-K9 | Diseases of the digestive system | 16 | 2,6 |
| N00-N99 | Diseases of the genitourinary system | 13 | 2,1 |
| J00-J99 | Diseases of the respiratory system | 12 | 2,0 |
| D50-D89 | Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism | 4 | 0,7 |
| M00-M99 | Diseases of the musculoskeletal system and connective tissue | 4 | 0,7 |
| S00-T98 | Injury, poisoning and certain other consequences of external causes | 4 | 0,7 |
| G00-G99 | Diseases of the nervous system | 3 | 0,5 |
| L00-L99 | Diseases of the skin and subcutaneous tissue | 3 | 0,5 |
| F00-F99 | Mental and behavioral disorders | 2 | 0,3 |
| Q00-Q99 | Congenital malformations, deformations and chromosomal abnormalities | 2 | 0,3 |
| H00-H59 | Diseases of the eye and adnexa | 1 | 0,2 |
| Total | | 607 | 100 |

Table 2. The structure of concurrent lung diseases in patients with COVID-19

| n/n | Lung diseases | Incidence | Percentage |
|---|---|---|---|
| 1 | Long-term effects of respiratory tuberculosis and unspecified tuberculosis | 2 | 5,3 |
| 2 | Malignant neoplasm of the bronchi and lung of unspecified localization | 2 | 5,3 |
| 3 | Neoplasm of an undetermined or unknown nature of the trachea, bronchi and lung | 2 | 5,3 |
| 4 | Chronic obstructive pulmonary disease | 2 | 5,3 |
| 5 | Combined asthma | 10 | 26,3 |
| 6 | Tuberculosis of the respiratory system confirmed bacteriologically and histologically | 20 | 52,6 |

It should be noted that in the groups of patients with comorbid disease in the form of diabetes mellitus and a disease characterized by high blood pressure, non-invasive and invasive lung ventilation was required in 10.71% and 4.52% of cases respectively. It was somewhat surprising that patients with initial lung damage as a result of various lung diseases

and those suffering from a new coronavirus infection did not require any ventilation support, either in the form of non-invasive or invasive lung ventilation. The analysis showed that in patients with malignant and benign neoplasms of the bronchi and lung, chronic obstructive pulmonary disease, combined asthma, as well as respiratory tuberculosis, including its long-term consequences, the course of SARS-COV-19 infection was not accompanied by severe lung damage that required ventilation correction. The immunity of deliberately altered lung tissue to the effects of coronavirus infection requires additional research. The reason for this discrepancy may lie in the initial constant therapy which the specified patients receive for their concurrent disease.

**Conclusion**. The presence of comorbid lung pathology in patients with new coronavirus infection is not a risk factor for the severity of the course and mortality in patients with COVID-19.

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# STUDY OF HELICOBACTERIOSIS IN PATIENTS WITH COVID-19 POSITIVE DIAGNOSIS

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**Abstract**. The article deals with the study of *Helicobacter pylori* in patients with COVID-19 positive diagnosis. To study the course of COVID-19 in patients diagnosed with *Helicobacter pylori*. Both of SARS Cov 2 (COVID-19) PCR and *H.pylori* antigen test is positive, PCR test for COVID-19 positive and mild to moderate clinical examination. The examination was carried out in patients with symptoms, but also with problems with GIT and positive for *H. pylori* (fecal antigen test). It was suggested that COVID-19 infected *Helicobacter pylori* patients have more complications than controls. Thus, the symptoms of abdominal pain and diarrhea are more pronounced. This aggravates the clinical course in patients with a confirmed diagnosis of COVID-19. An exacerbation of inflammatory processes in the GIT associated with the generation of *H. pylori* may be associated with ACE 2 cells.

**Key words**: *Helicobacter pylori (H. pylori)*, COVID-19 (SARS Cov 2), gastrointestinal tract (GIT), diarrhea.

**Introduction**. More than 50% of the world and 70% of developing countries are infected with *Helicobacter pylori (H. pylori)*. The main reasons for the widespread occurrence of *H. pylori* are difficulties in diagnosing and treating the disease, as well as increasing resistance in recent years to antibiotics used to kill bacteria. Antibiotic eradication therapy for *H.pylori* is currently the gold standard treatment. However, pathological reactions during this treatment process cause serious problems. Therefore, during eradication therapy with antibiotics, we are faced with symptoms of varying severity and frequency, especially from the gastrointestinal tract. Increased antibiotic resistance significantly reduces the effectiveness of treatment, which, in turn, can lead to candidiasis and other complications leading to dysbiosis.

At the same time, the cells of the immune system respond to this process. *In vitro* and *in vivo* studies of the effects of immune cells on *H.pylori* are of great importance, and *H.pylori* is considered to represent a completely new approach to both the pathogenesis and treatment of *Helicobacter pylori*. If *H.pylori* is believed to enhance the expression of ACE-2 receptors in the gastrointestinal tract, it is no longer a secret that the SARS COV 2 (COVID-19) virus binds to these receptors and infects cells.

For this reason, during COVID-19, we are faced with various clinical symptoms, as well as certain problems in treatment, the solution of which can lead to an improved prognosis of patients with COVID. SARS COV 2 (COVID-19) infection also requires a special approach to the treatment of GIT in patients with *H.pylori*. Therefore, the study of the effect of *H.pylori* on the clinical course of patients with SARS COV2 (COVID-19) aroused great interest in terms of studying various symptoms, frequency of reactions and complications of GIT in H.pylori.

**Materials and methods.** To study the course of COVID-19 in patients diagnosed with *Helicobacter pylori*. Both of SARS Cov 2 (COVID-19) PCR and *H.pylori* antigen test is positive, PCR test for COVID-19 positive and mild to moderate clinical examination. The

examination was carried out in patients with symptoms, but also with problems with GIT and positive for *H. pylori* (fecal antigen test).

For this, 50 people aged 18-7 years, 18 women and 32 men with COVID were examined. At the same time, 5 women and 5 men were selected for examination as a control group in patients with COVID 19, but without the H. pylori antigen test.

**Conclusions.** In conclusion, our study suggests that COVID-19 infected *Helicobacter pylori* patients have more complications than controls. Thus, the symptoms of abdominal pain and diarrhea are more pronounced. This aggravates the clinical course in patients with a confirmed diagnosis of COVID-19. An exacerbation of inflammatory processes in the GIT associated with the generation of *H. pylori* may be associated with ACE 2 cells.

# EXPERIENCE OF USING FOOD SUPPLEMENT CONTAINING OMEGA-3, OMEGA-6 FATTY ACIDS AND IODINE IN COMPLEX REHABILITATION OF COVID-19 RECONVALESCENTS

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**Abstract**. The aim of the study was to study the use of a dietary supplement "Astaxanthin + Omega-3 + Omega-6 + Iodine" (AOOI) in the program of complex rehabilitation of convalescents of COVID-19 infection. The pilot group to study the influence of AOOI consisted of 10 people, the control group was 20 people. The average age is 54.3 years in the AOOI group and 54.0 in the control group. According to the survey data at the second visit, the tolerance by AOOI convalescents during the 30-day period was good, side effects and allergic reactions were not identified. According to our data, in the examined patients, the average total score on the MFI-20 asthenia scale was 58 and indicated its presence in convalescents. From the subscales, general asthenia prevailed - 16 points and decreased activity - 14 points. On the background of taking AOOI, there was a decrease in the overall mean score of asthenia, as well as a decrease in general asthenia and decreased activity. According to the data of a pilot study of COVID-19 convalescents while taking dietary supplements AOOI, there is a good tolerance of dietary supplements, a reducing the degree of asthenia. Considering the literature data on the role of astaxanthin, omega 3, omega 6 fatty acids in supporting immunity, it is possible to use dietary supplements AOOI for the rehabilitation of COVID-19 convalescents.

**Key words:** COVID-19, astaxanthin, omega-3 fatty acids, omega-6 fatty acids.

**Introduction.** The immune system exists to protect the body from harmful environmental agents, pathogenic organisms: bacteria, viruses, fungi or parasites. To cope with such an array of threats, the human immune system has created many cells to defend the body. The immune system is always active, and its activity is enhanced if a person has contracted an infection. This increased activity is accompanied by an increased metabolic rate, which requires energy sources, substrates for the biosynthesis of molecules. These energy sources ultimately come from the diet. Hence, an adequate supply of a wide range of nutrients is essential to support optimal immune function [1,2]. The second problem of COVID-19 infection is weight gain during the period of self-isolation or after an infection [3]. Without lifelong diet therapy, adequate physical activity, it is impossible to successfully reduce body weight and correct immunity. The high medical and social significance of overweight, low effectiveness in the long-term period of standard programs for correcting overweight [4] make it relevant to search for approaches to the prevention and correction of obesity in convalescents of COVID-19 infection, which will allow comfortable and significant weight reduction and support the immune system.

**The aim of the study** was to study the use of dietary supplements Astaxanthin + Omega-3 + Omega-6 + Iodine (AOOI) in a comprehensive rehabilitation program for convalescents of COVID-19 infection.

**Materials and methods.** An observational study was conducted in 2020 on the basis of the Center for Curative and Preventive Nutrition of the Clinical and Diagnostic Department of NIITPM in accordance with the National Standards of the Russian Federation GOST-R 52379-2005 "Good Clinical Practice" (ICH E6 GCP), with the obligatory observance of the ethical principles set out in the Declaration of Helsinki 1975 with the additions of 1983 [5], and obtaining informed consent from patients.

The study was approved by the local committee on biomedical ethics at the Federal State Budgetary Scientific Institution "Research Institute of Therapy and Preventive Medicine" (Research Institute of Therapy and Preventive Medicine - a branch of the Federal State Budgetary Scientific Institution "Federal Research Center Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Sciences ") (Protocol No. 23 dated May 26, 2020).

As part of the dispensary observation of COVID-19 convalescents, a pilot group of patients who underwent the disease in 2020 was examined - 30 women, the 1st group took AOOI - 10 women, the second control group - 20 women.

The object of research is a dietary supplement AOOI, developed in a Limited Liability Company, a research and production company “BIO Building” on the basis of a Patent for invention No. 2604299, a certificate of state registration of the Federal Service for Supervision of Consumer Rights Protection and Human Wellbeing dated 12.02.2016 . No. RU 77.99.11.003.E.000687.02.16. The composition of the dietary supplement for food AOOI includes: Astaxanthin 50 mg / 100g, omega-3 28 g / 100g, eicosapentaenoic acid 26.80 g / 100g, alpha-linolenic acid 1.18 g / 100g, omega-6 8 g / 100g, iodine 1.2 mg / 100g, lecithin 2.4 mg / 100g, MUFA 9 g / 100g, linoleic acid 2851 mg / kg, palmitoleic acid 4806 mg / kg, palmitic acid 6809 mg / kg, glycerol (esterified) 1531 mg / kg.

**Inclusion criteria:**

1. Women 40 - 60 years old.
2. Signing of informed consent to participate in the study.
3. Reconvalescents COVID-2019 (with code U07.1 or U07.2).
4. Ability to understand and comply with the requirements of the research protocol.
5. Absence of contraindications to the diagnostic procedures stipulated by the research protocol.

Criteria for premature exclusion: Refusal to further participate in the study.

**Non - inclusion criteria:**

1. Age under 40, over 60 years old.
2. Presence of exacerbation of chronic diseases, neoplasms, diseases of the blood and blood-forming organs, mental disorders and behavioral disorders, decompensated pathology of the circulatory system, respiratory and digestive organs.

The diagnosis of COVID-2019 was considered verified in the presence of a positive laboratory test for SARS-CoV-2 RNA (using nucleic acid amplification methods) or SARS-CoV-2 antigen (using immunochromatographic analysis), regardless of clinical manifestations [6].

At the first stage, women who applied to the Center for Curative and Preventive Nutrition of the Clinical and Diagnostic Department of NIITPM for a consultation, after reading the information sheet about this study, signing an informed consent and consent to the processing of personal data, underwent: examination by an endocrinologist, identification of

eating disorders, level of asthenia, physical, anthropometric, biochemical examination and the patient's compliance with the inclusion / non-inclusion criteria was assessed.

At the second stage, an open, single-center clinical study of the efficacy and safety of dietary supplements AOOI 1000 mg during breakfast and dinner for 30 days was performed. We also assessed adverse events (presence / absence and nature of manifestations of allergic reactions), repeated measurement of the severity of asthenic symptoms, physical, anthropometric, biochemical and instrumental examination.

Tolerability of AOOI was assessed based on the analysis of the frequency of occurrence of adverse reactions recorded independently by the patient or doctor, regardless of the alleged connection with the studied dietary supplement. The following tolerance criteria were used:

- good: no adverse reactions associated with taking AOOI;
- satisfactory: the presence of adverse reactions associated with the intake of dietary supplements, but not requiring therapeutic intervention;
- unsatisfactory: the presence of adverse reactions associated with the intake of dietary supplements, requiring additional therapeutic intervention.

The level of asthenia was assessed using the MFI-20 asthenia scale [7]. Normally, the total number of points should not exceed 20-30. In addition to the overall result on the scale, the state can be assessed according to the following subscales: General asthenia (questions 1, 5, 12, 16); Decreased activity (questions No. 3, 6, 10, 17); Reduced motivation (questions No. 4, 9, 15, 18); Physical asthenia (questions No. 2, 8, 14, 20); Mental asthenia (questions No. 7, 11, 13, 19). If the total score on one of the subscales is higher than 12, then this may be a preliminary basis for the diagnosis of asthenic syndrome.

Statistical data processing was performed using the SPSS 13 software package. To assess the nature of the distributions of the analyzed features, the Kolmogorov – Smirnov test was used. Descriptive analysis of the numerical characteristics of the features was performed.

**Research results and discussion.** It is known that the immune system works all the time, but cells become activated in the presence of pathogens. This activation leads to a significant increase in the demand for substrates for the immune system for energy (glucose, amino acids and fatty acids). The activation of the immune response causes the production of lipid-derived mediators such as prostaglandins and leukotrienes and many different types of proteins, including immunoglobulins, chemokines, cytokines, cytokine receptors, adhesion molecules, and acute phase proteins. This requires fatty acids and amino acids, respectively. [one]. Good nutrition creates an environment in which the immune system is able to respond appropriately to a challenge, regardless of the nature of the task. In order to reduce the deficiencies of omega 3,6 fatty acids that occur in most cases after a previous infection, the effect of AOOI on persons who have had a COVID-19 infection was studied.

The pilot group to study the influence of AOOI consisted of 10 people. The average age is 54.3 years. According to the survey data at the second visit, the convalescents tolerated AOOI well within a 30-day period, no allergic reactions were detected. We obtained similar data in persons with metabolic syndrome in 2018 [8,9].

According to the literature, in a post-COVID-19 cohort of 143 hospital patients in Italy, 125 (87.4%) reported symptoms: 76 (53.1%) reported asthenia, 62 (43.4%) reported shortness of breath and 23 (16%) - about coughing - 2 months after discharge [10]. In an observational study of patients with COVID-19 conducted in the UK, the proportion of patients who remain symptomatic 5 weeks after infection is estimated at 21.0% (95% CI 19.9-22.1%) - in first place there was asthenia, cough was the second most frequent persistent symptom (11.4% [10.5–12.2%]) [11].

According to our data, in the examined patients, the average total score on the MFI-20 asthenia scale was 58, and indicated its presence in convalescents (Table 1). From the

subscales, general asthenia prevailed - 16 points and decreased activity - 14 points. While taking AOOI, there was a decrease in the total average asthenia score, as well as a decrease in general asthenia and decreased activity in comparison with the control group.

The resulting effect can also be explained by the mechanism of action of astaxanthin, omega-3.6 fatty acids and iodine on the body. Astaxanthin is a natural antioxidant that is a lipophilic, pinkish-orange carotenoid found in algae, seafood (crustaceans, shells, crabs, shrimp, fish) and various plants, giving them their own distinctive color. The highest concentration of astaxanthin was found in the green microalga Haematococcus pluvialis, which accumulates astaxanthin under stress conditions: high salinity of the habitat, nitrogen deficiency, high temperature and light [12]. The main sources of astaxanthin as dietary supplements for humans and animals are seafood and H. Pluvialis extract [13]. Astaxanthin protects the human body from adverse environmental factors, including UV radiation, neutralizes free radicals that can lead to cell damage in the body, diseases and aging, performs an energy function, and increases muscle endurance [14].

Table 1. Dynamics of scores on the MFI-20 asthenia scale

| | AOOI Group | | Control Group | |
|---|---|---|---|---|
| Subscales | 1 visit | 2 visit | 1 visit | 2 visit |
| General asthenia | 16 | 10 | 15 | 14 |
| Decreased activity | 14 | 12 | 14 | 14 |
| Reduced motivation | 8 | 8 | 8 | 8 |
| Physical asthenia | 12 | 10 | 12 | 11 |
| Mental asthenia | 8 | 8 | 10 | 10 |
| Total points | 58 | 48 | 59 | 57 |

Omega-3 PUFAs help stabilize the state of cell membranes and lipid metabolism, correct the ratio of high and low density lipoproteins, provide additional nutrition for the central nervous system, prevent the formation of blood clots, and also help restore the walls of blood vessels, accelerate the immune response and restore tissues, participate in the synthesis of group vitamins In [15]. The human body is not able to independently produce omega-3 PUFAs, so they must come from outside. However, most people do not consume enough cold water fish or nuts to get the right VFA balance. To address this important challenge, either increase your intake of fatty cold water fish to at least twice a week or start taking supplements containing omega-3 acids [16]. The biological role of Omega-6-PUFA is to participate in tissue repair, lipid metabolism (maintain normal blood cholesterol levels), increase blood viscosity and blood clotting [17].

Iodine regulates the work of the thyroid gland and pituitary gland, has a pronounced effect on the metabolism of proteins, fats, carbohydrates, water-salt balance.

Thus, the addition of dietary supplements AOOI to the diet of convalescents will compensate for the developed deficiencies and, according to our data, reduce the degree of asthenia.

**Conclusion.** According to a pilot study of convalescents after a previous infection with COVID-19, while taking dietary supplements AOOI, there is a good tolerance of dietary supplements, a decrease in the degree of asthenia. Considering the literature data on the role of astaxanthin, omega-3.6 fatty acids in supporting immunity, it is possible to use dietary supplements for the rehabilitation of convalescents of COVID-19 infection.

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# ANALYSIS OF THE SCHEMES OF APPLICATION OF PULSE THERAPY AND IMMUNODEPRESSIVE MEDICINES IN PATIENTS WITH CORONAVIRAL INFECTION (COVID-19) WITH SEVERE PULMONARY INFECTION

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**Abstract.** The efficacy and safety of the combined use of the glucocorticosteroid methylprednisolone and the IL-6 inhibitor with the combined use of the glucocorticosteroid dexamethasone and the Janus kinase inhibitor in patients with severe coronavirus pneumonia aged 58 to 70 years was compared. The use of two different treatment regimens for severe patients with new coronavirus infection with severe lung damage (methylprednisolone-IL-6 inhibitor and dexamethasone-Janus kinase inhibitor) showed efficacy, accompanied by a decrease in signs of inflammation and respiratory failure by 3 days of intensive therapy. There was no statistically significant difference in the dynamics of changes in the state depending on different treatment regimens.

**Key words:** SARS-COV-19, cytokine storm, JAK1 and JAK2, IL-6, GKS.

**Introduction.** With a severe course of a new coronavirus infection (COVID-19), pneumonitis develops with damage to the lung tissue, against the background of autoimmune systemic inflammation ("cytokine storm"). Cytokine storm is a cascade uncontrolled increase in the level of cytokines in the blood, which can lead to an excessive immune response, damage to organs and tissues [1]. There is no specific therapy for the novel coronavirus infection (COVID-19), therefore it is necessary to search for an effective and safe anti-inflammatory treatment [2]. It is recommended to include IL-6 receptor blockers, Janus kinase inhibitors and glucocorticosteroids in the pathogenetic therapy of patients with severe / critical course of coronavirus infection. Currently, clinical studies of the efficacy and safety of targeted drugs in patients with severe / critical coronavirus infection are ongoing. Baricitinib is a selective immunosuppressant, reversible inhibitor of Janus kinase 1 and 2 (JAK1 and JAK2). Janus kinases (JAKs) are enzymes that transduce intracellular signals from cellular receptors for a number of cytokines and growth factors involved in hematopoiesis, inflammation, and the immune response [3]. As part of the intracellular signaling pathway, Janus kinases phosphorylate and activate STAT (signal transporters and transcriptional activators), which in turn activate gene expression in the cell. Baricitinib modulates these signaling cascades, partially inhibiting the enzymatic activity of JAK1 and JAK2, thereby decreasing phosphorylation and activation of STAT [4].

**Objectives.** To compare the efficacy and safety of the combined using of the glucocorticosteroid methylprednisolone and the IL-6 inhibitor with the combined using of the glucocorticosteroid dexamethasone and the Janus kinase inhibitor.

**Material and Methods.** The study included 47 patients with severe coronavirus pneumonia (CT-3, CT-4) aged 58 to 70 years, who received standard intensive care, including non-invasive ventilation, glucocorticoids, anticoagulants, anti-inflammatory drugs, antibacterial and antiviral drugs, according to clinical guidelines [1]. In the first group, which

included 19 patients, during the first five days of admission to the intensive care unit, the patients were administered the glucocorticoid methylprednisolone 500mg for 5 days and the IL-6 inhibitor (Levilimab 162mg) for the first two days. In the second group, which included 28 patients, during the first five days of admission to the intensive care unit, the patients were administered the glucocorticoid dexamethasone at a dosage of 12 mg in the morning and 8 mg in the evening and a Janus kinase inhibitor 1 and 2 at a dosage of 5 mg. The severity of the patients' condition was assessed using the following scales: Glasgow Coma Scale (GCS), Pneumonia Severity Index (PSI), Multiple Organ Failure Scale (MOSF), ICU Pain Assessment Scale (ICU). The degree of respiratory failure was assessed by the level of blood oxygen saturation, respiratory rate and Horowitz index - PO2 / FiO2. The dynamics of the inflammatory process was assessed by the level of C-reactive protein, procalcitonin and ferritin in the blood plasma, the number of leukocytes in the blood and the leukocyte formula, as well as by the level of alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, and urea in the blood plasma. The level of D-dimer was monitored. Statistical analysis was carried out in the Statistica 6 program using nonparametric parameters.

**Results.** The comparison groups were comparable in age ($p = 0.85$) and gender composition ($p = 0.81$). Both in the first and in the second observation groups, in the first three days of intensive therapy, a decrease in the degree of respiratory failure was observed with a decrease in shortness of breath and an increase in the parameter of blood oxygen saturation. However, there was no statistical difference in the timing of positive dynamics between the comparison groups ($p = 0.59$). Similarly, in the comparison groups, there was no statistically significant difference in the length of stay in the intensive care unit ($p = 0.67$) and the length of hospital stay in the hospital ($p = 0.74$). Initially, in the comparison groups, the level of C-reactive protein was increased and amounted to 153 [130; 170] U / L in the first group and 151 [138; 165] U / L - in the second ($p = 0.67$). By the 3rd day of observation, there was a decrease in the level of this indicator by an average of 43.5% in the first group and by 40% in the second ($p = 0.42$). The initially high body temperature in both the first and second groups tended to decrease by an average of 2° per day after the start of intensive therapy ($p = 0.53$). Despite of the ongoing anticoagulant therapy, an increase in the level of D-dimer in the blood plasma of patients of both observation groups was recorded by the 5th day of being in the intensive care unit ($p = 0.64$). So, in the first group, the increase in this indicator compared to the initial indicators upon admission to the intensive care unit was 38%, in the second - 72% and was equal to 1.6 mg / l in the first and 2.9 mg / l - in the second.

**Conclusion.** The use of two different treatment regimens for severe patients with new coronavirus infection with severe lung damage (methylprednisolone-inhibitor of IL-6 and dexamethasone-inhibitor of Janus kinase) showed efficacy, accompanied by a decrease in signs of inflammation and respiratory failure by the third day of intensive therapy. There was no statistically significant difference in the dynamics of changes in the state depending on different treatment regimens.

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# COURSE OF CORONAVIRUS INFECTION IN PATIENTS WITH ACUTE SURGICAL PATHOLOGY

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**Abstract**. Cases of a combination of a new coronavirus infection and acute abdominal surgical pathology were analyzed at the National Surgical Center (NSC) under the Ministry of Health of the Kyrgyz Republic. Today, the NCC is one of the leading scientific, medical and preventive institutions in the capital to provide emergency surgical care to the population.

**Key words**: coronavirus infection, "acute abdomen", surgical pathologies.

Analysis of the Global Health Security Index (GHS) conducted as part of a joint project by the Johns Hopkins Center for Health Security and the NTI Nuclear Threat Initiative with The Economist Intelligence Unit in 195 countries across six categories, 34 indicators and 140 questions, based on data from WHO, the World Organization for Animal Health, the Food and Agriculture Organization of the United Nations and the World Bank, showed that no country in the world is fully prepared for epidemics or pandemics, and every country has serious gaps that need to be eliminated.

The average overall GHS score for 195 countries for 2019 was just over 40 out of 100 possible. The general index of Kyrgyzstan is 49.3 points, and ranks 47th out of 195 countries of the world (Table 1).

Table 1. Comparative index of the CIS

| Country | GHS Index | Rating |
|---|---|---|
| Average score of high-income countries | 51,9 | |
| Average score of other countries | less than 50 | |
| Kyrgyzstan | 49,3 | 47 |
| Russia | 44,3 | 63 |
| Kazakhstan | 40,7 | 83 |

The first case of COVID-19 in Kyrgyzstan was registered on March 17, 2020. Identified among three people who returned on the same plane from Saudi Arabia on the night of March 12-13, 2020, among people who performed a small hajj. In total, for the period from March 17 to the present day, according to official statistics, there were two waves of increase in the incidence with peaks in mid-July 2020 and in mid-November 2020.

The aim of our work was to study the features of the course of coronavirus infection in combination with acute surgical pathology of the abdominal organs at the National Surgical Center (NSC) under the Ministry of Health of the Kyrgyz Republic, from July 1 to July 31, 2020. For the studied period of time, a unified tactic of treatment and management of this category of patients was not developed and doctors had to face certain problems in making a diagnosis, determining the timing of surgery and the characteristics of postoperative management.

In total, during this period, emergency medical care was provided to 70 patients, including 34 women and 36 men. The patients' age ranged from 17 to 80 years, hospital stay from 2 to 29 bed-days.

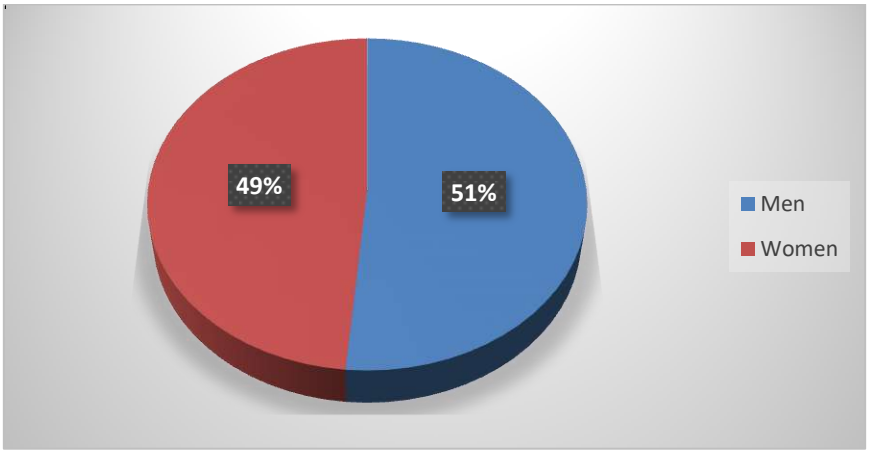


Figure 1. Distribution of patients by sex.

Table 2. Basic diagnoses on admission

| № | Diagnosis on admission | Number of patients |
|---|---|---|
| 1. | Acute appedicity | 25 |
| 2. | Acute cholecystitis | 23 |
| 3. | Acute pancreatitis | 15 |
| 4. | Acute adnexitis | 2 |
| 5 | Gastrointestinal bleeding | 3 |
| 6 | Uterine bleeding | 1 |
| 7 | Postpartum sepsis | 1 |
| | **TOTAL:** | **70** |

Of the total number of patients (70), due to the pronounced clinical picture of the “acute abdomen” and the phenomena of peritonitis, 11 patients, despite the presence of signs of confirmed bilateral pneumonia, underwent various surgical interventions.

Table 3. Name and number of surgical interventions in coronavirus patients

| № | Operations | Number of patients |
|---|---|---|
| 1. | Appendectomy | 1 |
| 2. | Laparoscopic cholecystectomy | 2 |
| 3. | Traditional cholecystectomy with drainage of the subhepatic space | 2 |
| 4. | Laparotomy. Omentobursostomy | 2 |
| 5. | Tubectomy | 3 |
| 6. | Laparotomy. Amputation of the uterus | 1 |
| | **TOTAL:** | **11** |

Of the 11 operated patients, two cases were fatal on the second day after surgery. In the first case, a laparotomy, omentobursostomy was performed for acute destructive pancreatitis, in the second - uterine amputation due to postpartum sepsis.

In all cases, according to clinical and laboratory data, it was observed:

1. Increased ESR (35 mm / h - 60 mm / h)

2. Severe leukopenia (3.2 - 4.0)
3. Lymphocytosis (38 - 52)
4. High numbers of CRP (80 - 90 mg / l) and procalcitonin (above 0.5 ng / ml)
5. Increase in D-dimer (above 1500)
6. Increased ferritin values (451 μg / L - 575 μg / L)
7. PCR - analysis in 15 cases “+”, 55 “-”
8. In all 70 patients, bilateral pneumonia was confirmed by X-ray and MSCT

**Conclusion**: Thus, the severity of the patients' condition, in addition to the main emergency abdominal pathology, was aggravated by the presence of symptoms of respiratory failure with a pronounced intoxication syndrome. All patients, in addition to traditional antibiotic therapy to prevent symptoms of intoxication, were on high-flow oxygen, anticoagulant and antiplatelet therapy, and the strictest pron-position.

# AGENT-BASED MODELLING OF THE COVID-19 SPREAD IN REGIONS OF THE RUSSIAN FEDERATION

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**Abstract**. The ongoing COVID-19 has heralded a global crisis in national healthcare systems, economy and politics. Comprehensive approaches are needed to reduce losses as well as to assist prevention of the disease spread. In turn, it requires adequate models allowing to predict an effect of different factors on the disease spread. Derivatives of a SIR model suffer from not accounting for random factors. Our agent-based model allows accurately accounting for age structure of a population, variations in self-isolation and laboratory testing, a role of super-spreaders etc. In this paper we report on our results of predicting the further spread of COVID-19 in regions of Russia. The model integrates the following key epidemiologic characteristics: the timing of infection, and age-dependent probability of a severe disease. It is demonstrated, that despite local features of different regions, the daily epidemic curves can be correctly predicted for different territories with the same model parameters, except the initial number of infected persons, which serves as a tuning parameter of the model.

**Key words**: COVID-19, prediction, agent-based models, Monte-Carlo, emerging infection.

**Introduction**. Reliable tools for epidemic spread simulations are required to predict the further development of COVID-19 pandemic as well as to choose the optimal strategy for vaccination and non-pharmaceutical interventions. Several classes of models are currently employed for the prognosis of the spread of infections.

Regression models are known to provide rapid estimations of the spread of infections [1-4]. Dynamic Bayesian networks are employed only for short-term prognosis and predominantly in the form of Markov models [5]. Neural networks and other machine learning methods can be applied only for short-term prognosis. Only feedforward neural networks and backpropagation algorithm are applicable for the prognosis of infections spread [6].

Compartmental models based on differential equations are the class of models employed for long-term prognosis based on the pioneering work by Kermack and McKendrick [7]. Modern compartmental models employ a large number of groups within entire population, accounting for susceptible, infected, recovered exposed, hospitalized, critical , dead , and those at the quarantine or isolation, which dynamics are governed by a system of differential equations. Compartmental models are widely employed for the modeling of the spread of coronavirus-induced infections (SARS, MERS, COVID-19). For example, SEIR model has been applied for modeling of COVID-19 spread in different countries [8-11]. Early COVID-19 spread and the efficacy of governmental measures are discussed in paper [12] also with the application of SEIR model.

Individually-oriented models primarily employ so-called agent-based approaches, which can be applied both for short-term and long-term prognosis of the spread of infection. Every member of population (agent) is described by number of parameters which govern his behavior and interaction with other agents in a probabilistic way in accordance with the predetermined rules. Agent-based models were proved to be effective in the description of the propagation of infections, such as Ebola [13] and flu [14], for different sizes of

population. Agent-based models were also applied for the modeling of COVID-19 spread, for example, the modeling of the development and the regress of the infection in the city of Helsinki is described in [15]. NotreDame-FRED model [16], based on previously developed FRED model (Framework for Reconstructing Epidemic Dynamics) for the prediction of flu pandemics in the year 2009. The modeling of the second wave of COVID-19 after the cancellation of the restrictive measures was also performed within agent-based model [17]. The use of sophisticated mathematical modelling of the spread scenarios will facilitate fitting such crucail factors as reinfection rate, lab tests coverage (PCR, ELISA), an association between various vaccination strategies and morbidity rates as well as possible patterns of the third waves of COVID-19.

The aims of the present work are as follows: the development of an agent-based model capable of predicting the progress of the COVID-19 burst in different regions of the Russian Federation, and determininig the key model parameters that provide the agreement of the simulated dynamics and actual statistics concerning daily incident cases and COVID-19-associated deaths.

**Agent-based COVID-19 spread model**. In this study, we developed a general pool agent-based model, in which all the individuals (agents) may interact with each other [18]. Conditional on a simulated scenario, each agent has the following binary states, governed by the Monte Carlo based random values: susceptible, infected, contagious, with disease manifestations, critical, recovered. Time resolution of a simulation is one day, since general statistics on newly registered cases and deaths is available on the daily basis. The model accounts for the population age structure based on the information on different disease progression in different age groups. Typical lengths of disease manifestation, progression, critical, and symptomless periods are introduced in accordance with the available data.

The average number of individuals *R*, to which an infected agent may transmit the infection within one week given that no restriction measures are applied, is considered as the main model parameter directly related to infection transmission coefficient. Given that the probabilities to be infected from different agents are independent, the infectation probability for an agent interacting with the general pool in a particular day is calculated as:

$$P = \frac{RN_i}{7N_t},$$

where $N_\mathrm{i}$ is the number of infected individuals presenting in the general pool in the current day and $N_\mathrm{t}$ is the total number of agents in the considered population. The $N_\mathrm{t}$ number is chosen in accordance with a population of the simulated region.

The model accounts for the efficiency of the following restrictive measures introduced by employing a so-called self-isolation index. This is an empirical value introduced by Yandex (Russia), which represents a cumulative parameter reflecting population activity based on both traffic information and activities in different internet services. The isolation index varies in the range between 0 and 5, and in simulation it is assumed that the index is proportional to the percentage of agents that obey the restrictive rules and do not interact with the general pool in the current day. For the days, when the restriction measures are applied, official data on self-isolation index by Yandex are employed. For the prognosis, the two approaches were applied. In the first one, the extrapolation of the detected dynamics of the self-isolation index was employed. Since general trend at the day of the prognosis generation demonstrated the decreases of the self-isolation index with time, this scenario is attributed as “negative”. An alternative scenario was produced by the introduction of constant self-isolation index values for particular time intervals. Since this scenario accounts for constant self-isolation index, it was attributed as “positive”.

Depending on the introduced anti-epidemic measures accounted in the simulation, an agent also may get a binary status “isolated”, if the agent has a positive COVID-19 test, or

under the self-isolation, if in current day he/she follows the restrictive measures and does not interact with the general pool.

The introduced rules of testing are an important part of the model, since the real data that are usually compared with the results of simulation are daily statistics on number of newly revealed cases and deaths. Obviously, the former number depends on the testing strategy within a given region and, therefore, its accurate description is of huge importance. In the model, the number of daily tests for each region is either taken from official statistics or determined from the daily number of cases for the entire Russian Federation in proportion to the region population. The testing model also accounts for the increase in the accuracy of COVID-19 tests with time and variation of testing strategy with pandemic development. While the early stage implied systematic testing of the individual with suspicious manifestations and their recent contacts, the limited capacity of the testing system during the second wave implied primarily testing the individuals with pronounced manifestations.

**Results**. Figures 1a, b demonstrate the results of simulations of the negative and positive scenarios of the epidemic progress in Moscow ($N_t = 11.4\times10^6$) made on May, 20$^{th}$ 2020. To provide a best-fit scenario, we manipulated with three key parameters of the model. They were the number of initial infected agents, percentage of deaths among agents in the critical state $p_d$ and virus transmission coefficient $R$. Each scenario was constructed by averaging five scenarios that are the closest to the real statistical data over a total of 20 realizations with the same parameters. Due to the stochastic origin of the developed model, similar starting parameters may result in totally different scenarios of an epidemic progress.

In Fig. 1 circles show the original data employed for determination of the model fitting parameters, while triangles denote the official statistical data reported after prediction by the model. It is worth noting that the prediction for Moscow was obtained for the transmission coefficient value $R = 4.6$ and death percentage of $p_d = 3\%$. Of note, the prediction was made during the epidemic peak in Moscow (Fig. 1a, b), in this connection, the positive scenario for daily newly registered cases provides the best fit supposing preservation of the restrictive measures combined with the increase in the accuracy of testing.

To predict the second wave of the epidemic developed in autumn 2020, the same disease transmission coefficient was employed, while isolation factor was treated as a fitting parameter for the wave start that was also responsible for negative of positive scenario. Fig. 1c,d show two prognoses for the second wave development in Moscow (daily new cases and deaths) based on assumptions that no restriction measures are introduced (negative scenario) or restrictions similar to that introduced in spring are applied (positive) scenario. The demonstrated prognoses were made on October 5$^{th}$ and show significantly different epidemic progression. Since the restrictive measures in the second wave were not that strict that in the spring period, the real pandemic developed through an intermediate scenario.

Prediction for other regions of Russia demonstrated that the fitting parameters determined in simulations for Moscow can be successfully translated to other locations leaving initial number of infected and isolation index as fitting parameters.

**Conclusion**. In this paper we presented an agent-based model of COVID-19 epidemic spread widely employing the rigorous methodology of Monte Carlo simulation principles. The model is able to account for the age-dependent disease development, restrictive measures as well as testing system. It was validated on the statistical data for daily new cases and deaths which were officially reported for the Moscow city. Moreover, 1-month-long predictions of further epidemic spread were made on 21, May, 2020 considering two scenarios, “negative” and “positive”, implying weakening or preservation of the introduced restrictive measures, respectively.

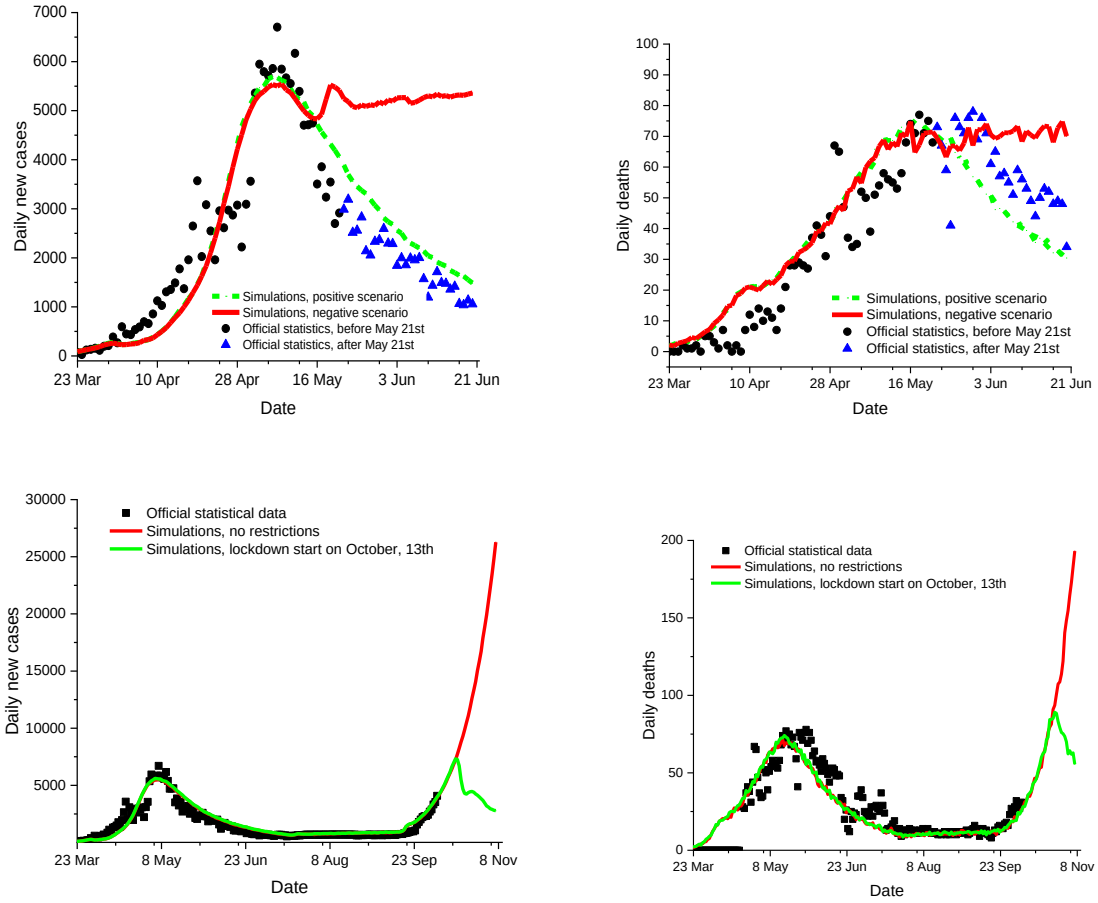


Figure 1. Comparison of simulated (positive and negative scenarios) and real statistical data for daily new COVID-19 cases (a, c) and deaths due to COVID-19 (b, d) in Moscow city at the peak stage of the first wave (a, b) and the beginning of the second wave (c, d).

The same approach was employed to predict the second wave of the epidemic given that the basic parameters determined at the first wave simulations are preserved. It was shown, that the epidemic spread fitting parameters derived from simulations for Moscow could be successfully incorporated for prognosis of the disease spread in other regions.

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# SPONTANEOUS RECTUS SHEATH HAEMATOMA IN COVID-19 PATIENT: CASE REPORT

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**Abstract.** Spontaneous rectus sheath hematoma (SRSH) is a rare clinical condition, frequently associated with abdominal trauma and anticoagulant therapy. The correct diagnostis of this pathology is still delayed because of absence of pathognomonic signs and simptoms. In the current conditions of the pandemic world and COVID-19 patients this diagnosis must be taken into consideration in each patient presented with acute abdominal pain and abdominal palpable mass with a sudden onset. We present a case report of a patient diagnosticated with COVID-19 and treated in the intensive care unit for its complications. She developed a progressive rectus sheath haematoma and underwent an emergency surgery.

**Keywords.** Haematoma, rectus muscle, COVID, anticoagulation.

**Case report.** 54 years old patient, refered from another institution to the ICU with the diagnosis: Polysegmental viral pneumonia, severe degree of damage. Bilateral pleurisy., confirmed COVID-19, without comorbidities. A progressive respiratory failure was noticed, decrease in $SO_2$ (80% on ambient air). A chesttubes were placed bilateral The patient underwent thoracentesis with pleural drainage. The condition was progressively worsening, she developed episodes of dry, harrowing, long-lasting cough. IV infusion therapy, anticoagulants and hormonal therapy were prescribed. The condition suddenly worsened 8 days after admission. A soft fluctuating mass appered in the lower part of the anterior abdominal wall, painfull on palpation. The skin on this level with massive bruising (Fig. 1), Carnett's sign apparently positive. The patient develops a clinical picture of hemorrhage, with the decrease of the CBC values: from Hb - 125 g / l to Hb - 93 g / l; Er - 4.5 x $10^{12}$ - to 3.3 x $10^{12}$, associated with hypotension and oligoanuria. The ultrasonographic examination revealed: a mass in the pelvis with heterogenous content (clot conglomerate and liquid blood component), with irregular contour, scalloped capsule, without central and peripheral Doppler signal; dimensions approx. 128x154x103 mm, aprox. volume – 1000 ml. Angiographic computed tomography was performed – pelvic fluid collection with anterograde compression of the bladder was described (Fig. 2).

In order to tule out bladder involvement, the decision to perform retrograde cystography was taken – cranial movement of the bladder, without communication with the liquid collection (Fig. 3). The progressive deterioration of the general condition, the increase in size of the mass, the progressive decrease of the CBC values (Hb - 67 g / l), the compression of the bladder and the right ureter, associated with hemodynamic instability imposed the deciosion for emergency surgery. Spinal anesthesia, and a middle-lower incision was performed in the projection area of the hematoma. An 850 ml preperitoneal haematoma (clots and blood) was opened.

Figure 1. Massive bruising on the anterior abdominal wall.

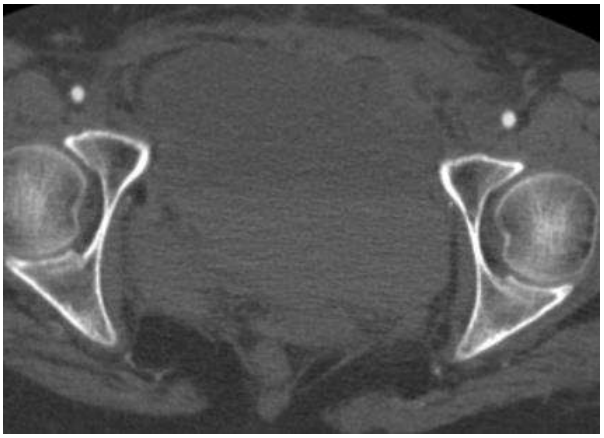

Figure 2. Angi CT

Figure 3. Retrograde cystography: compression of the bladder

During exploration a canal that communicated with a collection of the rectus sheat on the left, in the cavity blood clots and blood were found (Fig.4). The cavity was drained with 2 tubes. Postoperatively, the patient required transfusion of blood components. The evolution was favorable, including the underlying disease and the patients was discharged at 16 days postoperatively.

Figure 4. Blood clots from the collection of the rectus sheath

**Discussion.** Hematoma of the sheath of the rectus muscle is a relatively rare condition, which occurs either due to damage to the lower epigastric artery or due to the actual injury of the muscles. This pathology is correlated with abdominal trauma and with anticoagulant therapy [1]. The reported incidence is up to 1.8-2% [1]. Apparently, being a pathology with self-limiting potential, according to data from the literature, it has a mortality rate that can reach to 25% in patients undergoing anticoagulant therapy, an actual fact in the treatment for COVID-19 [1, 2].

The essential problem in the emergency surgery is the differential diagnosis of SRSH with false peritoneal irritation syndrome and acute surgical abdomen, to prevent unnecessary laparotomies [3], which are significantly aggravating in COVID-19 patients. In this context, the anamnestic is an useful tool in establishing the diagnosis of SRSH, because there are a number of risk factors that can lead to the appearance of this type of haematoma:

• direct abdominal trauma [4];

• recent surgery - iatrogenic [5];

• anticoagulant therapy - the most common predisposing factor, with a higher level of mortality due to severe hemorrhage [6]. The rate of anticoagulant therapy is showing a permanent increasing in the last decades [8, 9]. The current pandemic conditions, with the need of the anticoagulant therapy in the most of the patients with an aggressive clinical form of COVID-19, due to the coagulant potential of this virus, have significantly increased the risk of developing SRSH.

• cough - due to intense contraction of the muscles [1], there exist reported cases when exacerbation of asthma and respiratory infections led to the development of SRSH [10].

• pregnancy and birth [7].

The clinical signs are not pathognomonic, often the irritating mechanism on the parietal and peritoneal nerves endings leads to the false acute abdomen - Reily syndrome [3]. The most common clinical sign is abdominal pain, which is present in up to 97% of patients: exacerbates on movements, is acute, with sudden onset, does not irradiate and does not subside; followed by palpable mass (92%), muscle rigidity (49 %) [11]. The Carnett"s sign is useful for the differential diagnosis. Clinical signs may vary individually, depending on the localization and size of the colection and general condition of the patient.

Currently, the rate of the early diagnosis of SRSH is increasing due to imaging possibilities, ultrasonography and computed tomography being the imaging methods of choice. And if in the case of ultrasonography the diagnosis rate is up to 90%, then computed

tomography has a specificity of 100%, with the determination of a hyperdense colection, located posterior to the rectus abdominis muscles, with the enlargement of the ipsilateral muscle [12].

The SRSH treatment is dependending on the clinical picture and the patient's general condition, two treatment choices existing: conservative or surgical. Usually, taking into account the self-limiting nature of the pathology, conservative treatment is prefered: adequate fluid resuscitation, analgesia, compressive bandages, cessation of anticoagulant therapy. This type of treatment is only applicable to hemodynamically stable patients with a hematoma that does not increase in size. Hemodynamic instability, the impossibility of stopping anticoagulant therapy, as was previously reported, or the lack of adequate response to volume resuscitation, associated with a progressive increase of the haematoma size – require surgery for hemostasis [12].

**Conclusions**. SRSH should be considered for differential diagnosis in patients with abdominal pain, palpable abdominal mass, altered general condition and a history of COVID-19 with anticoagulant therapy. The imaging method of choice is angio computed tomography, which provides information about the location, extension and size of the hematoma. The therapeutic management will be selected individually, taking into account the general condition of the patient, hemodynamic parameters, CBC values and the evolution of hematoma dimensions.

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# COVID-19 AND PSYCHOEMOTIONAL DISORDERS

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**Abstract**. The SARS-CoV-2 virus can cause not only the severe damage to the central nervous system, but also can change brain function: violation of mental status, personality change, abnormal behavior or speech impairment, etc.

The lack of knowledge of this problem about the effect of the virus on the psychoemotional sphere of a person substantiated the purpose of this work - to study the psychoemotional state of people after suffering COVID-19 infection.

**Key words**: SARS-CoV-2, psychoemotional disorders, stress resistance, aggressiveness, situational anxiety.

**Introduction**. There are a large number of neurotropic viruses. There are more than 30 groups of RNA viruses and more than 20 groups of DNA viruses capable of infecting the human central nervous system [1]. Until recently, the question of whether the SARS-CoV-2 virus infects the structures of the nervous system has remained unsolved. The first reports, since the beginning of the COVID-19 pandemic, about the virus affecting the central and peripheral nervous system, began to appear in foreign sources from the beginning of April 2019.

The mechanisms of possible involvement of the central nervous system against the background of infection with the SARS-CoV-2 virus are different, among them there are three most probable variants [2, 3].

First, it is possible that the development of respiratory failure accompanying a new coronavirus infection is associated with the involvement of not only the lower respiratory tract in the pathological process, but also the respiratory center in the brain trunk. Epidemiological research shows that during the process of development of coronavirus infection, the average time from the first symptoms to the development of respiratory insufficiency is 5 days. During this time, the virus can penetrate the blood-brain barrier through the blood or transsynaptic way and affect the neurons of the brain stem, thereby disrupting the work of the respiratory center.

Secondly, the neuroinvasive potential of COVID-19 is being studied on the example of coronaviruses close to it in structure. SARS-CoV-1 was found in the brains both of patients and experimental animals, which means that it is possible that penetration into the central nervous system is possible for SARS-CoV-2. To invade cells, COVID-19 uses type 2 angiotensin-converting enzyme (ACE2) as a receptor that is found on the surface of neurons and glial cells in the brain. The interaction of coronavirus with these receptors can lead to direct damage of neurons without the development of inflammation. A similar picture has been demonstrated in a series of clinical cases of SARS-CoV-1 infection.

The other mechanisms of damage of the nervous system caused by a new coronavirus infection are also being taken into consideration. Special attention is paid to immune mechanisms; the possibility of autoimmune effects is not excluded. The development of a cytokine storm during coronavirus infection increases the permeability of the blood-brain barrier, making it possible for viruses, bacteria, immune cells, toxic metabolites and inflammatory agents to enter the CNS structures without control. The impact of these factors

on the brain tissue and its membranes can lead to the development of neurological symptoms without direct penetration of SARS-CoV2, but these conditions may still be considered associated with this infection [2, 3].

Neurological symptoms which have patients with COVID-19 appear as cerebral edema. The data were confirmed by the results of postmortem studies of the patients who died from the effects of COVID-19 infection [4, 5].

On March 31, 2020, a case of COVID-19-associated acute necrotizing hemorrhagic encephalopathy was described in the Radiology journal. The described condition is rare and can be associated with viral infections, but its connection with COVID-19 was established for the first time [6]. The International Journal of Infectious Diseases described the first case of meningitis and encephalitis associated with COVID-19 [7].

One of the characteristic clinical symptoms of a new coronavirus infection is anosmia, sometimes in combination with hypogeusia. The reason for the development of anosmia, in the case of a viral infection, is considered by most researchers to be congestion in the nasal mucosa.

However, with some patients, anosmia becomes permanent, which may be associated with irreversible viral damage of neurons. It is necessary to point out that ACE2, the receptors required for the invasion of SARS-CoV-2, are expressed in the olfactory epithelium [8].

On April 1, 2020, the first case of Guillain-Barré syndrome associated with COVID-19 was described in the Lancet magazine [9].

In addition to the above-described severe lesions of the central nervous system, the presence of viruses can form nonspecific clinical manifestations, symptoms of changes in brain function are possible, such as: violation of mental status, personality change, abnormal behavior or speech impairment, etc.

The first research works devoted to this problem have already appeared [10]. However, the lack of knowledge about this problem: the effect of the virus on the psychoemotional sphere of a person substantiates the relevance and purpose of this work - to study the psychoemotional state of convalescents after the transferred COVID-19 infection.

**The data and methods of research.** 99 volunteers (36 boys and 63 girls) from the students of the FSBEI HE Kirov SMU MOH Russia took part in the research.

The average age of the volunteers was 19.9 ± 0.17 years. 2 groups were formed: group 1 - experimental (16 boys and 24 girls) - had had coronavirus infection (from 3 to 6 months have passed after the disease), group 2 - test group (20 boys and 39 girls). The research was conducted in March 2021at that time, the testees had no signs of diseases and belonged to the group of practically healthy individuals.

The level of stress resistance was determined by the stress resistance self-assessment test by S.Cohen and G.Willianson. Aggressive behavior was assessed according to L.G. Pochebut, identified verbal aggression, physical aggression, objective aggression, emotional aggression, self-aggression and the general level of aggression. Situational anxiety was identified ин the scale of situational anxiety CH.D.Spielberger in the adaptation of Y.L.Khanin.

Statistical analysis of the research results was carried out by Excel spreadsheets and the Statistica Advanced 10 for Windows RU computer program.

The Shapiro-Wilk test was used to check normal distribution of data and, if the data obeyed the law of normal distribution or had a distribution close to normal, then the results were presented as the arithmetic mean (M) and standard error of the mean (± m).

In this case, the parametric Student's t test was used to compare the quantitative indicators of two independent samples. The results of nonparametric processing methods are presented as median (Me) and interquartile range as 25 (Q1) and 75 (Q3) percentiles. To compare two independent samples, the nonparametric U-Mann-Whitney test was used. The

frequency of occurrence of the trait was assessed using the chi-square test. Correlation analysis was carried out according to Spearman's criterion. Differences and correlations were considered statistically significant at $p < 0.05$.

**Results.** At the first stage, gender differences were assessed by comparing the average indicators of stress resistance, aggressiveness, anxiety and the frequency of occurrence of a low level of stress resistance, a high level of aggressiveness and anxiety among all the boys and girls who took part in theresearch, regardless of the incidence of COVID-19 (Table 1).

Table 1. Comparison of indicators of stress resistance, aggressiveness and anxiety among the boys and girls

| Index | Indicator value (M ± m) or Me (Q1; Q3) | | The share of people (%) with a low level of stress resistance, high levels of aggressiveness and anxiety among | |
|---|---|---|---|---|
| | boys, n = 36 | girls, n = 36 | boys, n = 36 | girls, n = 36 |
| stress tolerance | 14,33±1,13* | 18,29±0,74* | 2,7** | 17,5** |
| aggressiveness: | 15,5 (11,0;17,0) | 14,0 (11,0;17,0) | 8,3 | 1,6 |
| verbal aggression | 3,0 (2,0;4,0) | 3,0 (2,0;4,0) | 13,9 | 14,3 |
| physical aggression | 2,0 (1,0;4,0) | 1,0 (0;2,0) | 22,2 | 17,9 |
| objective aggression | 3,0 (1,0;4,0) | 2,0 (2,0;3,0) | 16,7 | 14,3 |
| emotional aggression | 2,5 (1,0;4,0) | 2,0 (2,0;4,0) | 8,3 | 11,1 |
| self-aggression | 4,0 (2,0;5,5) | 4,0 (3,0;6,0) | 41,7 | 41,3 |
| situational anxiety | 40,69±1,83 | 43,84±1,20 | 41,7 | 55,6 |
| Notes:<br>1. "*" - reliability of differences between boys and girls in terms of p = 0.003<br>2. "**" - reliability of differences between boys and girls in terms of p = 0.03 | | | | |

From the data presented in Table 1, it is clearly seen that the girls have significantly higher ($p = 0.003$) than the boys, the average value of stress resistance. The average indicators of aggressiveness, types of aggression and situational anxiety did not have gender differences. According to the frequency of occurrence of the assessed indicators: 55.6% of the girls and 41.7% of the boys have a high level of situational anxiety; 41.3% of the girls and 41.7% of the boys have a high level of self-aggression. Less common were high levels of other types of aggression. Comparing the indicators among the boys and girls, we can conclude that the low level of stress resistance is significantly more often ($p = 0.03$) observed among the girls (in 17.5% of cases) than among the boys (in 2.7% of cases). The frequency of occurrence of high levels of types of aggression and situational anxiety differed slightly among the boys and girls.

At the second stage, the comparative analysis of the indicators of stress resistance, aggressiveness and anxiety in the experimental and control groups was carried out (Table 2).

From the data presented in table 2, we can conclude that, according to the analyzed indicators in the experimental and control groups, there were no significant differences in the average values. Qualitative analysis of the data also did not reveal any differences in the frequency of occurrence of the low level of stress resistance, the high level of aggressiveness and situational anxiety in the experimental and control groups.

**Conclusion.** The conditions of the pandemic caused various changes in the psycho-emotional state of people. It is possible that the high frequency of occurrence of situational anxiety and self-aggression among students in our research is also determined by the stressful impact of living conditions nowadays. Since it was not possible to compare the indicators of

the examined individuals in dynamics (before and during the pandemic), it is difficult to draw unambiguous conclusions about changes in the level of anxiety and aggressiveness. In the compared groups, there were no significant differences in the researched indicators. Probably, the possibility of finding all the people without exception in the situation of a chronic stress leveled these differences.

Table 2. Comparison of indicators of stress resistance, aggressiveness and anxiety in the experimental and control groups

| Index | Indicator value (M ± m) or Me (Q1; Q3) | | The share of people (%) with a low level of stress resistance, high levels of aggressiveness and anxiety among | |
|---|---|---|---|---|
| | experimental group, n = 40 | control group, n = 59 | experimental group, n = 40 | control group, n = 59 |
| stress tolerance | 15,38±1,10 | 17,84±0,78 | 10,0 | 16,9 |
| aggressiveness: | 14,5 (10,0;17,0) | 14,0 (11,0;17,0) | 2,5 | 1,7 |
| verbal aggression | 3,0 (2,0;4,0) | 3,0 (2,0;4,0) | 13,5 | 15,3 |
| physical aggression | 2,0 (2,0;4,0) | 1,0 (0;3,0) | 20,0 | 8,5 |
| objective aggression | 2,0 (2,0;4,0) | 3,0 (2,0;4,0) | 10,0 | 18,6 |
| emotional aggression | 3,0 (2,0;4,0) | 2,0 (1,0;4,0) | 15,0 | 6,8 |
| self-aggression | 4,0 (2,5;5,5) | 4,0 (3,0;6,0) | 32,5 | 47,5 |
| situational anxiety | 42,52±1,72 | 42,81±1,27 | 47,5 | 52,5 |

Thus, the results obtained is the initial experience in studying the characteristics of the psychoemotional state of people who have undergone coronavirus infection. At the second stage, we will conduct research in groups of elderly people who have undergone coronavirus infection, who are more susceptible to stress and adapt worse to a changing life situation. Nevertheless, a great number of questions appear, the answers to which will allow obtaining new knowledge about the effect of coronavirus on the human central nervous system.

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# CHILDREN CORONAVIRUS INFECTION OF PAVLODAR REGION OF KAZAKHSTAN

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**Abstract**. The emergence of a new anthropo-zoonotic infection SARS-CoV-2 in the world in December 2019 was a new stage in the study of the impact of viral infection on humanity. Children, as the most vulnerable part of society, this time found themselves in more favorable conditions with the incidence of a new coronavirus infection. The new coronavirus (SARS-CoV-2) causes disease in children of all age groups, starting with newborns, which occurs in a milder form than in adults [1]. Epidemiologically, children have a reduced risk of infection due to fewer trips, communication and movements. Perhaps the low incidence of children is associated with higher levels of circulating ACE2 (and lack of antihypertensive receptor-blocking drugs), or children have some features of innate immunity that disappear in ontogenesis [2, 3]. This article analyzes the incidence of children with coronavirus infection on the example of Pavlodar region of Kazakhstan. The observed trends in the incidence, course and complications of coronavirus infection in children do not differ from those in the world medical literature. Short-term follow-up does not allow long-term conclusions to be drawn regarding further complications after the disease and this dictates constant dynamic follow-up of children of ill SARS-CoV-2.

**Key words**: children, new coronavirus infection, COVID-19, monitoring, lethality, multisystemic inflammatory syndrome.

**Introduction.** At the end of 2019, humanity faced an insidious infection caused by a new strain of human coronavirus (SARS-CoV-2), characterized by relatively high lethality, which, according to various studies, varies widely (from 0.5 to 15%). The leading pathogenetic syndrome of a new coronavirus infection leading to patient death is severe respiratory failure. Its development is associated with nonspecific acute respiratory distress syndrome. At the same time, an important factor aggravating the course of infection is the ability of SARS-CoV-2 to affect various organs and organ systems [4].

Coronavirus infection (COVID-19) is an acute infectious disease caused by a new strain of coronavirus SARS CoV-2 a saerosol-droplet and contact-household transmission mechanism. Pathogenetically, COVID-19 is characterized by viremia, a local and systemic immune-inflammatory process, a hyperactivity coagulation cascade, endotheliopathy, hypoxia, which leads to the development of micro- and macrotromboses; It proceeds from asymptomatic to clinically pronounced forms with intoxication, fever, damage to the endothelium of the vessels, lungs, heart, kidneys, GIT, central and peripheral nervous systems with a risk of complications (ARDS, RD, PE, sepsis, shock). In children and adolescents, there may be a clinical course variant in the form of multisystemic inflammatory syndrome temporarily associated with COVID-19 [5]

Multisystem inflammatory syndrome temporarily associated with COVID-19 in children and adolescents, other names of Kawasaki are similar syndrome or the following names are found in foreign literature: Paediatric inflammatory multisystem syndrome - PIMS-TS; Multisystem inflammatory syndrome in children, MIS-C. MVA is a new syndrome that is temporarily associated with exposure to the SARS-CoV-2 virus and can lead to a severe and life-threatening course of the disease. MIS associated with COVID-19- is a delayed immunological phenomenon associated with the development of inflammation following symptomatic or asymptomatic COVID-19 infection. [6]

The first coronaviruses detected were the cause of respiratory infection in children and adults, which were not particularly dangerous and severe. It has been established that coronaviruses (not causing COVID-19) are found in respiratory secrets in a large number of healthy children. In the Vanderbilt study, coronavirus was found in about 5% of samples from upper AW (VDP) and in 8% of lower AW (EAW) in acute respiratory disease. Most clinically relevant coronavirus infections were found in children under 2 years of age, although a severe course of coronavirus infections could occur in older children [7]. However, in general, children are sick less frequently and more easily than adults. A number of authors associate this with the anatomical-physiological features of the childhood body and the lifestyle of children other than adults: 1) children have a less active innate immune response (a more vigorous immune response in adults may also explain hyperergic immune responses that lead to the development of acute respiratory distress syndrome); 2) children have healthier airways because they have not been exposed to the same amount of cigarette smoke and air pollution as adults; 3) children have fewer chronic somatic diseases [8].

According to WHO data for February 20, 2021 in the world 111,427,508 cases of infection with COVID-19 coronavirus are recorded. Over the past day, the number of infected has increased by 341,651 people. The total number of deaths from coronavirus infection in the world is 2,467,296 people, today there are 8,720 deaths. 22,685,111 people are in the active phase of the disease, of which 95,233 are in critical condition. Fatality rate: 2.21%. Confirmed cases of complete cure of the virus today, February 20, 2021 in the world: 86 299 638 [5].

As of February 20, 2021 in Kazakhstan 256,388 cases of infection with COVID-19 coronavirus are recorded. Over the past day, the number of infected has increased by 766 people. The total number of deaths from coronavirus infection in the country is 3150 people, today there are 2 deaths. Confirmed cases of complete cure of the virus today, February 20, 2021 in the country: 231 667 [9].

Table 1. Statistics COVID-19

| | Recorded (total) | Recorded (per day) | Death (Total) | Death (per day) | In active phase | In critical condition | Recovered |
|---|---|---|---|---|---|---|---|
| World | 111 427 508 | 341 651 | 2 467 296 | 8720 | 22 685 111 | 95 233 | 86 299 638 |
| RK | 256 388 | 766 | 3150 | 2 | 16641 | 336 | 191 097 |
| Pavlodar region | 16939 | 100 | 162 | 0 | 352 | 28 | 77 |

Coronavirus infection continues to spread in Kazakhstan, the second wave covered Pavlodar region. Today, on February 20, 2021 the number of cases in the software was 16939 (+ 100), among the cases there are children and adolescents under the age of 18 (according to the UZ as of February 20, 2021 with the diagnosis: U07.1Coronavirus infection is under supervision (outpatient) 193 children, Infectious hospital ODB-7, of which:* transfer from the isolator - 3 children, * diagnosed: KVI -4 children:- up to 1 year - 1 child, - 1-5 years - 2 children, - over 5 years - 4.

With diagnosis U07.2 Coronavirus infection COVID-19 (Virus not identified) are on inpatient treatment - 11 patients [10].

It is noted that children with coronavirus infection are less common than adults. Their clinical symptoms are less pronounced, they are less likely to require hospitalization, and their disease occurs more often in asymptomatic and mild form. Although, cases of a serious course of the disease are not excluded. In many countries of the world, as well as in Kazakhstan, multi-inflammatory syndrome (MVS) is recorded among children who have a mild or asymptomatic form of coronavirus. This is a delayed immunological phenomenon

associated with inflammation after an infection. The syndrome is considered a rare occurrence. Most of the reports of its occurrence come from the USA, Great Britain and the EU, so it is difficult to establish how it manifests in other regions. WHO has developed preliminary, valvulitis or coronary artery lesions; signs of coagulopathy; acute symptoms associated with the gastrointestinal tract (diarrhea, vomiting, or abdominal pain). According to the PODB, three cases of MVS in children with favorable outcomes were recorded in Pavlodar region. Risk factors for such a severe and complicated course of COVID-19 are: children under 1 year of age; children with body weight deficiency > 30%; congenital malformations in decompensation; diabetes mellitus; obesity; bronchial asthma; autoimmune and oncological diseases; primary immunodeficiency; other hereditary diseases; coinfection (respirate-syncytial virus, rhinovirus, bokavirus, adenovirus, etc.).

The aforementioned concomitant pathology in a child with COVID-19 aggravates the course of the disease and leads to damage to the lower respiratory tract (pneumonia, bronchiolitis). In general, children are less likely and easier to tolerate coronavirus infection, complicated courses were extremely rare in our region (3 cases of MIS). Children in an asymptomatic and mild form of infection are much more likely to infect adults, which is important for them to comply with anti-epidemic measures (hand hygiene, distance, wearing personal protective equipment).

As for the asymptomatic forms, the high level of carriage is noteworthy. We can assume two probabilities underlying this phenomenon: on the one hand, it is a characteristic feature of SARS-CoV-2, on the other hand, inapparent seroconversion cannot be ruled out, in which a humoral immune response can develop even in the absence of a manifest form of infection [4].

**Purpose of the study** is to establish the age, gender, prevalence of coronavirus infection in Pavlodar region among children under 18 years of age, to compare the rate of spread with world data on COVID.

**Materials and research methods:** Statistical data on coronavirus infection of the Pavlodar region health center. Time series analysis (absolute growth, growth rate, growth rate, value of 1% growth, visibility indicators).

**Results.**

Table 2. Time series by the number of children who received inpatient treatment with coronavirus infection in Pavlodar region

| | number of children | absolute increase | indicators of visualization | rate of growth | rate of increase | value of 1% increase |
|---|---|---|---|---|---|---|
| Jan. 2020 | 1 | | | | | |
| Feb. 2020 | 1 | 0 | 100 | 100 | 0 | 0 |
| Mar. 2020 | 23 | 22 | 2300 | 2300 | 2200 | 0,01 |
| Apr. 2020 | 46 | 23 | 4600 | 200 | 100 | 0,23 |
| May. 2020 | 60 | 14 | 6000 | 130,4348 | 30,43478261 | 0,46 |
| Jun. 2020 | 101 | 41 | 10100 | 168,3333 | 68,33333333 | 0,6 |
| Jul. 2020 | 117 | 16 | 11700 | 115,8416 | 15,84158416 | 1,01 |
| Aug. 2020 | 159 | 42 | 15900 | 135,8974 | 35,8974359 | 1,17 |
| Sep. 2020 | 125 | -34 | 12500 | 78,61635 | -21,3836478 | 1,59 |
| Oct. 2020 | 65 | -60 | 6500 | 52 | -48 | 1,25 |
| Nov. 2020 | 28 | -37 | 2800 | 43,07692 | -56,92307692 | 0,65 |
| Dec. 2020 | 63 | 35 | 6300 | 225 | 125 | 0,28 |
| Jan. 2021 | 41 | -22 | 4100 | 65,07937 | -34,92063492 | 0,63 |
| Feb 2021 | 42 | 1 | 4200 | 102,439 | 2,43902439 | 0,41 |

The incidence of coronavirus infection in the population of Pavlodar region is uneven. The rate of change in incidence rates is different, the highest growth rate is observed in June 2020. The highest incidence rate in August 2020.

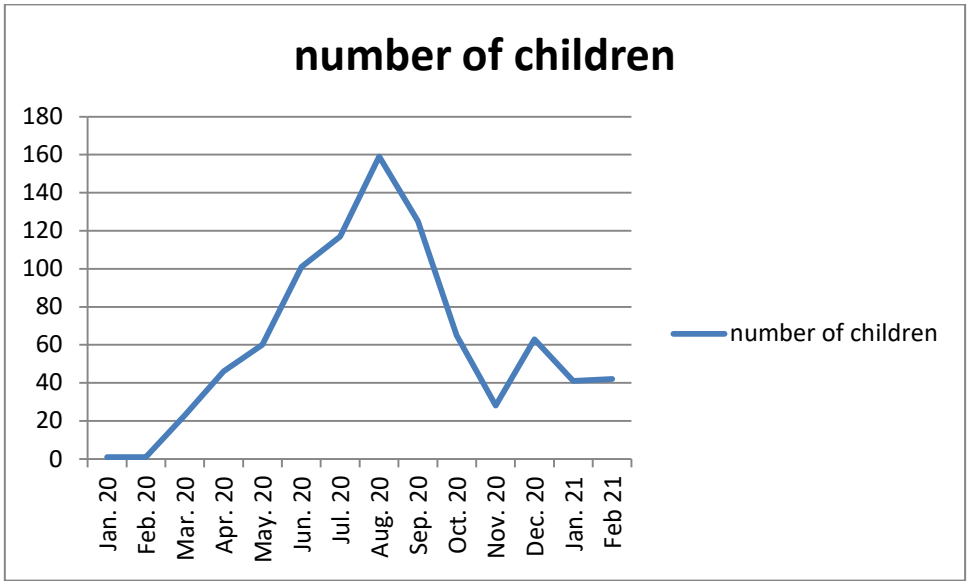


Figure 1. The number of children who received inpatient treatment with coronavirus infection in Pavlodar region by months

The number of children who received inpatient treatment with coronavirus infection in Pavlodar region for months from January 1, 2020 to February 20, 2021 was 872 children, of which 498 were boys and 374 were girls. And also up to a year 156 children, 1-5 years old 296 children, 5-18 years old 420 children.

**Conclusions.**

1. Children in the structure of the diseased population in the Pavlodar region account for 965 children (1.9%). According to World statistics, it is from 3 to 7%.
2. The course of the disease in children in 70% of cases is asymptomatic or mild, less often moderate. In Pavlodar region 675 children were asymptomatic, 272 children were of moderate severity, 18 children were severe.
3. Mortality in children with new coronavirus infection is relatively low, in Pavlodar region there was no mortality from CVI.
4. Girls get sick less often than boys. There are 548 fry and 417 girls in Pavlodar region.
5. Children of school age get sick more often than children of preschool age.
6. The COVID-19 epidemic continues and evolves rapidly, with many affected children still hospitalized.
7. For a better understanding of the course of COVID-19 infection in children, for more detailed information of patients and their parents, further research is needed on this urgent problem that has challenged humanity.

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# EXPERIENCE OF PREPARATION AND APPLICATION OF IMMUNE ANTI-COVID-19 PLASMA IN KAZAKHSTAN

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**Abstract**. This article analyzes the production and use of immune anti-COVID-19 plasma (hereinafter referred to as immune plasma), reflecting the main effects, methods of obtaining and using plasma in clinical practice in the Republic of Kazakhstan. In the process of organizing the procurement of immune plasma, the mechanisms for selecting donors, determining the concentration of class G antibodies against SARS COV-2, the titer of neutralizing antibodies, the effect of virus inactivation with amotosalenom + UV on the concentration of class G antibodies against SARS COV-2 were studied.

**Key words**: donor, donation, plasma, apheresis, anti-COVID-19.

**Introduction**. An outbreak of COVID-19, caused by SARS-CoV-2 [1], has spread rapidly, causing a progressive increase in the number of infected patients.

Currently, the determination of SARS-CoV-2 RNA in nasopharyngeal swabs is carried out using the method of real-time polymerase chain reaction (hereinafter - PCR) [2]. However, molecular tests can sometimes give false negative results [3]. With this in mind, serological tests can be useful for detecting IgG antibodies, assessing the degree of immunization, and selecting for immune plasma donations [4].

With a sharp increase in those who have had coronavirus infection and who want to donate immune plasma without confirming PCR tests, as well as a change in approaches to the admission of donors based only on clinical signs in the anamnesis, it was necessary to improve the quality of the plasma obtained, namely, antibody indicators.

Currently, the COVID-19 pandemic remains the major crisis facing healthcare systems around the world. A mass vaccination campaign has begun, including in the Republic of Kazakhstan, but it is still too early to predict the development of the epidemiological situation. The creation of methods and tools for etiotropic therapy for COVID-19 is a major challenge. It is known from the example of other human coronaviruses that the circulation of coronaviruses is possible in immune populations, so the need for treatment will exist even if everyone is vaccinated. Globally, there is a tremendous need for therapies aimed at suppressing the replication of the SARS-CoV-2 virus, the causative agent of COVID-19. Recently, British colleagues have shown that dexamethasone, a steroidal anti-inflammatory drug, is effective in seriously infected patients who develop a systemic inflammatory response leading to lung damage and other organ dysfunction [5]. However, this drug should not be used for all patients, who may indeed have very serious side effects. As an experimental etiotropic therapy, treatment with the introduction of immune plasma is used [6].

Virus neutralizing antibodies (VNA) are antibodies that bind to viral particles and suppress infectivity. VNAs are usually a small fraction of the total antibodies induced during infection.

According to the results of studies of the effectiveness of the use of immune plasma in the treatment of MERS-CoV infection, it was found that in order to achieve a therapeutic effect with the help of convalescent plasma transfusion, the VNA titer should be higher than 1:80. There is a requirement of the American regulatory body (FDA) for immune plasma: the VNA titer must be at least 1: 160. VNA titers are not constant and tend to decrease over time after recovery. In this regard, for the success of therapy with immune plasma, the main task is to find donors who have recovered with the necessary titers.

Transfusion of immune plasma remained the only possible resource for etiological treatment, while the development of vaccines against coronavirus took a long time to be introduced. The use of pathogen-inactivation technology was considered as a reliable means in terms of preventing transmissible infections during transfusion of convalescent plasma. Therefore, we had a basis for investigating possible qualitative changes in the specific antibodies of the treated plasma.

According to the materials studied in the world practice, Gudbjartsson and other researchers showed that there were no signs of a decrease in the level of antibodies up to 4 months after infection [7]. We assessed the concentration of antibodies to SARS-CoV-2 4-6 months after the first wave of the pandemic in participants with predominantly moderate to severe COVID-19.

It was considered expedient to inactivate pathogens in the plasma of convalescent donors; however, the effect of inactivation of pathogens on the level of protective antibodies has not been studied enough.

**Materials and methods**. Doses of immune plasma from patients' coronavirus infection were prepared by plasmapheresis using PCS2 Hemonetics devices. Generally accepted guidelines for donor selection, blood testing and product rejection have been applied in accordance with Blood Service standards. The target volume of collected plasma was 600 ml.

The content of class G antibodies to the SARS-CoV-2 nucleocapsid protein in blood serum was determined using:

- immunochemiluminescence assay (hereinafter - IHLA) with reagents manufactured by ABBOTT on Architect i2000sr equipment (ABBOTT, USA);

- enzyme-linked immunosorbent assay (hereinafter - ELISA) on the test system “ELISA EDI for the detection of IgG antibodies to the new coronavirus COVID-19”, EPITOPE DIAGNOSTICS, INC.

Research was carried out in our own laboratory. The laboratory has a safety level of class 2 (especially hazardous), which were approved by the Ministry of Health of the Republic of Kazakhstan [8].

VNA titration against SARS-COV-2 was performed at the National Center for Biotechnology, in Nur-Sultan city. For titration, a museum preparation of the SARS-COV-2 virus “B00001” with a titer of 2.4 × 105 PFU / ml, Vero E6 cells, EMEM medium (BioWhittaker BE12-668F), 2% low-melting agarose (iNtRON Biotechnology 32035) was used.

For the study, we used frozen serum samples of immune plasma donors, tested before donation using reagents manufactured by ABBOTT on Architect i2000sr equipment (ABBOTT, USA) and having class G antibodies to the SARS-CoV-2 nucleocapsid antigen.

Confirmatory testing was performed on semi-automated equipment (TECAN) for ELISA studies. The study was carried out using ELISA reagents: “GA CoV-2 IgG +” (GA Generic Assays GmbH, Germany). The specificity of antibodies against the main immunodominant antigens of SARS-CoV-2 (Spike Glycoprotein 1, Spike Glycoprotein 2, Nucleocapsid) was determined.

The plasma tested for vector-borne infections was treated with amotosalene + UFO using the Intercept System (CERUS) technology.

A special reporting form was developed to assess the effectiveness (or to monitor transfusion) of anti-COVID-19 virus-inactivated immune plasma in the treatment of patients with COVID-19. This report allows you to assess the health status of patients on the WHO progression scale (from 1 to 9) at the beginning of treatment with the use of immune plasma and at certain intervals (Table 1), and also contains a number of other indicators that allow us to assess the dynamics and likely effectiveness of the use of immune plasma.

Table 1. WHO progression scale

| **OMS Progression Scale** | **Description** | **Score** |
|---|---|---|
| Uninfected | Uninfected; Virus RNA not detected | 0 |
| Ambulatory | Asymptomatic; Virus RNA detected | 1 |
| Ambulatory | Symptomatic; manages independently | 2 |
| Ambulatory | Symptomatic; needs outside help | 3 |
| Hospitalized: moderate course | Hospitalized; without oxygen therapy | 4 |
| Hospitalized: moderate course | Hospitalized; oxygen through a mask or nasal oxygen supply | 5 |
| Hospitalized: severe course | Hospitalized; oxygen through non-invasive ventilation or high-flow | 6 |
| Hospitalized: severe course | Intubation and mechanical ventilation, $pO_2 / FIO_2 \geq 150$ or $SpO_2 / FIO_2 \geq 200$ | 7 |
| Hospitalized: severe course | Mechanical ventilation ($pO_2/FIO_2 < 150$ or $SpO_2/FIO_2 < 200$) or vasopressors (norepinephrine > 0.3 μkg/kg/min) | 8 |
| Hospitalized: severe course | Mechanical ventilation, $pO_2/FIO_2 < 150$ and vasopressors (norepinephrine > 0.3 μkg/kg/min), or dialysis or ECMO | 9 |
| Death | Death | 10 |

In this study, the STATA 16 statistical program was used to conduct descriptive and inferential analysis. Quantitative variables were described as means and standard deviations. Qualitative variables in the form of quantities and percentages. To assess the relationship between the two quantitative variables, the Pearson correlation coefficient was used, as well as simple linear regression analysis to obtain the relationship coefficients and confidence intervals. Indicators below the 0.05 level were considered statistically significant.

**Results**. As of March 25 of this year, 2,032 people became immune plasma donors in the Republic of Kazakhstan, of which 424 people donated plasma twice. Received 7215 doses of immune plasma, issued to medical organizations 3152 doses.

In June-July 2020, studies were carried out for IgG anti-SARS Cov-2 antibodies in 498 potential donors of immune plasma, of which husband - 82%, wives - 18%. The average age was 37 ± 7.5.

The positivity coefficient (Index S / C) was:

ELISA min-0.233, max-2.915, average 1.528 ± 0.574 (number of tests performed - 223),

IHLA min-0.010, max-9.450, average - 4.783 ± 1.929 (the number of tests performed was 275).

The number of negative samples was 170 (34%).

Positive results were found in 328 donors.

For the preparation of effective immune plasma, with a sufficient amount of antibodies, a threshold barrier was established by the positivity coefficient (CP) obtained during the study. Thus, the CP in the study by the ELISA method should have been more than 1.4, the CP in the study by the IHLA method should be above 3.0. This threshold was exceeded in 257 (52%) potential donors.

Also, in order to determine the titer of neutralizing antibodies, immune plasma obtained from 10 convalescent donors was examined, the average age was 40 ± 5.4 years. The positivity coefficient of IgG antibodies against SARS-COV-2 before donation is 8.18 ± 0.40. In 6 samples, the VNA assessment showed titers > 1: 1600, in 3 samples - titers from 1:50 to 1: 400, and in one sample the effect of antibody-dependent intensification of infection was found. Out of 10 samples, only 2 samples showed insufficient VNA titer to effectively treat patients with SARS-CoV-2 infection.

Since all doses of immune plasma were inactivated by the virus, we decided to study the effects of amotosalene + UV on the concentration of IgG antibodies against SARS COV-2. The total number of tested immune plasma samples was 50, of which 31 were tested by ELISA, and 19 samples were tested by CLIA. A paired t-test was used to compare the IgG concentration before and after the inactivation procedure. In both tests, there was a slight decrease in the level of specific IgG antibodies, but a smaller decrease in the ELISA test (from 1.46 ± 0.53 to 1.43 ± 0.54) with less significance ($p = 0.45$) and a greater decrease in the CLIA test (from 4.96 ± 2.02 to 4.50 ± 1.80 ) with greater significance ($p < 0.01$).

In order to assess the concentration of antibodies to SARS-CoV-2 4-6 months after the first wave of the pandemic in convalescent donors with predominantly moderate and severe COVID-19, a study was conducted. The study involved 52 participants, of whom 94.2% were men. The average age was 41.0 ± 9.6. The number of days after the first analysis (mean ± SD) - 162.7 ± 31.8. The positivity coefficient after the first analysis was (mean ± SD) 5.8 ± 1.6, the second (mean ± SD) - 2.2 ± 1.6, decrease (mean ± SD) by 3.6 ± 1.6. In 22 (42.3%) participants, the analysis showed a negative result.

Immune plasma was used in the treatment of 1128 patients, 2168 doses were transfused. Of the total number of recipients, 214 continue treatment, of which 181 with improvement. 666 patients were discharged, 248 people died.

**Discussion**. The first patients with COVID-19 in the republic were registered in mid-March 2020. At the same time, one of the main requirements for donors was the absence of any clinical manifestations of the disease COVID-19 for two weeks before donation.

Meanwhile, in June 2020, a number of international directives, including the European Guidelines, changed the requirements for the selection of donors, stating that the fact of the transferred disease can be confirmed by testing for the presence of antibodies to SARS-Cov2 without PCR testing or other methods of instrumental diagnostics of COVID-19.

In this regard, the national standard for the selection of immune plasma donors has also been changed. According to the new approach, the fact of the disease can be confirmed by the history data without seeking medical help, in addition, laboratory diagnostics is aimed at identifying and determining the level of antibodies to the causative agent of COVID-19, provided that serological tests with high quality characteristics are used.

To understand the correspondence of donor plasma to the patient's needs for a certain level of immunoglobulins G, it was necessary to organize screening of donors for the presence and titer of anti-SARS-Cov2 antibodies.

An analysis of the available offers from manufacturers of reagents for antibodies to SARS-Cov2 was carried out.

Considering the almost complete absence in March and April 2020 on the market of immunological tests, the choice was made on test systems for enzyme immunoassay for the

determination of antibodies Epitope Diagnostics Inc., USA, with high specificity and sensitivity.

After the appearance on the Kazakhstan market of test systems manufactured by ABBOTT Laboratories (USA), most blood centers began screening donors for antibodies to SARS-Cov2 using Architect analyzers, which are used to detect markers of transfusion infections in routine practice.

Thus, the production of anti-COVID-19 immune plasma in Kazakhstan began in May 2020, and already in June 2020, immune plasma began to be produced in almost all regions of the republic.

The data obtained from the regional blood centers and the NPCT laboratory made it possible to assess the main statistical characteristics of the results and, based on the assessment, determine the threshold for the positivity coefficient, below which the level of antibodies could be considered insufficient.

It was specifically stipulated that in the absence of tests for neutralizing antibodies, a test for the presence of anti-SARS-CoV-2 antibodies should be performed before the blood component is dispensed.

Meanwhile, British, Spanish, Italian specialists, doctors from the United States announced the possibility of only serological testing of donors with a preliminary establishment of a correlation between the results of serological tests and tests for determining the VNA of immune plasma.

Plasma VNA assessment was carried out by National Center for Biotechnology specialists in August 2020. Of 10 samples sent to National Center for Biotechnology, 1 has a titer of 1:50, 2 samples 1: 100, 1 - 1: 400, the remaining 6 samples have a titer of 1: 1600.

The performed work on the presence or absence of neutralizing antibodies to the Spike antigens of SARS-CoV-2 showed that all samples of immune plasma had antibodies to the antigens Nucleocapsid and Spike Glycoprotein 1, respectively, the immune plasma contains neutralizing antibodies that block the interaction of the receptor-binding domain of the S protein SARS-CoV-2 with target cells.

The pathogen inactivation process slightly reduces the concentration of specific anti-SARS-CoV-2 IgG antibodies in the collected immune plasma. ELISA and CLIA test results show their reproducibility and more research is required to identify a more specific method.

A relationship was established between a decrease in antibody concentration after 4-6 months (r -0.54; 95% CI: -0.03; p <0.001). The decrease in antibodies did not depend on the age of the participants (r 0.06; 95% CI: 0.01; p 0.66). This is encouraging, but the concentration of antibodies needed to protect against reinfection has yet to be established. Thus, large follow-up studies are warranted to establish protection against reinfection and / or disease and the duration of antibody protection.

A severe or rapidly developing life-threatening course of COVID-19 with one or more of the following symptoms has been identified as indications for immune plasma transfusion: short breathing (dyspnea), respiratory rate ≥30 / min, blood oxygen saturation ≤93%, ratio of arterial blood oxygen partial pressure to fraction of inspiratory oxygen <300, development of pulmonary infiltrate> 50% within 24-48 hours.

As of March 25 of this year, questionnaires for the treatment of 375 patients from all over the Republic of Kazakhstan were received.

The analysis of the questionnaires showed that the most effective application was in the first two weeks from the onset of the disease. On average, immune plasma was applied on the 11th day of hospitalization, while in patients with recovery - on average on day 10, in patients with fatal outcome - on average on day 12.

According to the WHO scale, at the beginning of the use of immune plasma, the state was assessed as corresponding to 4-7 points in 338 patients and in 37 patients, the state

corresponded to 8-9 points. The comparison showed that patients who started treatment at a stage corresponding to 4-7 points on the WHO scale were discharged in 69.2% of cases, patients with an assessment of 8-9 points - in 29.7%. In general, the proportion of patients discharged with recovery in the total number of recipients in the Republic of Kazakhstan was 58.6%.

Despite the limited number of observations, certain conclusions can be drawn: starting treatment at a relatively early stage of the disease is more effective in comparison with the use of immune plasma at stages requiring mechanical ventilation with support of vascular pressure by vasopressors. The most effective, given the severity of the disease, can be considered the use of the progression scale at stage 6 (43% of recipients requiring high-flow oxygen therapy were discharged) and at stage 7 of the scale (33.3% of recipients requiring intubation and mechanical ventilation were discharged).

Taking into account the data obtained, changes were proposed to the clinical protocol for diagnostics and treatment: contraindications to the use of immune plasma were introduced, among which - "despair therapy" in patients with subtotal (more than 75%) or total lung damage, who are on mechanical ventilation for more than 72 hours; the duration of the disease is more than 10-12 days; multiple organ failure.

Taking into account the severity of the disease, the use of plasma can be considered the most effective at stage 6 of the progression scale (43% of recipients were discharged who required high-flow oxygen therapy) and at stage 7 (33.3% of recipients were discharged requiring intubation and mechanical ventilation).

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# FACTORS ASSOCIATED WITH THE RISK OF DEATHS IN COVID-19

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**Abstract**: Available evidence and lessons learned from the COVID-19 pandemic show that COVID-19 ranges from mild respiratory infections to severe viral infections with complications and deaths. The mortality rate from COVID-19 in the Kyrgyz Republic is 1.7%. We analyzed 79 COVID-19 deaths to assess risk factors for poor outcomes. It was found that advanced age > 60 years, male sex, the presence of concomitant diseases, late admission, lymphopenia, high levels of C-reactive protein and D-dimer, the development of ARDS, sepsis, acute thrombosis are associated with a severe course and an unfavorable outcome.

**Key words**: COVID-19, mortality, disease, complication.

**Introduction.** For more than a year, as the coronavirus (SARS-CoV-2), which was registered in December 2019 in China, is rapidly spreading around the world. At the end of March 2021, more than 127 million cases of COVID-19 were registered in the world, of which 2.78 million were deaths. According to published studies, a new coronavirus infection can be asymptomatic in 17-25% of people. However, in 80% of cases, COVID-19 proceeds with clinical manifestations of a mild to moderate form, but 15% develop a severe illness requiring oxygen support, and 5% have an extremely severe course with complications such as acute respiratory distress syndrome (ARDS), sepsis and septic shock, thrombosis and / or multiple organ failure [1].

According to most published studies, severe COVID-19 was more common among older people [2, 4]. In publications from China, it was noted that 87% of patients with COVID-19 were between the ages of 30-79 years, with the disease being more common among women [3]. Studies in the UK showed that the average age of hospitalized patients was 73 years and was dominated by men (60%) [4]. In US publications, elderly patients (≥65 years of age) accounted for 53% of all ICU admissions and 80% of deaths, with the highest incidence of severe outcomes in patients ≥85 years of age [5].

Patients with comorbidities, who are at increased risk of serious illness, also deserve special attention, and the more comorbidities, the higher the risk. In the UK, the most common comorbidities were cardiovascular disease (31%), diabetes mellitus (21%), chronic lung disease (18%) and chronic kidney disease (16%) [3, 4]. In the United States, patients with COVID-19 reported hypertension (56%), obesity (49%), metabolic disorders (42%), and cardiovascular disease (33%). Cancer, chronic kidney disease, diabetes mellitus, and hypertension were independently associated with mortality [5, 6].

The severe course of COVID-19 in the elderly and with concomitant pathology is possibly associated with the development of macrophage syndrome, cytokine storm, severe lymphopenia, microcirculation disorders due to thrombus formation and hypoxemia.

There also appeared information about factors associated with severe forms of the disease, such as smoking, pregnancy, immunosuppression, ethnicity, A (II) blood group, vitamin D deficiency, environmental factors [6].

Despite numerous scientific studies, there are still many questions, including the risks of severe forms and deaths.

**The purpose** of study is to assess the main risk factors for adverse outcomes in COVID-19 based on the materials of the Republican Clinical Hospital for Infectious Diseases.

**Materials and methods**. Based on the statistical data of the Ministry of Health and the SR of the Kyrgyz Republic, an analysis of the incidence and mortality from COVID-19 in the Kyrgyz Republic for 2020-2021 was carried out. 79 medical records of the disease who died from COVID-19 in the Republican Clinical Hospital for Infectious Diseases, from November 2020 to January 2021. All patients were laboratory-confirmed SARS-CoV-2 coronavirus infection by PCR. The presence of pneumonia is confirmed by x-rays or computed tomography of the lungs. The severity and treatment were established in accordance with the "Interim Clinical Guidelines for the Diagnosis and Treatment of COVID-19" (version-4) of the Ministry of Health of the Kyrgyz Republic No. 649 dated 25.08.20 [7].

**Discussion.** As of March 31, 21, 88 thousand 374 cases of COVID-19 (1368.7 per 100 thousand population) and 1499 deaths (23.2 per 100 thousand population) were registered in the Kyrgyz Republic. The first cases of COVID-19 were detected on March 18, 2020 in 3 Kyrgyzstanis who returned after performing a small hajj (umrah) in Saudi Arabia. Subsequently, there was a constant increase in the number of new patients with COVID-19. However, a sharp increase in the incidence began to be recorded from June 2020, as soon as restrictive measures were lifted in the republic. (Figure 1.) The maximum number of newly detected cases was observed in the first half of July 2020, the peak value was 9239 cases per week (07.13-19.07. 20 g). It should be noted that during this period the highest rates of the detection rate of SARS-CoV-2 RNA were recorded, which reached a maximum value of 23.1%. From the second half of July to the end of August, a gradual decrease in the number of COVID-19 cases was noted (as of 31.08-06.09.20, the total number was 560 per week). At the same time, a decrease in the average frequency of detection of SARS-CoV-2 RNA among a conventionally healthy population was noted to 1.8%.

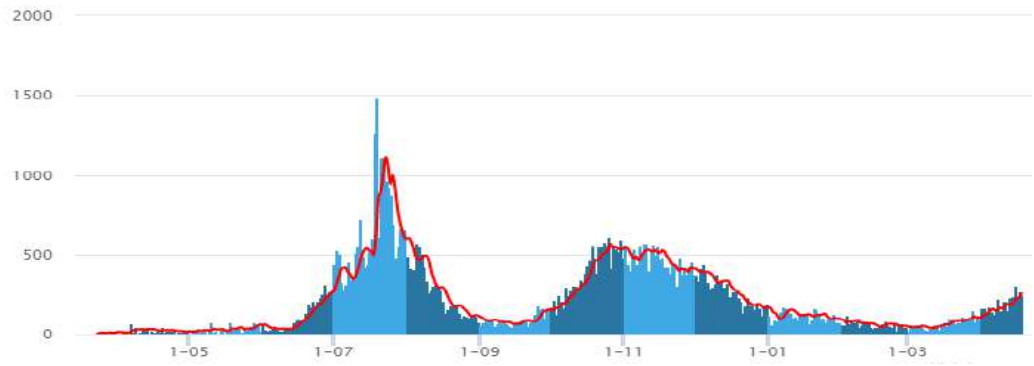


Figure 1. Dynamics of the incidence of COVID-19 in the Kyrgyz Republic from March 18, 2020 to April 10,2021.

The second wave of an increase in the incidence was noted in October-December 2020. In the period from 02.11 to 08.11.20, the maximum number of detected new cases was observed, which was 3941, but by the end of December, up to 932 cases per week were registered (28.12.20). Since January, the number of detected cases of COVID-19 has continued to decline, with an average of 806 cases per week, and 446.3 in February-March.

The incidence in the regions of the republic varied significantly. Over the entire period of the epidemic rise, the highest incidence was recorded in Bishkek (34.2%) and Chui oblast (15%), the lowest rates were noted in Talas (3%) and Naryn (2.5%) oblasts.

An important characteristic of the severity of the consequences of the COVID-19 epidemic is the general case fatality rate (CFR) and for Kyrgyzstan it was 1.7%. According to this indicator, the republic ranks 6th among the Commonwealth of Independent States. The maximum number of deaths was recorded in July and November 2020 at the peak of the incidence (1316 and 126 cases, respectively). (Figure 2.) 50.1% of all registered deaths occur in Bishkek, due to the high incidence rate and the frequent transfer of critically ill patients from the regions to the central hospitals of the city.

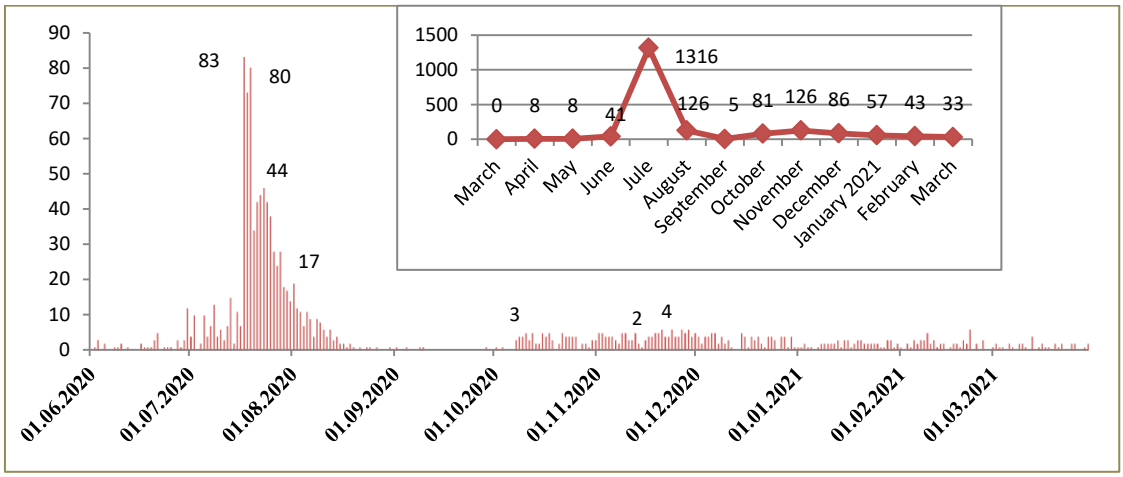


Figure 2. Dynamics of registered deaths from COVID-19 in the Kyrgyz Republic from March 1, 2020 to March 31, 2021

To study the risk factors for deaths, we analyzed 79 case histories of patients who died in the intensive care unit of the Republican Clinical Hospital for Infectious Diseases. The age of the deceased patients ranged from 17 to 86 years, averaging 66.7 years, with men predominating (64.6%). Thus, in the age structure, more than 70.9% of patients were over the age of 60, while in 33% of cases - from 61 to 71 years, in 26.5% - from 72 to 81 years, and 11.4% of cases - over 82 years old. It should be noted that there were differences in gender in different age categories. Thus, in the group of persons under 71 years old, men predominated (68.6% versus 49.9% of women), however, in the group of persons over 72 years old, women prevailed (50.1% versus 31.4% of men). Among patients with COVID-19, there were mainly residents of Bishkek (46.2%), as well as Chui and Osh regions (35.8%). Contact with a probable or confirmed case of COVID-19 was detected in patients only in 13.9% of cases.

It should be noted that the vast majority of patients (78.5%) were treated independently at home, while 58.2% of patients took antibiotics, 27.8% of patients - anticoagulants, and in 16.5% of cases - steroid hormones, which was cause of late admission and late hospitalization. 45.6% of patients were admitted on the 6-10th day of illness in a severe and extremely serious condition, 15.2% of patients - on the 11-15th day of illness, 8.9% - on the 16-30th day. According to the severity of the condition, 56.9% of patients were immediately admitted to the intensive care unit and intensive care unit, the rest were transferred due to the worsening of their condition.

The absolute majority of the observed patients (96.1%) had chronic non-infectious diseases, only in one case the patient had no concomitant pathology. Among concomitant diseases, in 68.4% of cases, patients with COVID-19 suffered from cardiovascular diseases (hypertension, CHD, IHD, etc.), while this pathology prevailed among men (72.5% versus 60.7% in women). It should be noted that in 27.8% of cases there was a combination of cardiovascular diseases with diabetes mellitus, which was more common among women (35.7%) than among men (23.5%). 37.9% of patients suffered from chronic liver diseases

such as fatty hepatosis (56.7%), chronic hepatitis (30%), liver cirrhosis (13.3%). Obesity was detected in 7.6% of patients, chronic kidney disease in 5.1% of patients, chronic pancreatitis in 8.9%, anemia in 3.8%, malignant neoplasms in 2.5%, tuberculosis in 1.3% of patients. It should be noted that chronic liver disease and obesity were more common in women (42.9% and 14.3%, respectively) than in men (35.3% and 3.9%). Consequently, patients with cardiovascular diseases, often in combination with diabetes mellitus, as well as chronic liver diseases should be included in the group at greatest risk of developing adverse outcomes of COVID-19.

The most typical clinical manifestations on admission in patients with a severe course of the disease were fever (97.2%), cough (95.5%), shortness of breath (94.5%), weakness (100%), anosmia and ageusia (69.3%), chest pain (60.5%), poor appetite (78.1%), joint pain (35.3%), myalgia (39.4%), diarrhea (13.4%). It should be noted that symptoms such as chest pain, arthralgia, myalgia and diarrhea were more common among men.

From laboratory blood tests, the greatest changes in patients occurred on the part of lymphocytes. The high incidence of lymphopenia in severe patients is associated with the targeted invasion of SARS-CoV viral particles, which damage the cytoplasmic component of the lymphocyte and cause destruction. In our study, lymphopenia was observed in 84.8% of patients, while the level of lymphocytes less than 5% was observed in 45.6% of cases. It should be noted that severe lymphopenia was more common among women (57.1%) than among men (39.2%). Thrombocytopenia was observed in 29.4% of cases, but 2 times more often it was observed in men (35.7% versus 17.6% in women). An increase in CRP was noted in 60.8% of patients, while a rate above 100 mg / l was noted in 50.2% of cases. An increase in fibrinogen was noted in 85% of cases, while indicators in the range from 400 to 800 mg /% were found in 58.8% of patients, in the range from 800 to 1200 mg /% - in 19.6%, more than 1200 mg /% in 14.2% of cases. An increase in D-dimer was observed in 93.5% of patients, while the indicator from 0.5 to 2 mg / ml was noted in 40.5% of cases, from 3-5 mg / ml - in 24.6% of cases, from 6- 10 mg / ml - at 34.9%. High levels of D-dimer in the range from 6 to 10 mg / ml were 3 times more common in men (51.6%) than in women (18.2%).

Patients were treated in accordance with the interim clinical guidelines for the diagnosis and treatment of coronavirus infection COVIL-19 (version 4) of the Ministry of Health of the Kyrgyz Republic No. 649 of 08.25.20. Despite the ongoing therapy, 41% of patients died within the first 7 days of hospital stay, in 44.9% of patients in the period from 8 to 14 days, in 14.1% - from 15 to 22 days. The main causes of death in 77.3% of cases were the development of ARDS and severe respiratory failure, in 17.6% in combination with disseminated intravascular coagulation syndrome, in 2.5% of cases from acute thrombosis and thromboembolism, in 2.5% - sepsis with multiple organ failure.

**Conclusion.** For Kyrgyzstan, the overall case fatality rate (CFR) from COVID-19 was 1.7%. Risk factors for the development of unfavorable outcomes of COVID-19 include advanced age >60 years (70.9%), male gender (64.6%), the presence of concomitant diseases (96.1%) with the prevalence of cardiovascular pathology (68.4 %), especially in combination with diabetes mellitus (27.8%), as well as chronic liver diseases (37.9%). The risk of death increased due to late admission, late hospitalization, and unjustified prehospital therapy. Critically ill patients had severe lymphopenia (84.4%), high levels of C-reactive protein (60.8%), fibrinogen (85%), and D-dimer (53.2%). The main cause of death in patients with COVID-19 was the development of complications - ARDS, sepsis, thromboembolic complications.

Our results are consistent with some published data, but further research is needed to assess the prognosis of adverse outcomes depending on clinical features, laboratory parameters, the presence of comorbidities and complications of COVID-19.

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# PAEDIATRIC INFLAMMATORY MULTISYSTEM SYNDROME TEMPORALLY ASSOCIATED WITH (COVID-19): (LITERATURE REVIEW AND OUR CLINICAL OBSERVATION)

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**Abstract**. The literature review summarizes information on the peculiarities of the course of COVID-19 in children. In most cases, COVID-19 is milder in children than in adults. However, since March 2020, there have been reports from several European countries and the United States of children with a new disease, showing signs of Kawasaki disease (KD) and toxic shock syndrome (TSS). One of the names given to this disease is pediatric inflammatory multisystem syndrome (PIMS) associated with COVID-19. The greatest number of clinical and laboratory-instrumental manifestations and outcomes of PIMS associated with COVID-19 were performed in Italy, France, Switzerland, England, and United States. We present our own clinical observation, analysis of the medical history of a patient with PIMS.

**Key words**: COVID-19, pediatric inflammatory multisystem syndrome, Kawasaki disease, clinical observation.

**Introduction.** Acute respiratory viral infections (ARVI), which include a new coronavirus infection, COVID-19, declared a global pandemic by the World Health Organization (WHO) in 2020, are one of the serious problems of global public health due to their high prevalence among all groups and segments of the population. Because of the COVID-19 pandemic, all of the world's health resources and efforts are focused on the diagnosis and treatment of this infection. [1].

According to the literature, there are currently seven known coronaviruses that cause human disease. Over the past 20 years, there have been three epidemics with a large number of severe cases, a high mortality rate and the carrying of the infection from a primary focus to other countries in the world with the subsequent formation of epidemic foci. In all three epidemics of coronavirus infection (CVI), children, including newborns, were involved in the epidemic process [2].

Pathogenetically COVID-19 is characterized by viremia, local and systemic immunoinflammatory process, hyperactivity of coagulation cascade, endotheliopathy, hypoxia, which leads to the development of micro- and macrothrombosis; proceeds from asymptomatic to clinically pronounced forms with intoxication, fever, vascular endothelial damage, lung, heart, kidney, gastrointestinal tract, central and peripheral nervous system with the risk of complications: acute respiratory distress syndrome (ARDS), acute respiratory failure (ARF), *pulmonary embolism* (PE), sepsis, shock. Children and adolescents may have a variant clinical course in the form of an inflammatory multisystem syndrome associated with COVID-19. [3.4].

Clinical manifestations in children are usually less severe than in adults. In more than 90% of cases, COVID-19 is asymptomatic in children, in a mild or moderate form [5.6]. The frequency of hospitalizations among children is also low. According to a CDC report, this rate in the United States was nearly half as high (5.7% vs. 10% in adults), including fewer intensive care unit (ICU) admissions. [7].

However, since March 2020, there have been reports from several European countries and the United States of children with a new disease, showing signs of KD accompanied by the development of a severe hyperinflammatory response associated with infection SARS - CoV-2 in previously healthy children. Some children showed signs of TSS, myocarditis with cardiogenic shock. One of the names given to these sings is a pediatric inflammatory multisystem syndrome associated with COVID-19. Other names of the syndrome found in foreign literature: Kawasaki-like syndrome; Paediatric inflammatory multisystem syndrome - PIMS TS; inflammatory multisystem syndrome in children -MIS –C. [8. 9.10].

Inflammatory multisystem syndrome (IMS) is a new syndrome that is temporarily associated with exposure to the SARS-CoV-2 virus and can lead to a severe and life-threatening course of the disease.

IMS associated with COVID-19 is a delayed immunologic event associated with the development of inflammation after symptomatic or asymptomatic COVID-19 infection.

**Purpose of study.** Purpose of the work: to conduct a systematic search of scientific publications on children with a new disease - PIMS associated with COVID-19, criteria for diagnosis and treatment.

**Materials and Methods.** A search for publications devoted to PIMS associated with COVID-19 in the PubMed database, Web of Science, Google Scholar, Clinical Trials, and in the CyberLeninka digital scientific library was performed to obtain information.

We analyzed case histories of patients who received inpatient care in the Infectious Disease Center of the Regional Clinical Hospital and Children's Hospital of Karaganda city for the period August to December 2020. The authors' own observations were used in this work.

Five children were admitted to hospitals with a diagnosis of IMS associated with COVID-19. Patients ranged in age of 1 year 3 months to 11 years, the average age was 7 years old. The number of males was 4, females - 1 patient. The average duration of hospitalization was $17 \pm 0.4$ days. The disease was severe in 100% of cases.

The diagnosis of IMS associated with COVID-19 in all patients was made by a consilium of specialists at the national level (national centers, universities) on the basis of detection of Ig class G, despite negative PCR results for COVID-19.

Clinical and laboratory examinations, diagnosis and treatment of patients were performed according to the current clinical protocol of diagnosis and treatment. Coronavirus infection COVID-19 in children, RK No. 117 dated 16.10.2014, approved by the Joint Commission on the Quality of Medical Services of the Ministry of Health of the Republic of Kazakhstan. [4].

**Results and Discussion.** We summarized the current information on PIMS associated with COVID-19 in 120 children from Italy, France, Switzerland, England, and the USA with similar features. [11]. Three cross-sectional groups of patients were identified during clinical observation. The first group (23 children) was characterized by persistent fever, pronounced inflammatory activity resembling the clinical presentation of KD and TSS. 29 children from the second group developed cardiogenic shock due to left ventricular (LV) dysfunction confirmed by EchoCG (62%, 18/29 patients), accompanied by elevated troponin levels (66%, 19/29 patients). The third group consisted of 7 children who clinically met the diagnostic criteria for KD, one of them developed shock. One child died of an ischemic stroke [12].

In the United States, a case series of 17 children hospitalized between April 18 and May 5, 2020, was described on June 8, 2020. Children were admitted with prolonged fever, systemic inflammation, shock, organ dysfunction, symptoms resembling KD (complete form - 8 children, incomplete form - 5) or TSS, reduced LV function, with evidence of recent COVID 19. Levels of inflammatory markers were elevated in all patients. 88% of patients required ICU treatment, 59% required inotropic support, 71% received methylprednisolone,

21% - hydrocortisone, 76% - intravenous immunoglobulins (IGIV), 65% - enoxaparin, and one patient received tocilizumab. One patient developed abdominal aortic coarctation (ACA). [13].

Information about a new disease in children on the background of COVID-19 and the accumulated experience of managing such patients allowed a number of European countries and the United States to publish diagnostic criteria for pediatric inflammatory multisystem syndrome and phenotypically similar diseases that require a differential diagnosis. Experts from the Royal College of Paediatrics and Child Health (UK) published their reports on May 1 [14], CDC (USA) - on May 14 [15], WHO - on May 15, 2020 [16].

The International Classification of Diseases of 10th revision does not have a code for this disease, it is suggested to indicate COVID-19 as the main diagnosis if it is proven (code UO7.1), and concomitant KD (code M30.03) [17]. PIMS associated with COVID-19 is cross-referenced with KD complicated by shock. This condition can be regarded as a systemic microangiopathic clinical "mask" of COVID-19. [18]. It is still unclear whether PIMS arising at 1-6 weeks from the onset of COVID-19 is its post-infectious complication or a manifestation, as reflected in the numerous synonyms of PIMS, but initial clinical observations suggest a correlation. It has previously been shown that other members of the coronavirus family (not only SARS-CoV-2) can be triggers of KD [19, 20]. On May 23, 2020, the first PIMS diagnostic and therapeutic guidelines of Western New York State (USA) incorporating the CDC criteria and providing an algorithm for patient management, were published. According to this algorithm, therapy depends on clinical manifestations and severity. Generalization of the current information on pediatric inflammatory multisystem syndrome (PIMS) associated with COVID-19, its manifestation of the diagnostic and therapeutic algorithm, made it possible to formulate criteria and significantly facilitate diagnosis. [9.21].

We present our own clinical observations of patients diagnosed with IMS associated with COVID-19. It was known from the history data that the patients had no confirmed case of COVID-19. The onset of the disease was acute. The most common clinical manifestations of IMS associated with COVID-19 during the initial period were elevated body temperature to febrile fever (100.0%), dry cough (40.0%), weakness (100.0%), bright red rash without itching (80.0%), conjunctivitis (40.0%), diarrhea, and nausea (40.0%). Four children developed cardiovascular complications in the form of coronary artery disease and myocarditis during the first week.

Due to the severity of their condition, they had changes in their hemogram. Thus, WBC count ranged from 1.7 to 21 $\times$ $10^9$units/l, and it was higher than normal in 60.0%. But no changes in the WBC differential were observed. In 80.0% of cases, the ESR was higher than the reference values and reached 37 mm/h. The platelet count was within the permissible limits of 100.0%, despite signs of hypercoagulability in the coagulogram. For example, 4 (80.0%) patients had increased fibrinogen and averaged 4, 96 g/l. D-dimer levels were elevated in 100.0% of cases and averaged 3039 ng/ml. Much attention was paid to such predictors of inflammation as CRP (C-reactive protein), procalcitonin. CRP levels were 100.0% higher than normal and ranged from 11.5 to 198 mg. In 4 (80.0%) patients, procalcitonin was elevated, with a maximum value of 17, 9 ng/ml. To rule out lung involvement, all children underwent chest CT scans, and a picture of effusion in the pleural cavities of both lungs was detected only in one case. Electrocardiography (ECG) and echocardiography (ECHO-CG) were performed to assess cardiac function, timely diagnosis of myocarditis, cardiomyopathy, cardiac tamponade, pericarditis, coronary artery dilatation or coronary artery aneurysms. ECG showed no specific changes, all children had sinus tachycardia. Diffuse dilatation of the right coronary artery lumen was observed in 3 (60.0%)

patients during ECHO-CG. One child showed signs of coronary artery disease: fusiform dilation of the main trunk of the left coronary artery and the trunk of the anterior descending artery, with inflammatory infiltration of the coronary artery region. All patients were treated according to this protocol. The principal medication included: intravenous immunoglobulins (IGIV), anticoagulants (heparin), antiplatelets (acetylsalicylic acid), glucocorticosteroids (prednisolone, dexamethasone, methylprednisolone), antimicrobials agents (azithromycin, cefuroxime, ceftriaxone), antiviral agents (Viferon).

Clinical observation:

**Boy Zh.** A 9-year-old boy (born on 27.10.2010) was admitted to the clinic on 18.08.2010 with complaints: vomiting, loose stools up to 10 times a day, anxiety, body rash, conjunctival hyperemia, eyelid swelling, palmar erythema, abdominal pain, weakness, fever, poor appetite.

**Anamnesis morbi:** he has been ill since 14.08.2020, when he had a fever (above 38°C), abdominal pain, loose stools. The next day a skin rash appeared, then conjunctival hyperemia, followed by palmar erythema. At home, he took Cef3 500 mg x 2 times for 3 days, Rehydron, Smecta, activated charcoal, Paracetamol, Ibufen - with no effect, and therefore he was taken to the hospital with the diagnosis of acute intestinal infection (AII).

**Epidemiological history:** denies contact with an infectious patient and does not associate the disease with anything.

**Objective data: as of** 18.08.2020. Respiratory rate - 22 per minute, Temperature - 37.5 C. Blood pressure - 90/60 mm Hg. Saturation - 96%. Condition of moderate severity due to symptoms of intoxication and dyspeptic syndrome. Clear consciousness, comes into contact, the state of health is moderately impaired. Regular build, satisfactory nutrition. Pale skin, maculopapular rash on the body, extremities. Palmoplantar erythema. Warm extremities. Capillary imbibition rate - less than 3 sec. Visible mucosa and tongue are wet, clean. The eyes are not hollow, the skin fold is immediately deployed. Sufficient salivation, wet lips. Conjunctival hyperemia and edema of both eyes are noted. No peripheral edema. Lymph nodes: anterior cervical - up to 1 cm in diameter, in other groups - up to 0.5 cm, painless, motile. The musculoskeletal system has no visible deformation, joint movements are not limited. Easy nasal breathing. Pharynx - moderate mucosal hyperemia, the labial mucosa is dry, hyperaemic, no cough. Percussion - vesicular resonance. Auscultatory - vesicular breathing, no dyspnoea. Satisfactory peripheral pulse. Cardiac borders are according to age. Loud heart tones, regular rhythm, tachycardia, short systolic murmur on the top and in the secondary aortic area, no irradiation. The abdomen is soft, stomach gurgling, painless on palpation mostly in the paraumbilical region. No symptoms of peritoneal irritation. Gastric peristalsis is not heard, the anus is occluded. The liver and lien are not enlarged. Urination is free, painless. Loose stool. Negative meningeal symptoms.

**Laboratory and Diagnostic Examinations:**

18.08.2020. **ESR** -10 mm/hour; Complete Blood Count (6 parameters) on analyzer - relative (%) monocytes-4.0%; eosinophils-4.0%; lymphocytes-16.0%; neutrophils-76%; hematocrit-33.9%; WBC-8,4%; platelets-183.0/l; RBC-4.20/l; haemoglobin-120.00000 g/l. **Coagulogram** dated 18.08.2020. D-dimer -2202.20 ng/ml; Quick's value-101%; fibrinogen 4.9 g/l; APTT-47.9 seconds, TT (thrombin time) 11 seconds; INR -1.08; PT -12.1. **Biochemical blood test** dated 19.08.2020**.** Total protein-67g/l; albumin-33g/l; urea-18.7 mmol/l; creatinine-243mmol/l; glucose-5.1 mmol/l; CRP- 407.9 mg/l; rheumatoid factor+; troponin 1.49 mg/ml; BNP – (natriuretic peptide) less than _ 0.05 ng/ml; ferritin368,4 ng/ml; procalcitonin -17.9 ng/ml; interleukin- 842.5 ng/ml

**COVID-19 test:** Nasopharyngeal smear PCR – SARS-CoV-2 RNA not identified **(**serologic examination) ELISA - SARS-CoV-2 IgM - 0.65, ELISA - SARS-CoV-2 IgG - 8.7, indicates a past infection.

**Plain chest** X-ray (I view) dated 20.08.2020. Impression: No X-ray abnormality identified in the lungs.

**ECG** dated 18.08,20.08,21.08.2020: sinus tachycardia. Metabolic disorder in the myocardium. Incomplete right bundle branch block. QT interval prolongation. ECHO-CG dated 21.08.2020: Bicuspid aortic valve, partially undivided commissure between the right and left coronary cusps, mild aortic regurgitation, dilatation of the ascending aorta. Typical for Kawasaki disease - diffuse dilation of right coronary artery lumen, mild hydropericardium. Hypokinesia of the basal inferior segment of the left ventricular myocardium, no abnormalities of contractility were confirmed in the regional deformation study mode. Dilation of the left ventricular cavity, mild mitral regurgitation.

**Cardiologist Consultation:** dated 20.08.2020. Impression: Inflammatory Multisystem Syndrome (Kawasaki-like Syndrome) Associated with COVID-19.

**Nephrologist Consultation**: dated 20.08.2020. Renal ultrasound - enlarged, GFR (glomerular filtration rate) according to Schwarts formula - 24.7 ml/min. Impression: Acute renal damage (prerenal), neoliguric form, as part of an inflammatory multisystem syndrome (Kawasaki-like syndrome) associated with COVID-19.

Taking into account fever for 5 days on admission, conjunctivitis, scleritis, without pathological discharge, recurrent maculopapular skin rash, Palmoplantar erythema, bright hyperemia and dryness of labial mucosa, abdominal pain, diarrhea, laboratory activity in the form of a significant increase in CRP, obtained positive diagnostic IgG values, indicating a past infection, the following diagnosis was made: **Inflammatory Multisystem Syndrome (Kawasaki-like Syndrome) Associated with COVID-19.**

Treatment: i.v. Kiovig 2 g/kg-80 g in 24 hours, i.v. methylprednisolone 750 mg + 0.9% NaCl solution 200 ml from 20.08.2020 - 3 days, followed by the prescription of methylprednisolone orally at a dose of 1 mg/kg (according to prednisolone), i.v. Cef 3 - 2g x 2 times daily, orally: acetylsalicylic acid 500 mg x 3 times, s.c. heparin 200 units/kg per day in 4 injections -20.08.2020 and 300 units/kg per day in 4 injections from 21.08.2020, i.v. Quamatel 20 mg once daily from 19.08.2020. Against the background of Kiovig administration, some positive dynamics were noted: abdominal pain stopped, conjunctival hyperemia decreased. The skin rash persisted, pain in the neck in the area of the posterior cervical lymph nodes was noted; upon change of the body position, he had a feeling of rapid heartbeat and some difficulty in breathing. On 20.08.2020, pulse therapy with methylprednisolone on the basis of 18.7 mg/kg was started. After administration of methylprednisolone, body temperature was normal, well-being improved, skin rash became pale. The patient needs an expert panel consultation to determine the indication for prescription of anti-TNF: infliximab, taking into account the coronary artery lesions, according to the international recommendations for the treatment of IMS.

**Transfer Summary:** 23.08.2020. Temperature: 37. Pulse: 86. Blood pressure: 95/65. Saturation: 97.

The condition is closer to severe, the severity of the condition is associated with symptoms of intoxication, skin syndrome, and renal failure. The patient is conscious, reacted adequately to examination, did not feel worse, sub-febrile temperature (below 38.0 °C). Enteral nutrition is ingested, no dyspeptic phenomena. The skin is pale pink, the skin fold is deployed. Scattered elements of a pale pink papular rash are in the area of the ankle joint. Wet mucosa. Free breathing, no rale. Moderate heart sounds. Systolic murmur in the secondary aortic area of the same intensity. Peripheral pulse is of satisfactory tension. The abdomen is soft, painless, non-tense. The liver is of the same size. Free urination.

As for further treatment, the patient was moved to the National Research Center for Maternal and Child Health of the Republic of Kazakhstan (Nur-Sultan city) for biological

therapy in connection with the preserved inflammatory activity in the blood and changes in echocardiography.

**Conclusions:**

1.Inflammatory multisystem syndrome temporarily associated with (COVID-19) may develop 1-6 weeks after COVID-19.

2.Difficulties in diagnosing IMS are connected with the fact that COVID-19 in children often has a mild and asymptomatic form, based on the diagnostic criteria of the disease, it is very important to diagnose it in time, to distinguish it from KD due to its more severe course.

4.Patients who had IMS need follow-up due to the risk of developing dilatation or ACA, as indicated by clinical observations.

5.Diagnostic criteria of the disease, therapeutic approaches to the treatment of children with IMS carried out in the Republic of Kazakhstan meet all international standards.

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# ANALYSIS OF CLINICAL LABORATORY DATA OF PATIENTS FROM THE POINT OF VIEW OF COVID-19 IMMUNOGENESIS

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**Abstract**. The article presents data on the immunogenesis of COVID-19 infection. The immunological mechanisms of the development of a cytokine storm and indicators that are most involved in this process are described. In addition, the article analyzes the clinical and laboratory data of 22 patients with a severe form of COVID-19 infection in the intensive care units of the city of Kirov. The results of the analysis of clinical and laboratory data obtained in this scientific work confirmed the available theoretical data on the scale of developing processes in the body of patients with a severe form of COVID-19 infection.

**Key words**. COVID-19, cytokine storm, clinical and laboratory data, multiple organ failure.

**Introduction**. Coronaviruses are a family of RNA viruses containing 43 species, one of which is SARS-CoV-2 [4]. The interaction of this virus with a cell is determined by an external S-protein in its structure. It consists of two domains, and its S-1 subunit also contains two domains - an amino-terminal domain and a receptor-binding domain (RBD). It is the latter that has the ability to bind to angiotensin-converting enzyme-2 (ACE-2) [2]. In addition, the SARS-CoV-2S-protein contains a furin-like cleavage site that is activated by the cellular serine protease TMPRSS2.

ACE2 is found in type 2 alveocytes, endotheliocytes, and enterocytes of the small intestine. The main route of transmission of SARS-CoV-2 is airborne, therefore, in the vast majority of cases, the first cells that come in contact with the virus arealveocytes.However, the virus also enters the central nervous system [1, 3].

After entering the cell, the viral genome replication occurs, which eventually causes pyroptosis of the affected cells. This releases pathogen-associated molecularpatterns and damage-associated molecularpatternsinto the environment, such as viral RNA, ATP, cellular DNA, and ASC protein oligomers. They are recognized by the surrounding alveolar macrophages, which then produce IL-6, TNFα, IL-1β, IL-8, IL2R. These chemokines, in turn, cause increased migration of monocytes and T-lymphocytes to the inflammation focus, with a decrease in their level in the peripheral blood.

In patients with a mild form of infection recruited cells cleanse the body of the virus and the patient recovers. At the same time, in those with the severe form an abnormally high concentration of IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), IP-10, MCP1, macrophage inflammatory protein 1α (MIP1α) and tumor necrosis factor (TNF) is observed. Also, there is an increase in capillary permeability with the formation of edema.

Indirect laboratory signs of the cytokine storm are: an increase in the level of serum ferritin more than 600 ng / ml, a decrease in platelets less than $180 \cdot 10^9$ / l and leukocytes less than $3.0 \cdot 10^9$ / l.

Ultimately, these manifestations lead to the transition of infection from local to systemic and the appearance of new symptoms: multiple organ failure, progressing respiratory failure and the development of DIC [5].

This is scientific research data. What are the results of assessing the developing processes in the human body against the background of COVID-19 during their hospitalization? What is the real clinical and laboratory data in patients with severe COVID-19?

**Materials and research methods.** The studies were conducted in 22 patients (11 men and 11 women) with identified COVID-19 infection. The median age was 67 years (43-93). All patients had a severe form of infection and were treated in intensive care units in Kirov. The identification of the virus was carried out using test systems for the determination of the SARS coronavirus 2 RNA protein from Litekh, by the method of polymerase chain reaction on Bio-Rad CFX96 amplifiers. The analysis of laboratory data was carried out retrospectively according to the results presented in the patient records. Statistical processing of the research data was carried out using the Microsoft Office Excel 2016 spreadsheet editor, in particular, its Data Analysis modules and the Statistica 13.0 for Windows software package for statistical data processing. Quantitative indicators were assessed for compliance with the normal distribution, for this, the Shapiro-Wilk test was used, as well as indicators of asymmetry and kurtosis. Aggregates of quantitative indicators, the distribution of which differed from normal, were described using the values of the median (Me) and the lower and upper quartiles (Q1-Q3). To assess the reliability of differences in quantitative characteristics in the compared groups, the method of nonparametric statistics (Mann-Whitney test) was used. In all cases, the difference between the individual indicators was taken as significant at $p < 0.05$.

**Research results.** According to the results of the analysis of patient histories, it was revealed that each patient was prescribed, on average, a general blood test, urine test, inflammation markers, a coagulogram, markers of cytolysis, as well as markers of azotemia. In order to monitor the condition of patients, as well as to prevent the development of a late stage infection, namely the addition of respiratory distress syndrome and the development of multiple organ failure, C-reactive protein, fibrinogen, and ferritin tests were prescribed over time. According to the results of the assessment of these indicators, an increase in the level of C-reactive protein (CRP) was detected in 95%, fibrinogen in 72%, ferritin in 86% of patients, and the marker of bacterial infection was increased in 13% of patients. The reliability of the increase in indicators relative to the norm was $p <0.037$.

Analysis of interleukin levels, which is done in order to determine the onset of the cytokine storm in patients with a severe form, is not possible in every laboratory. This limitation is caused both by the limitation of the range of test systems intended for their determination, and because of their cost. In this regard, the study of the level of ferritin in patients, which was carried out on the 4-5th day of their stay in the hospital, was an alternative option for analyzing the development of a cytokine storm. The production of pro-inflammatory cytokines by macrophages stimulates the liver to produce protective proteins. Thus, an increase in the level of ferritin in the blood serum indirectly indicates an increase in the level of cytokines. Analysis of the level of ferritin rise, assessed as a marker of the acute phase of inflammation, significantly correlated with other proteins of the acute phase ($p <0.026$).

Also, changes were observed in the general blood test, namely: a decrease in hemoglobin to the level of mild anemia - in 41% of patients. A statistically significant dependency ($p <0.047$) between the diagnosed anemia and the development of respiratory acidosis was revealed according to the results of the analysis of the acid-base state. Thrombocytopenia was detected in 43% of patients, leukocytopenia in 68% of patients. These indicators also correlated with an increase in ferritin according to the principle of negative feedbackloop. In patients with thrombocytopenia and leukocytopenia, ferritin values were increasing over time. Lymphocytopenia was detected in 82% of patients, and a decrease in monocytes in 63%, which can be explained by the presence of an inflammatory process in the body, where monocytes and lymphocytes actively migrate to, as a result of which their number in the peripheral blood decreases.

The results of the analysis of the coagulogram are of interest. Changes in the level of prothrombin, activated prothrombin time (APTT), platelet count and D-dimer were observed

in 100% of the examined patients. With the progression of the infection, the inflammatory process in the vessels is activated. D-dimer is a marker of thrombosis. When blood clots appear, the mechanism of their destruction is triggered, and large quantities of D-dimer are formed. This was confirmed in our study as well. An increase in the D-dimer was observed in half of the subjects. Also, there was a statistically significant relationship between thrombocytopenia and an increase in D-dimer ($p < 0.037$).

The state of azotemia, caused by an increase in creatinine and urea, was noted in 32% of the subjects. Dysfunction of the kidneys, accompanied by azotemia, on the one hand, may be associated with thrombosis in the smallest blood vessels of the kidneys, which occurs on the background of an inflammatory process. On the other hand, azotemia may indicate decompensation of chronic diseases. In fact, 50% of patients with a severe form of COVID-19 infection are patients with a large number of concomitant diseases, including diabetes mellitus, pathology of the cardiovascular system, etc. An increase in the enzymes ALT and AST was noted in 29% of the subjects, but no statistically significant relationships with other indicators could be identified.

The fact of liver dysfunction can also be explained by the development of multiple organ failure, which develops on the background of COVID-19 infection.

Thus, according to the results of the analysis of clinical and laboratory data, confirmation of the available theoretical data on the scale of developing processes in the body of patients with a severe form of COVID-19 infection was revealed.

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# RUSSIAN AND FOREIGN VACCINES AGAIST COVID-19

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**Abstract:** This article provides an overview of the Russian and foreign vaccines available on the market, which are designed to solve the problem of further spread of COVID-19. The main results of clinical trials are considered. Data on the effectiveness and safety of vaccines are presented. The side effects of some vaccines against the background of their use, which prevent the introduction of these vaccines in the system of mass vaccination of COVID-19, are analyzed.

**Key words:** Russian and foreign vaccines; Sputnik V; EpiVacCorona; KoviVac, AZD1222; CoronaVac; CNBG.

**Introduction**. 2020 has become one of the most difficult for humanity. It was this year that everyone learned about the new coronavirus infection. This disease, caused by the SARS-CoV-2 coronavirus, was discovered in late 2019 in the city of Wuhan in China. It was not immediately possible to identify the mysterious infection, as a result of which pneumonia of unknown etymology rapidly spread around the world, claiming hundreds of thousands of lives. Every country has made enormous efforts to prevent the spread of the coronavirus, but the number of infected and dead increased every day. Restrictive measures alone were not enough to reduce the rate of infection, so decisions were made at the state level in each country to develop a vaccine.

The world's first coronavirus vaccine, Sputnik V (Gam-Covid-Vac), was registered by Russia on August 11, 2020. The development of this vaccine was carried out by the Gamalea Center. The vaccine against the coronavirus (COVID-19) Sputnik V was created in a short time due to the fact that Russian virologists already had a ready basis for this – namely, the platform that was used to create a vaccine against Ebola hemorrhagic fever.

Ebola has been well studied since the 1950s, and the platform has long been proven safe, as it has already been used to vaccinate more than 10 million people. The Gamalei Center created an effective drug against Ebola in early 2014. In 2018, the same Center also developed a candidate vaccine against Middle East respiratory syndrome (MERS). It was these two "blanks", two stages passed in advance, that helped scientists quickly switch to work on the future Satellite V.

As with all vaccines in development, the Sputnik V vaccine research was conducted in two stages:

At the preclinical stage, the drug was tested on mice, monkeys, and hamsters. The purpose of this test was to determine the safety and effectiveness of the new drug (the formation of an immune response and its long-term duration). The vaccine has successfully passed this stage of the trial.

At the clinical stage, the drug was tested in humans. The research was divided into three phases. First, the tolerability and immunogenicity (the property of the antigen to cause an immune response) were evaluated, then the selection of doses and the mode of administration was carried out. Finally, at the third stage, the effectiveness of the drug in the selected dosage was evaluated. Safety was checked at all stages [1].

76 people took part in the first two phases. In all of them, the drug formed a " stable and humoral, and cellular immune response." Side effects "were mostly mild," with the most frequent being pain at the injection site, fever up to 37-38°C, headache, asthenia, and muscle

and joint pain. The study was open-ended and non-randomized, meaning no placebo was used, and all participants received the vaccine. According to the results of this stage, it was concluded that the drug is well tolerated and causes an immune response. No one was infected with the coronavirus after vaccination. The third phase was carried out after the registration of the vaccine. According to the results of tests on 19,866 volunteers, of which 14,964 received the vaccine and 4,902 received a placebo, the effectiveness of Sputnik V was 91.6 %. No life-threatening side effects were detected by the test organizers. They recorded several deaths, but considered that their causes were not related to vaccination. The vaccine was also effective in a sample of elderly (60-87 years old) volunteers [2].

As of November 24, 2020, researchers had recorded 175 cases of COVID-19 (79 in the vaccine group and 96 in the placebo group) after the first injection. Of the 175 volunteers, 66 of them became ill in the first two weeks after vaccination - that is, before immunological memory had had time to form. Another 31 volunteers became ill in the last week before the second injection. Based on this data, the researchers calculated that the effectiveness of the first dose itself was 73-86%.

After the second injection, the researchers recorded an additional 78 cases of COVID-19: 16 volunteers (0.1%) fell ill from the group that received the vaccine and 62 (1.3%) from the placebo group, corresponding to an average efficacy of 91.6% ($p < 0.0001$). The efficacy was higher than 90% in all age groups, including the elderly. In women it was slightly lower and averaged 87.5% versus 94.2% in men [3].

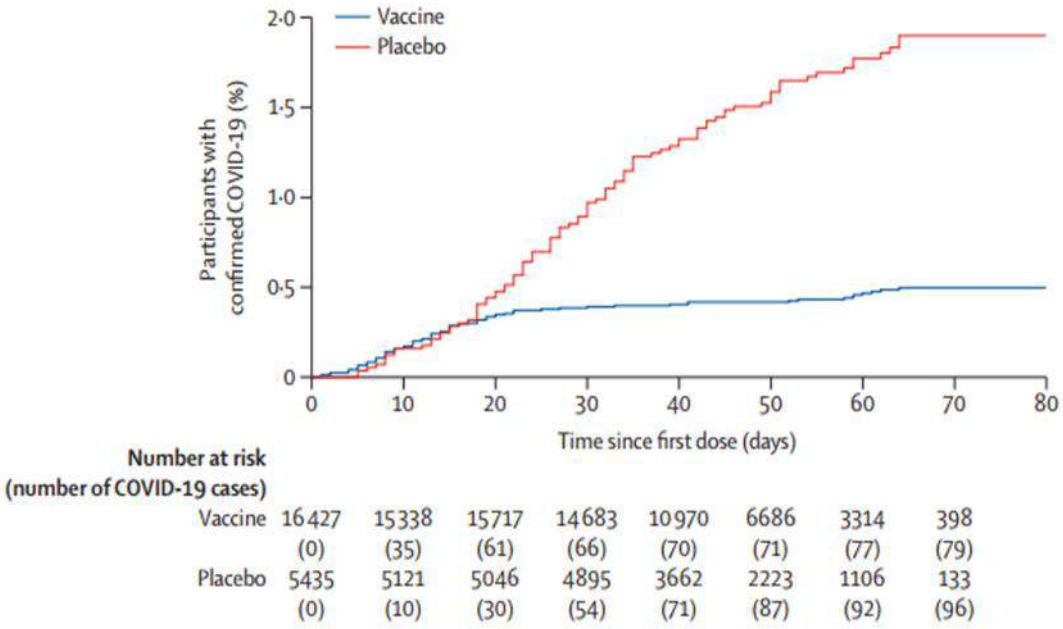


Figure 1. Incidence of COVID-19 in the placebo group (red) and the vaccine group (blue) [*Logunov et al. / The Lancet, 2021*]

The effectiveness against moderate and severe forms of COVID was higher - it was estimated at 100%, as the researchers did not find any such cases in the vaccine group, while there were 20 in the placebo group. Thus, all patients in the vaccine group had a mild illness with COVID-19 - that is, with a temperature below 38.5 oC, normal blood oxygen saturation, and no dyspnea or signs of pneumonia [3].

At this point, some populations have been left untested, such as pregnant and nursing women, people with some severe comorbidities, and children and adolescents. This is the next step in studying the effectiveness of Sputnik V.

Sputnik V is a great achievement of Russian scientists. Its use in the fight against COVID-19 has already been approved in 50 countries.

| | Total cases | Vaccine group | Placebo group | Vaccine efficacy (95% CI) | p value |
|---|---|---|---|---|---|
| **First COVID-19 occurrence from 21 days after dose 1 (day of dose 2)*** | | | | | |
| Overall | 78 | 16/14 964 (0·1%) | 62/4902 (1·3%) | 91·6% (85·6–95·2) | <0·0001 |
| Age group (years) | | | | | |
| 18–30 | 5 | 1/1596 (0·1%) | 4/521 (0·8%) | 91·9% (51·2–99·3) | 0·0146 |
| 31–40 | 17 | 4/3848 (0·1%) | 13/1259 (1·0%) | 90·0% (71·1–96·5) | <0·0001 |
| 41–50 | 19 | 4/4399 (0·1%) | 15/1443 (1·0%) | 91·3% (73·7–96·9) | <0·0001 |
| 51–60 | 27 | 5/3510 (0·1%) | 22/1146 (1·9%) | 92·7% (81·1–97·0) | <0·0001 |
| >60 | 10 | 2/1611 (0·1%) | 8/533 (1·5%) | 91·8% (67·1–98·3) | 0·0004 |
| Sex | | | | | |
| Female | 32 | 9/5821 (0·2%) | 23/1887 (1·2%) | 87·5% (73·4–94·2) | <0·0001 |
| Male | 46 | 7/9143 (0·1%) | 39/3015 (1·3%) | 94·2% (87·2–97·4) | <0·0001 |
| Moderate or severe cases | 20 | 0/14 964 | 20/4902 (0·4%) | 100% (94·4–100·0) | <0·0001 |
| **First COVID-19 occurrence after dose 1†** | | | | | |
| Any time after dose 1 | 175 | 79/16 427 (0·5%) | 96/5435 (1·8%) | 73·1% (63·7–80·1) | <0·0001 |
| From 14 days after dose 1 | 109 | 30/14 999 (0·2%) | 79/4950 (1·6%) | 87·6% (81·1–91·8) | <0·0001 |
| **First COVID-19 occurrence after dose 2 (28 days after dose 1)*** | | | | | |
| All | 60 | 13/14 094 (0·1%) | 47/4601 (1·0%) | 91·1% (83·8–95·1) | <0·0001 |

Data are n/N (%), unless otherwise stated. *Includes those who received both doses. †Includes participants who received at least one dose.

Figure 2. Number of COVID-19 cases in different groups and final vaccine efficacy [*Logunov et al. / The Lancet, 2021*]

EpiVacCorona is the second Russian coronavirus vaccine registered on September 30, 2020. Unlike Sputnik V, the drug developed by the Vector Center is peptide-based (based on artificial peptides replicating coronavirus fragments) and it is made from the three constituent parts of the coronavirus genome that are most resistant to mutation. Like GAM-Covid-Vac, it does not cause serious side effects and is even less reactive than Sputnik V. The drug also has a twice-daily administration regimen with an interval of at least 14-21 days. Vaccine recipients develop antibodies in 94% of cases. The expected protection against coronavirus is at least one year, in contrast to Sputnik V (2-year protection) [4].

A distinctive feature of the vaccine is that it can be used in adults 18-60 years old. Efficacy and safety in this age group have been confirmed by clinical trials.

The vaccine also has a certain list of contraindications, which are no different from those recommended for other types of vaccines.

Vaccination can be done not earlier than one month after recovery or remission. In non-serious acute respiratory infections, acute infectious diseases of the gastrointestinal tract the vaccination is given after the temperature has returned to normal [5].

Another variant of the vaccine developed in Russia is CoviVac. The vaccine was created at the Chumakov Federal Scientific Center for Research and Development of Immunobiological Preparations of the Russian Academy of Sciences. It was registered by the Russian Ministry of Health on February 20, 2021, and the WHO pre-registration procedure is planned, as well as registration in foreign countries. The vaccine is whole-virion inactivated -

based on "killed" whole coronavirus. This is a classic type of vaccine, widely produced and used since the last century. It is administered twice intramuscularly with an interval of two weeks. The immunological efficacy is 85% (antibody formation occurs within the defined immune response time, but the developers do not exclude that the immune response can form somewhat later). The timing of the immune response is not yet known and will be clarified after the end of clinical trials. No serious adverse events after vaccination were detected in the volunteers, 15% of the participants had mild local reactions. General reactions were accompanied by headache and mild fever in a few trial participants. The age limit for vaccine use was 18-60 years.

A special feature of this vaccine is that it can be used in people with immunosuppressive and immunodeficiency conditions.

It is contraindicated in pregnant, lactating women and children, since no studies have been done on these groups. Also not used in people who have had severe postvaccination complications from any previous vaccinations, or in people with severe allergies. Temporarily contraindicated: in acute febrile states, acute infectious and exacerbation of chronic diseases. Vaccination is done 2-4 weeks after recovery [5].

Among foreign vaccines is AZD1222, a drug developed by the Anglo-Swedish pharmaceutical company AstraZeneca. The AstraZeneca vaccine, like Sputnik V, is a vector vaccine - although it is not based on human adenovirus, but chimpanzee. vector. It is based on a weakened version of the adenovirus that causes infections in chimpanzees and contains the genetic material of the SARS-CoV-2 virus. After vaccination, a protein is formed that causes the immune system to attack the SARS-CoV-2 virus if it later infects the body. The vaccine is administered twice at 4-12 week intervals. The effectiveness is about 70%. The developers also suggested a method of administering this vaccine with an interval of a month - first half a dose, and after a month - a full dose. This way of administering the vaccine, according to scientific research can provide 90% efficiency. On September 6, 2020, scientists announced a pause in all trials, which was needed to study data on the safety of the vaccine. AstraZeneca said it could not disclose additional medical information. However, according to the Paul Ehrlich Institute, seven cases of a special, very rare form of cerebral vein thrombosis, three of which resulted in the death of patients, were reported in Germany after vaccination with the AstraZeneca vaccine for 1.6 million vaccinees.

Despite concerns about adverse effects on vaccine administration, trials have now been resumed and are being conducted in the United Kingdom [6].

Another foreign vaccine by CanSino Biological Inc. The vaccine of the Chinese company is based on their own vector vaccine technology platform. Also adenovirus-based, like AZD1222, is the Russian vaccine from the Gamaleya Research Institute. According to the company's website, it was previously used to develop a vaccine against the Ebola virus. According to one of the most respected medical journals, The Lancet, the results of the second phase of clinical trials showed that it is safe and causes an immune response without side effects. China's State Intellectual Property Office has already approved the first patent for this candidate vaccine [7].

Inactivated vaccine CoronaVac (Sinovac) was developed by Chinese company Sinovac Biotech. The disadvantage of this vaccine is that it must be stored at a certain temperature - in a refrigerator at 2-8°C. Two doses are required for immunization. Data on the effectiveness of Sinovac vaccine varies. Recent trials in Brazil have shown 50.4% efficacy, while Indonesia and Turkey have shown 65.3% and 91.5%, respectively. The vaccine has been approved for emergency use in high-risk groups in China since July 2020. The use of this vaccine was approved by Turkish authorities on January 13, 2020. Several Asian countries-Singapore, Malaysia, and the Philippines-as well as Brazil and Ukraine have signed CoronaVac purchase agreements.

Another Chinese inactivated vaccine, CNBG (Sinopharm), was developed by China National Biotec Group (CNBG) (a division of Sinopharm). This vaccine does not require a negative storage temperature and is administered in two doses two weeks apart. On December 30, Sinopharm announced that the drug showed 79% efficacy in Phase III trials. However, the United Arab Emirates (UAE), which approved Sinopharm's vaccine, said the vaccine was 86% effective. In addition to China and the UAE, Sinopharm vaccine is undergoing clinical trials in Bahrain, Jordan, Peru, and Argentina. In China, Sinopharm has been used as part of an emergency vaccination program since July 2020, and on December 31, 2021, the State Administration of Medicines of China approved the drug for widespread use [6].

The German company BioNtech developed the vaccine Pfizer-BioNTech together with the American company Pfizer. In the third phase of clinical trials, the drug showed 95% efficacy. The vaccine has a mandatory condition for use: it must be stored at a temperature not higher than minus 70 $^{o}$C, and after defrosting it is suitable for five days. The developed vaccine is administered in two doses three weeks apart. The UK was the first country to approve the use of Pfizer-BioNTech, followed by Canada, the US and countries in Europe and the Middle East. Mass vaccination with the drug will begin in the US and Canada on December 14, 2020, and in European countries on December 27, 2020. Serious side effects of the vaccine included anaphylactic shock. There have been reports of side effects after vaccination with the drug in several countries. In particular, on January 22, 135 cases of side effects from the Pfizer-BioNTech vaccine were reported in Finland, of which 31 were serious, including cases of rhythm disturbances [6].

The Janssen vaccine was developed by the American Johnson & Johnson Corporation. On March 11, 2020, it was approved by the European Union. Earlier, the U.S. Food and Drug Administration (FDA) approved the emergency use of the drug. The drug is also on the emergency list of the WHO. During clinical trials with 44,000 participants from the U.S., South Africa and Latin America, the drug showed efficacy of 67%. Janssen vaccine is stored at minus 20°C. The big advantage is that the vaccine can be stored at the temperature from 2 to 8°C for three months, and, what is the most important, the vaccine ensures the effective immunity after a single injection. Among the possible severe reactions to administration of the vaccine declared by the manufacturer are also severe allergic reactions, which can occur within minutes to one hour after the dose is administered. Signs of a severe allergic reaction may include difficulty breathing; swelling of the face and throat; palpitations; severe rashes all over the body; and dizziness and weakness [6].

Thus, all countries of the world have joined forces to fight the pandemic caused by COVID-19. There may be political differences between countries, but the fight against a global problem of humanity, aimed at developing means of prevention, blurs the boundaries of misunderstanding. Joint efforts of all countries to develop vaccines against SARS-CoV-2 have helped stabilize the situation worldwide. Currently 17,155,585 people have been vaccinated in Russia and 223,329,095 worldwide. As of April 2021, the number of those infected had dropped significantly. Residents who have had the coronavirus vaccine carry the infection in a mild form.

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# PULMONARY EMBOLISM IN PATIENTS WITH ANAMNESIS OF COVID-19 - A COMPLICATION IN A LATE PERIOD

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**Abstract.** Introduction: we studied the features of the course and outcomes in patients with pulmonary embolism diagnosed in the long-term period with COVID-19. Methods and Results: 147 patients with or without a history of COVID-19 were studied. Mortality in patients with a history of COVID-19 was 29.2%. In a subgroup without a history of infection, the mortality rate was 11.6%. Subgroup analysis was carried out, typical signs of pulmonary embolism at patients with history COVID-19 were identified. Conclusions: Patients with pulmonary embolism and previous COVID-19 have a worse prognosis. Characteristics and outcomes are likely to be determined by prior COVID-19 infection.

**Key words:** pulmonary embolism, thrombosis, COVID-19, emergency care.

**Introduction.** Since March 11, 2020 of the novel coronavirus (SARS-CoV-2) pandemic, more than 123 million people have been infected worldwide to date. Studies have shown an increased thromboembolic risk for patients with novel coronavirus infection 2019 (COVID-19). Inflammation associated with an increased level of cytokines, platelet activation, endothelial dysfunction is accompanied by coagulopathy and a general prothrombotic state [1]. An increase in the level of D-dimer, prothrombin time, changes in the level of platelets can be used to determine the risk as highly sensitive, but nonspecific criteria [2]. COVID-19 has been associated with thrombotic rather than hemorrhagic events. Up to 40% of patients may have thrombotic complications, 79% of them are venous thrombotic complications. Hemorrhagic events are not more than 21% [3]. The incidence of venous complications varies from 10 to 60% in different works. This is associated with a different mortality rate, according to some data, exceeding 30% [4]. The likelihood of their development is largely determined by the severity of the course of the infection. The detection rate also depends on the screening activity and the diagnostic methods used. The incidence of identified complications is higher according to autopsy data, it is reaching 60% [5]. Pulmonary embolism (PE) is one of the most significant thromboembolic complications. The morbidity rate may vary, on average it is about 20% in moderately severe patients [2, 4]. For comparison, in previous years, the incidence of PE in patients with severe influenza was no more than 7.5% [4]. In many cases, it is difficult to determine the mechanism of thrombotic lesion of the lungs. In COVID-19, complications can be manifestations of a primary thrombotic process at the level of small vessels of the lungs, not associated with deep venous thrombosis [6]. The prognostic role of PE is unclear. Patients are treated in intensive care units, have a longer treatment period, more often mechanical ventilation therapy. It is not clear the role PE at worsening prognosis. One of the multicenter cohort studies involving 1240 COVID-19 patients showed that PE is not associated with increased mortality [7]. What is the effectiveness of thromboprophylaxis? There is no evidence on the anticoagulants effectiveness. The risk of PE in COVID-19 does not consider into traditional thromboembolic risk factors. An increased thromboembolic risk is associated with the male sex, the time from the onset of infection to hospitalization, the level of C-reactive protein, the use of prophylactic and therapeutic doses of anticoagulants before and during hospitalization [7]. Clinical and laboratory signs associated with inflammation are perhaps more important for risk assessment. The duration of COVID-19 disease is difficult to predict. The timing of the

development of thrombotic complications, the duration of thromboprophylaxis not sufficiently studied. Complications may develop after elimination or "outside" the diagnosis of the SARS-CoV-2 virus. The diagnosis, treatment and determination of the prognosis in the late period of COVID-19 may influence outcomes at the patients.

**Methods.** The retrospective observational study included patients admitted to the cardiology department of the Center for Cardiology and Neurology with a diagnosis Pulmonary embolism from March 2020 to February 2021. The diagnosis was established in accordance with the European guidelines for the diagnosis and management of pulmonary embolism [8]. The mandatory inclusion criterion was the confirmation of the diagnosis by computer tomography angiography. To confirm / exclude COVID-19 infection, PCR diagnostics and determination of antibodies to SARS-CoV-2 were performed. Patients with suspected acute infection and positive PCR result with nasal and pharyngeal swabs were excluded from the study. At included in the study patients the demographic characteristics were determined, hospital mortality was analyzed. In 30 of the total number of patients (15 from the group of patients with a history of COVID-19 and 15 without a history), a comparative analysis of the clinical, laboratory and instrumental parameters was carried out. The typical characteristics of patients with pulmonary embolism and previous COVID-19 infection were determined. Statistical analysis was carried out using the Statistica software package. Parametric and nonparametric methods of statistics were used, Student's, Mann-Whitney's tests. X-square (x2) and Fisher's exact test for qualitative features. Differences were considered significant at $p < 0.05$.

**Results.** 147 patients with PE were hospitalized. According to the hospital's reported data - 88 patients were hospitalized for the same period of the previous years. Thus, during the pandemic, the number of PE cases increased at the hospital by 67%.

All 147 patients are Caucasian, 70 men (47.6%), mean age 63.6 ± 15.2 g. Of 147 patients, 28 were excluded from the analysis: 26 showed signs of an acute form of COVID-19, patients were transferred to infectious diseases departments, in 2 the diagnosis was not confirmed by the results of CT angiography. In some patients, the history of COVID-19 was confirmed immunologically - by the presence of immunoglobulins G to SARS-CoV-2.

Depending on the presence of COVID-19 2 subgroups were identified: 24 patients with PE and a history of COVID-19 and 95 patients without symptoms and the history COVID-19. In the group with a history of infection, 13 (54.2%) - men, mean age 63.5 ± 12.7 g. In the group with no history of infection, 46 (48.4%) - men, mean age 63.0 ± 16.2 d. 7 (29.2%) patients died in the group of patients with PE and COVID-19. 11 (11.6%) patients died in the group of patients without prior COVID-19. $p = 0.031$ ($x2 = 4.66$). Thus, prevalence of mortality in patients with prior COVID-19 was more than a two fold higher.

Typical signs of PE in subgroups were assessed - 15 patients were randomly selected at each subgroup. The average time period from COVID-19 manifestation to symptoms and confirmation of PE was 30.3 ± 12.1 days (Table 1).

A comparative analysis of the subgroups main characteristics was done. Patients did not differ in the prognostic indexes PESI, sPESI. All patients characterized by a similar frequency of PE of intermediate-high and high risk, a similar profile of concomitant pathology (Table 2). In patients with a history of COVID-19 thrombotic lungs damage was significantly less associated with deep vein thrombosis. At patients with previous infection, a lower level of troponin was recorded, right ventricular dysfunction by transthoracic echocardiogram and classic ECG signs of PE was less common. There were no significant differences in PE therapy in the subgroups.

**Discussion.** The results demonstrates the presence of features in the symptoms of patients with PE and a history of COVID-19. Patients with a history of infection are less likely to have the classic signs of PE (Figure 1). Patients with COVID-19 have a worse

prognosis – hospital mortality is higher. The classic signs of PE severity do not adequately predict the outcomes in these patients. Probably, the severity of previous COVID-19 infection affect the prognosis in the late period. In our study 8 of 15 patients had a previous lung damage > 50%.

Table 1. Characteristics of patients with history of COVID-19.

| **Variables** | **Value** |
|---|---|
| COVID19 – PE period M±σ, days | 30,3±12,1 |
| Lungs damage >50%, n (%) | 6 (40) |
| Anticoagulants prior to PE, n (%):<br>Prophylactic regimen;<br>Therapeutic regimen;<br>Without anticoagulants;<br>No data | <br>6 (40)<br>1 (6,7)<br>6 (40)<br>2 (13,3) |
| Corticosteroids prior to PE, n (%):<br>All;<br>High doses | <br>8 (53,3)<br>4 (26,6) |
| Antibiotics prior to PE, n (%):<br>Multiple combinations;<br>No data | <br>7 (46,6)<br>4 (26,6) |

Table 2. Characteristics of the patients with or without history of COVID-19.

| Variables | PE with prior COVID-19, n=15 | PE without prior COVID-19, n=15 | P-value |
|---|---|---|---|
| PESI, M±σ | 102,2±35,3 | 98,8±29,8 | 0,777 |
| High sPESI, n | 13 | 10 | 0,389* |
| CTPA thrombotic localization, n:<br>segmental<br>lobar<br>main | <br>7<br>4<br>4 | <br>0<br>8<br>7 | **0,01 ($x^2$=9,152)** |
| PE intermediate-high or high risk, n | 9 | 13 | 0,215* |
| spO2, M±σ,% | 88,7±5,8 | 86,7±6,2 | 0,397 |
| Deep venous thrombosis, n | 7 | 14 | **0,014** |
| Arterial hypertension, n | 10 | 12 | 0,682* |
| Coronary artery disease, n | 2 | 1 | 0,612* |
| BMI, M±σ, кг/$m^2$ | 32,8±8,6 | 30,6±4,5 | 0,445 |
| Diabetes mellitus, n | 5 | 2 | 0,389* |
| Cerebrovascular disease, n | 4 | 4 | н/з |
| Chronic kidney disease, n | 5 | 5 | н/з |
| Heart failure, n | 10 | 8 | 0,489* |
| Oncology, n | 4 | 1 | 0,186* |
| D-dimer, Me (Q1; Q3), мсg/l | 3480(1345;6290) | 5470(2860;15610) | >0,05** |
| Troponin, Me (Q1; Q3), ng/l | 23(20,75;40) | 63(35;144) | **<0,05**** |
| PT, M±σ, sec. | 14,6±2,5 | 13,5±3,3 | 0,487 |
| C-RP, Me (Q1; Q3), mg/l | 88,6(26,5;133,8) | 34,5(33,5;79,5) | >0,05** |
| RBC, M±σ, $10^{12}$ /l | 4,3±0,7 | 4,3±0,5 | 0,928 |
| WBC, M±σ, $10^9$ /l | 8,6±4,3 | 9,0±3,5 | 0,752 |
| Platelets, M±σ, $10^9$ /l | 197,1±119,5 | 213,5±87,0 | 0,671 |
| GFR, M±σ, ml/min | 72,5±23,7 | 67,8±16,6 | 0,542 |
| Bilirubin, M±σ | 16,2±9,5 | 14,1±3,7 | 0,445 |
| ECG, QIII SI TIII (McGinn-White | 2 | 5 | 0,235* |

| | | | |
|---|---|---|---|
| sign), n | | | |
| ECG, (-)T waves at precordial leads (Kosuge sign), n | 2 | 12 | **0,00035*** |
| ECG, RBBB, n | 6 | 4 | 0,699* |
| Transthoracic echocardiogram (TTE), RV enlargement, n | 8 | 14 | **0,035*** |
| TTE, RV(4c), M±σ, mm | 44,6±9,1 | 48,5±6,1 | 0,206 |
| TTE, RAindex, M±σ, mm/m$^2$ | 22,8±4,2 | 26,9±3,8 | **0,018** |
| TTE, LV, M±σ, mm | 42±3,4 | 42,4±4,6 | 0,805 |
| TTE, EF, M±σ, % | 62,4±5,9 | 62,6±9,1 | 0,952 |
| TTE, pulmonary artery systolic pressure, M±σ, mm Hg. | 57,3±15,2 | 55,5±14,3 | 0,746 |
| Fibrinolysis, n | 5 | 2 | 0,389* |
| Heparin, n | 11 | 12 | 0,695* |
| NOACs, n | 10 | 10 | NS |
| Oxygenation, n | 9 | 12 | 0,427* |
| ACE, ARBs, n | 7 | 4 | 0,449* |
| CCB, n | 5 | 10 | 0,085* |

* - Fisher test; **- Mann-Whitney test.

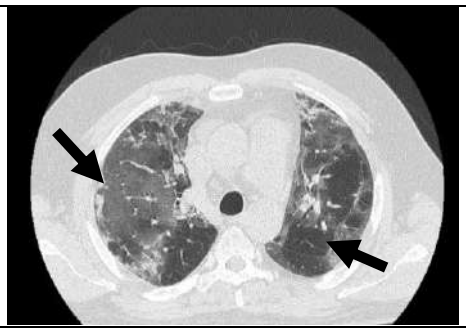
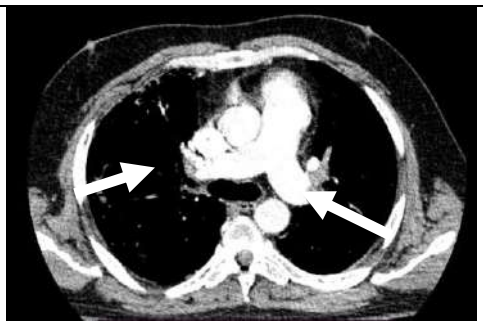
<table>
<tr><td colspan="2">1. «COVID19 to PE» period – 30,3 days</td></tr>
<tr><td colspan="2">2. Interstitial residual abnormalities (A). More distal thrombotic lesions (B)</td></tr>
<tr><td>A. Lung phase</td><td>B. Arterial phase</td></tr>
<tr><td>  </td><td>  </td></tr>
<tr><td colspan="2">3. Less right ventricular dysfunction.</td></tr>
<tr><td colspan="2">4. Less troponin levels.</td></tr>
<tr><td colspan="2">5. No deep venous thrombosis</td></tr>
<tr><td colspan="2">6. No classic ECG signs</td></tr>
</table>

Figure 1. Signs of patients with PE and history COVID-19.

**Conclusions.** Patients with PE and previous COVID-19 have a worse prognosis. The causes and pathophysiologic mechanisms of fatal outcomes require further investigations. Probably, the embolic thrombotic complications have a less role. It is more often may be direct thrombotic lung damage in a long-term period of COVID-19.

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# COVID-19 IN CHILDREN, DIAGNOSTIC DIFFICULTIES: CLINICAL OBSERVATION

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**Abstract**. A clinical case of one observation is presented. Infant 3 months old with coronavirus infection, nasopharyngeal PCR smear positive, but not on first examination, had an unusual neurological lesion in the form of bulbar syndrome

**Key words**: COVID-19, children, diagnostics.

**Introduction.** Many authors, from the first weeks of registration of cases of covid in the foci, and subsequently during the period of an avalanche-like increase in the incidence both in regions and countries, and up to a pandemic, drew attention to the fact that the proportion of children among those infected with this infection is significantly lower than in other age groups. It was also noted that children have a milder course of the disease and much less frequent complications and adverse outcomes [1-5]. For example, studies conducted in Johan [1-3]. Revealed a new coronavirus infection (CVI) in only 1.6% of all examined children. Even with the increase in morbidity, the proportion of children remained significantly lower than that of adults. A review based on 45 publications showed that in the age structure of diagnosed cases of COVID-19, children account for 1-5% (2-6). At the same time, the reason for hospitalization was hyperthermia above 39°C. All authors noted that in the case of infection of children with a new coronavirus, asymptomatic or mild forms of the disease prevailed in them [3–6], so observation of 171 children with CVI revealed the presence of asymptomatic forms in 15.8% of patients, pneumonia was only radiologically detected in 7% children, i.e. without clinical manifestations [5]. Clinically manifest forms of infection in children proceed as in adults, but fever (41.5%) and respiratory symptoms, such as hyperemia of the tonsils and pharynx, and cough predominate [5]. Pneumonia with CVI is classified as atypical and has features of manifestation in children compared with adults. And also in children less often than in adults, severe pneumonia develops. In general, pneumonia occurred in 32.7% of the observed children, while in all cases there was bilateral lung damage. [2,5] In infants under 1 year of age, compared with other age groups, severe forms of pneumonia were diagnosed, but in this group, not everyone had confirmed cases of CVI, so pneumonia could have a different etiology [2,4]. In general, the proportion of severe and critical cases was the highest for the age group under 1 year old - 10.6% [7]. Only 1.7% of all hospitalized patients required intensive care and mechanical ventilation. These were children with severe comorbid pathology (hydronephrotic transformation of the kidneys, leukemia, intestinal intussusception). Only one child had a fatal outcome of the disease [5]. On the part of the peripheral blood picture, lymphopenia (3.5%), leuko- and thrombocytopenia [7] were noted less frequently than in adults, while the levels of CRP and PCT were normal or moderately elevated. Also, laboratory parameters indicating an inflammatory process were changed less often: increased levels of interleukin (IL) 6 and lactate dehydrogenase, CRP> 200, PCT> 0.5, ferritin> 2500, D-dimer> 2500 [7]. In cases where a positive PCR result for COVID-19 RNA is absent, which is quite possible in pediatric practice, then characteristic changes on CT of the lungs should be the basis for their management as covid patients. At the same time, it must be remembered that using only CT data can lead to overdiagnosis of COVID-19, [7]

**Clinical observation.** Child A., 3 months old, was in the Children's Infectious Diseases Clinical Hospital (DIKB) in Almaty from 08.01 to 21.01.2021 (case history 577). The child was admitted with complaints of anxiety, refusal of the mother's breast during the day, fever up to 39°C, cough.

**Anamnesis morbi.** The child fell ill on 06.01.2021 with an acute increase in temperature to 38°C, the mother turned to an emergency doctor for help, in turn they took the child to the admission department of the DIKB, a diagnosis of ARVI was made, hospitalization was offered, but the parents refused hospitalization. In dynamics, the child continued to have a fever, but already at high numbers (up to 39°), he was restless, and a cough joined in. In the treatment took ospamox from the evening of 06.01. Due to the ongoing fever and the mother's breast refusal, the parents themselves came to the admission department of the children's surgical hospital, where the child was examined and examined, with a CT scan of the brain for acute cerebrovascular accident. This diagnosis was excluded and the patient was referred to the DIKB, where he was hospitalized.

**Anamnesis vitae**. A boy from the II pregnancy, which proceeded with early toxicosis and pyelonephritis. Childbirth II, urgent, weight - 3560 g, Apgar score 8/9 points. Before the present disease, he grew and developed according to his age.

**Epidemic anamnesis:** At home, everyone considers themselves healthy

**Status praesens.** The condition is serious, unstable. T-36.5°C, respiratory rate - 36 / min., Heart rate - 143 / min., BP-92 / 58mm Hg. Art., saturation-98%.

Consciousness is clear, lethargic, reacts to examination and painful stimuli with a quiet cry. He opens his eyes, follows his gaze. On the part of 12 pairs of cranial nerves without disturbances. The large fontanelle is at the level of the bony margins, not tense. Lessage's symptom is negative. Bulbar disorders are noted: does not suck, does not swallow, there is no cough reflex. Hyporeflexia. He receives liquid and food through a probe, assimilates. The probe is clean without pathological secretions. The skin is clean, pale in color. Visible mucous membranes are pale pink, clear. The nasolabial triangle is pale in color. The skin fold is straightened immediately. Above the lungs, percussion from the right behind in the lower sections is a shortening of the sound, above the rest of the sections with a box shade. Auscultatory hard breathing, except for the area behind, on the right in the lower sections, is weakened, here there are fine bubbling rales. The exhalation is lengthened. Hemodynamics are compensated. Heart sounds are rhythmic, muffled. The abdomen is unchanged, palpation is available. The liver protrudes from under the edge of the costal arch by + 3.5 + 3.5 + 4.5 cm. The spleen protruded from under the edge of the costal arch by +1.5 cm. There was no chair on the last day, urinating as usual.

**Laboratory research data.**

Spinal puncture was performed, cerebrospinal fluid analysis - colorless, transparent, cytosis - 3 cells, lymphocytes - 100%, protein - 0.135 g / l

In the KLA on the day of admission: anemia 1 tbsp. (HB-112g / l), leukocytosis (26.8 thousand), neutrophilia, ESR accelerated (18 mm RT.article). In dynamics in the UAC from 12.01. anemia worsened (Нв-104g / l), leukopenia appeared - 3.15 thousand, ESR decreased to 7 mm Hg.

Biochemical analysis on admission: normal values.

Coagulogram: prothrombin index is reduced (51.8%), APTT is 34.4 seconds, fibrinolytic activity is 2.44 per minute (reduced), thrombin time is 29 seconds (lengthening). VSK according to Lee-White - 8min.

OAM: ketone bodies are more than 15.6, other indicators are normal.

CT scan of the brain: a consequence of the postponed hypoxic-ischemic brain lesion, cyst of the posterior cranial fossa.

CT of the chest: a picture of 2-sided polysegmental pneumonia, more likely of viral etiology, with lung involvement of about 25-50%.

PCR for COVID-19 from 08/01/21 - neg., From 12/01. - gender.

**Main clinical diagnosis.** Coronavirus infection, severe. Confirmed case (nasopharyngeal smear RNA PCR positive from 01/12/2021), acute course, associated polysegmental pneumonia, CT scan 2. Extrapulmonary manifestations: bulbar syndrome

The state in dynamics as of January 20, 2021 is stable, the temperature is consistently normal, the consciousness is clear, follows the gaze, the bulbar disorders persist, the pneumonia resolved. For further treatment, the child was transferred to the neurological department.

**Conclusion.** This observation once again demonstrates the variety of coronavirus lesions. Although many authors testified about the presence in children of mostly mild forms of the disease, among patients with severe cases of CVI, children under one year of age predominated, especially in the first 3 months of life, which was in our observation. Among the variety of clinical symptoms in CVI described in the literature, we did not find such neurological symptoms as in our observed one. Bulbar syndrome, which appeared with the onset of the disease, persisted after the relief of the severity of the disease. If we talk about confirmed cases of the disease, then it was in the age group under 1 year that there was the most number of suspected cases of COVID-19 and the minimum confirmed. So it was in our case, when the first PCR study of a nasopharyngeal smear for COVID-19 was negative, the reason for re-examination was the signs of viral pneumonia on CT. Therefore, if you suspect CVI, you cannot limit yourself to one or two PCR tests.

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# STATE OF COVID-19 VACCINE DEVELOPMENT IN RUSSIA

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**Abstract**. An informational overview of three different types of vaccines (vector, inactivated and gene) developed by scientific organizations in Russia, designed to combat the coronavirus COVID-19, is presented. The analysis of properties, parameters, characteristics and possibilities of using Russian vaccines for clinical purposes is presented.

**Key words**: coronavirus, vaccines, parameters, characteristics, application.

**Introduction**. According to official sources, including the health authorities of China and the WHO (January-February 2020), work [1] provides an extensive overview and analysis of the epidemiological and clinical characteristics of coronavirus infection (COVID-19), as well as an assessment of possible options for the development of the epidemic. It is known from literary sources that the virus spreads by airborne droplets. The disease can occur both in a mild form and in a very severe (critical) form, depending on the degree of damage to the upper respiratory tract.

A feature of the new coronavirus infection is its spread throughout the world, as well as the lack of clarity on the further direction of the COVID-19 epidemic. Nevertheless, the leading countries of the world are taking the necessary measures to combat the new infection. These include both the development of non-invasive methods of diagnosis, monitoring and control of the condition of patients with COVID-19 infection, and the creation of vaccines against coronavirus infection.

Currently, Russia has developed three vaccines made on different technological platforms. This allows doctors to select the most suitable vaccine for patients for vaccination, taking into account certain characteristics of the human body. For example, restrictions may arise if a person is allergic to any of the components of the vaccine. In this case, it is possible to inoculate such a patient with another drug.

Russian scientific organizations at the moment have developed three types of vaccines approved for use in Russia, namely: Gam-Covid-Vak (trademark “Sputnik V”, manufacturer of the Gamaleya Research Center), “EpiVacCorona” (manufacturer of the State Research Center “Vector”) and in February 2021, another vaccine against COVID-19 was registered – “Kovi-Vac”, developed by the Chumakov Center of the Russian Academy of Sciences (this is a “mild” vaccine produced using classical technology).

This paper provides an informational analysis of data on these types of vaccines in order to disseminate scientific information on the possibilities of their use for the prevention of coronavirus infection and bringing it to a wide range of stakeholders.

**1. Comparative information analysis of Russian vaccines.**

When developing a vaccine against the novel coronavirus [2], the focus is on three types of vaccines: live, inactivated, and DNA or mRNA vaccines. A brief description of Russian vaccines is shown in Table 1.

Any new vaccine goes through three phases of testing before being used for clinical purposes. Table 2 provides information on the main stages of testing new Russian vaccines before their use for clinical purposes.

A large group of people are vaccinated. Then the effectiveness of the vaccine is analyzed, namely, whether the number of sick people is decreasing.

After passing through three stages of testing, the vaccine is registered with the World Health Organization (WHO). After that, the production of the drug begins.

Table 1. Brief characteristics of Russian vaccines

| n/n | Test phase | The purpose of this stage of testing | The essence of the tests | Appointment |
|---|---|---|---|---|
| 1. | The first | Determination of the ratio of dosage, effectiveness and side effects. | A small group of healthy volunteers receive a dose of the vaccine being tested. | security check |
| 2. | The second | Determination (finding) of the optimal dose. | The vaccine is beginning to be tested on hundreds of subjects. | People of different ages and health conditions. |
| 3. | Third | It is carried out in the so-called "natural conditions of the disease". | A large group of people (thousands) are vaccinated. | This is usually the longest phase. |

Table 2. The main stages of testing Russian vaccines

| n/n | Vaccine type | Structure | Application | Note |
|---|---|---|---|---|
| 1. | Vector or just a vector (live vaccine) - foreign genes are inserted into the genome of the virus. | The basis for the creation of a live vaccine is the neutralized virus itself. It does not cause disease, but it is able to multiply in the cells of the body. | Previously used against smallpox, the Ebola virus. | As a result, the immune system begins to produce antibodies, which helps prevent real infection with the disease. |
| 2. | Inactivated | Contains selected viral proteins or inactivated viruses - pathogens that have been killed. | It is used against influenza, polio, whooping cough, hepatitis. | Dead viruses cannot multiply, but the body recognizes them and produces antibodies. |
| 3. | Gene | Contains pure genetic information in the form of coronavirus DNA or RNA. | When the vaccine enters the body, it begins to form harmless viral proteins that create immune protection. | Separate pieces of genetic information from the pathogen are packed into nanoparticles and introduced into cells. |

At present, the first vaccine in Russia has been developed and registered with the "Gam-Covid-Vac" vaccine (trade mark "Sputnik V"). In addition, it is already registered in more than 30 countries around the world, an application has been submitted for registration in the EU and for approval by the WHO.

This is a genetically engineered vector vaccine based on two strains of live human adenoviruses. It is introduced twice with an interval of 3 weeks. The effectiveness is 91.4%, against a severe course of the disease - 100%. It is expected that immunity is formed for two years (for 9 months - already proven). The vaccinated may experience a flu-like syndrome: fever (sometimes up to 38-39 degrees), muscle and joint pain, weakness, headache. If necessary, it is recommended to take antipyretic drugs. Symptoms usually resolve within 1–2 days. Less commonly, nausea, dyspepsia, decreased appetite, and sometimes an increase in regional lymph nodes are noted. Recommended for adults (18-60 years old), and also allowed for use at the age of 60+. Contraindicated in pregnant and lactating mothers. Research on children under 18 is planned. It is not recommended for use in case of hypersensitivity to any component of the vaccine; history of severe allergic reactions; acute infectious diseases, exacerbation of chronic ailments. The vaccine can be given 2-4 weeks after recovery or remission.

With mild ARVI - after the temperature has returned to normal. In case of severe complications after the introduction of the first dose (for example, anaphylactic shock, convulsive syndrome, temperature above 40°C, etc.), the introduction of the second component is also prohibited. It can be used with caution in chronic liver and kidney diseases, diabetes mellitus, severe diseases of the hematopoietic system, epilepsy, strokes and other diseases of the central nervous system, a history of myocardial infarction, ischemic infection, primary and secondary immunodeficiencies, autoimmune diseases, lung diseases, asthma and COPD.

The second, developed by the FBSI SSC “Vector” of Rospotrebnadzor, the “EpiVacCorona” vaccine is a genetically engineered peptide vaccine based on artificial peptides that copy fragments of the coronavirus. Registered in Russia and Turkmenistan. It is injected twice intramuscularly with an interval of 2-3 weeks. Immunological efficiency 100%. The immune defenses are expected to last for at least a year. No significant adverse events were identified. Few have pain at the injection site and fever up to 38.5.

The vaccine is recommended for adults (18-60 years old), admission is expected for patients 60+. Contraindicated in pregnant and lactating women, studies on children under 18 years of age are planned. Features of the vaccine: it is forbidden to vaccinate in case of hypersensitivity to the components of the drug (aluminum hydroxide, etc.); with severe allergies; primary immunodeficiency, neoplasms, post-vaccination complications during the previous administration of the vaccine; acute infectious and non-infectious diseases, exacerbation of chronic diseases. The vaccination can be done no earlier than a month after recovery or remission. With mild ARVI, vaccination is carried out after the temperature has returned to normal.

Developed by FSBNU named after M.P.Chumakov RAS, Russia, the third new vaccine “KoviVac” - inactivated whole-virion, based on the “killed” whole coronavirus. This is a classic type of vaccine that has been produced on a large scale and has been used since the last century. It is injected twice intramuscularly with an interval of two weeks. Registered by the Ministry of Health of Russia on February 20, 2021, it is planned to carry out the WHO approval procedure, registration in foreign countries.

The immunological effectiveness of this vaccine is 85%. The duration of the immunity will be announced after the end of clinical trials. No serious adverse events were reported after vaccination. In rare cases, there was mild pain and induration at the injection site. Headache and mild fever were reported in a few participants. No serious adverse events were reported after vaccination. In rare cases, there was mild pain and induration at the injection site. Headache and mild fever were reported in a few participants.

The vaccine is recommended for adults 18-60 years old. Contraindicated in pregnant women, lactating women and children, since studies on these groups have not been conducted. Also not used in people with severe post-vaccination complications to any previous vaccinations, as well as with severe allergies.

Temporarily contraindicated: in acute febrile conditions, acute infectious and exacerbation of chronic diseases. The vaccination is done 2-4 weeks after recovery. The possibility of vaccination is allowed for chronic diseases of the kidneys, liver, neuroendocrine system, severe diseases of hematopoiesis, autoimmune, allergic diseases, bronchial asthma, etc. The patient's condition and the possibility of vaccination, taking into account the benefit-risk factor, are assessed by the attending physician.

**1. The first results of scientific and practical research of developed vaccines.**

The Gamaleya Center is the first developer of the first Russian vaccine against the COVID-19 coronavirus "Sputnik V", registered in August 2020. Now this drug is approved in more than 60 countries with a total population of over one and a half billion people.

In terms of the number of approvals received by state regulators, the Russian vaccine ranks second in the world. The results of the third phase of clinical trials of "Sputnik V", published in the scientific journal Lancet in early February, confirm its high efficacy and safety: the drug fully protects against the severe course of COVID-19.

"Interfax", citing the head of the center A.Gintsburg, reports that the Gamaleya Center continues to test the vaccine in order to identify the possibility of its use to protect immunity from several strains of coronavirus. The new technology is able to protect the immune system not to one, but to four or five variants of the virus. In this case, as A.Gintsburg said, "you don't have to make 3-4-5 different "Sputnik V", it will be a kind of cluster warhead" (Rossiyskaya Gazeta, www.rg.ru)

The vaccine "EpiVacCorona", developed by the FBSI SSC VB "Vector" of Rospotrebnadzor, is recognized as safe for the prevention of COVID-19. The results of clinical studies in volunteers aged 18 to 60 years have confirmed the safety and efficacy of this vaccine.

Taking into account the start of mass vaccination against COVID-19, including with the drug EpiVacCorona, and the high demand of Russian citizens for reliable information on the results of clinical trials of the developed vaccine among volunteers aged 18-60 years (I-II research phase), SSC "Vector" published the research results obtained in the journal "Infection and Immunity" 03/24/2021.

Published scientific materials indicate that the study was conducted in two stages:

1. An open study of the safety, reactogenicity and immunological activity of the vaccine (14 volunteers, 18-30 years of age participated);
2. A simple, blinded, comparative, randomized, placebo-controlled study (86 volunteers, 18-60 years old).

It was shown that the two-dose vaccination scheme caused the development of antibodies specific to the antigens that make up the vaccine in 100% of the volunteers.

In 100% of the volunteers, 21 days after receiving the second dose, seroconversion was recorded with a neutralizing antibody titer ≥ 1:20. According to the results of the study, Rospotrebnadzor concluded that the "EpiVacCorona" vaccine is an immunogenic and safe product for the prevention of COVID-19.

According to literary sources, over 4 months of mass vaccination in the United States, about 45 million people were vaccinated, in Israel - more than 4, 6 million, in Russia more than 6 million. But it is clear that this is not enough to stop the epidemic.

A very important question of vaccine effectiveness. Vaccine SIC named after N.F. Gamaleya demonstrates 92% efficiency and a very good result against new mutations of the

coronavirus. The use of the Pfiezer / BioNTech vaccine demonstrates an efficiency of 97% against symptomatic disease and 94% against asymptomatic infection, including infection with the "British" strain [1].

Russia is among the countries that do not need to wait for "favors from nature", namely, vaccines from other countries. Moreover, many people want to be vaccinated only with Russian vaccines. And above all, we are talking about the vector vaccine "GamKovidVac", better known as "Sputnik V". It is one of the three most sought after vaccines after Pfizer and AstraZeneca.

In February 2021 "Sputnik V" has been approved in 26 countries around the world; On March 4, an examination by the European Medicines Agency (EMA) began, which is necessary for the registration of a vaccine in the EU.

In an interview with "Reuters", Deputy Director of the Center named after Gamalei on scientific work, D.Logunov informed that during the study of the effectiveness of revaccination by "Sputnik", the vaccine "... shows a very good result against new mutations of the coronavirus, including against strains from the United Kingdom and South African Republic".

US chief infectious disease specialist Anthony Fauci, answering the question whether he would have been vaccinated with Sputnik or the Chinese vaccine, said: "The data that I know about "Sputnik" is quite good. I don't have enough information about the Chinese vaccine, but the Russian data looks good".

**Problems.** The coronavirus is not the flu. He does not have the ability to combine several surface antigens. On its surface there is only a thorn-like protein. Therefore, in terms of the effectiveness of vaccines against mutant strains, there are fewer problems with it.

The COVID-19 epidemic has dramatically changed the entire world. Health systems around the world were initially at a loss. Many issues have not yet been resolved. An effective treatment regimen has not yet been developed, including for cases of the first symptoms of the disease. The virus does not degenerate into a less dangerous virus, but slowly mutates and, at the same time, its pathogenicity contributes to an increase in infectivity.

Analysis of literature sources shows that COVID-19 remains a dangerous and insufficiently studied disease today, which can have unpleasant long-term consequences for those who have been ill (long COVID); the occurrence of chronic fatigue syndrome (about 20%); the emergence of cognitive disorders, including problems with memory and concentration (brainfog); impaired lung function, chest pain, palpitations, inflammation of the heart muscle; loss of smell.

Along with this, it should be noted also such possible consequences as: joint pain; depression; prolonged muscle and headache; hair loss; sleep problems; prolonged shortness of breath and / or cough. Damage to other organs that cause chronic inflammatory processes, for example, in the kidneys, is possible.

Three vaccines have been registered in Russia: the vector "Sputnik V" (Gamaleya Research Center), inactivated "KoviVac" (M.P.Chumakov Research Center) and "EpiVacCorona" ("Vector" Research Center of Rospotrebnadzor). In fact, now they are vaccinated mainly with Sputnik. There were no deaths or serious reactions associated with the vaccine [2]. The most typical reactions in the vaccinated are: temperature; pain at the injection site; drowsiness / weakness. "EpiVacCorona" and "KoviVac" are currently in the third phase of clinical trials.

Experts note that most candidate vaccines are likely to protect only against the development of the disease, but will not be able to prevent further transmission and spread of the virus. At the same time, it is still unknown how long-term immunity to COVID-19 will provide people with new vaccines.

**Conclusion.** Three vaccines have been registered in Russia: the vector "Sputnik V" (Gamaleya Research Center), inactivated "KoviVac" (M.P.Chumakov Research Center) and "EpiVacCorona" ("Vector" Research Center of Rospotrebnadzor). In fact, now they are vaccinated mainly with "Sputnik". There were no deaths or serious reactions associated with the vaccine [2]. The most typical reactions in the vaccinated are: temperature; pain at the injection site; drowsiness / weakness. "EpiVacCorona" and "KoviVac" are currently in the third phase of clinical trials.

Attention is drawn to the coincidence that WHO declared a pandemic, precisely when, thanks to scientific research, there have already appeared:

a) technologies that can decipher the genome in a matter of days;

b) the foreign companies Moderna and BioNTech already had developed technologies for the production of mRNA vaccines, and the named after N.F.Gamalei - a platform for creating vaccines based on adenoviral vectors has been developed.

Obviously, if the pandemic had happened 15-20 years ago, when there was still no such scientific groundwork, the problematic situation with the pandemic would have been a very difficult task to solve, and most importantly, with large losses of human lives.

Dr. Jeremy Farrah, Director of the "Wellcome" Foundation and Chair of the WHO Research and Development Program Advisory Group, said: "There is only one way to end the global pandemic - science." What is needed is "diagnostic tools to detect and contain this virus, vaccines to provide long-term protection to the population, drugs to save lives in the short term, and social science data to understand the behavioral and social impact of the pandemic."

The accumulation of scientific data shows that regardless of the degree of lung damage, the new SARS-CoV-2 coronavirus can affect the liver, kidneys, brain, eyes, intestines, provoke fat metabolism disorders, diabetes, heart disease and other diseases. A growing amount of data also indicates that often with COVID-19, the integrity of the vascular barrier is disrupted. At the same time, SARS-CoV-2 can disrupt vascular homeostasis by directly infecting endothelial cells through the ACE2 enzyme. This contributes to the development of venous and arterial complications of varying severity in a significant proportion of patients with severe disease (including young people and children). At the same time, many of the listed metabolic characteristics may remain unnoticed by doctors due to the impossibility of detecting them during routine laboratory testing. For this reason, some researchers believe that COVID-19 is also a multi-organ metabolic disease. In this regard, a scrupulous study of the pathogenesis of COVID-19 continues.

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# EFFECTIVENESS OF INTERFERONOTHERAPY IN TREATMENT OF NEW CORONAVIRAL INFECTION IN CHILDREN

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**Abstract**. Study of the efficacy and safety of interferon alfa-2b (VIFERON®, rectal suppositories and gel for external and local use) in the complex therapy of new coronavirus infection (COVID-19) in children. Examined 140 patients aged 1 to 17 years with a new coronavirus infection (COVID-19). Depending on the performed antiviral therapy, the observed patients were divided into two groups: the main group (I - 70 people, received VIFERON® drugs) and control (II-70 people, Arbidol® was prescribed, INN - Umifenovir). The criteria for the effectiveness of the therapy were the timing of the relief of the main clinical symptoms of the disease, the elimination of SARS-CoV-2 RNA in samples from the nasopharynx, the dynamics of the production of virus-specific IgM and IgG antibodies to SARS-CoV-2 in the blood serum. As a result of the therapy in the patients of the main group, compared with the control group, the time for relief of the main clinical symptoms of COVID-19 and the elimination time of SARS-CoV-2 RNA in nasopharyngeal smears were reduced, a statistically significant increase in the level of IgG antibodies to SARS-Cov-2 was revealed in blood serum.

**Key words**: children, COVID-19, interferons, VIFERON®, umifenovir.

**Introduction.** World statistics of the novel coronavirus infection (COVID-19) pandemic indicate that children and adolescents are less susceptible to the disease and make up from 1% to 7% in the structure of patients with diagnosed infection [1, 2]. In Russia in the first half of 2020 year, the number of children infected with COVID-19 amounted to 8.4% of all cases of this infection. The cause of infection of children with SARS-CoV-2 in 75% of cases was family contact with sick adults. The clinical picture of the disease is dominated by symptoms characteristic of an acute respiratory infection with a predominant lesion of the upper respiratory tract, while in a third of children the infection proceeds without clinical manifestations [3].

In the treatment of the new coronavirus infection COVID-19 in children, issues related to antiviral therapy are of particular importance today, since it is precisely childhood that limits the use of many drugs [4]. In this direction, of particular interest is the study of the effectiveness of recombinant interferons alpha-2b in the treatment of patients with COVID-19. The high sensitivity of SARS-CoV-2 to the action of interferon has been established. The results of a study examining the effect of interferon on the ACE2 receptor indicate that exogenous type 1 IFN activates inactive ACE2, preventing the attachment of the virus to the receptor and its penetration through the cell membrane [5]. At the same time, SARS-CoV-2, like its predecessors, uses many mechanisms to avoid the induction of type I antiviral IFNs in cells and tissues [6,7].

A promising direction for increasing the effectiveness of treatment of coronavirus infection COVID-19 is the use of the drug with the complex etiotropic and pathogenetic activity of IFN-α2b, VIFERON®, VIFERON® (manufactured by Feron LLC, Moscow, Russia). Many years of experience in the use of recombinant IFN-α2b in the treatment of seasonal acute respiratory viral infections, the availability of the drug, the form of release and

the relatively modest cost make it an excellent candidate for widespread use in the treatment of the new coronavirus infection COVID 19 [9,10].

Based on the foregoing, the aim of the study was to study the efficacy and safety of the drug VIFERON®, rectal suppositories (IFN-α2-b) 1,000,000 IU and 3,000,000 IU and VIFERON®, gel for external and local use (interferon alfa-2b) 36,000 IU / g in the complex therapy of new coronavirus infection (COVID-19) in children aged 1 to 17 years.

**Patients and methods.** A multicenter prospectively controlled scientific study to study the therapeutic efficacy and safety of combination therapy with VIFERON®, rectal suppositories and VIFERON® gel for external and local use as part of complex therapy in 140 children aged 1 to 17 years with a confirmed diagnosis of "New coronavirus infection COVID-19 "Hospitalized in the infectious diseases hospital of KGBUZ" Krasnoyarsk interdistrict children's clinical hospital No. 1 "of Krasnoyarsk for the period from 20.04.2020 - 01.08.2020.

From the moment of hospitalization, all patients underwent careful clinical and laboratory monitoring. To verify the etiology of COVID-19, the polymerase chain reaction (PCR) method was used, which allows the isolation of SARS-CoV-2 RNA in naso / oropharyngeal smears and feces. Determination of virus-specific antibodies IgM and IgG to SARS-CoV-2 in serum was carried out by enzyme-linked immunosorbent assay (ELISA).

Depending on the antiviral therapy carried out, the observed patients were divided into two groups - the main and the control. Patients with COVID-19 of the main group (70 people) received combination therapy with VIFERON® drugs according to the proposed schemes that differ depending on age: children from 1 year up to 7 years received VIFERON®, rectal suppositories (IFN-α2-b) 1,000 IU, 1 suppository twice a day, rectally 12 hours later. Children aged 8 to 17 years - VIFERON®, rectal suppositories (IFN-α2-b) 3,000,000 IU. 1 suppository 2 times a day after 12 hours rectally. Additionally, patients of the main group of both age groups were injected with VIFERON®, gel for external and local use (IFN-α2-b), 36,000 IU / g 5 times a day in each nasal passage at a dose of 4000 IU (a strip of gel not long more than 0.5 cm). The general course of therapy was 10 days.

Patients with COVID-19 in the control group (70 people) received the drug Arbidol® (INN - Umifenovir) as an antiviral therapy in a dosage form of a suspension, tablets or capsules in an age-specific dosage: a single dose for children from 2 to 6 years old - 50 mg, single the dose in children 6-12 years old is 100 mg, a single dose in children from 12 to 17 years old is 200 mg, the frequency of administration is 4 times a day, the duration of therapy is 10 days.

Patients of both groups were comparable in terms of age, sex, length of hospitalization, and severity of the disease. When studying the age characteristics of the comparison groups, it was found that in the group of patients receiving Umifenovir, children aged 8-17 years predominated with statistical significance (71%), while in the main group of patients, children aged 1-7 years predominated statistically more often ($p = 0.0058$). The median age of patients in the main group was 8 years [7; 10], in the control group 10 years old [9; 11] ($p = 0.0098$).

The criteria for the effectiveness of the therapy were the relief of the main clinical symptoms of the disease, the elimination of viral RNA in samples from the nasopharynx and feces, the dynamics of the production of virus-specific IgM and IgG antibodies in the blood serum in patients of the main and control groups.

Based on the results of the study, a database was formed in the MS Excel 2010 spreadsheet package, on the basis of which, using the statistical package IBM SPSS Statistics v.19, statistical analysis was carried out. The results of the nominal traits are expressed in absolute numbers, indicating the proportions (%). For continuous variables with an abnormal type of distribution, descriptive statistics were calculated: median, lower and upper quartiles

(Q1 and Q3, respectively). Due to the fact that all quantitative data did not obey the law of normal distribution, their description was carried out using the median (Me), 95% confidence interval (95% CI), as well as the minimum (min) and maximum (max) values. Differences were considered statistically significant at a significance level of $p < 0.05$.

**Results and Discussions.** Comparison of the severity and frequency of the main clinical symptoms of the new coronavirus infection COVID-19 in patients of the main and control groups at the time of admission to the hospital did not reveal a statistically significant difference. In most of the patients, the disease began acutely, with a rise in body temperature, the onset of symptoms of intoxication and catarrhal phenomena. 51% (72) of patients had severe weakness, headache 16% (22), muscle pain 7% (10).Regardless of age, signs of damage mainly to the upper respiratory tract were determined: difficulty in nasal breathing 54% (75), mucous discharge from the nose 66% (92), sore throat when swallowing 54% (76), coughing 47% (66). On an objective examination, attention was drawn to the development of catarrhal conjunctivitis 84% (118), hyperemia of the tonsils, arches, granularity of the posterior pharyngeal wall 83% (116), enlargement of regional (cervical) lymph nodes 53% (75). At the same time, 26% (37) of children had a cough already from the first days of the disease: dry 16% (23), wet 10% (14). Along with the pathognomonic signs of ARVI, 10% (14) of patients had abdominal pain and diarrheal syndrome in 20% (28). In 28% (39) of the observed patients, there was a violation of smell (anosmia) and taste (dysgeusia) in 19% (26). It is important to note the dependence of the incidence of individual clinical symptoms of COVID-19 on age. Thus, in patients 8-17 years old, taste disturbance (dysgeusia) 100% (26; $p = 0.00001$) and smell (anosmia) 97% (38; $p = 0.00001$) prevailed with statistical significance, severe nasal congestion 88% (66; $p = 0.00001$), lesion of the mucous membrane of the eyes 58% (69; $p = 0.00001$). While in patients 1-7 years of age, the development of diarrheal syndrome was more often observed in 64% (18; $p = 0.053$).

Among the patients with COVID-19 we observed, the mild form of the disease was most often diagnosed in 61% (86), the moderate form was found in 39% (54) of patients. When studying the incidence of various forms of severity in patients with COVID-19 in the compared groups, a statistically insignificant prevalence of a mild form of the disease in the control group was found 66% (46). The moderate form of the disease, on the contrary, prevailed in the main group of patients in 43% (30), while the differences were also not statistically significant.

In a comparative study of the duration of the main clinical manifestations of COVID-19 in the compared groups, statistically significant differences were found in the relief of such symptoms of the disease as: coughing (rare dry cough) ($p = 0.017$), impaired smell ($p = 0.001$) and taste ($p = 0.002$), nasal congestion ($p = 0.001$), sore throat ($p = 0.004$), hyperemia of the oropharynx ($p = 0.001$), enlarged neck lymph nodes ($p = 0.001$), conjunctivitis ($p = 0.001$) in the group of patients receiving as part of complex therapy preparations of recombinant IFN-α2b compared with children who received Umifenovir as antiviral therapy (Table 1).

In 69% (97) of patients, the manifestation of clinical manifestations of COVID-19 began with the appearance of complaints of “impaired sense of smell.” At the same time, in the main group of patients receiving combined therapy with recombinant IFN-α2b preparations, olfactory disorders were observed in 24% (17), in the control group - in 37% (26) patients. Against the background of the therapy, it was found that in the children of the main group, the recovery of “smell” was statistically significant 6 days earlier than in the control (($p = 0.0004$). The median of the symptom “impaired smell” in the main group was 4 days versus 10 days in the control ($p = 0.0004$). The average value of the duration of “taste disturbance” in patients in the main group was also 6 days less than in the control group ($p = 0.003$).

Table 1. Average duration of the main clinical symptoms in patients with COVID-19 of the main and control groups, depending on the therapy (days)

| Indicator | Comparison groups | | | | | | p |
|---|---|---|---|---|---|---|---|
| | Viferon (n=70) | | | Umifenovir (n=70) | | | |
| | Me | 95% CI | min-max | Me | 95% CI | min-max | |
| Conjunctivitis (days) | 3 | [2;4] | 2-10 | 5 | [6;7] | 1-16 | p=0,012 |
| Rhinitis (runny nose) (day) | 4 | [4;5] | 1-10 | 5 | [5;7] | 1-14 | p>0,05 |
| Nasal congestion (days) | 3 | [4;6] | 2- 4,0 | 7 | [7;8] | 4-9 | p=0,0001 |
| Smell disorder (days) | 4 | [4;8] | 3-11 | 10 | [9;11] | 5-14 | p=0,001 |
| Taste disturbance (days) | 4 | [1;8] | 1-10 | 10 | [8;11] | 4-14 | p=0,015 |
| Weak cough (days) | 5 | [5;6] | 2-14 | 7 | [6;8] | 3-11 | p=0,047 |
| Sore throat (days) | 3 | [3;4] | 1-8 | 8 | [6;8] | 2-14 | p=0,0001 |
| Oropharyngeal hyperemia (days) | 5 | [5;6] | 1-14 | 10 | [9;10] | 2-14 | p=0,0001 |
| Increased cervical l / nodes (day) | 4 | [4;6] | 1-14 | 10 | [8;10] | 2-14 | p=0,0001 |
| Abdominal pain (days) | 3 | [2;4] | 1-5 | 3 | [2;4] | 1-4 | p>0,05 |
| Diarrhea (days) | 3 | [3;4] | 2-4 | 4 | [3;4] | 2-5 | |

For all patients in the compared groups, the “total score” was calculated as the sum of the manifestations of the main clinical symptoms of COVID-19, depending on the therapy. We found that the median duration of preservation of at least one clinical symptom in the main group was 4 days less (4 (3.0 - 6.0)) than in the control group (8 (7.0 - 11.0)). When comparing relief of the main clinical symptoms of COVID-19 in the compared groups, statistically significant differences were observed from 3 to 12 days of illness (p = 0.01). At the same time, in the main group of patients, the relief of clinical symptoms ended already on day 5, while in patients of the control group, the symptoms of COVID-19 were stopped much more slowly and persisted until the 12th day of hospitalization (p = 0.001).

The dynamics of the elimination of the viral antigen in the compared groups, depending on the therapy, was assessed based on the results of taking nasopharyngeal swabs on days 5, 11, 13 and 21 of the observation of patients. Analysis of the duration of SARS-CoV-2 viral clearance in the observed patients showed statistically significant differences depending on the therapy. It was found that in 97% (64/66) of patients of the main group, the elimination of the pathogen occurred already on the 5th day after the start of combination therapy with IFN-α2b drugs, while in patients receiving Umifenovir, only 39% of patients underwent sanitation during these periods (27/69) patients. The results of nasopharyngeal swabs for SARS-CoV-2 taken on the 11th day by the end of the course of antiviral therapy showed that all children of the main group had elimination of SARS-CoV-2 RNA, while in the control group only 75% (52/69). Only 86% (60) children of the control group had negative smear results for SARS-CoV-2 on day 13, and 13% (9) continued to excrete the virus, which was the basis for continuing antiviral therapy. In general, the average duration of virus elimination in nasal / oropharyngeal swabs in patients with COVID-19 was 6 days in the study group, and 11 days in the control group.

The study of the dynamics of changes in the level of virus-specific antibodies IgM and IgG to SARS-Cov-2 in blood serum in the compared groups was carried out on days 5, 11 and 21 after the appointment of antiviral therapy.

Analysis of the results obtained indicates that in patients receiving IFN-α2b as antiviral therapy by the end of the course of therapy, there was a statistically significant increase in the level of IgG antibodies to SARS-Cov-2 by 11 and 21 days from the start of treatment compared with children of the control group receiving therapy with Umifenovir ($p = 0.05$). At the same time, the level of antibodies of the IgM class by day 21 was statistically significantly reduced in the main group of patients, which indicates the sanitation of the body from SARS-Cov-2 and the formation of antiviral immunity. At the same time, in patients of the control group by day 21, the level of virus-neutralizing IgG antibodies was statistically significantly lower ($p = 0.001$).

At the time of admission to the hospital, along with positive results of PCR smear from the nasopharynx in 25% (35) of the observed COVID-19 patients (18 of the main and 17 control groups), SARS-CoV-2 was found in the feces. At the end of the course of antiviral therapy, analysis of fecal PCR results on days 11-13 showed statistically significant differences in viral shedding depending on the therapy. In the main group of patients receiving preparations of recombinant IFN-α2b with antioxidants in 90% (16) of cases, the results of fecal PCR for SARS-CoV-2 were negative, and only 10% (2) of children continued to shed the virus. At the same time, only 24% (4) of patients in the control group receiving antiviral therapy with Umifenovir obtained negative results of fecal PCR for SARS-CoV-2, the remaining 76% (13) continued viral shedding ($p = 0.05$). Thus, when combined therapy with IFN-α2b drugs was prescribed, sanitation occurred 2.5 times more often than in patients receiving Umifenovir.

**Conclusion.** The results of the clinical study confirmed the high efficacy and safety of the appointment of combination therapy with IFN-α2b (rectal suppositories with antioxidants and gel for external and local use) in the treatment of COVID-19 in children aged 1 to 17 compared with standard therapy with Umifenovir. Combined therapy with VIFERON® drugs, by 4 days, reduces the total duration of the main clinical symptoms of COVID-19, having a high sanitizing activity by 5 days, it reduces the elimination time of SARS-CoV-2 in swabs from the nasopharynx and intestines, contributes to a statistically significant increase in the level of virus-specific IgG antibodies, which indicates on the formation of stable antiviral immunity. The proven efficacy and safety of combination antiviral therapy with VIFERON®, rectal suppositories with antioxidants in high dosages in combination with VIFERON®, gel for external and local use is the basis for widespread introduction in pediatric practice in the treatment of patients with new coronavirus infection COVID-19.

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# RESULTS OF COVID-19 TREATMENT USING RECOMBINANT INTERFERON AS PART OF COMPLEX THERAPY

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**Abstract**. The article is devoted to assessing the results of treatment of the new coronavirus infection COVID-19 using recombinant interferon as part of complex therapy. The data obtained show the high efficiency of therapy regimens with the inclusion of the interferon alpha-2b drug and the safety of its use in combination with symptomatic agents, antibiotics, anticoagulants, which makes it possible to recommend the study drug for inclusion in standard treatment regimens for patients with new coronavirus infection COVID-19.

**Key words**: COVID-19, Interferon, antibiotics, IFN-alpha-2β

**The relevance of research**. Approaches to the therapy of COVID-19 change over time, evidence and display of these changes in Russia are 1-10 versions of the Temporary guidelines for the diagnosis and treatment of COVID-19 of the Ministry of Health of Russia. The effectiveness of recombinant interferons in the treatment of COVID-19 has been discussed since the beginning of the epidemic in China. Recombinant interferon - alpha has established itself in the treatment and prevention of acute respiratory viral infections and influenza, further research on the effectiveness of these drugs in COVID-19 seems promising.

**Purpose**. Evaluation of the results of treatment of a new coronavirus infection COVID-19 using recombinant interferon as part of complex therapy.

**Patients and methods**. A prospective comparative controlled study included 140 patients with COVID-19, randomized into 2 groups: the main (MG) - 70 patients who received standard therapy for coronavirus infection in combination with IFN-alpha-2β (rectal suppositories 3,000,000 IU, 1 suppository three times per day and gel 36,000 IU/g 5 times a day on the surface of the mucous membrane of the nasal passages and palatine tonsils for 14 days), and the comparison group (GC) - 70 patients who received only standard therapy. There were 32 (45.7%) men in the MG, the average age was 52.31 ± 1.203 years; in the HS - 38 (54.3%) men ($\chi 2 = 1.029$; $p = 0.311$), average age - 49.49 ± 1.214 years ($t = 1.65$; $p = 0.101$).

**Results**. The severity of manifestations of intoxication and bronchopulmonary syndromes in patients in the comparison groups (CG) did not differ. In the main group (MG), dyspnea was recorded 17.1% more often ($p = 0.029$), taste disturbances were found 15.7% more often in the CG ($p = 0.029$). The average value of $SpO_2$ in the exhaust gas was 94.7 ± 0.53%, in the CG - 94.9 ± 0.39% ($t = -0.188$; $p = 0.851$). Oxygen therapy was carried out in 18 (25.7%) patients in the MG and 15 (21.4%) in the MG ($\chi^2 = 0.357$; $p = 0.551$).

In patients with MG, the reverse development of symptoms of intoxication was 2–8 days faster: headache and myalgia stopped by the 3rd day from the start of treatment (in CG - by the 4th and 5th days ($p < 0.001$), weakness - by 5th day (in CG - by the 11th day ($p < 0.001$). Cough in patients of the main group disappeared by the 5th day from the start of treatment, in the comparison group - on the 10th day of standard therapy ($p < 0.001$) Manifestations of rhinitis (runny nose, nasal congestion) were recorded in MG within 3 days, in CG - within 5–8 days ($p < 0.001$). CG - by the 10-11th day ($p < 0.001$). Shortness of breath in the MG stopped by the 3rd, in the HS - by the 5th day from the start of therapy ($p < 0.001$).

The body temperature in MG patients returned to normal (36, 9 ± 0.04°C) by the 7th day from the start of treatment, in the CG (36.05 ± 0.74) - by the 8th day (t = 1.15; $p$ = 0.253).

Elimination of the pathogen in patients with MG occurred 1-6 days faster (*Me* 9; $Q_{25}$ 1 / $Q_{75}$ 13) than in CG (*Me* 10; $Q_{25}$ 1 / $Q_{75}$ 17) (Mann – Whitney test, $p$ <0.001).

By the 15th day of observation, positive dynamics of changes in the lung tissue (according to the results of CT) was noted in 72.8% of patients with MG and 64.7% in the CG ($p$ = 0.302). The number of patients with widespread processes in the lung tissue (51–75%) by the end of the course of treatment in the MG 1.4%, in the CG - 13.3% ($p$ = 0.019).

There were no adverse events associated with the intake of interferon alpha-2β or other drugs included in the treatment regimen for patients in the main group and the comparison group.

**Conclusion.** The data obtained show the high efficiency of therapy regimens with the inclusion of the interferon alpha-2β drug and the safety of its use in combination with symptomatic agents, antibiotics, anticoagulants, which makes it possible to recommend the study drug for inclusion in standard treatment regimens for patients with new coronavirus infection COVID-19.

# CLINICAL AND EPIDEMIOLOGICAL CHARACTERISTICS OF SEVERE COVID-19

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**Abstract.** COVID-19 is a respiratory tract infection caused by the SARS-CoV-2 virus. An analysis of 172 case histories of patients with severe and critical form of COVID-19 was carried out. It was found that severe and critical forms of COVID-19 more often (79.8%) develop in non-working people over 60 years old. The presence of combined comorbid pathology (arterial hypertension, diabetes mellitus, cardiovascular pathology, etc.) increases the risk of developing severe forms of COVID-19 by 2.9 times. Severe forms can occur with normal or low-grade fever (19.4%), the total duration of fever in coronavirus infection can reach 15 days. A positive PCR test was detected in 76.9% of patients. The duration of positive PCR tests was 5 days - in 17.5%, from 6 to 10 days in 4.9%, from 11 to 15 days in 26.3% and from 15 to 22 days - in 15.2% of patients. The most frequent complications of severe and critical forms of COVID-19 were acute renal failure (55.8%), SPON (53.5%), ARDS (53%), acute renal injury (12%).

**Key words**: COVID-19, SARS-CoV-2, severe form, risk factors, clinic, complications

**Introduction**. COVID-19 is a respiratory tract infection caused by the SARS-CoV-2 virus, which has caused the development of the novel coronavirus infection (NKVI) pandemic worldwide. At present, SARS-CoV-2 is the main respiratory pathogen that has "displaced" the seasonal pathogens of acute human respiratory infections of the influenza virus and other acute respiratory viral infections [1]. A new coronavirus infection is characterized by a lesion of the respiratory tract with the development of pneumonitis, respiratory failure, ARDS, thromboembolic complications and multiple organ failure syndrome in severe cases. People of all ages are susceptible to COVID-19 infection. 20% of COVID-19 cases are severe, and a quarter of patients require intensive care (ICU) [2].

At the moment, 142 million cases of COVID-19 have been registered in the world, of which ~ 3 million cases have been fatal. According to the Federal State Statistics Service, mortality in Russia in 2020 increased by 18%, or 323.8 thousand people, of which about half are those who died with COVID-19, and the rest are excess mortality. Thus, the mortality rate in Russia against the background of the pandemic has become a record for ten years [5].

**Purpose**. The aim of the study is to study the clinical and epidemiological features of severe forms of COVID-19.

Materials and Methods: a retrospective observational study was conducted, a case-control study design was carried out, 172 case histories of patients with severe COVID-19 were analyzed. The control group consisted of 62 case histories of patients with a moderate form of the disease. All patients received inpatient treatment at the Republican Clinical Infectious Diseases Hospital. Statistical processing of the research results was carried out using the programs "Excel" and "Statistica-6".

Results. Men accounted for 43%, women - 57% of the total number of patients with severe and critical form of Covid-19 ($p > 0.05$) (OR 1.15; 95% CI 0.32-1.28). Thus, there were no significant gender differences among patients with severe COVID-19, although according to other researchers, male gender is a risk factor for the development of severe forms of NKVI [2,3]. 79.8% of patients with severe Covid-19 were ≥60 years of age.

The majority (87.7%) of patients with severe forms of NKVI, the sources of infection were unknown. Intrafamily contacts were present in 12.3% of patients. 92% of patients with a severe form were non-working, among them pensioners predominated. Among working patients (8%), doctors (1.8%), drivers (1.3%), watchmen (1.4%), teachers (1.8%), managers (1.3%) dominated, i.e. representatives of professions with a large number of social contacts.

Patients were admitted to the hospital: on days 1-4 of the disease - 12.5% of severe and 11.3% of moderately severe, on days 5-9 - 50% of severe and 41.9% of moderate, on days 10-15 - 34.7% heavy and 40.3% moderate, more than 15 days - 2.8% severe and 6.5% moderate (Fig. 1).

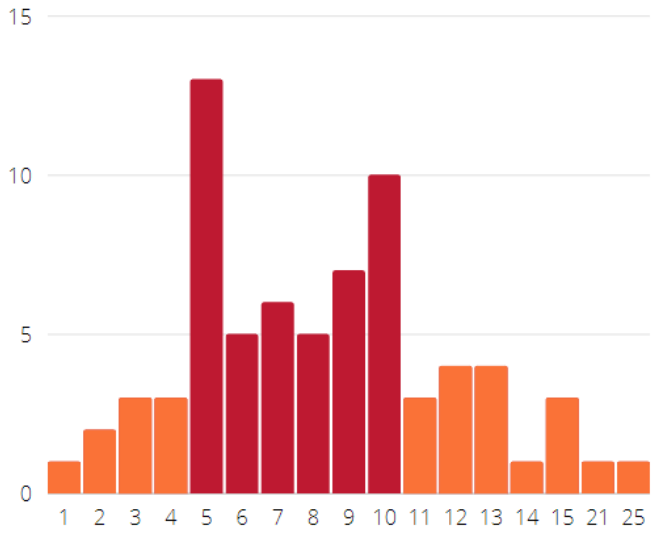


Fig. 1. The timing of admission of patients with severe forms of COVID-19 to the hospital (days of illness).

There were no significant differences between the timing of admission of patients with severe and moderate forms of COVID-19. 50% of severe and 41.9% of moderately severe patients were admitted to the hospital from 5 to 10 days of illness, which was associated with a worsening of the condition, persistence or repeated rise in temperature, and the appearance of shortness of breath. 48% of patients received antiviral therapy (AVT) at the prehospital stage, of which 37% took a combination of umifenovir + interferon alfa. 50% of patients with a severe form received antibiotics at the prehospital stage, mainly azithromycin.

Comorbid pathology was present in 91.7% of severe and 77.4% of moderately severe patients ($p < 0.05$). Most often, patients in both groups suffered from obesity (50% severe and 54.2% moderate, $p > 0.05$), diabetes mellitus (45.5% and 37.5% $p > 0.05$), arterial hypertension (80.3 % and 64.6%, $p > 0.05$), postinfarction cardiosclerosis (6% and 4.2%, $p > 0.05$), oncological diseases (1.5% and 6.2%, $p > 0.05$ ). Combined comorbid pathology was significantly more frequent in severe (72.7%) than in moderately severe patients (47.9%) ($p < 0.05$) (95% CI 1.5 - 10.2). Combined comorbid pathology in patients with COVID-19 increased the risk of developing severe forms by 2.9 times (OR = 2.899; 95% CI 1.3 - 6.3).

Each patient underwent 5 studies of oropharyngeal and nasal swabs for SARS-CoV-2 PCR. The test was positive in 76.9%, negative in 23.1%. Patients with a negative test had a typical clinical picture of COVID-19 and typical changes in the lung CT scan, which allowed these patients to be diagnosed with “unconfirmed coronavirus infection”. The results of our studies confirm the low sensitivity of PCR in the diagnosis of coronavirus infection and the high frequency of false-negative analyzes. From our point of view, all patients with

“unconfirmed coronavirus infection” should have serological tests were performed for the detection of IgM, IgG antibodies to SARS-CoV-2, as well as detection of other respiratory viruses and influenza, since the CT picture of viral pneumonia can be. similar. The duration of positive PCR tests in critically ill patients with COVID-19 was: 5 days - in 17.5%, from 6 to 10 days in 4.9%, from 11 to 15 days in 15 (26.3%) and from 15 to 22 days - in 15.2% of patients.

Most often, upon admission to the hospital, patients with severe forms complained of fever (91.7%), weakness (91.7%), difficulty breathing (83.3%), cough - dry or with scanty sputum (70.8%). ), chest pain (16.7%), anosmia (8.3%) and diarrhea (5.6%). Fever in severe patients was absent in 4.2%, subfebrile - in 15.2%, febrile - in 52.8%, pyretic - in 27.8% of cases. The duration of the fever was: 1-7 days in 51.7%, 8-15 days in 48.3%, more than 15 days in 1.4% of cases. Thus, in severe patients, the temperature can be normal or subfebrile in 19.4% of cases. It is also worth noting that the duration of fever in CVI often exceeds its duration in the uncomplicated course of influenza and ARVI, which is significant for the differential diagnosis of these diseases.

On admission in severe patients, pneumonia with a lesion volume of CT-1 was diagnosed in 8.3%, CT-2 in 23.6%, CT-3 in 43.1% and CT-4 in 25% of patients. Desaturation in 20.8% of severe patients developed on the 4-5th day of illness, from 5 to 10 days - in 41.7%, from 11 to 15 days - in 30.6% and 15-20 days - in 6.9% patients. The restoration of saturation against the background of oxygen support, pathogenetic and syndromic therapy in 43% of patients with severe CVI occurred within 25 days, in 37% of patients desaturation lasted more than 25 days.

The most frequent complications of severe forms of coronavirus infection were: acute respiratory failure (100%), acute cardiovascular failure (55.8%), multiple organ failure syndrome (53.5%), acute respiratory distress syndrome (53%), acute renal injury (12%), hypoxic encephalopathy (9.7%), pulmonary edema (8.8%), hydrothorax (8.8%), hematoma (4.7%), edema-swelling of the brain (4.7 %), acute cerebrovascular accident (1.4%), etc. 59.8% of patients developed several complications. The most frequent laboratory abnormalities observed in patients with severe forms were: neutrophilia without left shift, lymphopenia, increased CRP, increased D-dimers, ferritin, fibrinogen, lactate dehydrogenase, ALT and AST.

**Conclusions**:

1) Severe and critical forms of Covid 19 are more likely to develop in non-working people over 60 years of age. Combined comorbid pathology (arterial hypertension, diabetes mellitus, cardiovascular pathology, etc.) increases the risk of developing severe forms of Covid-19 by 2.9 times.

2) 48% of patients received antiviral drugs at the outpatient stage, 50% of patients with Covid 19 receive antibiotics unreasonably at the pre-hospital stage The timing of hospitalization and desaturation of Covid 19 patients basically corresponds to the timing of the development of a cytokine storm (from 5 to 15 days). Restoration of saturation against the background of pathogenetic and syndromic therapy in 43% of patients with severe CVI occurs within 25 days, in 37% of patients desaturation lasts more than 25 days.

3) The most frequent complications of severe and critical forms of COVID-19 are acute renal failure (55.8%), SPON (53.5%), ARDS (53%), acute renal injury (12%)

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# FIBROTIC PROCESS IN LUNGS OF PATIENTS WITH NEW CORONAVIRAL INFECTION COVID-19 AND APPLICATION OF BOVHIALURONIDASE AZOXYMER FOR ITS PREVENTION AND TREATMENT

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**Abstract**. The new coronavirus infection COVID-19 can lead to the development of pulmonary fibrosis, which, in turn, can affect the duration and quality of life of patients. The article provides data on the pathogenesis and morphological changes that occur in the lungs during the infectious process caused by SARS-CoV-2, necessitating the use of antifibrotic treatment. The possibility of using azoximer bovhyaluronidase, a Russian-made drug, which is a conjugate of the proteolytic enzyme hyaluronidase, as a drug for these purposes, is substantiated; treatment regimens recommended for patients with COVID-19 during the period of convalescence are given.

**Key words**: coronavirus infection, pulmonary fibrosis, antifibrotic therapy, antifibrotic treatment, bovhyaluronidase azoxymer.

The infection caused by a previously unknown coronavirus, dubbed SARS-CoV-2, first registered in the People's Republic of China, and then leading to the development of a pandemic of a disease called COVID-19, posed many new challenges for specialists, one of which is preventing or minimizing adverse the consequences of the transferred infectious process. One of the possible consequences is pulmonary fibrosis [1, 2, 3, 4].

Fibrosis is a pathological condition characterized by abnormal fibroblast proliferation and increased deposition of extracellular matrix components [5]. Accordingly, pneumofibrosis is a fibrotic lesion of the lung tissue, which is one of the targets for a new coronavirus infection [6]. It is the lung damage with COVID-19 that most often determines the severity of the course of the disease, becomes the cause of the death of patients [7]. This is due to a number of reasons, primarily the aerogenic mechanism of transmission of coronavirus infection, in which the upper respiratory tract is the main entrance gate of the infection and the breeding ground for the virus. Rapid replication of the pathogen can cause massive death of epithelial and endothelial cells and increased vascular permeability, leading to the production of a large number of proinflammatory cytokines and chemokines [8].

In the acute period of the disease, interstitial pneumonia often develops in the lungs after the SARS-CoV-2 viruses get there, in severe cases with the formation of acute respiratory distress syndrome (ARDS), systemic inflammatory response, “cytokine storm”. A systemic inflammatory response caused by a viral infection, tissue damage and realized, among other things, in the form of a “cytokine storm” can also have adverse outcomes and complications in the delayed and long-term period [6, 9].

The inflammatory response that occurs in the lungs after exposure to a pathogen is largely mediated by macrophages and granulocytes. The synthesis of pro-inflammatory cytokines increases, incl. IL-1, TNF, which are potent inducers of hyaluronic acid-2 synthetase in the CD31+ endothelium, adhesion molecules in the alveoli, are recruited and divided by fibroblasts [10]. The accumulation of fibrin in the vessels of the lungs is facilitated by a decrease in the content of fibrinolysis activators in the pulmonary endothelium. Fibrin can escape into the interstitium and lead to the formation of sclerosing alveolitis. The release

of fibrin into the lumen of the alveoli is favored by the increasing defeat of pneumocytes. Fibrin extravasates in the alveoli cause the formation of hyaline membranes [11].

Immunocompetent cells, primarily CD4+ T-lymphocytes, are involved in the regulation of the fibrotic process. They are capable of producing cytokines, chemokines and growth factors that can stimulate fibroblast proliferation and differentiation, as well as their production of collagen. Currently, certain subpopulations of CD4+ T-lymphocytes are considered as regulators of fibrosis, in particular: Th1, Th2, Th17 and Th22. The key role, perhaps, belongs to Th1 and Th2 - cells. Th1 cells and associated cytokines (IFNγ) contribute to the formation of a chronic inflammatory process and fibroblast proliferation. Th2 also play an important role in the formation of fibrous tissue, each of the Th2-produced cytokines (IL-4, IL-13 and IL-5) plays a role in the regulation of tissue remodeling: receptors for IL-4 and IL-13 are found on tissue subpopulations fibroblasts. Extracellular matrix protein synthesis and myofibroblast differentiation are induced by stimulation of IL-4 or IL-13. These interleukins, by suppressing the pro-inflammatory activity of macrophages, can counteract the inflammation associated with COVID-19, depending on the phase of infection. Despite the fact that IL-4 and IL-13 are not directly involved in the process of inflammation in the lungs in patients with COVID-19, they can indirectly modulate the cytokine storm and the development of fibrosis as mediators that regulate Th1 and Th17 immune responses [12, 13 ]. In the serum of severe patients with COVID-19, significantly increased levels of Th1 and Th2 cytokines are noted. Th2-type cytokines such as IL-4, IL-6 and IL-13 stimulate B lymphocytes to produce Ig and also stimulate collagen synthesis by fibroblasts. The risk of pulmonary fibrosis is higher in patients with severe COVID-19 [13, 14].

Pathomorphological features of the inflammatory process in COVID-19 include: priority of endothelial damage with micro- and macrothrombus formation; relatively late development of the exudative phase of inflammation; tendency to develop pulmonary fibrosis [15]. Damage to the vascular bed of the lungs (microangiopathy, thrombosis, in some cases - destructive-productive vasculitis) occurs in stages: first, there is an exudative phase of diffuse alveolar damage - alveolar-hemorrhagic syndrome (viral interstitial pneumonia with vascular and hemorrhagic component of ARDS, which is a sub ), then - the proliferative phase of diffuse alveolar damage, early stage. It usually develops after 7-8 days or more from the onset of the disease (with COVID-19, it is often significantly delayed). Characterized by the accumulation of fibrin in the lumen of the alveoli with polypoid growths of connective tissue. Typical are the confluent fields of obliterating bronchiolitis and organizing pneumonia or areas of loose fibrosis with slit-like structures lined with metaplastic squamous epithelium. The proliferative phase of diffuse alveolar damage, a late stage, is characterized by the fact that organizing pneumonia and changes characteristic of fibrosing alveolitis (macroscopically - with the formation of a “cellular lung”) develop mainly in the lower lobes of the lungs. Late changes in the form of pathological regeneration with metaplasia of the epithelium, collapse and sclerosis of lung tissue, vascular walls, their recanalization after thrombosis, neoangiogenesis and persistent vasculitis can be called pulmonary cirrhosis [16].

In addition to the processes provoked by the pathogen, the triggers of long-term complications can be ongoing therapeutic measures leading to damage to lung tissue (long-term use of mechanical respiratory support using oxygen or an oxygen-air mixture can cause negative effects and provoke the development of pulmonary fibrosis) [17].

As for the incidence of fibrosis in coronavirus infection, it is possible to draw analogies with previous outbreaks caused by other variants of coronaviruses: in the long-term period of SARS-CoV, 27-45% of patients who underwent infection developed fibrosis from the respiratory and cardiovascular systems [18].

After suffering SARS-CoV-2 infection, almost half of the survivors after COVID-19, after 3 months of observation, have residual effects in the lungs [19]. According to a study in

China, where a meta-analysis of data on 50,466 patients hospitalized for COVID-19 was carried out, 14.8% of patients developed ARDS, 20% of those who underwent it developed pulmonary fibrosis, and 3 and 6 months after infection it was found in 36% and 30% of patients, respectively [20].

The prognosis for pulmonary fibrosis is generally very serious. For example, about 40% of patients with idiopathic pulmonary fibrosis end up dying from respiratory failure, with a low 5-year survival rate of 20%. Chronic persistent pulmonary fibrosis allows a patient with such a diagnosis to survive for no more than three to five years [21].

Around the world, the number of people who have recovered from COVID-19 is steadily increasing. The available data on the pathogenesis, clinical course, complications and outcomes give reason to expect in the near future an increase in the number of patients with delayed lesions of various organs and systems, and, first of all, respiratory, which requires the development of effective treatment regimens and prevention of fibrotic changes [9, 22, 23].

Who should prevent the development and progression of pulmonary fibrosis after a previous COVID infection? These are patients with reduced exercise tolerance, regardless of CT results, patients with risk factors for the development of pulmonary fibrosis [10]. Risk factors for the development of extensive pulmonary fibrosis after COVID-19 are: a large area of lung damage, the use of mechanical ventilation, ARDS, a history of fibrosis [1, 24]. Additional risks of developing pneumofibrosis at all times, “dock-like” and “COVID”, are: smoking, external inhalation exposure (inhalation of organic and inorganic dust), gastroesophageal reflux, type II diabetes mellitus, genetic factors (familial fibrosis) [1, 21].

Considering all of the above, it is advisable to carry out pathogenetic treatment aimed at suppressing the development of the fibrotic process in the lungs in patients with COVID-19 [9, 22, 23]. One of the drugs that can be used for this purpose is bovhyaluronidase azoxymer (Longidase®), which has anti-fibrotic activity (belongs to the pharmaco-therapeutic group “enzyme drugs”), registered on the Russian market. It is a conjugate of the proteolytic enzyme hyaluronidase with a high molecular weight carrier from the group of poly-1,4-ethylenepiperazine N-oxide. Bovhyaluronidase azoxymer has hyaluronidase activity. Its substrate is mucopolysaccharides - glycosaminoglycans, which form the basis of the extracellular matrix of connective tissue. Due to its enzymatic activity, hyaluronidase is able to break down glycosaminoglycans (which include hyaluronic acid, chondroitin, chondroitin-4-sulfate, chondroitin-6-sulfate), which are essentially a “cementing” substance of connective tissue. As a result of depolymerization (hydrolysis) under the action of hyaluronidase, glycosaminoglycans lose their viscosity, the ability to bind water, metal ions. As a result, edema decreases, tissue trophism improves, scar tissue decreases in volume, becomes more elastic, and the formation of new collagen fibers in the focus of chronic inflammation becomes more difficult. The efficiency of bovhyaluronidase azoxymer is much higher than that of native hyaluronidase, because conjugation increases the resistance of the enzyme to temperature and inhibitors, increases its activity and prolongs its action [25].

Previous studies have shown that the introduction of azoxymer bovhyaluronidase led to the destruction of hyaluronic acid. This explains the anti-fibrotic property, which manifests itself not only in the weakening of the progression of fibrosis at an early start of treatment, but also in the regression of the formed granulomatous nodules. Bovgialuronidase azoxymer is effective both at the stage of prevention and treatment of early development of the pneumofibrotic process, and at the stage of formed fibrosis in the lung tissue. Clinical data have confirmed experimental studies that revealed a decrease in clinical and instrumental markers of pneumofibrosis, which made it possible to improve the quality of life of patients [26].

In Russia, this drug is produced under the trade name Longidaza® in two forms: a lyophilisate for the preparation of a solution for injection and vaginal and rectal suppositories.

Indications for its use in pulmonology according to the instructions: treatment of pneumosclerosis, fibrosing alveolitis, tuberculosis (cavernous-fibrous, infiltrative, tuberculoma). To achieve the effect, taking bovhyaluronidase azoxymer should be carried out in a long course: 1 injection every 3-5 days for 2-3 months [25].

Lyophilisate for the preparation of a solution for injections of 3000 IU is applied according to the scheme: intramuscularly once every 5 days with a course of 15 injections (2.5 months). It should start from 21 days after the diagnosis of COVID-19 by PCR, preferably no later than 2 months later. Longidaza® rectal suppositories of 3000 IU are used according to the scheme: 1 suppository every 2-4 days with a course of 10-20 injections, from 20 days to 2 months. With a fibrotic process in the lungs in patients with COVID-19, it is possible to carry out STEP therapy: Longidaza® lyophilisate for the preparation of a solution for injection of 3000 IU, intramuscularly once every 5 days with a course of 15 injections, then, if necessary, long-term maintenance therapy, - 1 suppository 1 time in 5-7 days for 3-4 months [27].

**Conclusion.** Thus, the fibrotic process that occurs in the lungs of patients with COVID-19 is the basis for the inclusion of drugs with antifibrotic activity in the complex of rehabilitation measures for convalescents of this disease. Their appointment is pathogenetically justified and expedient.

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# DYNAMICS OF ANTIBODY LEVEL TO SARS-CoV-2 INFECTION IN 10 MONTHS AFTER ILLNESS

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**Abstract**. The new SARS-CoV-2 posed a global challenge to medicine and, in particular, laboratory diagnostics. Antibody detection methods are simpler and more accessible than molecular methods. Although antibody responses to COVID-19 of varying severity within 5 months already well characterized, the question of the durability of antibody responses to the virus remains unanswered. Our task was to assess the dynamics of the emergence of specific IgG antibodies to SARS-COV-2 in 10 months after recovery, and to find out if there is a difference in the level of antibodies among the medical staff and residents of Vladimir.

**Key words**: new coronavirus infection, specific IgG antibodies, SARS-CoV-2.

Severe acute respiratory syndrome COVID-19 caused by the novel SARS-CoV-2 coronavirus has sparked a global pandemic with millions of infected and more than 1 million deaths. The new SARS-CoV-2 posed a global challenge to medicine and, in particular, laboratory diagnostics. Methods based on the polymerase chain reaction are very sensitive and specific, but depend on the quality of the material taken and the presence of mutations. If the virus is in the lungs, it may not be detected on nasopharyngeal swabs [2]. On the other hand, methods for determining antibodies, which are simpler and more accessible than molecular methods, are not applicable in the early stages of the disease, since the formation of an immune response takes at least a couple of weeks. Although antibody responses to COVID-19 of varying severity over 5 months have been well characterized [6], the question of the reliability, functionality and durability of antibody responses to the virus remains unanswered. In the clinical diagnostic laboratory of the Regional Clinical Hospital in the city of Vladimir (OKB Vladimir), we conducted a dynamic observation of the level of antibodies to COVID-19 during 10 months.

The aim of this work is to determine the dynamics of the appearance of specific IgG antibodies to SARS-COV-2 in patients and to assess the level of antibodies after 10 months.

Materials and methods. We used 30 samples of sera of the employees of the COVID hospital of the OKB Vladimir and 29 residents of the city of Vladimir who had recovered from a new coronavirus infection. The surveyed signed an informed consent to participate in research and the processing of personal data. The studies were conducted from June 2020 to March 2021. The patient's vaccination history was collected prior to enrollment.

According to the Interim Recommendations of the Ministry of Health of the Russian Federation, Version - 10 dated 02/08/2021 [4], when assessing the strength of immunity by enzyme immunoassay, it is advisable to determine antibodies to the receptor-binding domain (anti-RBD antibody). Therefore, we determined specific antibodies of the IgG class to SARS-COV-2 using highly effective sets of reagents SARS-COV-2-IgG-ELISA-BEST [5] (AO "Vector-Best", Novosibirsk region). The kit uses a recombinant full-length trimerized glycoprotein S (Spike) SARS-COV-2. When evaluating the results, the positivity coefficient (CP) was used, the sample was considered positive if the CP> 1.1; borderline 0.8-1.1; negative if CP <0.8. Dolgov V.V. and the authors in his book emphasize the differences in the errors of spectrophotometers when measuring the analyte at different intervals of optical

density. He recommends a working (linear) range of measured optical densities equal to 0.2 - 2.0 pu. [3]. In our work, a CP higher than 10 is unreliable; titration of the biomaterial was not performed [6].

Detection of SARS-CoV-2 RNA by PCR using MNA was performed on an automatic station for the isolation of nucleic acids KingFisher Flex 96 and amplifiers Real-time CFX96 using the diagnostic kits “RealBest RNA SARS-CoV-2” and “RealBest UniMag”. (AO “Vector-Best”, Novosibirsk region).

Computed tomography (CT) of the chest for COVID-19 was performed on a Philips Ingenuity computed tomography scanner 128 slices.

After 2-3 weeks from the onset of the disease and the clinical appearance of COVID-19, specific IgG antibodies to SARS-COV-2 were determined in the employees of the covid hospital and patients. All staff and patients were found to be positive. From the onset of the disease, the CP values ranged from 1.1 to 4.7 (mean CP 2.6). By PCR, the diagnosis was confirmed in 48 (80%), in 11 (20%) PCR was negative (analysis was performed at least 2 times). All subjects had mild to moderate clinical signs of COVID-19. According to the CT scan of the chest in patients, lung lesions were 15-36% in 16 (%) people out of 59. Two weeks after the first analysis, a repeated study of specific antibodies was carried out. The CP values have increased from 3.8 to 12.7, the average CP is 8.7. After another 2 weeks, the CP values continued to increase, reached 6.7-13.8, the average CP value was 12.1. Disease severity did not affect antibody levels. During the period of testing for antibodies, the subjects did not show new signs of COVID-19 and complications of the previous disease, there were no deaths.

3 months later (October, November 2021) since the beginning of the second wave of the epidemic of a new coronavirus infection and the reopening of the covid hospital, all subjects were tested for specific IgG antibodies to SARS-COV-2. It was found that all employees and patients gave a positive result, the CP values ranged from 7.7 to 12.6 (the average CP value was 9.9).

In February, March 2021, 10 months after the onset of the disease, blood was taken from all those who had been ill for testing for specific IgG antibodies to SARS-COV-2. In this study, we divided patients into two groups: medical staff (30 people) and residents of Vladimir (29 people) in order to assess the level of antibodies. According to experts, the causative agent of the virus is very widely present in enclosed spaces [1]. We assumed that medical personnel are constantly at risk, in contact with patients with a new coronavirus infection, and we were interested to see if there is a difference in antibody levels among medical personnel and residents of Vladimir. The medical staff had a CP from 6.8 to 12.8 (the average CP was 10.3), the residents of Vladimir city had a CP from 6.8 to 12.0 (the average CP was 10.3), there were no significant differences ($p < 0.001$ ).

We cannot provide conclusive evidence that these antibodies protect against reinfection; we consider it highly likely that they reduce the chances of reinfection and may weaken the disease in the event of reinfection. Given the half-life of immunoglobulin G of about 21 days, the persistent antibody levels seen here over 10 months are likely to be produced by long-lived plasma cells in the bone marrow. We believe that studying and establishing the period of action of antibody protection against SARS-CoV-2 infection, understanding the kinetics of antibodies to glycoprotein S (Spike) SARS-COV-2 will not shape the policy regarding the COVID-19 pandemic and the effectiveness of vaccination against COVID-19 .

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# FEATURES OF THE CLINICAL PICTURE OF COVID-19 INFECTION IN THE PERIOD OF DISEASE RESOLUTION

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**Abstract**. On February 11, 2020, the World Health Organization officially named the disease caused by the new coronavirus, Corona Virus Diseases (COVID-19). On March 11, 2020, WHO recognized the international emergency declared on January 30, 2020 as the COVID-2019 pandemic [1, 2]. The simultaneous disease of COVID-19 in many people leads to an increase in the number of hospitalizations and congestion of health systems. If sufficient collective immunity is developed among the population, the pandemic will end [2]. In this regard, the intensity and relevance of the study of COVID-2019 has increased dramatically.

**Key words**: clinic, COVID-2019

**Introduction**. On February 11, 2020, the World Health Organization officially named the disease caused by the new coronavirus, Corona Virus Diseases (COVID-19). On March 11, 2020, WHO recognized the international emergency declared on January 30, 2020 as the COVID-2019 pandemic [1, 2]. The simultaneous disease of COVID-19 in many people leads to an increase in the number of hospitalizations and congestion of health systems. If sufficient collective immunity is developed among the population, the pandemic will end [2]. In this regard, the intensity and relevance of the study of COVID-2019 has increased dramatically.

**Purpose**. to analyze the clinical picture of COVID-19 infection in the period of disease resolution.

**Materials and methods**. A retrospective analysis of 53 outpatient records of patients (44 women and 9 men) who went to a therapist after a COVID-19 infection was carried out by the continuous sampling method. The median age was 52+13 years. All patients had negative results of laboratory tests of biological material for the presence of SARS-CoV-2 RNA. Statistical data were processed using the Microsoft Excel 2010 version 11.0 program. The correlation analysis was carried out by the Spearman method using the Cheddock scale.

**The results of the study**. The analysis of outpatient records showed that in 48 (91%) of the treated patients, COVID-19 infection was complicated by bilateral pneumonia of varying severity. At the time of examination, the following changes were visualized in patients whose course of COVID-19 infection was complicated by bilateral pneumonia of varying severity according to X-ray studies (CT or lung X-ray): a decrease in the size of the areas of consolidation and "frosted glass" (pneumonia in the resorption phase) – 93% of patients; the formation of fibrous changes (pneumonia in the resorption phase) – 5%; pathological changes were not detected – 2% of patients.

Complaints were made by 87% of patients (Figure 1). The clinical picture was dominated by complaints of dry cough, which was registered in 47% of patients. Cough disturbed patients mainly in the morning. Difficulty breathing during physical activity was experienced by 26% of patients, it should be noted that previously these symptoms did not occur at all in patients or worsened against the background of the course of the disease. In 23% of cases, patients complained of “dissatisfaction with breathing”, which occurs independently of physical and psychoemotional stress, during daytime hours, short-term, and self-relieving.

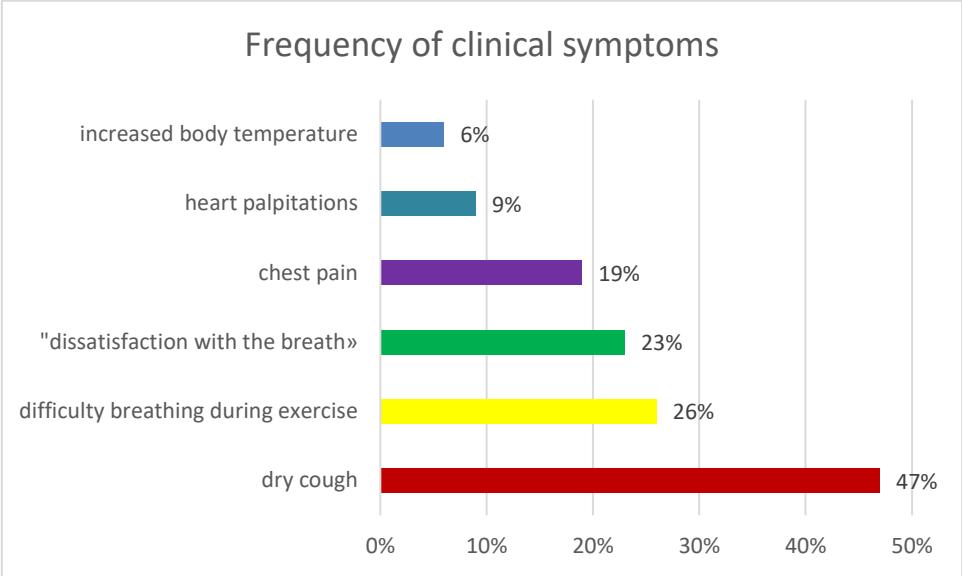


Figure 1. Frequency of clinical symptoms in patients with COVID-19 infection during the disease resolution period

19% of the analyzed patients had chest pain, more often in the sternum, not associated with physical exertion and emotional overstrain, without irradiation, often long-term, self-relieved. Complaints of palpitations were made by 9% of patients, attacks occurred at any time of the day, regardless of physical activity, and could be permanent. At the same time, before the disease, none of the patients experienced this symptom. Complaints of an increase in body temperature predominant in the second half of the day were registered in 6% of patients. The temperature increase was in the range of 37.2-38.0°C.

The analysis of clinical symptoms and data of radiological changes showed that even in patients with uncomplicated course of COVID-19 infection and the absence of pathological changes on radiographs, there were complaints indicating damage to the bronchopulmonary system. Correlation analysis of the clinical picture and radiological changes showed the presence of a significant weak correlation between the signs (rs-0.256, p=0.03).

**Conclusion**. The majority of patients after COVID-19 infection presented various complaints, most often related to the pathology of the bronchopulmonary system. At the same time, there was no correlation between the data of X-ray examinations and the clinic. All changes in the clinical picture can be considered as manifestations of post-ovoid syndrome, which requires medical rehabilitation of these patients.

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# INFLUENZA AND COVID-19 COINFECTION (REVIEW)

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**Abstract**. The article discusses the nature of the possible ecological interaction between the influenza virus and SARS-CoV-2 by the type of competition, and also substantiates the main reasons that determine the viruses success in the competition. The author made an assumption about what the season of viral infections will be in the current and next year.

**Key words**: ecology, influenza virus, SARS-CoV-2, COVID-19

The science of ecology studies interaction between living organisms. Organisms interact with each other in many different ways. The two major kinds of their interaction are symbiosis and antibiosis. Acute respiratory viral infection (ARVI), or flu, and COVID are of similar nature. Both of them are contagious respiratory diseases transmitted from person to person via infected respiratory droplets and infecting the airways and the lungs. It means that flu and COVID compete with each other. This type of cooperation is called antibiosis. The factors that determine the virus advanatages in the competition are the following.

1. *Reproduction rate.* With simultaneous infection, the virus that multiplies faster wins. Such a virus captures cells more efficiently, and its rival does not have enough resources to reproduce. As a result, the fast virus suppresses the slow virus multiplication [4, 5].

2. *The penetration order into the body*. If virus begins to multiply in cells first, it gains unimpeded access to all target cells [4].

3. *The number of viral particles that have entered the body.* The advantage is given to the virus that has entered the body in large quantities. A large number of virions capture cells faster.

4. *Cell penetration time.* If the influenza A virus enters the cell simultaneously with the respiratory syncytial virus, then it blocks its reproduction. And if the influenza virus enters the cell 12 hours after the respiratory syncytial virus has already appeared there, then the flu could no longer affect its growth [9].

Under certain conditions, different viruses can get along with each other. [6]. This can lead to the exchange of genetic material between viruses, resulting in chimeric viruses [7].

How SARS-CoV-2 interacts with its competitors is not yet known. But certain facts are known that help to understand this mechanism.

1. Both, the influenza virus and SARS-CoV-2 use different receptors to enter the cell, here they do not compete [2]. However, type II alveolar cells, which SARS-CoV-2 prefers, are the main site of influenza A virus replication [3].

2. Cases of co-infection of one person with SARS-CoV-2 and other viruses are less common than co-infection cases with other respiratory viruses. Either SARS-CoV-2 suppresses the multiplication of most other respiratory viruses, or vice versa, other viruses suppress the SARS-CoV-2 multiplication [4].

3. The main factor on which the virus victory in competition depends is the rate of its reproduction in the cell. SARS-CoV-2 growth rate is slower than that of other respiratory viruses [1]. It means that the influenza virus and many other pathogens must defeat it. SARS-CoV-2 has a chance of co-infection only if it enters the cell 5 days before the flu virus. And he can defeat a competitor only if another virus invades the body 10 days after infection with SARS-CoV-2.

4. In a human in whose body both viruses settle, the risk of dying increases 6 times, and 2 times - in comparison with those who contracted only COVID-19 [10].

5. Influenza viruses and ARVI viruses are the most common ones and have been with us for ages, so the human immune system is able to protect itself against them. While the coronavirus is a relatively "young" infection, immunity from which has appeared only recently in vaccinated and recovered coronavirus patients. Therefore, the coronavirus has an advantage.

6. In the 2020-2021 season, according to the US Centers for Disease Control and Prevention (CDC), the incidence of influenza in the United States fell to 0.9%, which is significantly below the baseline of 2.6%. There were no such indicators for 10 years.

It is difficult to judge what the cold season will be this year. It is believed that the season of colds will shift by several months. Perhaps some of the flu strains will disappear [8]. But the disappearance of some viral strains may open the way for new, more severe pathogens. Also, during the lockdowns, mankind has lost its antiviral immunity, it is likely that the coming season of colds will be worse than the previous ones.

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# CONSISTENT RESPONSE OF THE IMMUNE SYSTEM TO MOLECULAR REBUILDING OF THE ANTIGEN

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**Abstract.** The dynamics of the immune system has been studied using the principles of synergetics. The concentration of the antibody was chosen as the order parameter of the system. A new mechanism of antibody-antigen interaction is proposed and conditions for dynamic instability of the stationary state of the immune system are found. By applying the method of synergetic modeling to study nanoscale processes, a criterion for bifurcations of the stationary state of the immune system was found depending on the size and dimension of the antigen. Based on this criterion, a description of some of the features of the COVID-19 virus has been carried out. It has been shown that an increase in the size of the virus leads to an increase in the relaxation time of its biologically active configuration.

**Key words**: antigen, structure, synergetics, self-organization, relaxation.

**Introduction**. Synergetics offers a new concept for the study of biological systems, which are distinguished by a unique ability to self-organization [1]. In recent years, a new method has been developed for modeling electron-ion processes of self-organization in polymer nanosystems [2]. In this work, the dynamics of the immune system of living systems is investigated using a method called synergistic modeling. The results are used to describe some of the properties of COVID-19.

**Research results**. Let us consider the dynamics of the process of antibody production by the body's immune system and its interaction with the antigen, by representing its elementary stages by the following equations:

1. External environment ≥ Y;
2. A ≥ X`;
3. X`+Y ≥ X+Y;
4. Y ≥ External environment.

The first equation describes the process of penetration of the virus - Y into the human body. The second is production, the universal form of the antibody - X`. The third selective form of the antibody is X. The last equation characterizes the metabolic stage of the antigen. The interaction of the antigen with the universal form of the antibody leads to the formation of a biologically inactive complex - XY, which, in the process of dissociation, leads to the formation of a selective form of the antibody. These stages of the immune response are described by the following interconversion scheme:

$$X`+Y \geq XY;$$
$$XY \geq X+Y.$$

Assuming that the complex decays much faster than its formation, this scheme of interconversions is described above by one equation (3). This scheme characterizes the dynamics of the response of the immune system, which is integrally described by the scheme bone marrow ≥ antibody.

We choose - X 'as the order parameter, and write the rate equation for the order parameter in the following form:

$$\frac{dx`}{dt} = k_2 A - k_3 x`y \quad (1)$$

where $k_i$ - are the rate constants of the i-reaction, A is the productivity of the bone marrow. The concentrations of antigen - y and universal antibody - x` are related by the ratio:

$$y+x`=N - const.$$

The stationary state of the dynamic system "antigen + antibody" is determined from the condition:

$$\frac{dx`}{dt} = k_2A - k_3x`y = 0.$$

Analysis of this kinetic potential by the methods of "catastrophe theory" [3] leads to an elementary catastrophe of the "end" type - E, described by the following expression for the stationary antigen concentration $y_s$:

$$y_s^2 + u = 0 \qquad (2)$$

where, the control parameter - u of the immune system depends on the values of the parameters of the kinetic model in the following form:

$$u = \frac{4Ak_2 - N^2k_3}{4k_3} \qquad (3)$$

In the space of the control parameter - u, the immune system has a bifurcation point at u = 0. When u < 0, the immune system has two steady states in terms of antigen concentration. For u > 0, there is no stationary state of the system. It will be more clearly and conveniently presented graphically (Fig. 1)

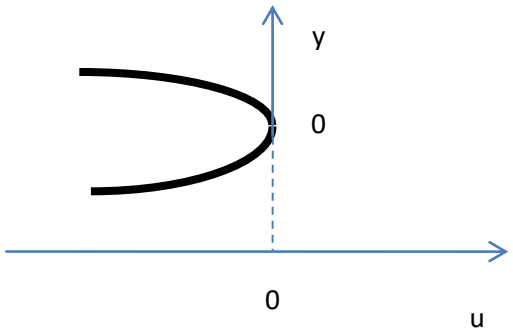


Figure 1. The Critical Diversity of an Elementary “end”-type Catastrophe

The steady state of the immune system is described by a parabolic dependence. The upper branch corresponds to a steady state. If the system is in this state, then with an increase in the control parameter - u, the value of the stationary antigen concentration decreases. At the same time, an increase in the relaxation time of fluctuations of antigen concentrations is observed (the first sign of approaching bifurcation is a critical slowdown) and an increase in the dispersion of the antigen concentration distribution (the second sign of approaching the bifurcation point is anomalous dispersion). As can be seen from equation (3), this occurs either with an increase in the value of bone marrow productivity - A, or with a decrease in the concentration of antigen - *y*, which is consistent with the data of clinical studies. Of particular interest is the comparison of the results of synergistic modeling of the immune system with the data on COVID-19. It has now become known that of the two strains of the virus, the British strain, which is characterized by a lower molecular weight, is the most biologically active. Within the framework of our model, this is explained by an increase in the reactivity of a local group of atoms of macromolecules with a decrease in its size. Microscopic analysis of the stability of atomic rearrangements of the LHA macromolecule based on vibronic representations shows that in low-dimensional systems, the vibronic labilization of the adiabatic potential along the reaction coordinate of the LHA macromolecule leads to a significant change in the reaction rate constant along the reaction coordinate for the order

parameter [2]. According to this model, this manifests itself in the processes of increasing the rate constants of the reactions $k_2$ and $k_3$.

**Conclusion**. Synergetic modeling makes it possible to determine the order parameter of a nonlinear dynamic system by analyzing the stability of a local group of atoms of a macromolecule and constructing its kinetic potential. This modeling method provides semi-empirical schemes for the analysis of self-organization processes in complex systems.

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# COVID-ASSOCIATED PANIC DISORDERS IN PATIENTS WITH A CORONOVIRAL PROFILE

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**Abstract.** This article discusses the panic attacks and panic disorders observed in patients with coronavirus profile. These mental disorders were identified clinically, through questionnaires and psychological tests. A relationship was found between the age of patients with COVID-19 and the presence of panic attacks, and a greater prevalence of panic affectivity among women was revealed.

**Key words**: panic attacks, panic disorder, coronavirus infection, derealization, depersonalization.

**Purpose of the study** is to identify the presence of a panic profile in patients with coronavirus infection in the provisional departments of the Mental Health Center of the Healthcare Department of Almaty.

**Relevance of the research.** The most common phenomena in psychiatric practice are panic disorder and panic attacks. Panic disorder significantly affects a person's quality of life, can lead to depression, disability. By order of the Almaty City Health Department, our Mental Health Center has been receiving coronavirus patients for more than a month. Patients with COVID-19 in the provisional part of our institution received drug therapy in accordance with the Clinical Protocols of the Ministry of Health of the Republic of Kazakhstan. The main symptoms of coronavirus infection, depending on the severity of the condition, were limited to the following range: weakness, lethargy, cough, shortness of breath, loss of appetite, smell, gastrointestinal disorders. In some patients, along with the underlying disease, there were complaints of panic conditions, namely, sudden attacks of panic, anxiety lasting an average of 20-30 minutes, with palpitations, “interruptions” in the heart, nausea and discomfort in stomach, various kinds of fears. These comorbid conditions prompted the idea of conducting a diagnostic and psychological examination of patients with the above complaints for the presence of panic disorders. As psychologist Mikhail Kors said: “A panic attack is not only the result of the coronavirus. The point is in the mechanism of its occurrence. For a reason unknown to science, sometimes there is a state of feeling of being driven out within the framework of some circumstances”.

First, you need to clarify what panic attack and panic disorder in general are. A panic attack is a sudden, short-term episode of severe anxiety that peaks within a few seconds, accompanied by severe anxiety, fear of loss of control or fear of death, as well as four or more somatovegetative symptoms (palpitations, shortness of breath, choking, sweating, tremors, paresthesias, pain or discomfort in the chest or abdomen, fainting, chills, fever). Sometimes panic attacks can be combined with derealization, depersonalization, fear of “losing control of yourself”, fear of “going crazy”. Panic attack is characterized by the so-called “vicious circle”, which is characterized by vegetative symptoms, fright, sympathicotonia, increased vegetative symptoms, increased fear, vegetative symptoms.

Panic disorder, or episodic paroxysmal anxiety according to ICD-10 (F41.0), in turn, is an independent nosology, which is characterized by repeated panic attacks that are not limited to a specific situation or circumstances and therefore are unpredictable. Also, ICD-10 writes that there may be several attacks within a month. The DSM-V classification (2013) gives the

following characteristic of panic disorder: “At least one attack per month, if it causes significant anxiety about repeated attacks and / or significant maladaptive changes in behavior”. Although we know from practice that the incidence of panic attacks varies from several times a day to a couple of cases per year. However, panic attacks are not pathognomonic only for panic disorder. They can occur in conjunction with other anxiety disorders, together with mood disorders, psychotic disorders, and substance use disorders. According to foreign guidelines (DSM-V), panic disorder can be diagnosed if repeated unexpected panic attacks occur, followed by one or more months of constant concern that the attacks might happen again and the formation of avoidant behavior.

Panic attacks can arise from direct effects of substance use (such as marijuana) or general health conditions (such as hyperthyroidism), but they cannot occur solely for these reasons. Also, panic disorder is not diagnosed if the symptoms are associated with another disorder. For example, when anxiety is associated with a social phobia of public speaking. The hallmark of patients with panic disorder is the apparent physical distress of the patient, not cognitive. The etiology of panic disorder is not well understood, but there is a well-founded opinion about the multifactorial nature of this disease. Genetics plays an important role in its development. First-degree relatives have a 40% risk of developing the syndrome if someone in the family has already been diagnosed with panic disorder or other anxiety disorders, manic-depressive psychosis, or depression. In addition, patients with panic disorder are also at high risk of developing other mental health disorders. The neuroanatomical substrate of panic disorder is the amygdala-hippocampus-thalamus-prefrontal cortex axis, which is characterized by increased glucose uptake during arousal. There is also evidence of hypertrophy of the amygdala with persistent anxiety. Of the personality traits of a person, an important role is played by general negative affectivity, increased sensitivity to experiences, a tendency to negatively evaluate life experience. From social factors, the formation of panic disorder is influenced by: the experience of abuse, violence (both domestic and sexual) in childhood, early withdrawal or refusal of parents (especially mothers). Several studies show that adverse childhood conditions can lead to panic disorder in adulthood. New research suggests that neural circuits may play a more important role in panic disorder, when certain areas of the brain in people become overexcited, and this can make them prone to developing the disorder [1]. From a number of theories of the occurrence of this disorder, it should be noted that the first was benzodiazepine, however, since the work of Donald Klein in the early 60s, it is well known that sedatives of the benzodiazepine type have little effect on the frequency of panic attacks, while antidepressants are more effective in suppressing such attacks. which speaks in favor of the serotoninergic theory. She suggests that susceptible patients lack the appropriate neurochemical mechanisms that would normally inhibit serotonin, and that this elevated serotonin level causes changes in the autonomic nervous system's network fear pattern. The noradrenergic theory is supported by the observation that individuals with panic disorder had higher plasma levels of norepinephrine compared to controls without such dysfunctions [2]. The role of the hypothalamic-pituitary system in the regulation of fear is also being studied, but it is worth mentioning that, despite fear, panic is possibly accompanied by suppression of the activation of the hypothalamic-pituitary-adrenal glands (HPA), and tachycardia and other forms of psychophysiological activation during panic are caused by vagal (parasympathetic) withdrawal rather than sympathetic arousal [3]. The main approaches to the treatment of panic disorder include both psychological and pharmacological interventions. Psychological interventions consist of cognitive behavioral therapy. As an added benefit for patients with panic disorder, who also have comorbidities, there are components of therapeutic regimens that can also secondarily improve their condition. Antidepressants and benzodiazepines are the mainstay of pharmacological treatment. Among the different classes of antidepressants, selective serotonin reuptake

inhibitors (SSRIs) are recommended over monoamine oxidase inhibitors and tricyclic antidepressants. SSRIs are considered a first-line treatment option for patients with panic disorder. In patients with comorbid conditions or in patients with severe symptoms, benzodiazepines such as alprazolam are preferred. Patients with substance use disorder and panic disorder are advised to use gabapentin and mirtazapine. The patient needs a detailed familiarization with the disease in order to realize that there is no immediate danger to life. The patient needs to be educated about the various treatments available and the need to follow them. In addition, the physician should warn the patient against alcohol or recreational drug use. The patient should be taught to recognize triggers and avoid them.

**Materials and Methods**. The material for the study was stationary cards, psychological tests and questionnaires of patients in provisional departments at the clinical base of the Mental Health Center in Almaty. To assess the severity of panic disorder, we used the Panic Disorder Severity Scale (PDSS). It is a questionnaire designed to measure the severity of panic disorder and is considered a reliable tool for monitoring treatment outcomes. The Panic Disorder Severity Scale Self-Reporting Form (PDSS-SR) is used to identify possible symptoms of panic disorder and indicate the need for a formal diagnostic assessment. The PDSS consists of seven items, each scored on a 5-point scale from 0 to 4. Items assess the frequency of panic, panic distress, panic-focused anticipatory anxiety, phobic avoidance, phobic avoidance of physical sensations, work disruption and social disruption, functioning. The overall score is based on the total score, which is calculated by summing the scores for all seven items. Total scores range from 0 to 28. PDSS-SR is used for screening, and a score of 9 or higher suggests a formal diagnostic evaluation is required.

All patients involved in the study filled out a questionnaire with the obligatory signing of a voluntary informed consent.

**Results and discussion.** 30 people were examined who were admitted to inpatient treatment at the provisional center at the clinical base of the Mental Health Center in Almaty, of which 15 men and 15 women from 20 to 40 years old with a diagnosis: Coronavirus infection, concomitant: Panic disorder or approximate to him. The results showed that 93.33% (28 people) of the respondents, after the PCR test for COVID-19 was confirmed, became susceptible to panic attacks with varying degrees of severity. The remaining 6.67% (2 people) had the results corresponding to the norm. Of the patients with identified symptoms, 35.71% were men (10 people), the remaining 64.29% were women (18 people). Pronounced phobic avoidance and disabilities were found in the age group from 20 to 29 years - 57.14% (16 people), panic-oriented anticipation of anxiety was detected at the age of 30-35 - 28.57% of cases (8 people), the least susceptible panic attacks in frequency and distress age group 36-40 years - 14.29% (4 people).

| Distribution by the number of points scored | | | |
|---|---|---|---|
| Age group | 20-29 лет | 30-35 лет | 36-40 лет |
| Average points | 19,75 | 13,8 | 9,25 |

Thus, the results show the prevalence of the prevalence of female panic reactions in patients with a COVID-19 profile over that in men. You can also notice a tendency for a decrease in the severity of panic attacks with increasing age of the individual. Thus, we confirm the data of many studies that a significantly smaller proportion of older people are susceptible to the development of anxiety disorders and the escalation of panic attacks. However, it is worth noting that although the incidence of panic disorder in this age group is

lower, they are more difficult to respond to therapy (pharmacotherapy, psychotherapy), which requires further research. It is possible that with an increase in life experience and wisdom, the threshold of affectivity rises in people, and, therefore, they are less worried. A larger study is required to investigate this issue.

Diagram 1

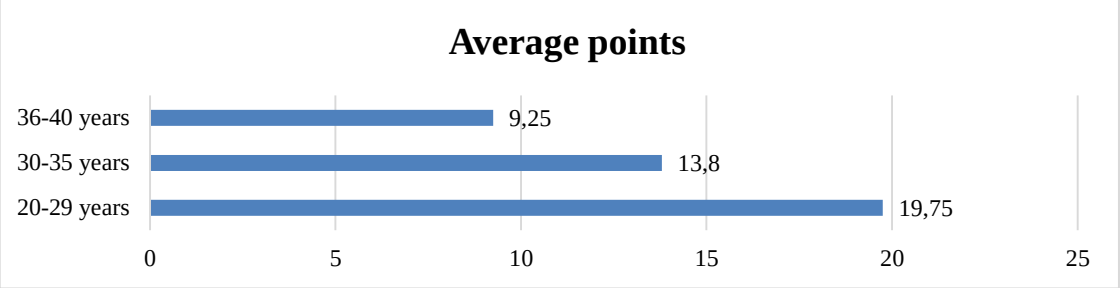
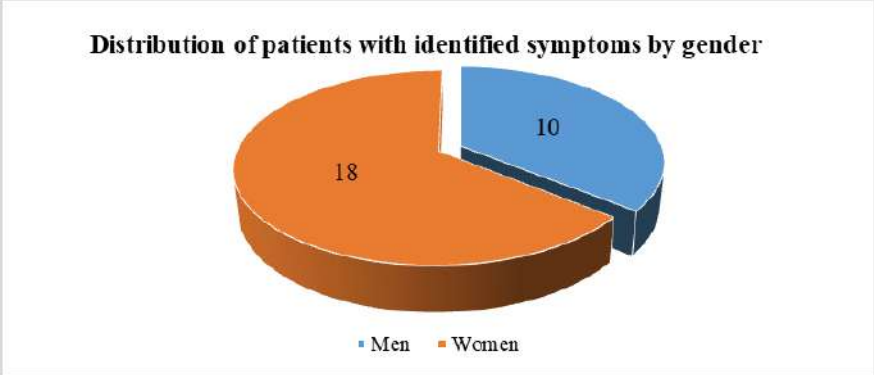



Diagram 2




**Conclusions**.

1. Our study indicates a possible inverse relationship between age and severity of symptoms of panic disorder and coronavirus infection.

2. The prevalence of panic affectivity in women is higher than in men.

3. Each panic episode should be carefully diagnosed and its connection investigated not only with various somatic pathologies, with other mental disorders, but also with the psychological situation in the patient's micro-society.

4. Measures should be taken to improve the recognition and treatment of panic disorders at a younger age, not only at the health-care level of psychiatric hospitals, but also in the infectious-level network.

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# INFLUENCE OF THE INTESTINAL FORM OF COVID-19 AND INTESTINAL PARASITOSES ON THE BODY IMMUNE STATE

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**Abstract**. It is known that cells of the immune system able to recognize foreign agents and respond to them with an immune response. The intestinal immune system provides local protection against the penetration of foreign bacteria and viruses. This article is about current data on the intestinal form of the new viral infection COVID-19. Only in 30% of cases, hereby can be of leading importance, and in 20% of patients with COVID-19 with high fever and respiratory symptoms have gastrointestinal disorders. This work aims to study some clinical aspects of intestinal biocenosis. The positive effects of probiotic drugs in coronavirus infection are widely reflected in foreign literature. These studies show the effectiveness of probiotics in the treatment of diarrhea in patients with the intestinal form of COVID-19 and with intestinal parasitosis.

**Key words:** intestinal COVID-19, parasitosis, immunological parameters, probiotics.

**Introduction**. The study finds that students with intestinal parasitic invasions (giardiasis, ascariasis, and enterobiasis) are more susceptible to different morbidity rather than people of this age without them. The objective of the study is to determine the role of cytokines, in particular, IL-4, IL-6, IL-10 in blood serum and some immunological parameters of CD3+, CD4+, CD8+, CD4+/CD8+ in students with intestinal parasitic invasion without concomitant diseases. Examination and identification of 188 students with giardiasis, ascariasis, enterobiasis and mixed intestinal parasitosis aged 19 to 23 years. As the result finds an increase in the content of IL-4, IL-6, IL-10 in the blood serum was revealed.

Based on the results of the immunological study, inference should be drawn that mixed pathology (e.g. Giardiasis cholecystitis), is a factor affecting the immune state of these patients. No drastic changes in the content of immunocompetent cells were observed. Assertedly, this is due to the duration of chronic mixed parasitosis with bacterial infections. As cytokines, in particular IL-4 in the blood serum, is involved in the initiation of immunological processes in intestinal parasitosis, this can significantly increase the effectiveness of the fight against intestinal parasitosis and reduce the risk of pathological processes.

Intestinal parasitoses have a negative effect on the human body. They lead to allergization, the development of polyhypovitaminosis, impaired blood formation and vascular permeability, hormonal imbalance, lead to the development of chronic diseases (cholecystitis, pancreatitis, colitis, bronchial asthma, etc.). The basis of allergic reactions in intestinal parasitoses is a mechanism formed as a protective reaction of the host organism, aimed at fighting the parasite [1,2]. This reaction or immune response is held by effector cells, macrophages, neutrophils, eosinophils, platelets, specific antigens A, M, G, E. The immunological response develops according to the Th-2 type. While the parasite antigens (polysaccharides, glycopeptides) attack the human body, they interact with macrophages and present them to T-lymphocytes. T lymphocytes release cytokine molecules that activate B lymphocytes. An important functional property of cytokines is the regulation of the development and behavior of cells of the immune system effectors. B-lymphocytes are converted into plasma cells synthesizing JgE [3, 4]. JgE binds to receptors on the surface of mast cells, which leads to the release of vasoactive amines and an increase in eosinophils, initially in the blood, and then

their active migration to the site of invasion. Further, as the parasitosis evolved, endogenous intoxication of the macroorganism holds [5,6].

**Relevance**. The relevance of the work is associated with the high prevalence of various forms of intestinal parasitosis and intestinal COVID-19. The intestinal microflora is active in the work of the immune system. The cells of the immune system are concentrated in the intestinal mucosa. They provide local protection against the penetration of foreign bacteria and viruses, participate in the general immunity of the body, activating special cells and synthesizing special proteins, such as B-lymphocytes, which produce immunoglobulins (antibodies).The intestinal microflora is an essence of the immune defense aimed pathogenic microorganisms and viruses to be disarmed.The gastrointestinal manifestations of COVID-19, according to our data, are featured by an increase in stool frequency up to 8 times a day. Diarrhea lasted, in patients with COVID-19, up to 16-20 days and could even precede the appearance of respiratory complaints, which confirms information about alternative methods of transmission of the virus in addition to airborne droplets. disruption of the intestine leads to serious complications on the body's immune system, which contributes to the penetration of bacteria and viruses into the human body, including the new viral infection COVID-19.

Fact that ability to cause gastrointestinal disorders such as abdominal pain, diarrhea, loss of appetite, nausea and vomiting being as a feature of the coronavirus has been confirmed in foreign scientific studies. The new COVID-19 coronavirus is an intracellular parasite that causes disease while penetrates inside a cell. First, viral particles attach to cells using their receptors, with which they went in the cell. Pursuant to the latest data, the cellular receptors using the COVID-19 coronavirus for penetrating the cell (angiotensin converting enzymes) are found in large quantities both in the mucous membrane of the respiratory tract, and in the intestinal cells.

3 patients with intestinal COVID-19 were observed. In these patients, abdominal pain, nausea, lack of appetite, and diarrhea lasted 2 months. Despite the treatment, these gastrointestinal tract phenomena are pursued. Patients received Bifidumbacterin 20 doses x2 times a day 40 minutes before meals for 21 days, and repeated the 2nd course of treatment with probiotics since a 14-day break was over.

Patients are subject of intestinal microflora being imbalanced. Is provoked by prolonged use of antibiotics, which strongly affect the intestinal microflora. Also, dysbiosis occurs against the background of inflammatory diseases of the mucous membrane. If a new infection ingested the digestive system, this is the first thing being occurred in intestines. The stomach begins to prick, and bad breath with flatulence is possible.

It should be considered that such a symptom also followed with improper diet, strong physical exertion and prolonged stress. Therefore, an accurate diagnosis requires to be surveyed.

Nausea and vomiting are signs of the coronavirus. They are as first, usually appear and precede the loss of smell and taste. In the main, nausea, vomiting proceeds to stools-diarrhea. Diarrhea is one of the most common symptoms. In some cases, the disorder last before cough and fever. Diarrhea and the frequency of stools last individually and depend on the general immunity of the person.

Another sign as loss of appetite, and inappetence are often associated with a general decline in the body's strength, weakness and nausea. The process must be monitored to prevent the development of anorexia.

Loss of appetite often results the loss of taste and smell. Constitutionally, neutral food is not attractive. But the stomach cannot lie fallow for a long time, otherwise an ulcer and concomitant diseases develop.

**Purpose**. The objective of this study is to determine fluctuations in the concentration of cytokines JL-4, JL-6, JL-10 and some immunological parameters in the blood during intestinal parasitosis.

**Materials and methods.** The study included 188 students with giardiasis, ascariasis, enterobiasis and mixed parasites at the age of 18 to 23 years. There were girls. The parasitological study of students included the collection of a parasitological anamnesis according to a special questionnaire compiled by us, general analyzes of urine, feces, blood, feces for worm eggs. The analysis of immunograms in the process of diagnostics and dynamics of treatment, determination of general and specific JgE, i.e. investigated the nature of the immune response in intestinal parasitosis [7, 8].

The following indicators of the immune state were studied: the content of CD3+, CD4+, CD8+, CD4+/CD8+ lymphocytes. The determination of the concentration of immunoglobulin M, G, A total IL-4, IL-6, IL-10 in blood serum was also carried out using the ELISA method. Solid phase heterogeneous immune ELISA (enzyme linked immunosorbent assay) analysis. IFA is based on the immune response of an antigen with an antibody, and the addition of an enzyme label to antibodies makes it possible to consider the conclusions of the antigen-antibody reaction by the appearance of enzymatic activity or by a change in its level.
The digital data obtained were subjected to statistical processing by methods of medical statistics, considering modern requirements. The average values of the obtained data (M), their standard deviations (d), standard errors (m). For a preliminary estimate of the difference between the variation series, the parametric t as a Student's t-test and assessment of the difference between the shares.

Based on the data obtained, the patients were divided into appropriate groups: Group I consisted of 46 patients with giardiasis.

Group II consisted of 40 patients with ascariasis without concomitant pathology. Group III consisted of only 26 patients.

Group IV consisted of 67 students with mixed parasitosis. The control group consisted of 22 students.

**Discussion and conclusions**. The analysis of clinical manifestations in the examined students revealed polymorphism of the manifestations of parasitosis. As shown by Table 1, the number of lymphocytes was determined in the composition of the blood formula as a percentage of the total number of leukocytes, as well as their absolute number, since the significance of these indicators in the composition of the leukocyte formula is very important. A significant (more than 2 times) increased number of eosinophils is characteristic of enterobiasis [7, 8].

A significant increase in the number of eosinophils JgE, IL-4, IL-6, ID-10 are characteristic of intestinal parasitosis.

The results of some immunological studies leads to the conclusion giardiasis paracytosis is a factor involved in the immune state of a person [5].

| T-indicators | Giardiasis n=49 M ±m | Ascariasis n=46 M ±m | Control group n=22 |
|---|---|---|---|
| $CD3^+$ | 63,72±0,76 | 66,30±0,73 | 65,8±2,91 % |
| $CD4^+$ | 37,49±0,5% | 38,40±0,470% | 39,6±2,10% |
| $CD8^+$ | 30,35±0,63% | 31,83±0,515% | 26,2±2,33% |
| $CD4/CD8^+$ | 2,59 | 1,2 | 1,5 |
| $p < 0,05$ | | | |

To study the intensity of immune reactions in students of the intestine by parasitic invasion, the indicators of cellular and humoral immunity were analyzed for each group of examined students. While the indicators of the immune state of students are analyzed, significant changes were found.

**T-cells versus controls**. Indicators of the T-cell link of the immune state in the blood serum of students with intestinal parasitic invasion prior to and after treatment.

Thus, the total number of T-lymphocytes (CD3+) was significantly reduced (55±9,4) (<0,05), which reflects the deficiency of T-cell defense mechanisms, which carries out immunological surveillance of antigenic homeostasis in the body. Calculation of the relative number of T-helpers (CD4+) also showed (38±7,97) ($p<0,05$) a decrease in this subpopulation of T-lymphocytes, T-helpers are cells that regulate the strength of the body's immune response to a foreign antigen, control the constancy of the internal the environment of the body (antigenic homeostasis) causing this indicator indicates an immunological deficiency. The trends of insignificant decrease (28,6±8,96) ($p<0,05$) of the level of T-suppressors (CD8+) became visible as a result of its analysis, although the difference was not significant. But, despite the changes in the subpopulation composition of T-lymphocytes, there was no significant violation of the T-helper/T-suppressor index, the determined immunoregulatory index, in the students we observed did not have.

Thus, in students with intestinal parasitic invasion. Especially the giardiasis and ascariasis groups are without the parameters of cellular immunity to be normalized. Some deviations were revealed compared with the control group in the study of the humoral factors of the immune state.

Indicators of the humoral link of peripheral blood immunity in students with giardiasis and ascariasis invasion.

| Indicators | Giardiasis n=49 M ±m | Ascariasis n=46 M ±m | Control group n=22 |
|---|---|---|---|
| JgA | 2,71±0,14 | 3,0±0,091 | 0,8±0,2 |
| JgM | 1,38±0,07 | 1,69±0,076 | 0,9±0,1 |
| JgG | 11,2±0,31 | 13,24±0,228 | 9,4±0,1 |
| JgE | 412,19±35,80 | 369,67±26,271 | 95,32±5,28 |
| p<0,05 | | | |

Thus, Comparative analysis of indicators of humoral and cellular immunity in blood serum of students with intestinal parasitic invasion revealed the most significant positive relationships between indicators of CD3+ and CD8+ ($p<0,001$) and the level of JgE ($p<0,001$).

Firstly, despite minor changes in the quantitative content of immunocompetent cells, the functional component of serum JgE, the main cytokine IL-4 is significantly increased. Thus, the content of serum JgE in the study group increased by more than 7 times, the content of IL-4 by more than 4 times.

Segmented neutrocytosis is characteristic of the ongoing inflammatory process from other organs. The increased number of eosinophils (almost 2 times) indicates the sensitization of the patient's body. No sharp changes in the content of immunocompetent cells were observed. Apparently, this is due to the duration of chronic mixed parasitosis.

At the same time, a slight decrease in the content of JgA in the blood serum is observed. Moreover, the content of JgE in them is increased by 4.5 times ($p<0,05$). Evidently, the reason for this is the addition of bacterial infections, e.g., giardiasis cholecystitis.

As a result of the study, an increase in the content of IL-4, IL-6, IL-10 in the blood serum was revealed in patients with enterobiasis, ascariasis and giardiasis. Moreover, with enterobiasis, the content of IL-4 in the blood serum averaged 22,3±3,2 pG/ml ($p<0,05$), ИЛ-6 14,2±2,8 pG/ml ($p<0,05$). Serum IL-4 values were positively correlated with each other. An increase in the concentration of IL-4 in the blood serum also indicates the presence of hypersensitivity and hyperreactivity on the part of Th-2.

Blood cell morphology differentials and the content of immunocompetent cells in students with giardiasis and mixed parasitosis (m±m).

| Indicator | Giardiasis n=49 | Mixed parasitosis n=67 | Control n=22 |
|---|---|---|---|
| Leukocytes | 5,90±0,12·$10^9$ | 0,127±6,48x$10^9$/л | 6,1±0,35x$10^9$ |
| Neutrophils banded (%) | 3,29±0,15% | 2,96±0,159% | 3,5±0,7x0 |
| Neutrophils s/n (%) | 53,12±0,62% | 67,46±0,442% | 53±121$^c/_0$ |
| Monocytes (%) | 4,95±9,21% | 4,76±0,189 | 5,2±0,09% |
| Eosinophils (%) | 8,98±0,38% | 7,49±0,209% | 4±1,45% |
| Lymphocytes % Lymphocytes abs | 29,66±0,58% | 22,32±0,477% | 1,2±0,64 |
| $CD3^+$ T-lymphocytes | 1,04±0,08·$10^9$/л | 1,42±0,083·$10^9$/л | 65,8±2,91(%) |
| $CD4^+$ lymphocytes | 63,72±0,76% | 63,01±0,739% | 39,6±2,10(%) |
| $CD8^+$ lymphocytes | 37,49±0,54% | 38,40±0,470% | 26,2±2,33(%) |
| $CD4^+/CD8^+$ lymphocytes | 2,59 | 1,2 | 1,5 |
| JgM g/l | 1,38±0,07 | 1,69±0,076 | 0,9±0,1 |
| JgG g/l | 11,21±0,31 | 13,24±0,282 | 9,4±0,1 |
| JgA g/l | 2,71±0,14 | 3,0±0,091 | 0,8±0,2 |
| JgE m/ml | 712±53,80 | 469±67±2,62±1 | 95,32±5,28 |
| IL-4 | 201±3,2 | 5,4±0,07 | 1,7±2,2 |
| IL-6 (n-42) | 16,55±11,87 | 22,9±2,39 | 4,13±0,22 |
| IL-10 (n-42) | 6,4±5,2 | 8,0±0,12 | 14,2±2,1 |
| $p<0,05$ | | | |

With COVID-19, there is a so-called cytokine storm, uncontrolled inflammation, leading to damage to the body's own tissues.

Thus, the atopic genesis of enterobiasis and ascariasis was confirmed. On the other hand, it was shown that the determination of the levels of IL-4 in the blood serum is a valuable diagnostic criterion for the differential diagnosis of various forms of intestinal parasitosis. Be noted that given the direct correlation of IL-4, IL-6, IL-10 indicators in blood serum in various intestinal parasitosis, it can be recommended for practical use.

Based on the above results of the immunological study, it can be concluded that mixed (mixed) intestinal parasitosis is a factor that affects the immune state of patients with parasitosis (enterobiasis, ascariasis, and giardiasis).

Thus, it is necessary to decipher many more factors and mechanisms of induction or suppression of immunity, the launch of immunological processes in intestinal parasitosis, in which cytokines are involved, since their targeted use in preventive measures for the therapy of parasitosis can significantly increase the effectiveness of the fight against parasitosis and reduce the risk of pathological processes.

Thus, consider the global role of normal intestinal microflora for keeping health, to provide primarily a normal immune system and other defense mechanisms, modern comprehensive programs for the treatment and rehabilitation of patients with intestinal dysbiosis should be extremely used.

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# MEDICAL-PHILOSOPHICAL AND THEOLOGICAL ASPECTS OF PUBLIC HEALTH PROTECTION DURING THE COVID-19 PANDEMIC

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**Abstract**. The sociological survey reveals the impact of Islamic moral and ethical values on human health and the formation of a healthy lifestyle, and emphasizes their role in protecting the health of the population. The provisions contained in the Qur'an and the "Tibbi-Nabawi" are presented as an alternative means of protecting public health and are assessed within the framework of preventive principles. It is known that gradually developing high faith increases the body's resistance to risk factors by strictly following religious rites. That is, the assessment of the role of religious rituals in terms of increasing the body's resistance to various harmful factors is relevant.

**Key words**: Coronavirus pandemic, risk factors, quarantine, "Tibbi-Nabawi", healthy lifestyle

The coronavirus pandemic is characterized by a massive increase in morbidity and mortality worldwide from 2020 onwards. In addition to disrupting the economies of countries, quarantine measures also create conditions for serious socio-psychological and material tensions of people, as well as food disorders. Risk factors that negatively affect the health of the population, according to WHO experts - alcohol abuse, smoking and drug use, including psychosocial stress, malnutrition - obesity, low physical activity (WHO, 2005; Ilyachenko I.N., 2001; WHO, 2005; Macura M., 2002) are now more relevant against the background of quarantine measures.

Lifestyle changes due to the pandemic, including the ineffectiveness of attempts to reduce the activity of risk factors (Myagkikh N.I. 2007; Drygas W., 2005), the inability to prevent these risk factors as a whole, drawing attention to the Islamic factor The study of protective measures is of interest, increasing the body's resistance to various damaging factors - the assessment of the role of religious rites in terms of developing reactivity is relevant.

According to the WHO, 50% of the world's population suffers from neuropsychiatric disorders. Studies show that mental disorders, such as depression and anxiety, are common in general health practice. According to the WHO (2001), depression will be the second leading cause of death in the world in 2020. (Chobanov R.A., Badalova A.O. 2016).

It is during the pandemic period that the moral and spiritual values presented by Islam are of paramount importance in strengthening mental health, preventing eating disorders, preventing the decline of physical activity, in short, eliminating the consequences of complex risk factors. Tolerance to psychological depression lays the foundation for a new stage in further strengthening the health of the individual.

Worship in Islam is part of the "Tibbi-Nabawi". Worship, such as prayer, fasting, pilgrimage, almsgiving, supplication, and remembrance of Muslims (Qur'an, 2/152; 33/ 35,41), have both protective and healing effects on physical and mental health. It can be assumed that the increase in gymnastic activity with the performance of prayer can prevent hydrodynamics, which is a risk factor in lifestyle. The role of fasting in the

prevention of eating disorders, the psychological effects of prayer and remembrance, and the social effects of aids such as zakat and almsgiving have already been proven by Islamic researchers to bring psychological relief to a person.

**Materials and methods**. For the first time in Azerbaijan, sociological surveys conducted to identify the impact of Islamic religious and moral values on human health, the formation of a healthy lifestyle and the role of public health in the study are included in the research material. Also included in the list of research materials are translations and interpretations of the Quran, a collection of narrations (hadiths) of the words of the Prophet, relevant works of Eastern and Western scholars.

**Conclusions and discussions**. Thus, when studying the relationship between respondents' observance of religious rites (746 people) and their state of stress, those who did not observe religious rites under stress (26.0 ± 6.2%) were more likely than those who did (17.4 ± 2.0%). in the case of excessive exposure, on the contrary; those who observe religious rites (40.9 ± 2.6%) are more tolerant than those who do not (18.0 ± 5.4%). An accurate correlation ($\chi 2 = 34.02$) between stress tolerance and adherence to religious rites was most likely ($P<0.001$).

Hypodynamics, which is a risk factor in lifestyle, can be assumed to be prophylactically prevented at the same time as performing high-will prayers. In order to prevent low physical activity, the recommended norm for training is the time spent by the average statistical believer in daily prayers (150 to 300 minutes per week) (Potemkina R.A. 2006; Caspersen C.J., Pereira M.F., Curran K.M. 2000) with full performance of prayers It is paid 3 times more.

As the duration of prayer increases over the years, there is a decrease in exposure to negative emotions and a number of negative psychological characteristics. Respondents in the survey are optimistic and justify this by following the Qur'an and the recommendations of the Prophet Muhammad. It is stated in the hadiths, “When infectious diseases spread in a place, do not leave that place.” Among the conditions of quarantine, it is important to maintain cleanliness and follow hygienic rules. Among the hadiths of the Prophet, “Keeping a Muslim's body, mind and spirit healthy,” is purity of faith; Cleanliness is half the faith; Religion is driven by purity; God is pure and loves to be clean.”

An important condition for getting rid of the coronavirus is social distance and strict adherence to the rules of personal hygiene. Believers have noted that there are hadiths regarding the closing of the mouth during sneezing and coughing and the avoidance of saliva and sputum. Therefore, the exemplary moral behavior of believers - following the hadiths - is important in terms of preventing the spread of pathogenic microorganisms and viruses in saliva through the air.

In true faith, the enrichment of the mind and spirit, which is a test in Muslim theology, is claimed to be charity for sins. The Prophet said: “There is no fatigue, no discomfort, no sorrow, no sorrow, no pain, no pain, not even a thorn in the side of a Muslim that Allah will not forgive him.” “If the body, family and wealth of a believing man and a believing woman are afflicted until they meet God, there will be no sin on them.” “There is not a person who does not get sick and the reward of his worship while he is healthy is not written for him (even now).” The above-mentioned hadiths play an important role in the formation of the physical health of a believer who lives a life of this belief, along with his spiritual enrichment.

The high impact of religious observance on stress tolerance and the increase of willpower against harmful habits makes people more likely to be in good health. In short, “quantity passes to quality.”

Of the 708 people who assessed their health status, 359 (50.7%) were full

adherents of religious rites, 301 (42.5%) were partial adherents, and 48 (6.7%) were non-adherents.

Quantitative changes show that respondents believe that their health status is good (60.7±1.8%) and relatively good (35.3±1.8%). The large number of people who fully and partially observe religious rites here indicates a new quality.

The discovery of an accurate relationship ($\chi^2$ = 27.05; P<0.05) between observance of religious rites and good health and the application of one-factor analysis of variance revealed that the impact of religious observance on human health is much higher ($\chi_x^2 \pm m\eta_x^2$ =2,0 ± 0,27%; p<0,01).

As a result, respondents argue with the verses of the Qur'an that they will restore their health through worship (prayer, prayer, fasting, etc.). “Our God said, 'Pray to me, and I will answer you” (Qur'an 40:60). “He is the God who heals me when I am sick” (Qur'an 26:80).

# PANCREATIC PSEUDOCYSTS TO CHILDREN. ETHYOLOGICAL SPECTER. DIAGNOSTIC AGREEMENT. TREATMENT

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**Introduction**. Pediatric surgery is still facing with the problem treating pancreatic pseudocysts. Although, in recent decades, the diagnosis of pancreatic pseudocysts became easier due to the endowment of medical institutions with high-performance devices, treatment remains to be a serious problem. The difficulty consist in the anatomical and surgical features of the child's pancreas and different therapeutic approaches are needed from adults cases.

**Key words**: pancreatic pseudocyst, surgery.

**Introduction**. Pediatric surgery is still facing with the problem treating pancreatic pseudocysts. Although, in recent decades, the diagnosis of pancreatic pseudocysts became easier due to the endowment of medical institutions with high-performance devices, treatment remains to be a serious problem. The difficulty consist in the anatomical and surgical features of the child's pancreas and different therapeutic approaches are needed from adults cases. The pseudocyst is a liquid collection formed in the pancreas of non-infectious etiology, without its own wall and lining endothelium, which is formed by the structures of neighboring organs. Its contents represent necrotic tissue, blood, pus that communicates with the ductal system in most cases (Gudumac et al., 2013). At children, it usually occurs as a result of traumatic injuries (road accidents, blows to the region of the epigastrium, falls) (Amulya K Saxena, MD, PhD, DSc, FRCS(Glasg); Chief Editor: Harsh Grewal, MD, FACS, 2019) .

**The purpose of the present study**. To evaluate the incidence of pancreatic pseudocysts at children and the role of clinical-paraclinical diagnosis to improve treatment and reduce the number of complications.

**Materials and methods**. An analysis was performed of 4 children aged between 6 and 14 years with pancreatic pseudocyst, examined and treated in the National Scientific-Practical Center for Pediatric Surgery “Natalia Gheorghiu” during 5 years.

**Results and discussions.**

**Case No.1** B.M patient, 14-year-old boy from rural areas, presented on 01.12.2019 in the Pediatric Surgery Clinic with the following accusations: vomiting after each meal, lack a 4-day stool, general weakness, abdominal pain located mainly in the epigastrium with irradiation in the left hypochondrium.

The anamnesis found out about the enduring of a blunt abdominal trauma that took place at school on 11/22/2019. He was then urgently hospitalized in the Ceadir-Lunga district hospital where he was examined, the injury of the internal organs was excluded and he was treated conservatively. Three days later, he was discharged in a satisfactory state. One day after discharge, postprandial vomiting and abdominal pain reappeared, which led the child and his mother to return to Ceadir-Lunga District Hospital for re-examination. Then the ultrasonographic examination of the abdomen and the simple X-ray were performed. On 1st December 2019, the patient was transferred to the Institute of Mother and Child in Chisinau in serious state with the above symptoms.

The objective examination found a general condition of medium severity, pale pink skin, clean. Slightly bloated abdomen, on superficial palpation the muscular defense is

missing, on deep palpation sensitive on the whole area, but, with predilection in the epigastrium and in the left hypochondrium Examination of the other systems pathological changes did not reveal.

Panendoscopy to the duodenum was performed at the Mother and Child Institute (02.12.2019). This highlighted: the lumen of the stomach and the deformed duodenum (possibly because of external compression). Ultrasonography and computed tomography revealed the presence of a fluid collection with high protein content in the retroperitoneal region, at the head of the pancreas and the D2 segment of the duodenum with dimensions 8.6 cm (vertical) x 4.2 (antero-posterior) x 5.8 (transverse ) with the effect of the mass exerted on the head of the pancreas, duodenum and gallbladder. Moderate dilation of the common bile duct. Biochemical examination of the blood showed increased amylase (192 U/l, N:0-90U/l); Also increased, alanine aminotransferase and aspartate aminotransferase, conjugated bilirubin, fibrinogen, urea.

Firstly, the patient was treated conservatively in order to stabilize the state and prepare him for surgery. The surgery was performed on the 3rd day after hospitalization. The subtotal excision of the pancreatic pseudocyst, marsupialization of the cavity and external drainage were performed. After the intervention were administered for the purpose of correction perfusion therapy, antibiotic therapy, spasmolytics, proton pump inhibitors, hemostatic analgesia was done with Promedol solution. The diagnosis of pseudocyst of the pancreas was confirmed by morphological examination. He was treated in the intensive care unit for four days. Postoperative evolution without complications. He was discharged 14 days postoperatively. He was registered for dispensary and outpatient treatment. The repeated examination over 6 months showed that the child is healthy.

**CaseNo.2** C.D patient, 10-year-old boy , from rural areas, presented on 18.12.2018 in the Pediatric Surgery Clinic with the following accusations: general weakness, abdominal pain located mainly in the epigastrium, nausea, adynamia, loss of appetite, palpable abdominal tumor in the region of the epigastrium, pain.

On 10th Dec 2018, the patient suffered a blunt abdominal trauma (blow), following which the above-mentioned accusations appeared a few hours later. They first went to the Rezina District Hospital where he was investigated. At the ultrasonographic examination (12.12.2018) was detected the presence of a formation in the body region of the pancreas. He was treated conservatively for 4 days, but the patient's state did not improve, which is why the decision was to transfer him to the Institute of Mother and Child in Chisinau.

At the primary examination the patient was in a state of medium severity, pale skin, bloated abdomen, no signs of peritonitis, on superficial palpation the sensitive abdomen on the whole area, at the deep one there was stiffness in the epigastrium. Investigations were performed such as: ultrasonography, computed tomography in which the presence of a massive cystic formation was detected at the body of the pancreas with dimensions 8.2 cm (vertical) x 6.0 cm (antero-posterior) x 8.3 (transverse). Amylase within normal limits. After two days of hospitalization, after adequate preparation, the patient underwent surgery under general anesthesia. Subtotal excision of the pseudocyst of the pancreas, marsupialization of the cavity and external drainage was made. Postoperatively, the patient received a complex treatment with infusions, spasmolytics, anagenic, hemostatic, proton pump inhibitors. Postoperative evolution without complications. He was discharged eight days postoperatively. He was registered for dispensary and outpatient treatment. Finally, repeated examination after 3 months showed that the child is healthy.

**Case No.3.** Patient A.V, a 6-year-old girl from a rural area, presented at the Pediatric Surgery Clinic on 14.09.2016 with the following accusations: diffuse abdominal pain, more pronounced in the epigastric region, sickness, loss of appetite, repeated postprandial vomiting.

The patient is considered ill for more than a year, since the above symptoms appeared, in a milder form. Over time, the symptoms became more intense, and the girl lost considerable weight. No traumas, blows, accidents, intoxications or other causes that would cause a pancreatic pseudocyst were not revealed.

At physical examination: the patient's condition of medium severity, pale pink skin, bloated abdomen, sensitive to superficial palpation throughout the area. At deep palpation, the presence of an abdominal mass in the epigastrium region was revealed, painful at the slightest pressure. Pathological changes were not revealed by other organ systems. She was hospitalized on suspicion of acute abdomen. Within the Institute of Mother and Child was performed ultrasound of the abdomen, computerized tomography in which the massive liquid formation with dimensions 22.0cm x 16.0cm was highlighted in the region of the tail of the pancreas. Biological tests showed moderate hyperamylasemia. Surgery was performed, after adequate preoperative training to stabilize the patient's state (22.09.2016). Surgical technique consisted of subtotal excision of the pseudocyst of the pancreas, marsupialization of the cavity and external drainage. Postoperatively, the patient received a complex treatment with infusions, spasmolytics, anagenic, hemostatic, proton pump inhibitors. The diagnosis of pseudocyst of the pancreas was confirmed by morphological examination. Postoperative evolution without complications. She was discharged 11 days postoperatively. She was registered for dispensary and outpatient treatment.

After 3 months from the discharge (17.12.2016), the patient was hospitalized again in the Institute of Mother and Child with the same accusations. Following ultrasonography and Nuclear Magnetic Resonance, the recurrent pancreatic pseudocyst was detected at the tail of the pancreas. It was decided to perform Nuclear Magnetic Resonance instead of computed tomography in angiography because increased creatinine in blood (99 mmol / l; Norm for children 4-9 years 44 mmol / l). This time, conservative treatment was used, as the detected formation was very small (22mm x 24mm), and the probability of a resolution of drug therapy was very high. Analgesics, spasmolytics, proton pump inhibitors, Wobenzym, vitamin E, infusion therapy were administered. The patient's state improved after a few days, and a week after the hospitalization the patient was discharged with evidence at the family doctor. Finally, over 6 months control showed that the girl is healthy.

**Discussions.** Pancreatic pseudocysts are rare at children. In this study was investigated the files of all patients admitted to the Emergency Surgery Department during 4 years, through which were found only 4 cases with the diagnosis of pancreatic pseudocyst. The incidence of pancreatic pseudocysts decreased twice if we compare the present study with the previous study conducted on this topic in which the report was 4 cases per year. (Gudumac et al., 2013) However, pancreatic pseudocyst (PP) is the most common cystic lesion of the pancreas. (Kloppel, 2000) . Unlike adults, trauma is the most common cause of PP at children, while gallstones and alcohol are considered the main causes at adults (Adrén-Sandberg et al., 2004) In all cases presented, the diagnosis of pancreatic pseudocyst was confirmed by ultrasonography, computed tomography and histological analysis of the material collected after the operation.
Two of the three patients, the cause of the pancreatic pseudocyst was the abdominal trauma, this being the most widespread etiological factor worldwide, constituting 23% of all cases of pancreatic pseudocyst at children. (Andre Hebra, MD; Chief Editor: Carmen Cuffari, n.d.). In the third case the etiology is unknown. The surgical intervention was performed only in combination with the conservative treatment, which minimize the complications, with recurrence occurring only in the third case. It consisted of excision surgery and drainage of pseudocyst wall. External drainage is the best method because of the low postoperative complications compared with other methods. But for its carrying out it is

necessary to satisfy the following conditions: pseudocyst walls must be sufficiently mature to support the drainage system, the location of the pseudocyst, presence of complications.

**Conclusions.** The incidence of pancreatic pseudocysts decreased almost twice compared to previous studies Their etiology as a child is abdominal trauma. In addition to the clinical picture that highlights violent abdominal pain, palpable tumor and signs of compression of adjacent organs, also are necessary imaging techniques, biological tests to establish the complete diagnosis. Ultrasonography and computed tomography remain the imaging methods of choice in assessing the nature of the tumor, with few exceptions when the latter may be contraindicated. It is necessary to make the differential diagnosis with hepatic and pancreatic hydatid cyst, other cystic formations with retroperitoneal site, pancreatic carcinomas, etc. Surgical necessity and technique of operation in the pancreatic pseudocyst are directly related to the dimensions of the pseudocyst (unique, small ones with diameter under 4-6 cm, which do not increase, in the conditions of communication with the ductal system), of the clinical-evolutionary phase, parietal maturation, etc. The clinical-paraclinical monitoring allows to concretize the moment of the operation. The approach of a new diagnostic and therapeutic management of pancreatic pseudocyst allowed to avoid deaths, to minimize complications and to improve the results of the treatment, these being in the majority of cases the complete healing. (Gudumac et al., 2013)

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# COVID-19: IMMUNOLOGICAL ASPECTS OF PATHOGENESIS, TREATMENT AND PREVENTION

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The report presents four main pathogenic links leading to the development of a severe form of a new coronavirus infection: SARS-CoV-2 evasion, hyperinflammation, hypercoagulation, and dysimmunoregulation.

The results of studies of drug groups for COVID-19, including anti-inflammatory, antiviral drugs, anticoagulants and immunomodulators, are discussed.

A generalized and systematized material of the role of interferons in the pathogenesis of COVID-19 and using in the treatment and prevention of infections caused by SARS-CoV-2 is presented. The concept of early prescription of type 1 interferon drugs to prevent the severe form of the disease and anti-inflammatory therapy to control the development of cytokine breeze / storm and / or other pathways of damage has been proposed. Data on the role of endotypes of bronchial asthma in the protective / enhancing effect on the form of COVID-19 are presented. The data on the antibody response in terms of protection and duration after infection and after vaccination are presented.

The final part of the report is devoted to a discussion of the complex relationship between different types of immune response to SARS-CoV-2 and the multifactorial nature of the disease.

# CLINICAL AND LABORATORY CHARACTERISTICS OF THE COURSE OF COVID-19 IN PATIENTS OVER THE AGE OF 60.

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**Abstract.** The paper deals with the study clinical and laboratory parameters, the proportion of concomitant pathology and complications affecting the severe course of COVID-19 in people over the age of 60. Materials and Methods: retrospective analysis of medical records of 134 COVID-19 patients over the age of 60 with concomitant pathology and complications was performed. Results and Discussion: severe adverse course of COVID-19 was associated with the presence of concomitant cardiovascular diseases (coronary heart disease, arterial hypertension, myocardial infarction) - 115 (85.8%). The severe adverse course of the disease was associated with concomitant diseases. In COVID-19 patients over the age of 60, the most frequent concomitant diseases were cardiovascular diseases (coronary heart disease, arterial hypertension, myocardial infarction) - 115(85.8%). Concomitant respiratory pathology was noted in 16 (11.9%), type 2 diabetes mellitus was noted in 36 (26.9%) cases, and oncopathology - in 8 (5.9%) cases. The development of complications also influenced the course of the disease; the most common event was pneumonia, leading to RF and ARDS. According to the existing classification under CT findings, the lung damage was between 10 and 90%. Persistent leukopenia, which was observed in patients transferred to the ICU, was a formidable sign of a severe course of the disease. Valuable laboratory criteria were neutrophilia, lymphocytopenia, increased levels of D-dimer, C-reactive protein.

**Key Words:** COVID-19 coronavirus infection, concomitant diseases, elderly and senile age, complications.

**Introduction.** Coronavirus infection (COVID-19) is an acute infectious disease caused by a new strain of the SARS CoV-2 coronavirus with airborne and contact-type transmission mechanisms.

Pathogenetically COVID-19 is characterized by viremia, local and systemic immunoinflammatory process, hyperactivity of the coagulation cascade, endotheliopathy, hypoxia, which leads to the development of micro- and macrothrombosis. Intensity and severity of clinical manifestations of COVID-19 depend on the massiveness of infection (infecting dose of virus) on the one hand and individual characteristics of the macroorganism on the other hand (age, sex, strength of immune response, presence of concomitant diseases-risk factors, etc.) [1].

To date, COVID-19 coronavirus infection remains the leading cause of death among the elderly. [2]. Already the first data from China indicated enormous differences in mortality depending on age - 0.2-0.4% at the age under the age 50, 1.3 at 50-59 years, 3.6% at 60-69 years, 14.3% at 80 years and older [3]. In Italy, where 23% of the population is over 65 years of age, 89% of COVID-19 deaths occur in those over the age of 70 years (31% between the ages of 70 and 79 and 58% over 80) [4,5].

SARS-CoV-2 differs from other viruses affecting the upper respiratory tract by its high virulence, posing a particular threat to the elderly and the senile people, since the disease in the latter is more severe than in younger people. The risk of a severe course of the disease and adverse outcomes in patients of older age groups is associated with an age-related

decrease in the functions of the immune system, a decrease in physiological reserves, polymorbidity [2].

Also, the cause of the severe course of the disease is the presence of concomitant diseases such as coronary heart disease, arterial hypertension, chronic pulmonary disease, diabetes mellitus, obesity and the development of severe complications: acute respiratory distress syndrome (ARDS), acute respiratory failure (ARF), sepsis, septic shock, pulmonary embolism (PE), acute cerebrovascular disease (ACD), acute myocardial infarction (AMI) [6.7].

However, in clinical practice, some patients have no pronounced comorbidity, but the disease is also severe. Such patients need oxygen support and/or artificial lung ventilation (ALV) [8].

In the current situation, due to the lack of evidence base for the treatment of COVID-19, the use of etiotropic drugs in COVID-19 patients is acceptable if the potential benefit to the patient exceeds the risk of their use, and if patients (relatives, guardians, etc.) have previously signed the informed consent [1].

**STUDY MATERIALS AND METHODS.** The retrospective analysis of 134 patients over the age of 60 receiving inpatient care in the Infectious Disease Center of Regional Clinical Hospital of Karaganda city for the period from 01.03.2021 to 31.03.2021 was performed.

The authors' personal observations were used in the work. A total of 282 patients were hospitalized with the diagnosis of COVID-19, of which 134 were over the age of 60. The age of the patients ranged from 60 to 90 years. The average age was 75.

Patients were divided into two age categories: 89 elderly patients (60 to 74 years old) and 45 senile patients (75 to 90 years old). The number of males was 64, females - 70 patients. The average duration of hospitalization was $11 \pm 0.2$ days.

The disease in 66.4% was moderate and in 33.6% - severe. Criteria of COVID-19 severity in patients were severity of hypoxemia, the presence/absence of pneumonia. The severity of the condition directly correlated with the presence of concomitant diseases. Concomitant cardiovascular pathology (coronary heart disease, arterial hypertension, myocardial infarction) was observed in 115 patients, which was 85.8%; concomitant respiratory pathology was noted in 16 (11.9%) cases, the presence of type 2 diabetes mellitus - in 36 (26.9%) cases, oncopathology - in 8 (5.9%) cases.

The diagnosis of coronavirus infection in all patients was confirmed by PCR of a nasopharyngeal swab. Laboratory tests of patients were performed in accordance with the current clinical protocol of the Republic of Kazakhstan dated 06.12.2020.

**RESULTS AND DISCUSSION.** The incubation period for COVID-19 ranged from 5 to 14 days, with an average of 7 days. Analysis of the clinical study of COVID-19 patients of different age groups did not reveal any reliable differences in the course, severity and outcomes of the disease, which was the reason for combining them into one group.

The most common clinical manifestations of COVID-19 in the initial period were elevated body temperature from subfebrile to febrile fever (88.2%), dry cough (95.0%), shortness of breath (87.2%), weakness and feeling unrested (80.6%), feeling of chest tightness (30.4%), headaches (40.0%), diarrhea, and nausea (3.1%). All admitted patients developed pneumonia in the first week, more often with the development of respiratory failure (RF).

Signs of grade RF 1 to RF 3 respiratory failure were revealed in 119 (88.1%) patients on admission. The oxygen saturation level on admission ranged from 53% to 97%, and the respiratory rate - from normal values to 50 per minute. The data are given in figure 1.

Figure 1. shows that most patients had signs of grade 1 to 3 RF on admission to the hospital. There were approximately equal numbers of patients with grade 1 and 2 RF, with

more patients with grade 3 RF (16.4%) than with grade 0 RF (11.9%). This confirms that the disease is more severe in people over the age of 60.

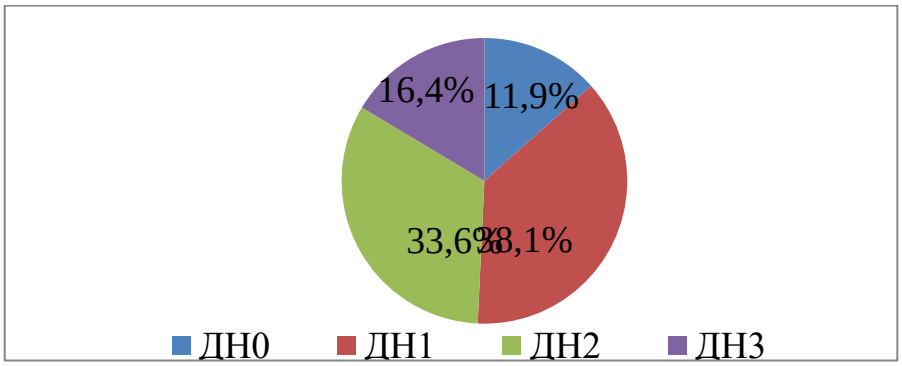


Figure 1. Percentage of patients with RF on admission

COVID-19 pneumonia is characterized by its "silent" course at the beginning of the disease, since the damage appears in most cases in the "aphonic breathing zones," which makes auscultation ineffective. Given this fact, the diagnosis of pneumonia was confirmed in 100% of cases before hospitalization by computed tomography, according to the existing classification [1].

CT-1 (small) damage grade of less than 25% signs: no more than 3 foci of ground glass opacity - < 3 cm in maximum diameter.

CT-2 (moderate) damage grade 25-50% signs: more than 3 foci of ground glass opacity - >3 cm in maximum diameter.

CT-3 (medium) damage grade 50 -75% signs: ground glass opacity - combined with foci of consolidation.

CT-4 (large) damage grade > 75% signs: diffuse thickening of lung tissue in the type of ground glass opacity and consolidation combined with reticular changes.

The data given in Table 1., show that the percentage of lung damage ranged from 10 to 90%. The largest percentage were patients with grade 2 lung damage (50.7%), followed by grade 3 (26.2%), grade 1 and 4 respectively (14.1% and 9.0%).

During the observation period, 23 (17.1%) patients were transferred to the ICU, of which 14 (10.4%) patients required ALV. Due to the development of complications, 21 (15.6%) cases were fatal. The data are given in Table 2.

Table 1. Diagnosis of pneumonia and assessment of the grade of lung damage in COVID-19 patients by CT findings.

| CT grades | Percentage of damage | Number of patients |
|---|---|---|
| CT-1 | less than 25% | 19 (14.1%) |
| CT-2 | 25-50% | 68 (50.7%) |
| CT-3 | 50-75% | 35 (26.2%) |
| CT-4 | more than 75% | 12 (9.0%) |

Due to the fact that such indicators as interleukin-6, procalcitonin, ferritin were not always possible due to difficult availability or lack of reagents, it became an urgent task for clinicians to find simple, easily reproducible markers of a severe course of the disease.

For example, persistent leukopenia, ranging from 2.2 to 4.4 per $10^{12}$ liters was observed in 11.9% of cases, and lymphocytopenia - from 2 -17% was noted in 64.1% of

patients in clinical blood count, which was an indirect sign of a severe course of the disease with the risk of “cytokine storm” development.

Table 2 Complications developed in patients transferred to ICU.

| Complications | Number of patients |
|---|---|
| Sepsis | 2 (1.5%) |
| Grade 3 ARF | 23 (17.1%) |
| ARDS | 14 (10.4%) |
| PE | 3 (2.2%) |
| Acute myocardial infarction | 2 (1.5%) |

Laboratory tests of patients were performed according to the current clinical protocol [1]. Neutrophilia of 73 to 94% was observed in 64.9% of cases, clearly indicating bacterial infection or activation of opportunistic pathogenic flora.

In biochemical studies of the hemogram, C-reactive protein and glucose levels were indicative markers of a severe course (in persons without diabetes mellitus or a history of metabolic syndrome). C-reactive protein levels were higher than normal in 110 (82.0%) cases and averaged -12.5 mg. Hyperglycemia on admission was noted in 53 (39.9%) patients, with a maximum blood glucose value of up to 11.7 mmol/l.

An important part of the laboratory examination was the coagulogram, where hypercoagulation was a characteristic change. For example, 60 (44.8%) patients had increased fibrinogen and averaged 4.96 g/l. D-dimer levels were elevated in 77.6% of cases and averaged 898.6 ng/ml. Critical elevation of D-dimer level up to 10,000 ng/ml was observed in three patients transferred to the intensive care unit (ICU).

All patients were treated according to this protocol. The principal medication included: anticoagulants (heparin, fraxiparin, enoxaparin sodium), anti-inflammatory agents (prednisolone, dexamethasone, methylprednisolone), antibacterial agents (azithromycin, ceftriaxone, cef4, meropenem, levofloxacin and moxifloxacin). Antibacterial therapy, which was administered in 100% of cases, was associated with the addition or activation of secondary bacterial flora (appearance of purulent sputum, increase in CRP level, neutrophilia, bacterial excretion during the bacteriological examination of sputum). Monoantibacterial therapy was administered in 78 (58.3%) cases and combination therapy in 56 (41.7%).

Prone-positioning and vibromassage were used in all patients, with simultaneous active ventilation of the basal areas of the lungs. Continuous oxygen therapy via nasal cannulas or Venturi masks was required in 116 (86.5%) patients for up to 5 days on average.

Thus, COVID-19 in the elderly and senile people was moderate in 66.4% and severe in 33.6%. Criteria of COVID-19 severity in patients were severity of hypoxemia, the presence/absence of pneumonia.

According to the existing classification under CT findings, the lung damage was between 10 and 90%.

The severe adverse course of the disease was associated with concomitant diseases. In COVID-19 patients over the age of 60, the most frequent concomitant diseases were cardiovascular diseases (coronary heart disease, arterial hypertension, myocardial infarction) - 115(85.8%).

Concomitant respiratory pathology was noted in 16 (11.9%), type 2 diabetes mellitus was noted in 36 (26.9%) cases, and oncopathology - in 8 (5.9%) cases. The development of complications also influenced the course of the disease; the most common event was pneumonia, leading to RF and ARDS. Due to the development of complications, 21 (15.6%) cases were fatal.

Persistent leukopenia, which was observed in patients transferred to the ICU, was a formidable sign of a severe course of the disease. Valuable laboratory criteria were neutrophilia, lymphocytopenia, increased levels of D-dimer, C-reactive protein.

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