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Editorial

Dear readers!

This is a special issue dedicated to fighting a new disease, COVID-19, that emerged in China in December 2019 and spread rapidly worldwide as a pandemic.

The lead article by *M.V.Samsonova, A.L.Chernyaev, Zh.R.Omarova et al.* "Features of pathological anatomy of lungs at COVID-19" reports a study of the pulmonary morphological changes in patients who died from COVID-19 in Moscow from March 20 to June 06, 2020. The pulmonary pathomorphological changes in the patients with COVID-19 have been demonstrated to comply with diffuse alveolar damage during viral interstitial pneumonia. The article also describes the indirect histological signs of a coagulation disorder.

The article by *L.V.Shogenova, S.D.Varfolomeev, V.I.Bykov et al.* "Effect of thermal helium-oxygen mixture on viral load in COVID-19" presents a method of treating COVID-19 patients with a thermal helium-oxygen mixture (t-He/O_2). The study aimed to assess the effect of t-He/O_2 on viral load, markers of inflammation, and antibody synthesis. When t-He/O_2 was included in the standard inhalation treatment regimen for patients with an infectious disease caused by SARS-CoV-2, the viral load and the levels of inflammation markers decreased.

The aim of a randomized clinical study by *K.V.Lyadov, E.S.Koneva, V.G.Polushkina et al.* was to determine the efficacy of the protocol of pulmonary rehabilitation in patients with an oxygenation index of < 400 and > 200 with spontaneous breathing or oxygen support in comparison with patients who did not undergo the rehabilitation. The article "Randomized controlled study on pulmonary rehabilitation in COVID-19 patients with pneumonia" demonstrates that when patients perform a set of selected exercises in the acute phase of the new coronavirus infection, the efficacy of treatment increases due to an early reduction in the need for oxygen support.

The article by *L.S.Namazova-Baranova and A.A.Baranov* "COVID-19 and children" presents the latest data on the course, treatment, and outcomes of the new coronavirus infection in children. For the first time in pediatrics, adults develop a serious illness and die, while children virtually stay out of the spread of the infection. The collaboration between scientists and clinicians gave answers to some of the questions. However, most of the information on the coronavirus's impact on the child's body cannot be introduced into the routine practice so far.

The review by *E.L.Nasonov* "Coronavirus disease-2019 (COVID-19): value of IL-6 inhibitors" shows that the development and introduction into clinical practice of monoclonal antibodies (mAbs) that inhibit IL-6 is one of the major achievements in the treatment of critical conditions within the scope of "cytokine storm" syndrome, including COVID-19. The article discusses numerous studies devoted to the efficacy and safety of mAbs against the IL-6 receptor (tocilizumab), etc., which inhibit the activity of IL-6 in COVID-19.

The article by *G.M.Galstyan* "Coagulopathy in COVID-19" presents a detailed review of the pathogenesis, clinical manifestations, methods of diagnosis and treatment of the coronavirus-induced coagulopathy. It is emphasized that hypercoagulability is detected with the onset of COVID-19; consumption coagulopathy and disseminated intravascular coagulation are usually observed in the late phases of the disease. The article provides recommendations for the treatment with low molecular weight heparins.

The article by *S.N.Avdeev* "Non-invasive ventilation in patients with novel coronavirus infection COVID-19" summarizes the experience of using non-invasive ventilation for hypoxemic acute respiratory failure in patients with COVID-19. This approach was highly effective.

The published materials show that the new viral infection not only damages the lungs, heart, liver, kidneys, skin but also induces pronounced anxiety and depression. So the information on the latest methods of diagnosis, therapy, and rehabilitation of patients that is provided in this special issue is extremely relevant for the practitioners.

Chief editor *Aleksandr G. Chuchalin*

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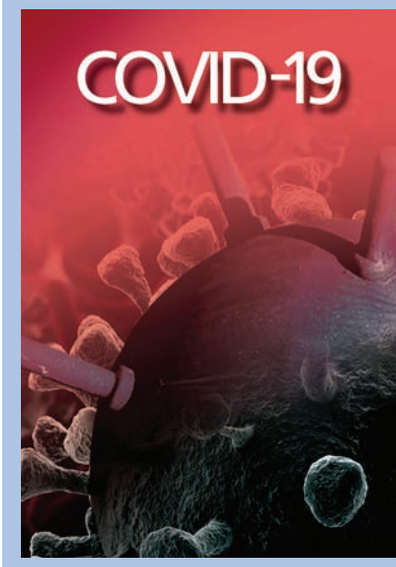

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Features of pathological anatomy of lungs at COVID-19

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Abstract

The research aim is to study the morphological features of COVID-19 in the lungs of patients who died in Moscow from March 20 to June 6, 2020. **Methods.** Autopsy material of the lungs from 123 deceased (54 women, 69 men) with COVID-19 coronavirus infection (confirmed by PCR) was analyzed, the median age was 71 (30 – 94) years, and the duration of the disease was 14 (3 – 65) days. In all cases, the patient's medical records and autopsy reports were analyzed. Macro- and microscopic changes in the lungs were evaluated in all the observations. **Results.** The pathology of the lungs in COVID-19 corresponds to various phases of diffuse alveolar damage (DAD). The exudative phase of DAD was detected in 54 (43.9%), the proliferative phase – in 21 (14.63%), and their combination – in 51 (41.46%) of the deceased. Histological features of different phases of DAD are described. **Conclusion.** An analysis of autopsy material revealed a mismatch between the duration of the course of the disease and the phase of diffuse alveolar damage. A significant portion of the dead found a combination of exudative and proliferative phases of the disease. Histological signs that indirectly indicate a violation of the coagulation system during COVID-19 are described.

Key words: COVID-19, viral interstitial pneumonia, pathology, coagulopathy.

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Особенности патологической анатомии легких при COVID-19

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Резюме

Целью статьи явилось изучение особенностей морфологических изменений в легких у умерших от COVID-19 в Москве за период 20.03.20–06.06.20. **Материалы и методы.** Проанализирован аутопсийный материал легких умерших от коронавирусной инфекции COVID-19 больных (n = 123: 54 женщины, 69 мужчин; средний возраст – 71 (30–94) год; продолжительность заболевания – 14 (3–65) суток), подтвержденной методом полимеразной цепной реакции. Проанализированы медицинские карты всех стационарных больных и все протоколы вскрытий. По данным всех наблюдений оценены макро- и микроскопические изменения в легких. **Результаты.** Патоморфологические изменения в легких соответствовали различным фазам диффузного альвеолярного повреждения (ДАП). Экссудативная фаза ДАП выявлена у 54 (43,9 %), пролиферативная – у 21 (14,63 %), их сочетание – у 51 (41,46 %) умершего. Описаны патогистологические особенности изменений в разные фазы заболевания. **Заключение.** При анализе аутопсийного материала установлено несоответствие между продолжительностью течения заболевания и фазой ДАП. У значительной части умерших обнаружено сочетание экссудативной и пролиферативной фазы заболевания. Описаны гистологические признаки, косвенно указывающие на нарушение системы коагуляции в течении COVID-19.

Ключевые слова: COVID-19, вирусная интерстициальная пневмония, патологическая анатомия, коагулопатия.

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Information about the epidemiology, clinical features, prevention, and treatment of the new coronavirus infection COVID-19 is still limited and is updated almost daily. In December 2019, an outbreak caused by the new coronavirus began in Wuhan, Hubei Province, China, leading to a pandemic declared by the World Health Organization (WHO) on March 11, 2020 [1]. According to phylogenetic studies, the pathogen was named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and the disease was named COronaVIrus Disease-2019 (COVID-19).

The high infectivity of the coronavirus, the lack of effective antiviral drugs and vaccines, and the potentially large number of asymptomatic patients have made it extremely difficult to prevent the spread of COVID-19. Unfortunately, about 20% of infected patients develop severe disease. On July 2, 2020, the mortality rate from COVID-19 in the world was 4.86%, according to the WHO data [2].

It is known that the most severe clinical manifestation of a new variant of coronavirus infection is viral interstitial pneumonia in the form of diffuse alveolar damage (DAD) (clinically ARDS), less often with the development of thrombohemorrhagic syndrome and septic shock. The respiratory distress syndrome that develops in patients with severe COVID-19 may differ from classic acute respiratory distress syndrome (ARDS). However, patients demonstrated the relatively intact lung mechanics in the presence of severe hypoxemia, characterized by high respiratory compliance and a high shunt fraction. Therefore, the pathology and pathophysiology of COVID-19 may differ from the known ARDS [3]. Dysregulation of the immune response during COVID-19 is characterized by a pro-inflammatory phase with the development of subsequent immune suppression [4]. Furthermore, it is assumed that microvascular disorders are a fundamental pathogenetic aspect leading to death in the most severe course of the disease [5].

Thus, the pathophysiology of the disease is not well understood. Data on the pathomorphological features of the disease are accumulating, but at the moment the number of such publications is limited.

The purpose of this article is to study the pathological changes in the lungs of those who died from COVID-19 in Moscow for the period from March 20 to June 6, 2020.

Materials and methods

The autopsy material of the lungs from 123 dead people (54 women, 69 men) was analyzed, the median age of the dead was 71 (30 – 94) years. In all observations, the inpatient's medical records and autopsy reports were analyzed. All these people had a new coronavirus infection, COVID-19, confirmed in vivo by Polymerase chain reaction (PCR) of nasopharyngeal smears. The duration of the disease (from the onset of symptoms to death) was 14 (3 – 65) days, the duration of hospitalization was 6 (1 – 65) days. Some of the patients underwent mechanical ventilation, the median duration of which was 4 (1 – 30) days.

Table 1
Basic clinical and laboratory findings
Таблица 1
Основные клинические и лабораторные показатели

Characteristic	Value
Sex, female/male	54/69
• Age*, years	71 (30 – 94)
• COVID-19 diagnosis (RT-PCR – naso-, oropharyngeal smears)**, *n* (%)	123 (100)
Time from the onset of symptoms to death, days*	14 (3 65)
The duration of hospitalization, days*	6 (1 – 62)
The duration of mechanical ventilation, days*	4 (1 – 30)
Comorbid diseaes**, *n* (%):	
Diabetes mellitus, type II	39 (32,5)
Obesity	19 (15,83)
• Arterial hypertension	61 (49,59)
• Chronic ischemic heart disease	30 (24,39)
• Chronic cerebral ischemia	4 (3,25)
• Myocardial infarct	3 (2,5)
• Leukemia, lymphomas	9 (7,5)
• Malignant tumors	5 (4,16)
• Chronic respiratory diseases	15 (12,5)
• HIV	4 (3,33)
• Kidney transplantation	1 (0,83)
• Lung tuberculosis	1 (0,83)
• Paraproctitis	1 (0,83)
• Laboratory parameters:	
• Total leucocyte count (× 10^9/L)***	11,24 ± 7,29 (1,4 – 31,4)
Absolute lymphocyte count (× 10^9/L)*	0,6 (0 – 9)
CRP, mg/ml*	170 (15 – 431)

Note: RT-PCR, Polymerase chain reaction in real time; CRP, C-reactive protein; *, median (minimum–maximum) for normal distribution quantitative variables; **, absolute values (%); ***, mean values ± standard deviation (minimum/maximum); reference values: for total number of leukocytes – (4.0 – 11.0) × 10^9/l, for absolute number of lymphocytes – (1.5 – 4.5) × 10^9/L, and for C-reactive protein concentration – < 5 mg/L.

Примечание: * – медиана (минимум–максимум) для количественных переменных с нормальным распределением; ** – абсолютные значения (%); *** – средние значения ± стандартное отклонение (минимум–максимум); референсные значения: для общего числа лейкоцитов – (4,0–11,0) × 10^9 / л, для абсолютного числа лимфоцитов – (1,5–4,5) × 10^9 / л, для концентрации С-реактивного белка – < 5 мг / л.

Table 2
The frequency of occurrence of histological signs; n (%)
Таблица 2
Частота встречаемости гистологических признаков; n (%)

Histological signs	Number of cases
Edema	104 (84,55)
Starch bodies	9 (7,32)
Hyaline membranes	99 (80,49)
Cytotoxic pneumocyte changes	63 (51,22)
Bronchial epithelium desquamation	92 (74,80)
Bronchial epithelium metaplasia	35 (28,45)
Pneumocyte desquamation	91 (73,98)
Alveolar metaplasia	60 (48,78)
Megakaryocytes	37 (30,08)
Intraalveolar macrophages	89 (72,36)
Intraalveolar plasmatic cells, lymphocytes	73 (53,35)
Intraalveolar neutrophils	40 (32,52)
Intraalveolar erythrocytes	93 (75,6)
Intrabronchial erythrocytes	15 (12,2)
Siderophages/haemosiderin in alveoli	46 (37,36)
Infarcts/hemorrhages	51 (41,46)
Thrombus in arteries	60 (42,78)
Thrombus in veins	31 (25,20)
Microthrombus (in capillaries, arterioles, venules)	12 (9,76)
Edematous myxoid stroma	11 (8,94)
Interstitial inflammation	69 (56,1)
Fibrin in alveoli	80 (65,04)
Fibrin in bronchi	6 (4,9)
Fibroblastic tissue	61 (49,59)
Fibrosis of alveolar septae	16 (13,01)
Alveolar capillary congestion	17 (13,82)
Acute swelling	15 (12,20)
Aspiration	3 (2,44)
Intraalveolar ossification	7 (5,69)
Vasculitis/microvasculitis	10 (8,13)
Bacterial pneumonia	30 (24,39)

Statistical analysis

Parameters with a normal distribution are presented as mean values ± standard deviation, those without a normal distribution are presented as a median (minimum–maximum). Qualitative variables are presented in terms of frequency and percentage distribution. The statistical software package Statistica, version 13 was used for the analysis.

At the autopsy a pronounced plethora of internal organs, especially the lungs was revealed; in some patients, multiple fine hemorrhages in the parietal and visceral pleura, shock kidneys were observed. The lungs usually filled the entire chest cavity. The weight of the lungs was 1,450 (700 – 3,200) g. Gross examination revealed a typical picture of "shock lungs": the lacquered appearance of the dark cherry surface of the lungs, the rubbery density of the tissue, in the section from dark cherry to brownish red in color (Figure 1).

A crimson, opaque, thick liquid, which was hardly squeezed out of the tissue, flowed from the cut surfaces. In some cases, areas of acute swelling were observed, more often in the anterior parts of the lungs. One could see atelectasis (distelectasis), hemorrhagic infarctions, as well as hemorrhages of various sizes, merging with each other, sometimes spreading on the whole lobes. In some patients, obstructing blood thrombi were found in the branches of the pulmonary arteries and veins. At later stages, the lungs were compacted; on the incision in these areas, the tissue was grayish or grayish-yellow in color (Figure 2).

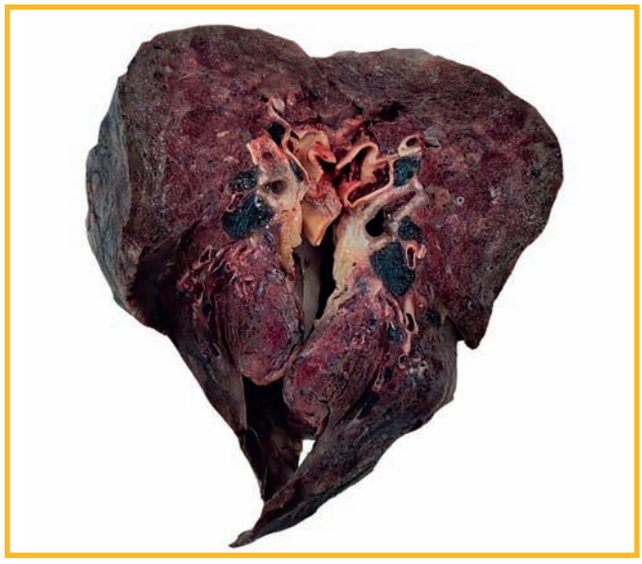

Figure 1. Gross cross section of the lung. "Shock lung": red surface with focal dark red areas (hemorrhage) under the visceral pleura

Рис. 1. Макропрепарат легкого. «Шоковое» легкое: на разрезе – ткань с чередованием участков красного и темного-красного цвета (кровоизлияния) под висцеральной плеврой

Figure 2. Gross cross section of the lung. Organizing pneumonia: large areas of gray-yellow color

Рис. 2. Макропрепарат легкого. Организующаяся пневмония: обширные участки серо-желтого цвета

Histological examination of the lungs revealed signs of viral interstitial pneumonia in the form of diffuse alveolar damage (DAP) in its various phases.

The exudative phase of DAP was detected in 54 (43.9%) deaths, the median duration of the disease in them was 11 (4 – 37) days. Histological examination in this group showed pronounced intraalveolar edema, hyaline membranes lining the contours of respiratory bronchioles, alveolar ducts, and sacs, alveoli in the form of strips of different thicknesses (Figure 3). There was damage to the epithelium associated with viral exposure desquamation of bronchial and bronchiolar epithelium, type I and II pneumocytes, a proliferation of type II pneumocytes (Figure 4).

Most of the deceased showed signs of cytopathic damage to the epithelium with the appearance of ugly pneumocytes characterized by a variety of shapes, changes in the nucleus with the appearance of nucleoli, atypical mitoses; in some of the cells, enlightenment around the nucleus in the form of a halo, as well as round particles in the cytoplasm of cells, were found. In the lumens of the alveoli, small symplasts were often found, and in some of the dead multinucleated pneumocytes. Along with changes in the alveolar epithelium, epithelial cells with enlarged

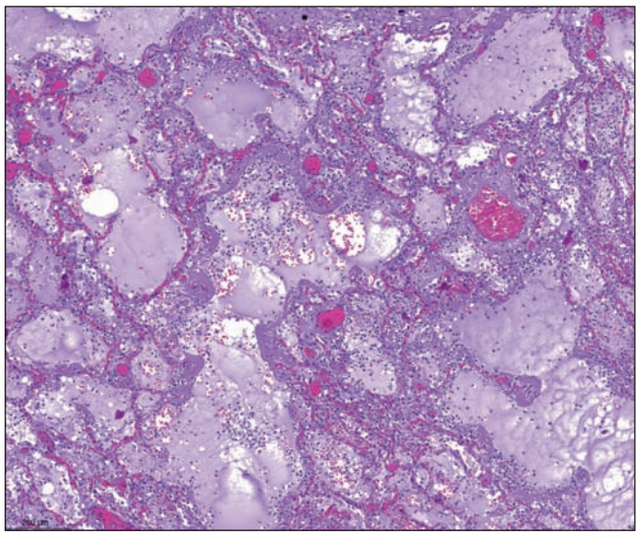

Figure 3. Intraalveolar edema with hyaline membranes lining the alveoli. H&E, × 100

Рис. 3. Внутриальвеолярный отек и гиалиновые мембраны по контуру альвеол. Окраска гематоксилином и эозином, × 100

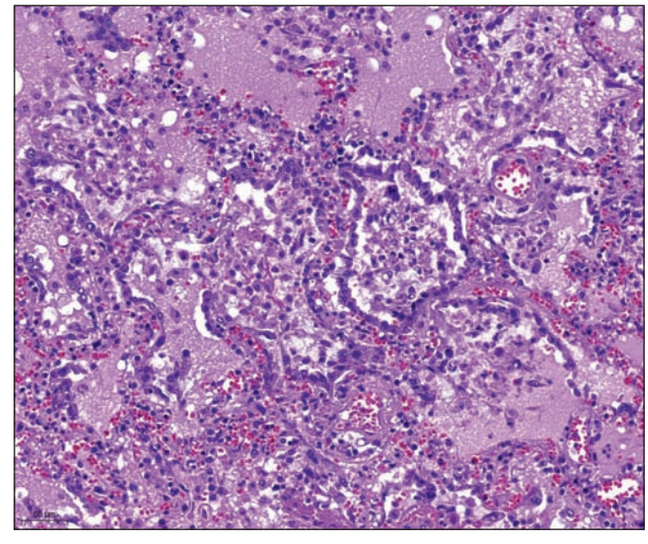

Figure 4. Intraalveolar edema, macrophages, desquamation of pneumocytes. H&E, × 200

Рис. 4. Внутриальвеолярный отек, пласты десквамированного альвеолярного эпителия и макрофаги в просветах альвеол. Окраска гематоксилином и эозином, × 200

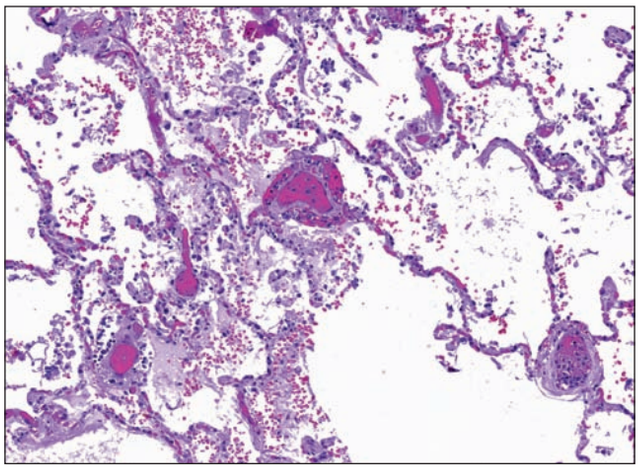

Figure 5. Mild intraalveolar edema, macrophages, lymphocytes, organizing thrombus in the arteriola, congestion of the arterioles. H&E, × 100

Рис. 5. Небольшой внутриальвеолярный отек, макрофаги, лимфоциты в просветах альвеол, организующийся тромб в артериоле, полнокровие артериол. Окраска гематоксилином и эозином, × 100

nuclei were observed among the desquamated bronchial epithelium. In some cases (6 deaths), fibrin was found in the lumens of the bronchi and bronchioles. Some patients were found to have blood vessel's congestion (branches of the pulmonary arteries and veins, capillaries of the interalveolar septa) with damage and desquamation of endothelial cells, with the sludge of erythrocytes, organizing and fibrin thrombi (Figure 5), foci of perivascular hemorrhages, erythrocyte accumulation in the bronchial lumen. A third of the deceased from this group had focal hemorrhages and/or hemorrhagic infarctions. In the vascular endothelium of patients with COVID-19, overexpression of FVIII was found (Figure 6). Interstitial inflammation in this phase was represented by lymphoid infiltration of the interalveolar septa. In some cases, there was a rather pronounced intraalveolar accumulation of lymphocytes and macrophages. In rare cases, phagocytosed cell fragments and erythrocytes were observed in the cytoplasm of alveolar macrophages (Figure 7).

The proliferative phase of DAP was detected in 21 (14.63%) dead with a disease duration of 17 (9 – 23) days and was characterized, along with the changes described above, by the appearance of intraalveolar fibrin accumulations of varying degrees of maturity; edema of interalveolar septa of varying severity, with their infiltration by lymphocytes, plasma cells, macrophages, sparse neutrophils. In this phase of the disease, some patients were found to have myxoid edematous stroma in the interalveolar septa and perivascular spaces. There was a proliferation of fibroblasts, as well as deposits of collagen in the walls of the alveoli. In some patients, interstitial inflammation was quite pronounced, which was manifested by an enlargement of the alveolar septa. In this phase, the organization of fibrin was observed with the appearance of scattered fibroblasts, a proliferation of fibroblastic polypoid tissue in the lumens of the alveoli and respiratory bronchioles. In some patients, starch bodies were found in the alveoli as a result of prolonged edema.

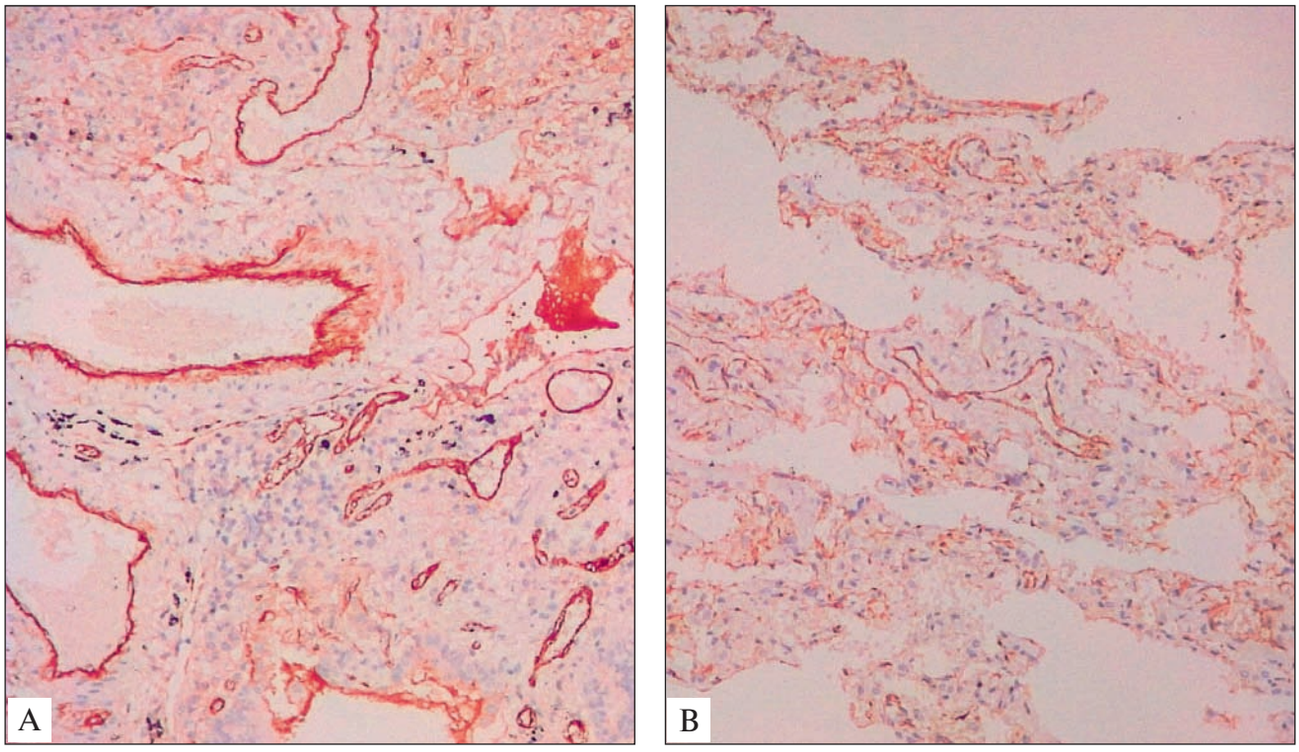

Figure 6. FVIII expression in endothelium: A, COVID-19 viral pneumonia; B, Control surgical material from the patient operated for lung cancer, unaffected area). IHC, × 200

Рис. 6. Экспрессия FVIII в эндотелии сосудов: А – при вирусной пневмонии COVID-19; В – в контрольном наблюдении (операционный материал пациента, оперированного по поводу рака легкого, неизмененный участок ткани). Иммуногистохимическое окрашивание, × 200

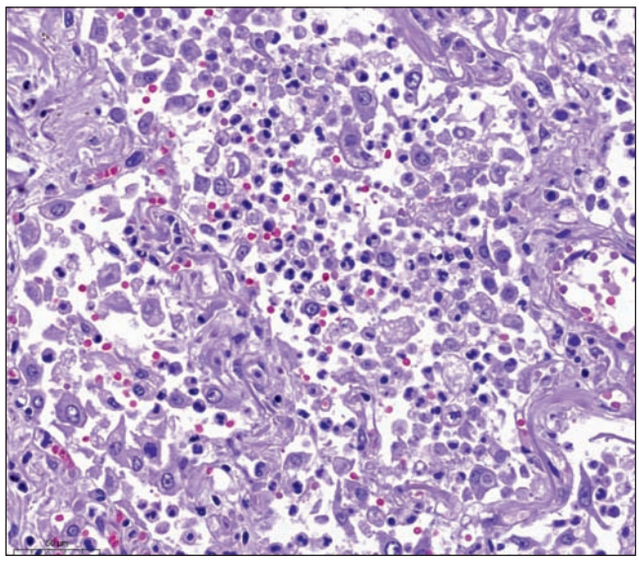

Figure 7. Intraalveolar accumulation of desquamation of pneumocytes with cytopathic changes, macrophages, autophagy: cell fragments it the cytoplasm of macrophages. H&E, × 250

Рис. 7. Скопления в просветах альвеол десквамированных альвеолоцитов с цитопатическими изменениями, макрофагов, аутофагия: клеточные фрагменты в цитоплазме макрофагов. Окраска гематоксилином и эозином, × 250

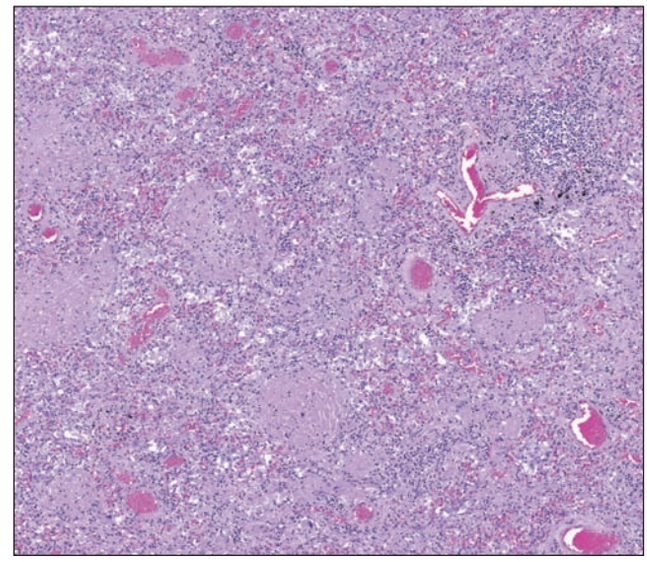

Figure 8. Intraalveolar fibroblastic tissue in the form of glomeruli, the focus of lymphoid infiltration. H&E, × 40

Рис. 8. Фибробластическая ткань в просветах альвеол в виде клубочков, очаг лимфоидной инфильтрации. Окраска гематоксилином и эозином, × 40

Intraalveolar accumulation of macrophages, lymphocytes, and plasma cells, more often found in the exudative phase, was also detected in some of the deceased in the proliferative phase of the disease. The last was characterized by the presence of reparative changes in the bronchiolar and alveolar epithelium in the form of proliferation of type II pneumocytes and squamous cell metaplasia. In some patients, focal areas of young connective tissue in the form of "glomeruli" were found (Figure 8). There were also areas of fibrotic atelectasis, consisting of delicate connective tissue with a small number of collagen fibers and smooth muscle proliferation (Figure 9). However, no significant fibrosis with collagen deposition was found in any of the dead. In 7 out of 54 deaths with signs of the proliferative phase of DAP, fragments of bone tissue were found within alveoli, with localization in one case among desquamated and metaplastic pneumocytes.

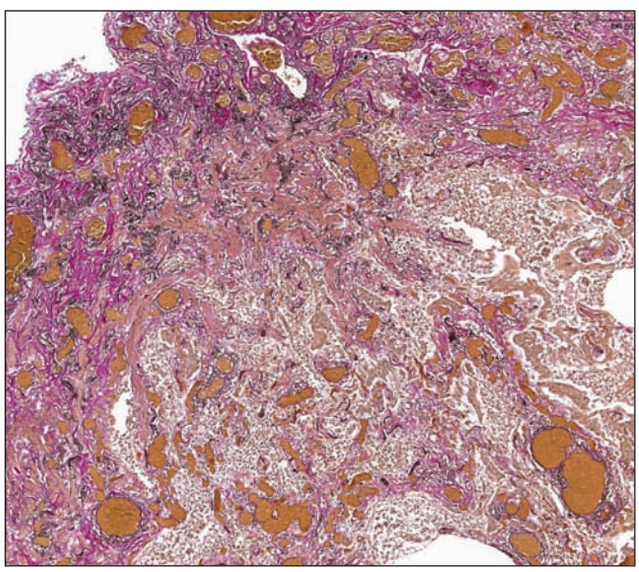

Figure 9. Subpleural fibrosis: connective tissue with a small number of collagen and elastic fibers, smooth muscle proliferation, angiomatosis. Stained with picrofuchsin by Van Gieson, × 50

Рис. 9. Подплевральный участок фиброза: соединительная ткань с небольшим числом коллагеновых и эластических волокон, пролиферацией гладких мышц, ангиоматоз. Окраска пикрофуксином по Ван Гизону, × 50

With COVID-19 infection, a combination of exudative and proliferative phases of diffuse alveolar damage was often observed in 48 (39.02%) dead, the median duration of the disease was 15 (11 – 65) days. So, in these cases, in some areas of the lung, there was an acute process with the presence of edema and hyaline membranes, in others, signs of a proliferative phase were revealed the organization of fibrin, foci of organizing pneumonia, sometimes quite abundant or foci of granulation tissue.

In some patients with a prolonged course of the disease (more than 15 – 20 days), in areas of the lung with typical signs of proliferative changes, edema, hyaline membranes and pronounced desquamation of pneumocytes, including those with signs of cytopathic changes, were revealed (Figure 10). With a long course of the disease, the appearance of siderophages in the alveoli was observed, as well as the deposition of iron-containing pigment in the endothelium and the vascular wall.

Histological changes, which could indirectly indicate the impairment of coagulation, namely the appearance of intraalveolar hemorrhages, blood clots in pulmonary arteries and veins, were found in all phases of the disease. Lymphoid infiltration of the vessels with sparse cells as minimal signs of vasculitis was found in 10 deceased (Figure 11), while acute vasculitis and endotheliitis were observed only in cases complicated with bacterial

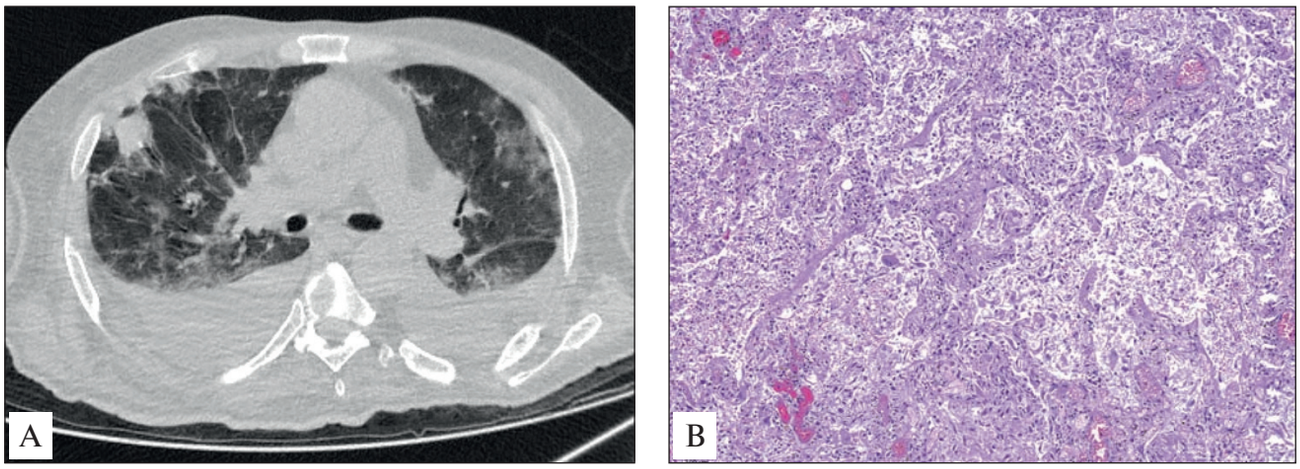

Figure 10. Patient 70 years old. SARS-CoV-2+. The duration of the disease is 65 days. The exudative with proliferative phase of diffuse alveolar damage: A, Computer tomogram of the lungs. Disease progression: foci of heterogeneous "ground-glass" opacity in the lingular of the left lung, areas of the round shape consolidation in the cortical zones of the right lung, bilateral pleural effusion; B, Fibroblastic tissue, desquamated pneumocytes with cytopathic changes, macrophages in the lumens of the alveoli, fibrosis of the alveolar septa. H&E, × 100

Рис. 10. Пациент 70 лет. SARS-CoV-2+. Продолжительность заболевания – 65 дней. Экссудативно-пролиферативная фаза диффузного альвеолярного повреждения: А – компьютерная томография легких. Прогрессирование заболевания (неоднородный участок уплотнения по типу неоднородного «матового стекла» в язычковых сегментах левого легкого, участки консолидации округлой формы в кортикальных отделах правого легкого, двусторонний плевральный выпот); В – фибробластическая ткань, десквамированный альвеолярный эпителий с цитопатическими изменениями, макрофаги в просветах альвеол, фиброз межальвеолярных перегородок. Окраска гематоксилином и эозином, × 100

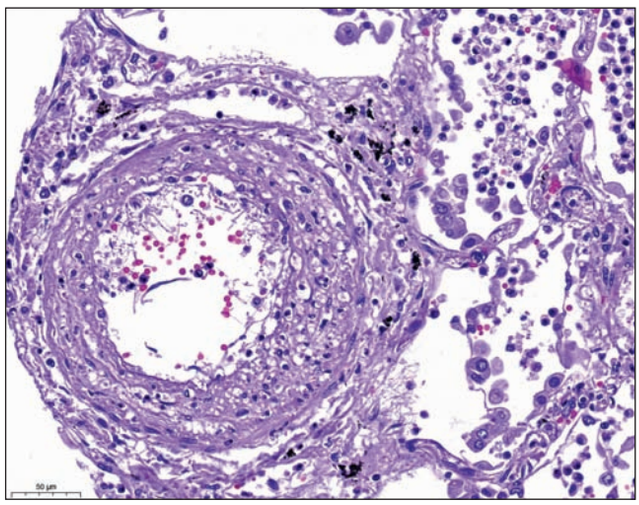

Figure 11. Immune inflammation in the vessel wall: lymphocytes in the intima and lumen of the branch of the pulmonary artery, reticular fibrin. H&E, × 100

Рис. 11. Иммунное воспаление в стенке сосуда: лимфоциты в интиме и просвете ветви легочной артерии, сетчатый фибрин. Окраска гематоксилином и эозином, × 100

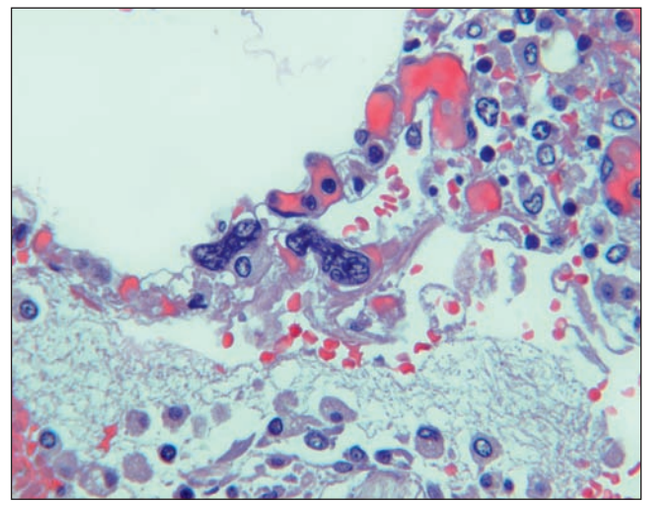

Figure 12. Megakaryocytes in the capillaries of intraalveolar septa, scanty macrophages and filaments of fibrin in the lumen of the alveoli. H&E, × 100

Рис. 12. Мегакариоциты в капиллярах межальвеолярных перегородок, единичные макрофаги и нити фибрина в просвете альвеолы. Окраска гематоксилином и эозином, × 100

pneumonia. In the capillaries of the interalveolar septa, megakaryocytes were found in more than one-third of the observations (Figure 12). In three cases of dead with confirmed COVID-19 infection (the duration of their disease was 4, 27, and 32 days, respectively), only minimal signs of intra-alveolar edema with single hyaline membranes were found in the lungs (Figure 13). At the same time, sludges of erythrocytes were found in the capillaries of the interalveolar septa, as well as fibrinous microthrombi or sludge of erythrocytes with their partial lysis and in the pulmonary arteries and veins.

Discussion

This study analyzed autopsy material of 123 deaths with a new coronavirus infection COVID-19 for the period from March 20 to June 6, 2020. At the beginning of our work, there were only a few descriptions of the lung pathology caused by the SARS-CoV-2 virus in the literature. To date, about 30 papers have been published, however, our study presents the analysis of the largest autopsy material to date.

A severe course of viral infection is characterized by the development of viral interstitial pneumonia, the typ-

ical morphological manifestation of which is diffuse alveolar damage. Histological changes in COVID-19 are similar to those previously described in severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and influenza A(H1N1) [7–9].

The most impressive feature of the morphological manifestations of COVID-19 is, in our opinion, is the discrepancy between the duration of the course of the disease and the phase of DAD. So, the changes characteristic of the exudative phase were observed on the 3rd – 37th day of the disease, and in some patients, the signs of proliferation could be detected as early as on the 7th day after the onset of symptoms. The latter fact can probably be explained by the fact that some patients have a long period of an asymptomatic or almost asymptomatic course of the disease. Besides, in 41.46% of cases, we identified a combination of exudative and proliferative phases of the disease. In a study by *A.N.Duarte-Neto et al.* a combination of exudative and proliferative phases of the disease was found in 8 out of 10 deaths [7]. The authors believe that this is due to the temporal evolution of the damage, as well as to mechanical ventilation. We suppose that a distinctive clinical course of the disease may be a possible explanation for this phenomenon. It is well known that in some patients a temporary improvement in the condition, as well as clinical and laboratory parameters, is followed by a repeated deterioration, which is probably associated with the sinuosity of the virus replication process in the epithelium of the lower respiratory tract and pneumocytes. This can also explain the fact that in some patients in the late proliferative phase of diffuse alveolar damage, we observed desquamation of the alveolar epithelium with marked cytopathic changes (see Figure 10). It cannot be ruled out that this may be due to the long-term persistence of the virus, which can be detected in the lung tissue for many days and could be a trigger for repeated lung injury and disease progression [10, 11]. However, in some patients in the late phase of the course of the disease, the viral RNA is no longer detected in the material of nasopharyngeal smears. In our opinion, this temporal heterogeneity distinguishes the course of COVID-19 from other types of viral pneumonia. During the epidemic caused by the influenza A(H1N1) virus, morphological changes corresponded to the duration of the disease and the phases of DAD [12].

Cytopathic changes in the epithelium are most likely due to direct viral cell damage. Bronchiolar epithelium, pneumocytes I and, predominantly, type II express receptors for angiotensin-converting enzyme-2 (ACE2), which allows the virus to enter the cell. The SARS-CoV-2 virus has been detected in the alveolar epithelium in a number of studies [11, 13]. Multinucleated pneumocytes are not characteristic of the influenza virus, they have also not been described in SARS and MERS, however, some authors indicate their presence in COVID-19 infection [14, 15]. The appearance of multinucleated epithelial cells probably reflects an impairment of the process of cell proliferation and normal epithelial repair. However, such cells were uncommon in our material.

The issue of viral damage to lymphocytes, mainly $CD4^+$ T-cells, is discussed in the literature. Although there are no receptors for ACE2 on lymphocytes, there is an assumption that the virus can enter the cell through membrane fusion and endocytosis. As a result, some of the lymphocytes may die, as is assumed by apoptosis or pyroptosis [16]. The fragments of cells and erythrocytes which we identified in the cytoplasm of macrophages may be indirect evidence of apoptosis of lymphocytes, but this requires further confirmation. The detection of such macrophages may also be indirect evidence of massive activation of the macrophage system, partially similar to that in secondary hemophagocytic lymphohistiocytosis [17]. Previously, signs of hemophagocytosis were found in the lymph nodes, spleen, bone marrow, heart, and liver [18]. Such changes were revealed in the exudative phase, during a certain period of which the most pronounced intraalveolar accumulation of macrophages, lymphocytes, and plasmocytes is determined, along with inflammatory infiltration of interalveolar septa. It is seeming that this occurs in the phase of the "cytokine storm" accompanied by a prompt decrease in the absolute number of lymphocytes in the blood of patients.

A number of morphological studies based on autopsy material from dead with COVID-19 have demonstrated a high incidence of thromboembolic events in the lungs. Thus, in a study by *D.Wichmann et al.* [19], a high incidence of deep venous thrombosis is indicated, which amounted to 58% in a group of 12 deaths, in the work of *C.Edler et al.* in 40% in a group of 80 deaths [20]. Many studies have confirmed the high frequency of blood clots and microthrombi in the lungs [21, 22]. However, in our opinion, despite the available data on systemic coagulation, in most cases these changes in the lungs should be regarded as thrombosis, not thromboembolism (except for clearly identified thromboembolism at autopsy). We took into account the nature of the intravascular contents from sludge erythrocytes to fibrinous thrombi, as well as reticular fibrin in the lumens of blood vessels in some cases. We found the organized fibrinous thrombi in the pulmonary artery only in two cases. At the same time, a high frequency of intrapulmonary thrombosis and microthrombosis is shown in many studies [20, 21]. *M.Ackermann et al.* depicted the 9 times higher incidence of capillary microthrombosis in COVID-19 than in influenza A(H1N1) [20]. Using scanning and convection corrosion electron microscopy, the authors demonstrated the presence of viral particles in the vascular endothelium of the lungs, as well as signs of capillary angiogenesis.

Coagulopathy is common in severe COVID-19. So, in a study of 191 patients with COVID-19, 50% of the deceased had signs of thrombotic disorders versus 7% in the survivors. A high concentration of D-dimer (> 1,000 μg/mL) is an unfavorable prognostic factor associated with a high risk of death [22]. However, it has been shown that in patients with COVID-19 there is no significant decrease in the proportion of platelets and the concentration of fibrinogen. As a rule, patients with new coronavirus infection do not develop disseminated intravascular coagulation syndrome (DIC). The latter was de-

tected in only a small portion of patients in the terminal stage of the disease. In this regard, coagulation syndrome in COVID-19 was proposed to be called "diffuse pulmonary intravascular coagulopathy" [17, 23].

Activation of the coagulation system has been described for some viral pneumonia, including coronavirus, as well as those caused by the Ebola virus, HIV, and dengue virus [24, 25]. Coronavirus infection can be a trigger for disturbance of the coagulation system, the pathogenetic mechanisms of which are complex and include endothelial dysfunction characterized by increased production of von Willebrand factor, systemic inflammation with activation of *Toll*-like receptors, as well as activation of procoagulant factors. It is assumed that the process of thrombus formation may be associated with hypoxia, which causes activation of transcription factors, and immune damage associated with the action of antiphospholipid antibodies [13, 25–28]. Some authors point to the presence of endotheliitis, including leukocytic, as a cause of endothelial damage [29]. In our observations, in 8.13% of patients, infiltration with sparse lymphocytes of the blood vessel's wall was detected. Thereby, the picture does not fit into the common picture of vasculitis; apparently, it is worth talking about immune vascular damage that develops after viral and cytokine damage [17].

Congestion and microthrombosis of the capillaries of the alveolar septa are one of the vivid morphological signs of viral pneumonia COVID-19 [19, 30]. *C.Magro et al.*, *C.Edler et al.* showed that in patients with plethora and microthrombosis of capillaries, the signs of diffuse alveolar damage were less pronounced [3, 20]. Such changes can be detected already in the early stages of the disease. However, in our work, in 4 patients, plethora and microthrombosis of the capillaries of the interalveolar septa in the presence of a minimal severity of edema and scarce hyaline membranes were detected 5 – 35 days after the onset of symptoms. In these patients, CT changes in the lungs indicated the presence of minimal viral pneumonia (see Figure 13). We assume that one of the possible causes of death in COVID-19 infection is impaired coagulation in the late stages of the disease, with almost complete resolution of viral pneumonia. The mechanisms of such damage require further study and clarification.

The appearance of megakaryocytes in the capillaries of the alveolar septa, in all likelihood, is also a sign reflecting an impairment of coagulation. Megakaryocytes in the capillaries of alveolar septa have been described by some authors in infection caused by SARS-CoV-2 [11, 13, 17, 31]. In the work of *V.V.Kungurova*, *S.V.Khasanyanov* it was shown that megakaryocytes can be found in the capillaries of alveolar septa and other organs in shock conditions of various etiologies [32], including sepsis [33]. Normally, megakaryocytes rarely leave the bone marrow, however, under the condition of hypoxia, the appearance of these cells in the capillaries of the lungs indicates intense hematopoiesis and can lead to local platelet formation. Besides, there are suggestions that some viruses, including dengue virus, can directly damage megakaryocytes, leading to impaired platelet production and thrombocytopenia [34]. The latter is one of the laboratory signs of COVID-19.

Squamous metaplasia of the bronchiolar and alveolar epithelium has been previously described in other viral pneumonia SARS, MERS, influenza A(H1N1). Some authors point to pronounced squamous cell metaplasia in COVID-19 [7, 22, 31, 35], which is most likely associated with direct viral damage to the epithelium, as well as with

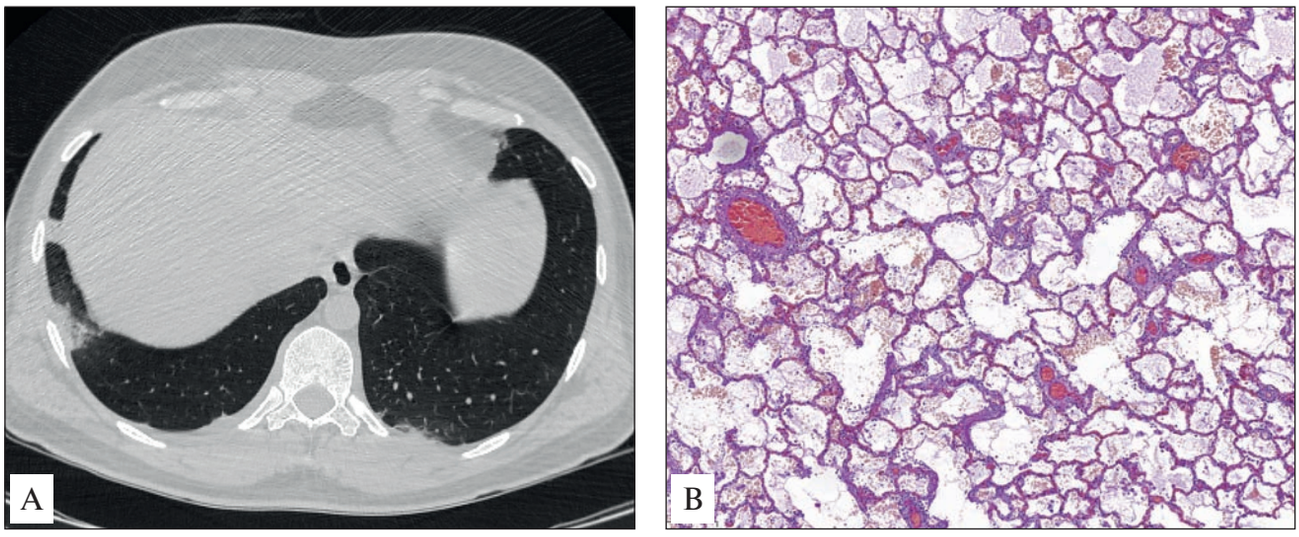

Figure 13. Patient 34 years old. SARS-CoV-2+. Concomitant disease: dilated cardiomyopathy. Disseminated intravascular dissemination: A, Computer tomogram of the lungs: Residual effects of viral pneumonia: subpleural site of heterogeneous consolidation in the lower lobe of the right lung, subpleural linear opacity in the lower lobe of the left lung; B, Minimal signs of intra-alveolar edema, single hyaline membranes, capillary congestion, erythrocyte sludges in the branches of the pulmonary artery

Рис. 13. Пациент 34 лет. SARS-CoV-2+. Сочетанное заболевание: дилатационная кардиомиопатия. Синдром диссеминированного внутрисосудистого свертывания. А – компьютерная томография легких. Остаточные явления вирусной пневмонии: субплевральный участок неоднородной консолидации в нижней доле правого легкого, субплевральное линейное уплотнение в нижней доле левого легкого; В – минимальные признаки внутриальвеолярного отека, единичные гиалиновые мембраны, полнокровие капилляров межальвеолярных перегородок, сладжи эритроцитов в ветвях легочной артерии

the effect of oxygen during ventilation in patients with the severe course of the disease. Previously, it was shown that the protein E of the coronavirus leads to damage to intercellular contacts [36] and subsequent impairment of repair processes.

In our study, in 5.7%, bone metaplasia was observed in the lungs during the proliferative phase of diffuse alveolar damage in COVID-19. The presence of bone metaplasia in the lungs with a new coronavirus infection is indicated by some authors [15]. The processes of calcification and ossification in the lungs can be associated with an increase in the serum concentration of calcium and phosphate, the activity of alkaline phosphatase, as well as with a local disturbance of pH in the tissue. Additional studies are needed to clarify the possible pathogenetic mechanisms of such a rapid (within 1 – 1.5 months) formation of calcifications and ossifications in the lungs in viral pneumonia [37].

In our study, the frequency of detection of histological signs of acute pulmonary distention was 12.2%, in half of the observations with invasive ventilation of the lungs, and in half in conditions of high-flow mask ventilation with oxygen. Probably, the toxic effect of oxygen can cause damage to the surfactant lining of the alveoli with the subsequent focal expansion of the alveoli and alveolar ducts.

Although the most dramatic changes in COVID-19 occur in the lungs, as a result of viral exposure, as well as the development of a systemic inflammatory response and thrombohemorrhagic syndrome, damage to other organs occurs. However, we did not set out to describe them as our goal in this work [38].

Conclusion

The pathology of the lungs in COVID-19 corresponds to viral interstitial pneumonia in the form of DAD. An analysis of 123 cases revealed a discrepancy between the duration of the course of the disease and the phase of DAD. In a significant portion of the patients, a combination of exudative and proliferative phases of the disease was found. Histological signs are described that indirectly indicate an impairment of the coagulation system during COVID-19.

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Effect of thermal helium-oxygen mixture on viral load in COVID-19

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Abstract

In this paper, we will discuss the use of t-He/O_2 in the treatment of patients with the viral disease COVID-19. **The aim** of the study is to evaluate the effect of thermal helium-oxygen therapy on viral load, inflammatory markers, and antibody synthesis. **Methods.** A single-center, randomized, prospective study included 60 patients with COVID-19. Patients were divided into two groups: 1 (n = 30; 17 male, 13 female) – t-He/O_2 therapy was included in the standard COVID-19 treatment Protocol; 2 (n = 30; 16 male, 14 female) – standard therapy in accordance with the clinical recommendations of Healthcare Ministry of Russia for patients with COVID-19. Of the 60 patients included in the study, 28 (46.7%) were medical professionals. The median age of patients in the study was 56.7 (45 – 61) years old. In the group 1 – 58 (45 – 59.5) years old, in the group 2 – 55 (46 – 66) years old. All patients had a positive test of SARS-CoV-2 coronavirus RNA, CT signs of "ground-glass opacity" type lung damage, and areas of air space consolidation. Patients were comparable by gender, age, body mass index (BMI), area of lesion of the pulmonary parenchyma, laboratory data. **Results**. As a result of the use of t-He/O_2, the elimination of the SARS-CoV-2 virus occurred within 48 – 72 hours from the start of inhalation and was confirmed by PCR test. The following changes were found in all patients: synthesis of IgM and IgG antibodies, increase in lymphocytes level, decrease of C-reactive protein, restoration of alanine aminotransferase and aspartate aminotransferase levels, D-dimer, and ferritin. These signs became more pronounced in the 1st group within 72 – 168 hours, compared with the 2nd group, where these results were achieved on the 10th day of therapy. **Conclusion**. The inclusion of thermal inhalation a gas mixture of helium and oxygen (t-He/O_2) in the standard therapy of patients carrying infectious disease caused by SARS-CoV-2 with CT signs of COVID-19 pneumonia (CT1, CT2 grades) reduces the viral load by stimulating antibody synthesis, as the type of immunoglobulin G, and immunoglobulin M causing the effect of "termovaccination"; increases the effectiveness of treatment, reducing the markers of inflammation.

Key words: thermal helium-oxygen mixture, helium, PCR, immunoglobulin G, immunoglobulin M, COVID-19.

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Влияние термической гелий-кислородной смеси на вирусную нагрузку при COVID-19

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Резюме

Представлен метод лечения больных COVID-19 при помощи термической гелий-кислородной смеси (t-He/O_2). **Целью** исследования явилась оценка влияния t-He/O_2 на вирусную нагрузку, маркеры воспаления и синтез антител (АТ). **Материалы и методы.** В одноцентровое рандомизированное проспективное исследование включены больные COVID-19 (n = 60; медиана возраста – 56,7 (45–61) года). Пациенты рандомизированы в 2 группы: в стандартный протокол лечения больных COVID-19 1-й группы (n = 30: 17 мужчин, 13 женщин; средний возраст – 58 (45–59,5) лет) включена терапия t-He/O_2; у пациентов 2-й группы (n = 30: 16 мужчин, 14 женщин; 55 (46–66) лет) проводилась стандартная терапия в соответствии с клиническими рекомендациями Министерства здравоохранения Российской Федерации для больных COVID-19. Из 60 пациентов, включенных в исследование, 28 (46,7 %) являлись медицинскими работниками. У всех больных результат теста РНК коронавируса SARS-CoV-2 был положительным, выявлены компьютерно-томографические (КТ) признаки поражения легких по типу «матового стекла» и участки консолидации. Пациенты были сопоставимы по полу, возрасту, индексу массы тела, площади поражения легочной паренхимы, лабораторным данным. **Результаты**. В результате применения t-He/O_2 элиминация вируса SARS-CoV-2, подтвержденная методом полимеразной цепной реакции, происходила в течение 48–72 ч от момента начала ингаляции. У всех пациентов обнаружены следующие изменения: синтез АТ иммуноглобулина (Ig) M и -G, повышение уровня лимфоцитов, снижение уровня С-реактивного белка, восстановление уровней аланин- и аспартатаминотрансферазы, D-димера, ферритина. Эти признаки становились более выраженными у пациентов 1-й группы в течение 72–168 ч по сравнению с таковыми у больных 2-й группы, где эти результаты достигались на 10-е сутки терапии. **Заключение**. При включении ингаляций t-He/O_2 в стандартную терапию пациентов, переносящих инфекционное заболевание, вызванное SARS-CoV-2, с КТ-признаками пневмонии I и II степени тяжести отмечено снижение вирусной нагрузки и уровня маркеров воспаления, повышение эффективности лечения; происходит также стимуляция синтеза АТ IgG и IgM, вызывая эффект «термовакцинации». В настоящее время изучается ответ на воздействие t-He/O_2 у пациентов с КТ-признаками пневмонии III степени тяжести. Продемонстрирован положительный эффект у тяжелых больных, однако при этом требуются дальнейшее изучение и статистический анализ результатов терапии.

Ключевые слова: термическая гелий-кислородная смесь, гелий, полимеразная цепная реакция, иммуноглобулин G, иммуноглобулин M, COVID-19.

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

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The first outbreak of the new coronavirus disease 2019 (COVID-19) began in December 2019 in Wuhan, China and has evolved into a major pandemic [1, 2]. A severe acute respiratory syndrome coronavirus (SARS-CoV-2) was later identified as the causative agent. This virus is enveloped in a positive-stranded RNA [3, 4]. About 28,506,254 cases of COVID-2019 and 915,920 deaths (as of) were registered globally by September 11, 2020 [1]. The fight against the coronavirus infection is an extremely acute issue that requires the development of new methods to expand the therapeutic and preventative options. WHO have not recommended any medicinal product for the treatment of COVID-19 yet. The currently recommended and used therapeutics are supportive. Some repurposed anti-HIV and antiviral drugs are currently in use, including hydroxychloroquine, remdesivir, lopinavir/ritonavir, interleukin 6 (IL-6) receptor inhibitors, and plasma therapy [5–8].

Great hopes are set on the development of synthetic vaccines that affect the antibody synthesis and specifically interact with certain proteins of the virus. The issue of finding new methods for treatment of COVID-19 is pressing.

We have developed a new method based on the use of thermoheliox (inhalation of a high-temperature mixture of helium and oxygen – t-He/O_2).

Helium is an inert gas. It was discovered by *P.Janssen* and *N.Lockyer*, and both reported the discovery independently to the French Academy of Sciences in 1868. Academician *P.L.Kapitsa* played an important role in the study of the physicochemical properties of helium. He began his research during his internship in Rutherford laboratory in London (1938), and continued it in Moscow together with Academician *D.L.Landau* [9–13]. Both scientists were awarded the Nobel Prize for their research on the physical properties of helium.

The authors of this article have more than 20 years of clinical experience with heliox. Initially, we used a thermal helium-oxygen mixture in patients with hypoxemic respiratory failure, and then in patients with hypercapnic respiratory failure [2, 3].

In the recent years, this experience has been used in a neurological clinic for the treatment of patients with ischemic stroke [14, 15] and in obstetrics to correct the oxygen status of pregnant women in the III trimester [4].

[1] *https://news.mail.ru/story/incident/koronavirus*

[2] Kutsenko M.A. [Using an oxygen-helium mixture to treat acute respiratory failure in patients with an exacerbation of chronic obstructive pulmonary disease]: Thesis for a candidate degree in medical sciences. Moscow; 2000 (in Russian).

[3] Shogenova L.V. [The efficacy of heliox therapy in patients with acute respiratory failure against an obstructive pulmonary disease]: Thesis for a candidate degree in medical sciences. Moscow; 2003 (in Russian).

[4] Patent No.RU2727750C1 registered in the Russian Federation as of November 08, 2019. Shuginin I.O., Panin A.A., Chuchalin A.G., Petrukhin V.A., Shidlovskaya N.V., Lysenko S.N. [A treatment method for pregnant women with placental insufficiency]. Available at: *https://patenton.ru/patent/RU2727750C1* (in Russian).

Our clinical study was preceded by a theoretical analysis of the development of acute viral infection with an assessment of the potential therapeutic effects of t-He/O_2 inhalation. The kinetic model included a description of growth and reproduction of the virus in the human body, the viral damage to the recipient cells, the effects of thermal destruction of viruses, and the antibody response. Theoretical analysis predicted the potential effects of inhalation of t-He/O_2, i.e. the production of antibodies against the proteins of the destroyed viral particles [16]. The analysis of the protein composition of the patient's exhaled air condensate confirmed the safety of thermoheliox [17].

This article discusses the use of t-He/O_2 in the treatment of COVID-19.

Materials and methods

Study group. A single-center, randomized, prospective study included 60 patients with COVID-19. Patients were divided into two groups. Group 1 (n = 30) received the standard COVID-19 treatment protocol together with the t-He/O_2. Group 2 (n = 30) received the standard treatment in accordance with the clinical recommendations of the Ministry of Health of the Russian Federation "Prevention, diagnostics, and treatment of the novel coronavirus infection COVID-19" [version 5 (approved by the Ministry of Health of the Russian Federation on March 08, 2020), version 6 (approved by the Ministry of Health of the Russian Federation on April 28, 2020), version 7 (approved by the Ministry of Health of the Russian Federation on June 3, 2020)] [18]. Of the 60 patients included in the study, 28 (46.7%) were medical professionals. The male/female ratio was 17/13 in Group 1, and 16/14 in Group 2. The groups were matched by the sex ratio, p = 0.403. The median age of the patients was 56.7 years (45 to 61 years). The median age was 58 years (45 years; 59.5 years) in Group 1 and 55 years (46 years; 66 years) in Group 2. The groups were matched by age, p = 0.537. The general characteristics of the patients at the enrollment are shown in Table 1.

The clinical symptoms in Groups 1 and 2 are characterized in Table 2. The symptoms included: a loss of smell and taste, runny nose, shortness of breath, dyspnea, weakness, fever, headache, muscle pain, sore throat, and dry cough.

All patients who were enrolled in the study according to the protocol No.11 – 20 dated April 20, 2020, approved by the Ethics Committee on Biomedical Ethics of the N.V.Sklifosovsky Research Institute for Emergency Medicine of Moscow Department of Health received treatment for pneumonia caused by the SARS-CoV-2 virus from April 21 to June 2020 both inclusive.

The diagnostic procedures included specific molecular tests of the respiratory samples (throat and nasopharyngeal swab) (detecting amplifier CFX-96 REAL TIME, Bio-Rad, USA), lung CT scan, express analysis of the gas composition of arterial blood on an automatic analyzer ABL-500 (Radiometer Copenhagen, Denmark), measurement of serum IgM and IgG on an immunochemiluminescent analyzer (Mindray 6000, USA), complete blood count, analyses of serum markers (D-dimer, C-reactive protein [CRP], ferritin, lymphocytes, aspartate aminotransferase, AST, and alanine aminotransferase, ALT).

Table 1
General characteristics of patients in groups at the time of inclusion in the study
Таблица 1
Общая характеристика пациентов на момент включения в исследование

Parameter	Group 1 (n = 30)	Group 2 (n = 30)
Age, years	56 [45; 59.5]	52 [46; 66]
Sex, male/female	17/13	16/14
Duration of the disease, days	2 [1; 4]	3 [1; 5]
Respiratory rate, min^{-1}	25.9 [22; 28]	24.9 [20; 27]
Heart rate, min^{-1}	110.6 [89.3; 122.1]	115.2 [91.7; 128.4]
SpO_2, %	94 [88; 96]	93 [87; 95]
Positive PCR for coronavirus, n	30	30
CT signs of pneumonia (lesion volume in %)	25.2 [21; 42.5]	26 [25; 41.7]
NIV / high flow oxygen therapy, n	24	23
D dimer, ng/mL	358 [270; 387]	354 [294; 432]
C-reactive protein, mg/L	65.1 [45.2; 75.6]	62.1 [39.1; 67.4]
Ferritin, mg/L	568.8 [423.2; 620.8]	602.8 [529.4; 75.3]
Lymphocytes, %	15.4 [12.8; 23.2]	17.2 [14.7; 28.1]
AST, U/L	35.4 [30.2; 49.1]	34.2 [28.9; 43.5]
ALT, U/L	38.1 [34.1; 42.1]	36.2 [32.1; 39.2]
Immunoglobulin IgM, COI	0.8 [0.62; 3.21]	1.2 [0.79; 3.18]
Immunoglobulin IgG, U/mL	16.5 [12.2; 22.1]	17.1 [15.1; 25.1]

Note: SpO_2, saturation of hemoglobin with oxygen; PCR, polymerase chain reaction, CT, computed tomography of the lungs; AST, aspartate transaminase; ALT, alanine aminotransferase. The quantitative data are presented as median (lower and upper quartiles).

Примечание: количественные данные представлены как медиана (нижний – верхний квартиль).

All patients had a positive test of SARS-CoV-2 coronavirus RNA, the ground-glass opacities in the lung CT, and the areas of air space consolidation.

The inclusion criteria were:

- Age > 18 years;
- Positive RNA test of SARS-CoV-2 coronavirus
- CT signs of viral pneumonia (CT1, CT2);
- Oxygenation index ⩾ 150 according to the Berlin classification;
- Increased CRP and ESR.

Table 2
General characteristics of clinical symptoms in group 1 and 2; n
Таблица 2
Общая характеристика клинических симптомов у пациентов 1-й и 2-й групп; n

Symptoms	Group 1 (*n* = 30)		Group 2 (*n* = 30)	
	yes	no	yes	no
Loss of smell and taste	27	3	25	5
Runny nose	25	5	24	6
Shortness of breath	28	2	27	3
Dyspnea	28	2	27	3
Weakness	26	4	25	5
Fever	29	1	30	0
Headache	24	6	29	1
Muscle pain	25	5	29	1
Sore throat	27	3	25	5
Dry cough	28	2	28	2

The exclusion criteria were:
- an oxygenation index < 150;
- mechanical ventilation;
- severe impairment of consciousness (score on the Glasgow scale less than 10);
- unstable hemodynamics (systolic blood pressure < 90 mm Hg, heart rate < 50 min or > 160 min);
- hemoglobin < 115;
- profuse sputum secretion;
- vomiting that interfered with the use of masks;
- acute cerebrovascular accident (ACV);
- acute myocardial infarction (AMI) within the last 6 months, and pregnancy.

Study design

All patients underwent swabs from the mucous membrane of the nasal cavity and oropharynx to detect SARS-CoV-2 coronavirus RNA; sampling of venous blood for IgG (semiquantitative) and IgM (semiquantitative) antibodies of SARS-CoV-2 coronavirus by the standard enzyme immunoassay method, for CPB, D-dimer, ferritin, lymphocytes, AST, and ALT levels. Schedule of the examinations is presented in Table 3. The study design is shown in Figure 1.

Treatment with gas mixtures

The t-He/O_2 therapy was performed on the Heliox-Extreme apparatus (LLC Medtekhinnovatsii Russia, medical device code: 944460 (TU 9444-001-0116489960-2915)) through separate oxygen and helium ports. Oxygen was supplied from a centralized hospital oxygen distribution system. Medical helium "A" from a 10-liter metal cylinder under a pressure of 200 atm through a 15 atm pressure regulator (GCE, China). In this work, we used medical helium grade "A" (99.995%; TU 20.11.11-005-45905715-2017, NII KM, RF). The apparatus was mixing two gases (helium and oxygen) in accordance with the specified concentrations. Then the mixture of He and O_2 through the breathing filter Inter-Guard™ (Intersurgical Ltd, UK) and the Flextube hose (Intersurgical Ltd, UK) was fed into the thermistor of the Heliox-Extreme apparatus, which was connected to the exhalation valve (Intersurgical

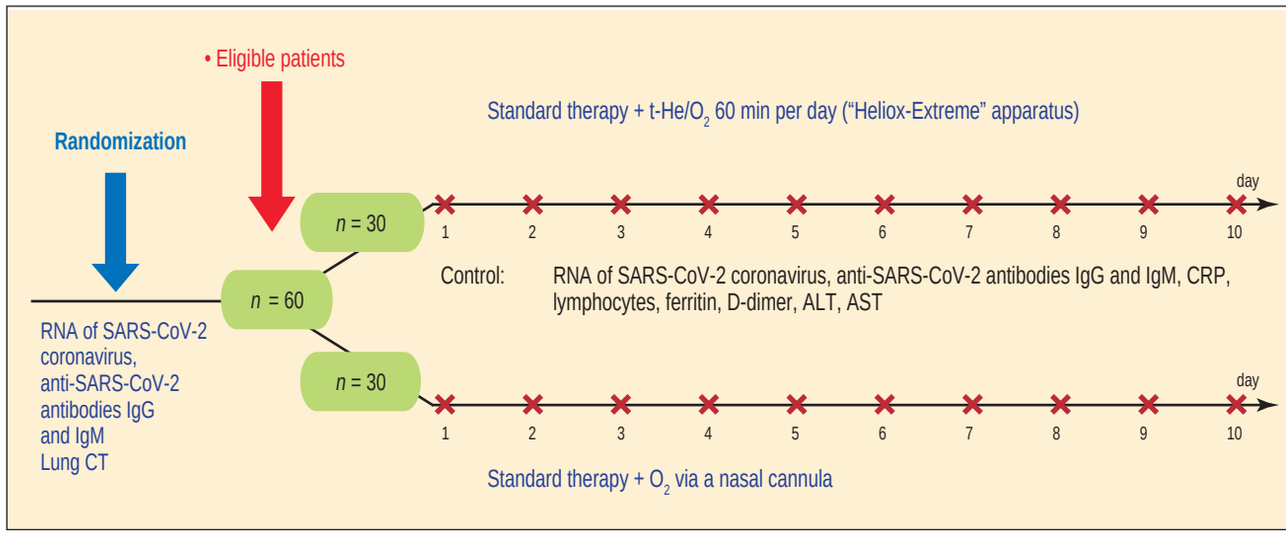

Figure 1. The design of the study (randomized simple comparative) in parallel group ($n = 60$)
Note: t-He/O_2, thermal helium-oxygen mixture; Ig, immunoglobulin; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CT, computed tomography.

Рис. 1. Дизайн исследования (рандомизированное простое сравнительное) в параллельных группах ($n = 60$)

Table 3
Monitoring interval by day in the study groups
Таблица 3
Интервал мониторирования по дням в исследуемых группах

Parameter	Screening/Randomization	Day									
		1	2	3	4	5	6	7	8	9	10
PCR	+	+	+	+	+	+	+	+	+	+	+
Immunoglobulin IgG, U/mL	+			+				+			+
Immunoglobulin IgM, COI	+			+				+			+
CRP, mg/L	+	+	+	+	+	+	+	+	+	+	+
D dimer, ng/mL		+		+				+			+
CRP, mg/L		+		+				+			+
Ferritin, mg/L		+		+				+			+
Lymphocytes, %		+		+				+			+
AST, U/L		+		+				+			+
ALT, U/L		+		+				+			+

Note: PCR, polymerase chain reaction; Ig, immunoglobulin; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Ltd, UK) and the facial anesthetic mask QuadraLite (Intersurgical Ltd, UK).

The patients underwent 4 daily inhalation procedures for 15 minutes with 15-minute intervals. The concentration of He and O_2 was selected individually for each patient in the range from 79 to 50% (He) and from 21 to 50% (O_2) to maintain SpO_2 within 97 – 99% at temperatures from 75 to 96 °C, depending on the saturation index, tidal volume, and the patient comfort.

At $SpO_2 \geqslant 93\%$, the inhalation of t-He/O_2 started with 79% He and 21% O_2 at a temperature of 85 – 96 °C with a gradual increase in O_2 fraction by 2% every minute until the target SpO_2 97 – 99%.

At $85 \leqslant SpO_2 \leqslant 92\%$, the inhalation of t-He/O_2 started with 70 He and 30% O_2 at a temperature of 85 – 96 °C with a gradual increase in O_2 fraction by 2% every minute until the target SpO_2 97 – 99%.

At $SpO_2 < 85\%$, the inhalation of t-He/O_2 started with 65% He and 35% O_2 at the temperature of 75 – 84°C with a gradual increase in O_2 fraction by 2% every minute. The O_2 fraction did not exceed 50%, i.e. the ratio of helium and oxygen not more than 50 : 50% while maintaining SpO_2 97 – 99%.

The maximal allowed tidal volume (TV) was 1,000 mL. If the TV was more than 1000 ml, we interrupted the breathing cycle from the circuit of the apparatus and the patients made one or two breaths of an air mixture with FiO_2 21%. Then, the face mask was put back on, and breathing with t-He/O_2 was continued with the same concentration of He and O_2. SpO_2 was monitored using an OxyShuttle pulse oximeter (Sensor Medics, USA). The TV was monitored with a monitor built into the Heliox-Extreme apparatus.

Statistical analysis

The statistical processing of the data was carried out using the SPSS 17.0 software package (SPSS Inc., USA). The quantitative parameters are presented as median (Me) and quartiles (lower and upper quartiles). The nonparametric statistic methods with Mann–Whitney U-test were used to compare the variables between the groups. Friedman rank analysis of variance followed by paired comparison with the Wilcoxon test was used to assess the changes over time in each group. The differences were considered statistically significant at $p < 0.05$.

Results

No patients had any objective procedure-related side effects during the inhalation therapy with t-He/O_2. One patient refused inhalation therapy on Day 2 because he did not tolerate the fever well. From that moment on, 29 patients in Group 1 and 30 patients in Group 2 continued the therapy. None of the patients were transferred to mechanical ventilation. There were no lethal outcomes in both groups. All patients were discharged. The median hospital stay was 15 (13.35) [12,7; 34,6] days.

Changes of the PCR results over time. Group 1 showed statistically significant decrease in positive RNA tests for the SARS-CoV-2 coronavirus. According to our observations, most COVID-19 patients from Group 1 who received inhalation of t-He/O_2 had a negative PCR on Day 3 and some patients had a negative result as early as 1 day after the start of therapy. The patients in the standard therapy group has a positive test for the viral antigen from 7 days to 4 weeks from the onset of the disease, in some cases even longer (Figure 2).

Changes in the D-dimer test results over time. Group 1 showed a statistically significant decrease in the D-dimer level on Day 3 as compared to Day 7 in the Group 2. The change of D-dimer level within 10 days was significantly higher in the Group 1 (Figure 3).

Changes in the ferritin level over time. The ferritin level stayed high in both groups. The statistically significant decrease in the ferritin level was observed on Day 7 and Day 10 (Figure 4).

Changes in the CRP level over time. The standard therapy group kept a statistically significant increase in CRP on Day 3 and the statistically significant decrease on

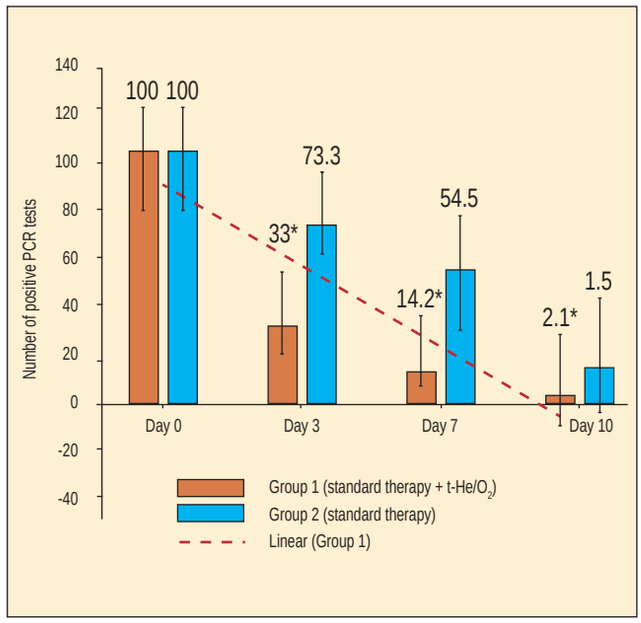

Figure 2. Number of the positive polymerase chain reaction tests in comparison groups
Note: PCR, polymerase chain reaction; t-He/O_2, thermal helium-oxygen mixture; *, $p < 0.05$.

Рис. 2. Количество положительных тестов при проведении анализа методом полимеразной цепной реакции в группах сравнения
Примечание: * – $p < 0,05$.

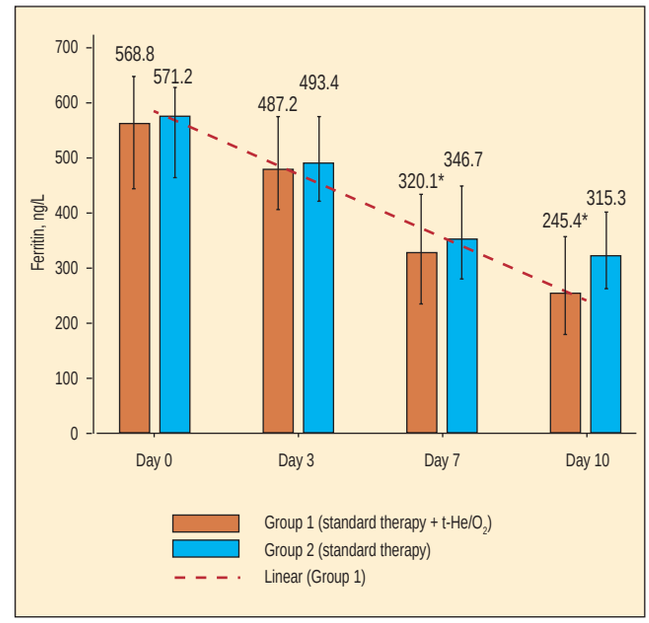

Figure 4. Dynamics of the ferritin indicator in comparison groups
Note: t-He/O_2, thermal helium-oxygen mixture; *, $p < 0.05$.

Рис. 4. Динамика изменения уровня ферритина в группах сравнения
Примечание: * – $p < 0,05$.

Day 7 and Day 10. Group 1 showed a statistically insignificant increase in CRP on Day 3. The decrease in CRP level on Day 7 and Day 10 in Group 1 was statistically significant as compared to Group 2 (Figure 5).

Changes in lymphocyte levels over time. Low lymphocyte levels were reported in Groups 1 and 2 at baseline. The addition of t-He/O_2 to the complex therapy made it possible to significantly increase the level of lymphocytes

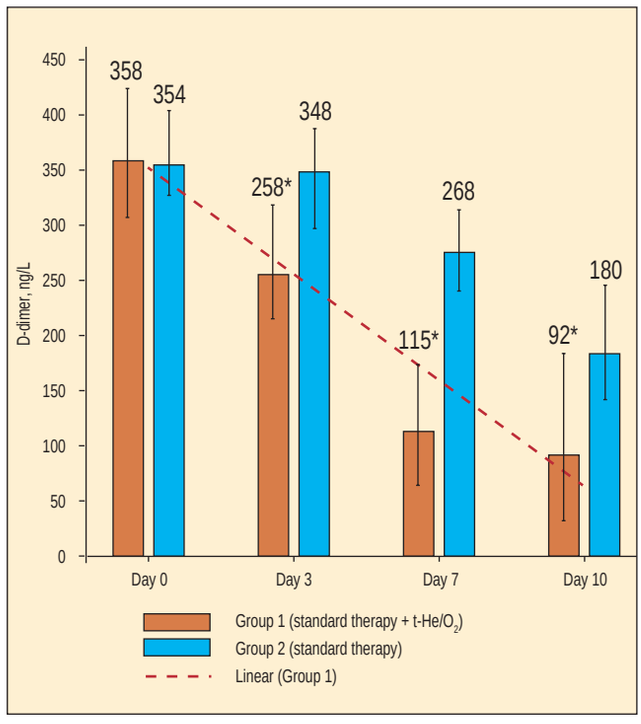

Figure 3. Dynamics of the D-dimer indicator in comparison groups
Note: t-He/O_2, thermal helium-oxygen mixture; *, $p < 0.05$.

Рис. 3. Динамика изменения уровня D-димера в группах сравнения
Примечание: * – $p < 0,05$.

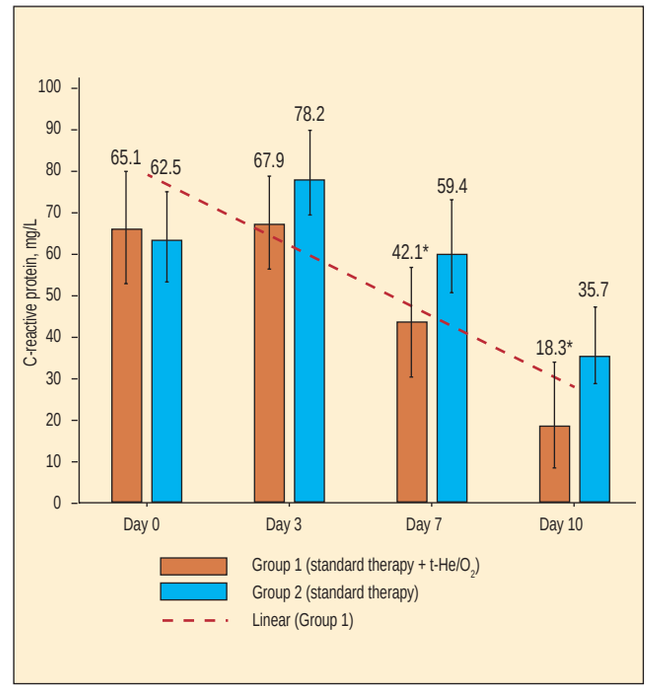

Figure 5. Dynamics of the DRR indicator in comparison groups
Note: t-He/O_2, thermal helium-oxygen mixture; *, $p < 0.05$.

Рис. 5. Динамика изменения уровня С-реактивного белка у пациентов групп сравнения
Примечание: * – $p < 0,05$.

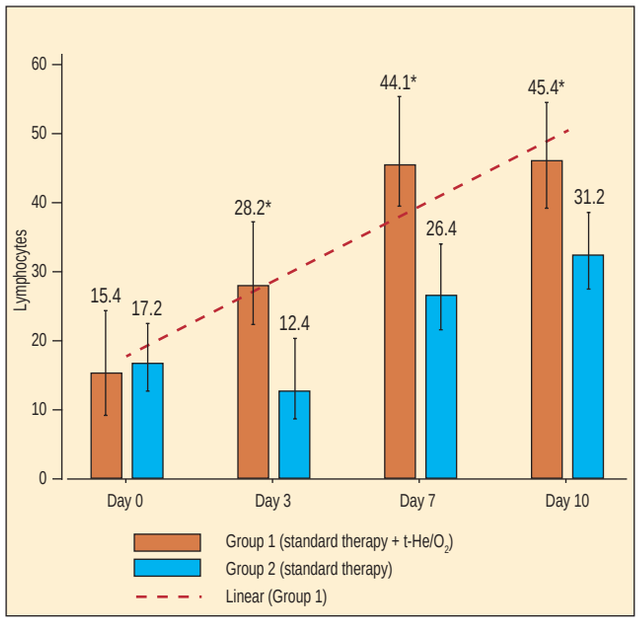

Figure 6. Dynamics of lymphocytes in the comparison groups
Note: t-He/O_2, thermal helium-oxygen mixture; *, $p < 0.05$.

Рис. 6. Динамика изменения уровня лимфоцитов в группах сравнения
Примечание: * – $p < 0,05$.

in the Group 1 on Day 3 and to achieve full recovery on Day 7. Group 2 showed a statistically significant decrease in lymphocyte level on Day 3 as compared to the baseline. The lymphocyte level increased significantly on Day 3 and Day 7, but the growth was significantly lower than in Group 1 (Figure 6).

Changes in ASTs over time. High AST levels were reported in Groups 1 and 2 at baseline. Group 1 showed a statistically significant decrease in AST level on Day 3 and a continued decrease on Days 7 and 10. Group 2 showed an increase in AST on Day 3, and the difference from the baseline was statistically significant. The AST level dropped on Days 7 and 10, but a lesser extent than in Group 1 (Figure 7).

Changes in ALT levels over time. High ALT levels were reported in Groups 1 and 2 at baseline. Group 1 showed a statistically significant decrease in ALT level on Day 3 and a continued decrease on Days 7 and 10. Group 2 showed a continued growth of the ALT level on Day 3. The ALT level decreased on Day 3 and 7 but it was still significantly higher than the baseline. The ALT level decreased on Days 3 and 7 but to a lesser extent than in Group 1 (Figure 8).

Changes in IgM levels over time. The immune response was confirmed in both groups at baseline. The immune response showed a statistically significant peak on Day 7 and decreased by Day 10 in Group 1. Meanwhile, Group 2 showed the peak immune response on Day 10 (Figure 9).

Changes in IgG levels over time. Group 1 had a statistically significant increase in IgG levels on Day 3 of the t-He/O_2 therapy and a continued significant growth on Days 7 and 10. The Group 2 had a statistically insignificant increase in IgG levels on Days 3 and 7 of the standard therapy. The statistically significant increase in the IgG levels was reported on Day 10 as compared to the baseline. The increase in the IgG levels on Days 3, 7, and 10 in Group 1 was significantly higher than in Group 2 (Figure 10).

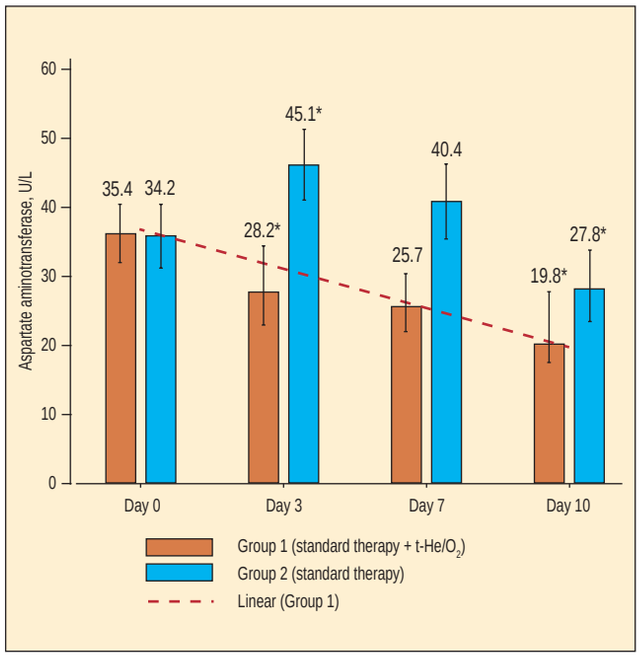

Figure 7. The dynamics of aspartateaminotransferase in the comparison groups
Note: t-He/O_2, thermal helium-oxygen mixture; *, $p < 0.05$.

Рис. 7. Динамика изменения уровня аспартатаминотрансферазы в группах сравнения
Примечание: * – $p < 0,05$.

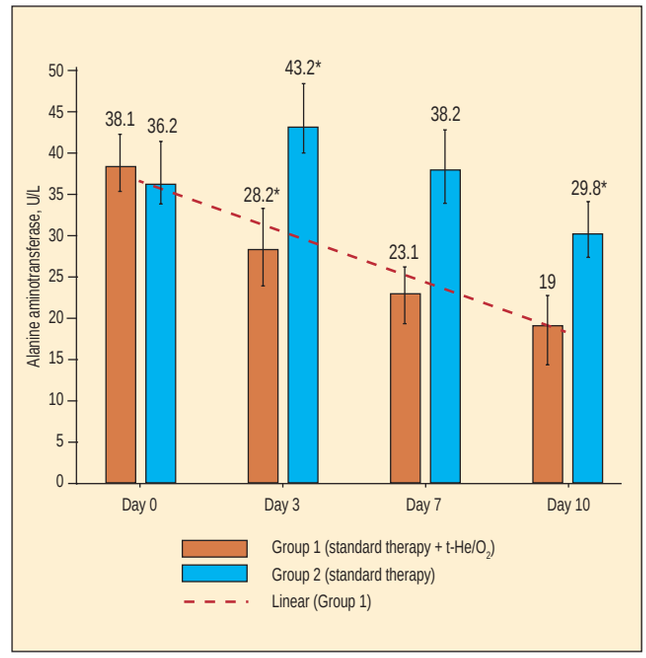

Figure 8. The dynamics of alanineaminotransferase in the comparison groups
Note: t-He/O_2, thermal helium-oxygen mixture; *, $p < 0.05$.

Рис. 8. Динамика изменения уровня аланинаминотрансферазы в группах сравнения
Примечание: * – $p < 0,05$.

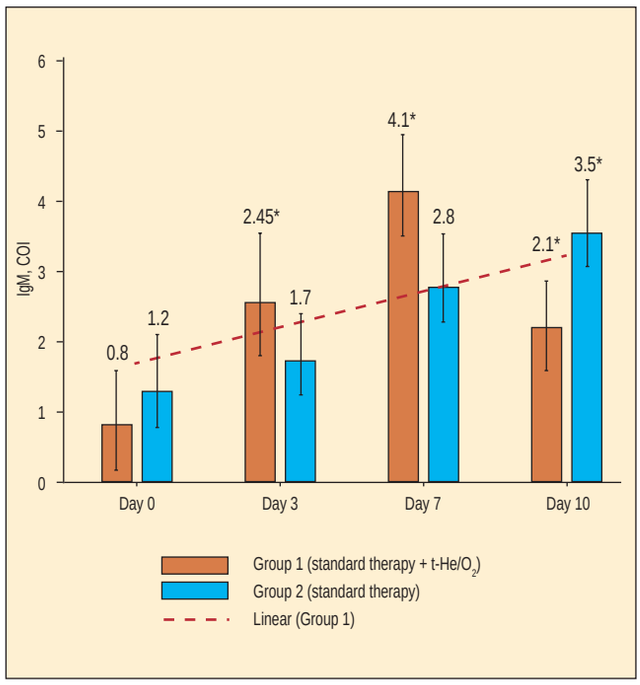

Figure 9. The dynamics of IgM in the comparison groups
Note: t-He/O_2, thermal helium-oxygen mixture; *, $p < 0.05$.

Рис. 9. Динамика изменения уровня IgM в группах сравнения
Примечание: * – $p < 0,05$.

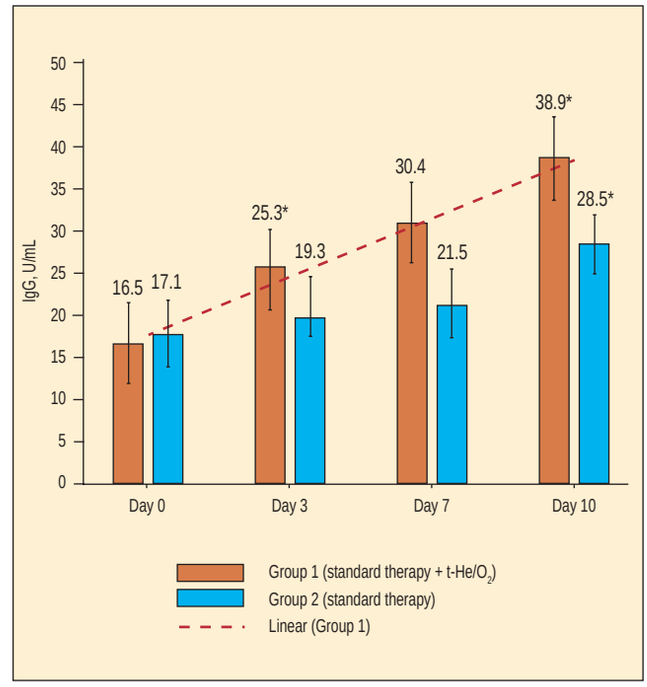

Figure 10. The dynamics of IgG in the comparison groups
Note: t-He/O_2, thermal helium-oxygen mixture; *, $p < 0.05$.

Рис. 10. Динамика изменения уровня IgG в группах сравнения
Примечание: * – $p < 0,05$.

Discussion

The findings demonstrate that the full-size viral particles detected by PCR are eliminated by days 2 – 3 of t-He/O_2. The antibody production is continued, apparently, as a response to the protein products of the thermal destruction of the virus. The use of t-He/O_2 stimulates the synthesis of IgM and IgG from the first procedure. 60% of patients in Group 2 that did not receive the t-He/O_2 inhalations, had almost no IgM and IgG antibodies during the first three days. Antibody synthesis begins on the second or third day after the induction period.

The changes in the IgG and IgM levels over time clearly demonstrate that t-He/O_2 leads to activation of the immune system and stimulates production of specific antibodies in patients with the coronavirus infection.

The immune response is complex and involves various biochemical systems. In particular, CRP is considered one of the components of a complex chain of biochemical processes and one of the first respondents to bacterial and viral infections. We compared the changes in the accumulation and reduction of CRP in the course of standard treatment and treatment with t-He/O_2 inhalations. A significant difference in the response was found.

A relatively slow accumulation of CRP occurs in the typical course of the disease. In most cases, the CRP level reaches maximum on Days 2 – 4 of treatment. The CRP level decreases as the treatment is continued. In our study, inhalations with t-He/O_2 stimulate the rapid accumulation of CRP with the subsequent exponential decrease in the level of CRP.

Stimulation of the immune response with t-He/O_2 can be defined as “thermal vaccination”. Our study showed that the full-size viral particles detected by PCR are eliminated by Days 2 – 3 of t-He/O_2. Apparently, the antibody production is continued as a response to the protein products of the thermal destruction of the virus. A “classical” vaccination with a weakened or destroyed antigen takes place. The fundamental positive difference is that the process takes place in vivo with the participation of natural viral proteins, and the “thermal vaccination” can have a wide-range specificity.

The mechanism of the observed effect of stimulation of the immune response with t-He/O_2 requires further research. The kinetic model that was developed and evaluated by us [2] [13] explains the observed effects by an increase in the antigen concentration during thermal destruction of the virus.

Conclusion

The addition of thermal inhalation of a gas mixture of helium and oxygen (t-He/O_2) to the standard therapy of patients with the infectious disease caused by SARS-CoV-2 and with CT signs of COVID-19 pneumonia (CT1, CT2 grades) reduces the viral load by stimulating both IgG and IgM antibody production. This effect of “thermal vaccination” increases the effectiveness of treatment and reduces the markers of inflammation. We are currently studying the response of patients with the CT3 signs of pneumonia to t-He/O_2. The intermediate results demonstrate a positive effect in the critically ill patients. The results require further research and statistical analysis.

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COVID-19 in cystic fibrosis patients

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Abstract

Since the beginning of the COVID-19 epidemic, the European cystic fibrosis society (ECFS) has decided to launch a special ECFS-COVID-19 program to collect information on the of COVID-19 characteristics in the patients with cystic fibrosis (CF). The results of the program should help timely and efficiently provide the patients with CF with the necessary care. Initially, it was assumed that COVID-19 would be severe in CF patients. **The aim**. To assess the prevalence and characteristics of COVID-19 in patients with cystic fibrosis (CF) in the Russian Federation (RF). **Methods.** 6 cases (4 children and 2 adults) of COVID-19 in Russian CF patients were analyzed. **Results**. There are 405,843 infected with SARS-CoV-2 in Russia, the incidence of coronavirus infection in Russia was 1.4 cases per 1 thousand people. According to the Ministry of Health of the RF, as of December 2019, there were 3,931 patients with CF (2,823 children and 1,108 adults). The incidence of COVID-19 was 1.5 per 1000 patients with CF (1.4 : 1,000 for children and 1.8 : 1,000 for adults). The incidence was not higher than in the General population. The diagnosis of COVID-19 was confirmed in 4 boys and 2 women, 3 of the patients were infected with *Pseudomonas aeruginosa* and 2 – with *Achromobacter spp*. Mild disease was seen in 5 patients including all the children. Pneumonia was registered in 3 patients. One child with COVID-19 had abdominal syndrome. 2 patients – 1 adult and 1 child – needed in-patient care. Additional antibiotics were given to 4 patients, 2 of them received i/v antibiotics. One adult patient was on the lung transplantation waiting list. This woman had long-term oxygen therapy and BiPAP noninvasive respiratory support before the infection with SARS-CoV-2, FEV_1 was 24%$_{pred.}$ **Conclusion.** Despite the fact that patients with CF are at risk of severe COVID-19, to date, in the described cases, COVID-19 infection has not led to a significant deterioration of the symptoms of CF. Not a single fatal outcome in Russian patients with CF has been recorded.

Key words: cystic fibrosis, COVID-19, incidence, pneumonia, antibacterial therapy.

Conflict of interests. The authors declare the absence of conflict of interests.

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COVID-19 у больных муковисцидозом

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Резюме

С начала эпидемии COVID-19 Европейским обществом по муковисцидозу *(European Cystic Fibrosis Society* – ECFS) инициирована специальная программа наблюдения ECFS-COVID-19 для сбора информации по особенностям течения COVID-19 у пациентов с муковисцидозом (МВ). Ожидается, что данная программа должна помочь своевременно и качественно оказывать необходимую помощь пациентам с МВ. Первоначально предполагалось, что на фоне МВ COVID-19 протекать будет тяжело. **Целью** исследования явилась оценка распространенности и течения COVID-19 у пациентов с МВ в Российской Федерации. **Материалы и методы.** Проанализированы 6 (4 ребенка и 2 взрослых) случаев заболевания COVID-19 у российских пациентов с МВ. **Результаты.** В Российской Федерации SARS-CoV-2 инфицированы 405 843 человека, заболеваемость коронавирусной инфекцией составила 1,4 случая на 1 тыс. населения. Учитывая численность пациентов в регистре МВ (по данным Министерства здравоохранения Российской Федерации, на декабрь 2019 г. в регистр включен 3 931 пациент: 2 823 ребенка и 1 108 взрослых), заболеваемость SARS-CoV-2 составила около 1,5 на 1 тыс. пациентов с МВ (1,4 : 1 000 – для детей и 1,8 : 1 000 – для взрослых), что не превышает таковую в общей популяции. Заболеваемость COVID-19 на 01.08.20 среди пациентов с МВ составила 3,8 (0,38 %) на 1 тыс. пациентов (2,1 : 1 000 – для детей и 8,8 : 1 000 – для взрослых). Диагноз COVID-19 подтвердился у 4 детей (все мальчики) и 2 взрослых женщин, при этом 3 больных были инфицированы *Pseudomonas aeruginosa*, 2 – *Achromobacter spp*. В легкой форме заболевание протекало у 4 из 6 пациентов, включая всех детей, пневмония зарегистрирована у 3 пациентов. У одного из 4 детей с COVID-19 отмечался абдоминальный синдром при отсутствии респираторных проявлений; 2 пациента (1 взрослый и 1 ребенок) нуждались в стационарном лечении. Антибактериальная терапия назначена 4 пациентам, двум из них – внутривенно. Одна взрослая пациентка, объем форсированного выдоха за 1-ю секунду у которой составлял 24 $\%_{долж.}$, зарегистрирована в листе ожидания на трансплантацию легких, до заражения SARS-CoV-2 у нее проводились длительная кислородотерапия и неинвазивная респираторная поддержка BiPAP. При подтверждении коронавирусной инфекции она была выписана из больницы. **Заключение.** Несмотря на то что пациенты с МВ находятся в группе риска тяжелого течения заболевания, на сегодняшний день в описанных случаях COVID-19 инфекция не привела к значительному ухудшению состояния по основному заболеванию. У российских пациентов с МВ не зарегистрировано ни одного летального исхода.

Ключевые слова: муковисцидоз, COVID-19, заболеваемость, пневмония, антибактериальная терапия.

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COVID-19 cases have been reported in many countries around the world since February 2020. WHO declared a pandemic on March 11, 2020 [1]. Isolated cases of COVID-19 were reported in the Russian Federation as early as at the end of January 2020. The incidence is growing steadily from the second half of March.

Patients with cystic fibrosis (CF) are at risk for bacterial respiratory tract infections due to dysfunction of the CFTR (chloride) channel caused by CFTR gene mutations [2]. By the Decree of the Government of the Russian Federation No.432 dated April 3, 2020, the routine medical exams and check-ups were suspended temporarily to ensure patient safety. The Order of the Healthcare Ministry of Russia No.198n dated March 19, 2020 recommended the management of healthcare institutions to postpone the scheduled in-patient medical services, if possible. In this regard, the health care professionals and the patient community were extremely concerned about changes in patient care and the threat of COVID-19. There was an urgent need to understand the risk of infection and the clinical course of coronavirus infection in CF patients. Outpatient CF treatment became highly relevant.

The updated reports from WHO [3] show that most patients (about 80%) recover spontaneously without the need for hospitalization. About one in five cases of COVID-19 is severe and is associated with respiratory failure or acute respiratory distress syndrome (ARDS), which can be leathal.

The disorders of the bronchopulmonary system in CF patients are characterized by airway obstruction, chronic bacterial infection, and inflammation. These processes damage the lung tissue and lead to bronchiectasis. Almost all lethal outcomes are caused by respiratory disorders. The bronchopulmonary conditions increase the predisposition to Pseudomonas aeruginosa infection, which occurs in 53% of patients with CF [4].

Neutrophils are the primary cells of the inflammatory process in CF. They infiltrate the airways, damage the lung tissue, and cause the obstruction. Cytokine inflammation is also typical for CF [2, 5]. Thus, both CF and COVID-19 are characterized by neutrophilic inflammation and cytokine release, which determine the severity of damage to the respiratory tract and the vascular system [6].

The diagnostic criteria for the cytokine release syndrome in COVID-19 have not been developed yet. It should be suspected in patients with a rapid deterioration in lung function in combination with increased levels of C-reactive protein (CRP) and ferritin, cytopenia (thrombocytopenia and lymphopenia), coagulopathy (low platelet and fibrinogen levels and increased D-dimer level), signs of liver damage (increased activity of lactate dehydrogenase and aminotransferases) [7]. Dornase alpha is traditionally used in CF patients to eliminate the extracellular traps and digest the extracellular DNA that is present in the viscous bronchial secretions in large quantities.* Dornase alpha is being studied as a potential component of combined therapy of COVID-19* [7].

The European Cystic Fibrosis Society (ECFS) launched the ECFS-COVID-19 surveillance program in April 2020 to collect information on the course of COVID-19 in patients with CF. It was decided to collect the data through national registers. In our country, the national register of CF patients was created in 2011, and its data are included in the European Cystic Fibrosis Society Patient Registry.

* Voronkova A.Ju. [Clinical efficacy and safety of dornase alfa ("Pulmozyme") in the treatment of children with cystic fibrosis]: Thesis for a candidate degree in medical sciences. Moscow; 2004 (in Russian).

Eight data reports have been published already [8]. The Organizing Committee of the Cystic Fibrosis Patient Registry in the Russian Federation decided to support the European surveillance program ECFS-COVID-19.

Initially, COVID-19 was assumed to take a severe course in patients with CF. However, the studies have shown that the disease is less common and is often mild in CF patients.

A multinational report to characterize SARS-CoV-2 infection in people with cystic fibrosis included 40 patients from 8 countries – Australia, Canada, France, Ireland, Netherlands, New Zealand, UK, and USA. The report showed (as of April 13, 2020) that the incidence of COVID-19 in patients with cystic fibrosis (0.07%) was lower than the average prevalence in the studied countries (0.15%) [9].

Another study described 30 cases of COVID-19 in CF patients (Lombardy (Italy), France, Germany, Spain). No deaths have been reported by April 15, 2020. The absence of fatal outcomes among CF patients by April 2020 may be associated with the relatively low incidence of COVID-19, the effective self-isolation methods, as well as with the young age of patients. But it is too early to make any final conclusions [10].

Study objective: To assess the prevalence and course of COVID-19 in patients with cystic fibrosis (CF) in the Russian Federation.

Materials and methods

We analyzed 6 Russian patients with CF (4 children and 2 adults) with COVID-19. Inclusion criteria: diagnosis of cystic fibrosis, a positive PCR-test for SARS-CoV-2 coronavirus RNA (or a positive test by another method), or a positive enzyme-linked immunosorbent assay for anti-SARS-CoV-2 IgG immunoglobulin [11]. Exclusion criteria: no laboratory confirmation of COVID-19 and no signed informed consent. The characteristics of patients with cystic fibrosis and COVID-19 are shown in Table 1.

Results

Per the study objective, 6 cases of COVID-19 among patients with cystic fibrosis were analyzed. 2 patients were over 18 years old.

Case No.1

A boy born in 2015 lives in Moscow and is under the care of the CF department of the Children's Clinical Multidisciplinary Center of the Moscow Region and the Morozov Children's City Clinical Hospital. The child was diagnosed with CF at the age of 3 months based on the positive neonatal screening and the positive sweat test on a Nanodact device (120 mmol/L against the upper reference level of 50 mmol/L), confirmed by the genetic testing (a pathogenic homozygous variant of the *CFTR F508del gene*). The child had left-sided upper lobe pneumonia at 3 months of age. He was hospitalized for pseudo-Bartter syndrome at 4 months of age. At 2 years of age, the chest X-ray showed distorted vascular markings and a peribronchial infiltration in the upper medial part of the left lung. The infiltrative changes were resolved after the treatment. *S. aureus* (MSSA) and *K. pneumoniae* were identified in sputum cultures for a long time. *P. aeruginosa* was first identified in August 2017. Inhaled sodium colistimethate and oral ciprofloxacin were administered to eradicate the bacteria. *P. aeruginosa* was identified again in September 2018 and 2019. MRSA was first identified in December 2018 and was detected in the cultures until May 2019, despite the antibiotics. *P. aeruginosa* was detected intermittently since September 2019. The boy received courses of inhalation therapy with sodium colistimethate 2 million units 2 times a day, oral ciprofloxacin for respiratory infection, and an alternate course of azithromycin. The basic therapy also includes dornase alpha, pancreatic enzymes, vitamins, ursodeoxycholic acid, and kinesitherapy. No severe exacerbations of the chronic bronchopulmonary process and no hospitalizations were reported last year. The child was examined by an otolaryngologist for nasal polyps and by an allergist for allergic rhinitis associated with a history of sensitization to alder, birch, and house dust.

At the beginning of May 2020, the child developed abdominal pains, followed by vomiting and fever up to 39.3 °C the next day. The O_2 saturation was 98%. The child was examined by a pediatrician, who diagnosed an acute intestinal infection. The fever and abdominal pain persisted for 2 days. The doctor prescribed Enterofuril, sorbents, and daily azithromycin. Oropharynx and nasal swabs for PCR for COVID-19 were taken from all family members because both parents had malaise and subfebrile body temperature previously. The child received a positive result the next day. The second test also turned out to be positive, and the next two were negative. The child was dismissed after 21 days from the onset of the illness. The tests of both parents were negative.

Case No.2

A child born in 2018, a resident of the North Caucasus Federal District, has been under the care of the Clinic of the Research Institute of Pediatrics of Federal State Autonomous Institution of the Ministry of Health of the Russian Federation of the Ministry of Health "National Medical Research Center for Children's Health" since August 2018 (the age of 4 months). The diagnosis was established by the neonatal screening and sweat test and confirmed by genetic testing (a homozygous pathogenic variant of the *CFTR W1282X gene*).

The child has a history of severe pseudo Bartter syndrome. *P. aeruginosa* was identified in culture from the upper respiratory tract, and the child received intravenous antibiotics therapy. The basic therapy included dornase alpha (inhalation), enzyme replacement therapy (Creon), ursodeoxycholic acid, vitamins, and inhaled colistimethate sodium.

The child had febrile fever for one day with no other symptoms in mid-May 2020. The SARS-CoV-2 infection was confirmed in his parents and his 4-month sister. The SARS-CoV-2 infection was confirmed by PCR in the patient. The chest X-ray showed no infiltrative changes. The blood lymphocyte level was 58%.

The treatment was outpatient and included azithromycin 10 mg/kg per day for 7 days in addition to the current medications. The control smears for PCR were taken on May 29 and 31, and the results were negative.

Table 1
Characteristics of the patients with cystic fibrosis and COVID-19
Таблица 1
Характеристика пациентов с муковисцидозом и COVID-19

Parameter	Patients					
	1	2	3	4	5	6
Age, years	13	4	32	24	2	1
Sex	Male	Male	Female	Female	Male	Male
Pancreatic insufficiency	+	+		+	+	
FEV_1 before COVID-19, %			24	54		
BMI before COVID-19	15,2	15,8	19,8	16,7	19,4	16,9
Lung bacteriological status for 12 months:						
• *P. aeruginosa*		+	+		+	
• *S. aureus*	+	+				+
• *Achromobacter spp.*			+	+		+
• *MRSA*		+				
			Respiratory failure	Vasculitis		
Comorbidities						
CF treatment > 3 months:						
• Dornase alpha	+	+	+	+	+	+
• Inhalations with 7% NaCl	+	+				+
• Inhaled antibiotics		+	+	+		
• Tablet antibiotics			+	+		
• Inhaled GCs			+	+		
• Azithromycin		+	+	+		
Course of COVID-19:						
• Pneumonia	+		+	+		
• ARVI		+	+	+	+	+
• Abdominal syndrome		+				+
• Others			Hemoptysis			
Symptoms:						
• fever	+	+	+	+	+	+
• pharyngitis	+			+		
• rhinitis	+					
• increased cough	+		+	+		+
• diarrhea		+				+
• vomiting		+				
• abdominal pain		+				+
• fatigue		+	+	+		
Course of the disease						
• mild	+	+		+	+	+
• severe			+			
Treatment:						
• in-patient			+			+
• outpatient	+	+		+	+	
Therapy:						
NSAIDs			+	+		
Oral antibiotics	Azithromycin, Cefixime	Azithromycin	Azithromycin	Ciprofloxacin, Minolexine, Azithromycin	Azithromycin	
Duration (days)	15	≤ 7	14	10	≤ 7	16
Intravenous therapy			Meropenem / Ceftazidime / Amikacin			Ampicillin / Sulbactam
Hydroxychloroquine				+		
Antivirals						Interferon α2b
NIV (BIPAP, CPAP)			BiPAP			
CT lesion volume, %			25			
Diagnostics:						
• PCR (nasal and oropharyngeal swabs)	+	+		+	+	+
• Serum (antibodies)			+			
Outcome:						
• Recovery	+	+	+	-		+
• Ongoing treatment				+	+	

Note: FEV_1, forced expiratory volume during the 1st second; BMI, body mass index; MRSA, Methicillin-resistant *Staphylococcus aureus*; CF, cystic fibrosis; GCs, glucocorticoids; ARVI, acute respiratory viral infection; NSAID, non-steroid anti-inflammatory drugs; NIV, noninvasive ventilation; BIPAP, Biphasic Positive Airway Pressure; CPAP, Constant Positive Airway Pressure; CT, computed tomography; PCR, polymerase chain reaction.

Case No.3

A child (boy) born in 2019, living in Moscow, is under the care of the Morozov Children's City Clinical Hospital. Cystic fibrosis was diagnosed at the age of 2 months based on positive neonatal screening and positive sweat test and was confirmed by genetic testing (F508del/E92K). The fecal level of pancreatic elastase-1 was 96 μg/g.

Achromobacter xylosoxidans was identified in one culture at the age of 3 months. The antibiotic therapy included intravenous meropenem + amikacin + oral ciprofloxacin for 2 weeks, and inhaled fluimucil-antibiotic IT for 3 months. Only *S. aureus* (MSSA) was detected in the subsequent cultures. The basic therapy includes inhaled dornase alpha, 3% NaCl, ursodeoxycholic acid, and vitamins A. D, E, K. The boy received enzyme replacement therapy at a minimum dosage up to 1 year of age. The therapy was canceled after a repeated fecal level of pancreatic elastase of more than 200 μg/g.

The grandmother had ARVI symptoms 1 week before the COVID-19 onset in the boy. The grandmother's PCR test for COVID-19 was positive. The child had an acute onset of the disease with a fever up to 38.8 °C. He was examined by a pediatrician the next day, and a swab from the throat and nose was taken for the PCR test. Cough and hoarseness developed a day later. The smear was positive, and the child was hospitalized on the 3rd day of illness.

His state was of moderate severity upon admission. Pale skin, symptoms of intoxication, and decreased appetite were noted. The respiratory system showed difficulty in nasal breathing with mucous discharge and moderate pharyngeal hyperemia. The cough was rare and unproductive. The child had no dyspnea at rest. The breathing was harsh, no wheezing. The results of the total blood counts are shown in Table 2.

Urinalysis: all parameters were within the reference range. The blood biochemistry showed an insignificant elevation of AST (40 U/L) and the lipase level of 71 U/L. Other parameters were within the reference range. The tests for the coronavirus (COVID-19) were positive on days 4, 11, and 16.

Table 2
Results of the general blood test of a child born in 2019 (clinical observation No.3) in dynamics
Таблица 2
Результаты общего анализа крови ребенка 2019 года рождения (клиническое наблюдение № 3) в динамике

Parameter	Day of the illness		
	3rd (admission)	8th	13th
Hemoglobin, g/L	116	119	116
Hematocrit, %	37.9	40	39.7
Red blood cells, 10^{12}/L	4.58	4.84	4.8
White blood cells, 10^9/L	7.2	11.5	6.4
Neutrophils, %	13.5	3.7	18.9
Lymphocytes, %	82.8	92.5	77
Monocytes, %	3.7	3.8	4.1
Platelets, 10^9/L	328	441	450
ESR, mm/h	22	5	2

Note: ESR, erythrocyte sedimentation rate.

The chest X-ray on the 4th day of illness showed a slight heterogeneous decrease in pneumatization of the right upper internal parts without clear contours. The pulmonary vascular markings were increased and distorted, prominence of the interstitial pattern was increased. The right root was dilated, poorly structured, and not visible on the left behind the shadow of the mediastinum. The chest X-ray on the 11th day of illness showed no focal infiltrative changes. The pulmonary vascular markings were increased and distorted.

Diagnosis: COVID-19, the virus was confirmed. SARS-CoV-2 infection, moderate right-side pneumonia, RF-0.

IV ampicillin/sulbactam for 9 days, and rectal suppositories with interferon alpha-2b 500,000 IU/day were prescribed. The mother had a positive smear on day 18. The child was discharged with improved symptoms and isolated at home.

Case No.4

A boy born in 2006 and living in the Leningrad Region is under the care of the Leningrad Regional State Budgetary Health Care Institution "Children's Clinical Hospital".

The diagnosis of cystic fibrosis was established by a positive sweat test and the reduced level of pancreatic elastase. The child had recurrent bronchitis from 7 months or age. At the age of 10 months, he had surgery for congenital heart disease, a ventricular septal defect. *S. aureus* is identified in the cultures from 2 years of age. In 2019, computed tomography showed bronchiectasis in *S 2*, *3*, *4*, *5* of the right lung and S 5 of the left lung. Spirometry indices were normal: FEV_1 – 85%; $SatO_2$ – 95%. The child has 3 – 4 exacerbations per year associated with ARVI and received oral antibiotics. The basic therapy included pancreatin, ursodeoxycholic acid, inhaled dornase alpha, vitamins D, A, E, K, and nutritional support.

The coronavirus disease was mild with symptoms of fever, pharyngitis, rhinitis, and increased cough. The X-ray revealed right lower lobe pneumonia. The PCR test for coronavirus by (COVID-19) was positive. Azithromycin for 5 days and the cefixime for 10 days were prescribed in addition to the basic therapy of CF.

Case No.5

The patient was born in 1987. She has been under the care of the Research Institute of Pulmonology and the D.D.Pletnev City Clinical Hospital under the Moscow Department of Health since 2009.

The patient had bronchitis from early childhood. CF was diagnosed at the age of 15 based on the clinical picture. She had recurrent bronchitis from early childhood. A right-sided upper lobectomy was performed in 1995. The respiratory tract was infected with *P. aeruginosa* since 1995. The diagnosis was confirmed by a positive sweat test (sweat chlorides 62,76 mmol/L). The genetic testing identified pathogenic variants of the *CFTR* gene: *CFTRdele2,3 and 3849+10kbC>T*. In recent years, the patient's condition deteriorated: the number of respiratory episodes increased, she developed shortness of breath, hemoptysis, reduced periods of remission after antibiotic therapy, and more frequent need for such treatment. The patient is on noninvasive ventilation in a protective mode since the summer of 2015 as the

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part of kinesitherapy. The patient developed hypoxemic respiratory failure in the autumn of 2017 and was prescribed oxygen therapy. A gastrostomy was installed in January 2019. The patients gained about 10 kg of body weight within a year of nocturnal hyperalimentation. The patient was included in the waiting list for lung transplantation due to respiratory failure, low respiratory function (FEV_1 within 20 – 27% of the reference value since 2016), and more frequent episodes of bronchopulmonary exacerbations in spring 2019. She receives daily inhalations of dornase alpha, a short-acting bronchodilator, budesonide/formoterol, and ambroxol, courses of inhaled tobramycin and colistimethate sodium, ursodeoxycholic acid preparations, omeprazole, and azithromycin as anti-inflammatory therapy. She also receives intravenous antibiotics 3 – 4 times a year and oral antibiotics every three months.

The cough, hemoptysis, and shortness of breath have brcome more severe in association with fever, and the volume of purulent sputum has increased to 100 mL/day since the second half of April 2020. Intravenous antibiotic therapy on an outpatient basis had no significant effect. This treatment failure, previous contact with a COVID-19 patient, and the severe baseline condition of the patient required inpatient treatment.

The general state was of moderate severity upon admission. SpO_2 was 85% on room air and 92% with O_2 – 4 L/min. The respiratory rate was 24 per minute. The blood pressure was 115/65 mm Hg. The heart rate was 88 per minute. Influenza was ruled out by the express test immediately upon admission, and nasal and oropharyngeal swabs were taken to test for COVID-19. The laboratory tests showed that the lymphocyte level was 15% with the number of leukocytes of 7.6×10^9, and the level of C-reactive protein was 83.0 mg/L. The chest CT (Figure 1) on April 29, 2020 showed that the volume of the right lung is reduced due to the upper lobectomy. The right upper part (S6) showed an area of pronounced pneumopleurofibrosis associated with a bullous transformation with a bulla size up to 52 mm.

The left upper lobe contained bullae up to 16 mm, one of them with a horizontal content level. Focal pneumosclerosis were seen in all parts of both lungs, but more on the right. Dilation of bronchi of III/IV degree with cylindrical and saccular bronchiectasis was reported in association with ground-glass opacities, mainly in the middle and lower right lobes, as well as in the upper and lower left lobes. Bronchiectasis were of various sizes, with perifocal infiltration, and some contained fluid. The mediastinum was structurally intact and displaced to the right. The trachea and the main bronchi were not deformed. The heart was in the standard location; the configuration was intact. The heart chamber sizes were regular. The thoracic aorta was intact. The diaphragm is in the normal location, the contours are even and clear. The pleural cavities were intact. Lymphadenopathy was not reported. The soft tissues and chest bone structures were intact. Conclusion: History of right-sided upper lobectomy. CT picture of cystic fibrosis. Bullae in both lungs. CT signs of suspected COVID-19 infection (the correlation with clinical and laboratory data have not been established).

CT scan on May 11, 2020 (Figure 2) showed persistent ground-glass opacities, primarily in the lower parts of the lungs. The upper left lobe contained bullae up to 16 mm, no fluid levels were detected. Otherwise, the CT findings were unchanged. Conclusion: CT signs of viral pneumonia. The intensity of typical COVID-19 signs complies with CT degree 1 (mild). History of right-sided upper lobectomy. CT picture of cystic fibrosis. Bullae in both lungs.

The PCR tests for COVID-19 with smears that were taken on the day of admission and on May 02, 2020 turned out to be negative. The patient had a serum test for IgM and IgG antibodies to the virus. The results confirmed COVID viral infection: IgM was 2.82 U/mL (the reference range is 0 – 0.99), IgG was 143.17 U/mL (the reference range is 0 – 10).

The 14-day therapy included intravenous meropenem, ceftazidime, tranexamic acid, and paracetamol; inhaled dornase alpha, budesonide/formoterol, and sodium colistimethate; oral azithromycin, ursodeoxycholic acid, omeprazole, and acetylcysteine. The patient also received noninvasive ventilation and oxygen therapy. The nocturnal hyperalimentation via the gastrostomy was continued.

The patient improved during the treatment. The body temperature steadily returned to normal, the systemic inflammation regressed, the intensity of purulent-obstructive bronchitis decreased, the hemoptysis was resolved, and the severity of respiratory failure decreased (SpO_2 – 92%).

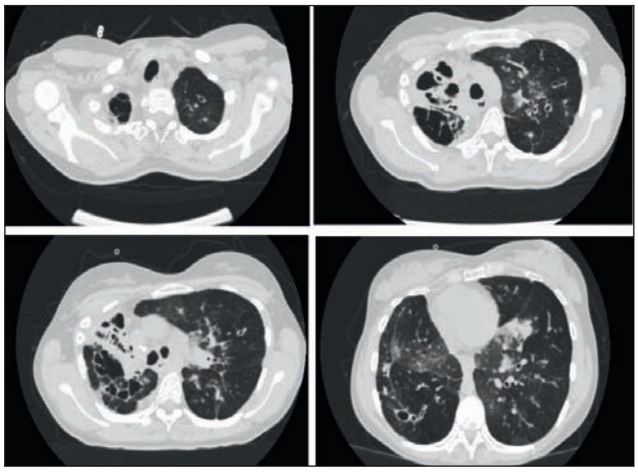

Figure 1. Computer chest tomography of the patients (case 5) dated 29.04.20

Рис. 1. Компьютерная томография органов грудной клетки пациентки (клиническое наблюдение № 5) от 29.04.20

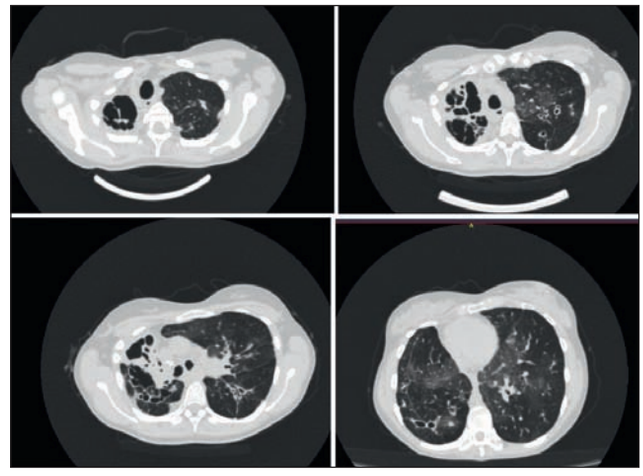

Figure 2. Computer chest tomography of the patients in dynamics (5 cases) dated 11.05.20

Рис. 2. Компьютерная томограмма в динамике (клиническое наблюдение № 5) от 11.05.20

Case No.6

The patient was born in 1995. She has been under the care of the Research Institute of Pulmonology and the D.D.Pletnev City Clinical Hospital under the Moscow Department of Health since 2013.

She was diagnosed with cystic fibrosis at the age of 3 years based on the typical clinical picture (pancreatic insufficiency from the first weeks of life) and a positive sweat test. The patient had a respiratory tract infection with *P. aeruginosa* from 3 years of age, and *Pseudomonas alcaligenes/Achromobacter spp*. from 12 years of age. The patient received outpatient intravenous antibiotic therapy every three months, and oral antibiotic treatment twice a year. The patient received daily inhalations with hypertonic NaCl solution, dornase alpha, inhaled mannitol, budesonide/formoterol, thiamphenicol glycinate acetylcysteine, and receives oral prednisolone, pancreatin, ursodeoxycholic acid, ambroxol hydrochloride, vitamins, and alternate azithromycin.

The patient deteriorated in early May 2020. The symptoms included increased coughing and shortness of breath, and body temperature of 38.0 °C. COVID-19 was diagnosed in the patient's father, who lives with her. The repeated swabs (PCR) from the nose and oropharynx tested positive and confirmed the diagnosis of COVID viral infection.

The treatment was outpatient, considering normal oxygen status (SpO_2 – 97%), FEV_1 – 58%, and insignificant symptoms of intoxication. The therapy included daily azithromycin, ciprofloxacin, and minolexin together with inhalations of dornase alpha twice daily.

The patient improved. The body temperature steadily returned to normal on the 5th day of therapy, and the respiratory symptoms improved.

Discussion

405,803 patients with SARS-CoV-2 have been registered in Russia by May 31, 2020. By this date, 6 CF patients with COVID-19 were identified. Their medical history is discussed in this article. 15 cases of the coronavirus infection were registered in patients with CF (6 children and 9 adults) by August 01, 2020.

3,931 patients (2,823 children and 1,108 adults) with cystic fibrosis were registered in Russia in the register of the Ministry of Health of the Russian Federation as of December 2019. The incidence of COVID-19 among them was 1.5 per 1,000 patients (0.15%) (1.4 : 1,000 for children and 1.8 : 1,000 for adults), which is higher than 0.07% in Europe on April 13, 2020, according to a European study [12].

At first, COVID-19 was reported in children with CF more often as compared to the adults (4 *vs* 2). This fact can be explained with the predominance of children among CF patients of the Russian Federation [3]. In European countries, adults account for 50% or more of the CF population [8]. The COVID-19 statistics have changed in Russia by August 01, 2020. The proportion of adults with CF and COVID-19 is now higher, as it is in other countries.

According to WHO, COVID-19 is rare and milder in the general pediatric population [13]. This trend is also observed in patients with cystic fibrosis. The state of 5 out of 6 patients that are discussed in this publication was mild (including all children). Pneumonia was diagnosed only in 3 patients. One of the four children had abdominal syndrome, which is typical for children [13]. 2 patients (adult and child) required hospitalization. 4 patients received antibiotic therapy, 2 of them – intravenously. One adult patient was on NIV. This patient suffered from hypoxemic respiratory failure and received long-term oxygen therapy prior to the infection with SARS-CoV-2. In general, our findings comply with the reported course of COVID-19 in CF patients in other countries [9, 10].

According to the data from the European Cystic Fibrosis Society ECFS-COVID-19 surveillance program as of May 27, 2020, COVID-19 cases in CF patients have been reported in 13 out of 35 countries that participate in the data collection. 79 patients were reported, including 72 cases with a detailed description (34 men and 38 women, 16 children), including Russian patients. 17 patients were asymptomatic, 27 had mild disease, 7 had severe disease, and 3 were critically ill. In total, 41 patients were hospitalized. 6 of them needed intensive care, 2 were ventilated, and 3 died [12].

As of July 29, 2020, 128 cases of the disease were registered in 18 countries (men : women – 69 : 59) out of 38 European countries that submitted information to the ECFS-COVID-19 program. These cases included 33 children (*https://www.ecfs.eu/covid-cf-project-europe*). 80 patients had mild disease, 6 patients were severe, and 5 patients were critically ill. No other fatal outcomes were reported, so 3 patients died in total. 22 patients were asymptomatic. 68 patients were hospitalized, 3 were on mechanical ventilation, and 1 patient needed ECMO. The five most common symptoms were fever, cough, fatigue, increased amount of sputum, and headache.

Conclusion

Thus, both foreign and Russian data show that most patients with CF develop a mild course of COVID-19. The incidence of COVID-19 is not higher than in the general population, which is associated with both the young age of patients, their early and strict isolation, skills in preventing infection, and, possibly, with basic therapy. Different researchers suggest that the following drugs protect patients with CF from the severe course of COVID-19: dornase alpha, azithromycin used for anti-inflammatory purposes against chronic *P. aeruginosa* infection, and frequent courses of antibiotic therapy [9, 10]. Further data will help to draw more accurate conclusions.

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COVID-19 in individuals adapted to aerobic exercise

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Abstract

Analysis of COVID-19 features in individuals who regularly practice aerobic training. **Methods.** Asymptomatic persons and patients with COVID-19 older than 30 years, 293 people (180 men and 113 women), 214 of them – inhabitants of the Moscow region (the beginning of the sampling – 2nd decade of April 2020) and 79 – inhabitants of the Belgorod region (the beginning of the sampling – 2nd decade of May 2020), adapted (27 people – 1st group) and unadapted (266 – control group) to aerobic training (AT). Computer tomography of the chest, RNA test for SARS-CoV-2 in smears from the nasopharynx-oropharynx, the clinical blood sample and level of antibodies to SARS-CoV-2 were studied. The criterion for adaptation to aerobic loads was considered compliance with the rules of the American Heart Association, 2008. **Results.** Adapted to AT individuals, in contrast to the control group, characterized with the prevalence of asymptomatic ($p = 0.045$) and absence of severe forms of COVID-19, limited cataral simptoms of the disease ($p < 0.001$), rare pneumonia with absence (1) or presence (2) of acute respiratory failure ($p_1 = 0{,}028$; $p_2 = 0{,}034$), along with lower prevalence of diseases, potentiating this infection ($p = 0.03$). **Conclusion.** Patients adapted to AT have less severe course of COVID-19.

Key words: COVID-19, adaptation, aerobic exercise.

Conflict of interests. The authors declare the absence of conflict of interests.

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COVID-19 у лиц, адаптированных к аэробной нагрузке

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Резюме

Целью исследования явился анализ особенностей течения COVID-19 у лиц, регулярно практикующих аэробный тренинг. **Материалы и методы.** В исследовании принимали участие лица старше 30 лет с бессимптомной формой и больные COVID-19 ($n = 293$: 180 мужчин, 113 женщин), жители ($n = 214$) Московского региона (начало формирования выборки – 2-я декада апреля 2020) и жители ($n = 79$) Белгородской области (начало формирования выборки – 2-я декада мая 2020), адаптированные (1-я группа; $n = 27$) и неадаптированные (контрольная группа; $n = 266$) к аэробным нагрузкам. У всех пациентов проводились компьютерная томография органов грудной клетки, тест на РНК SARS-CoV-2 в мазках из носо-, ротоглотки, общий анализ крови, определение антител к SARS-CoV-2. Критерием адаптации к аэробным нагрузкам считалось соответствие правилам *American Heart Association* (2008). **Результаты.** У адаптированных к аэробным нагрузкам лиц, в отличие от контрольной группы, отмечены преобладание бессимптомной ($p = 0{,}045$) и отсутствие тяжелой формы COVID-19, ограниченная острая респираторная вирусная инфекция, клинический вариант болезни ($p < 0{,}001$), низкая частота случаев пневмонии с отсутствием (1) или наличием (2) острой дыхательной недостаточности ($p_1 = 0{,}028$; $p_2 = 0{,}034$) наряду с меньшей распространенностью заболеваний, потенцирующих данную инфекцию ($p = 0{,}03$). **Заключение.** Пациентов, адаптированных к аэробным нагрузкам, отличает менее тяжелое течение COVID-19.

Ключевые слова: COVID-19, адаптация, аэробные нагрузки.
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The significant results of adaptation are improved reliability of biological systems and body as well as increased resistance to external disturbances [1]. In this regard, the search for clinical inhomogeneity patterns of COVID-19 should focus on characterisation on initial respiratory system fitness, more specifically – adaptation to aerobic exercise (AE). However, the issue "CoV-2 – adaptation to AE" is wider than the issue "CoV-2 – sports", even when the question is about the so-called cyclic sports (field-and-track athletics, rowing, swimming, cycling). This limitation, especially in case of professional sports, is due not only to the age (sportspeople are relatively young), but also to the influence of key elements of a sports process affecting harmonious development: immunomodulating competitive stress, infection-promoting crowding during workouts and competitions, and highly commercialised nature of sports. Therefore, a few researches on the specifics of COVID-19-pathology in physically trained individuals, specifically in sportspeople, are not able to resolve the issue of natural sanitation mechanisms, resulting, in some cases, in asymptomatic disease and, in some cases, in severe pneumonia associated with corona virus infection [2, 3].

This paper, initiated during the period of higher uncertainty and mysteriousness of the new disease for the Russian healthcare system, is aimed at assessment of COVID-19 characteristics in individuals adapted to AE. At the same time, the initial knowledge about the lower incidence and relatively good outcomes in younger population was a prerequisite for sampling patients over 30 years old only.

Materials and methods

The study included asymptomatic individuals and COVID-19 patients over 30 years old, 293 individuals (180 men and 113 women), with the median and interquartile age of 54.5 (44 – 65) years old, 214 of them were citizens of Moscow and Moscow region (sampling initiation: 2nd decade of April 2020) and 79 citizens of Belgorod region (sampling initiation: 2nd decade of May 2020). 56 subjects (21.1%) previously visited endemic regions abroad (including 49 citizens of Moscow and Moscow Region). COVID-19 was diagnosed in accordance with The Temporary Guidelines for Prevention, Diagnosis and Management of a Novel Corona Virus Infection of the Ministry of Health of the Russian Federation (revision 4 dated March 27, 2020 and revision 5 dated April 08, 2020), where 3 severity levels (mild: 146 individuals, moderate: 63 individuals, and severe: 53 individuals) and 6 clinical patterns are identified; only 4 of them were recorded in the study: ARVI, pneumonia without respiratory distress (RD), pneumonia with severe RD, acute respiratory distress syndrome (no sepsis and septic shock cases were recorded). Due to uneven capability (especially in outpatient settings) to perform a full set of diagnostic procedures, assessment was based on computer-aided chest tomography (CT), SARS-CoV-2 RNA smears from the nasopharynx – oropharynx, clinical blood assay with differential white blood cell count, and antibody levels (IgG and IgM).

Asymptomatic cases included cases (31 patients if the incubation stage of the disease is excluded) limited to positive SARS-CoV-2 RNA smear PCR tests and/or increased IgG (over 10 U/mL) and IgM (over 2 U/mL) titre against SARS-CoV-2 (ELISA). Any other medical history data, excluding asymptomatic cases, were obtained only from COVID-19 survivors.

In order to characterise "adaptation to AE", the modified American Heart Association criteria (AHA, 2008) were used, where an individual had highly intensive aerobic physical exercises during previous 12 months (min. 150 minutes/week) or combined intensive exercises (min. 75 minutes/week) with moderate exercises (min. 150 minutes/week). Intensity levels corresponded to AHA classification, based on the heart rate (HR) during exercises: moderate intensive exercises if the HR was 50 – 70% of the maximum value ($HR_{max.}$ = 220 – age), intensive exercises if the HR was > 70% – ⩽ 85%$_{max}$. However, such an estimation precision of exercises duration and HR in clinical settings is rather an aim, not a real possibility, recorded only in patients who were aware of and used the principles of self-control. All other subjects were included into the group with adaptation to AE if during the previous 12 months they regularly (at least 5 times weekly) went running outside or on a treadmill (min. 30 minutes), stationary bike exercises (min. 40 minutes), stair stepper exercises (with an overall duration of 30 min.) or intensive nordic walking (60 – 90 minutes). In AHA guidelines (2008), such aerobic exercises are included into "intensive exercises". Eventually, these criteria were met by 27 individual (17 men, 10 women), with the median and interquartile age of 54 (42 – 67) years old (group 1). The remaining 266 individuals from the main group not adapted to AE (163 men and 103 women aged 55 (43 – 66) years) were controls (group 2). As there were no individuals with markedly depressed immunity (administration of system glucocorticosteroids, cytostatic agents, exhaustion, etc.) or persons from close communities (orphanages, retirement homes) in group 1, these characteristics were exclusion criteria in controls as well.

Regular intensive exercises are one of the endurance and stamina features of an individual – determination, adding to other endurance and stamina features: bravery, independence, self-command, etc. For additional characterisation of patient personality and determination specification, we used the "persistence"

scale from the Willed Self-Regulation questionnaire by *A.V.Zverkov – E.V.Eidman* [4]. Of note, the objectivity of results in such an analysis is greatly dependent on trusted relations between the patients and his/her physician; and the formal nature of tests with filling out questionnaires sometimes compromises the method. This is especially true with COVID-19 patients who had a psychological trauma. Therefore, in order to maintain the principles of medical paternalism, the 16 questions (where pronouns "I", "My", "Me" were replaced with "You", "Yours", "For you") were distributed along the conversation with the patient, and the operator calculated the final result after listening to the recorded dialogue. The results were processed using variation statistical methods in Statistica 6.0 (StatSoft, Inc., USA) and Biostatistics for Windows 4,03.

Results and discussion

In the groups of COVID-19 patients from Moscow, Moscow Region and Belgorod Region, the share of individuals who regularly do aerobic exercises was 9.2% (27 individuals). There were 3 patients over 80 years old: 2 men of 81 and 83 years old and a 80-year old woman who went for 5 – 7 km of nordic walking every day. As far as disease severity is concerned, individuals adapted to AE did not have severe pathology; they were mostly asymptomatic ($p < 0.05$), only 1 patient had a moderate disease (see Table 1). It is worth mentioning that this regularity was identified during provisional analysis, when the groups were formed, during the period of the highest uncertainly as to the correct search direction, when in addition to very limited amount of information about the infection and lack of experience in COVID-19 patient management, we have already had some references to severe course of COVID-19 in an individual highly adapted to AE. It was a 38-year old Italian marathon runner who spent over 2 weeks on mechanical ventilation, and on 27 February the Daily Mail named him a super-spreader of the infection in Lombardy [5].

The rate of mild cases in group 1 (excluding asymptomatic cases) was 95%, whereas in group 2 it was 66.5%; the rate of moderate and severe cases in group 2 was 11.6% and 21.9%, respectively. This severity ratio is quite different from the currently accepted values for COVID-19 (81, 14 and 5%); this is probably due to a small sample number, age limitations (individuals under 30 years old were excluded) and the criterion of no marked immune depression.

In individuals adapted to AE, very often the disease was limited to ARVI only ($p < 0.001$), while pneumonia with severe RD was diagnosed only in 1 patient (a 57-year old man) who had moderately severe disease. In controls, pneumonia with severe RD was diagnosed in 42.9% ($p < 0.05$), and the rate of pneumonia without severe RD was a bit lower (44.7%). Also, the unadapted group of patients included 3 men and 1 woman who suffered from ARDS.

Analysis of individual signs in COVID-19 patients (20 individuals in group 1 and 242 individuals in group 2) demonstrates fewer symptoms of respiratory abnormalities in patients adapted to AE: they had caught, dyspnea and chest X-ray abnormalities less frequently (see Table 2). When all symptomatic cases were excluded, this group included only 6 individuals with typical CT pattern: 1 man with right unilateral "ground glass" areas in S6 and 10 (CT stage: I), 4 patients had bilateral pneumonia stage, and one patient had a bilateral disease with CT stage II. In controls, CT changes were recorded in 234 individuals ($p < 0.05$), including 22.4% (53 individuals) with stage 3 and 3 – 4 ($p = 0.087$).

Table 1
Severity structure and clinical variants of COVID-19 in individuals adapted (group 1) and unadapted (group 2) to aerobic training; n (%)
Таблица 1
Структура тяжести и клинические варианты COVID-19 у лиц, адаптированных (1-я группа) и неадаптированных (2-я группа) к аэробной нагрузке; n (%)

Characteristics	Group 1 $n = 27$	Group 2 $n = 266$	p
Mild disease	19 (70.4)	161 (60.5)	N/a
Moderate disease	1 (3.7)	28 (10.5)	N/a
Severe disease	–	53 (19.9)	0,042
Asymptomatic disease	7 (25.9)	24 (9.0)	0,045
ARVI	14 (51.9)	8 (3.0)	< 0,001
Pneumonia without RD	5 (18.5)	153 (57.5)	0,028
Pneumonia with RD	1 (3.7)	77 (28.9)	0,034
ARDS	–	4 (1.5)	N/a

Note: ARVI, acute respiratory viral infection; RD, acute respiratory distress; ARDS, acute respiratory distress syndrome; p confidence for χ^2; N/a, no data available.
Примечание: достоверность p по критерию χ^2.

Because of a variable conception of the disease duration by patients (whether presence of symptoms or duration of hospitalisation or sick leave), we used fever duration as a criterion, taking into account that the majority of patients remembered quite a unique, usually two-phase ARVI. In adapted patients, the median duration was 2 days shorter than in controls ($p < 0.01$); the maximum fever duration in group 1 was 12 days, while in group 2 it was 27 days.

Regular aerobic exercises did not prevent group 1 patients from having diseases that potentiate COVID-19; however, this group included only 7 patients with obesity, arterial hypertension (AH) and diabetes mellitus (DM), whereas in controls these conditions were recorded in approx. 70% ($p < 0.05$, see Table 3). Intergroup differences in comorbidity were caused by various combinations of obesity and DM ($p < 0.05$), but not AH. Of note, among individuals adapted to AE there was one individual with obesity, DM and AH (a 54-year old man). We have been following this patient up for 2 years; his hyperglycemia is corrected with a combination of antihyperglycemic agents

Table 2
Frequency of individual signs* COVID-19 in patients adapted (group 1) and unadapted (group 2) to aerobic training; n (%)
Таблица 2
Частота отдельных признаков* COVID-19 у больных, адаптированных (1-я группа) и неадаптированных (2-я группа) к аэробной нагрузке; n (%)

Characteristics	Group 1 *n* = 19	Group 2 *n* = 242	*p*
Fever	16 (84.2)	241 (99.6)	N/a
Fever duration, days, *Me* (*Q1 – Q2*)	3 (3–5)	5 (3–14)	0,001**
Cough	3 (15.8)	227 (93.8)	0,003
Dyspnoe	1 (5.2)	112 (46.3)	0,023
Runny nose	18 (94.7)	181 (74.8)	N/a
Impaired olfaction	17 (89.5)	231 (95.5)	N/a
Headache	5 (26.3)	107 (44.2)	– " –
Impaired sense of taste	1 (5.2)	60 (24.8)	– " –
Diarrhea	–	18 (7.4)	– " –
Myalgia, arthralgia	6 (31.6)	148 (61.2)	– " –
All CT positive cases	6 (31.6)	234 (96.7)	0,025
Severe CT positive cases:			
• I	5 (26.3)	134 (55.4)	N/a
• II	1 (5.2)	39 (16.1)	N/a
• II – III	–	8 (3.3)	– " –
• III	–	50 (20.7)	– " –
• III – IV	–	3 (1.2)	– " –
Lymphocyte depletion (lymphocyte count < 20%)	–	28 (11.6)	

Note: CT, computered tomography; p confidence for χ^2; *, for paraclinic signs, when the test was repeated, we used a result with the highest deviation; **, *p* confidence for Mann – Whitney test; *Me* (*Q1 – Q2*) – median, quartile 25 – 75%; N/a, no data available.

Примечание: * – для параклинических признаков при неоднократности выполнения исследования использован результат с наибольшим отклонением; ** – достоверность *p* по критерию Т Манна–Уитни; *Me* (*Q1–Q2*) – медиана, квартиль 25–75 %.

and a two-component antihypertensive regime, including ACE inhibitors; also, he has been regularly exercising on a stationary bike for 14 months (45 – 90 min/day); his disease was a 5-day ARVI without impaired olfaction.

Analysis of mean values for "persistence", modified Willed Self-Regulation questionnaire did not allow revealing a significant difference between patients who regularly exercise and those who do not use aerobic exercises in their daily life. In group 1, the value was 12 (7 – 13) points, whereas in group 2 it was 10 (6 – 12) points, with the difference of 16.7%, just trending towards confidence ($p = 0.093$), without any statistically significant difference. A probable reason might be both inadequate specificity of the method used and a small number of subjects in the test and control groups.

Without getting into details of effects from adaptation to AE, three mechanisms should be named that can contribute to favourable COVID-19 course in patients adapted to physical exercises. On the one hand, long-term adaptation to AE (or stamina training) has a very important characteristic: it results in sparing use of regulatory respiration elements during regular stress and enhanced reserves of the respiratory system, together with the ability to mobilise more efficiently when required. Favourable cross effects from such adaptation for antioxidant and immune systems are well known as well [1]. A typical inflammation manifestation is energy deficit in the inflamed site; frequent sympathicotonia and resulting phospholipase activation and lipide peroxidation are associated with cytopathy. On the contrary, in adaptation to AE, with increase in antioxidant enzyme levels in tissues (superoxide dismutase and glutathione peroxidase) and mitochondria genesis, this effect significantly reduces [6, 7]. Also, aerobic exercises promote improved density and adrenoreceptor affinity in breathing muscles, bronchi smooth muscle cells, bronchial arteries, glands and epithelium. First, it allows improving the rate and amplitude of inhale and exhale muscle contraction (their strength) in response to significantly lower (non-toxic) adrenaline concentrations, synchronising their activity with other skeletal muscles participating in locomotor behaviour; second, it efficiently reduces resistance in the bronchial tree as a result of more marked bronchodilation; and third, it improves the quality of bronchi mucosa sanitation due to ciliary activity stimulation and less viscous secretion passage [1, 6].

Most prominent changes in COVID-19 are found in the alveolar-capillary membrane (ACM), and the virus enters the cell through membrane protein – angiotensin converting enzyme 2 (ACE II) [8]. In addition to the growth in the pulmonary capacity, AE are known to modify the ACM structure and to improve its diffusion capacity. During overall diffusion capacity tests with carbon monoxide (DL_{CO}), trained subjects demonstrated significantly higher values *vs* untrained individuals not only at rest, but specifically during exercises; a similar difference was noted for blood volume in pulmonary capillaries (V_c) and diffusion capacity of membrane ($D_м$) [9]. In our study, untrained patients were distinguished for a large number of cases with high body mass index and DM. Obesity and DM significantly disturb the ACM structure and function [10]. For an experimental model, increased thickness, reduced elasticity and diffusion capacity both in normal state and in hypoxic events were proven. Also, in obesity associated with hypoxia, the number of type II alveolar epithelial cells and alveolar macrophage are significantly reduced; oxidised defective DNA are more numerous, thus promoting impaired overall resistivity of ACM [11]. Now it is difficult to give an unambiguous answer to the question: is it only the training of the respiratory system that increases the level of its resistance to coronovirus, or the small number of comorbid diseases – obesity and diabetes mellitus – is also important here, presented in this work in the group of persons adapted to AN. Most likely today, both factors should be taken into account, but the degree of signifi-

Table 3
Diseases that potentiate COVID-19 in the compared groups; n (%)
Таблица 3
Заболевания, потенцирующие COVID-19 в сравниваемых группах; n (%)

Disease	Group 1 n = 27	Group 2 n = 266	p
Obesity + DM	–	53 (19.9)	0.043
Obesity + AH	–	16 (6.0)	N/a
AH + DM	–	3 (1.1)	N/a
Obesity + DM+ AH	1 (3.7)	22 (8.3)	– " –
Obesity	2 (7.4)	52 (19.5)	– " –
DM	–	1 (0.3)	– " –
AH	4 (14.8)	38 (14.3)	– " –
All cases with obesity	3 (11.1)	143 (53.8)	0.009
All cases with DM	1 (3.7)	79 (29.7)	0.031
All mentioned diseases that potentiate COVID-19	7 (25.9)	185 (69.5)	0.03

Note: DM, diabetes mellitus; AH, arterial hypertension; p confidence for χ^2; N/a, no data available.
Примечание: достоверность p по критерию χ^2.

cance of each of them must be specified in the course of a subsequent study with an increase in the volume of the experimental and control groups.

ACE II, an ACE homolog which differs from ACE in its physiological effects, is a component of counterregulatory axis (ACE II/AT (1 – 7)/MasR). Regular physical exercises reduce ACE II levels in tissues [12, 13]; therefore, they should have facilitated corona virus penetration to the cell and made COVID-19 more aggressive. However, clinical and experimental trials of ACE inhibitors and angiotensin II receptor blockers (their pharmacological mechanism causes increase in ACE II level) show quite another pattern: administration of medicines is associated with reduced risks of death of COVID-19 patients; during the experiment, medicines reduced mortality and prevented acute damages of lungs in mice challenged with SARS-CoV [8, 14, 15]. Other arguments for physical exercises and ACE II growth are presented in a study by *D.M.Magalhães et al.* (2020): as exemplified by physically trained men who were doing highly intensive aerobic exercises, blood and urine ACE II levels significantly rise, and in moderate exercises, renal elimination of ferment is significantly increased [16]. It is clear that they are free, unbound (solubilized) protein fractions. Therefore, it is possible that ACE II split from cell membranes is increased in AE; therefore, in adapted individuals, the probability of virus entering the cell via this receptor is reduced.

The human and animal immune system is affected by the overall physical activity and AE [17]. Adaptation to AE impacts cell and humoral elements of inborn and acquired immunity: regular exercises modify the ratio of natural killer cells increasing the number of younger (CD56-bright NK) colonies; the neutrophils/lymphocytes ratio and the density of *Toll*- and NOD-like receptors increase; Th1, Th2, Th_{reg}, secretory IgA levels change in upper respiratory tract mucosa, etc. [18, 19]. All these factors improve body resistance to respiratory infections, neoplasms, toxic and even radiation impacts [1, 6, 20, 21]. Still, there are negative cross-effects from such adaptation. They result from excessive exercises (J-effect by *D.C.Nieman*, 1994), when the risk of respiratory infections increases. It is true about long AE [22–24]. An additional condition is physical epithelium damage (bronchial and alveolar) resulting from long-term hyperventilation in case of inadequate training conditions [25]. It is likely that all these conditions were present in references, where COVID-19 in individuals adapted to AE was severe (only 2 cases were recorded among numerous marathon runners and only 1 among professional cyclists) [2, 3]. Unfavourable consequences from adaptation to AE can be prevented by following the rules established by the Russian school of physiology: "prevention... Is first of all sustainable limitation of physical exercises and adequate selection of ontogeny stage when exercises can be done (or increased); second, use of combined adaptation when the body adapts to several factors", thermal (cold water treatment), hypoxic, etc. regimen [1].

Conclusion

In this study of physically active individuals of 30+ years old adapted to AE, as opposed to patients who are not used to aerobic exercises, COVID-19 was mostly asymptomatic or was associated with limited clinical ARVI, rare pneumonia (or CT positive cases), together with lower morbidity of rates that potentiate this infection, especially obesity and DM; the degree of their participation and the independent role of the adaptation factor to AE in changing the severity of COVID-19 is planned to be clarified in the course of a subsequent study.

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The multispiral computed tomography in the early diagnosis of pneumonia caused by SARS-CoV-2

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Abstract

The high informative value of chest computed tomography in the diagnosis of pneumonia caused by SARS-CoV-2 is generally recognized, but there is no enough data on the diagnostic capabilities of this method within 5 first days of the clinical manifestations of the disease. The paper presents the results of chest multispiral (multislice) computed tomography (MSCT) of 56 patients with COVID-19 pneumonia in the early days of the disease. **The aim** of the study was to analyze the semiotics of pathological changes in the lungs in the first days of the onset of clinical symptoms of COVID-19 and to clarify the methodology for conducting MSCT. **Methods.** The data of chest MSCT of 56 patients with clinical symptoms of a new coronavirus infection SARS-CoV-2 were analyzed. MSCT was carried out in the first 4 – 5 days of the disease. **Results.** Five variants for the development of the disease were revealed, including atypical, characterized by the prevalence and CT semiotics of lung damage and apparently due to the different response of the patients to SARS-CoV-2 infection. The leading signs of COVID-19 pneumonia in the early stages of the disease were foci of ground glass opacification (GGO), multifocal lesions of the lungs, edema of the interalveolar pulmonary interstitium, which distinguishes it from pneumonia of another etiology. **Conclusion.** Comparison of MSCT data and the clinical picture of the disease during the first 5 days suggests with high confidence the pneumonia associated with COVID-19. A prerequisite for conducting MSCT in case of suspicion of this type of pneumonia is the implementation of thin 0.5 – 1.5 mm sections, MSCT performance at suspended full inspiration, post-processing of unenhanced tomogram data in MinIP mode.

Key words: multispiral computed tomography, semiotics, pneumonia, SARS-CoV-2, COVID-19 pneumonia.

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Мультиспиральная компьютерная томография в ранней диагностике пневмонии, вызванной SARS-CoV-2

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Резюме

Высокая информативность компьютерной томографии (КТ) органов грудной клетки (ОГК) в диагностике COVID-19-ассоциированной пневмонии общепризнанна, однако данные о диагностических возможностях и особенностях выполнения этого метода в первые 5 суток клинических проявлений заболевания отсутствуют. В работе представлены результаты мультиспиральной КТ (МСКТ) ОГК пациентов (n = 56) с COVID-19-ассоциированой пневмонией в первые 4–5 суток развития симптомов болезни. **Целью** исследования явилось изучение семиотики патологических изменений в легких в первые дни появления клинических симптомов COVID-19 и описание особенностей методики проведения МСКТ. **Материалы и методы.** Проанализированы данные МСКТ ОГК пациентов с клинической симптоматикой новой коронавирусной инфекции SARS-CoV-2. МСКТ выполнялась в первые 4–5 суток заболевания. **Результаты.** Выявлено 5 вариантов развития заболевания, включая атипичный, различавшихся распространенностью и КТ-семиотикой поражения легких и обусловленных, по-видимому, различной реакцией организма пациентов на инфекцию SARS-CoV-2. Ведущими признаками COVID-19-ассоциированной пневмонии в ранние сроки заболевания являлись очаги «матового стекла», мультифокальность поражения легких, отек межальвеолярного легочного интерстиция, в чем и состояли отличия COVID-19-ассоциированной пневмонии от таковой другой этиологии. **Заключение.** Сопоставление данных МСКТ и клинической картины заболевания в течение первых 5 суток заболевания позволяет с высокой достоверностью предположить наличие пневмонии, ассоциированной с COVID-19. Необходимым условием проведения МСКТ при подозрении на пневмонию данного типа является выполнение тонких (0,5–1,5 мм) срезов, контроль за полнотой вдоха пациента, постпроцессинговая обработка данных нативной томограммы в MinIP-режиме.

Ключевые слова: мультиспиральная компьютерная томография, семиотика, пневмония, SARS-CoV-2, COVID-19-ассоциированная пневмония.

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On January 26, 2020, the National Health Commission of the People's Republic of China registered a total of 2,744 confirmed cases of pneumonia caused by the novel SARS-CoV-2 (2019-nCoV) coronavirus infection from 30 provinces (districts and cities), including 461 severe cases and 80 deaths. Despite the unprecedented measures to limit the spread of infection that were taken by the Chinese and International sanitary authorities, the World Health Organization has announced the COVID-19 pandemic on March 11, 2020. As of July 7, 2020, over 11.4 million cases in over 188 countries and territories were registered, resulting in more than 535,000 deaths; over 5.14 million people recovered [1–5]. Studies have demonstrated the high diagnostic efficiency of multispiral computed tomography (MSCT) of the chest in pneumonia caused by SARS-CoV-2 [6–9]. Although this conclusion was questioned in some publications [10]. However, most publications are devoted to the MSCT semiotics of lung tissue damage, assessment of the extent of the process, and its development. The diagnostic significance of MSCT at the early stage of COVID-19, recognition and correct interpretation of lung damage within the first 3 days from the onset of the symptoms have been studied insufficiently.

The aim of the study was to analyze the MSCT semiotics of pathological changes in the lungs in the first days of COVID-19 clinical symptoms and to clarify the methodology of MSCT in patients with suspected SARS-CoV-2 pneumonia.

Materials and methods

The single-center, non-randomized prospective study included patients (n = 56) with clinical symptoms of the novel coronavirus infection SARS-CoV-2, who had chest MSCT for diagnostic purposes during the first 4 – 5 days of the disease. 29 (51.8%) patients complained of nasal congestion, sore throat, increased fatigue, low-grade fever. 27 (48.2%) patients experienced an increase in body temperature up to 38 – 39 degrees during the first two days. Subsequently, the diagnosis of COVID-19 was confirmed by laboratory tests in all examined patients.

MSCT was performed on days 1 to 5 after the onset of clinical symptoms. The scan was performed twice with an interval of 2 – 3 days in 18 (32.1%) patients. The MSCT data were evaluated for typical signs of viral pneumonia (Cov19Typ), according to the classification in the Expert Consensus Statement of Radiological Society of North America [11]. The MSCT findings of lung damage were compared with the severity of clinical symptoms (fever, dry cough, nasal congestion, weakness, and others). 2 (3.6%) patients had no clinical signs or symptoms at the time of MSCT but still showed CT findings of COVID-19 pneumonia and had SARS-CoV-2 confirmed by PCR.

Data analysis

The study results demonstrated there are several rules to be followed during MSCT in the case of suspected COVID-19, such as ensuring that the scan is performed at the complete inhalation. This approach will help avoid false positives in the form of pseudo ground areas (gravity-dependent atelectasis) associated with an incomplete inhalation or exhalation of the patient. The scanning should use thin sections of no more than 1.5 mm. Post-processing in the mode of minimum image intensity (MinIP) followed the previously described method [12]. The main goal of the post-processing is to improve the visual assessment of the native CT data. The MinIP

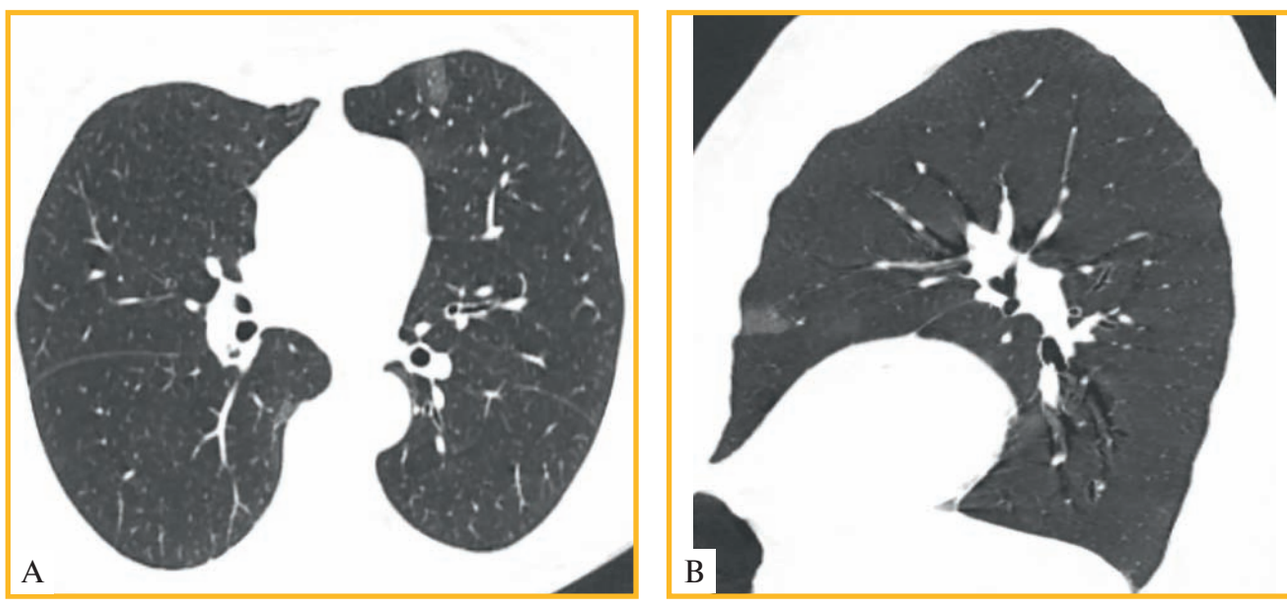

Figure 1. Multispiral computed tomography of the chest (1 mm slices) on the 2nd day of clinical onset of COVID-19 pneumonia: A, Axial slice. A ground glass opacity in the left lingular segment; B, Sagittal reconstruction in MinIP mode provides clearer visualization of the findings

Рис. 1. Мультиспиральная компьютерная томография органов грудной клетки (срез 1 мм) на 2-й день клинических проявлений COVID-19-ассоциированной пневмонии: А – аксиальный срез – очаг «матового стекла» в язычковом сегменте левого легкого; В – сагиттальная реконструкция в MinIP-режиме – более четкая визуализация изменений

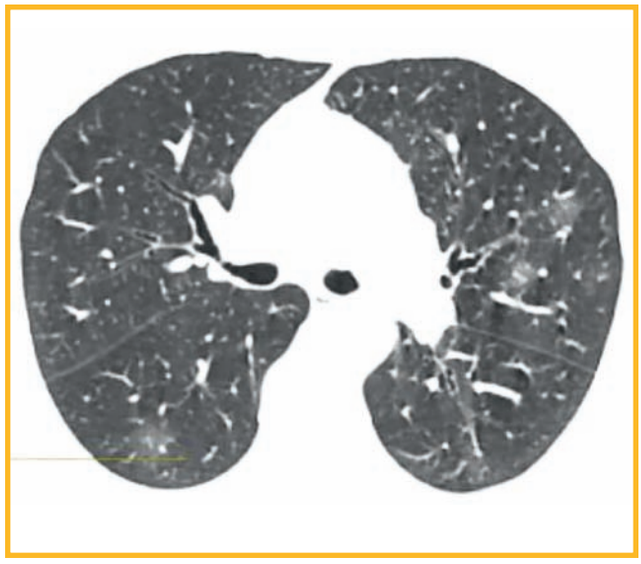

Figure 2. Multispiral computed tomography of the chest (1 mm slices) on the 3rd day of clinical onset of COVID-19 pneumonia; Axial slice – polisegment two-side micro ground glass opacities

Рис. 2. Мультиспиральная компьютерная томография органов грудной клетки (срез 1 мм) на 3-й день клинических проявлений COVID-19-ассоциированной пневмонии, аксиальный срез: полисегментарная двусторонняя локализация мелкоочаговых изменений по типу «матового стекла»

program isolates the elements of the air-filled structures of the lung. This improves the detectability of the ground glass opacities and allows to assess the state of the bronchi. It is an expert method for proving the presence or absence of ground glass findings, especially with low intensity, in borderline cases. Comparative analysis of the native MSCT data and the data obtained with a contrast enhancement demonstrated that contrast enhancement does not improve visualization of COVID-19 pneumonia. A contrast agent is optional unless the patient has other indications for it.

The data analysis identified various early CT signs of viral pneumonia caused by SARS-CoV-2.

Pneumonia with focal lesions and a limited extent of damage was detected in the first days of the disease in 17 (30.4%) patients. MSCT showed one or more small ground-glass opacities (up to 30 mm) in I – III segments of one or, less often, both lungs. The lesions had unclear outer edges and were localized mainly at the periphery (Figure 1, 2). Some ground-glass opacities included clearly distinguishable areas of high density (Figure 3). 7 out of 17 (41.2%) patients had increased pulmonary vascularity with a reticular consolidation of the interstitium at the periphery of the lesions. 2 out of 17 (11.8%) patients with single ground-glass opacities had no clinical signs of COVID-19 at the time of CT scan (the scan was conducted at the request of the patient due to the illness of a family member). 3 out of 17 (17.6%) patients had MSCT performed on the 3rd day of clinical symptoms of COVID-19, and the scan did not reveal the typical findings in the lungs. However, MSCT was repeated on the 5th day (2 days after the initial examination) in one patient after a rapid deterioration. The scan revealed signs of COVID-19 pneumonia in the lung tissue. One of these cases is described below:

Clinical case

Patient G., 53 years old, reported pain, sore throat, dry cough, and subfebrile temperature up to 37.4 °C on April 04, 2020. Chest MSCT was performed on April 06, 2020. The scan showed no significant pathological findings in the lungs and mediastinum. On April 07, 2020, the patient's condition worsened. The body temperature rose to 39.5 °C in the evening, and the patient reported weakness, headache, myalgia, and intensified cough. The chest MSCT was repeated on April 08, 2020. Both pulmonary fields showed multifocal ground-glass opacities, mostly round, in all segments as compared to the scan on April 06 (Figure 4). No fluid in the pleural cavity and intrathoracic lymphadenopathy were confirmed. Conclusion: The patient's status worsened as compared to the scan on April 06, 2020. MSCT signs of COVID-19 viral pneumonia.

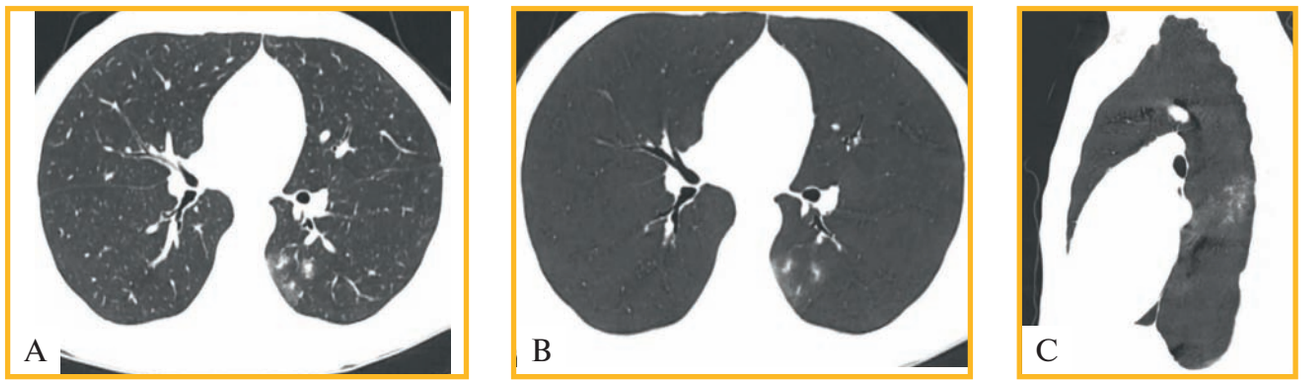

Figure 3. Multispiral computed tomography of the chest (1 mm slices) on the 2nd day of clinical onset of COVID-19 pneumonia: A, Axial slice. The pathological ground glass opacities with high density focal findings cover the whole left IV segment; B, C, Axial projection and saggital reconstruction of the findings in MinIP mode

Рис. 3. Мультиспиральная компьютерная томография органов грудной клетки (срез 1 мм) на 2-й день клинических проявлений COVID-19-ассоциированной пневмонии: А – аксиальный срез – патологические изменения «матового стекла» полностью охватывают IV сегмент левого легкого, на фоне которого выделяются очажки высокой плотности; В, С – аксиальная проекция и сагиттальная реконструкция зоны изменений в MinIP-режиме

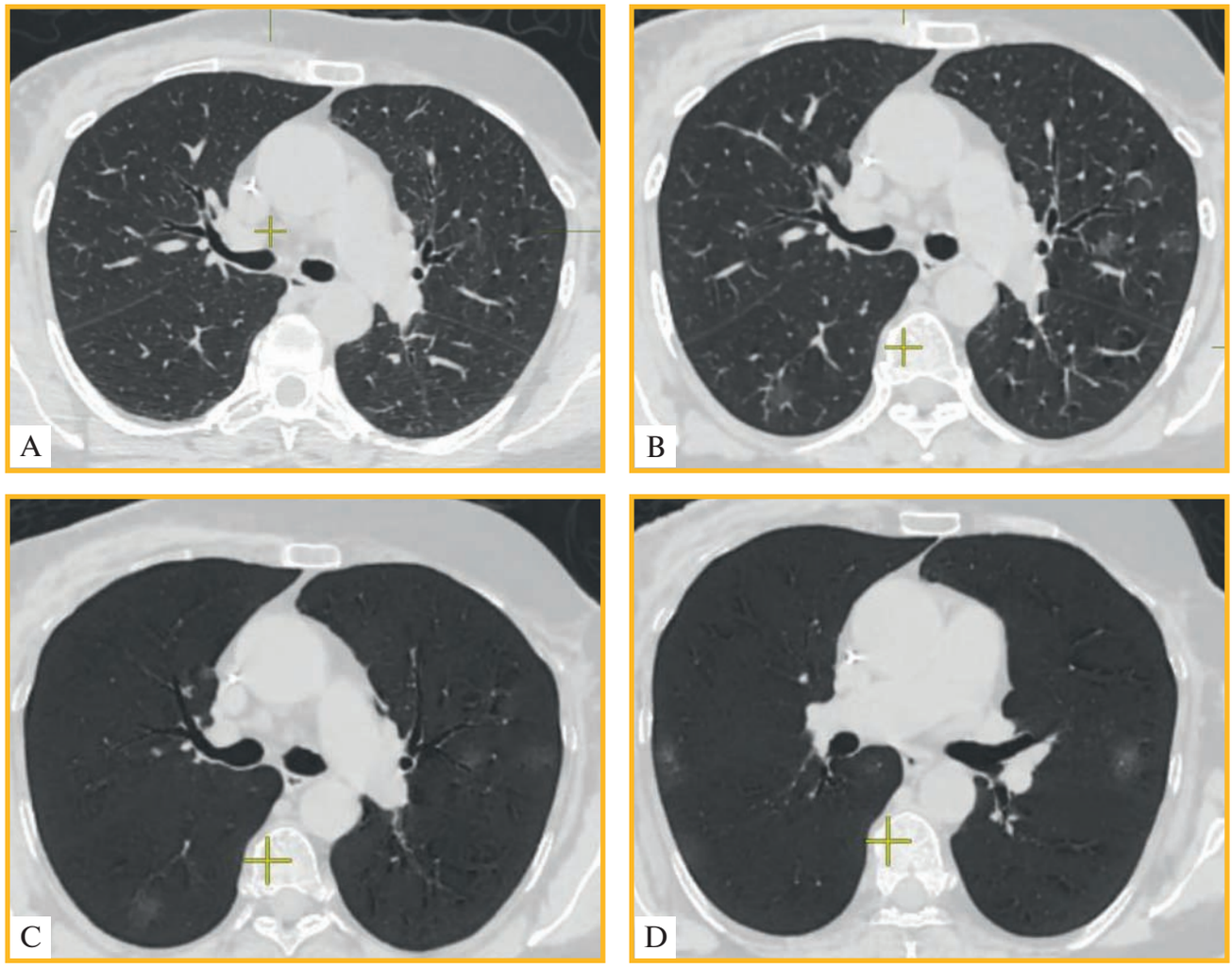

Figure 4. Chest multispiral computed tomography, 1 mm axial slices: A, Day 2 of COVID-19 clinical symptoms, no findings that suggest pneumonia; B, The same patient on day 4 of COVID-19 clinical symptoms. The ground glass opacities appeared in both lungs; C, D, A clearer visualization of the findings in MinIP mode. COVID-19 pneumonia

Рис. 4. Мультиспиральная компьютерная томография органов грудной клетки, аксиальные срезы 1 мм: A – 2-й день клинических проявлений COVID-19, данных за наличие пневмонии не получено; B – та же пациентка, 4-й день клинических проявлений COVID-19 – появление в левом и правом легких очагов «матового стекла»; C, D – более четкая визуализация изменений в MinIP-режиме – COVID-19-ассоциированная пневмония

Multifocal bilateral ground glass opacities up to 30 – 45 mm in size in 3 to 5 lung segments were found in 15 (26.8%) patients. These lesions had unclear, blurred outer edges with a pericissuritis type reaction of pleura and thickening of the interstitium along the periphery of the foci. This group of patients differed from the previous one both by the variable macrostructure of the lesions and by the chaotic distribution of areas of the affected lung tissue. In total, the findings were observed in all parts of the lungs, both subpleurally, in the middle and hilar zones of the lungs, and in the mediastinal pleura. 2 out of 15 (13.3%) patients showed extensive bilateral findings with polysegmental ground-glass opacities. Areas of swollen alveolar tissue were visualized against the opacities (Figure 5).

Polysegmental bilateral lung lesions with a predominantly peribronchial localization were observed in 13 (23.2%) patients. Several segments (possibly in different lobes) of the lungs were involved in the process. The entire segment or part of it was affected. High-density infiltration was observed against the ground glass opacities in the central zone. Other findings included air bronchogram sign, crazy paving sign, honeycombing of the interalveolar and pulmonary interstitium, mediastinal lymphadenopathy, limited pleural effusion in some cases, and dilatation of the pulmonary veins of the affected area. In contrast to the previous group, these patients showed predominantly peribronchial localization of the pathological findings, dilatation, and thickening of the bronchial walls, the air bronchogram sign, and mediastinal lymphadenopathy. Some patients showed local pleural effusion, areas of cobblestone-like increased pulmonary interstitial pattern, rough, cord-like consolidation of the interstitium and interlobar pleura. The dense infiltrate was larger in the central part of the focal ground-glass opacities. Individual groups of alveoli were “swelled”. Probably, the respiratory bronchioles were damaged, and inflammation led to the ball-valve ventilation of individual groups of alveoli.

7 (12.5%) patients had **infiltrative lobar lesions** along with focal changes. The pneumonia was localized in

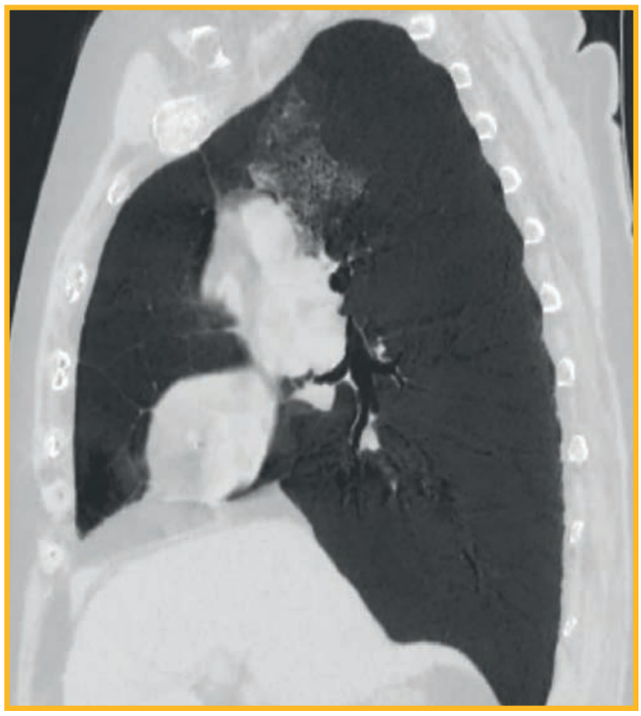

Figure 5. Multispiral computed tomography of the chest (1 mm slices) on the 1st day of clinical symptoms of COVID-19 pneumonia. The saggital reconstruction in MinIP mode showed extensive lesions in the left upper lobe and the low intensity ground glass opacities in the upper and lower lobes of the right lung

Рис. 5. Мультиспиральная компьютерная томография органов грудной клетки (срез 1 мм) на 1-й день клинических проявлений COVID-19-ассоциированной пневмонии. При сагиттальной реконструкции в MinIP-режиме выявлены обширные изменения в верхней доле левого легкого, «матовое стекло» низкой интенсивности в нижней и верхней долях правого легкого

II – V lobes of the lungs. The focal ground-glass opacities, dense infiltrations in the central zone, polysegmental infiltrations, air bronchogram sign, thickening of the bronchial wall, cobblestone sign in the interstitium, reticular consolidation of the interstitium, pleural reactions in the form of pleural effusion and thickening, mediastinal lymphadenopathy, and dilatation of the peripheral pulmonary veins within the lesions (Figure 6) were also found.

4 (7.1%) patients had **atypical findings** in the lungs. 3 (75.0%) patients had increased pulmonary vascularity due to diffuse consolidation of the interstitium with damage to both lungs and thickening of the bronchial walls. No ground-glass opacities were found. 1 (25.0%) patient had a bilateral lesion. Single ground-glass opacities associated with a pronounced infiltration of the left lower lobe, thickening of the bronchial walls and interstitial tissue, and dilatation of the pulmonary veins were found.

Discussion

Analysis of the data of patients with suspected COVID-19 pneumonia showed that MSCT is a highly sensitive diagnostic method that reveals pathological findings in lung tissue in the first days of the disease.

The most common signs of pneumonia are variable ground-glass opacities (infiltration in the central zone, unclear or blurred outer edges). The pulmonary vascularity is intensified due to the cord-type interstitial edema, a reticular macrostructure, up to the cobblestone appearance. If the lesion is subpleural, the pleura is consolidated. The most likely reason for the cobblestone sign in the first days of the disease is the pronounced edema of the interlobular interstitium associated with the ground-glass opacities. The findings could be localized in any part of the lung. The disease affected the alveolar tissue and caused a reaction of the interalveolar and pulmonary interstitium. We observed these CT signs of pneumonia in the early days of COVID-19 in 32 (55.6%) patients.

13 (23.2%) patients had extensive infiltrations along with the ground-glass opacities. The changes were mainly peribronchial, the bronchial walls were thickened due to edema, and mediastinal lymphadenopathy developed. Our data coincide with the opinion of most researchers [1–11]. Only one publication did not confirm lymphadenopathy in patients with SARS-CoV-2 pneumonia [6].

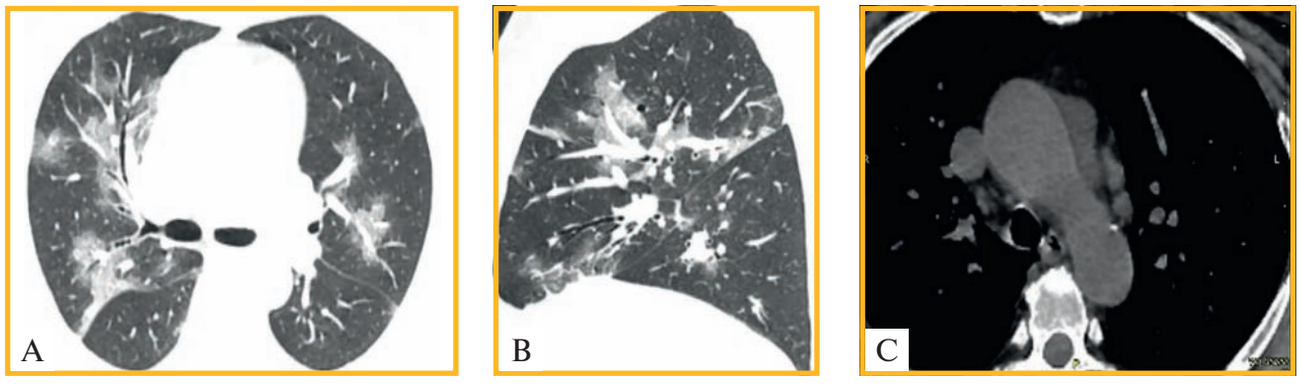

Figure 6. Multispiral computed tomography of the chest (1 mm slices) on the 4th day of clinical symptoms of COVID-19 pneumonia: A, B, Axial slices. The saggital reconstruction shows multilobar polysegmental lung damage, pericissuritis, high density lesions associated with the ground glass opacities, air bronchogram symptom; C, Indurated and enlarged lymph nodes in the aortic window in the region of aortic arch

Рис. 6. Мультиспиральная компьютерная томография органов грудной клетки (срез 1 мм) на 4-й день клинических проявлений COVID-19-ассоциированной пневмонии: A, B – аксиальный срез. Сагиттальная реконструкция – многодолевое полисегментарное поражение легких, перициссурит, участки высокой плотности на фоне «матового стекла», симптом «воздушной бронхограммы»; C – уплотненные, увеличенные лимфатические узлы в аортальном окне, области дуги аорты

7 (12.5%) patients had infiltrative lobar changes along with the focal findings. These cases of severe pneumonia were characterized by extensive damage to the lung tissue and polymorphic MSCT findings in the lung parenchyma, bronchial wall, interstitium, pleura (in the form of pleural effusion and thickening), mediastinal lymph nodes, and peripheral pulmonary veins within the affected area.

Also, 4 (7.1%) patients with COVID-19 had atypical MSCT findings in the lungs. These findings have not been described in COVID-19 patients before and included a pronounced increase in the pulmonary vascularity caused by an interstitial consolidation (edema) and dilation of the peripheral pulmonary veins along with the ground-glass opacities.

The variable prevalence and inter-patient semiotics of COVID-19 pneumonia indicate a variable response to the infection. All authors emphasize the need to comply with specific methodological requirements when performing MSCT in patients with suspected pneumonia caused by SARS-CoV-2. In particular, the scan should be performed with thin slices, since the ground glass can be skipped in slices of more than 5 mm [12]. However, we did not find any references to the need for post-processing of native MSCT data in the mode of minimum image intensity in the available literature.

Note that MSCT signs of COVID-19 pneumonia can appear earlier or later than the clinical symptoms. Several authors report that the pathomorphological changes in the lungs in the first days of pneumonia associated with SARS-CoV-2 infection are mediated by dilatation and congestion in the alveolar capillaries, exudation of fluid into the alveolar cavity, and edema of the interlobular interstitium. These processes are seen in the MSCT scan as single or multiple ground-glass opacities, reticular consolidation of the interstitium, fusing of the lesions, and the appearance of high-density foci against the ground glass opacities [5–9].

Special attention should be paid to the differentiation between pneumonia caused by SARS-CoV-2 and pneumonia of a different etiology. COVID-19 pneumonia should be distinguished from pneumonia associated with influenza, parainfluenza, adenovirus, human metapneumovirus, respiratory syncytial virus, as well as bacterial and atypical pneumonias (mycoplasma, chlamydia, and others). Some non-infectious diseases (vasculitis, dermatomyositis, and organizing pneumonia) can cause changes in the lung tissue similar to the ones caused by COVID-19 pneumonia [13–17]. An important differential diagnostic sign of COVID-19 pneumonia, as opposed to the above-mentioned diseases, is that the typical findings can be located in any part of the lungs, the changes are multifocal, and the ground glass symptom can be combined with infiltrative changes and interstitial edema. The breakdown of lung tissue in COVID-19 pneumonia does not lead to the formation of cavities. The changes that are associated with viral pneumonia of a different etiology, mycoplasma or chlamydial infection are localized mainly in the basal or hilar parts of the lungs. Bacterial pneumonia is usually associated with infiltrative changes in the alveolar tissue in specific segments or lobes. The infiltrations are often prone to decay and are typically complicated by exudative pleurisy. Bacterial pneumonia is not associated with the ground-glass opacities [18].

In our opinion, pneumonia caused by SARS-CoV-2 can be suggested after the comparison of MSCT data with the clinical picture and after MSCT monitoring.

Conclusion

- MSCT at the early stages of COVID-19 pneumonia shows a specific macrostructure that allows for a conclusion about the causative agent.
- Thin-section MSCT is a highly effective method for diagnosing COVID-19 pneumonia and can be used when patients show clinical signs of the disease or for monitoring of persons who had contact with an infected patient.
- Post-processing of the native MSCT data in the mode of minimum intensity projection provides additional information about the macrostructure of the findings and the state of the bronchi.
- MSCT is necessary for patients with suspected COVID-19 pneumonia, especially in hospitals with different specialization.

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Randomized controlled study on pulmonary rehabilitation in COVID-19 patients with pneumonia

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Abstract

Pulmonary rehabilitation in COVID-19 patients with pneumonia is associated with better treatment outcomes. However, existing protocols have never been evaluated in randomized control studies. **The aim.** To evaluate the effectiveness of newly-developed pulmonary rehabilitation protocol compared to basic Russian COVID-19 guidelines for patients with oxygenation index (OI) between 200 and 400 points without IMV. **Methods.** Based on literature reviews and own clinical experience, standard rehabilitation protocol was designed and tailored for specific needs of low-OI patients. Two clinical centers participated in the study and included total 73 patients in main group. Control group included 73 retrospective patients based in propensity score; this patients received standard protocol of early pneumonia activation from official COVID-19 guidelines. Ten-days clinical outcomes were assessed based on parameter distribution type. **Results.** Evidence show significant difference in required time of continuous oxygen support in (5.1 ± 3.3 *vs* 8.0 ± 4.6 days for main and control group respectively. Main group also had mildly better functional. We've observed less mortality in main group, but attribute it not to the program, but for growing experience of health professionals and decreased loads on health system. Malignancy as comorbidity was considered a significant cofactor also. **Conclusion.** New pulmonary rehabilitation protocol improves clinical outcomes in critical COVID-19 patients by decreasing the demand fox oxygen support.

Key words: rehabilitation, COVID-19, breathing exercises, oncology, survival rate.

Conflict of interests. The authors declare the absence of conflict of interests.

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Дыхательная реабилитация у больных вирусной пневмонией на фоне новой коронавирусной инфекции

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Резюме

При использовании дыхательной реабилитации при пневмонии, ассоциированной с новой коронавирусной инфекцией (НКИ), отмечено улучшение результатов лечения. Однако типовые протоколы дыхательной реабилитации для тяжелых форм коронавирусной пневмонии по данным рандомизированных исследований до настоящего момента не оценивались. **Целью** рандомизированного клинического исследования, проведенного в 2 клинических центрах, явилось определение эффективности протокола дыхательной реабилитации у больных с индексом оксигенации < 400 и > 200 при самостоятельном дыхании или кислородной поддержке по сравнению с пациентами, у которых реабилитация не проводилась. **Материалы и методы.** В исследовании приняли участие пациенты (n = 146) с ДН, отобранные методом ретроспективной псевдорандомизации среди больных, проходивших лечение ранее. Разработан протокол из 5 последовательных упражнений дыхательной гимнастики. Пациентам основной группы (n = 73) к лечению в течение 10 дней добавлена исследуемая реабилитационная программа, затем оценивались результаты. **Результаты.** Получено достоверное различие продолжительности непрерывной кислородной поддержки между группами (5,1 ± 3,3 дня *vs* 8,0 ± 4,6 дня). При анализе в подгруппах важной самостоятельной ковариатой исхода оказалось наличие онкологического заболевания. **Заключение.** При

использовании комплекса лечебной физической культуры в остром периоде течения НКИ повышается эффективность лечения за счет раннего снижения потребности в кислородной поддержке, ускоренной нормализации индекса оксигенации, повышения толерантности к физической нагрузке.

Ключевые слова: реабилитация, новая коронавирусная инфекция, дыхательная гимнастика, онкология, выживаемость.

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The new COVID-19 infection (NCI) created an unprecedented challenge to healthcare systems around the world. The combination of high virulence with a severe course of the disease, in the clinical picture of which viral pneumonia phenomena dominate, resulted in a situation where in-patient departments quickly filled with patients who have confirmed COVID-19 infection or suspected of it [1].

Early activation improves the prognosis for the life of patients with severe pneumonia in an evidence-based manner [2]. However, clinical practice showed that for COVID-19 infection, it is relevant to develop specific restorative complexes with respect to the extremely high risk of breathing with resistance and severe asthenization of patients. In addition, in the context of the NCI pandemic, the problem of attracting professional exercise therapeutists and instructors for these tasks, the deficiency of which was observed earlier, becomes especially acute. This makes it desirable to use techniques that are available to all personnel involved in the treatment of patients, as well as suitable for their implementation by patients themselves. Finally, while the researchers proposed several options for rehabilitation protocols for the new COVID-19 infection, there were no comparative studies between them – this does not allow making a definitive conclusion about the reasonability of their inclusion in the treatment program [3].

This paper describes a clinical study comparing the effectiveness of the respiratory rehabilitation protocol developed by us with the standard treatment of patients with the NCI complicated by respiratory failure.

The purpose of the study was to evaluate the effectiveness of the respiratory rehabilitation protocol in patients with the oxygenation index between 200 and 400 on spontaneous breathing or with oxygen support in comparison with patients without rehabilitation support.

Objectives:

- To create the protocol for the first stage rehabilitation of patients with the COVID-19 infection under the conditions of respiratory failure based on literature data and clinical experience.
- To select the treatment group from among patients who meet the inclusion and exclusion criteria and received an appropriate early rehabilitation according to the protocol.
- To form the comparison group using the pseudo-randomization method from the number of patients who meet the inclusion and exclusion criteria, but have not received an appropriate early rehabilitation according to the protocol.
- To compare clinical results in the two groups.

Materials and methods

Study design

Primary endpoint was the period from the start of treatment to the refusal of oxygen support

Secondary endpoints:

- Frequency of transferring patients to artificial lung ventilation (ALV)
- Dynamics of the oxygenation index measurement.
- Evaluation of subjective general state according to SF-36 on the 1st and 10th days.
- Break-in exercise therapy for 2 or more days.
- Patient survival rate in 10 days from starting exercise therapy.

In our opinion, the duration of the period from starting the treatment to normalizing oxygenation sufficiently to terminate the oxygen support is the most adequate indicator of the effectiveness of treatment for assessing the significance of the proposed protocol.

Endpoints 3 and 4 were ultimately excluded from the study because of the impossibility of collecting relevant data in the control group due to the lack of this information in the source medical records. To ensure data collection, endpoint 3 was replaced with data from medical records for self-care of patients, who, according to the literature, can make an adequate contribution to the assessment of the program [4]. To assess the indicator, a binary model was used, in which “1” corresponded to patients who were able to get out of the bed on their own, dress themselves to a limited extent and move around the ward at the end of 10 days, and “0” corresponded to those who could not perform any of these actions.

After releasing several updates to the temporary protocol of the Ministry of Health of Russia on the treatment of the new COVID-19 infection in the course of the study, as well as an obvious increase in clinical experience, we decided to put aside the assessment of the survival rate as an endpoint. In our opinion, a sufficient number of fundamental changes were added to the treatment protocol that directly affects the survival rate. However, we included the survival rate in the study summary for the interpretation of the ANOVA data.

Inclusion criteria:

- Age over 18 years old;
- Patients with the IO < 400 in the ICU.

Exclusion criteria:

- Patients on ALV;
- Patients with the IO < 200;
- Patients inaccessible to the productive contact;

- Patients with the following contraindications (extensive contractures of the extremities; severe pain syndrome; ostomy patients; patients with severe decompensation of a concomitant disease);
- Patients who cannot leave the pron position without a prolonged (over 2 minutes) cough or a steady decrease in oxygen saturation by more than 3%;
- Patients who did not comply with the protocol during the study.

Comparison groups. The treatment group consisted of the patients who met the inclusion criteria, had no exclusion criteria, and underwent the selected rehabilitation program.

The control group consisted of the patients who underwent pseudo-randomization according to archival data. The control group was formed by the pseudo-randomization method after assessing the nature of the parameter distribution using the Kolmogorov–Smirnov method; parametric distribution was carried out by Student's t-test, binary distribution was carried out by McNamar's χ^2 test, and non-parametric distribution was carried out by Mann–Whitney's U-test. Pseudo-randomization in the retrospective group was performed based on the concordance of the sample by the following parameters:

- Gender;
- Age;
- Oxygenation index at the date of starting the treatment;
- Therapy with tocilizumab;
- CIRS (Cumulative Illness Rating Scale) [5].

Analyses in subgroups:

- By gender and age groups;
- By the number of accompanying complications;
- By the APACHE/SOFA index;
- By the frequency and multiplicity factor of the exercises performed;
- By routing the start of the exercise therapy (initial admission to the ICU in compliance with the inclusion criteria; transferring to the ICU for deterioration and in compliance with the criteria; transition to exercise therapy after ALV).

Estimated number of patients

100 people in each of the main and control groups or reaching the first endpoint.

Patient selection principle

Patients were included in the study on the first day of admission to the ICU if they met the inclusion criteria and had voluntary informed consent for participation in the study. The distribution into groups was carried out randomly. Rehabilitation assistance was provided according to the protocol specifying the actual number of exercises performed. The endpoints were assessed for 10 days.

Data analysis

The database was formed based on source medical records in SPSS Statistics (IBM, USA). The odds ratio (with a significant difference of 3% and 95% CI) was calculated for the primary endpoint. The ANOVA analysis by subgroups was carried out for the primary and secondary endpoints.

Group recruitment and treatment

The recruitment of groups was carried out on a multi-center principle with the participation of two clinical centers: City Clinical Hospital No.40 of the Moscow City Department of Health and Mytishchi City Clinical Hospital, State Budgetary Institution of Health Care of the Moscow Region. The selection and rehabilitation process at the clinical center ware managed by a full-time exercise physician or the Head of the ICU, and the actual implementation of patient education was carried out by doctors, nurses and/or volunteers of the clinical base, whose competence included control of the frequency and accuracy of exercises by patients.

Treatment protocol

Protocol development

The protocol was developed based on the analysis of literature data and our own clinical experience. The work of Chinese specialists, from which we made three main conclusions about the factors that directly affect the effectiveness of the early rehabilitation process, formed a methodological backbone of the protocol:

- Rehabilitation should begin as early as possible, as soon as the patient's condition allows, to prevent the vicious circle of asthenization, weakening of the respiratory muscles, and worsening respiratory failure.
- There is a high risk of further damage to the lung tissue with techniques that significantly increase resistance to expiration or force expiration.
- Rehabilitation techniques in the format of respiratory exercises, which mainly stimulate the auxiliary respiratory muscles, improve the indicators of external respiration function in an evidence-based manner [6–11].

In the Chinese research protocols, traditional Chinese exercises were mainly used; however, due to the lack of prior experience working with it, the Chinese exercises were replaced with traditional ones in Russian exercise therapy, with respect to the recommendations for the muscle groups involved.

In the period from March to April 2020, the protocol was tested within the separate exercises, performed first by patients with mild respiratory failure (with the IO over 400 and breathlessness), and then by individual patients in the ICUs. During approbation, the initial list of exercises for ICU patients was reduced to 5, which was close to the maximum tolerable one-time physical activity on the one hand and made it possible to quickly train patients and staff on the other hand.

To ensure the greatest availability of data, the reference performance of the exercises with comments was recorded in a video lesson format, which was then posted on a public website on the Internet. Given the absence of any data on how long a patient should do respiratory exercises, we recommended all patients to continue the exercises until the health authorities form a procedure for screening and rehabilitating such patients, and for this purpose, we also recorded specific videos with the entire complex of exercises and instructions on their own implementation tested by us.

Formalized protocol

- For the first time, the exercises shall be performed jointly by the patient and medical staff; then the medical staff shall control the patient's doing exercises himself/herself.
- The exercises shall be performed only in the presence of productive contact with a patient, with a properly operating oxygen saturation sensor put on.
- The supine position shall be a starting position.
- The exercises shall be repeated 3 to 10 times, in a given order (Table 1). The frequency of approaches is 4 – 6 per day at a patient's request, while the range and number of repetitions performed within one approach shall not be regulated. If less than four approaches were performed per day, the mark "no exercises were performed" was recorded in the research protocol for such a patient.
- The exercises shall be terminated under the following conditions:
  - If initial SaO_2 > 92: with a decrease in SaO_2 below 88. If the indicator is restored within 30 seconds or less, it is possible to continue the exercise.
  - If initial SaO_2 was within the range of 87 – 92: with a decrease in SaO_2 below 80. If the indicator is restored within 30 seconds or less, it is possible to continue the exercise.
  - If initial SaO_2 < 80 (a sensor malfunction is suspected; the current acid-base balance should be clarified): the exercises shall be performed only in the presence of the attending physician.
  - In the case of the patient's complaints of severe fatigue, weakness, dizziness, or nausea, the exercises shall be terminated at any time.

The exercises were performed in the order shown in Table 1.

Compliance with Ethical standards

The study protocol and the patient's brochure were approved by the Protocol No.2 of the Ethics Committee of the City Clinical Hospital No.40 of the Moscow City Department of Health, State Budgetary Institution of Health Care of the City of Moscow, dated May 11, 2020. All study participants signed informed voluntary consent in accordance with the Declaration of Helsinki. Patients who refused to participate in the study received standard treatment in accordance with the current edition of the Interim Methodological Guidelines for the Prevention, Diagnostics, and Treatment of the New COVID-19 Infection and (since 21.05.20) in accordance with the Interim Methodological Guidelines for Medical Rehabilitation in the New COVID-19 infection.

In total, 146 patients were included in the study: 73 patients each in the treatment and control groups. The gender and age structure of the patients studied and the indicators selected for calculating the Propensity score are presented in Table 2.

Results and Discussion

During the study, the primary endpoint was reached with a significantly lower need for oxygen support in the treatment group. The results were systematized in Table 3.

Table 1
Order and description of program's excercises
Таблица 1
Порядок и описание упражнений программы

No.	Description
1	In the starting position, the patient shall make breathing-in. Then sliding the heel along the bed, the patient shall bend his/her leg in the knee and make breathing-out to painless level
2	Hands to the shoulders, spread the elbows to the sides – the patient shall make breathing-in. Then lower the elbows, press them against each other to the chest and bend in the stomach (if possible) – the patient shall make breathing-out
3	Support on the elbows, raise the chest – the patient shall make breathing-in. Then straighten the arm diagonally and make a reach for the arm by tearing off the shoulder blade – the patient shall make breathing-out ("Boxing" exercise)
4	One hand is behind the head. Twist the body in the opposite direction (with the pelvis staying the same place) and with the other hand clapping himself/herself on the side on the ribs – the patient shall make breathing-in. Then take the starting position with the hand put behind – the patient shall make breathing-out
5	Being supported by the elbows, raise the chest so that the shoulder blades go towards each other – the patient shall make breathing-in. Then relax – the patient shall make breathing-out

Table 2
Pseudo-randomization parameters structure
Таблица 2
Характеристика пациентов исследуемых групп по параметрам псевдорандомизации

Parameter	Treatment group	Control group	Significance of differences
Group size	73	73	< 0.05
Males, %	57.5	53.4	< 0.05
Average age	59.2 ± 14.4	60.3 ± 15.3	< 0.05
BMI	27.2 ± 4.1	29.2 ± 3.9	> 0.1
Average oxygenation index at the date of starting the treatment	330 ± 36	332 ± 54	< 0.05
Patients receiving tocilizumab, %	5.4	6.8	< 0.05
Cumulative Illness Rating Scale-Geriatric (CIRS-G), the average score	3.4 ± 2.3	3.3 ± 2.8	< 0.05

Note: BMI, body mass index.

Table 3
Study results
Таблица 3
Результаты исследования

Endpoint	Treatment group	Control group	Difference
The period from the start of treatment to the refusal of oxygen support	5.1 ± 3.3	8.0 ± 4.6	Significant ($p < 0.05$)
Daily average dynamics of changes in the oxygenation index	± 28.3 ± 39.0	± 14.3 ± 32.3	Significant ($p < 0.05$)
Self-service status assessment	0.6 ± 0.3	0.3 ± 0.5	Non-significant ($p = 0.12$)
Fatal outcomes, *n* (%)	1 (1.4)	4 (5.5)	Significant ($p < 0.05$)*
Transfer to ALV after treatment, *n* (%)	2 (2.7)	6 (5.5)	Non-significant ($p = 0.17$)

Note: ALV, artificial lung ventilation; *, They were excluded from the study analysis.

As the data in the table show, the study reached the primary endpoint – there is a significant difference in mortality rates between the groups. At the same time, the interpretation of the result requires several clarifications presented below and related to the peculiarities of patient selection in studies without the existing standard comparator intervention.

When analyzing the subgroups, no significant differences were revealed in age and sex. Among concomitant diseases, the difference in mortality rates in the presence of an oncological disease detected in 8 patients and accompanied by 3 (37.8%) fatal outcomes turned out to be significant. Moreover, cancer turned out to be a significant covariate of another indicator – exercise tolerance in those patients in whom it was managed to reliably measure it. At the same time, the ANOVA analysis did not reveal significant outcome covariates among the parameters entered.

When evaluating data on the mortality rate, it is necessary to take into consideration a combination of organizational and methodological factors, which, in our opinion, do not allow us to say about the presence of a causal relationship between this indicator and the treatment performed. First of all, most of the patients of the treatment group entered it in the period from May to June 2020, when the treatment protocols for patients with the new COVID-19 infection were well developed, and doctors gained experience in working with this category of patients. In contrast, the majority of the patients in the control group entered it in the period from March to April 2020 when many treatment principles were still being developed. It is necessary to say that during May, hospital occupancy also began to decrease, which led to the fact that the medical staff burden became lower, and they were able to more efficiently allocate time between patients.

In addition, attention should be drawn to the fact that in the existing method of patient selection, the treatment group definitly consisted of the patient contingent motivated for active prevention, while the control group, among other things, could have a high proportion of low-active patients with the severe depressive syndrome, high subjective asthenization, and low culture of physical activity in general. This is partly supported by a significantly higher BMI of the patients in the control group.

With regards the analysis in subgroups, the result is probably self-evident – the patient group was quite homogeneous in terms of age and sex composition, while patients with oncological diseases, especially those who underwent the course of anticancer therapy, dramatically stand out against it by the severity of their condition [12, 13].

The lack of ANOVA analysis results can be explained by two main classes of reasons having the opposite direction to a certain extent. First of all, probably, there were too many parameters for the relatively small sample, even for the minimal list of partition that was used in the study. And secondly, a large number of factors that could turn out to be significant covariates were not taken into consideration: for example, the study did not involve using the depression scale, recovery motivation scale, assessment of haemocoagulative parameters, interpretation of signs of a systemic inflammatory response in individual indicators (levels of interleukins, TNF-α, etc.). Moreover, we used the integral comorbidity parameter, while the literature data highlight very specific and diverse predictors of fatal outcomes depending on the number and nature of the concomitant disease [14–21].

Providing insight into the prospects for further studying the topic, we consider it reasonable to develop a comparator program with conducting a further study on their comparative assessment in conditions of COVID-19 infection. However, the primary objective is to form the evidence base for the first stage of rehabilitation in uncomplicated patients, as well as the second and third stages of rehabilitation. From our point of view, these objectives are largely related, since only the specification of the long-term medical and social effects of the new COVID-19 infection can give a clue to promising rehabilitation methods.

The use of larger samples allowing to better estimate the outcome covariates, in our understanding, is not reasonable, since the presented technique is only an auxiliary tool of the treatment protocol. And in contrast, comparing different early rehabilitation protocols as covariates in large population studies devoted to different complex treatment protocols can come useful.

In such a way, currently, we can say for sure that the proposed algorithm of respiratory exercises significantly accelerates the recovery of patients with severe respiratory failure against the background of the new COVID-19 infection, and it is associated with a better life prognosis for them. It is currently impossible to conclude the long-term effects of rehabilitation, but this assessment is included in our research strategy.

Conclusion

Using the complex of exercise therapy in the acute period of the new COVID-19 infection reduces the need for oxygen support in patients with respiratory failure and the oxygenation index of more than 200 and less than 400 against the background of the new COVID-19 infection. This results in a decrease in the inpatient unit burden under the epidemic conditions, and it was associated with an accelerated recovery rate of patients and reduced rates of transferring to ALV and mortality rates, for which, however, there were probably more significant success cofactors.

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Lung ultrasound: the possibilities of diagnosing of lung damage associated with the new coronavirus infection COVID-19

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Abstract

This publication is devoted to the ultrasound method of lung examination, which has gained particular relevance during the pandemic of the new coronavirus infection 2019. The lecture discusses the general provisions of lung ultrasound, ultrasonic signs of lung damage, features of ultrasound semiotics in the viral nature of lung lesions, differences from the bacterial nature of lung damage, presents aspects of the use of lung ultrasound during the pandemic of the coronavirus infection 2019. The lecture is based on the experience of domestic and foreign researchers, as well as on the authors' own experience, which demonstrates the value of this method both in intensive care units and in a therapeutic clinic.

Key words: lung ultrasound, ultrasonic artifacts, consolidation, lung damage, coronavirus infection.

Conflict of interests. The authors declare the absence of conflict of interests.

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Ультразвуковое исследование легких: возможности диагностики повреждения легких, ассоциированного с новой коронавирусной инфекцией COVID-19

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Резюме

Данная публикация посвящена ультразвуковому методу исследования легких, который приобрел особую актуальность в период пандемии новой коронавирусной инфекции COVID-19. Рассмотрены общие положения ультразвукового исследования легких, ультразвуковые признаки поражения легких, особенности ультразвуковой семиотики при вирусном поражении легких в отличие от бактериального поражения легочной ткани, представлены аспекты применения ультразвукового исследования легких при пандемии коронавирусной инфекции COVID-19. Публикация основана на опыте отечественных и зарубежных исследователей, а также на собственном опыте авторов, продемонстрирована ценность данного метода как в условиях отделения интенсивной терапии, так и в терапевтической клинике.

Ключевые слова: ультразвуковое исследование легких, ультразвуковые артефакты, консолидация, поражение легких, коронавирусная инфекция.

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Lung ultrasonography (U/S) has become popular mostly in intensive care units and emergency departments and gained acceptance as a useful bedside diagnostic tool for detecting some thoracic pathologies [1–3]. At present, doctors more and more often use lung U/S not only in emergencies, but also in therapeutic divisions as an adjunctive tool to diagnose pulmonary disorders, including pneumonias [4, 5]. *R.Copetti* made a good point by saying that it is high time to consider ultrasound the best stethoscope in our hands [6], and this modality should be as widely introduced in our clinical practice as the stethoscope, which is the symbol of the medical trade and doctors' skills. So far, considerable knowledge and experience has been accumulated suggesting its high diagnostic significance and safety, which is coupled with its convenience and ability to provide rapid information. Ultrasonography can be performed using fixed or portable ultrasound machines with various degrees of technical sophistication.

The following types of transducers can be used: standard convex, micro-convex, and sector transducers with a frequency range of 1 – 6 MHz and linear transducers with a frequency range of 6 – 12 MHz reserved for evaluation of superficial structures and the pleura [7, 8]. This examination can be carried out when the patient is sitting or lying if there is a possibility to turn him or her to the side opposite the side being examined.

Depending on the purpose of the examination and time limitations, ultrasound scanning can be done in each lung intercostal space, with 72 zones being examined, or the number of scanned sites can be reduced [9]. It has been shown that reducing the number of scanned zones to 14 does not significantly influence the examination results [10]. For intensive care units, some authors [11] proposed the Bedside Lung Ultrasound in Emergency (BLUE) protocol with only six areas of investigation (three on each side of the thorax). Such units quite often use a more comprehensive protocol with 8 – 12 zones of examination [12, 13].

During the pandemic of the novel coronavirus infection 2019 (COVID-19), lung U/S stimulated particular interest and become a promising target for further development. Before discussing U/S signs of lung damage in patients with COVID-19, we will look at the overall potential of ultrasonography for examination of the lungs.

At the time of development and introduction of ultrasound diagnostic techniques, doctors avoided using them for a lung examination. Indeed, in normally aerated lung tissue the largest portion of an incident ultrasound signal is reflected from the air. The U/S wave reflection coefficient for air is 750 times higher than for a fluid medium [7]. Thus, unaffected lung tissue cannot be visualised (Figure 1). However, morphological abnormalities and thus changes in the physical properties of lung tissue result in the appearance of acoustic effects that can be detected by ultrasound.

Reduced aeration of lung tissue and its increased density greatly facilitate the transmission of an ultrasound signal to deeper layers of lung tissue, and in zones of consolidated tissue penetration of ultrasound waves is almost 50 times higher [7]. It is important to note that consolidation can be observed not only in various types of pneumonia, but also in other pathologies accompanied by an increase in lung density, such as atelectasis of various causes, pulmonary embolism, tumours, and lung contusion [12]. Consolidation appears as a hypoechoic zone with an ultrasound pattern similar to that of liver (the tissue-like sign). For this reason, this pattern is referred to as lung hepatisation, which actually means consolidation [14]. Nevertheless, ultrasonography fails to detect consolidations that do not extend to the pleura because, as mentioned above, the layer of normally aerated lung tissue reflects ultrasound waves.

Consolidations can be of different shape and size, which is important for differential diagnosis. For example, an inflammatory consolidation appears as an area of irregular shape, which is not true for pulmonary infarction, carcinoma, or metastases. The pleural line over a lung consolidation may be seen as a less well-defined, fragmented hypoechoic line. Inflammatory lesions are separated from normal aerated lung tissue by irregular, interrupted, a bit blurred borders with a staircase appearance [14, 15] (Figure 2).

The air bronchogram sign and its severity are important features of consolidation [14]. This sign is seen as the presence of acoustically dense hyperechoic structures appearing as small linear inclusions, small focal lens-shaped lesions or ramified structures (Figure 2). It is caused by the presence of air in the small bronchi [16, 17]. Areas of consolidation may show either relatively even or uneven distribution of these echo-positive structures. Another possible feature is the dynamic air bronchogram, i.e. hyperechoic structures moving with the respiratory cycle, the presence of which is explained by air movement during inspiration. The dynamic air bronchogram is defined as progression of the air bronchogram in inspiratory time toward the periphery (centrifugally). The presence of this sign in an area of consolidation is the most specific sign of pneumonia and rules out pulmonary atelectasis due to occlusion of a proximal bronchus [15, 18].

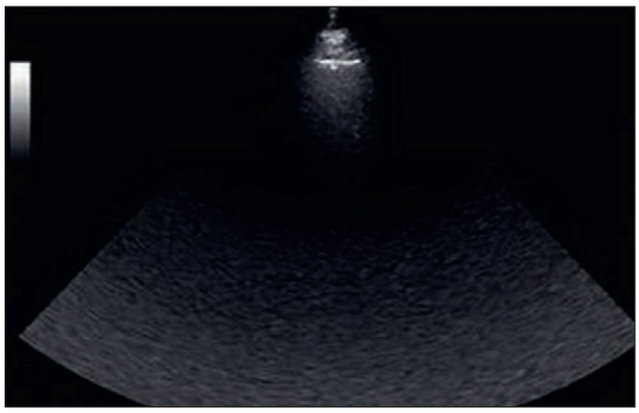

Figure 1. Ultrasound image of unchanged lung tissue (from the personal archive of G.V.Nekludova)

Рис. 1. Ультразвуковое изображение неизмененной ткани легкого (из личного архива Г.В.Неклюдовой)

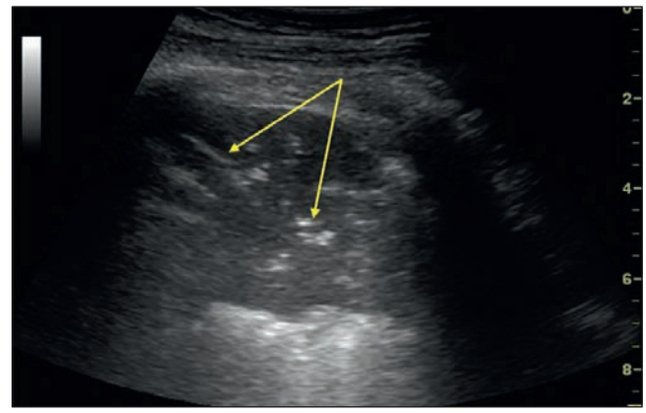

Figure 2. Ultrasound image of the lung consolidate (tissue-like sign), air bronchogram (arrows) (from the personal archive of G.V.Nekludova)

Рис. 2. Ультразвуковое изображение консолидата (*tissue-like sign*) воздушной бронхограммы (стрелки) (из личного архива Г.В.Неклюдовой)

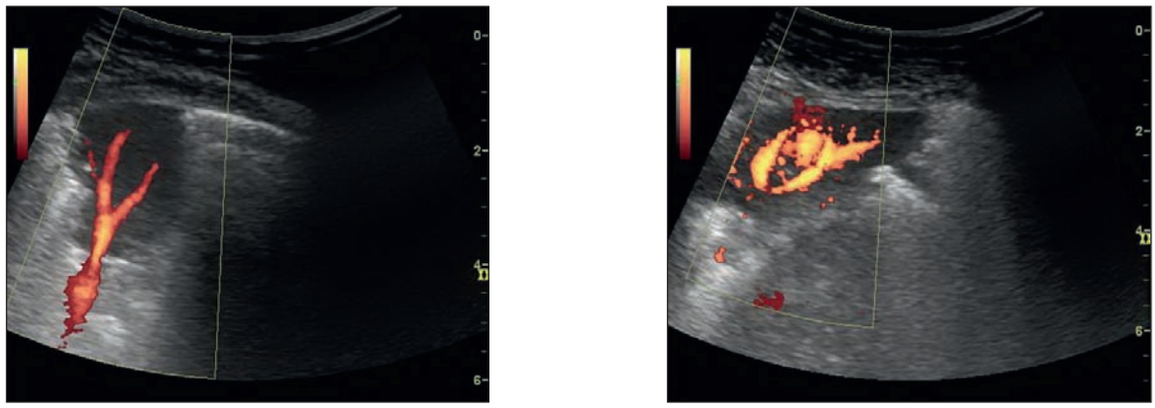

Figure 3. Ultrasound image of blood flow in the lung consolidate. Doppler blood flow analysis in the energy scanning mode shows increased vascularization, regular vascular pattern (from the personal archive of G.V.Nekludova)

Рис. 3. Ультразвуковое изображение кровотока в участке консолидации легочной ткани. Доплеровское исследование кровотока в режиме энергетического сканирования демонстрирует усиление васкуляризации, сосудистый рисунок регулярный (из личного архива Г.В.Неклюдовой)

Lung ultrasound may also show anechoic tubular fluid-containing structures, which represent fluid-clogged bronchioles, with surrounding consolidated lung. This phenomenon is referred to as the fluid bronchogram sign [2, 14]. The presence of this sign and its severity are also helpful diagnostically in identifying the causes of consolidation.

An important step in the evaluation of a consolidation area is an assessment of its vascularity, which could be increased or reduced with either a normal regular (Figure 3) or abnormal distorted vascular pattern [19, 20]. Analysis of these features is important in the differential diagnosis and the identification of the underlying causes of consolidation.

As the attenuation coefficient of ultrasound in fluids is minimal, ultrasonography is highly sensitive and highly specific for the detection of fluid in the pleural cavity and is superior in this regard to chest X-ray [21, 22]. Ultrasound can easily detect pleural effusion and, besides identifying the fluid itself, it can also provide detailed information about its location and nature, amount of fluid, and the condition of the pleural surfaces. It should be noted that lung U/S is more sensitive than chest X-ray for detecting not only pleural effusion, but also pneumothorax [23, 24].

In addition to identifying certain really existing pulmonary structures, ultrasound scans may show additional ultrasonographic effects representing acoustic artefacts. There are two main patterns of artefacts. The first, called A-lines, is reverberation artefacts that are generated by multiple reflections of the ultrasound waves at the pleura and appear as repetitive, horizontal, hyperechoic lines deep to the pleural line displayed at regular intervals (Figure 4). This artefact is indicative of normal or excessive amount of air in the alveolar spaces [9].

The most important ultrasound artefact is the one called B-lines, which are signs of an increased lung density and its reduced aeration [3, 11, 25]. On ultrasound scans they are seen as hyperechoic lines that originate from the pleural line and traverse the entire ultrasound screen vertically to the opposite edge. These hyperechoic lines extend radially, appear as a laser beam, and move in synchrony with lung sliding (Figure 5). B-lines appear when ultrasound waves reach the interface between a thickened interlobular septa and air-filled alveoli, i.e. the interface between two media with very different acoustic impedance,

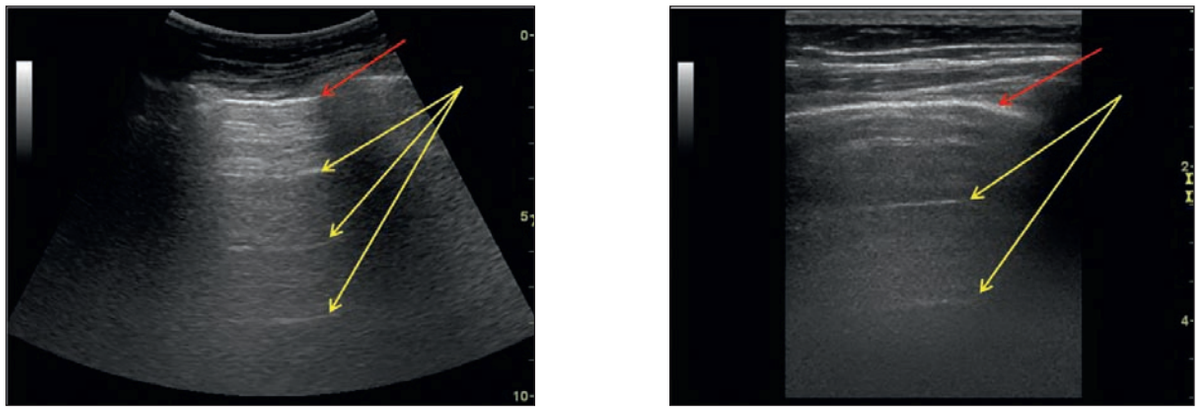

Figure 4. Unchanged lung tissue. Thin echo-positive pleural line (red arrow), A-lines (yellow arrows) (from the personal archive of G.V.Nekludova)

Рис. 4. Неизмененная легочная ткань. Тонкая эхо-позитивная плевральная линия (красная стрелка); А-линии (желтые стрелки) (слева – конвексный датчик, справа – линейный датчик) (из личного архива Г.В.Неклюдовой)

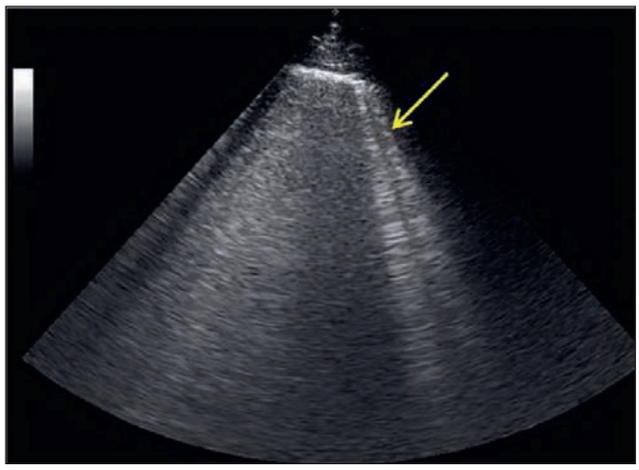

Figure 5. Ultrasound image of the B-line artifact (arrow) (from the personal archive of G.V.Nekludova)

Рис. 5. Ультразвуковое изображение артефакта В-линии (стрелка) (из личного архива Г.В.Неклюдовой)

which results in multiple vertical reverberations. This U/S phenomenon is not a specific sign, but it is characteristic of interstitial changes (interstitial syndrome). For instance, it can be observed in lung atelectasis, pneumonia, lung contusion, pulmonary embolism, diffuse parenchymal lung diseases, cardiogenic pulmonary oedema, and acute respiratory distress syndrome (ARDS) [3]. With progression of interstitial changes, B-lines become more numerous (Figure 6) and confluent (Figure 7), resulting in a single hyperechoic area in the most advanced cases. This phenomenon is referred to as white lung appearance (or the waterfall sign, which is seen when the transducer is placed longitudinally, perpendicular to the ribs) and represents alveolar-interstitial syndrome.

In different cases, depending on the etiology of interstitial syndrome and the severity of the pathogenic process, the pleural line can appear normal (not more than 2 mm thick) or thickened and be regular and smooth or irregular and interrupted [26] (Figures 6, 7).

It should be emphasised that since features and artefacts detected by U/S are not highly specific, they need to be thoroughly and comprehensively assessed together with clinical and laboratory data as well as findings detected by physical examination and additional investigations. This will definitely enlarge the diagnostic potential of sonography and improve the quality of diagnostic services in general.

As mentioned above, it was during the spread of coronavirus infection that this imaging diagnostic modality received enormous attention. What was the reason for such popularity of lung U/S during the pandemic of COVID-19?

Chest computed tomography (CT) is indisputably the tool of choice and the "gold standard" for the diagnosis of pulmonary damage. However, CT is not always available in intensive care units. Moreover, there are some limitations to using CT during a pandemic, including a large number of patients requiring diagnostic testing and treatment, the high infectivity of SARS-CoV-2, risks of transporting patients with hypoxemia and unstable haemodynamics, and difficulties associated with disinfection of CT scanners.

Some pilot studies have already demonstrated a correlation between the results of diagnostic CT and ultrasonography of the lungs in patients with suspected COVID-19-associated pneumonia [27, 28].

In turn, ultrasonography is more sensitive than conventional chest radiography for the detection of interstitial syndrome and subpleural consolidations. Ultrasonography is able to identify very small consolidations (< 0.5 cm) [29]. Moreover, in patients with COVID-19, pulmonary lesions strongly tend toward peripheral (subpleural) distribution, making ultrasonography an acceptable diagnostic tool for COVID-19-associated pneumonias. Also, ultrasound machines are affordable and relatively inexpensive devices, compared to other imaging equipment. Undoubtedly, ultrasound scanners are more mobile. Currently, specialists more and more often use pocket wireless ultrasound devices, which are a lot easier to be disinfected and protect-

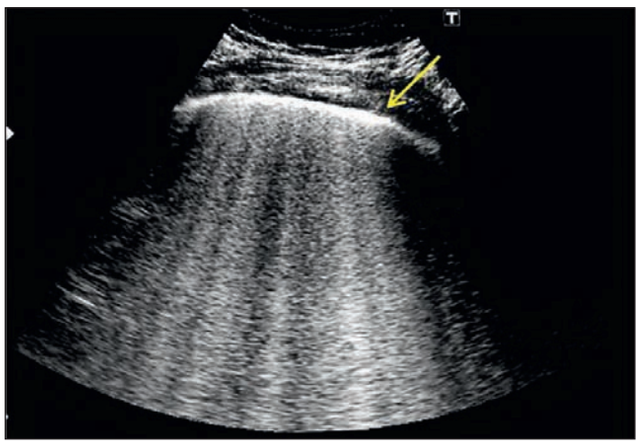

Figure 6. Severe interstitial syndrome, multiple B-lines, thickened pleural line (arrow) (from the personal archive of G.V.Nekludova)

Рис. 6. Выраженный интерстициальный синдром, множественные В-линии, утолщенная плевральная линия (стрелка) (из личного архива Г.В.Неклюдовой)

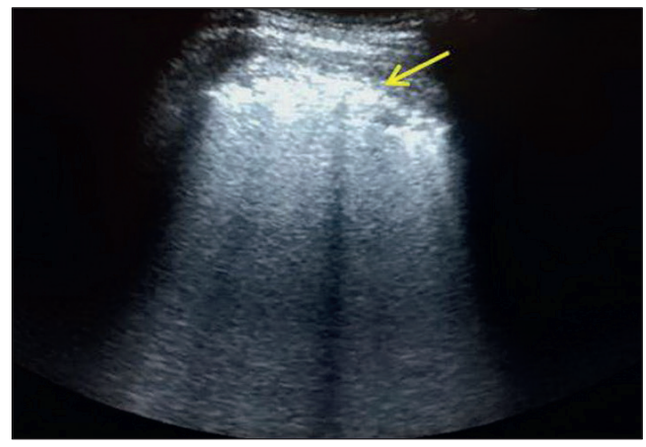

Figure 7. Confluent B-lines, "white lung", thickened, irregular, intermittent pleural line (arrow) (from the personal archive of G.V.Nekludova)

Рис. 7. Сливающиеся В-линии, формирование «белого легкого», утолщенная нерегулярная прерывистая плевральная линия (стрелка) (из личного архива Г.В.Неклюдовой)

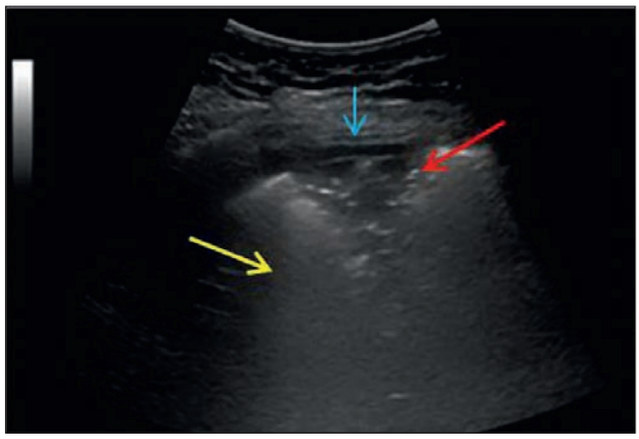

Figure 8. Consolidate with air bronchogram (red arrow) on the background of a pronounced interstitial syndrome, manifested by confluent B-lines (yellow arrow); a small amount of fluid (effusion) in the pleural cavity (blue arrow) (from the personal archive of G.V.Nekludova)

Рис. 8. Участок консолидации с наличием воздушной бронхограммы (красная стрелка) на фоне выраженного интерстициального синдрома, проявляющегося сливающимися В-линиями (желтая стрелка), незначительное количество жидкости (выпот) в плевральной полости (голубая стрелка) (из личного архива Г.В.Неклюдовой)

ed from contamination. An important advantage of ultrasonography is its ability to provide valuable information within a short period of time; besides, it can be used as a bedside method. Being radiation-free, ultrasound examinations can be repeated many times and used for follow-up assessment of the lesions detected.

However, as noted above, U/S signs of lung damage are not highly specific. This raises the question of whether this method can be helpful in the diagnosis of viral pneumonia. Are there any U/S signs specific to pneumonia of viral etiology?

Earlier studies conducted during the type A (H1N1) flu pandemic and outbreaks of avian influenza A (H7N9) analysed specific U/S signs of viral pneumonia and revealed some differences in this regard from bacterial pneumonias. A typical and obligatory feature of viral pneumonia is interstitial syndrome, which manifests by such U/S artefact as B-lines. Another additional sign of viral pneumonias is the presence of small subpleural consolidations [29, 30], while bacterial pneumonias mostly present with areas of consolidation usually seen as larger opacities with air bronchogram. Moreover, bacterial pneumonias are quite often associated with increased vascularity within consolidated lung. It is important to note another significant characteristic of viral lung damage that differentiates it from that in bacterial pneumonias, i.e. a multifocal, mosaic-like (a combination of interstitial syndrome and consolidations) distribution pattern of U/S signs, which are more extended and more often bilateral [31].

Are there any U/S signs specific to pulmonary abnormalities caused by coronavirus infection and not found in other types of viral pneumonia? From the accumulated experience, it is clear that U/S signs as well as CT signs of lung injury observed in patients with coronavirus infection are not specific. This means that ultrasonographic signs identified in patients with COVID-19-associated pneumonia can also be seen in people with other viral infections.

The most consistent and apparently essential finding is the presence of interstitial syndrome; and the greater extension of B-lines (their number and distribution along the pleural line) is correlated with more marked lung involvement as evidenced by morphology and CT [32]. This was proven by a meta-analysis of seven studies. This analysis showed that the pooled frequency of the abnormal B-pattern detected in patients with lung damage caused by COVID-19 was 97%, with a minimum range of frequency reported in different studies (90 to 100%).

The next most frequent sign is abnormalities of the pleural line (its thickening and/or irregularity). The pooled frequency of this sign was 70%, but its frequency reported in different studies ranged significantly from 10 to 100%.

Consolidation (Figure 8) was observed less consistently (its pooled frequency was 39%) and its frequency in different studies varied significantly from 20 to 75%, with minor subpleural consolidations usually with poor blood flow being more frequent (Figures 9 and 10) [28]. Of note, in patients with COVID-19 consolidates are almost always accompanied by signs of interstitial syndrome (multiple separate or confluent B-lines). When isolated consolidations or locally distributed B-lines associated with a consolidation lesion are observed, other underlying causes should be considered.

Pleural effusion is not typical (its pooled frequency was only 14%). This is especially true of a significant pleural effusion, which should prompt consideration of other causes of pleuritis. The same is absolutely true of pneumothorax [33].

These U/S signs, interpreted in combination with clinical data, are quite helpful in detecting lung injury caused by coronavirus and other viruses and differentiating it from bacterial pneumonia. Importantly, in terms of the severity, extent, and nature, U/S findings are correlated with those detected by high-resolution CT [33].

In clinical practice, loss of lung aeration is assessed by semiquantitative analysis of U/S signs. In the context of a pandemic lung examination needs to be performed as promptly as possible, thus it is feasible to modify an U/S protocol and limit the number of chest areas to be scanned to 12 or 14 [31, 34] and in intensive care units this protocol can be reduced even further. The following scoring system is used to assess the severity of lung aeration loss in each area: 0 – normal lung aeration (A-lines or not more than two B-lines), 1 – moderate loss of lung aeration (multiple separated B-lines), 2 – severe loss of lung aeration (coalescent B-lines or white lung appearance in the most severe cases and small subpleural consolidations in some cases), and 3 – consolidation (tissue-like pattern) [31]. Then the sum of all the areas is calculated to obtain the overall score for both lungs.

Some researchers use a modified lung ultrasound scoring system developed for interstitial pneumonia [33].

The severity of U/S-detected loss of lung aeration reflects the following histological changes: the first stage is marked by acute lung damage manifesting as exudative diffuse alveolar damage (DAD), alveolar oedema, formation of hyaline membranes, haemorrhage, and mixed cel-

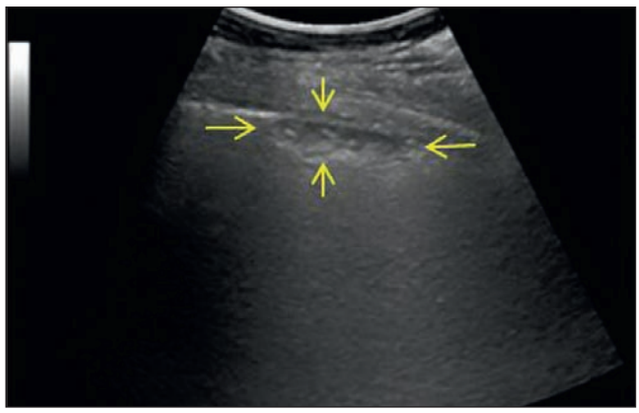

Figure 9. Subpleural consolidate (yellow arrows) on the background of a pronounced interstitial syndrome (confluent B-lines) (from the personal archive of G.V.Nekludova)

Рис. 9. Субплевральный консолидат (желтые стрелки) на фоне выраженного интерстициального синдрома (сливающиеся В-линии) (из личного архива Г.В.Неклюдовой)

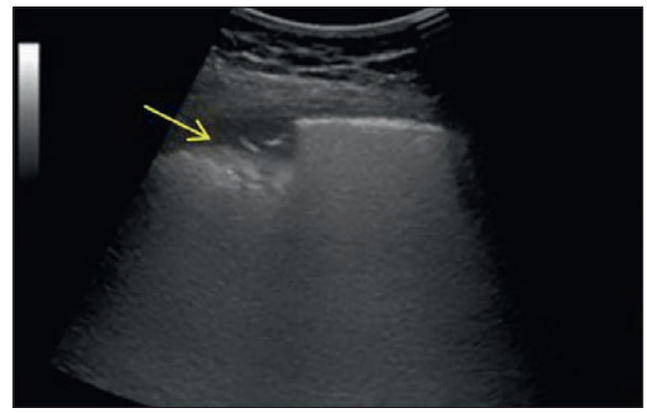

Figure 10. Subpleural consolidate (yellow arrow) on the background of alveolar-interstitial syndrome ("white lung") (from the personal archive of G.V.Nekludova)

Рис. 10. Субплевральный консолидат (желтая стрелка) на фоне альвеолярно-интерстициального синдрома («белое легкое») (из личного архива Г.В.Неклюдовой)

lular inflammatory infiltration; the following stage is characterised by early fibroproliferative changes combined with organisation of exudate, and deposition of loose extracellular matrix; and the next stage is dominated by fibroproliferation [35].

A semiquantitative ultrasound analysis of lung aeration loss not only allows for a one-time assessment of findings, but also offers the option of their follow-up. It can be used as a tool to assess the course and development of the disease, on the one hand, and the efficacy of various therapeutic interventions, on the other. *A.Pagano et al.* [36] used lung ultrasound imaging to assess the changes in lung aeration in patients with ARDS secondary to SARS-CoV-2 with non-invasive continuous positive airway pressure therapy (CPAP). They demonstrated that patients who did not reach an improvement in the oxygenation status with CPAP did not show any U/S signs of improved lung aeration. At the same time, patients whose oxygenation status improved with CPAP demonstrated lung recruitment of various degrees, which means that, besides an increase in lung aeration, in some cases there are probably other pathophysiological mechanisms resulting in the improvement in oxygenation. Thus, lung U/S provided a more comprehensive pathophysiological picture of alterations in patients with ARDS associated with SARS-CoV-2 infection, which helped optimise treatment protocols.

Initiating and maintaining the prone position (PP) is a widely used therapeutic strategy in patients with ARDS associated with COVID-19 [37–39]. PP allows for a more homogeneous overall lung ventilation and pulmonary blood flow, contributing to a reduction in ventilation/perfusion mismatch and improvement in oxygenation [40]. However, due to the individual dynamics of the disease not all patients respond equally positively to PP [38]. In patients with COVID-19 hypoxemic respiratory failure the intensity of positive response to PP is associated with the rate of intubation [41]. There is an increasing number of publications describing the potential of sonography to predict patients' response to PP. Based on the results of previous studies and our own experience, we believe that it is important to perform not only an overall assessment but also local analysis of the reduction in lung aeration, evaluating it in different regions. The following parameters may be regarded as potential predictors of a positive response to PP: the intensity of lung aeration loss and the area of poorly aerated lung tissue in the posterior portions and the degree of involvement of the anterior portions, as evidenced by ultrasonography. *G.Prat et al.* [42] reported that a normal U/S pattern of both anterobasal lung regions in supine position may predict a positive response to PP in patients with ARDS.

Resolution of the disease and normalisation of lung aeration is accompanied by the appearance of A-lines.

Conclusion

Thus, lung abnormalities associated with COVID-19 do not have any specific ultrasound signs that would be helpful in differentiating them from lung damage in other viral infections. There is, however, a set and combination of U/S findings that can suggest viral etiology of lung injury and distinguish it from that caused by bacterial pathogens. Therefore, in the context of a pandemic the identification of the above described signs may help raise the rate of early diagnosis and facilitate timely therapeutic decisions.

To summarize, during the COVID-19 pandemic lung U/S provides useful information for triage of symptomatic patients (patients with/without pneumonia), assessment of the severity and extent of lung involvement with subsequent identification of critically ill patients and their transfer to an intensive care unit, and monitoring the dynamics of lung injury with treatment [43].

In conclusion, it is important to emphasise that lung U/S is not a replacement for CT of the lungs and should not be viewed as an alternative to the latter. It is a promising adjunctive modality, useful for detecting lung abnormalities, and, in some cases, may substitute for conventional chest radiography, especially when the latter cannot be performed or when multiple examinations are required.

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An experience of using Laennec in patients at high risk of a cytokine storm with COVID-19 and hyperferritinemia

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Abstract

The probability of formation of the so-called "cytokine storm" accompanied by an avalanche-like growth of inflammatory markers – interleukins (IL)-1β, -6, interferon-γ, tumor necrosis factor-α, C-reactive protein (CRP), ferritin, etc. is high at a heavy current of COVID-19. In the absence of adequate treatment in the development of "cytokine storm" increases the risk of death, especially against the background of comorbid pathology. **Methods.** In April–May 2020, patients (n = 28: 12 men, 16 women; age 39 – 86 years) with long, chronic COVID-19 course were under observation, hospitalized on critical days of the disease. All patients reported anosmia, cough with poor sputum, signs of conjunctivitis. The patients had chronic diseases (n = 22: coronary heart disease, diabetes mellitus type 2, scleroderma). All patients were given standard therapy; half (n = 14) were additionally prescribed Laennec for 3 – 10 days (6 mL per 350 mL of 0.9% NaCl solution, intravenous infusion for the first 3 days, from day 4 – 6 mL per 250 mL of 0.9% NaCl solution) until stable remission is achieved. **Results.** The majority state (n = 25) stabilized; several patients died in the control group (n = 3; p = 0.067). In spite of the state stabilization, no reliable positive dynamics was noted in the control group for the tested parameters. Initially, liver dysfunction (level of alanine aminotransferase (ALT) – 113 ± 121, aspartate aminotransferase (AST) – 90.8 ± 87) was registered in 71% of patients, 8 U/L) and high risk of "cytokine storm" development (ferritin levels in men – 480 – 1,072 μg/L, in women – 274.7 – 493 μg/L, C-reactive protein – 5.0 – 52.6 mg/L, lymphocytes – < 25%). Positive clinical dynamics, a decrease in the level of ferritin (–282 μg/L – in men, –80 μg/L – in women; p = 0.039), an increase in blood oxygenation to normal values (p = 0.0029), a decrease in the area of lung injury according to CT data (on average – 10%); p = 0.0027), increase in relative lymphocyte content (+8%; p = 0.04), normalization of markers of liver dysfunction (AST, ALT), creatinine and systolic blood pressure (p < 0.05) were observed on prescription of Laennec. All patients who received Laennec recovered within 3 – 15 days from the start of the drug and were discharged with a negative test for SARS-CoV-2. **Conclusion.** Health condition is significantly improved, a wide range of hepatoprotective, immunomodulatory and regenerative effects are observed when the polypeptide Laennec is included in the complex therapy in patients with severe COVID-19. Laennec should be used primarily in patients with liver pathology, diabetes mellitus type 2, coronary heart disease, including high ferritin levels.

Key words: COVID-19 therapy, comorbid conditions, ferritinemia, Laennec, predictive modeling, intellectual data analysis.

Conflict of interests. The authors declare the absence of conflict of interests.

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Опыт применения препарата Лаеннек у пациентов с высоким риском развития «цитокинового шторма» на фоне COVID-19 и гиперферритинемии

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Резюме

При тяжелом течении COVID-19 высока вероятность формирования т. н. «цитокинового шторма», сопровождающегося лавинообразным нарастанием маркеров воспаления – интерлейкинов (IL)-1β, -6, интерферона-γ, фактора некроза опухоли-α, С-реактивного белка (СРБ), ферритина и др. В отсутствие адекватного лечения при развитии «цитокинового шторма» повышается риск летального исхода, особенно на фоне коморбидной патологии. **Материалы и методы.** В апреле–мае 2020 г. под наблюдением находились пациенты (n = 28: 12 мужчин, 16 женщин; возраст – 39 – 86 лет) с длительным, застойным течением COVID-19, госпитализированные в критические дни заболевания. У всех пациентов отмечены потеря обоняния, кашель со скудной мокротой, признаки конъюнктивита. У больных отмечались хронические заболевания (n = 22: ишемическая болезнь сердца, сахарный диабет 2-го типа, склеродермия). У всех пациентов проводилась стандартная терапия; половине (n = 14) дополнительно назначался препарат Лаеннек в течение 3–10 суток (6 мл на 350 мл 0,9 % раствора NaCl, внутривенно капельно в первые 3 дня, с 4-го дня – 6 мл на 250 мл 0,9 % раствора NaCl) до достижения устойчивой ремиссии. **Результаты.** Состояние большинства (n = 25) стабилизировалось; несколько в группе контроля скончались (n = 3; p = 0,067). Несмотря на стабилизацию состояния, в группе контроля достоверной положительной динамики по исследованным параметрам не отмечено. Исходно у 71 % пациентов отмечены дисфункция печени (уровень аланинаминотрансферазы (АЛТ) – 113 ± 121, аспартатаминотрансферазы (АСТ) – 90,8 ± 87,8 ед. / л) и высокий риск развития «цитокинового шторма» (уровень ферритина у мужчин – 480–1 072 мкг / л, у женщин – 274,7–493 мкг / л, С-реактивного белка – 5,0–52,6 мг / л, лимфоцитов – < 25 %). При назначении препарата Лаеннек наблюдалась положительная клиническая динамика, отмечено снижение уровня ферритина (–282 мкг / л – у мужчин, –80 мкг / л – у женщин; p = 0,039), увеличение оксигенации крови до нормальных значений (p = 0,0029), снижение площади повреждения легких по данным компьютерной томографии (в среднем –10 %; p = 0,0027), повышение относительного содержания лимфоцитов (+8 %; p = 0,04), нормализация маркеров дисфункции печени (АСТ, АЛТ), креатинина и систолического артериального давления (p < 0,05). Все пациенты, получавшие Лаеннек, выздоровели в течение 3–15 дней с начала применения препарата и были выписаны с отрицательным тестом на вирус SARS-CoV-2. **Заключение.** При включении полипептидного препарата Лаеннек в комплексную терапию у пациентов с тяжелым течением COVID-19 существенно облегчается состояние здоровья, наблюдается широкий спектр гепатопротективных, иммуномодуляторных и регенеративных эффектов. Лаеннек следует использовать в первую очередь у пациентов с патологией печени, сахарным диабетом 2-го типа, ишемической болезнью сердца, в т. ч. на фоне повышенного уровня ферритина.

Ключевые слова: терапия COVID-19, коморбидные состояния, ферритинемия, Лаеннек, предиктивное моделирование, интеллектуальный анализ данных.

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

Для цитирования: Максимов В.А., Торшин И.Ю., Чучалин А.Г., Лазебник Л.Б., Ткачева О.Н., Стражеско И.Д., Громова О.А. Опыт применения препарата Лаеннек у пациентов с высоким риском развития «цитокинового шторма» на фоне COVID-19 и гиперферритинемии. *Пульмонология*. 2020; 30 (5): 587–598. DOI: 10.18093/0869-0189-2020-30-5-587-598

In 2019, the world was faced with COVID-19 – a previously unknown and highly contagious respiratory viral infection that implies risks of serious complications (primarily in patients with chronic diseases in presence of high levels of inflammation). Unlike other respiratory diseases, COVID-19 can be asymptomatic or relatively mild in most patients. However, COVID-19 causes severe pneumonitis and acute respiratory failure in a number of patients. The main goal of therapy is to prevent death. Various methods of treating the coronavirus infection are being currently tested.

Multiple organ pathology is inherent in the COVID-19 infection. In addition to damage to the lung tissue and the resulting respiratory dysfunctions, there are *dysfunctions of other organ systems*, including:

- impaired blood coagulation profile (including increased D-dimer levels) and disseminated intravascular coagulation [1];
- "cytokine storm", an avalanche-like increase in the levels of multiple inflammation markers in the blood (IL-1β, IL-6, CRP, TNF-α, IFN-γ, ferritin, etc.);
- liver dysfunction involving increased levels of AST and ALT markers, albumin and bilirubin [2] and gastrointestinal symptoms (nausea, vomiting, diarrhea);
- damage to the parenchima of the kidneys, heart and of the other organs [3, 4].

These multiple organ complications are associated with severe COVID-19 and a higher risk of death [5]. A faster treatment of these COVID-19 complications requires the use of certain pharmacological medications. Unfortunately, each of the above complications requires the use of separate drugs leading to inevitable polypharmacy that implies multiple and quite unwanted drug-drug interactions and an increase in the iatrogenic load on the hepatobiliary system.

Therefore, it is essential to make the right choice of a drug for the treatment of patients with COVID-19 in presence of multiple organ pathology, in order to tackle the main challenge of COVID-19 therapy, i.e. to decrease mortality. In our opinion, the polypeptide drug Laennec (ATX A05BA Drugs for the treatment of liver diseases, L03 Immunostimulants), developed by Russian and Japanese scientists, has a significant potential in the therapy of COVID-19.

Laennec is registered in Russia as a hepatoprotector and immunomodulator that increases the functional activity of phagocytes and T-cells, and prevents the death of hepatocytes and other parenchymal cells. Laennec is characterized by a high degree of pharmaceutical standardization and a multidirectional therapeutic effect. According to the nosological classification, Laennec (ICD-10) is indicated for patients *with liver diseases* (K76.9 Liver disease, unspecified, K70.0 Alcoholic fatty degeneration of the liver, K76.0 Fatty liver degeneration, not classified elsewhere), viral infections (B00.9 Herpesviral infection, unspecified) and diseases characterized by an *increased background of inflammation, including allergic* (L20 Atopic dermatitis) [6]. Accordingly, Laennec has the potential to

compensate for the multiple organ pathology associated with COVID-19.

The purpose of this study is to test the use of Laennec in middle-aged and elderly patients with a long and stagnant course of COVID-19 with liver dysfunction, hyperferretinemia and with a high risk of cytokine storm against the background of a high comorbid load (chronic diseases were in 22 (79%) of 28 patients). The patients were followed up in April and May, 2020.

Materials and methods

A group of patients with a moderate/severe course of COVID-19 (n = 28) had been treated at the COVID center deployed at the Russian Gerontological Research and Clinical Center (RGRCC). Patients aged 39 to 86 (12 men, 16 women) were observed; 12 patients suffered from ischemic heart disease (IHD), 8 had type 2 diabetes mellitus (T2DM), one patient had multiple sclerosis, and one patient had psoriasis. All patients received complex therapy in keeping with the 5th version of the Guidelines of the Ministry of Health of the Russian Federation as of April 08, 2020; full blood cell count and biochemical blood tests were performed using standard methods; ferritin was determined spectrophotometrically by enzyme immunoassay.

Patients had liver dysfunction (mean ALT values 113 ± 121 U/L, AST 90.8 ± 87.8 U/L) and a high risk of cytokine storm: CRP 5 – 52.6 mg/L, the relative lymphocyte count less than 25 in 71% of patients; ferritin (men) was 480 – 1,762 mcg/L, ferritin (women) was 274.7 – 493 mcg/L (given the references intervals of 20 – 250 mcg/L for men and 10 – 120 mcg/L for women). General and biochemical blood tests were performed using standard methods; ferritin was determined spectrophotometrically by enzyme immunoassay.

From the first day of the disease, all patients reported lack of appetite; increasing, overwhelming weakness that would not subside after sleep; sweating, and muscle pain. All patients showed loss of smell, cough with scanty sputum, and signs of conjunctivitis. On examination, dyspnea at rest was noted aggravated by exertion (walking, climbing stairs). The patients were underactive and quickly got tired. The patients had an increased temperature (37 – 39 degrees during 2 to 5 days), skin pallor, and rapid breathing. The semi-sitting position made breathing easier.

Upon admission to the RGRCC, the patients showed rapid breathing (28 – 30 per minute), decreased blood oxygenation (SpO_2 < 90%), decreased partial oxygen pressure (PaO_2 < 60 mm Hg), and decreased systolic blood pressure (SBP, less than 100 mm Hg). Six out of 28 patients required mechanical ventilation (ALV); the rest of the patients received high-flow nasal oxygenation. Before Laennec was used, there was no positive dynamics observed during 5 to 7 days.

The severity of COVID-19 in patients was assessed by computed tomography (CT). Bilateral changes were recorded in patients with a predominant lesion of the lower lobes (more than 3 foci of ground glass compaction with a maximum diameter of < 3 cm, in combination with foci of consolidation). According to the CT data, the total area of injuries (0 – 100%) and the degree of damage in points (0 – 5 points) were assessed. The degree of damage was calculated as the average for each of the five lobes of the lungs (1 point – < 5% tissue is involved, 2 points – 5 – 25%; 3 points – 26 – 49%; 4 points – 50 – 75%; 5 points – > 75%).

The patients were hospitalized between the 5th and 10th days from the onset of the disease that corresponds to the stage of progression (Days 5 to 8 of the disease) and the peak stage of COVID-19 (Days 10 to 13 of the disease). According to the CT, the stage of progression was characterized by an increase in the prevalence of ground glass symptoms, local reticular changes, and the appearance of consolidation foci. At the peak stage, the CT showed the formation of perilobular compaction.

14 patients were prescribed the polypeptide drug Laennec (Japan BioProducts Co. Ltd., registration certificate of the Healthcare Ministry of the Russian Federation No.013851/01), registered in Russia as a hepatoprotector and immunomodulator. Depending on the severity of a patient's condition, Laennec was used from 3 to 10 days (the first three days, 6 mL per 350 mL of 0.9% NaCl solution, intravenously, drip, from Day 4, 6 mL per 250 mL 0.9% NaCl solution daily). Patients were discharged after achieving a stable remission, with a comprehensive assessment of the general condition, taking into account the data of blood biochemistry, blood oxygenation, in the stage of pneumonitis resolution shown in the CT.

The standard processing of the research results included the use of methods of mathematical statistics, including the calculation of the numerical characteristics of random variables, testing statistical hypotheses using parametric and nonparametric criteria, and correlation analysis and ANOVA. The predicted and observed frequencies of occurrence of the studied features were compared using the χ^2 test, the Wilcoxon–Mann–Whitney test, and the Student's test. The application program Statistica 10.0 and Microsoft Excel spreadsheets were used.

In addition to standard statistical methods, modern data mining methods were applied in the study, including the method of analyzing metric condensations in the parameter space, the method of metric maps [7] and methods for predicting numerical target variables [8, 9]. The mathematical details of the methods used (including the comparison with other approaches and algorithms) are given in our series of works on topological data analysis [7–9]. The method of analysis of metric condensations is highly sensitive and enables the detection of clusters (condensations) of points, even if the differences in the point density do not exceed a few percent.

Results

The condition of 25 patients stabilized; three patients in the control group died (p = 0.067). Despite the stabilization of the state, there was no significant positive dynamics in the studied parameters in the control group. The use of Laennec resulted in positive clinical dynamics, a decrease in ferritin levels, an increase in blood oxygenation to the normal range, a decrease in the area of lung dam-

age according to the CT data, an increase in the percentage of lymphocytes, and the normalization of liver dysfunction markers (AST, ALT), creatinine and systolic blood pressure (all $p < 0.05$). All patients who received the medication achieved a stable remission within 3 to 15 days after the start of Laennec use and were discharged with a negative test for SARS-CoV-2 to be followed up by a physician at their place of residence to secure further rehabilitation.

The use of Laennec facilitated complex changes in the values of indicators of the patients' condition that are presented on the metric map (Figure 1). The metric map of a clinical trial is a visual diagram showing each of the studied indicators of the state (for example, the level of ferritin) in correspondence to two points on the plane: the values of the indicator before and after therapy ("ferritin, before" and "ferritin, after"). The distance between any two points of the metric map corresponds to the degree of the indicators' association. The condensations (clusters) of points correspond to indicators with the values closely interacting with each other.

The metric maps enable both the study of complex relationships between indicators of the patients' condition (see, for example, in studies [10, 11]) and a comprehensive assessment of the efficacy of therapy, as well as the choice of the most informative predictors for predicting the therapy efficacy and responders/non-responders (see below). With a low efficacy of therapy (considering all the studied parameters), the positions of the points hardly alter, and a single cluster of parameters is maintained. An effective therapy results in a significant rearrangement of the points corresponding to the studied parameters into separate clusters.

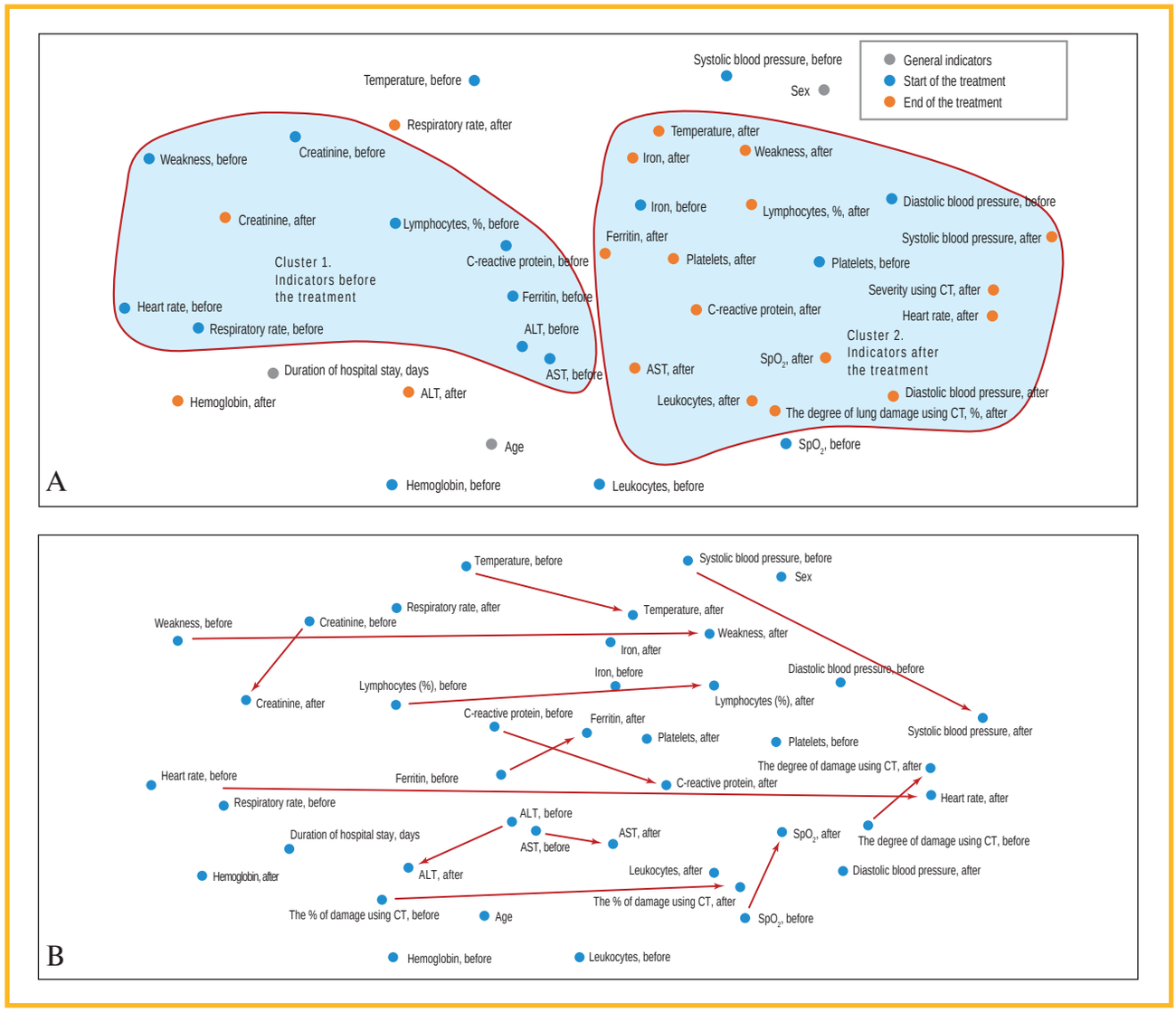

Figure 1. Metric card of the present study. The points on the metric map correspond to the indicators of the patient's condition. The distances between the points reflect the degree of interaction of indicators: the closer the points, the stronger the associations between the indicators: A, Metric condensations (clusters) of points on a metric map; B, Representation of the dynamics of treatment as a regrouping of points on a metric map.
Note: ALT, alanine transaminase; AST, aspartate transaminase; CT, computed tomography; SpO_2, blood oxygenation level.

Рис. 1. Метрическая карта настоящего исследования. Точки на метрической карте соответствуют показателям состояния пациентов. Расстояния между точками отражают степень взаимодействия показателей: чем ближе точки, тем сильнее ассоциации между показателями: А – метрические сгущения (кластеры) точек на метрической карте; В – представление динамики лечения как перегруппировки точек на метрической карте

In the present study it was found that the use of Laennec is associated with a clear division of the metric map into the cluster of parameter values before the start of therapy and into the cluster of parameter values after therapy (Figure 1A). No such division into clusters was observed in the control group. In other words, the use of Laennec in patients with a rather severe course of COVID-19 caused a coordinated complex change in many indicators of their condition corresponding to the movement of points "from left to right" on the metric diagram in Figure 1B. As the analysis of the individual parameters shows, this complex change corresponds to clear positive dynamics of the patient's condition: a decrease in inflammation, an improvement in the function, and a decrease in markers of liver and kidney dysfunction. In the control group, however, there was no clear positive dynamics in ferritin, CRP, AST and ALT ($p > 0.05$ according to Student's test and the rank criterion) and according to the CT data.

Laennec therapy in patients with COVID-19 primarily resulted in a *significant decrease in the levels of inflammatory markers (ferritin, CRP) and in an increase in the relative lymphocyte count compared to control* (Figure 2). Significant improvements in these parameters were observed both in the entire group of patients receiving Laennec, and in the male and female subgroups. On average, for the entire group, ferritin decreased from 603 ± 205 μg/L to 390 ± 124 μg/L ($p = 0.039$). At the same time, a significant decrease in ferritin was observed both in men (from 790 ± 249 to 462 ± 145 μg/L; $p = 0.033$) and in women (from 372 ± 86 μg/L to 244 ± 140 μg/L; $p = 0.034$).

The levels of C-reactive protein (a protein of the acute phase of inflammation), decreased from 23.1 ± 18.9 mg/L to 9.0 ± 6.8 mg/L ($p = 0.014$). Although after the end of therapy, CRP levels reached the upper range of normal (5 mg/L) in only 4 out of 14 patients; the median CRP (6 mg/mL) significantly approached the reference interval compared to the initial median value (14.2 mg/mL).

The relative content of lymphocytes (LYM%) indicating the state of antiviral immunity, significantly increased from 20.0 ± 10.9% to 27.8 ± 11.6% after treatment with Laennec ($p = 0.042$). Before treatment, LYM% values of more than 25% (the lower limit of the reference interval) were observed in only 3 of 14 patients, and after treatment, in 9 patients. This result corresponds to a significant reduction in the risk of LYM% values less than 25% according to the χ^2 test (OR, 0.15; 95% CI, 0.03 – 0.81; $p = 0.022$), that is, the activation of the antiviral system in the body.

The positive clinical dynamics corresponded to a decrease in inflammation markers during the use of Laennec (Figure 3): an increase in the degree of blood oxygenation according to pulse oximetry (SpO_2), a decrease in the degree and area of lung damage according to computed tomography, and a decrease in complaints of overwhelming weakness.

Laennec therapy resulted in an increase in the degree of blood oxygenation SpO_2 from 91.4 ± 4.6% to 96.2 ± 3.2% ($p = 0.0029$). SpO_2 values less than 95%, corresponding to respiratory failure, were observed in 11 patients before the start of therapy and only in 3 patients after therapy, which corresponds to a 13-fold decrease in the risk of respiratory failure (OR, 0.07; 95% CI, 0.01 – 0.45; $p = 0.0025$). It should be noted that already from Day 2 of Laennec therapy a significant decrease in respiratory rate

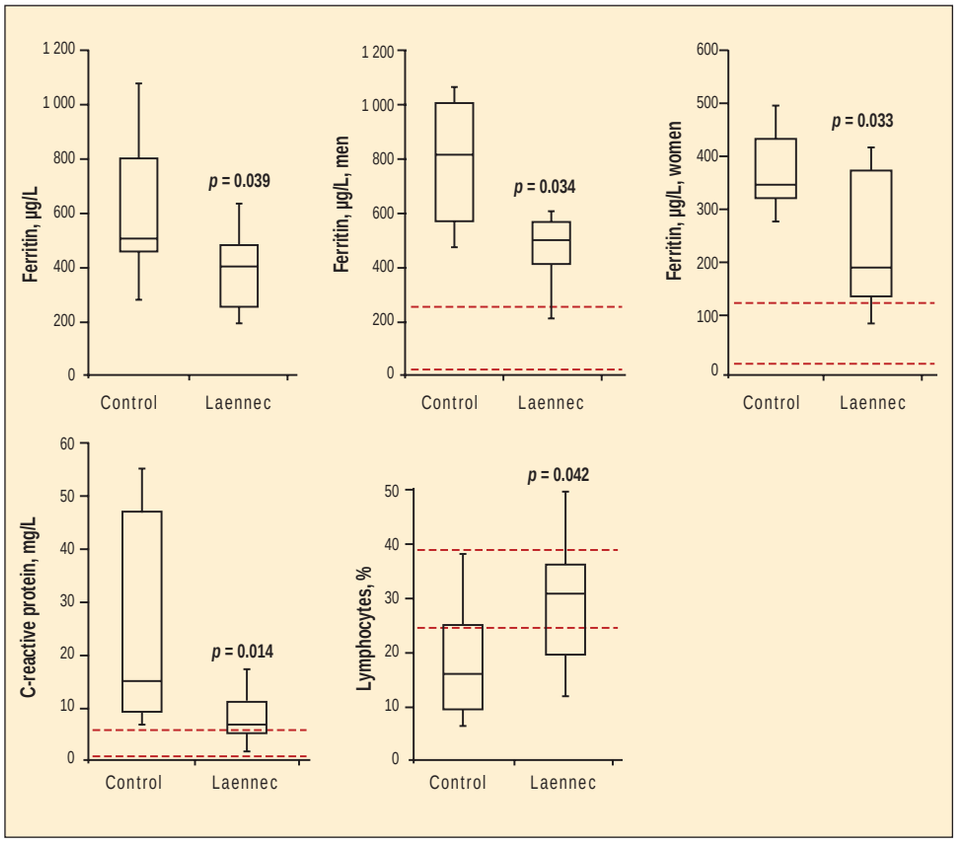

Figure 2. Dynamics of markers of inflammation/cytokine storm in patients with COVID-19 during treatment with Laennec. The rectangles represent the boundaries of 25 – 75% of the values, the lines within the rectangles are the median values of the parameters. Dash-dotted lines show the boundaries of the reference intervals
Note: CRP, C-reactive protein.

Рис. 2. Динамика маркеров воспаления / «цитокинового шторма» у пациентов с COVID-19 на фоне лечения препаратом Лаеннек. Прямоугольники обозначают границы 25–75%-ных значений, линии внутри прямоугольников – медианные значения параметров. Штрих-пунктирными линиями показаны границы референсных интервалов

was observed, from 18.9 ± 2.4 per minute to 17.5 ± 1.2 per minute ($p = 0.029$); the patients had improved sleep and improved mood.

The improvement in blood oxygenation was accompanied by a decrease in the degree of lung damage according to the CT data (a decrease in the score from 3.35 ± 0.50 to 2.71 ± 0.61; $p = 0.0027$) and a decrease in the area of lung damage according to the CT data from 73.4 ± 17.2% to 63.1 ± 13.9 % ($p = 0.047$). Along with the objective improvement in respiratory function, the patients complained less of the overwhelming weakness: before the start of therapy, 9 patients complained of general weakness, after therapy there were only two such patients (a 11-fold reduction in risk, OR, 0.09; 95% CI, 0.01 – 0.59; $p = 0.0068$).

The use of Laennec resulted in significant improvements in liver (ALT, AST levels; Figure 4) and kidney (creatinine levels) markers. The AST levels decreased from 121.3 ± 102.5 U/L to 45.7 ± 15.7 U/L ($p = 0.050$). Initially, there were elevated AST levels (more than 40 U/L) in 14 patients; after treatment, only in 7 (OR, 0.07; 95% CI, 0.007 – 0.70; $p = 0.0091$). The ALT levels decreased from 164 ± 155 U/L to 49 ± 28 U/L ($p = 0.049$). At the same time, abnormally high ALT levels (more than 41 U/L) were observed in 13 out of 14 patients at the start of therapy and in 8 patients after using Laennec (OR, 0.10; 95% CI, 0.01 – 1.00; $p = 0.029$). On average for the group, creatinine decreased from 105.3 ± 87.8 μmol/L to 20.5 ± 9.2 μmol/L ($p = 0.049$).

Discussion

Previous studies of the composition of Laennec did indicate considerable feasibility of using the drug in patients with COVID-19. In fact, peptides-inhibitors of the IKKB protein that were found in the composition of the drug do help to reduce systemic inflammation by inhibiting the NF-kB cascade. Further, a significant amount of the immunomodulatory element zinc necessary to activate innate antiviral defense systems in COVID-19 [3] and anti-inflammatory peptides-inhibitors of a number of kinases in human proteome were also found in Laennec. Earlier clinical experience with Laennec demonstrated normalized levels of pro-inflammatory cytokines (IL-6, TNF-α) and a significant decrease in the levels of AST and ALT enzymes in Laennec-treated patients [6]. Therefore, we hypothesized that the anti-inflammatory and anti-viral effects of Laennec could effectively inhibit the formation of a life-threatening cytokine storm in patients with severe COVID-19.

In this work, we considered ferritin, CRP, and the relative content of lymphocytes as biomarkers of a cytokine storm. It is known that patients with severe COVID-19

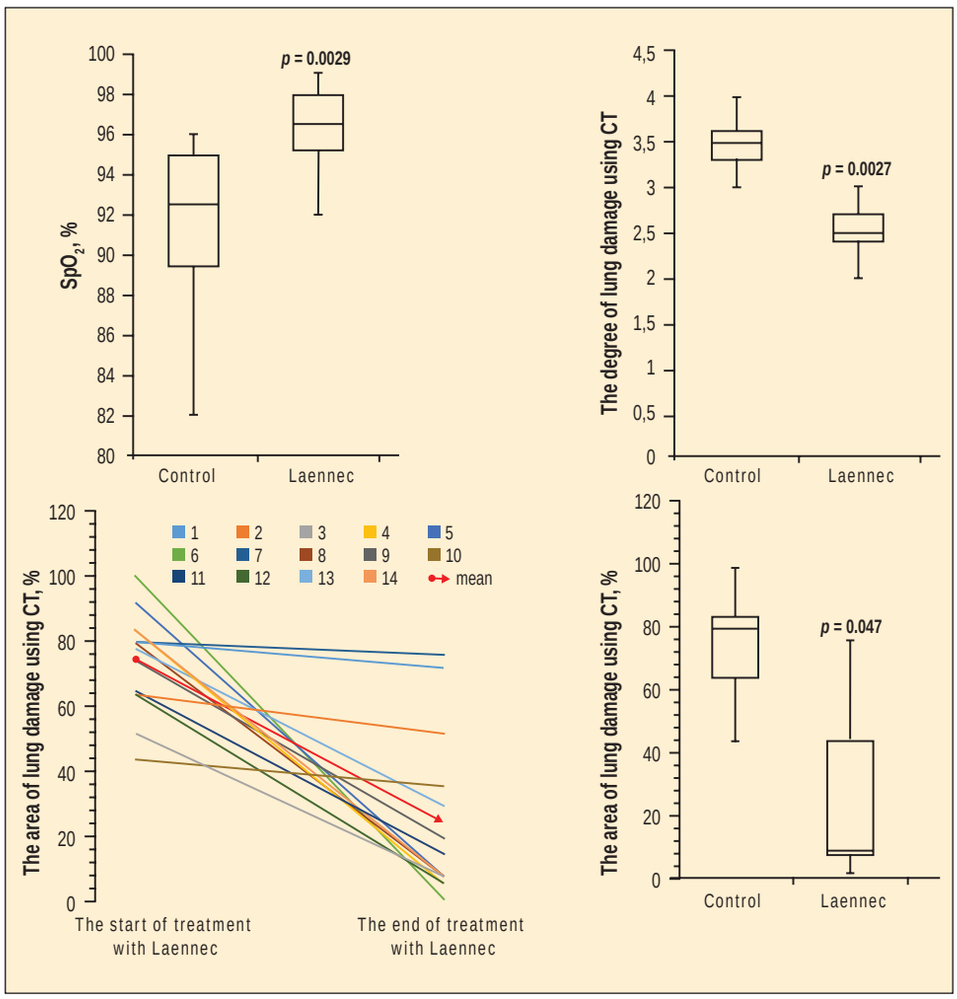

Figure 3. Improvement of respiratory function in the dynamics of Laennec therapy
Note: CT, computed tomography; SpO_2, blood oxygenation level.

Рис. 3. Улучшение дыхательной функции в динамике терапии препаратом Лаеннек

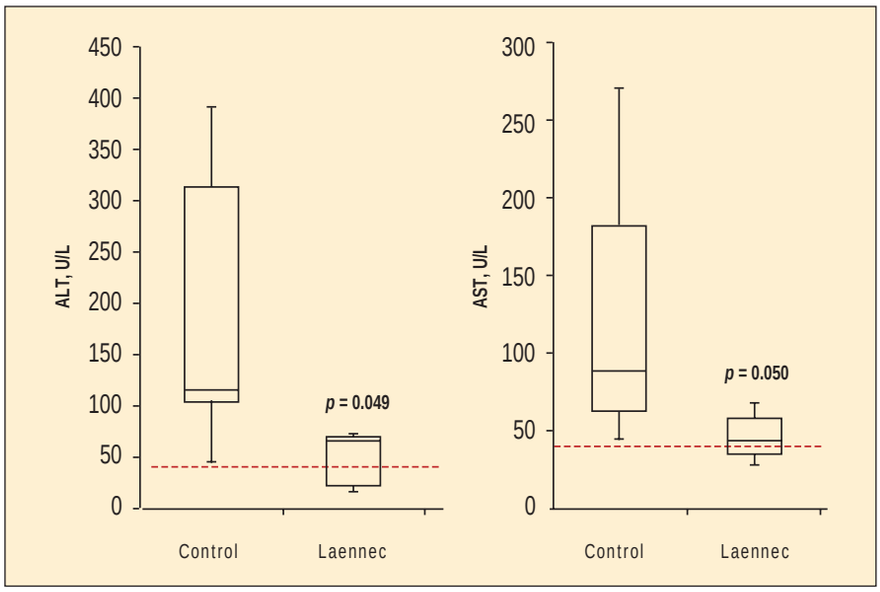

Figure 4. Levels of liver dysfunction markers in patients with COVID-19 in the dynamics of Laennec treatment. Dash-dotted lines show the boundaries of the reference intervals Note: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Рис. 4. Уровни маркеров дисфункции печени у пациентов с COVID-19 в динамике лечения препаратом Лаеннек. Штрих-пунктирными линиями показаны границы референсных интервалов

have increased ferritin levels associated with high mortality [5, 12]. Ferritin is an iron-carrying protein found in virtually all tissues. Normal levels of ferritin in the blood are 10–120 μg/L in women and 20 – 250 μg/L in men. Elevated serum ferritin levels are associated with disorders of iron accumulation in the body (hemochromatosis, etc.); they also indicate inflammation concomitant to severe ARVI, liver dysfunction, autoimmune or tumor diseases, etc.

In patients with COVID-19, ferritin levels dramatically increase both due to the acute phase of inflammation and through the mass death of red blood cells that enables the formation of the so-called "catabolic ferritin". When performing a biochemical blood test, it is impossible to distinguish "pro-inflammatory" ferritin from "catabolic" ferritin. Nevertheless, total ferritin is an effective marker of the severity of coronavirus infection: in patients with mild COVID-19, lower serum ferritin levels were observed (on average, by 282 μg/L; $p < 0.001$) [13, 14]. In the present study, a significant decrease in total ferritin was found in the dynamics of treatment (in men by 386 μg/L, in women by 80 μg/L).

The use of Laennec resulted in positive dynamics of C-reactive protein (another marker of the acute phase of inflammation that is produced in the liver). A meta-analysis that included 16 studies of COVID-19 patients (n = 3,962) confirmed that patients with less severe disease had lower levels of CRP (–41.8 mg/L; $p < 0.001$) and other markers of inflammation (IL-6, ESR, ferritin) [13].

In this study, the baseline CRP values in all the subjects were quite high (23.1 ± 18.9 mg/L while the reference interval is 0 – 5 mg/L; CRP levels >5 mg/L were found in 86% of patients). This indicated to us an extremely active inflammatory process that predisposes to the formation of microthrombi in the microvascular network of the lungs and in other tissues. Accordingly, a decrease in CRP during therapy to 9.0 ± 6.8 mg/L (p = 0.014) indicates both the extinction of the cytokine storm and a decrease in the risk of thrombotic complications of COVID-19.

Elevated CRP levels, leukocytopenia and lymphocytopenia are important features of the course of COVID-19 [15]. At the beginning of treatment, the relative content of lymphocytes (LYM%) was 20.0 ± 10.9% and the values within then reference interval of LYM% (25 – 40%) were found only in three patients. The course of COVID-19 with decreased contents of lymphocytes in the blood corresponds to an increased risk of a protracted disease and a decrease in the rate of rehabilitation. Therapy with Laennec led to a significant increase in LYM% up to 27.8 ± 11.6% (p = 0.042).

An increase in the content of lymphocytes in the blood corresponds to the activation of antiviral defense in the body. As noted earlier, a significant amount of zinc was found in Laennec that stimulates the body's interferon defense proteins against single-stranded RNA viruses (including SARS-CoV-2) [3]. Also, **14 peptides were found in the composition of the drug that produce antiviral effects at all stages of the life cycle of DNA/RNA viruses**. These 14 peptides of Laennec can inhibit the activation of viruses inside the cell (specific inhibition of the cellular HCFC1 protein), fusion of the viral envelope with the plasma membrane at the stage of infection with the host cell virus (inhibition of the cellular CD4 protein), viral replication (inhibition of the CTBP1 protein), maturation of the virion (inhibition of proteins CRM1, VPS4B, TPR, proline isomerase), and budding of viral particles from the cell membrane (inhibition of the NEDD4 protein) [16]. Therefore, an increase in the percentage of lymphocytes may be associated with the antiviral effect of peptides and zinc in Laennec.

Overcoming the cytokine storm and activated antiviral immunity are associated with improved respiratory function. SpO_2 blood oxygenation is a non-invasive but fairly objective method for assessing respiratory failure. The improved blood oxygenation in the dynamics of treatment with Laennec from 91.4 ± 4.6% to 96.2 ± 3.2% (p = 0.0029; SpO_2 levels > 95% were achieved in 11 of 14 patients) should be considered as the restored normal gas exchange between alveocytes and erythrocytes. The reduction in the

degree (–0.64 points; $p = 0.0027$) and the area of lung damage (–10.4%; $p = 0.047$), assessed using the CT data, correspond to a good rate of lung tissue regeneration as a result of treatment. This finding is supported by a significant reduction in patient complaints of overwhelming weakness (11-fold reduction in risk; $p = 0.0068$).

We should note that Laennec helps to increase the regenerative capabilities of the body and is used in the treatment of chronic fatigue syndrome (CFS). In particular, the positive effects of Laennec in CFS are associated with the modulation of mitochondrial function. **Laennec contains the peptides PGVSCR, HMVLLH, EALPGPL, LPGPLNP**, etc. that promote:

- inhibition of cell apoptosis under conditions of oxidative/toxic stress (via the activation of the antiapoptotic protein BcL-2);
- a decrease in hyperinsulinemia (activation of the PPARA receptor);
- an increase in the intensity of energy metabolism of mitochondria (inhibition of MAP kinases and kinases of pyruvate dehydrogenase) [6].

In addition, Laennec contains biologically active **peptides that stimulate the regeneration of damaged tissues** and improve the body's response to stress (fragments of proenkephalin A, peptides inhibiting CDK1, IKKB and mTOR kinases). An experimental study demonstrated geroprotective properties of Laennec: the addition of Laennec increased the lifespan of *Caenorhabditis elegans* under conditions of prolonged oxidative stress by 92% compared to the control [6].

The use of Laennec resulted in a significant improvement in liver (ALT, AST) and kidney (creatinine levels) markers. It should be emphasized that COVID-19 infection is associated with multiple organ pathology. First, chronic comorbid diseases aggravate the course of coronavirus infection. Second, infection with SARS-CoV-2 stimulates or worsens organ damage.

In COVID-19 patients is noted liver dysfunction (increased levels of AST, ALT markers, albumin, bilirubin) [2], renal dysfunction (proteinuria, hematuria) [17] and severe impairment of the blood coagulation profile (including an increase in D-dimer and fibrin degradation products) [1], which is associated with a higher risk of mortality from COVID-19. Liver dysfunction occurs in 24 to 37% of COVID-19 patients [18]; renal dysfunction occurs in 27 to 44% of patients [17].

In the present study, liver dysfunction was observed in all patients (AST and ALT levels were elevated). The use of Laennec resulted in a significant decrease in AST and ALT in all patients, and the AST/ALT ranges were achieved in half of the patients. This result is quite expected since Laennec is registered as a hepatoprotector (ATX A05BA). In experiment and in clinical practice, it has been shown that the drug eliminates hemosiderosis (chronic iron overload) of the liver, and reduces damage to hepatocytes and cells of other organs. The experiment demonstrated the cardioprotective effect of Laennec on the model of adrenaline damage to the heart and an increase in the antioxidant resource of the blood [6]. The molecular mechanisms of the regenerative action of Laennec on various tissues have been mentioned above.

Creatinine is a biomarker of the state of the renal filtration system; its elevated levels indicate impairment of renal filtration function [19]. Acute renal failure is an important risk factor for mortality in patients with COVID-19 [17]. At the start of treatment, creatinine levels in the patients examined were above the upper limits of the reference intervals (62 to 106 μmol/L in men, 44 to 80 μmol/L in women) in 5 out of 14 people in the therapy group. The use of Laennec promoted a significant decrease in creatinine from 105.3 ± 20.5 μmol/L to 87.8 ± 9.2 μmol/L ($p = 0.049$), i.e. towards the ranges of values corresponding to the reference intervals. Thus, Laennec has contributed to improved kidney function in COVID-19 patients.

We should also note that the analysis of the metric map (see Figure 1) reflecting the dynamics of the patients' condition during therapy, enables the design of effective algorithms for predictive modeling of various parameters at the time of the end of therapy. Such algorithms, based on the topological theory of pattern recognition [7–9, 20], facilitate the evaluation of the efficacy of COVID-19 therapy with Laennec based on the initial data in a particular patient. In particular, models were obtained and verified (in cross-validation) for predicting the duration of hospital stay (the correlation coefficient r (c) = 0.73), ferritin levels (r(c) = 0.49), CRP (r(c) = 0.50), ALT (r(c) = 0.62), creatinine (r(c) = 0.54), hemoglobin (r(c) = 0.84), platelets (r(c) = 0.57), the relative content of lymphocytes (r(c) = 0.65) and other important indicators of respiratory function such as Spo2 (r(c) = 0.88), respiratory rate (r(c) = 0.50), the degree of damage using CT (r(c) = 0.51) and lesions using CT (r(c) = 0.87). The developed algorithms for predictive modeling constitute the subject of a separate paper.

Here are two clinical cases that clearly illustrate the results of the treatment of COVID-19 using Laennec.

Case 1

Patient B., 63 years old, had diagnosis of T2DM (E11 MO ICD-10). The patient referred to the RGRCC with complaints of dry cough, fever up to 39 °C, air hunger, severe weakness, and sweating. Respiratory rate was 30 per minute and the patient had a positive PCR test for SARS-CoV-2 virus. According to the CT scan, the patient's lungs were affected by the 3rd degree, the lesion area was 52%. Baseline SpO_2 (on room air) was 94%. The temperature was high during 3 days, then it dropped to 37.6 °C.

Blood biochemistry: ferritin, 1,071.8 mcg/L (normal 20 – 250 mcg/L), ALT, 44 u/l (normal < 41 U/L), AST, 44 U/L (normal < 40 U/L), CRP, 52.6 mg/L (normal 0 – 5 mg/L), creatinine, 143 μmol/L (normal 80 – 115 μmol/L), hemoglobin, 153 g/L (normal 130 – 160 g/L), leukocytes, 6.1 × 10^9/L (normal 4 – 9 × 10^9/L), platelets, 169 × 10^9/L (normal 180 – 320 × 10^9/L), lymphocytes (LYM%), 26% (normal 25 – 40%).

In view of the fact that the patient had already been in a "cytokine storm" for a day (very high levels of ferritin, C-reactive protein, borderline lymphopenia), it was decided to prescribe Laennec i/v (6 mL in 350 mL of isotonic solution, 1 time per day, no. 10 daily).

The patient's clinical condition rapidly deteriorated and after the first use of Laennec by Day 3, the temperature increased to

38 °C, CRP, up to 64.7 mg/L, SpO_2 decreased to 89%, lymphocytes, to 7.4%. According to the CT data, there was lung lesion of the 4th degree, the lesion area was 80%. The use of Laennec continued. By Day 7 there was a decrease in ferritin to 408 μg/L, CRP, to 9.1 mg/L, and an increase in leukocytes up to 10.9%. On Day 11 there was a trend towards an increase in SpO_2 (91%), the state of the lungs according to CT improved to Grade 3, the lesion area decreased to 60%. The use of Laennec was stopped. The patient was followed up for another 5 days. 5 days after completing the course of Laennec, ferritin levels decreased almost to the normal range, 210 μg/L, and blood oxygenation SpO_2 increased to 97%. Respiration rate was 20 per minute. The patient was discharged in satisfactory condition.

Case 2

Patient A., 54 years old, was admitted to the RGRCC on emergency with complaints of paroxysmal cough with scanty sputum, hyperthermia up to 39 °C, severe weakness, and shortness of breath. She fell ill a week prior to being admitted to the RGRCC with the first symptoms of loss of smell and lack of appetite, after 3 days the temperature rose to 39 °C, and dry cough started. An RGRCC examination showed a positive PCR test for SARS-CoV-2.

The patient was in the RGRCC for three days on compulsory oxygen therapy. The temperature was high during three days, then dropped to 36.7 °C. Despite the hospital stay, the condition of the lungs worsened: the SpO_2 oxygenation in the air decreased to 82%, according to the CT data, there was 4th degree lung damage, the lesion area was 92%. There was a trend towards the formation of a cytokine storm, with ferritin 493.4 μg/L (normal 10 – 120 μg/L), a decrease in lymphocytes to 15.3% (normal 25 – 40%) with the developing liver dysfunction (ALT, 42 U/L, normal < 41 U/L, AST, 64 U/L, normal < 40 U/L). Blood pressure was 148/84 mm. Hg, heart rate was 91 per minute.

The patient was prescribed Laennec i/v (6 mL in 350 mL of isotonic solution, 1 time per day, no. 8 daily). Starting from the second day of using the drug, the patient's condition became significantly better: blood pressure returned to normal up to 110/80 mm. Hg, her heart rate decreased to 78 beats/min, blood oxygenation increased to 85%, and respiratory rate decreased from 20 to 18 per minute. There was a daily positive trend. On Day 7 SpO_2 increased to 97%, lymphocytes, up to 31.5% (normal 25 – 40%). According to the CT, the degree of lung damage decreased to the 3rd degree, the affected area was up to 80%, ferritin levels were up to 398 μg/L, weakness disappeared. The patient was discharged the next day in a satisfactory condition.

Conclusion

Various approaches to pharmacotherapy for COVID-19 are currently being tested. Decisions on the choice of pharmacotherapy should take into account all the important features of COVID-19 and, above all, the severe course of this coronavirus infection in presence of comorbid pathologies. It is well known that most of the drugs used in the treatment of viral diseases are highly toxic and cannot always be used in patients with liver dysfunction, coronary artery disease, T2DM and other chronic diseases. Therefore, in a severe course of COVID-19, especially against an unfavorable comorbid background, the requirements for the safety of the chosen pharmacotherapy are paramount.

The polypeptide drug Laennec has a good safety profile, a high degree of pharmaceutical standardization [21], and is characterized by reliable hepatoprotective, anti-inflammatory and immunomodulatory properties. The use of Laennec in the therapy of COVID-19 in patients with comorbid load (IHD, T2DM), liver dysfunction (increased AST, ALT by 2 – 3 times) and a high risk of a cytokine storm (increased CRP, ferritin, decreased lymphocyte count) have shown positive clinical dynamics and improvement in almost all studied laboratory parameters.

It is especially important to note the decreased ferritin levels ($p = 0.039$), an increase in blood oxygenation to the normal range ($p = 0.0029$) and a decreased area of lung damage according to the CT data ($p = 0.0027$). The sustained remission was achieved in all patients between 3 to 15 days after the start of Laennec; the patients were discharged with a negative test for the SARS-CoV-2 virus. The collected data allowed the development of algorithms for predictive modeling of the efficacy of COVID-19 therapy using Laennec.

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Chronic obstructive pulmonary disease and COVID-19: topical issues

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Abstract

The problem of comorbidity of new coronaviral infection (COVID-19) and chronic obstructive pulmonary disease (COPD) is acute, considering similarity of clinical manifestations, diagnostic difficulties, the potential severe disease course. Patients with COPD represent a vulnerable group of infected SARS-CoV-2, with a complicated disease course and frequent adverse outcome. Features of the spread of the virus limit treatment and diagnosis for patients with COPD, making it difficult to provide medical care during the pandemic. The negative results of some clinical studies of antiviral drugs for patients with COVID-19 indicate the need for a search for new drugs; for this reason, analysis of the anti-inflammatory effect on the lungs in infection COVID-19 of drugs of basic COPD therapy is promising.

Key words: COVID-19, chronic obstructive pulmonary disease, SARS-CoV-2, smoking.

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Хроническая обструктивная болезнь легких и COVID-19: актуальные вопросы

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Резюме

Актуальность проблемы коморбидности новой коронавирусной инфекции COVID-19 и хронической обструктивной болезни легких (ХОБЛ) обусловлена схожестью клинических проявлений, сложностью диагностики, потенциальной тяжестью течения и взаимоотягощением этих патологий. Больные ХОБЛ, инфицированные SARS-CoV-2, представляют собой уязвимую группу лиц с осложненным течением и часто неблагоприятным исходом болезни. Особенности распространения вируса накладывают значительные ограничения на многочисленные диагностические и лечебные мероприятия при ХОБЛ, затрудняя оказание медицинской помощи больным данной категории в период пандемии на всех ее этапах. Необходимость поиска новых терапевтических решений продиктована отрицательными результатами текущих клинических исследований по изучению эффективности применения ряда препаратов у больных COVID-19; перспективным представляется изучение действия на SARS-CoV-2 препаратов базовой терапии ХОБЛ с доказанным противовоспалительным действием на бронхолегочную систему.

Ключевые слова: COVID-19, хроническая обструктивная болезнь легких, SARS-CoV-2, курение.

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A new strain of coronavirus emerged in December 2019 in the Chinese city of Wuhan (Hubei province), spread rapidly across the world until the COVID-19 pandemic was officially announced by the World Health Organization (WHO) on March 11, 2020. It is a global challenge for healthcare that forced to consider strategic issues of diagnosis, treatment, and rehabilitation of other noncommunicable diseases exclusively in the context of the pandemic. The coronavirus was named SARS-CoV-2 on February 11, 2020. It enters the human body through the receptors of the angiotensin converting enzyme type 2 (ACE-2). It can infect type 2 alveolar cells, leading to diffuse alveolar damage to the lungs which is clinically seen as viral bilateral pneumonia and acute respiratory distress syndrome [1].

[1] Ministry of Health of the Russian Federation. [Temporary guidelines: Prevention, diagnostics, and treatment of the of novel coronavirus infection (COVID-19). Version 8 (03.09.2020)]. Available at: *https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/051/777/original/030902020_COVID-19_v8.pdf* (in Russian).

Chronic obstructive pulmonary disease (COPD) remains one of the leading reasons for the decline in the quality and duration of life. It is an unresolved medical and social problem, and the urgency has been growing over the years. According to various authors, the prevalence of COPD among the adult population ranges from 4 to 10%, which equals to about 210 million people around the world [1]. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), COPD is "a disease that can be prevented and treated". However, the choice of therapeutic strategies for patients with COPD remains challenging, and the ability to influence the endpoints and prognosis of the disease remains limited [2].

Given that both COPD and COVID-19 cause potentially severe lung damage, it is important to study the impact of SARS-CoV-2 infection on the course, complications, and outcomes of COPD, as well as the impact of the pandemic on the organization of medical care for chronic pulmonary patients. The similarities in the pathogenesis of COVID-19 and COPD make it possible to consider a number of drugs for basic COPD therapy as a potential treatment for the new coronavirus infection.

Impact of COPD and smoking on the risk of COVID-19 infection: the relevant pathogenetic features of SARS-CoV-2. *J.M.Leung et al.* conducted one of the first studies on the mutual influence of COVID-19, COPD, and smoking. Their article in the *European Respiratory Journal* highlighted the problem and caused a discussion in the scientific medical press. Professor *J.M.Leung et al.* examined smokers with COPD at St. Paul's Hospital (Vancouver, Canada) and assessed the expression of ACE-2 in the bronchial epithelial cells. The patients with COPD and smokers had increased expression of the ACE-2 gene in the respiratory tract as compared with the non-smokers and former smokers. The greatest changes were observed in the patients with COPD. Based on these data, the authors suggested an increased risk of SARS-CoV-2 infection in COPD patients and active smokers and presented immediate smoking cessation as one of the ways to reduce the risk of infection [2].

This position was also confirmed by the article of *P.Russo et al.* in the same print edition [3]. The researchers have found a significant increase in nicotine expression of ACE-2 via the α_7-nicotine-acetylcholine receptor (α_7-nAChR) of human bronchial epithelial cells. They suggested that exposure to nicotine increases the risk of SARS-CoV-2 entering lung cells; α_7-nicotinic receptors are found in nerve cells, vascular endothelium, and lymphocytes, so smoking can potentially negatively affect the pathophysiology of COVID-19 in many systems and organs, including the brain, as well as the clinical outcomes. In a response article, Professor *J.M.Leung* agreed that nicotine could act via α_7-nAChR receptors and that smokers with COPD can have increased expression of ACE-2 receptors and be prone to severe COVID-19 infection. In this light, he suggested considering selective antagonists of α_7-nicotine-acetylcholine receptors, such as methyllycaconitine and α-conotoxin, as potential antiviral drugs [4].

S.Sharif-Askari et al. indicate transmembrane serine protease 2 (TMPRSS2) as an entry gate for the virus, along with ACE-2. They also pointed out a low level of expression of these receptors in the upper and lower respiratory tract in children, and the increased expression in smokers and patients with COPD, which explains the different course of the disease in these groups and their different susceptibility to infection [5]. A significant decrease in the level of ACE-2 with an unchanged level of expression of TMPRSS2 was also found after infection with COVID-19. This prompted the authors to suggest serine protease inhibitor (camostat) for treatment of COVID-19.

On the other hand, a number of publications provide other data on the effect of smoking, nicotine, and COPD on the risk of infection with SARS-CoV-2 virus. Several Chinese studies and their meta-analyzes indicate an unusually low prevalence of COPD and tobacco smoking among COVID-19 patients. *J.J.Zhang et al.* studied comorbidities and allergic status in 140 patients with an average age of 57 (25 – 87) years old, with verified COVID-19, who were hospitalized at Hospital No.7 in Wuhan in January–February 2020. The study sample included only 2 active smokers and another 7 people with a history of tobacco smoking (6.4% of the sample). Active smoking and COPD were reported in only 1.4% of patients [6], which is lower than the prevalence of COPD and tobacco smoking in China (COPD occurs in 13.7% among adults over 40; 27.3% of the population are active smokers). These findings correlate with a wider study of the clinical status of COVID-19 patients in China by *W.J.Guan et al.* [7]. An analysis of 1,099 inpatient case histories (552 hospitals in 30 provinces) showed that only 1.1% of the patients had COPD as a comorbidity, and 12.6% of patients were active smokers.

According to a meta-analysis by *A.Emami et al.* that was also based on pooled data from Chinese researchers as of March 2020, the prevalence of COPD among those infected with SARS-CoV-2 was 0.95%. 7.6% of the patients were active smokers [8]. Nevertheless, the authors of the meta-analysis name COPD and smoking among the "common comorbidities" in patients with COVID-19 but, obviously, the incidence of these conditions is less than in the general population. Similar data on the relatively low prevalence of smoking and COPD among COVID-19 patients were obtained in the United States. Only 5.1% of 393 patients were active smokers with COPD [9]. In June 2020, the *European Respiratory Journal* published an article by *M.Rossato et al.* which emphasizes that all epidemiological data published to date show an extremely low prevalence of tobacco smoking among COVID-19 patients [10]. The authors cite their own analysis of hospitalizations at the University Hospital of Padua in March-April 2020. None of 132 patients with COVID-19 were smoking, 15.2% of patients had a history of smoking, and the latter did not correlate with the severity of the infection. At the same time, the percentage of active smokers in Italy in general and in the Veneto region, to which the

[2] Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Revised 2020. Available at: *www.goldcopd.com*

hospital belongs, is high and amounts to 25.7 and 22.7%, respectively.

T.Lupia et al. from Italy performed a meta-analysis of the data from China. They also showed a low prevalence of COPD in patients with COVID-19 1 – 2.9%, with a total prevalence of COPD in China equal to 1.2 – 8.9%. The results of the meta-analysis did not allow to attribute COPD to the common comorbidities in patients with the new coronavirus infection [11]. An article by Chinese authors from Zhejiang University indicates a higher prevalence of COPD among 136 elderly patients (⩾ 60 years old) with COVID-19 as compared with the younger population. However, the incidence of COPD in the elderly was 2.21% and cannot be considered high [12].

Professor *F.Polverino* of the Center for Asthma and Respiratory Diseases at the University of Arizona (USA) calls the relationship between tobacco smoking and COVID-19 a «complex interaction». The epidemiological data clearly put in question active smoking as a risk factor for COVID-19. At the same time, the author emphasizes the delicacy and complexity of the topic of the possible protective effect of nicotine in COVID-19, taking into account the proven unconditional and diverse negative effects of cigarette smoke on the lungs [13].

Greek authors *K.Farsalinos et al.* also argue with *J.M.Leung* and *P.Russo* say that additional research on the role of nicotine in the pathogenesis of COVID-19 is required. Their meta-analysis of the prevalence of active smoking in patients with COVID-19 in China and the United States showed that nicotine as an agonist of the cholinergic system can potentially limit the manifestation of the cytokine storm through α_7-nicotine-acetylcholine receptors. Taking this into account, the authors consider the use of α_7-nAChR (methyllycaconitine, α-conotoxin) receptor antagonists dangerous in patients with COVID-19 because of the possible growth of the systemic inflammation. They did not question the general harm of tobacco smoking, but still proposed to consider using pharmacological nicotine-containing drugs in the complex therapy of COVID-19 [14].

J.M.Leung et al. criticized the position of *K.Farsalinos et al.* The latter published a response letter in the *European Respiratory Journal* and admitted that they were also surprised by the small number of smokers among patients with new coronavirus infection. The authors suggest such possible reasons as the underestimated prevalence of smoking, the potential protective effect of inhalers, and a lower prevalence of tobacco smoking among the elderly – the main target population of COVID-19. In any case, Professor *J.M.Leung* urges to approach the epidemiological data with caution and not to consider smoking as a "protection" against COVID-19. He emphasizes that COPD still remains a factor associated with the severe disease and high mortality, despite the low prevalence of smoking and COPD in the infected population [15].

Impact of COPD on COVID-19 severity and outcomes. In the active discussion of the impact of COPD on the risk of infection with SARS-CoV-2, most experts agree on one thing – COPD is an undoubted risk factor for severe COVID-19 and increases the likelihood of an unfavorable outcome of the disease. Changes in the local and systemic inflammatory response in patients with COPD, a decrease in the immune status, an imbalance in the microbiota of the respiratory tract, impaired mucociliary clearance and bronchial architecture, and the consequences of prolonged use of inhaled glucocorticoids are considered the main pathogenetic grounds for this risk, along with increased expression of ACE-2 receptors in COPD patients and tobacco smokers [16].

One of the first meta-analyzes by Chinese authors included 6 studies (n = 1,558) of patients with COVID-19 and showed that the risk of severe infection in the patients with COPD is 5.9 times higher than in the patients without COPD. COPD was recognized to be an independent risk factor for the severe course of the new coronavirus infection along with arterial hypertension, diabetes mellitus, cardiovascular and cerebrovascular diseases [17].

Naturally, a similar small meta-analysis by Italian authors based on clinical information from China showed a similar result: COPD increases the risk of a severe course of COVID-19 by more than 5 times [16]. The authors of the review conclude that patients with COPD should be isolated to avoid contact with the virus and should be monitored carefully if infected.

A nationwide analysis from the People's Republic of China [18] assessed the effect of comorbidities on serious adverse outcomes (death, admission to the intensive care unit (ICU), the need for mechanical ventilation) in 1,590 patients COVID-19. 50% patients with COPD reached the endpoints. If the patient had two or more comorbidities, the prognosis became even worse. Thus, COPD can largely determine the unfavorable outcome of the coronavirus infection, which once again emphasizes the vulnerability of chronic pulmonary patients to COVID-19.

The meta-analysis by *V.Jain et al.* also confirms this conclusion. This meta-analysis assessed the prognostic factors of severe new coronavirus infection and hospitalization in the ICU. They analyzed the influence of various comorbidities on the prognosis in 1,813 patients in 7 studies that were conducted in China. Despite the generally relatively low prevalence of COPD among those infected with SARS-CoV-2, the concomitant COPD had the strongest prognostic value in relation to the severe course of COVID-19 (OR 6.42, 95% CI 2.44 – 16.9) and hospitalization in ICU (OR 17.8, 95% CI 6.56 – 48.2) [19].

Patients with COVID-19 who required repeated hospitalization after discharge had COPD as a comorbidity much more often than those who were hospitalized only once (6.8% *vs* 2.9%) [20]. *S.Shi et al.* studied myocardial injury in COVID-19 and revealed a more frequent increase in markers of myocardial necrosis in patients with several comorbidities, including COPD [21].

Finally, a systematic review of studies and a meta-analysis on the impact of COPD on mortality in COVID-19 patients was performed. *M.Parohan et al.* reviewed the histories of 29,909 patients with confirmed SARS-CoV-2 infection in 14 studies. A total of 1445 deaths were recorded. According to the review, concomitant COPD is associated with a high risk of mortality in COVID-19 patients (OR = 3.53, 95% CI = 1.79 – 6.96, p < 001). The other risk fac-

tors were arterial hypertension, cardiovascular diseases, diabetes mellitus, and age ⩾ 65 years [22].

A meta-analysis by *Q.Zhao et al.*, included a large number of studies (11) and assessed the impact of COPD and smoking history on the severity of COVID-19 [23]. The presence of COPD was associated with an almost four times higher risk of severe COVID-19. The conclusions regarding the active smoking status were contradictory. A meta-analysis showed a twofold increase in the risk of severe COVID-19 in active smokers. At the same time, the effect of smoking history on the severity of the infection became insignificant after one study [24] was excluded from the analysis.

A few other publications illustrate the impact of tobacco smoking on the severity and outcomes of COVID-19 and are largely contradictory to each other. A team of authors from Tiantan Hospital in Beijing published the results of a meta-analysis that investigated the relationship between clinical features and outcomes of COVID pneumonia. The authors reviewed data from 12 cohort studies that included 2,445 patients with COVID-19 and made an unambiguous conclusion that the severe course of infection is associated with a history of smoking. Also, they confirmed a strong relationship between severe COVID pneumonia and concomitant COPD (OR = 5.08, $p < 0.001$) [25]. Several other cohort Chinese studies have confirmed the severe course of the coronavirus infection in smokers. These studies have showed that current and former smokers have more pronounced symptoms, are admitted to ICU, and need mechanical ventilation more frequently [7]. The studies have also confirmed the relationship between smoking and the progression of COVID-19 [26].

At the same time, a large cohort study (1,007 patients) in several hospitals in China confirmed that COPD but not smoking is a risk factor for progression of mild or moderate COVID-19 to a severe disease. Moreover, the proportion of smokers was insignificantly ($p = 0.08$) lower in the COVID-19 progression group as compared to the group of stable patients [27]. Such conflicting data undoubtedly indicate the need for further research of the effect of nicotine and its analogs on the risk of infection with SARS-CoV-2, the severity and outcomes of the infection.

COVID-19 course in the selected groups of patients with COPD. A number of publications discuss the course of the new coronavirus infection in selected cohorts of patients with COPD. In particular, *L.Wang et al.* studied the course and prognosis of COVID-19 in elderly patients. They followed up 339 patients over 60 years old in Wuhan and showed that COPD was a predictor of an unfavorable outcome of the disease, among other comorbidities [28].

Authors of an article on the increased expression of ACE-2 receptors in overweight patients with COPD conclude that there is a risk of a more severe course of COVID-19 in these patients [29].

The Thoracic Surgery Department of Tongji Hospital in Wuhan City studied the features of COVID-19 in patients after thoracic surgery. The highest mortality was recorded in the group of patients with concomitant COPD [30].

In general, COVID-19 patients with lung cancer have a severe course of infection. The authors note that the markers of an unfavorable outcome of the disease were not specific features of cancer and its therapy, but the presence of certain comorbidities, including COPD [30].

Difficulties in diagnosing COVID-19 in patients with COPD. Several publications point out that diagnosing the new coronavirus infections in patients with COPD is challenging. First, there is an obvious similarity between the clinical symptoms of an exacerbation of COPD and COPD-19. The most common signs of SARS-CoV-2 infection are cough (up to 80% of cases), fever and intoxication (> 90% of cases), and shortness of breath (up to 30% of cases). These same symptoms often accompany an exacerbation of COPD [23, 31]. Thus, the infection with SARS-CoV-2 may be clinically unnoticeable and masked by manifestations of chronic lung pathology in patients with a relapsed or symptomatic COPD. The experts [32] recommend using clinical symptoms such as high fever, anorexia, myalgia, and signs of gastrointestinal tract damage for the differential diagnosis, because they are not pathognomonic for an exacerbation of COPD.

COPD Foundation experts warn that COPD patients may experience a sharp deterioration in 6 – 7 days and develop respiratory failure associated with the suppressed COVID-19 symptoms. The authors of the publication propose mandatory testing for SARS-CoV-2 in all patients with an exacerbation of COPD to avoid delayed diagnosis of COVID-19 in COPD [31].

An interesting clinical case was presented in the journal *American Family Physician* in May 2020 [33]. A 67-year-old patient with long-term COPD and a number of other chronic diseases (ischemic heart disease, diabetes mellitus) had watery diarrhea for 4 days. The patient did not report an increase in shortness of breath and cough, did not have a fever, and had stable hemodynamic parameters. Saturation was 92% against the oxygen therapy at home, which was typical for him. The stool analysis for *C. difficile* was negative. On the first day of the hospital stay, his cough intensified, and his body temperature rose to 38.9 °C, the oxygen saturation of the blood dropped to 88%, and bilateral interstitial changes were revealed by a CT scan. The COVID-19 test upon admission was positive. Mechanical ventilation was started because the patient deteriorated. This clinical example clearly illustrates the difficulties of diagnosing the new coronavirus infection against the underlying severe chronic lung pathology, especially with an atypical clinical form of COVID-19.

The difficulties in detecting COVID-19 in COPD patients are not limited to the clinical picture. Interpretation of computed tomography (CT) data in these patients is often also hard. Both false-positive and false-negative diagnoses are possible [34, 35]. Usually, the typical ground-glass opacities occur in patients with COPD against the background of a strongly altered X-ray picture: pulmonary emphysema, bullae, areas of fibrosis [34].

S.Salehi et al., who studied the features of CT in COVID-19 patients with various chronic bronchopulmonary pathologies, also noted that the CT signs

of COVID pneumonia in COPD patients are atypical. In particular, the formation of cavities is not typical for SARS-CoV-2 lung damage. However, small centrilobular emphysematous bullae are characteristic of a long-term COPD, and ground-glass interstitial changes around them create a picture of "pseudocavities" [35]. The authors note that the overlapping of coronavirus pneumonia (interstitial changes and areas of air space consolidation) and the underlying COPD can also mimic the CT picture of aspiration pneumonia or lung atelectasis.

Japanese authors described CT changes in a 78-year-old smoker with a long history of COPD and confirmed COVID-19. They noted multiple peripheral round and irregular ground-glass opacities against the background of emphysematous changes, which they figuratively call "Swiss cheese" [36].

Managing patients with COPD during the COVID-19 pandemic. The COVID-19 pandemic has made significant adjustments to the provision of health care across a range of noncommunicable diseases, and COPD is no exception. The period of self-isolation, the need to comply with restrictive measures during outpatient visits and inpatient treatment, mutual aggravation of COVID and COPD altogether have significantly changed the strategies for managing chronic pulmonary patients at all stages, i.e. prevention, diagnosis, treatment, and rehabilitation. In addition, the similarities in pathogenetic mechanisms of these two diseases require studying the effect of basic bronchodilator therapy for COPD on the course of COVID-19 and, vice versa, studying the effect of antiviral therapy on the clinical status of patients with COPD. Most of the authoritative national and international pulmonary communities have presented their guidelines and strategies for managing COPD during the COVID-19 pandemic.

The Global COPD Initiative (GOLD) responded to the pandemic with a short, patient-centered guide recommending to comply with all restrictive measures to prevent infection with SARS-CoV-2, continue the basic bronchodilator therapy during the pandemic, including the use of inhaled glucocorticosteroids, use oxygen therapy for standard indications, follow the national guidelines for COVID-19, and use the information provided by WHO [37].

Most national guidelines and medical publications repeat the basic principles for the management of patients with COPD listed above [32, 37, 38]. Swiss authors stressed the need to adhere to standard therapy for COPD and bronchial asthma during the COVID-19 pandemic. They also warned of the dangers of spirometry studies and the use of nebulizer therapy in the infected patients due to the increased risk of SARS-CoV-2 infection [32].

Experts from the *Canadian Thoracic Society* (CTS) have formulated general guidelines for COPD patients during the pandemic:

- stay at home as much as possible, including working remotely at home;
- follow national guidelines for the sanitary and hygienic rules, as well as the distance and isolation when going out;
- provide for a minimum 30-day supply of necessary medicines or a reliable channel for their delivery;
- foresee and, if possible, document the plans for hospitalization and resuscitation in case of severe COPD, and, accordingly, the potential risk of severe COVID-19 [38].

General principles of COPD therapy during the pandemic. All national and international guidelines do not recommend changing previously prescribed COPD drug therapy during the COVID-19 pandemic [31, 32, 37–39].

The article by *A.Attaway* (USA) discusses the possible challenges in the treatment of acute respiratory failure during an exacerbation of COPD. The standard methods such as nebulizer therapy, high-flow oxygen therapy through a nasal cannula, and positive pressure non-invasive ventilation (NIV) are associated with a high risk of SARS-CoV-2 infection. The following solutions are proposed: the use of individual metered dose inhalers, dry powder inhalers, and spacers instead of nebulizers; the personnel should use personal protective equipment (PPE) that provides maximum protection and use viral filters if nebulizer therapy and NIV are required; limiting oxygen consumption during oxygen therapy to 30 L/min. At the same time, a complete rejection of NIV is not recommended, given its proven efficacy in the treatment of respiratory failure in COPD [40]. High-flow oxygen therapy should not be used in patients with hypercapnia [32]. Therefore, the analysis of the gas composition of arterial blood is recommended for all patients with COPD and signs of respiratory failure [39].

The need for prophylactic therapy with anticoagulants in patients with a combination of COPD and COVID-19 is emphasized because the coronavirus infection causes coagulopathy while exacerbations and severe course of chronic obstructive pulmonary disease increase the risk of venous thromboembolism [41, 42]. Careful monitoring of the patient's clinical status, laboratory and instrumental parameters is required to exclude any thromboembolic complications [39].

If a patient with COPD uses low-flow oxygen therapy at home, it should be continued. The mode can be changed only after consultation (including remote) with the attending physician [38, 39].

Elements of rehabilitation are essential in the management of clinically severe patients with COPD and COVID-19. The rehabilitation can take the form of physical therapy and active nutritional support to correct the malnutrition and sarcopenia typical for COPD. Weaning from mechanical ventilation is a complex multistep process for the patient and his family because the ventilation can be still required for COPD.

The COPD Foundation experts emphasize that pulmonary rehabilitation is essential for patients with COPD [31]. Given the limited availability of rehabilitation facilities during the pandemic, a number of national and international pulmonary organizations offer web-based platforms for counseling on physical therapy and other methods of medical rehabilitation at home. When treating COPD at home, it is advisable to isolate the patient in his room, ideally, for him/her to have his/her own bathroom. The door to the room should be closed when the patient

uses a nebulizer and remain closed for several hours after the procedure [32].

The overall psychological climate deteriorated during the pandemic and COPD patients are susceptible to anxiety and depression, so the COPD Foundation has released a guide to maintaining the emotional well-being of COPD patients during the COVID-19 pandemic. The guide explains how to monitor and prevent negative thoughts, feelings, and reactions – the triggers of anxiety-depressive states. They also gave the recommendations to improve the psycho-emotional background during a pandemic [43]. CTS also offers an online resource for educating COPD patients and self-managing strategies for disease control and pulmonary rehabilitation during the pandemic (*https://cts-sct.ca/covid-19/*). Experts emphasize the importance of telemedicine technologies for monitoring and education, the importance of maintaining physical activity and strict implementation of the drug treatment plan [38].

Experts from the *Francophonie Pulmonary Society* (SPLF) believe that the huge harm from the COVID-19 pandemic lies in the suspension of most of the current clinical research on COPD. This could delay the introduction of innovative treatments for the disease by several years. In addition, lung transplantation is strictly limited during the pandemic, including for terminal COPD, except for the urgent cases. This may also have delayed adverse effects [39].

Inhaled and systemic glucocorticoids in the treatment of COPD during the COVID-19 pandemic. The problem of using both inhaled and systemic glucocorticoids (GCs) in COPD and COVID-19 is still largely the subject of scientific discussion. Most medical publications like the GOLD guidelines state no proven negative effect of GCs on the course of COVID-19. Therefore, infection with SARS-CoV-2 is not a reason to not prescribe or cancel these drugs in COPD patients [32, 37–39].

D.M.G.Halpin et al. suggest in their systematic review that the relatively low prevalence of COPD in those infected with SARS-CoV-2, which was mentioned above, can be explained, among other things, by the constant use of inhaled GCs. The analysis of a large number of literature sources (771 publications in international databases) regarding the impact of inhaled GCs on the course and outcomes of COVID-19, SARS, and MERS led to the conclusion that there is not enough data at the time [44]. A low evidence level study in Japan provides data on several cases of a positive effect of inhaled ciclesonide on the clinical course of COVID-19 in patients receiving oxygen therapy [45].

At the same time, American authors remind that GCs increase the viral shedding in MERS-CoV and SARS-CoV infections. Therefore, it is advisable to limit the dose of the drug and the duration of GCs therapy in COVID-19 if possible [32]. A number of previous studies indicate a higher prevalence of pneumonia and changes in the airway microbiome in COPD against the use of inhaled GCs, in particular, fluticasone [46, 47]. Glucocorticoids are believed to suppress the production of the antibacterial protective peptide cathelicidin in the lung epithelium [48]. Experts from the CTS believe that the benefit of prescribing prednisolone for an exacerbation of COPD outweighs the potential risk of increased viral shedding. At the same time, the effect of the drug on the course of COVID-19 is still questioned [38, 39]. The latest WHO Interim Guidance for the Clinical Management of COVID-19 advise against the use of systemic corticosteroids outside of clinical trials and the previously approved indications.

Most of the experts interviewed by the COPD Foundation confirmed that systemic glucocorticoids should be prescribed to patients with an exacerbation of COPD and suspected or confirmed COVID-19. A small number of experts said that the minimum doses should be used or that GCs should not be used at all. The question of whether systemic glucocorticoids are recommended for hospitalized COPD patients with COVID pneumonia and inflammatory infiltration of lung tissue has become more complex and controversial. The expert opinions were divided approximately 50/50 [49].

COPD medications with potential benefits for COVID-19. A large number of drugs of various groups are used for the complex treatment of COPD. Many of these medications have systemic and topical anti-inflammatory effects. Given the need to limit the massive systemic inflammation in SARS-CoV-2 infected individuals and to target the interstitial lung damage, many of the treatments for COPD are reviewed in the scientific literature in light of their potential beneficial effects in COVID-19.

As noted earlier, information on the effect of inhaled and systemic GCS in COVID-19 is ambiguous. *S.Matsuyama et al.* reported in a preprint the potential inhibitory effect of ciclesonide on replication of SARS-CoV-2 RNA *in vitro* and its cytopathic activity. A similar effect was found for mometasone [50]. Ciclesonide inhibits viral replication by targeting the non-structural protein NSP15. At the same time, budesonide, beclomethasone, or fluticasone do not have a similar effect [45]. According to another laboratory study, budesonide and formoterol can independently suppress the systemic activation of interleukin IL-6 in the acute lung injury in a mouse model [51]. *B.Lipworth et al.* assessed the general prospects for the use of inhaled GCS against the cytokine storm in patients infected with SARS-CoV-2. The researchers concluded that these drugs influence pro-inflammatory mediators via "crude" non-specific effects. Also, one should not forget that GCs suppress immune mechanisms and might increase the viral replication [47]. Several ongoing studies evaluate the effect of ciclesonide on the rate of eradication of SARS-CoV-2 in patients with mild COVID-19 infection (conducted in South Korea) and on the course of severe forms of COVID-19 pneumonia (conducted in Japan).

In addition, the literature mentions a possible positive effect of bromhexine on the course of COVID-19, given that it inhibits penetration of respiratory viruses via the transmembrane protease TMPRSS2. Also, the use of both agonists and antagonists of nicotine in the new coronavirus infection is discussed. The theoretical prerequisites for this treatment are set out in the previous chapter.

A joint publication by authors from the United Kingdom, Italy, Israel and Canada explores the possibility of using another group of drugs that are prescribed for COPD, i.e. phosphodiesterase-4 (PDE4) inhibitors. These drugs are assumed to have an anticytokine effect in patients with COVID-19, given their pronounced anti-inflammatory effect, which is successfully used in the treatment of skin and articular manifestations of psoriasis and other dermatoses, as well as in severe COPD. The authors discuss the possible positive clinical effect of apremilast, cilomilast, and roflumilast on COVID-19-associated pneumonitis and the associated immunothrombosis in elderly patients with the coronavirus infection. The presumed biochemical mechanism is the ability of PDE4 inhibitors to reduce the activity of key inflammatory mediators, such as tumor necrosis factor, interleukin-12, interleukin-17, and a number of chemokines, as well as to influence alveolar macrophages and neutrophil-mediated reactions. Roflumilast inhibits the interaction of leukocytes and platelets, as well as the prothrombotic functions of leukocytes. This antithrombotic effect is especially important to treat the COVID-19-associated coagulopathy.

The authors highlight that the use of roflumilast and apremilast is not associated with an increase in the incidence of upper respiratory tract infections in patients with COPD and patients with psoriasis. On the contrary, numerous animal studies showed the anti-inflammatory effect of PDE4 inhibitors in respiratory viral infections (not the coronavirus infection). All this suggests a favorable effect of PDE4 inhibitors in COVID-19, especially in the elderly patients, severe cases, and patients with the thromboembolic complications. Of course, the hypothesis must be proven by clinical trials [52].

The article by *B.L. Yen et al.* is also notable. They assessed the potential use of mesenchymal stem cells in COVID-19 therapy, based on a study on the use of stem cells in chronic lung pathology – COPD, bronchial asthma, and idiopathic pulmonary fibrosis. Currently, the use of mesenchymal stem cells in patients with COPD is being studied in 10 clinical trials at different stages. The authors reviewed the theoretical basis for the use of stem cells and the findings of the *in vitro* and animal preclinical studies. They suggested that this therapy might limit the systemic inflammatory response to the coronavirus infection by decreasing the level of the most active pro-inflammatory cytokines – interleukin-6 and tumor necrosis factor-α. At the moment, 31 studies have been initiated on the use of mesenchymal stem cells in patients with the new coronavirus infection COVID-19. A potential clinical target for this treatment method will be severe COVID-19 with ARDS and cytokine storm [53].

Conclusion

Thus, the need to search for new therapeutic solutions comes from negative results of the current clinical studies of the efficacy of several drugs in patients with COVID-19. It seems promising to study the anti-SARS-CoV-2 therapeutic effect of the basic COPD therapeutics with a proven bronchopulmonary anti-inflammatory effect.

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COVID-19 and children

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Abstract

In December 2019, the world became aware of an epidemic of a very severe infection caused by a new coronavirus. Later, WHO declared a pandemic. The pediatricians were ready for the worst. The novel infection was expected to promptly spread among the most vulnerable population, children. But the clinicians soon understood that the situation is unbelievable: adults develop severe disease and die, while the children remain almost excluded from the infection spreading. 9 months have passed in the "new reality". The humankind was learning to respond to the new infection challenge by empirical search for the potential therapeutic and diagnostic solutions and conducting wide clinical studies in parallel. A few questions have been answered because of consolidated and/or isolated actions of researchers and clinicians at the national, regional, and international levels. However, most aspects of how the new coronavirus affects the humans, including children, is still unclear and our knowledge of these aspects cannot be transferred in the routine practice. This review presents latest understanding of the course of the novel coronavirus infection in children, its treatment and outcomes.

Key words: children, COVID-19, SARS-CoV-2, anosmia, hyposmia, ageusia, dysgeusia, decreased cognitive functions, ferritin, D-dimer, Hac1, troponin, *pro*BNP, creatinine.

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COVID-19 и дети

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Резюме

В декабре 2019 г. началась эпидемия тяжелой инфекции, вызванной новым представителем семейства коронавирусов, позже объявленная Всемирной организацией здравоохранения пандемией. Педиатры приготовились к самому худшему – быстрому распространению новой коронавирусной инфекции (КВИ) среди самых уязвимых – детей, однако вскоре осознали, что впервые столкнулись с невероятной ситуацией, когда тяжело заболевали и умирали люди взрослые, а дети оставались практически вне распространения инфекционного процесса. В течение 9 мес. жизни в новой реальности человечество училось реагировать на новый инфекционный вызов в процессе его развития, чаще эмпирически нащупывая возможные лечебные или диагностические интервенции и параллельно широким фронтом осуществляя клинические исследования. В результате иногда разрозненных, иногда консолидированных действий ученых и клиницистов на страновом, региональном и международном уровнях на некоторые вопросы уже получены ответы, однако бóльшая часть информации, касающейся воздействия нового коронавируса на организм человека, в т. ч. ребенка, пока еще недоступна для внедрения в рутинную практику. В данном обзоре представлены современные представления о течении, лечении и исходах новой КВИ у детей.

Ключевые слова: дети, COVID-19, SARS-CoV-2, аносмия, гипосмия, агевзия, дисгевзия, снижение когнитивных функций, ферритин, D-димер, HAc1, тропонин, *pro*BNP, креатинин.

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Pediatricians know coronaviruses very well as causative agents of seasonal viral infections in children [1]. Most of these infections are caused by group 1 alpha-coronaviruses (HCoV-229E, HCoV-NL63) or line A group 2 beta-coronaviruses (HCoV-OC43, HCoV-HKU1). Such infections have been described in both children and adults in the second half of the 20th century and in the beginning of the 21st century. For example, a case of a boy from the United Kingdom was published in the 1960s. Group 1 alpha-coronavirus was identified in this patient. This coronavirus was first described as B814 isolate but was later defined as HCoV-229E. Another clinical case described US medical students (from the University of Illinois) who had similar symptoms of an acute respiratory infection with the same confirmed pathogen. A case of bronchiolitis in 7- and 8-month infants was published

in the Netherlands in 45 years. The condition was caused by the HCoV-NL63 coronavirus from the same subgroup of group 1 alpha-coronaviruses. In 1967 – 1972, the US National Institutes of Health reported several cases of ARI in adults that were caused by HCoV-OC43, a line A group 2 beta-coronavirus. A case of pneumonia in a 71-year-old Hong Kong resident caused by HCoV-HKU1, a line A group 2 beta coronaviruses, was published in 2004. In general, all the described cases had a moderate course and no lethal outcomes. Most patients were male [1].

The Russian and foreign pediatricians face a few cases of coronavirus infections in children with mild acute respiratory symptoms every season in the routine clinical practice. However, some children with coronavirus infection may develop a Kawasaki syndrome within 2 – 3 weeks. This complication is more often observed in Asian patients (approximately ⅔ of the cases) [2]. Veterinarians also regularly treat coronavirus infection in pets. The animals mostly show gastrointestinal symptoms and are infected with different types of coronaviruses as compared to humans [3].

Thus, humanity has lived with the idea that coronaviruses do not pose a danger to people, including children, until the early 2000. In 2003 – 2004, China has seen an outbreak of atypical pneumonia caused by SARS-CoV, a line B group 2 beta-coronavirus. This outbreak prompted a fresh look at this family of RNA viruses. The coronavirus infections are considered life-threatening after the outbreak of Middle East respiratory distress syndrome 8 years later in Saudi Arabia. This syndrome was caused by MERS, a line C group 2 beta coronavirus. The mortality rate was about 10% during the first outbreak and reached 40% during the second one. The fatal cases included patients under 18 years old. Thus, the current pandemic can be called the "third arrival" of the most dangerous varieties of coronaviruses (lines B and C group 2 beta-coronaviruses).

The attitude of humankind towards the new epidemic is different, though. The degree of respect (or fear) of the new infection is so high that the name of the pathogen and the disease itself was chosen differently [4]. The atypical pneumonia of the first outbreak was called **SARS** (**S**evere **A**cute **R**espiratory **S**yndrome), and the coronavirus that caused it was named **SARS-CoV**. The second was an outbreak of **MERS** (**M**iddle **E**ast **R**espiratory **S**yndrome) caused by a coronavirus called MERS-CoV. The current coronavirus was named **SARS-CoV-2** (**S**evere **A**cute **R**espiratory **S**yndrome **C**orona**V**irus-2). The new infection was named nCoV-2019 first and then renamed into **COVID-19** (**CO**rona**VI**rus **D**isease that arose in 20**19**). And that is an interesting fact.

In the early months of the new outbreak, the main presentation of COVID-19 was believed to be pneumonia, so the term "coronavirus pneumonia" was used as a synonym. Today, it is clear that SARS-CoV-2 causes multiple organ damage, so this term should only be used to describe one of the affected systems or one of the symptoms of the disease.

The role of the receptor for SARS-CoV-2, a type 2 angiotensin converting receptor, or ACE2, is described in detail in the literature [5]. This receptor is expressed in various organs and systems – lungs, intestines, kidneys, blood vessels, as well as in the oral mucosa. This explains both the multidirectional action of the virus, and the fact that the inflammation triggered by it affects various target organs (as mentioned above, not only and not so much the lungs).

In the first months of the pandemic, some publications stated that patients taking ACE inhibitors (as well as statins) may need to switch to other hypotensive drugs because their current drugs might facilitate the penetration of the new coronavirus into the host cells [6]. The Russian cardiologists and therapists published such opinions, as well. In May 2020, a review was published that ACE inhibitors, on the contrary, can protect elderly patients with hypertension and reduce their risk of hospitalization by 40% [7]. No such protective effect was found for young patients, including those under 18 years of age, for unknown reasons.

Bronchial asthma has been named another risk factor for a severe course of the disease in the beginning of the pandemic [8]. But clinicians, including Russian pediatricians [9], did not observe the high susceptibility of children with asthma to the new infection. This was explained in a publication in *Allergy Clinical Immunology* in the end of April 2020 [10]. It said that patients with allergic asthma have reduced expression rate of the *ACE2* gene in their airway cells and are less susceptible to the infection. Fortunately, asthma has an allergic (atopic) nature in more than 90% of pediatric cases. This means that children are less susceptible to the novel coronavirus disease.

Later other receptors were found that the virus used to penetrate the host cells. A publication in *Allergy Clinical Immunology* [11] on May 7, 2020 confirmed that mediators of T2 inflammation in patients with allergic rhinitis or asthma (with high production of T2 cytokines and expression of their genes) modulate the activity of both ACE2 and TMPRSS2, which also facilitate the entry of SARS-CoV-2 into the cells. However, these actions are multidirectional. One cytokine, IL13 (but not IL-4 and IL-5), reduces the expression of ACE2 and increases the expression of TMPRSS2 in epithelial cells of the upper and lower respiratory tract *in vitro* (*ex vivo*). The epithelial cells were sampled during bronchoscopy in pediatric and adult patients. The genes of these receptors are located on different chromosomes, which may explain the multidirectional action of cytokines. In any case, the results of this study also partly explain the low incidence of COVID-19 in children and adults with atopic allergic diseases.

The fact that men were diagnosed with COVID-19 and died more frequently than women was observed in Wuhan, other Chinese provinces, and in the adjacent and far away countries even before the pandemic was declared. The cases of coronavirus infection that were referenced in the beginning of this article describe mainly male patients. The ratio of sick men to women was about 2 : 1, and the risk of dying was significantly higher in men than in women during the outbreak in China. The mortality was 1.7% in women and 2.8% in men in China. The risk of intensive care or death was more than 2 times higher among men

than among women – 32 and 15%, respectively – in Hong Kong hospitals. This inequality was also noted in other regions of the world. However, the long-term consequences are usually worse in women than in men due to the social and psychological factors. This justifies the need for rehabilitation technologies after recovery that will be discussed at the end of the article. In any case, these facts forced *D.Gemmati et al.* to conduct a study, which explained that double X chromosomes in women are a protection against the new coronavirus. The gene of one of the receptors that the virus uses to enter the cell (ACE2, but not TMPRSS2) is located on the "female" chromosome [12]. In addition, X chromosome contains the gene that mediates both the cellular and humoral immunity and inflammation.

Another study clarified the differences in clinical symptoms at the onset of the disease. The study was published by *R.Zang et al.* and evaluated the expression of receptors for SARS-CoV-2 – ACE2 and TMPRSS2/TMPRSS4 – in enterocytes of the small intestine [13]. The authors have shown that the expression rate of ACE2 in the small intestine is maximal as compared to other human organs and tissues. The expression rate is much higher than in alveolocytes of the lungs. This may explain that COVID-19 starts with intestinal symptoms frequently, especially in children. The authors emphasized that the coronavirus is inactivated in the large intestine and the feces do not contain active and infectious forms of the virus. However, the fecal-oral route of infection cannot be excluded, since the experiment did not study the properties of the virus that is excreted with feces in the case of frequent stools (whether it is inactivated fully in a short time).

The epidemiological features of this viral infection have been analyzed in detail in many publications, including the Russian ones [14, 15]. Replication of the pathogen takes 2 – 3 times longer as compared to the seasonal influenza virus. Therefore, isolation and physical distancing in compliance with sanitary and hygienic requirements are highly effective, including for children. "Physical distancing" is a preferred term over "social distancing" because social isolation just does not happen in the "new reality". People stay connected not a bit less and maybe even more than before the pandemic thanks to the Internet and other means of communication. At the same time, the definition of the safe distance is being discussed today. Is 1.5 meters enough or is it better to maintain a distance of 5 meters or more? A scientific study showed that the minimum distance should be 5 – 6 meters. The results were even published, but then the publication was retracted. So, this study is not cited here.

An important fact about masks is that children under 3 years old are NOT recommended to wear masks at all. It is obvious that babies will not be able to describe breathing difficulties or adjust their breathing difficulties caused by the mask! Moreover, pediatricians agree that only children over 6 should wear masks [16].

COVID-19 quickly turned into a nosocomial infection, and today it is most dangerous for healthcare practitioners (more than 1,800 doctors from 64 countries have died already), as well as for adults who work or live in closed groups (nursing homes, hospitals, and so on), especially the elderly. At the same time, only one real outbreak in a children group have been described. It happened in a French high school in the first months of the pandemic.

One question has been discussed heatedly from the beginning of the pandemic: are children infected less often than adults, or are they infected with the same frequency but have much less pronounced clinical symptoms? The Chinese researchers wrote from the very beginning of the outbreak in China that children become infected and sometimes develop the symptoms, but much more rarely and milder than adults [16].

The scientists explain the supposed relative resistance of children to SARS-CoV-2 with several factors. Obviously, from the epidemiological point of view, children have a reduced risk of infection due to less travel, communication, and transportation. The low morbidity in children might be associated with higher levels of circulating ACE2 or other characteristics of the receptors [17]. Children may also have some features of innate immunity that disappear with age [18, 19]. Other possible reasons include a more favorable state of the mucous membrane of the respiratory tract due to the lower destructive active effects of cigarette smoke and air pollution, and a smaller number of chronic diseases, in contrast to adults. The maturity of the immune system may explain the unfavorable type of triggered immune response, which is associated with the development of acute respiratory distress syndrome in adult patients. And finally, the key factor might be that the children are regularly vaccinated, including live weakened vaccines that stimulate the innate immunity.

In any case, this fact has not been explained unambiguously from a scientific point of view yet.

Previously, it was believed that special attention should be paid to children of any age, since they play a huge role in the spreading the disease, including by excretion of the pathogen with feces [20]. From this point of view, the fecal-oral route of transmission was considered no less important as compared with the airborne and contact routes for SARS-CoV-2. This fact was especially relevant in areas where outbreaks of hepatitis A and rotavirus gastroenteritis are frequent and where wastewater can easily become a source of an outbreak of the novel coronavirus infection when it mixes with the groundwater. However, as mentioned above, it was found later that the virus is inactivated at the level of the large intestine and is excreted with feces in an inactive form [21]. Therefore, the fecal-oral route is most likely not the principal route in the spread of infection, but only one of the probable ones.

The opposite can be said about the possibility of children spreading the infection as asymptomatic carriers. The studies of the ways of spreading COVID-19 in Russia and other countries indicate that children become infected in families, in cluster sites, and not vice versa [9, 22–26]. That is why it is so important to follow the sanitary and hygienic measures in everyday life, in families, to teach the children hygiene from an early age.

COVID-19 is a severe illness in adult patients. Several authors [27] associate it with early functional depletion of innate (NK-cells) and acquired ($CD8^+$ cytotoxic lymphocyte) immunity. Although some researchers do not agree that the virus induces suppression of innate immunity [28]. Today all agree that the serious illness in adults is

associated with the so-called "cytokine storm". This reaction is similar to a pathological immune response in some rheumatic diseases (the so-called MAS – macrophage activation syndrome, or secondary HLH – secondary hemophagocytic lymphohistiocytosis, when a systemic inflammatory response is activated and damages multiple organs and systems) [29]. The key phrase above is "similar to", so COVID-19 patients cannot be treated as patients with a rheumatic disease and hemophagocytic syndrome, for example. Therefore, the treatment strategies for COVID-19 are both similar and different to those used in adult or pediatric rheumatology. And again, today it is obvious that not all adults develop the disease, or rather, the clinical symptoms in people of the same age and lifestyle can be completely different – from asymptomatic carriage to a critically serious condition. The factors that determine the course of the disease are still unclear. Some of these factors have already been described (those associated with a genetic predisposition) and some are still being studied.

The following observation also confirms that a cytokine storm is crucial in people vulnerable to SARS-CoV-2. The study showed that levels of fecal calprotectin are increased in patients with diarrhea (but without an inflammatory bowel disease) associated with COVID-19 [30], regardless of the presence of the virus in stool samples. The authors believe that it confirms that SARS-CoV-2 triggers the systemic inflammatory response and justifies the use of anti-cytokine therapy. The systemic inflammatory response apparently proceeds in 2 steps. The first is active viral shedding, but without the symptoms. The symptoms appear in the second step and are determined by the inflammatory changes in different organs and systems, i.e. the "cytokine storm". The patient is releasing almost no viral particles at this point. By the way, the ACE2 levels are sharply increased in patients with active inflammatory bowel disease (without treatment), which makes them vulnerable to SARS-CoV-2 [31], in contrast to patients with asthma and allergies.

There is another difficulty regarding the pediatric population. The children were not getting COVID-19 in large numbers for months, but then frightening messages suddenly appeared. On April 27, 2020, the UK Society of Pediatric Intensive Care issued the PICS Statement [32]. The global pediatric and parenting communities were informed about the increasing number of children with a new multisystem inflammatory disease associated with positive tests for SARS-CoV-2 (although not all patients had this connection confirmed by laboratory tests for the virus at admission). The disease proceeded as toxic shock syndrome and atypical Kawasaki disease (with abdominal pain, gastrointestinal symptoms, and heart damage). The patients had high levels of CRP, ferritin, troponin, proBNP, and red blood cell counts, as well as changes in the coronary arteries.

On May 6, *Lancet* [33] published an article describing 8 children aged 4 – 14 years, mostly boys, who were admitted to intensive care units in London in mid-April with Kawasaki-like syndrome. 6 children were of Afro-Caribbean origin and 2 were Asian. Half of the children got COVID-19 from their family members. The tests for SARS-CoV-2 with nasopharyngeal swabs and bronchoalveolar lavage were negative upon admission. Children were admitted with high fever (up to 40 °C), various rashes, edema, conjunctivitis, pain in the extremities, and severe gastrointestinal symptoms, which quickly led to vasoplegic shock. They were refractory to resuscitation and required norepinephrine. Almost all patients (7 out of 8) required mechanical ventilation to stabilize their cardiovascular system (not for the relief of respiratory failure). Signs of systemic inflammation were also reported, including pericarditis, pleurisy, ascites; increased levels of CRP, procalcitonin, ferritin, triglycerides, and D-dimer. Other pathogens (adenoviruses and enteroviruses) were isolated in only one of 8 patients. The ECGs were normal, but echocardiography showed signs of coronary aneurysm one week after discharge in one child. Another child developed severe arrhythmia with refractory shock, which required extracorporeal support. The patient died later from a massive cerebrovascular infarction. The increased levels of myocardial enzymes indicated inflammation of the heart muscle in all patients. All children received intravenous immunoglobulins (2 g/kg) in the first 24 hours and antibiotics (ceftriaxone and clindamycin). 6 children also received 50 mg/kg aspirin. 12 more children were admitted to the ICU in different parts of London over the next 7 days after this publication, in the end of April. Again, almost all of them were initially negative for SARS-CoV-2. The Royal College of Pediatrics and Child Health in the United Kingdom has promptly issued RCPCH Guidance, the clinical guidance to treat such pediatric cases [34].

A week later, on May 4, 2020, the Head of the New York City Department of Health (*Daskalakis*) also sent out a notification about the new disease – Pediatric Multisystem Inflammatory Syndrome (PMIS), that is potentially associated with SARS-CoV-2 [35].

A fairly large number of publications on multisystem inflammatory syndrome in children appeared in the next 3.5 months [36–41]. Some of them highlighted the racial and ethnic differences among the patients. The article from France states that 57% of the children hospitalized with this diagnosis in Paris were from African communities; the average age of these children was 7.9 years [39]. At the onset of the disease, all children had gastrointestinal disorders, 57% had symptoms of shock, and 76% had myocarditis. All received treatment with intravenous immunoglobulins, 48% received steroids. The average duration of hospitalization was 8 (5 – 17) days. All children recovered. The absence of the viral RNA in the biological loci and the presence of IgG antibodies strongly indicated that the disease develops not at the time of viremia, but after 2 – 3 weeks from the introduction of infection.

These inter-ethnic differences between the children with multisystem inflammatory syndrome did not come as a surprise. Clear inter-ethnic differences have already been noted in morbidity and mortality from COVID-19 earlier in the United States [42]. For example, Latin American communities represent 39% of all communities in California, but they represent more than half (56%) of cases and 46% of deaths from COVID-19. 8.5% of the fatal cases were African Americans (6% of the state's popu-

lation). But Caucasians (37% of California's population) contribute less to morbidity (17.5%) and mortality (30%) as compared to the Latin American communities.

Many children who died from systemic inflammatory syndrome were African Americans, including those with obesity. Although many aspects remain unclear. The higher morbidity and mortality rates among the ethnic population of the United States is explained by the worse economic situation, including the lower availability of highly qualified medical care and a higher incidence of obesity among the Afro-Caribbean and Latin American citizens as compared to Caucasians. However, these data contravene the global statistics, because the morbidity and mortality from COVID-19 is incomparably higher in developed countries compared to the developing countries: at the end of May, when more than 5.3 million cases of the disease and 350,000 deaths (more than 100,000 in the USA alone) were recorded worldwide, only 80,000 cases were confirmed and 2,000 deaths were reported at the African continent! [43]. Although, according to the authors, the "economic storm" caused by the new coronavirus in the emerging economies has led to a much larger number of mental health issues as compared to physical health. 2% of the population was suffering from severe depression requiring serious medication in the "precovid period", and now this number seems to have increased significantly. This is clearly confirmed by the study by *M.Taquet et al.* that was published in *JAMA Psychiatry* on July 29, 2020 and describes the change in the mood of 16.5 – 24 year old students in the Netherlands during quarantine compared to the pre-quarantine period [44]. The authors noted a significant decrease in "mood homeostasis", increased depression, especially in those students who had a family history of mental health problems. This again draws attention to the need for serious rehabilitation, including psychological, of children, youth, people of older age groups who have survived quarantine, and especially those who have recovered from COVID-19. Also, the current situation, when lots of citizens from different countries were left without the basic means of subsistence, will inevitably lead to an increase in violence, primarily in families under the lockdown.

From our point of view, the pediatric systemic inflammatory syndrome is the analogue of the COVID-19 disease in adults and occurs in few children around the world. To date, just over 600 cases have been described. The mortality rate is about 1 – 2%. This includes three hundred patients in the United States, mainly 5 – 14 years old, several deaths, and about 100 cases in the UK and other European countries. This syndrome is usually reported in children approximately 2 months after the onset of the outbreak in the country. In May, we wrote in our review on the website of the Union of Pediatricians of Russia (*www.pediatr-russia.ru*), that there will be such cases in the Russian Federation in the coming days/weeks. And so it happened. Over the past weeks, about 25 patients with systemic inflammatory syndrome have been admitted to hospitals in Moscow and other regions. The overwhelming majority of these patients were discharged home in 2 – 3 weeks, some of them with coronary vasodilation/aneurysm.

An interesting calculation was presented by *F.P.Wilson* from Yale University [45]. Knowing that the incidence of COVID-19 in the pediatric population is incredibly low, he made the following calculation: approximately 5% (5,000) of 100,000 children who can become infected with SARS-CoV-2, will require hospitalization, in theory. Among them, there may be 733 cases of multisystem inflammatory syndrome (Kawasaki-like syndrome), including 20 deaths (that is, the mortality rate in children with COVID-19 was estimated at 0.02%). This forecast was surprisingly accurate and was confirmed fully over the next months. This syndrome, in contrast to the true Kawasaki syndrome, is not associated with "raspberry" tongue and bilateral conjunctival injection. Also, rashes are less common, and the patients are about 2 times older. Unfortunately, the clinicians still use the wrong diagnosis in some regions of the Russian Federation. They call this condition "Kawasaki syndrome" or "Kawasaki disease" instead of "multisystem inflammatory syndrome in children" (or "Kawasaki-**LIKE** syndrome") and therefore use the irrelevant protocols for the children with true Kawasaki syndrome.

The routes of transmission of the pathogen in the child population are airborne, contact-household, and fecal-oral – the same as in adults.

The virus persists in aerosol form for about 2 hours, it survives on plastic/metal surfaces for up to 6 – 8 hours [46, 47], on hair for up to 3 days [48], in the room where the patient was staying for several days [49]. Although some scientists doubt these numbers and continue their research [50].

The virus transmission begins 1 – 2 days before the onset of clinical symptoms. The viral RNA can be detected in nasopharyngeal swabs of children for up to 6 – 22 days of illness and even longer (!), in feces – from 5 to 28 days and longer [51–57, 20], although not always in active form. The main question is whether the detection of a virus in a biological locus should be defined as a carrier status or considered a disease? On the one hand, it is obvious that the presence of a virus without clinical symptoms is just a coexistence of a microorganism and a macroorganism. On the other hand, how do we distinguish a disease that is caused by another pathogen in the presence of the novel coronavirus and the disease caused by this coronavirus, if the child has any relevant symptoms? Differential diagnosis should be mandatory for every pediatric case of COVID-19 because a child is surrounded by many potentially dangerous pathogens to which he has not developed the immunity yet.

The research also suggests that masks have advantages over other methods to prevent the spread of SARS-CoV-2 [58]. An aerosol that is released during a conversation, including particles with coronavirus, "hangs" in the air for 14 minutes and can be easily inhaled by other people during this time [59]. Another group of researchers found that SARS-CoV-2 continues to replicate in the small intestine but is inactivated in the colon. Most likely, it is inactive in feces [60]. That is, the fecal-oral route is hardly the main one, but it should not be dismissed so far. For example, American scientists also write that the fecal-oral route of transmission was confirmed in the US [61].

The viral load and duration of viral shedding does not correlate with the severity of COVID-19 [53, 54], although it was initially thought that patients with the severe disease shed the virus longer. The recent works confirm that viral shedding is directly related to the disease severity.

Vertical transmission of the virus has not been confirmed yet. Not a single case has been published worldwide that describes isolation of the viral RNA from a newborn, from the amniotic fluid, or placental tissues. The 2 published cases of neonates with SARS-CoV-2 IgM should be interpreted with caution [62–64].

There is no evidence that the virus is transferred through human milk [22, 65].

There is another important aspect. **Young people (!) rather than children** are the biggest "distributors" of the infection. It has been shown [66] that young people aged 15 – 34 years (first of all, people of 20 – 24 years old) make the greatest contribution to the spread of the virus in comparison with people of 35 – 49 years old and younger adolescents of 10 – 14 years old. Therefore, the preventative measures should be different for these age groups.

The incubation period in children is 4 – 6 days as in the adult population (with a range from 1 to 14 days or more). Although some studies show that the average incubation period in children is equal to 3 days with a range from 0 to 24 days [67].

The data on the actual incidence of COVID-19 in children is scarce. The Chinese Center for Disease Control and Prevention reported that 2.2% of the patients with the confirmed diagnosis were under 19 years old since the beginning of the epidemic of the novel coronavirus disease COVID-19 in China. Among this subpopulation, the disease was confirmed more often in the patients over 10 years old [68]. These numbers are a bit higher that the numbers in the first reports from China (0.25% for children aged 0 – 18 years) [16] but are still quite insignificant in comparison with adults. Currently, about 20 million cases and about 750,000 (3.75%) deaths have been reported worldwide. Children are still rarely mentioned among the sick and dead [69].

Here are some of the epidemiological data that were provided by researchers in different parts of the world:

- Switzerland: The morbidity rate in children under 10 years old is 0.4%, 10 – 9 years old – 2.6% of all patients with COVID-19.
- Sweden: Up to 10 years – 0.5%, 10 – 19 years – 1.3% of all cases [70].
- Spain: Children (under 18) – 0.8% of all cases [71].
- India: Children (under 10 years old) – 2.5%, 10 – 19 years old – 5% [72].
- Iceland: The population screening did not reveal any cases of children under 10 years old and confirmed 0.8% among older children [73].

Most children are infected in their families [9, 23–25, 52, 53, 56, 57].

On May 20, 2020, the Reuters news agency drew attention to the latest data from British scientists [74], who revealed 2 new facts:

- Children are less likely to develop symptoms than adults (about 20%).
- The acquired immunity to the novel coronavirus infection does not last long [75].

To date, all researchers and doctors admit that the disease is usually asymptomatic or mild in children, in contrast to adults [76–90].

As mentioned above, there are very few scientific publications on COVID-19 in children, but in general they all agree with the information above. These data were confirmed by a study [91] on the epidemiological characteristics of 2,143 pediatric patients with COVID-19. The cases were reported to the China CDC from January 16 to February 8, 2020. More than 94% children had asymptomatic, mild, or moderate disease. An important aspect is the number of patients with the severe/critical disease and deaths. The number of severely ill children among the 2,143 cases was 3 times less than among adults (18.5%). 5.9% of the children were in critical condition, and one child died (at the end of February). The disease was more severe among infants and children under 5 years of age with chronic conditions. However, the Chinese researchers emphasize that most of the described severe and critical cases did not have a positive laboratory test for coronavirus and could be caused by other pathogens (influenza, RSV, RV, etc.) in association with the underlying disease. In addition, there is no data on whether anosmia appeared in sick children as often as in adult patients. It is still unknown whether the patten of anosmia was different in children as compared to adults. Is there a difference in the course of COVID-19 in children and adults?

Thus, children accounted for a very insignificant part of the cases. The fatal outcomes were not registered in China until mid-February. The children had mild symptoms or were asymptomatic carriers [82, 90, 92, 93].

The patterns of the "children's epidemic of coronavirus" in China is repeated in other countries. An analysis of COVID-19 incidence in children in the United States from February 12 to April 02, 2020 was published [94]. During this time, more than 890,000 cases of the disease and more than 45,000 deaths were recorded worldwide, including over 239,000 cases and almost 5,500 deaths in the United States, and it was important for American clinicians to analyze the pediatric situation. Children of 0 – 17 years old currently make up 22% of the population in the United States. If children got sick as often as adults, the morbidity rate would be the same.

However, only 2,572 cases were described among children under 18 years of age (1.7%) out of 149,760 laboratory-confirmed cases of coronavirus disease from February 02 to April 04. Only ¾ of these patients had any symptoms, such as fever, cough, or difficulty breathing (almost all adults of 18 – 64 years old, 93%, had symptoms) and only 5.7% required hospitalization (this number was 2 times higher, 10%, among adults). 3 lethal outcomes were reported.

According to the Federal Children's Resuscitation and Advisory Center of the Russian Federation (operational data of the Ministry of Health of the Russian Federation), about 50,000 children in our country were diagnosed with COVID-19 by the end of June 2020. This equals to about a half of the patients with the U code (the rest were cases of pneumonia, the J code). These patients account for 6.6%

cases with both codes, 4.5% with the U code out of more than 450,000 infected Russians. About 50 children with a clinically or laboratory confirmed diagnosis of COVID-19 were treated in intensive care units. In June, the number of children in the intensive care units increased slightly (on average, up to 60 children were treated in intensive care throughout the country, some of whom were on mechanical ventilation). In July–August, the number of children in intensive care decreased to 50 – 40, then to 30. 42 deaths were reported in total (children make up 0.35% of the 12,000 deaths!).

Thus, the important distinctive features of the course of COVID-19 in the pediatric population are:

- the vast majority of pediatric cases are mild or moderate;
- children can be asymptomatic carriers significantly more often than adults (or COVID-19 is often not associated with such symptoms as fever, cough, and difficulty breathing in children);
- even though most children have a mild illness, there are those who still need hospitalization, including patients with obesity, diabetes, and other comorbidities associated with overproduction of coagulation factors, but not with allergies and asthma;
- in addition, children can still develop a systemic inflammatory response with a "cytokine storm" (fortunately, this is completely different from the classic "cytokine storm" in patients with rheumatic diseases) very rarely after COVID-19. As we predicted in May 2020, the systemic inflammatory syndrome was reported in Russian children in the end of May and during the first two summer months.

The detailed description of the clinical picture of COVID-19 in children also differs clearly from adults. In the first months of the pandemic (from January to April 2020), only a few articles were published in the world describing cases of COVID-19 in the pediatric population, mainly from China. Therefore, the patients of this country will also be mentioned in this review [83–90, 95].

According to the Chinese epidemiological data, the incubation period in children was 5 – 7 days. All patients in China had close contacts or were from clusters, including family ones. A small part of the patients had fever, unproductive cough, and signs of "general intoxication". The other patients were asymptomatic. An exceedingly small number of sick children had the upper respiratory tract symptoms (nasal congestion, rhinorrhea) or gastrointestinal disorders (nausea, vomiting, abdominal pain or discomfort, or diarrhea). Single patients had symptoms of lower respiratory tract damage (mostly bronchitis and a few cases of viral pneumonia).

In general, the coronavirus infection was mild in children, and they recovered within 1 – 2 weeks. It is noteworthy that not a single newborn from mothers with established COVID-19 infection had a positive test for the pathogen (this fact refuted the theory of transplacental transmission of SARS-CoV-2), and no newborn cases were reported until the end of February 2020. By the beginning of April, one of the first articles on this topic presented the results of treatment of 55 pregnant women infected with COVID-19, and 46 newborns with no clear signs of vertical transmission [96]. Later, publications appeared on a positive test for the RNA of the pathogen in a newborn 36 hours after the delivery [97]. But the authors of the article themselves are not inclined to consider this an evidence of intrauterine infection (the time interval was too much, and the tissues of the placenta and umbilical cord did not contain the viral RNA). The same interpretation was given by the authors who described 10 other newborns with positive tests for SARS-CoV-2 [98] and by the authors of the newspaper article [99] and in later publications. Moreover, WHO published a position statement saying that mothers with confirmed COVID-19 should continue breastfeeding (provided, of course, that all hygiene rules are observed!), because the virus was not excreted with milk in any of the women with coronavirus infection [100]. Cases of 33 newborns from mothers with COVID-19 clinic signs were published on April 07, 2020. 3 (9%) of these children also had a clinical diagnosis of coronavirus infection [101]. All three were born by cesarean section, had low APGAR scores (3/4/5) at 1, 5, and 10 minutes, the radiographic findings of pneumonia resolved by the 14th day of antibiotic therapy, and test for SARS-CoV-2 in nasopharyngeal and anal swabs were positive on the 2nd and 4th day of life and were negative on the 7th. According to the authors, the children were infected intrapartum, but vertical transmission cannot be ruled out completely. Later publications, including those in May and June, described the situation in the same manner.

Of course, the clinical picture of a new infection in the pediatric population should be closely monitored, and the clinicians should be able to respond quickly to new facts. It is noteworthy that child deaths were reported more often in previous epidemics of coronavirus infection (SARS and MERS), while the mortality rate of patients of all ages was significantly higher than the current epidemic (approximately 30 – 40% for MERS and 8.5 – 12% for SARS versus 3.5 – 5% for COVID-19 at the moment).

Thus, some clinical symptoms of COVID-19 in children are much less common and some are much more common than in adults. Some symptoms have been described in adults, but not described in children, and vice versa.

1. The common clinical symptoms in children include:
   - asymptomatic course;
   - fever (only in 40 – 56% of the cases);
   - cough (about every second child);
   - sore throat/pharyngitis (in 40% of the cases);
   - mild diarrhea;
   - co-infections (influenza A and B, *M. pneumoniae*, RSV, RV, etc.).
2. Clinical symptoms that are rarely seen in children:
   - rhinorrhea;
   - wheezing;
   - fatigue/headache/myalgia.
3. Symptoms that are common in adults and occur with an unknown frequency in children: anosmia/hyposmia (is considered a pathognomonic symptom in adults);
   - conjunctivitis (RT-PCR+);
   - acute kidney damage that requires renal replacement therapy is reported in 36.6% of hospitalized adults and in 90% of ventilated adults.

4. Manifestations that are common in children, but have not been reported in adults yet:
   - **"COVID fingers"** in the absence of other symptoms of the disease (fingers or phalanges with signs of cutaneous vasculitis, painful, like frostbite, were described in children in Spain, USA). New publications about this symptom appeared in Italy and Spain after the May 20. Also, the data from other countries (including US) say that this symptom can be used as pathognomonic to diagnose COVID-19 in children even without the laboratory confirmation.

Later, papulovesicular rash (as in chickenpox) in patients of all ages in Italy [102, 103] and neurological complications (*Guillain–Barré* syndrome, strokes, polyneuropathies, including transient ones), and also psychiatric complications (delirium followed by depression, increased anxiety, insomnia, and long-term consequences of post-traumatic stress) were described. A high burden of COVID-19 on mental health has been noted for Latin Americans, primarily those with language difficulties in the United States [104].

The number of publications on the neurological symptoms of the new coronavirus infection has increased in the last 2 – 2.5 months. The correlation of these symptoms with the severe symptoms of anosmia/hyposmia and ageusia/dysgeusia, as well as with the previously proven effect of SARS and MERS on the central and peripheral nervous systems was explored.

Italian scientists [105] described the neurotropic effects of SARS-CoV-2 using a clinical example of a 25-year-old woman who worked with patients in one of the hospital departments. The patient had a dry cough for 1 day, as well as loss of smell and taste, fever, and other symptoms of COVID-19. Her CT-scan and nasal endoscopy showed no changes in lungs and sinuses, respectively. However, MRI of the head 3 days after the onset of symptoms showed distinct changes in the form of hyperintense signals in the area of the right gyrus rectus and olfactory bulba, which disappeared after 28 days. Based on this, it has been suggested that the virus enters the central nervous system directly through the eye/optic nerve. This means that glasses or screens provide additional protection from the virus.

The fact that IgM antibodies to SARS-CoV-2 (but not the viral RNA) are detected in the cerebrospinal fluid may indicate that the pathogen stays in the central nervous system at the time of illness, which means that COVID-19 can indeed take the form of an acute encephalitis/encephalomyelitis [106]. Animal studies have confirmed that the virus can enter the brain (after the injection into the nasal fibers). The authors describe 3 cases (all African Americans), including 2 patients with encephalitis who recovered and were discharged and a woman with encephalomyelitis and concomitant sickle cell anemia who died.

Chinese researchers [107] retrospectively studied the case histories of 214 patients who received treatment in 3 specialized centers in Wuhan from January 16 to February 19, 2020 and described neurological changes in every third patient (36.4%). These neurological changes included cerebrovascular disorders, altered consciousness, skeletal muscle damage that was more pronounced with more severe symptoms of COVID-19 in older people with comorbidities (hypertension).

A review in *JAMA* dated May 29, 2020 draws attention to the fact that the virus can potentially enter the central nervous system by different routes (transsynaptic transfer directly through the infected neurons, penetration through the optic nerve or vascular endothelial cells, migration with leukocytes across the blood-brain barrier). And the most frequently described neurological symptoms are anosmia/hyposmia, ageusia/dysgeusia, headache, as well as stroke, impaired consciousness, seizures, encephalopathy, etc. [108].

We would also like to cite the publication of American researchers from the University of Maryland, published on July 31, 2020 in *JAMA Psychiatry* [109]. The authors emphasize that both the impact of the disease itself (the SARS-CoV-2 virus) and the measures that were taken to reduce the number of new cases (separation of people, quarantine, when families sometimes stayed in very cramped conditions for a long time, other restrictions in the everyday life, a significant drop in the economic indicators in all countries) led to a sharp increase in both the number of acute psychiatric conditions (delirium, primarily) and delayed psychiatric conditions (in the form of depression, increased anxiety, post-traumatic stress syndrome). The cognitive impairments caused by the direct effect of the new coronavirus on the central nervous system and by the indirect psychological mechanisms are even more subtle, but especially relevant for children. These impairments include, for example, disruption of the usual world order, fear of death, fear of "fantastic creatures in spacesuits" for hospitalized children, and others. In this regard, the author once again emphasizes the idea that any active or passive immunomodulatory treatment (vaccination, administration of passive antibodies, steroids, biological agents, and so on) that reduce the degree of immune inflammation caused by the virus will significantly improve the mental health of patients.

The researchers reported from the very beginning of the pandemic that laboratory diagnosis of COVID-19 in children is similar to that in adults. However, more recent publications indicate that leukopenia, lymphopenia, and thrombocytopenia are uncommon [52, 53, 80], and the levels of CRP and PCT are normal or moderately elevated in children in general. At the same time, adults with severe lung damage have lymphopenia (due to the decreased levels of NK cells and CD8 lymphocytes), an increase in the level of IL-6 and LDH, CRP > 200, PCT > 0.5, ferritin > 2,500, D-dimer > 2,500 [110, 111]. As mentioned above, similar changes are detected in children mainly in association with multi-inflammatory syndrome.

On May 19, the *Lancet* published the results of a new study (the largest one in the United States). It was a prospective follow-up of 1,150 patients from 2 Presveterian hospitals in New York [112]. The study showed that markers of inflammation and thrombosis are predictors of possible deaths in critical COVID-19 patients who require intensive care (257 (22%) patients of the study cohort). ⅔ of

them needed mechanical ventilation and ⅓ needed a renal replacement therapy. A 10% risk of death was noted for every 10% increase in IL-6 and D-dimer levels. These data confirm the pathogenetic significance of systemic inflammation that damages vascular endothelium and determine the prospects for future research of drugs with immunomodulatory and anticoagulant effects. The gender, racial and ethnic differences were also found. Among the critically ill patients (67% of them were men), 62% were Hispanic/Latino, 19% were African Americans, 3% were Asians, and only 12% were Caucasian. 82% of the patients (mean age 62 years) had at least one comorbidity, most often – hypertension (63%) and diabetes (36%). 41% of the critically ill patients were on mechanical ventilation and 39% died. The previously published data from the UK (a cohort of almost 11,300 patients) confirm the high mortality rates of patients on mechanical ventilation. In that cohort, 50% died within a month from the initiation of intensive care. Many researchers also emphasize that mortality is high in patients with both types of diabetes. The other risk factors include older age, obesity, and uncontrolled blood glucose levels (A1c).

Instrumental (radiation) diagnostics of COVID-19 in children is similar to that in adult patients. All patients with suspected or established diagnosis of coronavirus infection need chest CT as early as possible. The typical CT-scans show mono- or bilateral, mono- or multifocal, peripheral, more often subpleural characteristic changes in lung tissue in the form of "ground glass" or "watch glasses". The scans show no signs of pleural effusion and intrathoracic lymphadenopathy, which indicates that the lung tissue damage in non-infectious. The chest X-ray is rather uninformative [53, 87, 113].

The diagnosis of coronavirus infection in children is established with a positive epidemiological history (children who have traveled or live in the site of coronavirus infection within 14 days preceding the onset of the disease; children who have been in contact with people with high fever or respiratory symptoms from the site of infection; children from families or other sites of the new viral disease; newborns from mothers infected with the novel coronavirus infection). The children should also have any 2 of the clinical symptoms with laboratory confirmation:

- Fever (although many pediatric patients have subfebrile or normal body temperature), nonproductive cough, sore throat, diarrhea, papulovesicular rash, "COVID-fingers".
- Typical changes in the lung CT-scan.
- Normal blood counts at the onset of the disease (leukopenia and/or lymphopenia are also possible).
- Other pathogens that can cause similar clinical symptoms cannot be identified.

The diagnosis is confirmed by positive RT-PCR for SARS-CoV-2 in the samples from the upper respiratory tract (nasopharyngeal or oropharyngeal swabs) or blood or tissues of the lower respiratory tract (the urine is not tested!). RT-PCR for SARS-CoV-2 in samples from the lower respiratory tract obtained by bronchoscopy is more informative than nasopharyngeal swabs, especially in critically ill patients [97], but these samples are very rarely collected in children.

It should be noted that since about May 2020, more and more articles on the topic of "clinical intuition" began to appear, when the absence of laboratory confirmation of the diagnosis of COVID-19 (American clinicians report 2 – 30% of such patients) should not mislead the doctor. At the same time, it is necessary to continue to follow the treatment protocols. By the way, the US FDA monitors closely the diagnostics used to test the population and regularly recalls test systems from even highly respected manufacturers due to their frequent false negative or false positive results.

The course of COVID-19 can be different **in children**.

- The infection can be asymptomatic (that is often seen in patients of all ages), i.e. children with a positive test for SARS-CoV-2 and no symptoms.
- COVID-19 in the form of **acute viral infection of the upper respiratory tract** (often found in children and healthy adults) manifests with fever, cough, sore throat, nasal congestion, headache, fatigue, myalgia, discomfort, etc., but no radiographic signs of pneumonia or symptoms of a sepsis.
- Children with **mild pneumonia** (often asymptomatic, or mild to moderate pneumonia) might have fever, have respiratory symptoms (cough, etc.), radiological signs of pneumonia, but no signs of severe pneumonia.
- **Severe pneumonia caused by SARS-CoV-2 and requiring mechanical ventilation is very rare in children (isolated cases) and is associated with:**
  - increasing shortness of breath ⩾ 70 per minute for children in the first year of life, ⩾ 50 per minute for children over a year old when they are not crying and do not have their peak body temperature;
  - decrease in saturation < 92%;
  - hypoxia: need for respiratory support (nasal cannulas, etc.), cyanosis, intermittent breathing with episodes of apnea;
  - impaired consciousness.
- **The critical condition**, including patients with the systemic multi-inflammatory syndrome (all patients with a respiratory disorder who need mechanical ventilation, have shock or damage to other organs and systems should be transferred to the ICU).

Fatal outcomes in SARS-CoV-2 positive infants and children have been described, but the main causes of death have not been found. The first child death was reported in Germany on April 09, 2020. The rates of hospitalizations, transfers to ICUs, and deaths for infants are published more often. The data from China, Spain, USA, and Germany were published. The latest publication in *Pediatrics* confirms this suggestion [114]. The authors analyzed data on 177 pediatric patients who were treated in the Washington National Children's Hospital (33 hospitalized and 144 outpatients), the authors concluded that the smallest (infants in the first year of life) and the oldest (adolescents over 15 years old) children are hospitalized more often than the others. These two age groups accounted for 64% (32% each) of all hospitalized children. 9 children were in critical condition. About 25% of child deaths in the Russian Federation is accounted for by newborns, mainly premature. Their clinical course of the disease is still unknown.

Interesting data have emerged recently regarding some special groups of pediatric patients and pregnant women. Turns out, the fears of the relatively high potential mortality of these patients from SARS-CoV-2 are greatly exaggerated.

Children with IDS of different etiology and immunocompromised patients:

- **PID (Primary Immunodeficiency Disorders)**: The COVID-19 cases are rare and no fatal outcomes have been reported.
- **Oncological patients**: Several cases of the disease were described in China, Italy, Spain, and Switzerland. The results were predictable, no deaths were reported.
- **Patients after organ and tissue transplantation**: No severe cases in solid organ recipients have been reported from Italy [115].
- **Autoimmune diseases**: A benign course of the disease has been described in 8 patients with IBD receiving immunomodulatory therapy and biological agents.
- **Patients with asthma** (with a controlled course of the disease) rarely become infected and do not develop the severe disease [116]. It is recommended to continue inhalation therapy with inhaled glucocorticoids (but not through nebulizers!) and to replace it with metered-dose inhalers, including those with spacers. If the patient is receiving systemic steroid therapy, it is recommended to continue this therapy. Oral steroids should be used in a short course, if short-acting $beta_2$-agonists (salbutamol) are unavailable.

Patients with rheumatic diseases who receive TNF-α inhibitors have significantly lower risks (60%) of severe course and hospitalization with SARS-CoV-2 infection, as was shown by the Global Rheumatology Alliance COVID-19 Registry [117]. At the same time, the patients who received 10 mg or more of prednisolone per day, had 2 times higher (105%) risk of hospitalization compared with those who did not receive steroids. The registry was launched on March 24, 2020 and contained data on more than 1,300 patients, collected by 300 rheumatologists from 40 countries by the May 12. The analysis of data from the first 600 patients in the registry showed that 46% were hospitalized and 9% died. The risk factors for the severe course and hospitalization were the same as in the rest of the population and included age and comorbidities (diabetes, obesity, arterial hypertension, diseases of the cardiovascular system, kidneys, and lungs).The use of hydroxychloroquine (or other antimalarial drugs) did not affect the hospitalization rate. Notably, patients with systemic lupus erythematosus (SLE) had a higher risk of hospitalization (80%), in contrast to patients with rheumatoid arthritis (RA).

Analysis of data from 17 million UK residents, including 885,000 patients with RA, SLE, and psoriasis showed a 23% higher hospitalization rate in patients with existing comorbidity [118].

The new publication describes 347 patients with **multiple sclerosis (MS)** [119] from the Francophone registry who had COVID-19 from March 01, to May 21, 2020. Only 248 patients received disease-modifying therapy (DMT) for MS. Some of the patients (21%) suffered from a moderate disease (were hospitalized, but without mechanical ventilation) or severe disease, 12 (3.5%) patients died. The proportion of patients, who did not receive DMT, had the worst scores on the EDSS scale, were older, and had obesity, was significantly higher among the moderate to severe cases and the fatal cases.

Pregnant women

Most published cases describe **pregnant women** in the third trimester without any complications that would have been typical only for pregnant women [120].

According to the recent publications, the severity of COVID-19 is significantly lower than that of H1N1 flu. Follow-up of 86,293 pregnant women from March 1 to April 15, 2020 showed that the hospitalization rate due to severe COVID-19 disease was 4.9 per 1,000 pregnant women (2 times more pregnant women are hospitalized with flu, 8 per 1,000). Only 427 (0.5%) women were hospitalized due to the severity COVID-19.

The vertical transmission of the virus has not been documented yet [121–125].

Newborns

An asymptomatic course of infection (with a normal CT scan of the lungs) has also been described in newborns [113, 124, 126].

3 cases described newborns with early but rapidly terminated viral shedding.

Complications in the perinatal and postnatal period in uninfected infants from mothers with COVID-19 have been described [125].

Once again: COVID-19 viral infection (including pneumonia) in children is usually mild. Sometimes the disease causes the typical changes in the lung CT-scans that should be monitored over time. As children rarely have a positive PCR test for coronavirus RNA (for various reasons), the changes in the lung CT-scan should be the reason for managing the child as having COVID-19 infection and early initiation of adequate therapy. On the other hand, the decision-making based on the CT data alone can lead to overdiagnosis of COVID-19, especially if there is a co-infection or the disease has a similar clinical picture, but a different etiology.

As noted above, the COVID-19-like symptoms in children should be differentiated from the following infections:

- Influenza;
- Parainfluenza;
- Adenovirus infection;
- RSV infection;
- RV infection;
- Human metapneumovirus infection;
- SARS coronavirus infection;
- Other viral infections;
- Infections caused by *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*;
- Bacterial pneumonia.

At the end of May and the beginning of June, 2 important documents were published that described the princi-

ples of diagnosis, treatment, and rehabilitation of patients with a new coronavirus infection, both in adults and children. WHO published a document on May 27, 2020 (available through a link on the WHO website *https://www.who.int/publications/i/item/clinical-management-of-covid-19*), and CDC published a protocol on June 11 (*https://www.covid19treatmentguidelines.nih.gov*) [127].

The WHO document introduced a "traffic light" system for the guidelines that helps visually comprehend what is proven and therefore should be applied in clinical practice (**"green checkmarks"**), what should be avoided (**"red crosses"**), and what can be used only in specific circumstances (**"yellow exclamation marks"**). In addition, the WHO guideline covered the principles of screening and triage, laboratory diagnostics, therapy of patients with mild, moderate, and severe pneumonia, acute distress syndrome, septic shock, principles of prevention of severe complications of mechanical ventilation, the use of drugs with antiviral, immunomodulatory, and antibacterial effects, steroids, treatment of acute and chronic infections in patients with COVID-19, management of patients with neurological and mental problems, chronic noncommunicable diseases, rehabilitation of those who have recovered, as well as separate management of women during pregnancy and after childbirth, care and feeding of newborns and babies from mothers with coronavirus infection, caring for elderly patients, palliative care, ethical issues of the optimal organization of care during the pandemic and clinical trials, and the guidelines for reporting deaths.

It was emphasized that drugs such as chloroquine/hydroxychloroquine (with or without azithromycin), antivirals (lopinavir/ritonavir, remdesivir, umifenovir, favipiravir), immunomodulatory agents (tocilizumab, interferon-β-1a), and convalescent plasma should be avoided in the prevention and treatment of COVID-19 (outside of clinical trials!).

It is not recommended to use glucocorticoids for the routine treatment of viral pneumonia. They should be reserved for special cases (septic shock, antenatal prevention of miscarriage, etc.).

Antibiotics are **strictly not recommended** for the prevention and treatment of mild or moderate disease (only for severe cases of COVID-19) when therapy must be started within the first hour after the blood sampling for the initiation of antibacterial therapy.

It was emphasized that individualized rehabilitation of patients should begin in the in-patient settings (including in intensive care) and that **psychological rehabilitation** should be considered a priority, especially in patients with signs of disadaptation (sleep disturbance, etc.).

The mode of delivery should not be chosen based on the pregnant woman's COVID-19 status but should be solely determined by the state of the mother and her child. At the same time, pregnant women or women who have given birth and are feeling normal should not be hospitalized but must be monitored at home and admitted to a specialized hospital if necessary. All women with suspected or confirmed positive status for COVID-19 are recommended to initiate or continue breastfeeding of their babies.

A randomized, placebo-controlled clinical trial involving 821 patients shown that administration of hydroxychloroquine within 4 days after contact with an infected patient had no preventative effect [128]. In addition, several studies have re-emphasized the potential dangers of hydroxychloroquine (especially in combination with azithromycin) in patients with preexisting prolongation of the *QT* interval.

There were 3 important updates in the CDC manual: a special section dedicated to children was added, new data on the antiviral therapy were added, and information on kidney damage in COVID-19, laboratory diagnosis of the disease, oxygen therapy and mechanical ventilation, and the use of IL-1 and IL-6 inhibitors were updated.

The pediatric section focuses on the multisystem inflammatory syndrome. There are still no officially recommended treatment regimens for this condition. Most American centers propose to treat the syndrome with intravenous immunoglobulin and steroids, anticoagulants and antiaggregants, and other immunomodulatory agents (inhibitors of IL-1 and IL-6).

The guidelines on the use of remdesivir vary. It is recommended for hospitalized severe patients with COVID-19 with saturation less than 94% and non-compulsory oxygen support (AI) for 5 days (AI), on mechanical ventilation or ECMO (BI). If no improvement is seen within 5 days, the therapy can be extended to 10 days (CIII). This drug should not be used to treat mild or moderate disease. Chloroquine/hydroxychloroquine (also in combination with azithromycin) should **not be used** to prevent or treat COVID-19 (AI – AIII).

Lopinavir/ritonavir and other HIV/AIDS medications are **not recommended** for the treatment of COVID-19 (AI, AIII).

General principles for treatment of children with COVID-19

Bed rest, sufficient nutrition and adequate hydration, control of electrolyte balance and homeostasis, monitoring of vital functions and oxygen saturation, monitoring of the patency of the respiratory tract, and oxygen therapy (mostly non-invasive), if indicated, monitoring of blood and urine tests (CRP, electrolytes, liver and myocardial enzymes, renal parameters, and coagulogram) are recommended. Blood gases test and repeated X-ray of the lungs should be performed if indicated. **To date, there are no clinical studies on the efficacy and safety of individual drugs in children with COVID-19!**

Symptomatic treatment

Physical methods of cooling and paracetamol at age-appropriate dosages should be used in patients with the body temperature > 38.5 that causes discomfort. The recommendations to avoid NSAIDs (ibuprofen, etc.) are not supported by the EMA, WHO, and the expert community [129]. Anticonvulsants should be used in severe patients

(do not confuse with muscle twitching as a symptom of the disease!).

Oxygen therapy

Start oxygen therapy through a nasal tube or mask immediately in case of signs of hypoxia. High-flow oxygen therapy, non-invasive or invasive mechanical ventilation, and, if indicated, forced ventilation should be used in exceptional cases.

Antiviral therapy

At the moment, 3 drugs have a **proven *in vitro*** antiviral activity against SARS-CoV-2: remdesivir [130], a combination of **lopinavir/ritonavir** [131] and **hydroxychloroquine** [132]. But these drugs have also been excluded from the guidelines.

The results of one clinical trial of **remdesivir** in severe patients (without a control group) are available. The respiratory function improved by 68% [133]. The clinical trials of remdesivir are ongoing.

The clinical trials of **lopinavir/ritonavir** have shown **its inefficacy** [132].

At the beginning of the epidemic, studies appeared on the high efficacy of hydroxychloroquine (with or without azithromycin) in patients with COVID-19 [134, 135], as well as the reviews of its potential use that took into account its *in vitro* and *in vivo* antiviral activity [136]. An increasing number of publications in the last weeks showed **absence of positive results** in the treatment of COVID-19 with hydroxychloroquine. Moreover, the number of severe patients and patients with **heart failure is reported to be growing**, especially among those receiving hydroxychloroquine in combination with azithromycin. Therefore, hydroxychloroquine was excluded from the latest guidelines (WHO, CDC).

Oseltamivir and other anti-influenza drugs are recommended only for the treatment of influenza. Oseltamivir and other influenza drugs should only be used in patients with the influenza virus. Influenza A or B viruses were most often detected in Chinese children with COVID-19 (an exceedingly small percentage of the Chinese population, including children, is vaccinated against influenza).

Umifenovir and interferon preparations have been used in Chinese patients with COVID-19, but there is no evidence of their effectiveness and safety in specially organized clinical trials.

Antibiotics

Unjustified use of antibiotics, especially broad-spectrum ones, should be avoided. Children with a co-infection, signs of a bacterial or fungal infection should be monitored. When the pathogen is identified, antibacterial or antifungal therapy is prescribed. Azithromycin prolonged the *QT* interval in patients with COVID-19, so it is used only in hospital and with caution.

Glucocorticoids

The decision to start glucocorticoids (GCs) is based on the severity of the systemic inflammatory response, the degree of dyspnea (with or without signs of respiratory distress syndrome), changes in the X-ray picture of the lungs. GCs are prescribed for a short course of 3 – 5 days. The dosage of methylprednisolone should not exceed 1 – 2 mg/kg/day.

GCs were included in the guidelines at the very beginning of the pandemic because many patients had high blood levels of pro-inflammatory cytokines (IL-6, TNF-α, etc.).

The idea of using biological agents, for example, tocilizumab, was based on the same fact. Over the past months, biological agents were proven to be effective against COVID-19 (they arrest the "cytokine storm") and reduce the risk of hospitalization and severe disease for patients with various inflammatory diseases (rheumatic diseases, IBD, etc.). Many children with systemic inflammatory syndrome recovered without the biological agents in the Russian Federation.

Another option is zinc pyrithione, which has been proven to inhibit the activity of coronavirus *in vitro* [137]. The data on the use of vitamin D show that it reduces the likelihood of severe disease and hospitalization in the risk groups. Vitamin D was included in many clinical guidelines for adult patients.

Heparin

Heparin is indicated for all patients with blood coagulation disorders and with a family history of tendency to thrombosis or thrombosis. This drug should be used with coagulogram monitoring.

Immunoglobulins

These agents were used in severe patients at the beginning of the pandemic. Their effectiveness was not proved, and they were excluded from the latest guidelines. A new interest has emerged in recent weeks in connection with the systemic inflammatory syndrome in children.

Respiratory support

Non-invasive ventilation is preferred. Invasive ventilation should be used in life-threatening cases, and ECMO is indicated when the invasive mechanical ventilation is ineffective. Many studies show that fatal outcomes are reported more often in the patients who were mechanically ventilated. Fatal outcomes in ventilated children were reported in the Russian Federation.

Support of blood circulation

Monitor the volume of injected fluids, improve microcirculation, use vasoactive drugs, and hemodynamic moni-

toring, if needed. There is evidence that state of many patients worsened after the administration of unnecessarily large volumes of fluids (!).

Psychotherapy

Counseling is essential for a speedy recovery. Active psychological support and treatment is indicated for older pediatric patients, especially with sings of phobias, anxiety, and psychological disorders. In general, about 30% of children and adolescents show a decrease in cognitive functions. Primarily these are patients with pre-existing problems. That is why the psychological rehabilitation is necessary for all children after COVID-19, including mild and asymptomatic disease. The rehabilitation is described in detail in the guidelines of the Ministry of Health of the Russian Federation [15].

Prophylaxis

Do not stop the routine vaccination! On the contrary, it is necessary to continue the routine primary vaccination of infants to prevent the outbreaks and epidemics of such diseases as measles and poliomyelitis (WHO). Vaccination is described in detail in the corresponding section of the guidelines by Healthcare Ministry of Russian Federation and on the website of the Union of Pediatricians of Russia. For example, the United States CDC recommended strict adherence to the routine immunization schedule for children, especially the first 24 months of life, on March 24, 2020. On May 8, the CDC published a report [138] on the current situation with vaccination of children, that included an analysis of the number of vaccines ordered by doctors to immunize children from early January to late April 2020 (compared to the same period in 2019). The report assessed all vaccines recommended for children (except for influenza vaccines, which are seasonal), including a separate data on vaccines against measles-rubella-mumps (the use of which is calculated separately for children under 2 years of age and for children from 2 to 18 years old). The decrease in the number of ordered vaccines for the specified period amounted to hundreds of thousands and millions: more than 3 million children less were vaccinated in 2020 as compared to 2019, including 400,000 less against measles-rubella-mumps, primarily at the expense of children aged 2 – 18 years. Data from India indicate a 69% decline in measles-rubella-mumps vaccination among children [139].

Additional disappointing facts that indicate a significant decrease in the vaccination rate in 2020 as compared to 2019 were reported in different US states. The average decrease was 33%. The decrease by 60.5% was noted in people aged 19 – 49-years and by 83.1%, in those who are 65 and older [140]. The summer months should be used to restore the wide vaccination coverage. Priority should be given to vaccination of pregnant women against diphtheria-pertussis-tetanus (T_{dap}) with acellular vaccines, immunization against measles-rubella-mumps in adults, seasonal flu vaccination in late summer 2020, as well as against pneumococcus and *Haemophilus influenzae* type b.

Of course, immunization should be carried out in conditions that prevent the spread of coronavirus infection.

The primary immunization regimens in infancy, predominantly using combination vaccines, in strict accordance with the national immunization schedule and with standard guidelines should be a priority in the pediatric population. For people over 18 years old, it is important to vaccinate the susceptible individuals and patients from risk groups against pneumococcal infection, hemophilic infection type b, and seasonal flu before the autumn rise in the respiratory morbidity.

Supporting the immunity

A balanced diet, adequate physical activity, regular visits to the attending doctor, and avoidance of excessive physical exercise, as well as emotional stability and mental activity prevent the infection effectively. Recent works [141] put forward a hypothesis that "fermented vegetables" (sauerkraut, for example) and other fermentation products (homemade curdled yogurts, kefir, and kvass produced with homemade cultures, etc.) help reduce the morbidity and mortality from COVID-19. Vaccination is an effective way to prevent infection. The vaccines are being developed.

Information sources and the people's knowledge

Professor *J.Bousquet et al.* from Montpellier processed big data on queries in the Google search engine about the SARS-CoV-2 virus and such symptoms of COVID-19 as anosmia/hyposmia and ageusia/dysgeusia. They then superimposed these curves on the plots of new cases of coronavirus disease in different regions of the world. The researchers came to the surprising conclusion that the wave of inquiries anticipated the wave of cases by several days (unpublished data). Thus, Internet resources can kind of predict an "infectious tsunami", which, of course, is COVID-19 today. A bit more about the mass media. Indian researchers [142] surveyed 1,246 respondents (744 medical workers and 502 non-medical citizens). More than 94% of the respondents were ethnic Hindus. 80% of the doctors and 82% of the citizens were afraid of getting the novel coronavirus infection, and more than 90% of both groups took appropriate measures to protect themselves from the virus. 98% of the medical workers and 97% of the citizens considered "difficulty breathing" the main symptom of COVID-19. 28.9% of the healthcare practitioners and 26.5% of the citizens knew that there is no targeted antiviral therapy available. But the respondents drew the information from completely different sources: doctors, from official medical websites (WHO, CDC, NIH, NEJM, etc.); other people, from the media (from TV and from social networks such as WhatsApp, Instagram, Telegram, and TikTok).

This raises the relevant question of sources of reliable information on COVID-19, both in adults and children, for our citizens.

Conclusion

This review covers the latest views on the course, clinical manifestations, treatment, outcomes, and prevention of the new coronavirus infection in children and other groups of patients. However, the emerging further information about this disease should be carefully monitored and analyzed while the pandemic is ongoing.

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Coronavirus disease-2019 (COVID-19): value of IL-6 inhibitors

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has drawn attention to new clinical and fundamental issues in the immunopathology of human diseases. Since in COVID-19 it is the ''hyperimmune'' response, called cytokine storm syndrome, which forms the basis of the pathogenesis of acute respiratory distress syndrome (ARDS) and multiorgan dysfunction in COVID-19, special attention is drawn to the possibility of "repurposing" (drug repurposing) of some widely used for treatment immune-mediated inflammatory rheumatic diseases (IMIRDs) anti-inflammatory drugs, including glucocorticoids (GC), disease-modified anti-rheumatic drugs (DMARDs), biologic agents and ''targeted'' DMARDs. In the spectrum of cytokines involved in the pathogenesis of cytokine storm syndrome in IMIRDs and COVID-19, great importance is attached to the pro-inflammatory cytokine, interleukin IL-6. The development and introduction into clinical practice of monoclonal antibodies (mAbs) that inhibit the activity of IL-6 are among the major advances in the treatment of IMIRDs, and in recent years, critical conditions within the framework of the cytokine storm syndrome, including in COVID-19. The review discusses the materials of numerous studies devoted to the problems of the efficacy and safety of mAbs to the IL-6 receptor (tocilizumab) and other mAbs that inhibit the activity of this cytokine in COVID-19. Despite the effectiveness of inhibiting IL-6 in patients with severe COVID-19, many theoretical and clinical problems of immunopathology and pharmacotherapy of this disease require further study.

Key words: COVID-19, immune-mediated inflammatory rheumatic diseases, interleukin 6, tocilizumab.

Conflict of interests. The author declares the absence of conflict of interests.

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Коронавирусная болезнь-2019 (COVID-19): значение ингибиторов IL-6

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Резюме

Пандемия коронавирусной болезни-2019 (COVID-19) привлекла внимание к новым клиническим и фундаментальным проблемам иммунопатологии заболеваний человека. Поскольку при COVID-19 именно гипериммунный ответ, получивший наименование синдром «цитокинового шторма», составляет основу патогенеза острого респираторного дистресс-синдрома и мультиорганной дисфункции при COVID-19. При этом особенно привлекательной является возможность репозиционирования (drug repurposing) некоторых широкоприменяемых для лечения иммуновоспалительных ревматических заболеваний (ИВРЗ) противовоспалительных лекарственных препаратов, включая глюкокортикостероиды, базисные противовоспалительные препараты, генно-инженерные биологические препараты и таргетные базисные противовоспалительные препараты. В спектре цитокинов, принимающих участие в патогенезе синдрома «цитокинового шторма» при ИВРЗ и COVID-19, большое значение придается провоспалительному цитокину интерлейкину (IL)-6. Разработка и внедрение в клиническую практику моноклональных антител (мАТ), ингибирующих активность IL-6, относится к числу крупных достижений в лечении ИВРЗ, а в последние годы – критических состояний в рамках синдрома «цитокинового шторма», в т. ч. при COVID-19. В обзоре обсуждаются материалы многочисленных исследований, посвященных проблемам эффективности и безопасности мАТ к рецептору IL-6 (тоцилизумаб) и других мАТ, ингибирующих активность этого цитокина при COVID-19. Несмотря на эффективность ингибирования IL-6 у пациентов с тяжелым течением COVID-19, требуется дальнейшее изучение многих теоретических и клинических проблем иммунопатологии и фармакотерапии этого заболевания.

Ключевые слова: COVID-19, иммуновоспалительные ревматические заболевания, интерлейкин-6, тоцилизумаб.

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The global pandemic of the Coronavirus Disease 2019 (COVID-19) [1, 2] has drawn attention to the novel clinical and fundamental issues of immune and pathological mechanisms of human diseases. The data that was accumulated during the research of pathogenic mechanisms of inflammatory rheumatic diseases (IRDs) can help us un-

derstand the nature of pathological processes that underly severe and potentially fatal complications of COVID-19. Advances in pharmacotherapy of IRD could improve the treatment of the novel coronavirus disease [3, 4]. The hyperimmune response, rather than the cytopathic effect of the virus alone, causes acute respiratory distress syndrome (ARDS) and multiple organ dysfunction in patients with COVID-19 [5]. So there is a promising possibility to repurpose some anti-inflammatory drugs that are widely used in rheumatology [6], including glucocorticoids (GCs), disease-modifying anti-rheumatic drugs (DMARDs), biologic agents, and targeted DMARDs [3, 4, 7].

The pathogenetic mechanisms of COVID-19 were summarized in several reviews [8, 9]. COVID-19 is caused by the SARS-CoV-2 virus (severe acute respiratory syndrome coronavirus-2) that infects primarily type II pneumocytes and other cells expressing angiotensin-converting enzyme 2 (ACE II), which acts as the virus receptor. Replication of SARS-CoV-2 has a cytopathic effect on the target cells. The virus causes pyroptosis (a pro-inflammatory form of programmed cell death – apoptosis), which in turn induces the production of interleukin-1 (IL-1) and other pro-inflammatory cytokines by myeloid cells in the course of coordinated activation of innate and acquired immune responses. At the same time, SARS-CoV-2 suppresses the production of interferon (IFN) type I (IFN-α and IFN-β) and thereby weakens the antiviral immune response [10]. This promotes uncontrolled replication of the virus, and, as a consequence, the progression of the immune-inflammatory process that climaxes as the cytokine storm syndrome [11–14]. The clinical manifestations of the cytokine storm syndrome include primary and secondary hemophagocytic lymphohistiocytosis (HLH) [15], macrophage activation syndrome [16–18], and cytokine release syndrome as a complication of CAR-T-cell therapy (Chimeric Antigen Receptor T-Cell) of oncological disorders [19]. On the one hand, this syndrome is one of the most severe complications of some IRDs. On the other hand, it can be a consequence or stage of COVID-19 and manifests itself as ARDS, coagulopathy, and multiple organ dysfunction [20–22].

The pathogenetic basis of the cytokine storm syndrome is dysregulated production of a wide range of cytokines (both pro-inflammatory, immunoregulatory, and anti-inflammatory) and chemokines caused by the abnormal activation of innate and acquired immunity (Th1 and Th17 types). These substances include IL-1, IL-2, IL-6, IL-7, IL-8–10, IL-12, IL-17, IL-18, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor-α (TNF-α), IFN-γ-inducible protein 10, monocyte chemotactic protein 1 (MCB1), macrophage inflammatory protein-1α (MBB1α), and chemokines (CCL1, CCL3, CCL5, CXCL8, CXCL9, CXCL10, and others). A pronounced increase in the concentration of these cytokines (to varying degrees and in different combinations) is characteristic of severe and especially of critical course of COVID-19 [23–26]. The immune abnormalities typical to the severe COVID-19 include profound lymphopenia, a decrease in the peripheral blood levels of $CD4^+$ T-cells, $CD8^+$ T-cells, T-regulatory cells, B-cells, monocytes, eosinophils, and basophils, overexpression of the exhaustion markers (NKGA2, and others) on the membrane of natural killer (NK) cells and $CD8^+$ T-cells. The peripheral blood tests identify biomarkers that indicate the activation of the Th17-type immune response, namely the expansion of pathogenic $CCR4^+$ $CCR6^+$ Th17-cells [27, 28], as well as T-cells that produce GM-CSF. The latter activates $CD14^+$ $CD16^+$ monocytes and induces the production of IL-6 and other pro-inflammatory mediators [29].

Interleukin-6 (IL-6) is considered to play a crucial role in the development of cytokine storm syndrome in patients with inflammatory rheumatic diseases (IRD) [30, 31] and COVID-19 [32, 33]. IL-6 is an autocrine, paracrine, and hormone-like regulator of various 'normal' and pathological biological processes (inflammation, metabolism, psychosomatic reactions, and others) (see the figure). Biological effects and molecular mechanisms of action of this cytokine are based on its ability to activate target genes that regulate differentiation, survival, apoptosis, and proliferation of various immune and non-immune cells in the human body [34–36]. Pleiotropism of IL-6 is mediated by a unique signaling system that includes IL-6 receptors (IL-6R) and downstream signal molecules. IL-6R consists of two subunits – an IL-6-binding chain (IL-6Rα) and a transmembrane signal-transducing receptor gp130 (130 kDa glycoprotein, IL-6Rβ). The membrane-bound IL-6Rα (mIL6Rα) is expressed by a limited range of cells (macrophages, neutrophils, CD4 T-cells, hepatocytes, podocytes, megakaryocytes, and specific intestinal epithelial cells). On the other hand, gp130 (IL-6Rβ) is present on almost all human cells. Binding of the IL-6-IL-6R complex to two gp130 proteins initiates the IL-6 signal cascade. Dimerization of gp130 induces activation of Janus kinases (JAK) 1 & 2 and phosphorylation of tyrosine residues in the cytoplasmic region of gp130. As noted above, most human cells do not express mIL-6R and are therefore resistant to the biological effects of IL-6. However, soluble (s) IL-6Rα can be found in the blood plasma and tissues. This soluble form is released during proteolysis of the membrane-bound form by Zn^{2+} metalloproteinases ADAM (A Disintegrin and Metalloproteinase domain) 10 and 17. sIL-6-Pα protects IL-6 from enzymatic cleavage, increases its serum lifespan. Most importantly, sIL-6-Pα, in combination with IL-6, can bind to gp130 and activate cells that do not express mIL-6Pα. This process is called trans-signaling, while cell activation that is mediated by the interaction of IL-6 with mIL-6P is defined as classical (cis-) signaling. It is believed that trans-signaling mediates the pathogenic effects of IL-6 to a greater extent as compared to the classical signaling. At the same time, the classical signaling is also involved in the acute phase response, production of pathogenic Th17- and Th22-cells, and the suppression of T-regulatory cells. Recently, a new mechanism of IL-6 signaling has been characterized. It is called trans-presentation. IL-6 binds with IL-6Pα on the membrane of specific dendritic cells and is presented to the gp130 homodimer, which is expressed on the surface of adjacent T-cells. Researchers believe that this is how IL-6 induces the generation of a "pathogenic" subpopulation of Th17-cells [37].

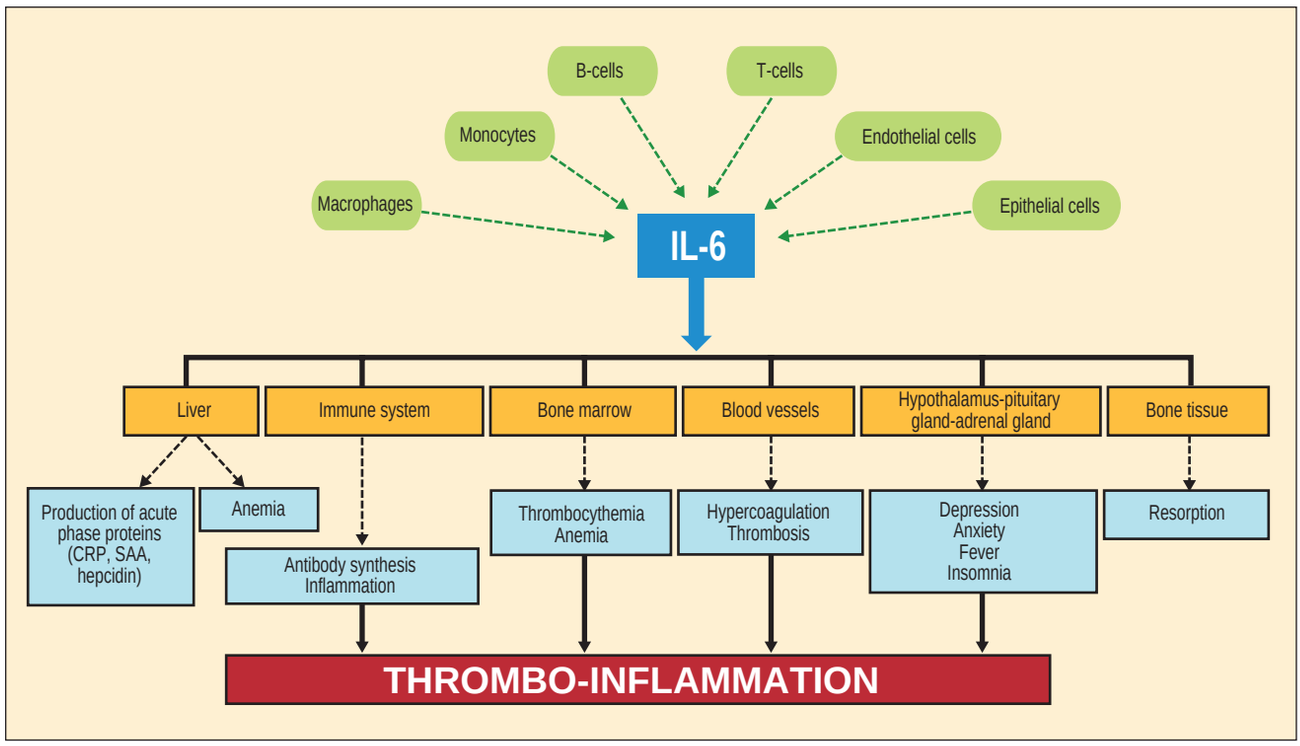

Figure. Main effects of interleukin-6
Note: CRP, C-reactive protein; SAA, Serum amyloid A protein.
Рисунок. Основные эффекты интерлейкина-6

The assumed important role of IL-6 in the immunopathogenesis of COVID-19 is supported by numerous studies that indicate an increase in the serum concentration of this cytokine in vivo [23, 38–40]. According to a meta-analysis, the level of IL-6 was 3 times higher in patients with severe COVID-19 (n = 1,302) as compared to patients with mild/moderate disease ($p < 0.001$). The baseline concentration of IL-6 correlates with bilateral lung damage ($p = 0.001$) and the intensity of fever ($p = 0.001$) [41]. Another meta-analysis [42] (n = 1,426 patients) showed that the mean baseline IL-6 concentration in severe COVID-19 was significantly higher than in non-severe COVID-19 ($p < 0.001$) and was significantly associated with increased mortality ($p = 0.03$). SARS-CoV-2 RNA (RNAmia) is detected in the serum of patients with severe COVID-19 pneumonia and is associated with a substantial increase in the IL-6 level [43]. This is consistent with the concept of viral sepsis as the leading cause of cytokine storm syndrome in COVID-19 [44].

One of the major advances in the treatment of IRDs [31, 35, 45–47] was the development and introduction into clinical practice of monoclonal antibodies (mAbs) that inhibit all IL-6 signaling pathways. In recent years, these drugs were approved for the treatment of critical conditions caused by the cytokine storm syndrome [48], including COVID-19 [39, 49, 50]. mAbs include (Table 1): tocilizumab (TCZ; Tocilizumab, Actemra, Roche, Switzerland), sarilumab (SAR; Sarilumab, Kevzara, Sanofi-Aventis, France) and, lately, siltuximab (SLT). A Russian drug, olokizumab (Artlegia, R-Pharm), has been registered for the treatment of RA recently. Olokizumab blocks IL-6, not IL-6R. A phase II randomized controlled trial of a Russian drug levilimab (BCD-089, BIOCAD) in RA is about to be completed. Levilimab is a human anti-IL-6R mAb. The IL-6 inhibitors have not been approved for use in COVID-19 yet, but these drugs (mainly TCZ) are used off-label to treat the most severe patients, often in a life-threatening condition.

Tocilizumab

Noncomparative studies (single arm) of Tocilizumab

The study by *P.Luo et al.* [51] included 15 patients. The TCZ doses varied from 80 to 600 mg (single intravenous injection). Three critically ill COVID-19 patients died on day 6 (n = 2) and day 7 (n = 1). The disease progressed in one patient. All other patients stabilized or improved, including three of the seven critical patients and all patients with moderate to severe disease. Notable, fatal outcome was associated with no positive changes in the concentration of CRP and IL-6. *X.Xu et al.* [52] presented a retrospective analysis of treating 21 patients with COVID-19 with TCZ. 18 patients received a single infusion of TCZ; three patients received two infusions within 12 hours. All patients showed normal body temperature, improved general symptoms, lesser need in mechanical ventilation (within 5 days in 75% of the patients), the disappearance of ground glass opacities on the CT-scans (n = 19), normal lymphocyte and CRP levels (84.2%) one day after the TCZ infusion. On average, the patients were discharged from the hospital after 15.1 days. The authors concluded that the treatment with TCZ should be started as early

Table 1
Comparative characteristics of IL-6 inhibitors
Таблица 1
Сравнительная характеристика ингибиторов IL-6

Characteristics	Tocilizumab	Sarilumab	Siltuximab
Antibody type	Humanized, IgG1	Human, IgG1	Humanized, IgG1κ
Therapeutic target	sIL-6R, mIL-6R	sIL-6R, mIL-6R	Circulating IL-6
Suppression of the signaling	Cis-, trans-signaling	Cis-, trans-signaling	Cis-signaling
Mode of administration	Intravenous and subcutaneous	Subcutaneous	Intravenous
Standard dose	8 mg/kg per month intravenously, 162 mg once a week subcutaneously	150 or 200 mg subcutaneously once every 2 weeks	11 mg/kg once every 3 weeks
Time of C_{max}	2,8 days after subcutaneous injection	2 – 4 days after subcutaneous injection	No data available
Volume of distribution, L	6,4 after subcutaneous injection	8,3 after subcutaneous injection	4.5
Elimination half-life, days	≤ 12	≤ 10	20.6
Approved indications for use	Rheumatoid arthritis, systemic and polyarticular juvenile idiopathic arthritis, giant cell arteritis, and cytokine release syndrome induced by chimeric antigen receptor T-cell (CAR-T) therapy	Rheumatoid arthritis	Multicentric Castleman's disease (MCD) in patients who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative

as possible if the disease progresses from moderate to severe, the patient shows ground glass opacities in the lungs and the increase in IL-6. *S.Scarscia et al.* [53] conducted a prospective multicenter study of TCZ, which included 63 patients with severe COVID-19. The administration of TCZ caused PaO_2/FiO_2 (oxygenation index) to change from 152 ± 52 to 283.73 ± 115.8 after 7 days and to 302.2 ± 126 after 14 days ($p < 0.05$). The overall mortality was 11% and was associated with high levels of basal D-dimer, but not IL-6. Initiation of TCZ therapy in the first 6 days after hospitalization increased the probability of survival (HR = 2.2; 95% CI: 1.3 – 6.7; $p < 0.05$).

The retrospective study by *R.Alattar et al.* [54] that included 25 patients with COVID-19 showed that TCZ treatment was associated with normalization of body temperature, a decrease in CRP level from 193 mg/L to less than 6 mg/L ($p = 0.0001$), and positive changes in lungs in 44% of the patients after 7 days and in 68% of the patients after 14 days. The number of patients on mechanical ventilation decreased from 84 to 60% after 7 days and to 28% after 16 days ($p = 0.001$). 9 (36%) patients were discharged, and three patients died during the follow-up period. *B.B.Uysal et al.* [55] noted a pronounced positive trend in 10 out of 12 patients with COVID-19 pneumonia after the infusion of TCZ. The positive effect was seen as normalization of the oxygen saturation (from 87.58 ± 3.12% to 94.42 ± 1%), body temperature, and CRP levels. The patients were discharged from the hospital within 18 days. *R.Marfella et al.* [56] found the patients with COVID-19 and hyperglycemia who received TCZ had significantly worse outcomes as compared to the patients with normoglycemia ($p < 0.009$). *V.Morena et al.* [57] assessed the efficacy of TCZ 51 patients with severe COVID-19 pneumonia (need for high nasal oxygen flow or mechanical ventilation, CRP > 40 mg/L; oxygen saturation < 93%). A significant decrease in the intensity of fever, CRP levels, and an increase in the level of lymphocytes was reported within 7 days after the intravenous infusion of TCZ ($p < 0.001$). After 34 days, 67% of the patients showed a decrease in the severity of pneumonia, 31 patients were discharged, 17 (33%) patients experienced deterioration, and 14 (27%) patients died. The risk of death was significantly higher in patients who needed mechanical ventilation at baseline (83.3%) as compared to the patients who needed the non-invasive oxygen support (20%) ($p = 0.0001$). The most common ADRs were an increase in the liver enzymes (29%), thrombocytopenia (14%), and fungal infection (27%). These data show the limited efficacy of TCZ in patients with a critical course of COVID-19 pneumonia who require mechanical ventilation and have a high risk of infectious complications. *P.Toniati et al.* [58] presented a prospective observation of 100 patients with COVID-19 and severe ARDS who needed mechanical ventilation: 43 patients received TCZ infusions in the ICU, and the remaining 57 received TCZ in the therapeutic department. 37 (65%) out of 57 patients showed improvement and switched to non-invasive ventilation, 7 remained stable, and 13 (23%) experienced a deterioration (10 patients died, three were transferred to the ICU). In the group of 43 ICU patients, 32 (74%) showed improvement (17 were weaned), two patients remained stable, and 10 died. Status of 77 (77%) patients improved or stabilized within 10 days. The ground glass opacities were no longer identified in the CT-scans of 66 of these patients. 15 patients recovered and were discharged from the

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clinic. The condition of 33 (33%) patients worsened. 20 of them died. According to *C.C.Price et al.* [59], patients with severe COVID-19 who were prescribed TCZ (n = 153) had a higher survival rate (83%), equal to the survival rate (91%) in patients with the non-severe disease (p = 0.11). 75% of the patients, who needed mechanical ventilation and received TCZ, survived. No severe ADRs were associated with TCZ.

Comparative studies of Tocilizumab (as compared to the standard treatment)

M.Roumier et al. [64] administered TCZ to 30 patients with COVID-19 pneumonia and a rapid increase in pulmonary insufficiency. The comparison group included 29 patients. The groups were matched by the main demographic characteristics and severity of the disease. There was a decrease in the need for mechanical ventilation (odds ratio (OR) 0.42; 95% confidence interval (CI) 0.20–0.89; p = 0.025), as well as mortality (OR 0.25; 95% CI 0.05 – 0.95; p = 0.04) in the main group as compared to the control group after 8 days (6.0 – 9.75 days). The risk of subsequent transfer to the ICU decreased for the patients who did not need the intensive care at baseline (23 patients in the main group and 16 patients in the control group) (OR 0.17; 95% CI 0.06 – 0.48; p = 0.0001). TCZ was tolerated well. Only one patient showed an increase in the hepatic enzymes, and one patient developed moderate pneumonia. A retrospective analysis of 111 patients was published. 42 received TCZ treatment, and 69 received standard therapy [65]. All patients in the TCZ group (n = 42) received antiviral therapy, and 40% of them received GC. 62% of patients in the TCZ group were mechanically ventilated. Three patients died (on average, after 17.8 days of follow-up). 7 of 26 remained mechanically ventilated, and 17 of 26 developed a bacterial superinfection. No deaths or bacterial infections were reported in the standard therapy group. At the same time, the basal concentration of CRP, IL-6 (p < 0.001), and neutrophils (p = 0.04) was significantly higher in the TCZ group. The levels of lymphocytes (p < 0.0001) were significantly lower in patients who were mechanically ventilated as compared to those who did not need it. An open-label case-control study included 86 patients. 21 of them received TCZ. It was found that TCZ was associated with a 75% reduction in the risk of death (RR 0.25; 95% CI 0.07 – 0.90) [66]. *E.C.Somers et al.* [67] studied the efficacy of TCZ in patients with COVID-19 who needed mechanical ventilation (n = 78). The comparison group included 76 patients who did not receive this drug. The average duration of follow-up was 47 days (28 – 67 days). The risk of death reduced significantly in the TCZ group (RR 0.54; 95% CI 0.02 – 1.00). The mortality rate was 18% *vs* 36%, respectively (p = 0.01). Important pieces of evidence of the efficacy of TCZ were an increase in the number of discharged patients (56% *vs* 40%; p = 0.04) and a decrease in the number of patients who required mechanical ventilation during the follow-up period (18% *vs* 47%). At the same time, the TCZ group showed a 2-fold increase in the risk of superinfection (54% *vs* 26%; p < 0.001), mostly in the form of ventilator-associated pneumonia (45% *vs* 20%; p < 0.001). The pneumonia was associated with *Staphylococcus aureus* in most cases in both groups. Notably, the superinfection did not affect the mortality in the TCZ group (22% *vs* 15%; p = 0.42). *R.Carpa et al.* [68] assessed the outcomes of COVID-19 pneumonia in 85 patients. 62 patients received TCZ in combination with the standard therapy (GC, lopinavir and ritonavir), and 23 patients received only the standard therapy. Administration TCZ (on average, in 4 days after the admission) led to a significant improvement in the survival as compared with the control group (HR 0.035; 95% CI 0.004 – 0.347; p = 0.004), adjusted for the initial severity of the condition. 2 of 62 patients died in the TCZ group and 11 of 23 patients died in the control group. 92% and 42.1% of patients recovered (i.e., were discharged), respectively. Improvement of the lung function was noted in 64.8% of patients in the TCZ group who stayed in the hospital. All patients of the control group showed deterioration of the lung function and needed mechanical ventilation. No infectious complications were reported in both groups. *T.Klopfenstein et al.* [69] found a decrease in mortality and the need for transfer to the ICU in patients treated with TCZ (n = 20) as compared to the control group (n = 25) (25% *vs* 75%; p = 0.002). Interestingly, the TCZ group included patients with more severe course of COVID-19, as was shown by the Charlson Comorbidity Index (5.3 *vs* 3.4; p = 0.014), the oxygen therapy (13 L/min *vs* 6 L/min; p < 0.001, lymphopenia (676/mm^3 *vs* 914/mm^3; p = 0.037), and CRP levels (158 mg/L *vs* 105 mg/L; p = 0.017). Recently, the results of a large observational study were reported. The study included 1,229 patients (10,673 patients/years) who were followed up in Spain. 260 (21%) patients received TCZ and 969 patients who did not receive TCZ [70]. The administration of TCZ to the patients with the baseline CRP levels over 150 mg/L was associated with a decrease in mortality (RR 0.38, 95% CI 0.16 – 0.72; p = 0.005) and the combined outcome (need for transfer to ICU and mortality) (HR = 0.38, 95% CI 0.19 – 0.81; p = 0.011). This trend was not confirmed for the patients with the baseline CRP levels below 150 mg/L. The propensity score matching in 21 patients with COVID-19 treated with TCZ and 21 patients on standard therapy was performed in the SMACORE study (SMAtteo COvid19 Registry) [71]. The preliminary analysis showed that TCZ does not reduce the need for transfer to ICU (OR = 0.11; 95% CI 0.00 – 3.38; p = 0.22) and mortality within 7 days after drug infusion (OR = 0.78, 95% CI 0.06 – 9.34; p = 0.84). *T.Kewan et al.* [72] conducted a retrospective analysis of the outcomes of 51 patients with COVID-19. 28 (55%) of the patients received TCZ treatment, and the rest received the standard therapy. Note that the patients on mechanical ventilation (regardless of the TCZ treatment) received systemic GC therapy (81% and 82%, respectively) and GC in combination with azithromycin (93% and 96%, respectively). Initially, the TCZ group included patients with a more severe condition as compared to the standard therapy group. So the TCZ group had a higher need for mechanical ventilation both at

baseline (68% *vs* 22%, respectively) and during the hospitalization (75% *vs* 48%, respectively). Nevertheless, the clinical state of the TCZ patients on mechanical ventilation improved faster (HR = 1.83, 95% CI 0.57 – 5.84) as compared to the control group. The clinical state of all TCZ patients also improved faster (HR = 1.14, 95% CI 0.55 – 2.38), regardless of the need for mechanical ventilation. The average duration of vasopressor therapy and mechanical ventilation was 2 days and 7 days in the TCZ group and 5 days and 10 days in the control group ($p = 0.039$ and $p = 0.11$, respectively). The incidence of infectious complications (18% and 22%) was similar. *R.M.Petrac et al.* [73] presented the results of a retrospective analysis of a multicenter study, which included 145 patients. 123 (84.8%) received one TCZ infusion, and 22 (15.2%) received 2 TCZ infusions. The overall mortality was 28.3%. At the same time, each additional day of delay in the administration of TCZ increased the risk of mechanical ventilation by 21% ($p = 0.002$) and did not depend on the use of GC ($p = 0.965$). The early administration of TCZ was associated with a decrease in mortality (13.5%) as compared to the later start of treatment (68.2%) ($p < 0.001$). The early administration of TCZ was also associated with a higher rate of discharge (59.5% *vs* 18.2%; $p < 0.001$). Late administration of TCZ was associated with a higher (17.8 times) mortality as compared to the early administration of the drug ($p < 0.001$). Thus, the early administration of TCZ reduced the need for mechanical ventilation and increased the possibility of recovery. Preliminary results indicate an improvement in lung damage during subcutaneous use of TCZ in patients with severe COVID-19 pneumonia ($n = 12$) and the absence of severe manifestations of cytokine storm syndrome [74]. The retrospective analysis of the TESERO (The Tocilizumab in Patients with Severe COVID-19 Pneumonia) study [75] is of great interest. This study enrolled 1351 patients with COVID-19, including 544 (40%) patients with severe COVID-19 pneumonia. All patients received the standard therapy (oxygen support, GC, azithromycin, antiviral therapy, low molecular weight heparin). 179 of 544 patients with COVID-19 pneumonia received TCZ (91 subcutaneously, 88 intravenously) in combination with the standard therapy, and 365 patients received the standard therapy only. Mechanical ventilation was initiated in 57 (16%) of 365 patients in the standard therapy group as compared to 33 (18%) of 179 patients who received TCZ ($p = 0.41$), regardless of the form of the drug (18% of those who received the intravenous injections and 19% of those who received the subcutaneous injections). Fatal outcomes were reported in 20% of patients in the standard therapy group and in 7% of patients who received TCZ ($p < 0.0001$). The mortality in the TCZ did not depend on the TCZ dosage form. It was 7% for the patients who received the intravenous injections and 8% for the patients who received the subcutaneous injections. TCZ was associated with a significant reduction in the mortality (RR = 0.61, 95% CI 0.40 – 0.92; $p = 0.02$) adjusted for gender, age, duration of symptoms, and the Subsequent Organ Failure Assessment Score (SOFA). However, the incidence of infectious complications in patients receiving TCZ (13%) was higher than in patients receiving standard therapy (4%) ($p < 0.0001$). *F.Perrone et al.* [76]. presented preliminary results of a prospective multicenter study TOCIVID-19 (phase IIa), which included 301 patients. 180 (59.8%) of them received TCZ (8 mg/kg, up to 800 mg). The null hypothesis said that mortality would be 20% (after 14 days) and 35% (after 30 days). TCZ decreased this outcome after 30 days (22.4%; $p < 0.001$), but not after 14 days (18.4%; $p = 0.52$). The efficacy of TCZ was higher in patients who did not require mechanical ventilation at baseline. *R.Rossotti et al.* [77] summarized the results of a retrospective analysis of the effectiveness of TCZ in 84 patients with COVID-19 (the majority of patients, 69.8%, were critically ill) in comparison with the control group ($n = 184$), who did not receive TCZ. The groups were matched by sex, age, severity, and comorbidities (Charlson Index). TCZ treatment was associated with improved survival (RR 0.499, 95% CI 0.262 – 0.952; $p = 0.035$), but longer hospital stay (HR 1.658, 95% CI 1.088 – 2.524, p = 0.019). The latter was primarily associated with the increased ADR rate. *L.M.Canziani et al.* [78] conducted a study that included 64 patients with COVID-19 who received TCZ. Another 64 patients were included in the control group. The mortality rate (27% and 38%, respectively) and the risk of death (RR 0.61, 95% CI 0.33 – 1.15) (within 30 days) did not differ between the groups. TCZ was associated with a decrease in the need for mechanical ventilation (RR 0.36, 95% CI 0.16 – 0.83, $p = 0.017$) and did not affect the risk of thrombosis, bleeding, and infection. *N. De Rossi et al.* [79] presented an analysis of a cohort study that included 158 patients with COVID-19 pneumonia at an early stage of pulmonary failure. 90 of these patients received TCZ (400 mg IV or 324 mg SC) along with the standard therapy. The mortality rate was 7.7% (7 out of 90 patients) in the TCZ group and 50% (34 out of 68 patients) in the comparison group. TCZ was associated with a significant reduction in the risk of death (HR: 0.057, 95% CI 0.017 – 0.0187), independent of the dosage form. Treatment with TCZ was not associated with infectious complications and other ADRs. *C.Campochiaro et al.* [80] assessed the outcomes of 65 patients with COVID-19 pneumonia. 32 of these patients received TCZ therapy. After 28 days, clinical improvement was noted in 69% of the TCZ patients and in 61% of the patients who received the standard therapy ($p = 0.61$). The mortality was 15% and 33%, respectively ($p = 0.15$). In the TCZ group, the predictor of mortality was older age, and the predictor of clinical improvement was a high basal PaO_2/FiO_2 ratio. The incidence of infectious complications did not differ between the groups (13% and 12%, respectively). *V.Carvalho et al.* [81] compared the efficacy of TCZ in 28 patients with severe COVID-19 who were in the ICU. Another 24 patients were enrolled in the control group. Despite the more severe condition at baseline (the need for GC, mechanical ventilation, a pronounced decrease in the gas exchange), there was no increase in mortality ($p = 0.3$) and the incidence of infectious complications in the TCZ group. On the contrary, CRP levels ($p = 0.009$), lymphocyte levels ($p = 0.02$), and lung function returned to normal

faster. *M.Mikulska et al.* [82] conducted an observational single-center study, which included 196 patients with severe COVID-19 pneumonia. 130 patients received anti-inflammatory therapy. 29 of them (22.3%) received TCZ (8 mg/kg, intravenously or 162 mg, subcutaneously), 45 (34.6%) received methylprednisolone (1 mg/kg for 5 days, intravenously) and 56 (43.1%) received TCZ and methylprednisolone (MP) in combination the with standard therapy. The other patients received the standard therapy only. It was found that the early prescription of TCZ (within 3 days after hospitalization) and/or MP was associated with 86.5% and 80.8% (after 14 and 30 days) survival rate as compared to the standard therapy (64.1%). This higher survival rate associated with a significant decrease in the risk of treatment failure (HR = 0.48, 95% CI 0.23 – 0.99, $p = 0.049$). A large observational study indicated the ineffectiveness of GC (as monotherapy or in combination with azithromycin) concerning mortality in patients with COVID-19 ($n = 2512$) [83]. The patients in the TCZ group ($n = 134$) showed a trend to a higher survival (HR 0.76, 95% CI 0.57 – 1.00) within 30 days – 46% as compared to 56% in the group of patients who did not receive TCZ. *N.Wadud et al.* [84] found that the survival rate of COVID-19 patients who received TCZ ($n = 44$) was significantly higher than in the control group ($n = 50$) (61.36% *vs* 48.0%, $p < 0.00001$). *G.Rojas-Marte et al.* [85] assessed mortality in 193 patients with COVID-19. 96 of these patients received TCZ, and 97 received the standard therapy. In general, the mortality rate did not differ between the groups (52% *vs* 62%, $p = 0.09$). However, TCZ patients who did not require mechanical ventilation showed lower mortality as compared to the control group (6% *vs* 27%, $p = 0.024$). A prospective study by *S.Ramino et al.* [86] enrolled 86 patients with COVID-19 who received TCZ and 86 patients in the control group. All patients received high doses of methylprednisolone (250 mg on the first day and 80 mg on days 2 – 5) and had clinical and laboratory signs of the cytokine storm syndrome. These signs included rapid progression of the respiratory failure and at least 2 out of 3 abnormal laboratory tests (an increase in the levels of CRP > 100 mg/L, ferritin > 900 μg/L, d-dimer > 150 μg/L). The indications for the use of TCZ (8 mg/kg, intravenously) were the progression of the lung function disorder within 2 days, despite the use of methylprednisolone. TCZ was associated with an increased likelihood of improved lung function and hospital discharge (RR 1.8, 95% CI 1.2 – 2.7) (on day 7), a 65% decrease in mortality (RR 0.35, 95% CI 0.19 – 0.65), and lesser need for mechanical ventilation (HR 0.29, 95% CI 0.14 – 0.65) as compared to the control group. The incidence of ADR was similar between the groups. The only exception was the increase in the incidence of pulmonary embolism in the TCZ group ($p = 0.0590$). *E.Moreno-Garcia et al.* [87] evaluated the use of TCZ in 77 patients with COVID-19 with ARDS in comparison with the control group ($n = 94$). TCZ treatment was associated with a decrease in the need for transfer to the ICU (10.3% *vs* 27.6%), $p = 0.005$), the need for mechanical ventilation (0 vs 13.8%, $p = 0.001$), as well as the combined outcome (transfer to the ICU and death) (OR 0.03, 95% CI 0.007 – 0.10, $p = 0.0001$).

Meta-analyzes of Tocilizumab use

2 meta-analyzes [88, 89] summarized most of the above studies of the efficacy of TCZ in patients with COVID-19. A meta-analysis by *A.Kaye et al.* [88] included 9 comparative studies [64, 68, 69, 71, 75, 80, 83–85]. Overall, these studied enrolled 618 patients who received TCZ and 1,057 patients in the control group. The mortality rate was 26.1% in the TCZ group and 41.5% in the control group (OR 0.492, 95% CI 0.326 – 0.713, $p < 0.001$). The mortality rate among the patients treated with TCZ was 13.5% in 12 uncontrolled studies ($n = 803$) [51, 53–55, 57–61]. Another meta analysis [89] was based on the results of 13 retrospective [64–66, 68–70, 72, 75, 80, 83–85, 87] and 3 prospective studies [67, 71, 82], which included 2,488 patients who received the standard therapy and 1,153 patients who received TCZ. The mortality in the TCZ group (22.4%) was significantly lower than in the control group (26.21%) (OR 0.57, 95% CI 0.36 – 0.92, $p = 0.02$).

Sarilumab and siltuximab

E.Gremese et al. [90] presented the data on SAR in 53 patients with severe COVID-19 pneumonia. 39 patients (66.7%) were administered SAR (1 infusion) in the therapeutic department, 14 patients (26.4%) were received it in the ICU (92.6% received 2 infusions). In the therapeutic department, 89.7% patients showed a significant clinical improvement (46.7% of the patients after 24 hours, 61.5% – after 3 days), 85.7% of patients no longer needed respiratory support, and 70.6% were discharged. 62.4% of those in the ICU were transferred to the therapeutic department, 35.8% remained in the ICU. The overall mortality rate was 5.7%, including 2.5% (1 patient) in the therapeutic department and 14.4% (2 patients) in the ICU. *E.Della-Torre et al.* [91] evaluated 28 patients with COVID-19 pneumonia who received SAR (400 mg, intravenous) and 28 patients in the comparison group. After 28 days, the clinical status improved in 61% of patients in the SAR group. The mortality rate was 7% in the SAR group. No significant differences were reported between the groups (64% and 18%, respectively) ($p > 0.05$). Predictors of clinical improvement in the SAR group were a basal PaO_2/FiO_2 ratio > 100 mm Hg and the lung lesion area < 17% in the CT-scan. Notably, the clinical status of patients with lung lesion area < 17% improvement faster (on average after 10 days) in the SAR group as compared to the standard therapy (on average after 24 days) ($p = 0.01$). *M.Benucci et al.* [92] noted an improvement in the lung function (SpO_2/FiO_2 ratio) in 7 out of 8 COVID-19 pneumonia patients treated with TCZ. The improvement was associated with an increase in lymphocyte levels and a decrease in the IL-6 and CRP concentrations. At the same time, preliminary results of a multicenter RCT (phase II / III) of SAR are disappointing. The study included 400 COVID-19 patients in a severe or

critical state (need for mechanical ventilation, high-speed nasal flow, and/or ICU) [93]. An interim analysis (within the phase II) did not reveal significant differences in the efficacy of SAR therapy at a dose of 400 mg intravenously ($n = 145$) as compared to the control group ($n = 77$) for all analyzed endpoints – mortality (23% *vs* 27%), the need for continued mechanical ventilation (23% *vs* 27%), clinical improvement (59% *vs* 41%), discontinuation of high-speed nasal flow procedures (58% *vs* 41%), and discharge (53% *vs* 41%). The exception was a more pronounced decrease in the concentration of CRP in the SAR group as compared to the control group (–79% *vs* –21%).

Preliminary results of the efficacy and safety of SLT in 21 patients with COVID-19 complicated by ARDS were reported [94]. In general, the efficacy is satisfactory. All patients showed normal CRP levels within 5 – 7 days. ⅔ patients showed improved or stable lung function. Nevertheless, the state of 5 patients worsened. All of them required mechanical ventilation, and one of them died.

Conclusion

Numerous uncontrolled studies show the efficacy of IL-6 inhibitors in patients with severe COVID-19 pneumonia (with and without the cytokine storm). Nevertheless, the fundamental theoretical and clinical issues of immunopathology require further studies [95–97]. The most pressing issues are related to the true place of IL-6 in complex pathogenetic mechanisms that differ at different stages of this disease. Let us consider just a few of these issues. The serum levels of IL-6 in severe COVID-19 that is complicated by cytokine storm syndrome is significantly lower (from 7 to 627 pg/mL) [98–102] than in ARDS caused by other viral infections (578 – 1,618 pg/mL) [103–105]. The serum levels of IL-6 reached 10,000 pg/mL in patients with cytokine release syndrome caused by CAR-T-cell therapy [106]. The IL-6 level can exceed 50 pg/mL during active inflammation in patients with IRDs in the absence of ARDS and other manifestations of cytokine storm [107–110]. Moreover, the administration of recombinant human IL-6 to patients with cancer at a dose of 10 μg/kg to 20 μg/mL leads to a pronounced increase in the serum levels of IL-6 (> 4,000 pg/mL). However, it is not accompanied by severe lung damage or multiple organ failure [111]. This suggests that the development of COVID-19 pneumonia is associated with severe local inflammation (that may be dependent on IL-6), rather than with the systemic hyperimmune response characteristic of ARDS associated with other viral infections. On the other hand, there is evidence of the "protective" antiviral and antimicrobial effects of IL-6 in the early phase of infections [112]. This evidence is consistent with the numerous studies that showed an increased risk of infectious complications during the treatment of rheumatoid arthritis with TCZ and SAR [31, 34, 45–47]. The data of the RECOVERY study (Randomized Evaluation of COVid-19 thERapY) are important when considering the potential use of IL-6 inhibitors in the treatment of COVID-19. This study showed efficacy of dexamethasone therapy (6 mg per day for 10 days) in reducing mortality (within 28 days) in patients with COVID-19 ($n = 2,104$) who were mechanically ventilated (from 40% to 28%; $p = 0.0003$) or needed oxygen support (from 25% to 20%; $p = 0.0021$) as compared to the control group ($n = 4,321$). Notably, the higher efficacy of dexamethasone was not reported in patients who do not require oxygen support ($p = 0.14$) as compared to the control group [113]. These data can probably be extrapolated to other GCs and draw special attention to the negative results of RCTs (phase II / III) regarding the use of SAR in severe COVID-19 [93]. Preliminary results of the COVACTA RCT were presented. The TCZ treatment (as well as SAR) was not more effective than placebo in patients with severe COVID-19, as to most "primary" and "secondary" endpoints: improvement of clinical status ($p = 0.36$), mortality within 4 weeks (19.7% *vs* 19.4%; $p = 0.94$), the number of days without ventilation (22 days *vs* 16.5 days; $p = 0.320$) and the incidence of infectious complications (38.3% *vs* 40.6%) and severe infections (21.0% *vs* 25.9%). Although the time to discharge (or "readiness for discharge") was less (20 days) in the TCZ group than in the placebo group (28 days) ($p = 0.03$), these differences were not statistically significant [114]. From a clinical point of view, all these results are not conclusive regarding the choice of therapy in patients with COVID-19. However, they emphasize the heterogeneity of the pathogenic immune mechanisms of critical conditions as a manifestation of cytokine storm syndrome. In this regard, attention should be paid to the unique position of GCs in the control of inflammation. GCs block the synthesis of not only IL-6 but a wider range of pathogenetically important pro-inflammatory cytokines (including IL-1α/β, IL-12, IL -17, IFN-γ, TNF-α, and others) [115]. Overproduction of these cytokines is associated with a poor prognosis in COVID-19 pneumonia.

Suppression of hyperinflammation in COVID-19 (as in other immunoinflammatory diseases in humans) cannot be based on GC alone in the 21st century. Numerous studies aim to find new therapeutic targets for the development of personalized immunomodulatory therapy for COVID-19 [116, 117] based on the concept of "taxonomy" of cytokine-dependent diseases [7, 118]. Efficacy of inhibition of various pro-inflammatory cytokines, other than IL-6, is being studied (or discussed): IL-1 [119, 120], TNF-α [121], GM-CSF [122], IL-17 [123], IL-18 [124], cytotoxic terminal products of the complement system activation, etc. [125]. A promising area of immunopharmacotherapy for COVID-19 is associated with the repurposing of JAK (Janus kinase) inhibitors, primarily baricitinib (BARI). BARI is a targeted basic anti-inflammatory drug that is widely used to treat RA, and more recently, other immune-inflammatory diseases [126–128]. BARI inhibits the activity of JAK1 and JAK2 and thereby suppresses signaling of a wide range of pro-inflammatory cytokines, including IL-6 and GM-CSF. BARI also has an antiviral effect because it prevents infection of target cells with SARS-Cov-2 and intracellular assembly of the virus [129, 130] (Table 2).

In a short time, many scientific and clinical research studies were started and conducted to explore the issue of the cytokine storm syndrome in COVID-19. These studied dived into the abnormal immune mechanisms

Table 2
Anti-inflammatory therapy for COVID-19
Таблица 2
Противовоспалительная терапия при COVID-19

Drugs	Mechanism	Use in COVID-19		Use in IRD
		Advantages	Disadvantages	
Corticosteroids	Suppression of inflammation and immune response [115]	Decrease in mortality of COVID-19 patients on mechanical ventilation [113]	Slowing the virus RNA clearance [131]	RA, SLE, SS, SV, other inflammatory diseases
			Development of ADR [132]	
Aminoquinoline agents (chloroquine, hydroxychloroquine)	Moderate anti-inflammatory and immunosuppressive effect: production of IL-6 and TNF-α ↓	Reduced viral load [133]	Efficacy was not proven; ADRs were reported [133]	RA, SLE, SS, SV, other IRDs
IL-6 inhibitors	Suppression of inflammation (see the text)	Reduced mortality	The efficacy was not confirmed in the RCT [113, 114], ADRs were reported (risk of infections, and others)	See Table 1
IL-1 inhibitors	Suppression of inflammation [119]	Reduced mortality, improved lung function [120, 134 – 142]	The efficacy was not confirmed in the RCT, ADRs were reported (risk of infections, etc.)	Autoinflammatory diseases [119]; sepsis [143], secondary HLH [144,145] and MAS [146]
Colchicine	Suppression of inflammation [147]	Effective against fever, skin lesions and myopericarditis [148,149]	The efficacy was not confirmed in the RCT, ADRs were reported (risk of infections, etc.)	Autoinflammatory diseases, gouty arthritis [147]
Janus kinase inhibitors (baricitinib, ruxolitinib)	Suppression of inflammation [126,127], prevention of infection of lung cells with SARS-CoV-2 [128, 129]	Improvement in COVID-19 pneumonia [150–152]	The efficacy was not confirmed in the RCT, ADRs were reported (risk of infections, etc.)	RA, PsA, UC, psoriasis, secondary HLH (ruxolitinib) [153–155]
Complement inhibitors • mAb to C5a (eculizumab) • Low molecular weight C3a inhibitor (AMI-101)	Suppression of complement-dependent inflammation [156]	Improvement in COVID-19 pneumonia [157, 158]	The efficacy was not confirmed in the RCT, ADRs were reported (risk of infections, etc.)	Atypical HUS Paroxysmal nocturnal hemoglobinuria Myasthenia gravis Optic neuromyelitis
GM-CSF inhibitors: • mAb to GM-CSF	Suppression of inflammation [159]	Improvement in COVID-19 pneumonia [160–162]	The efficacy was not confirmed in the RCT, ADRs were reported (risk of infections, etc.)	RA (phase III) [163]
Intravenous immunoglobulin	Modulation of the immune response [164, 165]	Improvement in COVID-19 pneumonia [166, 167]	The efficacy was not confirmed in the RCT, ADRs were reported (acute lung damage, thrombosis)	IRD (off-label)

Note: ADR, adverse drug reactions; RCT, randomized controlled trial; HUS, hemolytic uremic syndrome; RA, rheumatoid arthritis; PsA, psoriatic arthritis; UC, ulcerative colitis; SLE, systemic lupus erythematosus; SV, systemic vasculitis; SSS, systemic scleroderma; IIM, idiopathic inflammatory myopathies; HLH, hemophagocytic lymphohistiocytosis; IRDs, inflammatory rheumatic diseases.

and treatment of human immunoinflammatory diseases. One can hope that the efforts of scientists and physicians around the world will improve the prognosis for COVID-19, generate new knowledge for successful control of epidemics of viral infections that humanity may face in the future, and will improve the pharmacotherapy of widespread IRDs.

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Coagulopathy in COVID-19

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Abstract

Hemostatic disorders play an important role in the pathogenesis and clinical manifestations of COVID-19. The purpose of the research was a detailed consideration of the pathogenesis, clinical manifestations, and methods of diagnosing and treatment of coronavirus-induced coagulopathy (CIC). At the onset of COVID-19, hypercoagulability is detected, and consumption coagulopathy and disseminated intravascular coagulation (DIC) syndrome are usually observed at later stages of the disease. In the pathogenesis of hypercoagulation in patients with COVID-19, pro-inflammatory cytokines, hyperfibrinogenemia, increased blood levels of von Willebrand factor, factor VIII, neutrophilic extracellular traps, platelet activation, production of antiphospholipid antibodies, microvesicles are of importance. Laboratory findings show increased plasma concentrations of D-dimer, fibrinogen, a longer prothrombin time and a decrease in the number of platelets. The cumulative incidence of thrombotic complications ranges from 21 to 31%. Thrombosis risk factors are intensive care unit stay, leukocytosis, and a high plasma D-dimer concentration. Differential diagnosing of CIC should be carried out with disseminated intravascular coagulation, sepsis-induced coagulopathy, antiphospholipid, hemophagocytic syndromes, thrombotic microangiopathy, and heparin-induced thromocytopenia. CIC may be complicated by sepsis, antiphospholipid syndrome, hemophagocytic syndrome, thrombotic microangiopathy, and heparin-induced thrombocytopenia.

The main therapy is low molecular weight heparins treatment. Treatment recommendations are provided.

Key words: coronavirus infection 2019, heparin, coagulation, D-dimer, fibrinogen, prothrombin time.

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Коагулопатия при COVID-19

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Резюме

Нарушения гемостаза играют важную роль в патогенезе и клинических проявлениях COVID-19. Целью работы явилось подробное рассмотрение патогенеза, клинических проявлений, методов диагностики и лечения коронавирус-индуцированной коагулопатии (КИК). При дебюте COVID-19 выявляется гиперкоагуляция, а коагулопатия потребления, синдром диссеминированного внутрисосудистого свертывания (ДВС) регистрируются обычно на поздних стадиях заболевания. В патогенезе гиперкоагуляции при COVID-19 играют роль провоспалительные цитокины, гиперфибриногенемия, повышенное содержание в крови фактора Виллебранда, фактора VIII, нейтрофильных внеклеточных ловушек, активация тромбоцитов, выработка антифосфолипидных антител, микровезикулы. В лабораторных показателях выявляются повышенные плазменные концентрации D-димера, фибриногена, увеличение протромбинового времени и уменьшение количества тромбоцитов. Кумулятивная частота тромботических осложнений колеблется от 21 до 31 %. Факторами риска тромбозов являются пребывание в отделении интенсивной терапии, лейкоцитоз и высокая концентрация D-димера в плазме. Дифференциальный диагноз КИК следует проводить с ДВС-синдромом, сепсис-индуцированной коагулопатией, антифосфолипидным, гемофагоцитарным синдромами, тромботической микроангиопатией, гепарин-индуцированной тромоцитопенией. Возможно сочетание КИК с сепсисом, антифосфолипидным синдромом, гемофагоцитарным синдромом, тромботической микроангиопатией, гепарин-индуцированной тромбоцитопенией.

Основной терапией является лечение низкомолекулярными гепаринами. Приводятся рекомендации по лечению.

Ключевые слова: коронавирусная инфекция 2019, гепарин, коагуляция, D-димер, фибриноген, протромбиновое время.

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The novel COronaVIrus Disease 2019 (COVID-19) is an infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an enveloped RNA recombinant virus (genus Betacoronavirus) between the bat coronavirus and an origin-unknown coronavirus. The genetic sequence of SARS-CoV-2 is up to 79% similar to that of SARS-CoV [1, 2]. The first outbreak of this infection was reported in the Chinese city of Wuhan in December 2019, and as early as March 11 2020 the World Health Organisation (WHO) declared this outbreak as a pandemic. The world entered a "war to the knife", as was underscored by Italian specialists [3], which is not figurative, but literal. The infection starts when SARS-CoV-2 enters target cells expressing angiotensin-converting enzyme-2 (ACE2), a membrane receptor. ACE2 receptors are expressed in respiratory, renal, and cardiac cells as well as in the oesophagus, bladder, ileum, and central nervous system. However, type II alveolar cells are the major target, which is rapidly reached by the virus.

Viral infection of these cells leads to diffuse alveolar damage, which clinically manifests as acute respiratory distress syndrome (ARDS). This syndrome has been reported in 41.8% of patients, half of which died [4]. Nevertheless, if we continue comparing the fight with COVID-19 to a war, we can say that it is at least a two-front war: lung damage is the most evident clinical manifestation of COVID-19, but there is a second, often "invisible", front in this war, i.e. coagulation abnormalities, which are frequently inapparent and left undetected. Coagulopathies not only lead to clinically significant thrombotic events, but are also implicated in the pathogenesis of coronavirus infection, including lung injury. Alteration in microcirculation caused by microthrombi may significantly worsen acute respiratory failure in patients with COVID-19. Therefore, treatment protocols for COVID-19 must include therapies for haemostatic disorders. Evaluation of mechanisms underlying coronavirus-induced coagulopathy (CIC) helps not to only better understand the pathogenesis of the disease, but also improves the accuracy of its diagnosis and opens up new horizons for treatment.

The objective of this paper is to describe the pathogenesis and clinical manifestations of CIC and discuss methods used to detect and treat this condition.

Pathogenesis of coronavirus-induced coagulopathy

Cell penetration of SARS-CoV-2 is mediated by its spike (S) protein, which binds to the receptor on the surface of the host cell. This receptor is ACE2 on the surface of type II alveolar cells. Single-cell RNA-sequencing revealed that expression of the ACE2 gene is limited to a small population of type II alveolar cells and that endothelial cells and alveolar macrophages do not have ACE2 [5]. Receptor-mediated endocytosis results in release of the viral nucleocapsid into the cytosol, where the viral RNA serves as an mRNA for the synthesis of the pp1a and pp1ab polyproteins, of which, in the next replication/translation passage, a copy of the virus RNA is formed, as well as 8 separate mRNA templates for virus proteins that generate them indefinitely [6]. Released cytokines provoke interstitial inflammation, endothelial damage, and blood coagulation activation. Tissue factor is crucial in the pathogenesis of blood coagulation activation. It is exposed by monocytes and by damaged endothelial cells or those activated by the cytokines' burden.

The final result is thrombin production and consequent thrombosis of alveolar capillaries [7]. Although inflammation and coagulation are the key factors in the pathogenesis of CIC, the mechanisms underlying coagulation disturbances are different from those involved in disseminated intravascular coagulation (DIC) and sepsis-induced coagulopathy (SIC) [8].

The procoagulant response in sepsis involves damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) [8]. Sepsis is associated with release of proinflammatory cytokines such as interleukin (IL)-1β, IL-6, tumor necrosis factor, and complement system proteins, all of which induce coagulopathy [9]. In addition, tissue factor expression on monocytes and macrophages, neutrophil activation, and release of neutrophil extracellular traps (NETs) also produce activation of coagulation and thrombosis [10, 11]. NETosis is a type of programmed death of neutrophils. During this process necrotic neutrophils release a mixture of filaments mainly consisting of DNA, histone proteins, and nucleosomes, which also exhibit procoagulant activity and increase the risk of thrombosis. Such thromboinflammation leads to endothelial damage and an increased generation of thrombin [12]. SIC/DIC is associated with inhibition of fibrinolysis caused by an increased production of plasminogen activator inhibitor 1, which is accompanied by thrombosis and organ dysfunction [13]. To detect these abnormalities, the following parameters were included in the DIC criteria: severity of thrombocytopenia, elevated plasma levels of fibrin degradation products, including D-dimer, increased prothrombin time, and hypofibrinogenaemia [14]. The following parameters are the SIC criteria: increased prothrombin time, severity of thrombocytopenia, and severity of the patient's condition, as assessed by the Sequential Organ Failure Assessment (SOFA) [15]. Both DIC and SIC are associated with a reduced plasma activity of natural anticoagulants (antithrombin III and protein C) [16].

CIC occurs through other mechanisms. Several research groups have reported that coagulation profiles of patients with COVID-19 reflect severe hypercoagulation, but not consumptive coagulopathy or DIC [17, 18]. Consumptive coagulopathy is a typical manifestation of DIC/SIC, but it does not develop at the onset of COVID-19. In COVID-19 interleukin-1β and interleukin-6 may cause thrombocytosis and hyperfibrinogenaemia in patients with SARS-CoV-2-associated ARDS [19]. In early stages of COVID-19, inflammation and hypercoagulation are mainly observed in the lungs and DIC develops only if the diseases progresses to multiorgan dysfunction. Significantly elevated plasma levels of D-dimer are explained by impaired regulation of local alveolar fibrinolysis via urokinase-type plasminogen activator released from alveolar macrophages. These events lead to viral interstitial pneumonia, ARDS, and death of patients with coronavirus infection [19]. SARS-CoV-2 invasion of endothelial cells, which widely express the ACE2 receptor (receptor for SARS-CoV-2), results in massive release of plasminogen activator [20]. In healthy conditions, ACE2 enhances anticoagulant properties of vascular endothelium. SARS-CoV-2 binding to ACE2 induces expression of tissue factor and inhibits the protein C system [20].

As the severity of COVID-19 increases, procoagulant activity leads, over time, to fibrin generation, an increase in blood fibrinogen levels, and platelet activation. Damaged endothelial cells release von Willebrand factor and plasminogen activator inhibitor 1, which causes increased clot formation in pulmonary capillaries. Plasma activity of factor VIII, an acute-phase protein, is three times higher and concentrations of von Willebrand factor antigen are five times higher than those in healthy subjects [18].

As in sepsis, NETs have proven to be involved in COVID-19 Analysis of blood samples obtained from 50 patients with COVID-19 and 30 healthy subjects

showed that patients with coronavirus infection had higher levels of the following key markers of NETosis: cell-free DNA, myeloperoxidase(MPO)-DNA complexes, and citrullinated histone H3 Elevated blood levels of cell-free DNA associated with higher platelet levels. Plasma from individuals with COVID-19 added to neutrophils triggered NETosis of these cells *in vitro* [21]. Through electrostatic interactions, neutrophil extracellular traps activate the intrinsic (contact) phase of coagulation [22]. As compared with controls, patients with COVID-19 and thrombosis had higher blood levels of markers of NETs Levels of these markers were evaluated in a retrospective, case-control study of 11 patients with COVID-19 who developed thrombosis as compared with gender- and age-matched COVID-19 patients without clinical thrombosis [23]. Compared to the control group, patients with thrombosis had significantly higher blood levels of markers of NETs (cell-free DNA, MPO-DNA complexes, and citrullinated histone H3) There was a strong association between markers of NETs and D-dimer levels.

Production of antiphospholipid antibodies is another mechanism of involvement of haemostasis in the pathogenesis of COVID-19. Chinese authors [24] reported three cases of COVID-19 patients who developed thrombotic events (arterial thrombosis in the limbs and ischaemic stroke) on days 33, 10, and 18 from disease onset. More detailed testing showed the presence of anti-β_2-glycoprotein I IgA and IgG antibodies as well as anticardiolipin IgA antibodies. French researches [25] studied 56 patients with verified COVID-19 and reported that 25 (45%) of them had lupus anticoagulant, whereas anticardiolipin and anti-β_2-glycoprotein I antibodies were detected in only five of 50 tested patients (10%). In another study 50 (87.7%) of 57 tested COVID-19 patients had positive lupus anticoagulant [26]. In COVID-19 the insidiousness of lupus anticoagulant is that, on the one hand, patients have increased activated partial thromboplastin times (APTT) and, on the other, suffer from thrombotic events. Moreover, APTT cannot guide therapeutic decisions regarding heparin therapy in lupus anticoagulant-positive patients.

Some authors [18] focus considerable attention on the role of microvesicles in the development of hypercoagulation in COVID-19. These moieties are cytoplasmic microparticles stemming from platelets or monocytes and exhibit procoagulant properties.

Change in haemostatic parameters in coronavirus-induced coagulopathy

Apparently, a consideration of the pathogenic pathways is needed to understand what happens in CIC. In the pandemic environment, however, clinicians treating patients with COVID-19 need simple diagnostic criteria that would make it possible to detect CIC and choose appropriate therapy.

Plasma levels of D-dimer. The degree of increase in blood levels of D-dimer reflects the severity of patient's condition. A study of data regarding 1,099 patients with laboratory-confirmed COVID-19 from more than 550 hospitals in China showed that 260 (46.4%) out of 560 patients had plasma levels of D-dimer higher than 0.5 mg/L. Of note, elevated D-dimer levels were observed only in 43% of patients with mild disease and in 60% of patients with severe disease [27]. *C.Huang et al.* [28] noted that at the time of presentation patients with COVID-19 who required admission to an intensive care unit (ICU) had higher plasma D-dimer levels than those who did not: median D-dimer level 2.4 mg/L (0.6 – 14.4 mg/L) *vs* 0.5 mg/L (0.3 – 0.8 mg/L), $p = 0.0042$). *N.Tang et al.* [29] showed that higher plasma D-dimer levels in patients with COVID-19 were a predictor of death: mean D-dimer level 2.12 μg/mL (interquartile range 0.77 – 5.27 μg/mL) in non-survivors *vs* 0.61 μg/mL (interquartile range 0.35 – 1.29 μg/mL) in survivors ($p < 0.001$) (normal value < 0.50 μg/mL). Fibrin degradation product (FDP) levels, another marker of activation of coagulation and fibrinolysis, had the same predictive value. The mean FDP level was 7.6 μg/mL (interquartile range 4.0 – 23.4 μg/mL) in non-survivors *vs* 4 μg/mL (interquartile range 4.0 – 4.3 μg/mL) in survivors ($p < 0.001$) (normal value < 5.0 μg/mL). Italian authors [30], who measured plasma D-dimer levels in 388 patients with COVID-19 every three days (on days 1 – 3, 4 – 6, and 7 – 9 after admission), reported a tendency toward elevation of this parameter in more severe patients, which was more evident in patients transferred to an ICU. These levels were always higher in non-survivals than in survivals, indicating greater severity of their condition. In patients who were not transferred to an ICU elevation of D-dimer was not very high (median D-dimer level increased from 329 to 472 ng/mL in survivors and from 868 to 1,093 ng/mL in non-survivors), while in ICU patients these values were of different magnitude (median level increased from 615 to 3,137 ng/mL in survivals and from 1,022 to 7,746 ng/mL in non-survivals). *N.Tang et al.* [29] reported that patients had significantly high plasma D-dimer and FDP levels in the first days of COVID-19, but starting from day 10 this difference became especially pronounced. In a study of 201 patients with COVID-19, Coxregression analysis showed that elevated plasma D-dimer levels were a risk factor associated with the development of ARDS (hazard ratio [HR], 1.03; 95% confidence interval [CI], 1.01 – 1.04), $p < 0.001$ and death (HR, 1.02; 95% CI, 1.01 – 1.04), $p < 0.002$ [4]. In a study of 343 patients, ROC analysis showed that plasma D-dimer concentrations of ⩾ 2.0 μg/mL on admission in hospital, i.e. 4 times higher than normal, predicted in-hospital mortality with a sensitivity of 92.3% and a specificity of 83% [31]. Elevated plasma levels of D-dimer are not, however, pathognomonic only for COVID-19: comparison of haemostatic parameters of 449 patients with SARS-CoV-2 pneumonia and acute respiratory failure and those of 104 patients with pneumonia of the same severity and respiratory failure caused by other etiologic agents did not show any significant difference in their D-dimer levels [32].

APTT. This parameter does not significantly change in COVID-19. Nevertheless, prolonged APTT in patients with COVID-19 may be caused, as mentioned above, by the presence of lupus anticoagulant. It did not significantly differ between COVID-19 patients who required ICU treatment and those who did not (26.2 [22.5 –

33.9] s *vs* 27.7 [24.8 – 34.1] s, $p = 0.57$) [33] as well as between survivors and non survivors (41.2 [36.9 – 44.0] s *vs* 44.8 [40.2 – 51.0] s, $p = 0.096$) [29]. APTT was not a significant risk factor for ARDS (HR, 0.97 [95% CI: 0.94 – 1.01), $p = 0.13$) or death (HR, 0.96 [95% CI, 0.91 – 1.01], $p = 0.06$) [4].

Prothrombin time. Prolonged prothrombin time is not a disease-specific sign of COVID-19 [26]. This parameter did not significantly differ in patients with pneumonia induced by SARS-CoV-2 and non-SARS-CoV-2 pneumonia [32]. However, prolonged prothrombin time is associated with higher severity of COVID-19 and acts as a risk factor for the development of ARDS: (HR, 1.56 [95% CI, 1.32 – 1.87], $p < 0.001$) [4]. In patients with COVID-19 longer prothrombin times were observed in those who required ICU treatment compared to those who did not (12.2 [11.2 – 13.4] s *vs* 10.7 [9.8 – 12.1] s, $p = 0.012$) as well as in non-survivors compared to survivors (15.5 [14.4 – 16.3] s *vs* 13.6 (13.0 – 14.3) s, $p < 0.001$). Of note, although these differences are statistically significant, the absolute difference is just a few seconds, and if INR is measured and prothrombin time is not, these differences may not ne noted. A dynamic evaluation revealed prolongation of prothrombin time in non-survivors compared to survivors starting from day 10 after admission [29].

Plasma levels of fibrinogen. While DIC is associated with hypofibrinogenaemia, which is considered one of its diagnostic criteria [14], COVID-19 is more often associated with hyperfibrinogenaemia. In the study of 183 patients with COVID-19 conducted by *N.Tang et al.* [29] the median plasma fibrinogen level was 4.55 g/L (3.676 – 5.17 g/L), with the normal range being 2.0 – 4.0 g/L. Fibrinogen levels did not significantly differ in survivors and non-survivors, while a dynamic assessment showed that on days 10 and 14 from the onset of the disease non-survivors had higher fibrinogen levels than survivals [29]. Fibrinogen is an acute-phase protein, whose concentration increases in inflammation. This can explain a strong correlation ($R_2 = 0.506$) between plasma levels of fibrinogen and IL-6 in COVID-19 patients [34].

Antithrombin III. Unlike in sepsis, in COVID-19 plasma activity of antithrombin III was not reduced and in most patients it remained within the reference range or slightly decreased [18, 26, 29]. In general, activity of antithrombin III did not significantly differ between non-survivals and survivals [29]. However, daily monitoring showed that after the first week of hospital stay non-survivals had lower activity of antithrombin III (still generally within the reference range) than survivals [29]. This could be explained not only by consumption of antithrombin III due to infection, but also by heparin therapy, which itself causes depletion of antithrombin III.

Coagulation factor VIII. This coagulation factor is actually an acute-phase protein, thus in most patients with COVID-19 its plasma activity is 3 – 4 times higher than normal [18, 26].

Von Willebrand factor. In most patients with COVID-19 levels of von Willebrand factor antigen were 4 – 6 times higher than normal [18, 26], which reflected the severity of endothelial damage resulting in its release.

Platelets. At the onset, COVID-19 is typically associated with moderate thrombocytopenia. In a study of 1,099 patients with COVID-19, the median platelet level was 168×10^9/L. On admission, thrombocytopenia, which was defined as platelet count $< 150 \times 10^9$/L, was present in 36.2% of patients [27]. In pneumonia caused by SARS-CoV-2 thrombocytopenia is less severe than in those of other etiologies [32]. A meta-analysis including nine studies with 1,779 COVID-19 patients [35] showed that severe COVID-19 was associated with more significant thrombocytopenia than mild disease: weighted mean difference (WMD) was 31×10^9/L, this number shows how much lower the platelet count was. A subgroup analysis comparing patients by survival showed WMD of 48×10^9/L. Moreover, thrombocytopenia was associated with five-fold enhanced risk of severe disease (odds ratio [OR], 5.1; 95% CI, 1.8 – 14.6) and mortality in patients with COVID-19 [35].

Thus, the following parameters should be measured in all COVID-19 patients: plasma levels of D-dimer, prothrombin time, platelet count, and plasma levels of fibrinogen (specified in descending order of diagnostic value). The frequency of measuring D-dimer and fibrinogen levels, prothrombin time, and platelet count depends on the severity of COVID-19. Both an increase, and a decrease in these parameters are important changes. In hospital, the recommended frequency of measurements is every four-five days for patients with mild disease, every two days for those with moderate disease, and every day for those with severe disease. If the infection worsens, additional unscheduled testing for these parameters should be performed [36]. It can help triage COVID-19 patients by severity. The results of these tests have prognostic value [37].

Another option is integral diagnostic tests for COVID-19-associated haemostatic disorders. Some authors have reported using thromboelastography (TEG) in COVID-19 patients and showed that this method, as well as clotting tests, can detect hypercoagulation [18]. Another useful method is rotation thromboelastometry (ROTEM). The ROTEM panel includes INTEM, EXTEM, and FIBTEM tests which are able to detect hypercoagulation. In non-survivals the signs of hypercoagulation, as assessed by ROTEM tests, were most significant [17]. TEG and ROTEM can also be used to monitor treatment with heparin [38].

Clinical manifestations of coronavirus-induced coagulopathy

Whatever laboratory signs of haemostatic disorders are, what is most important is their clinical manifestations. Among 92 patients with COVID-19 who were admitted to an ICU, forty percent experienced thrombotic events, including venous (79%) and arterial (21%) thrombosis. Nineteen (21%) of these patients experienced haemorrhagic events [39]. Haemorrhagic events in COVID-19 may be caused by a direct effect of the virus, thrombocytopenia and DIC in severe cases, or anticoagulation therapy. In one study [40], these events were observed in 3% of individuals who received anticoagulants and in 1.9% of those who did not receive this treatment ($p = 0.2$).

Different authors report different data about the frequency and incidence of thrombotic events because these parameters are highly dependent on the examinations performed. Undoubtedly, some conditions are difficult to detect, such as pulmonary embolism (PE) in patients with ARDS, asymptomatic deep-vein thrombosis, or ischaemic stroke in patients on mechanical ventilation who are undergoing a medically induced sedation to an unconscious state.

In a study of 184 patients with verified COVID-19, PE was diagnosed in 13.6%, deep-vein thromboses and catheter-related thromboses in 1.6%, and ischaemic stroke in 1.6% of the patients. A cumulative incidence of thromboses was 31% [41]. These authors [41] emphasised that thrombotic events were especially difficult to detect in patients on mechanical ventilation.

In a study of 362 patients with COVID-19 who were treated an academic hospital in Milan, the rate of thrombotic events was 7.7%, corresponding to a cumulative rate of 21.0%, despite the fact that all patients had received thromboprophylaxis with low-molecular-weight heparin (LMWH) starting from day 1 of hospital stay. A cumulative rate of thromboembolic events was significantly higher for ICU patients (27.6%) compared to that for patients who were treated in general wards (6.6%). Most thrombotic events were diagnosed within 24 h of hospitaladmission. Overall, PE was detected in 1.2%, deep-vein thromboses in 1.4%, catheter-related deep-vein thromboses in 2.1%, ischaemic cerebral stroke in 2.5%, and acute coronary syndrome in 1.1% of patients. These data were obtained not in the whole population of hospitalised COVID-19 patients but only in those who had undergone relevant examinations that are able to detect the above-mentioned complications. This may explain great differences in the rate of thrombotic events because their detection was highly dependent on the examination protocol adopted in a hospital. In another study, contrast-enhanced computed tomography (CT-angiography) was performed in all 106 patients with COVID-19 and revealed PE in 32 (30%) patients [42]. Other authors performed ultrasound examination in all COVID-19 patients on mechanical ventilation and observed thrombotic events in 22.2% of cases, including deep-vein thromboses in 14.8%, three-fourths of which were catheter-related, and a thrombus attached to the tricuspid valve [43]. Therefore, regular CT-angiography and ultrasonography in all COVID-19 patients receiving hospital treatment will increase detection rates for thrombotic events, and longer hospital stays will be associated with higher rates of these complications. This was confirmed by a study conducted by *S.Middeldorp et al.* who reported that [44] 39 (20%) out of their 198 COVID-19 patients admitted in hospital were diagnosed with thromboembolism, despite thrombosis prophylaxis. The cumulative incidences of thromboses at 7, 14 and 21 days of hospital stay were 16, 33%, and 42%, respectively. For symptomatic thrombotic events, these were 10, 21, and 25%, i.e. almost 1.5 times lower. This once again proves that all patients with COVID-19 should be evaluated for thrombotic events irrespective of the presence of their clinical symptoms. The incidence of thromboses was significantly higher in ICU (26, 47, and 59% at 7, 14 and 21 days) than in general wards (5.8, 9.2, and 9.2% at 7, 14, and 21 days). In addition to ICU stay, leukocytosis and high plasma D-dimer levels were also risk factors for thrombotic events. Patients with thrombotic events had a 2.4-fold increased risk of death (HR, 2.4; 95% CI, 1.02 – 5.5) [44].

French authors compared CT-angiography data in 106 patients with ARDS secondary to COVID-19 and 54 patients with ARDS who did not have COVID-19. Pulmonary embolism was detected in 32 (30%) patients with ARDS secondary to COVID-19 and only in 6 (11%) out of 54 patients with ARDS without COVID-19, i.e. three times less often [42]. Thus, patients with ARDS secondary to COVID-19 develop PE significantly more often than those with ARDS of other etiologies. Eighty-two percent of patients with COVID-19 infection and D-dimer levels of > 5,000 μg/L had pulmonary embolus, while 78% of patients without pulmonary embolus had D-dimer levels < 5,000 μg/L [42].

CT pulmonary perfusion showed that early in the course of COVID-19, when D-dimer levels are below 500 ng/mL, there are multiple bilateral perfusion deficits due to microvascular obstruction. Pulmonary embolism is highly likely to occur at later stages of the disease and should be suspected if the person develops haemoptysis, unexplained tachycardia, or signs/symptoms of deep-vein thrombosis or have D-dimer level above 500 mg/L [45].

Autopsy of 12 patients who died of COVID-19 revealed thrombi in the deep veins of the lower extremities in 7 (58%) patients in whom thrombosis was not detected before death; pulmonary embolism was the direct cause of death in 4 (33%) out of these 12 patients [46].

Differential diagnosis of coronavirus-induced coagulopathy

Foremost, differential diagnosis of CIC should include DIC and septic coagulopathy. Unlike CIC, DIC and septic coagulopathy are more often accompanied by the following signs, which are also more severe in these disorders: thrombocytopenia, consumption of natural anticoagulants (protein C and antithrombin III), hypofibrinogenaemia, increased APTT, and prothrombin time (Table). Does it mean that COVID-19 cannot be accompanied by DIC? Research has shown that, although in most cases the onset of the disease is really marked by non-DIC hypercoagulation disorders, DIC may develop later, as the disease progresses and multiorgan dysfunction, infectious complications or sepsis appear. Thus, while in COVID-19 survivors DIC was reported only in 0.6% of cases, in those who died it was observed already in 71.4% of cases [29].

COVID-19 can be complicated by antiphospholipid syndrome, resulting in the appearance of such additional clinical and laboratory signs as venous and arterial thrombosis and increased APTT (Table).

Haemophagocytic syndrome (HFS) is characterized by hyperactivation of immune cells (macrophages, natural killers, and cytotoxic T-cells) and cytokine storm, which is similar to the pathogenesis of COVID-19 [47, 48]. HFS can be caused by various factors, including viral infections,

Table
Changes in hemostatic parameters in patients with various diseases and syndromes
Таблица
Изменения параметров гемостаза при различных заболеваниях и синдромах

Parameter	CIC	DIC/SIC	APS	HFS	HUS	TTP	HIT II
Thrombosis	Microthrombosis, venous thrombosis	Microthrombosis	Venous/arteri thrombosis	Microthrombosis, venous thrombosis	Microthrombosis, venous/arteri thrombosis	Microthrombosis, venous/arteri thrombosis	Venous/arteri thrombosis
Platelets	→↓	↓↓	↓	↓	↓	↓↓	↓↓
D-dimer	↑↑	↑	↑	→	→	→	↑
APTT	→	↑	↑↑	→			→
PT	↑	↑	→	→			→
Fgn	↑	↓↓	→	→	→	→	→
Antithrombin III	→	↓↓	→	→	→	→	→
APS-antibodies	+	No	++	No	No	No	No
Complement activation	+	No	No	No	+++	No	No
Von Willebrand factor multimers	No	No	No	No	+++	+++	No
Schizocytes	No	No	No	No	+++	+++	No
ADAMTS-13, %	> 10	> 10	> 10	> 10	> 10	< 10	> 10
HIT-antibodies	No	No	No	No	No	No	++

Note: CIC – coronavirus-induced coagulopathy; DIC – disseminated intravascular coagulation; SIC – sepsis-induced coagulopathy; aPL Ab – antiphospholipid antibodies; APS – antiphospholipid syndrome; HFS – haemophagocytic syndrome; HUS – haemolytic uraemic syndrome; TTP – thrombotic thrombocytopenic purpura; HIT – heparin-induced; thrombocytopenia; APTT – activated partial thromboplastin time; PT – prothrombin time; Fgn – fibrinogen; AT – antithrombin.

and may have similar clinical manifestations (Table) [47]. In one study 35 patients with COVID-19 were reported to have signs of haemophagocytosis in their bone marrow aspirate samples, two-line cytopenia, and hyperferritinaemia, which misled the authors to interpret their condition as HFS [48]. This led to objections of other researches, who believe that hyperinflammation and hypercytokinaemia in the acute phase of severe COVID-19 infection are not caused by HFS, but reflect the severity of ARDS and lung injury [49].

Atypical haemolytic uraemic syndrome (aHUS) and thrombotic thrombocytopenic purpura (TTP) are thrombotic microangiopathies and constitute a group of conditions with different pathogenesis but a similar clinical presentation of microvasculature damage, nonimmune microangiopathic haemolytic anaemia, consumptive thrombocytopenia, and ischaemic organ injury (Table). aHUS is caused by impaired regulation of the complement system, which leads to its uncontrolled activation [50, 51]. The pathophysiology of TTP involves reduced activity of ADAMTS13 (A Disintegrin And Metalloprotease with ThromboSpondin type 1 motif), a plasma protein regulating interaction of von Willebrand factor with platelets. Inactivity or reduced activity of ADAMTS13 leads to consumption of platelets in developing microthrombi that obstruct arterioles and capillaries and cause intravascular mechanical haemolysis and clinical manifestations of TTP [52]. These conditions are not typically associated with impairments in the plasma haemostasis system; they are defined by the following signs:

- multimers of von Willebrand factor circulating in blood;
- normal plasma levels of von Willebrand factor antigen;
- a blood smear showing a large number of schistocytes due to mechanical haemolysis.

In TTP microthrombi are found most extensively in the heart, brain, kidneys, and pancreas, whereas aHUS most commonly affects kidneys [52]. A group of authors [53] reported five cases of microvascular injury and thrombosis due to complement activation in patients with COVID-19 and respiratory failure. All patients had thrombocytopenia accompanied by such histological characteristics as fibrin deposits within vascular lumens and deposition of terminal complement components C5b-9 (membrane attack complex), C4d, and C3d7 in the skin and lungs, which is similar to HUS. These authors did not report nonimmune

haemolytic anemia or schistocytes in blood. They believe that SARS-CoV-2 affects the proximal complement via the lectin and classical pathways as well as the terminal components of the complement system via inflammation, activation of platelets and endothelial cells, and white blood cell recruitment [54]. Like other researchers, we have never seen schistocytes in blood or haemolysis [54] in our patients, and all of them had plasma activity of ADAMTS13 above 10%.

Type II heparin-induced thrombocytopenia (HIT) (see Table) is caused by antibodies against complexes of heparin and platelet factor 4 containing in platelet α-granules. The resulting complexes consisting of IgG, platelets, and platelet factor 4 bind platelet Fc receptors. This causes platelet activation, aggregation, and destruction, resulting in the release of procoagulant phospholipids [55]. Clinical manifestations of type II HIT appear about 5 – 14 days after the onset of heparin treatment and include thromboses and thrombocytopenia. Type II HIT is diagnosed based on the platelet count $< 100 \times 10^9$/L or 50% reduction of the platelet count from baseline, which appears between days 5 and 10 after the onset of heparin treatment; the appearance of arterial or venous thromboses; and exclusion of other causes of thrombocytopenia [55]. The incidence of HIT in patients receiving unfractionated heparin (UFH) and those receiving LMWH was 4.8 per thousand patients and 0.48 per thousand patients, respectively [56]. Coagulopathy is not typical for type II HIT. However, as most patients with COVID-19 receive heparin, the risk of type II HIT cannot be fully ruled out. A group of American authors [57] reported that the cumulative incidence of positive HIT immunoassay assay (positive antibodies to complexes of heparin and platelet factor 4) was 12% at 25 days. For all patients with positive antibodies, heparin treatment was replaced by argatroban.

Thus, CIC should be differentiated from other syndromes and disorders complicated by thrombotic events. It must, however, be kept in mind that, on the one hand, COVID-19 may be associated with other preexisting disorders, such as antiphospholipid syndrome (APS), TTP, etc., and on the other hand, these disorders may complicate the course of COVID-19, for example, lead to the appearance of lupus anticoagulant, type II HIT, sepsis, etc. In such cases CIC is accompanied by other haemostatic disorders.

Treatment of coronavirus-induced coagulopathy

LMWH is the main and widely available treatment for CIC [37]. There are several targets for heparin in CIC. In addition to its anticoagulant properties, heparin exhibits a number of other positive effects:

- in the lungs it reduces inflammation and clot formation, decreases the severity of ARDS, and improves oxygenation;
- in the heart it reduces clot formation in the coronary arteries and cardiac chambers, decreases the severity of cardiomyopathy and cardiac dysfunction caused by ischaemic hypoxia in the subendothelial tissue;
- in other organs it also reduces the severity of microvascular ischaemia, multiorgan dysfunction, the intensity of oedema and capillary leakage.

The anionic nature of heparin allows it to bind to several proteins and thus act as an effective inhibitor of viral attachment [58]. In an experimental model, heparin (100 μg/mL) reduced the number of infected cells in sputum of patients with SARS-CoV-2 pneumonia by 50% [59]. Moreover, the SARS-CoV-2 S1 protein receptor-binding domain interacts with heparin [60].

According to the International Society on Thrombosis and Haemostasis (ISTH) guidelines, prophylactic dose heparin should be considered in all patients (including non-critically ill) who require hospital admission for COVID-19 infection, in the absence of any contraindications (active bleeding and platelet count less than 25×10^9/L) [37]. Below is the treatment strategy for CIC based on a summary of guidelines on heparin therapy established by various communities (ISTH [37], Chinese experts [38], the Swiss Society of Hematology [61], and Russian guidelines [36]):

An assessment of haemostatic disorders in patients with severe COVID-19 infection should include medical history (congenital disorders of coagulation, thrombophilia, platelet dysfunction, treatment with anticoagulants or anti-platelet agents, etc.).

Prophylaxis of deep-vein thromboses of lower extremities/PE should be considered in COVID-19 patients who are quarantined and being treated at home if they are at high risk of venous thromboembolic events, but at low risk of haemorrhage and are not receiving anticoagulants for other indications. With regard to this, special attention should be given to patients with limited mobility, a history of thrombotic events, or malignancies, especially those who have additional risk factors of thrombosis.

LMWH, at least in prophylactic doses, should be given to ALL hospitalised patients and not discontinued at least until discharge. There is no evidence showing the superiority of a particular LMWH agent over others. If LMWH is not available or contraindicated, UFH can be used.

Routine monitoring of blood anti-Xa activity in patients receiving parenteral anticoagulants is not required. It can be considered in patients at higher risk of haemorrhage and/or thrombosis. The target levels of anti-Xa activity are 0.2 – 0.6 anti-Xa units/mL for preventive treatment and 0.6 – 1.0 anti-Xa units/mL for therapeutic treatment. In patients receiving LMWH, blood samples for anti-Xa activity are taken between four and six hours after drug administration (preferably after three-four injections), in patients receiving subcutaneous UFH it is done in the intervals between injections, and in those receiving intravenous (IV) infusions of UFH six hours after each dose adjustment.

After discharge prolonged prophylaxis (preferably with LMWH) can be in considered for COVID-19 patients if they are still at higher risk of venous thromboembolic events, but at low risk of haemorrhage and do not require therapeutic doses of anticoagulants for other indications.

Contraindications to the use of prophylactic doses of LMWH/UFH include continued bleeding, the platelet

count < 25 × 10^9/L, and severe renal failure (for LMWH). Prolonged prothrombin time and APTT are not contraindications for the use of LMWH/UFH.

Patients with thrombotic events should receive therapeutic doses of LMWH/UFH. Administration of LMWH/UFH in therapeutic doses can also be considered in patients with clinical signs suspicious for thrombotic events when the diagnosis cannot be verified. In ICU patients with significantly elevated plasma levels of D-dimer, severe inflammation, renal or hepatic dysfunction, or respiratory failure should receive therapeutic doses of LMWH/UFH. Possible causes of heparin resistance include high levels of acute-phase proteins (C-reactive protein, fibrinogen, and factor VIII) or von Willebrand factor, low plasma antithrombin III activity, and type II HIT.

In patients with fluctuations in the platelet count and/or heparin resistance, type II HIT should be excluded. In patients with type II HIT, venous thromboembolic events should be prevented and treated with fondaparinux sodium. Unlike LMWH/UFH, fondaparinux sodium does not produce potentially beneficial pleiotropic effects, but it does not cause heparin-induced thrombocytopenia.

LMWH and fondaparinux sodium should not be used in patients with severe renal failure or rapidly changing renal function.

There is no information about the use of direct oral anticoagulants in COVID-19. If patients with mild COVID-19 are receiving oral anticoagulants for other indications, they can continue this treatment. In case of unacceptable drug interactions with medications for COVID-19 (lopinavir/ritonavir) as well as severe COVID-19, patients should be switched to therapeutic doses of heparin (preferably LMWH).

In non-bleeding patients with consumptive coagulopathy, the platelet count should be maintained above 20 × 10^9/L and plasma levels of fibrinogen above 2 g/L. In patients with bleeding, the platelet count should be maintained above 20 × 10^9/L, plasma levels of fibrinogen above 2 g/L, and prothrombin ratio below 1.5. Fibrinogen levels of < 1.5 g/L, or FFMA < 10 mm (as measured by TEG), or MCFFIBTEM ⩽ 6 mm are indications for cryoprecipitate therapy. For non-bleeding thrombocytopenic patients, the threshold for platelet transfusion is 20 × 10^9/L and for bleeding patients and those awaiting lumbar puncture it is 50 × 10^9/L. If bleeding persists, recombinant activated factor VII can be used.

Patients with a creatinine clearance > 30 mL/min must receive LMWH. For patients with body weight above 100 kg, an increase in dose should be considered in advance.

Patients with a creatinine clearance < 30 mL/min must receive UFH either subcutaneously two or three times a day or as a continuous intravenous infusion.

Anti-Xa activity should be monitored in patients with renal failure who are receiving LMWH.

It is not necessary to monitor plasma antithrombin III activity, but it must be monitored in individual cases (in patients with DIC, sepsis or heparin resistance).

In patients with COVID-19, UFH therapy can be monitored using TEG with heparinase or ROTEM (INTEM and HEPTEM tests). Comparison of data obtained by TEG and ROTEM with and without heparinase helps evaluate the effectiveness of heparin therapy. The recommended parameters include the ratio of the R time in the control tube (without heparinase) to the R time in the heparinase tube (R/Rh ratio) or ROTEM (CTINTEM/CTHEPTEM ratio) data.

In COVID-19 patients receiving renal replacement therapy, UFH/LMWH should be used for systemic anticoagulation. If UFH is used for anticoagulant therapy, dose titration should be based on TEG (R/Rh ratio) or ROTEM (CT INTEM/CTHEPTEM ratio) data. If LMWH is used, it is administered as an intravenous bolus injection (60 – 80 IU/kg) 20 – 30 minutes before the procedure and additionally at a dose of 30 – 40 IU/kg every 4 – 6 hours. Anti-Xa activity should be maintained at 0.3 IU/mL. Systemic anticoagulation should not be used in patients undergoing citrate dialysis.

Patients undergoing extracorporeal membrane oxygenation should receive UFH with the aim of reaching activated clotting time of 180 – 220 s, or APTT 1.5 times higher than normal, or R/Rh ratio as measured by TEG, or anti-Xa activity of 0.3 – 0.7 IU/mL. Heparin therapy can improve treatment outcomes in COVID-19 patients. Comparison of treatment results in a group of patients (n = 449) with COVID-19, only 99 of whom received heparin (mainly LMWH) for 7 days or longer, did not show any difference in 28-day mortality between heparin users and nonusers (30.3% *vs* 29.7%, p = 0.910). However, the heparin treat was associated with lower 28-day mortality in patients with SIC score ⩾ 4 (40.0% *vs* 64.2%, p = 0.029) and in patients with D-dimer exceeding 6-fold of upper limit of normal (32.8% *vs* 52.4%, p = 0.017) [62].

The study conducted by *L.Ayerbe et al.* [63] included patients with COVID-19, admitted in 17 hospitals in Spain. Among them, 1,734 people received heparin and 285 did not. Among the heparin users 242 (14.0%) people had died, and among the nonusers 59 (20.7%) patients had died. Heparin was associated with lower mortality when the model was adjusted for age and gender, with OR (95% CI) 0.55 (0.37 – 0.82), p = 0.003. This association remained when hypoxaemia (SaO_2 < 90%), and fever (temperature > 37 °C) were added to de model with OR (95% CI), 0.54 (0.36 – 0.82), p = 0.003. *I.Paranjpe et al.* [40] conducted a study of 2,773 patients with verified COVID-19, only 786 (28%) of whom received systemic anticoagulation. In-hospital mortality did not significantly differ in patients who were treated with anticoagulants and those who were not (22.5% *vs* 22.8%). Patients who received anticoagulation were significantly more likely to require mechanical ventilation (29.8% *vs* 8.1%; p < 0.001), which can be explained by more severe disease in this subgroup. In patients who required mechanical ventilation, anticoagulation improved prognosis (mortality was 29.1% with a median survival of 21 days for those treated with anticoagulation as compared to 62.7% with a median survival of 9 days in patients who did not receive anticoagulation (HR, 0.86; 95% CI, 0.82 – 0.89, p < 0.001).

Nevertheless, besides systemic heparin therapy, there have been other attempts to treat CIC. A new trial of

inhalation therapy with heparin and N-acetylcysteine (nebulized Heparin-N-acetylcysteine in COVID-19 Patients by Evaluation of pulmonary function, HOPE) is being currently developed. The theoretical rationale for this type of therapy is that the SARS-CoV-2 virus has a Spike Protein that interacts with three molecules on the surface of lung cells: heparin sulfate, furin, an enzyme required for processing, and an ACE2 receptor [64]. These interactions are needed for the virus to infect cells. The combination of heparin and N-acetylcysteine impairs this interaction. Laboratory experiments showed that heparin and N-acetylcysteine interfere with SARS-CoV-2 infection *in vitro*. Both drugs are currently approved for use by injection and N-acetylcysteine is also approved in an inhalation formulation. The objective of the HOPE trial is to demonstrate that inhalation of heparin and N-acetylcysteine improves the pulmonary function and allows for elimination of mechanical ventilation [64].

Antifibrinolytics represent another attempt to treat haemostatic disorders in CIC. Authors have reported using tissue plasminogen activator (Alteplase) for treatment of three patients with COVID-19-associated acute respiratory failure [65]. Initially, all patients had severe acute respiratory failure (oxygenation index (PaO_2/FiO_2) 72, 73, and 82, respectively) and were placed on mechanical ventilation. For all these patients Alteplase was indicated because of their significantly high plasma levels of D-dimers (> 50,000 ng/mL, 20,293 ng/mL, and > 33,328 ng/mL, respectively). The drug was administered at a dose of 25 mg over 2 hours, followed by a 25 mg infusion over the subsequent 22 hours. Following thrombolysis, the oxygenation index in all patients increased up to 150, 135, and 125, respectively, but despite this treatment all of them died later.

Another treatment opportunity is eculizumab, a drug used to treat HUS, which is also associated with thrombotic events, resulting in multiorgan dysfunction. A group of authors reported using eculizumab in four patients with confirmed SARS-CoV-2 pneumonia. Eculizumab was administered once a week at a dose of 900 mg. Patients were also treated with enoxaparin 4,000 IU/day via subcutaneous injection, lopinavir 800 mg/day + ritonavir 200 mg/day, hydroxychloroquine 400 mg/day, ceftriaxone 2 g/day IV, and vitamin C 6 g/day for 4 days, and were on non-invasive continuous positive airway pressure. All patients survived and showed improvement in the lung disease. Normally, all candidates for eculizumab therapy should receive a meningococcal vaccine [66]. Because it was impossible for patients with rapidly developing COVID-19 infection, all of them received prophylaxis with ceftriaxone. It should be pointed out that in these cases eculizumab was used not to treat COVID-19-associated HUS, but to inhibit the complement system in infectious patients, i.e. as an anti-inflammatory agent. Some trials of eculizumab in patients with COVID-19 have even been announced on *ClinicalTrials.gov*. One is an open-label, multicenter trial that is being prepared by Alexion. It will include patients with a confirmed diagnosis of SARS-CoV-2 infection and severe pneumonia. They will receive up to seven (at least five) doses of eculizumab. The total duration of the programme will be 4.5 months. Another trial announced on *ClinicalTrials.gov* is being conducted by Hudson Medical. In this trial all patients with SARS-CoV-2 infection will receive eculizumab at a standard dose of 900 mg IV over 30 minutes every 7 days and ceftriaxone IV as an alternative prophylactic antibiotic covering infection caused by *Neisseria meningitis*. Complement blood levels will be measured every 72 hours. The duration of therapy will be determined by the investigator. Patients will be followed up at days 7, 14, and 28 after discharge from hospital. The recorded assessments include mortality, time in the ICU, and time on a ventilator.

Finally, a third trial will evaluate the use of ravulizumab (Ultomiris) for the treatment of COVID-19. Ravulizumab is a new drug developed by Alexion for the treatment of HUS. It is a humanized monoclonal antibody that binds specifically and with high affinity to the ясomplement protein C5, thereby inhibiting its activity. In fact, ravulizumab is an improved version of eculizumab with a higher specificity and a longer duration of action. The company plans to conduct a randomized, controlled trial of 270 patients with COVID-19. The following parameters will be assessed: survival at day 29, number of days free of mechanical ventilation at day 29, change from baseline in SpO_2/FiO_2 at day 29, duration of intensive care unit stay at day 29, change from baseline in SOFA score at day 29, survival at day 60 and day 90, and duration of hospitalisation.

Conclusion

In summary, treatment of CIC is an integral and necessary part of a combination treatment strategy for COVID-19. The effectiveness of CIC treatment influences the severity of COVID-19 infection and its prognosis.

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Imaging of lung pathology in COVID-19 (literature review and own data)

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Abstract

Novel coronavirus infection is predominantly manifests as lung tissue damage. Imaging methods, particularly, chest X-Ray and computed tomography, are of great importance for detecting pulmonary changes and differentiate them with other diseases (mainly other viral pneumonias). In the early disease stages the disease presents on CT with ground glass opacities, consolidations, crazy paving symptom. With time course, they can gradually decrease, evolve into organizing pneumonia or stay stable and even increase in volume with the spread of consolidation and formation of several signs of organizing pneumonia. Although radiological methods show high sensitivity in the detection of pulmonary changes, their specificity and prognostic ability are not so good today. Novel coronavirus infection can be complicated with pulmonary embolism, development thrombosis *in situ* in pulmonary small vessels, acute heart failure and subsequent development of cardiogenic pulmonary edema, bacterial superinfection, exacerbation or worsening of chronic lung disease and several iatrogenic issues (pneumothorax, pneumomediastinum, hematomas).

Key words: novel coronavirus disease, computed tomography, diffuse alveolar damage, organizing pneumonia, complication.

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Визуализация изменений в легких при коронавирусной инфекции (обзор литературы и собственные данные)

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Резюме

Одним из главных проявлений новой коронавирусной инфекции (КВИ) является поражение легочной ткани, при этом для выявления изменений в легких и их дифференциальной диагностики с другими заболеваниями (преимущественно иными вирусными пневмониями) большую роль играют методы визуализации, в первую очередь – обзорная рентгенография и компьютерная томография. В начале заболевания в большинстве случаев определяется уплотнение легочной ткани по типу «матового стекла» или консолидации, симптом «булыжной мостовой». Данные изменения при динамическом исследовании могут уменьшиться в объеме с постепенным восстановлением воздушности легочной паренхимы или нарастанием консолидации и формированием типичной картины организующейся пневмонии. Они могут сохраняться и даже увеличиваться с нарастанием консолидации, появлением типичной картины или отдельных признаков организующейся пневмонии. Однако при высокой чувствительности методов лучевой диагностики на сегодняшний день их специфичность и прогностическая способность остаются не столь высокими. Осложнениями КВИ являются тромбоэмболия легочной артерии, развитие тромбозов легочных сосудов *in situ*, острая сердечная недостаточность с развитием кардиогенного отека легких, бактериальная суперинфекция, обострение или ухудшение хронического заболевания легких и последствия проводимой терапии (пневмоторакс, пневмомедиастинум, гематомы).

Ключевые слова: новая коронавирусная инфекция, компьютерная томография, диффузное альвеолярное повреждение, организующаяся пневмония, осложнение.

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

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The world has been affected by the novel coronavirus infection (COVID-19) since December 2019, when the coronavirus SARS-CoV-2 was first isolated from patients in the Chinese city of Wuhan. Since then, the number of new cases worldwide has been increasing steadily. Lung damage is the main manifestation of this infection, which is seen almost in all cases and defined as "viral pneumonia". The need is clear for timely and accurate assessment of abnormal chest findings, appropriate assessment of these changes over time, and evaluation of the prognostic value of the main radiographic signs of organ damage. Imaging techniques are particularly important for detecting pulmonary changes caused by SARS-CoV-2, differentiating them from those caused by other disorders, assessing the severity of abnormal findings and changes in them over time, and evaluating the efficacy of treatment.

Imaging techniques

Imaging techniques used to detect pulmonary abnormalities in patients with COVID-19 include plain chest X-ray and chest computed tomography (CT), and, in some cases, pulmonary and pleural ultrasound. Magnetic resonance imaging and radionuclide imaging have no diagnostic significance for acute respiratory infections and are not used to detect lung damage in COVID-19.

During the first days of the disease, the sensitivity of routine X-ray for early changes in the lungs (ground-glass opacities) is relatively low, and this technique cannot be used to exclude COVID-19 during this period [1, 2]. At later stages, however, the diagnostic value of X-ray significantly increases as the disease becomes more generalised and pulmonary consolidation progresses. This method reliably detects severe viral lung disease and pulmonary oedema of various etiologies. Portable chest X-ray obtained using mobile units is the main diagnostic imaging modality for chest abnormalities in resuscitation and intensive care units. This type of X-ray is recommended in most clinical guidelines as the most readily available and epidemiologically safe imaging technique.

Computed tomography is the most sensitive tool to detect radiographic signs of COVID-19. CT is feasible for initial chest evaluation in patients with severe, progressive disease and patients with clinical signs of acute viral respiratory infections and evident risk factors for a severe course of infection. Also CT is necessary for differential diagnosis of the findings revealed and, in some cases, for follow-up evaluation. The main drawback of CT is its low specificity, which rarely exceeds 60%, as it reveals multiple unequivocal lesions, such as small ground-glass opacities or reticular lesions. The specificity of CT also depends on the prevalence of infection in a particular area [1, 3–6]. The higher percentage of people are infected, the more specific CT becomes, and vice versa. The specificity of CT scanning is also highly dependent on the probability of the disease in an individual patient. The lower the clinical probability is, the less specific CT findings are.

Due to their low specificity, none of imaging modalities is recommended as a screening tool to detect respiratory problems in asymptomatic persons and patients with mild disease. In addition, imaging techniques cannot identify the etiology of the disease and, therefore, cannot replace routine laboratory tests.

Ultrasonography is an adjunctive imaging tool, which does not replace or exclude CT scanning and X-ray. When its technique is well respected and the examination is performed by a qualified specialist, ultrasonography is highly sensitive for the detection of subpleural interstitial changes and consolidations in lung tissue, pleural effusion, and pneumothorax [7–9].

The role of ultrasound in assessing pulmonary abnormalities in COVID-19 patients is controversial. Despite their high sensitivity, ultrasound data are not helpful in assessing the actual extent of lung injury. Ultrasound findings do not always correlate with X-ray and CT data. Finally, ultrasonography is not a standard diagnostic tool to diagnose pneumonia and not included in clinical guidelines for the diagnosis and treatment of community-acquired pneumonia. Therefore, its diagnostic value depends largely on the experience and qualifications of physicians in a particular facility.

Comparison of radiographic morphological features

It has been established that SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2), a membrane receptor expressed mainly on the surface of nasal epithelial cells, lower airway cells, particularly type II alveolar cells, as well as cells in the upper third of the oesophagus, enterocytes of the colon, cholangiocytes, cardiomyocytes, and epithelial cells in the proximal renal tubules and the bladder. Therefore, the airway epithelium serves as the standard entry point for this infection; from there the virus moves to the blood and affects the most susceptible organs and tissues [11–13].

Viral exposure in the lungs usually triggers diffuse alveolar damage (DAD). This term is used to describe characteristic changes in all layers of the alveolar-capillary membrane, including its basal membrane [13–17]. DAD typically is a biphasic process, and includes exudative (oedematous) and proliferative phases.

The exudative phase develops within the first few days and manifests as inflammation in the area damaged by the virus. This is accompanied by breaches in alveolar epithelium and, in some cases, sloughing of alveolar epithelial cells from the basal membrane. Some histochemical reactions and the loss of the integrity of the alveolar-capillary barrier result in exacerbation of interstitial oedema and filling of the alveoli with a fluid rich in proteins, particularly fibrin. An important step of this process is the formation of hyaline membranes, one of the main morphological markers of DAD, in the alveolar spaces.

Partial filling of the alveoli with exudate, cellular debris, and hyaline membranes is responsible for ground-glass opacities, the earliest and the most typical sign of viral lung damage detected by various imaging modalities. As abnormal contents continues to accumulate in the alveolar spaces, images start to show consolidations, areas of completely airless lung parenchyma, which are usually surrounded by a peripheral ring of ground-glass opacity (halo sign).

Viral damage to the alveolar-capillary membrane may spread throughout the interstitial compartment and affect pulmonary capillary endothelial cells. Breakdown of capillary endothelial lining cells and those anchored to the basal membrane results in the following two consequences: damage to the capillary wall (basal membrane) and an outpouring of haemorrhagic exudate directly into the alveolar spaces and the interstitial compartment, on the one hand, and thrombosis of small pulmonary vessels [17].

Radiographically, accumulation of haemorrhagic exudate in alveoli also manifests as ground-glass opacities, which relatively rapidly develop into consolidation. Ground-glass opacity lesions often have areas of reticular abnormality seen as polygonal structures 5 to 15 mm in diameter, which are actually thickened intralobular or interlobular septa (Figure 1). This is the well-known crazy

paving sign. It is not specific for viral lung damage. It can also be seen in a number of other infections, as well as in neoplasms, interstitial disorders, pulmonary oedema of various etiologies, pulmonary haemorrhage, and in case of blood aspiration in patients with pulmonary bleeding [18–20]. Some studies showed that the crazy paving sign predicts a poor prognosis for coronavirus infection, which has been reflected in many recent guidelines [5].

On radiographic images, bleeding into the alveoli or blood accumulation in the alveolar spaces, on the one hand, and cellular debris with hyaline membranes in the alveoli, on the other, manifest identically, i.e. as ground-glass opacity and consolidation. Radiography does not provide reliable evidence to distinguish between these morphological changes. However, the prognostic value of these imaging signs and clinical features associated with them turn out to be completely different, even in patients with similar extent of lung injury. Haemorrhagic suffusion of lung tissue is often a harbinger of acute respiratory distress syndrome. Some authors believe that haemorrhagic oedema is the cause of exceptionally fast progression of pulmonary abnormalities in patients with an initially small area of lung involvement [21–24].

On a chest radiograph, thrombosis of small pulmonary vessels is seen as dilation of these vessels in areas of increased density with the ground-glass pattern, but not in consolidation areas, where vessels are not seen on a background of airless lung. This sign is most evident in the cortical lung zones within the first few days (see Figure 1).

The proliferative phase of DAD becomes more prominent over the second or third week of the disease. This period is marked by dissolution of hyaline membranes, formation of immature connective tissue in the alveolar spaces and respiratory bronchioles, hyperplasia of type II alveolar cells, and migration of fibroblasts, monocytes, and macrophages to damaged alveoli. Morphologically, this process is usually viewed as an organising pneumonia. In this phase, the course of the disease depends on the volume and depth of the affected parenchyma and the integrity of the alveolar-capillary membrane [18, 20]. When all components are involved and the basal membrane is degraded, which is typically seen in COVID-19, the convalescence phase is almost unavoidably manifests as organizing pneumonia (OP). When lung tissue is not so deeply affected, complete restoration of lung parenchyma is possible without elements of OP, similar to how it happens in common bacterial pneumonia [18, 20].

The radiographic findings of OP are well established and frequently described in literature (Figure 2). These often include signs of cryptogenic OP and OP of known etiologies, such as drug exposure, viral and other infections, radiation damage, and systemic connective tissue diseases [24–27]. A typical imaging sign of this disorder is the presence of multiple patchy ground-glass density lesions combined with consolidations. They can be located in subpleural, perilobular, or peribronchial regions. An obligatory feature is the air bronchogram sign, i.e. the phenomenon of air-filled bronchi being made visible by

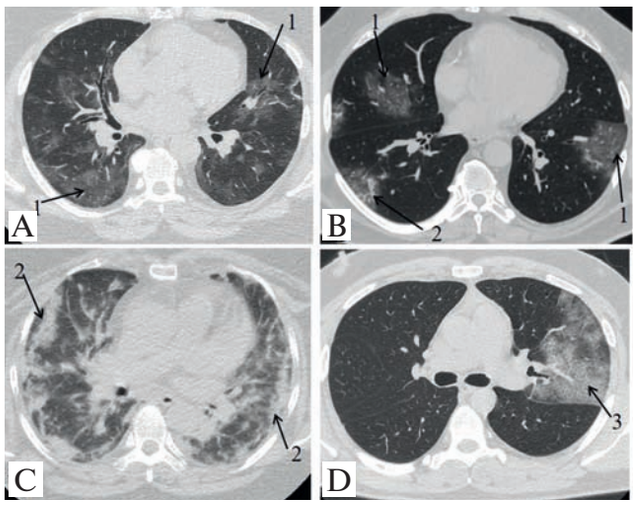

Figure 1. Variants of manifestation of COVID-19 (computed tomography on the 5 – 7th days of the disease): A, bilateral subpleural and peribronchovascular ground glass foci (1) of irregular shape; B, bilateral ground glass foci (1) with small consolidation areas (2) located subpleurally and in the central areas of lungs; C, bilateral subpleural confluent round areas of consolidation (2); D, crazy paving sign (3) in the upper left lobe

Рис. 1. Варианты манифестации COVID-19 (компьютерная томография выполнена на 5–7-е сутки от начала заболевания): A – билатеральные субплевральные и перибронховаскулярные участки «матового стекла» (1) неправильной формы; B – билатеральные участки «матового стекла» (1) в сочетании с небольшими участками консолидации (2) округлой формы, расположенные субплеврально и в центральных отделах легких; C – билатеральные сливные участки консолидации (2), расположенные преимущественно субплеврально; D – симптом «булыжной мостовой» (3) в верхней доле левого легкого

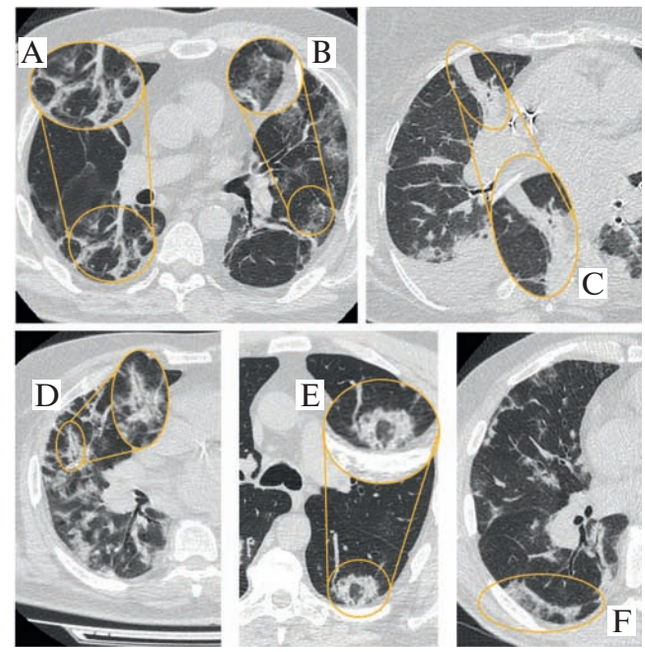

Figure 2. Common computed tomography signs of organizing pneumonia: A, perilobular reticular pattern; B, reticulation; C, linear consolidation; D, peribronchovascular consolidation; E, atoll sign (reversed halo sign); F, fibrous band parallel to pleura

Рис. 2. Типичные компьютерно-томографические признаки организующейся пневмонии: A – перилобулярный ретикулярный паттерн; B – ретикулярный паттерн; C – линейная консолидация; D – перибронхиальный участок консолидации; E – симптом обратного ободка («симптом атолла»); F – фиброзный тяж, параллельный плевре

the opacification of surrounding tissue. However, the key, but not disease-specific, sing of OP is the reversed halo sign, characterised by a central ground-glass opacity surrounded by a ring of consolidation. It was earlier often referred to as the atoll sign due to its appearance similar to that natural structure. It is typical to visualize on plain radiographs a gradual relocation of opacities from the visceral pleura towards deeper zones of lung parenchyma and apparent lung hyperinflation along the thoracic wall [26]. In some cases, it gives a false impression of emerging cavitating lesions or emphysematous bullae in the cortical regions.

So far, no evident temporal distinction has been determined between the DAD phases in the coronavirus infection. In many cases, it is just possible to note the predominance of a particular pathological process at a certain time point. Another specific feature of this infection is a paradoxical prolongation of any phase up to several weeks. Therefore, accurate evaluation of radiographic findings is very meaningful in practice, including in prognosis assessment.

In some patients SARS-CoV-2 specifically affects the immune system, causing uncontrolled and, in most cases, irreversible autoinflammatory response. This is accompanied by a rapid progression of the exudative phase of lung injury [22, 28, 29]. An X-ray examination reveals a rapid increase in lung involvement coupled with a fast progression of consolidation toward subtotal lung involvement (Figure 3) [30]. Pleural effusion is a frequent accompanying sign. Clinically, these findings are associated with acute respiratory distress syndrome (ARDS).

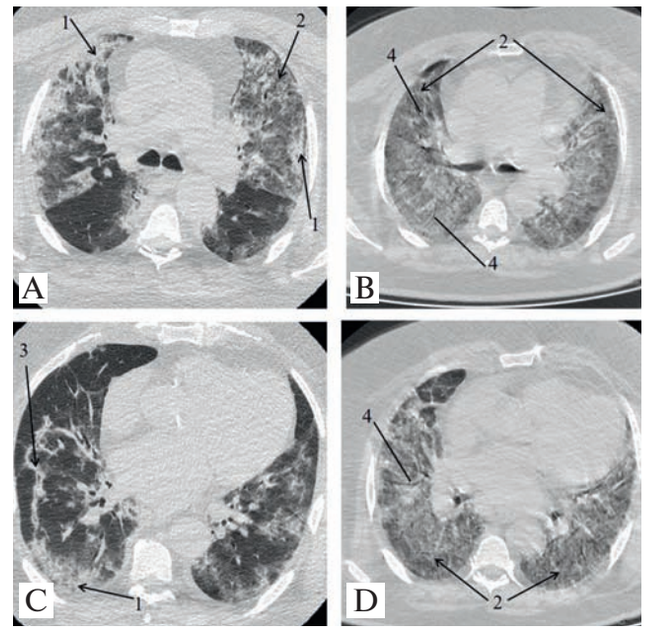

Figure 3. Patient S. 67 years old. Severe COVID-19 complicated by ARDS on the 20th day of the disease. Computed tomography, axial slices, 14th (A, B) and 20th (C, D) days of the disease; A, B, bilateral consolidation (1) and ground glass (2) foci and linear consolidation parallel to pleura (3); total lung involvement is more than 50%; C, D, total bilateral ground glass (2) spread with air bronchogram (4); damaged pulmonary area reaches 100%

Рис. 3. Пациент С., 67 лет. Тяжелое течение COVID-19 с развитием острого респираторного дистресс-синдрома на 20-е сутки заболевания. Аксиальные компьютерно-томографические срезы на: A, B – 14-е сутки заболевания; C, D – 20-е сутки заболевания; A, B – двусторонние участки консолидации (1) и «матового стекла» (2), линейный участок консолидации вдоль плевры (3); суммарная площадь поражения легочной паренхимы > 50 %; C, D – тотальное распространение «матового стекла» (2) с симптомом «воздушной бронхографии» (4); суммарная площадь поражения легочной паренхимы достигает 100 %

Prevalence of the primary radiographic signs

The radiographic signs of lung damage in COVID-19 patients have been described in many studies published in recent months, including large systematic analyses [31, 32]. Evaluation of CT data of more than 1,000 patients with verified coronavirus infection revealed the following most typical changes: ground-glass opacities (88.0%), bilateral lung involvement (87.5%), peripheral distribution in lung parenchyma (76.0%), and multilobar involvement (damage to more than one lobe) (78.8%) (Table 1). Isolated ground-glass opacities or accompanied by consolidation were the most common feature of the disease. Other, less common features, included intralobular and interlobular septal thickening, bronchiectasis, and pleural thickening. Pleural effusion, pericardial effusion, lymphadenopathy, cavitation, the halo sign, and pneumothorax were significantly less common (Table 2).

Changes in the radiographic signs over time

In their study *Y.H.Jin et al.* [34] described CT findings observed during five stages of COVID-19 infection, which they defined as ultra-early stage, early stage, progression stage, consolidation stage, and dissipation stage: In the ultra-early stage, one or two weeks after contraction, when patients usually had no clinical manifestations, CT scanning showed single or multiple ground-glass opacities, and patchy consolidations or nodules surrounded by ground-glass opacities. In the early stage (early clinical manifestations, 54% in this study), CT revealed single or multiple ground-glass opacities, combined with the crazy paving pattern. In the progression stage (3 – 7 days after the onset of clinical symptoms), the disease manifested on CT as large-scale consolidation with air bronchogram inside. In the consolidation stage (the second week of clinical manifestations), CT features may include consolidations in slighter density and smaller range. About two or three weeks after the onset of symptoms, CT scanning may show patchy consolidation, linear opacities, bronchial wall thickening, and interlobular septal thickening.

F.Song et al. [35] showed that CT data reflect progression of the disease, including a higher incidence rate of consolidations. *Y.Pan et al.* [36] examined 63 patients and assessed their follow-up CT obtained 3 – 14 days after the initial CT scans. In more than 85% of patients, they found radiographic signs of disease progression, including larger areas of ground-glass opacity and consolidation and interlobular septal thickening. In some patients with lung lesions on the initial CT scans, re-examination CT showed that the lesions increased and enlarged, and some of them merged.

Table 1
Frequent symptoms and distribution of changes on computed tomography Images of patients (n = 919) with coronavirus infection [32]
Таблица 1
Частые симптомы и распределение компьютерно-томографических изменений у пациентов (n = 919) с коронавирусной инфекцией [32]

Signs / Findings	Number of publications	Number of cases (%)	Total number of patients
Bilateral involvement	12	435 (87.5)	497
Peripheral distribution	12	92 (76.0)	121
Predominantly in the posterior segments	1	41 (80.4)	51
Multilobar involvement	5	108 (78.8)	137
Ground-glass opacities	22	346 (88.0)	393
Consolidation	10	65 (31.8)	204

F.Pan et al. [37] reviewed the changes in CT findings over time in 21 patients with confirmed COVID-19. In most patients, CT performed at early stages revealed more ground-glass lesions and involvement of fewer pulmonary lobes than follow-up CT scans obtained at later stages. However, when patients were re-examined some time later, their CT showed progression of reticular changes (increase in the crazy-paving pattern), involvement of more pulmonary lobes, and consolidations. On average, the CT features were most prominent on day 10 from symptom onset. After day 14 positive changes were observed in 75% of the patients and included involvement of fewer pulmonary lobes, disappearance of the crazy-paving pattern, and resolution of consolidation.

Following the initial examination, the radiographic features of viral lung damage can evolve in several ways, including the following (Table 3) [3–5, 33, 39–42]:

- Reduction in lung involvement accompanied by improvement in pulmonary aeration and dissipation of consolidations into ground-glass opacities and subsequent complete recovery of aerated lung volume. This process is reminiscent of the typical resolution stage of community-acquired pneumonia.
- Reduction in lung involvement accompanied by more prominent consolidation and appearance of a typical organising pneumonia pattern.
- Stability or even an increase in lung involvement accompanied by more prominent consolidation and appearance of a typical organising pneumonia pattern or separate signs of organising pneumonia.

The first variant is the most favourable because it indicates resolution of viral lung damage usually without any residual abnormalities. The second variant indicates a typical reparative process manifested by signs of organising pneumonia that appear in the second phase of DAD. It is a longer process, which may lead to residual pulmonary abnormalities. The long-term prognosis for patients with such abnormalities is now difficult to predict due to little evidence and requires further research. Until these radiographic findings keep improving on follow-up CT scans, they should not be interpreted as "fibrosis" or "sclerosis", i.e. disease resolution with sequelae. As in community-acquired pneumonia, the duration of resolution of lung abnormalities is not limited and does not correlate with the clinical manifestations of the disease.

Table 2
Variants of radiological manifestation of novel coronavirus infection [33]
Таблица 2
Варианты рентгенологической картины новой коронавирусной инфекции [33]

Typical	Equivocal	Atypical
Multiple bilateral peripheral (subpleural) ground-glass opacities:	–	Lobar consolidation
• including those accompanied by consolidation		Focal lesions (including the tree-in-bud sign)
and/or		Space-occupying lesions. Lung cavitation and areas of consolidation
• the crazy paving sign		Signs of pulmonary oedema: uniform interlobular septal thickening and pleural effusion
Multiple bilateral rounded ground-glass opacities deep in the lung parenchyma:	–	Subpleural reticulation (a mesh pattern)
• including those accompanied by consolidation		Lymphadenopathy without lung lesions
and/or		
• the crazy paving sign		
Signs of organising pneumonia: areas of increased density (ground-glass opacities combined with consolidation) and the reversed halo sign	–	

The third variant of the evolution of radiographic findings may cause difficulty in differentiating positive and negative changes (Figure 4). If the previous examination was performed before the disease peaked, the time when peak lung involvement is reached, a follow-up image may mislead to a conclusion of disease progression. Clinical manifestations are the key to the interpretation of radiographic findings, which can be accurately assessed only in combination with the clinical picture. If respiratory failure does not become more severe, it indicates regression of the disease, even if the changes in radiographic findings seem to be negative. Radiographic signs have some value too. The signs of OP may be suggestive of disease regression. Worsening of ground-glass opacities, consolidations, reticular changes, and, in many cases, pleural effusion without sings of OP more likely suggests negative evolution.

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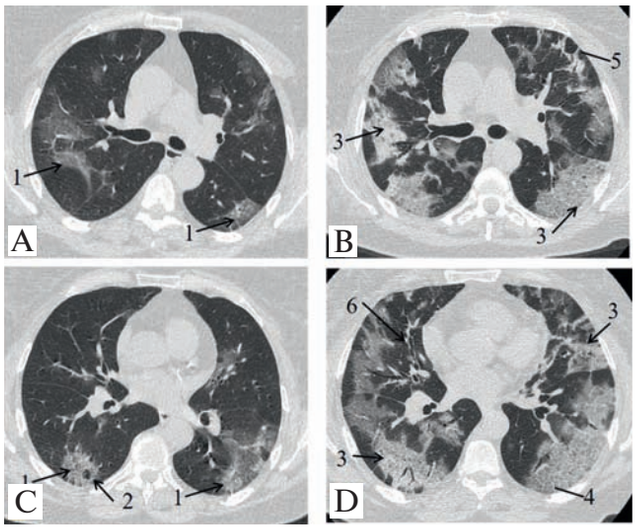

Figure 4. Patient N., 61 years. Moderate COVID-19. Computed tomography, axial slices; A, B, 8th, and C, D, 15th days of the disease. Clinically the patient is stable. A, B, few subpleural inhomogeneous ground glass foci (1) with sporadic secondary lobules with preserved aeration (2). Damaged pulmonary area is about 40%; C, D, multiple confluent areas of increased attenuation (3) predominantly on the periphery; crazy paving symptom (4), perilobular reticular pattern (5), dilated segmental bronchi (6). The lung involvement is about 70%

Рис. 4. Пациентка Н., 61 год. Среднетяжелое течение COVID-19. Компьютерно-томографические аксиальные срезы: А, В – 8-е, С, D – 15-е сутки заболевания. Клинически состояние пациентки стабильное. А, В – немногочисленные субплевральные негомогенные участки «матового стекла» (1) с единичными вторичными дольками с сохраненной воздушностью (2) в их структуре. Площадь поражения легочной паренхимы – около 40 %; С, D – множественные сливные фокусы снижения воздушности легочной паренхимы (3), преимущественно в периферических отделах легких; симптом «булыжной мостовой» (crazy paving) (4), уплотнение перилобулярного интерстиция (5), расширенные просветы сегментарных бронхов (6). Площадь поражения легочной паренхимы – около 70 %

Assessment of the extent of lung involvement

From the prognostic point of view, it is important to assess not only the nature of radiographic findings, but also their extent Assessment of the extent of lung involvement in patients with coronavirus infection can be based on:

- imaging data;
- data obtained using various semiquantitative scales;
- data collected using software for lung density analysis and generation of maps of lung density distribution, including computer-aided design (CAD) and artificial intelligence software solutions.

The literature describes a number of similar scales, developed to improve the early diagnosis of the coronavirus infection and assess its severity more accurately (Tables 4, 5). These scales are almost identical in terms of content and differ only in the total score [36, 40, 42]. It is worth noting that they do not usually consider the type of lung abnormalities (ground-glass opacities and consolidation), except for a 64-point scale developed by *F.Feng et al.* [44]. Their practical application is, however, hindered, because there is an increasing number of publications suggesting the absence of a direct correlation between the severity of clinical manifestations and the nature and extent of lung injury as assessed by CT [45, 46]. It should also be emphasised that such scoring systems are based on the experience of individual researchers, which leads to some inaccuracy of the results when using them in the general population.

Such semiquantitative assessment of the severity (volume and extent) of CT-diagnosed lung abnormalities associated with COVID-19 is possible, but it is not mandatory. These scales can be used by medical facilities as part of an agreed and approved treatment protocol for COVID-19 patients.

A group of Dutch researchers has proposed an assessment scheme for analysing pulmonary findings in patients with suspected COVID-19, using likelihood ratios (CO-RADS), and presented it on the Radiology Assistant website [47] (Table 6). It was developed as an analogue to previously existing scoring systems (PI-RADS, BI-RADS, etc.), which aim to standardise the assessment of likelihood of a certain diagnosis. Since the CO-RADS is not well known to practitioners and not widely used in inpatient facilities, it has no advantages over semiquantitative scales for assessment of lung abnormalities.

Correlation between imaging findings and infection severity

CT does not assess the severity of the disease and can only provide indirect indicators of its prognosis. Although specialists widely use such terms as “severity of CT findings”, “severity grading of CT findings”, and “severity grades of CT features, such as CT0, CT1, CT2, CT3, CT4, and sometimes CT5”, these data primarily reflect the extent of lung involvement. They poorly correlate with the clinical assessment of the severity of the patient’s condition at the time of CT examination, including such key parameters as the severity of respiratory failure and the degree of desaturation [45, 46].

Multiple publications have reported that patients with severe disease more often have more widespread lung involvement and more frequently develop certain symptoms, for example, reticular changes or pleural effusion. This does not, however, mean that patients with extensive CT or X-ray abnormalities are in critical condition. Importantly, lung lesions can also be found in a considerable number of asymptomatic patients. In the study conducted by *S.Inui et al.*, of 104 cases of coronavirus infection, 76 (73%) were asymptomatic, 41 (54%) of which had pneumonic changes on CT [49]. Our pilot analysis of radiographic and clinical manifestations of 92 patients with COVID-19 showed that two patients (6.9%) with mild infection had extensive lung lesions on a follow CT with > 50% lung involvement, while they did not demonstrate any clinical signs of respiratory failure.

In addition, our own unpublished data demonstrate that bronchodilation on CT obtained at presentation (6.7 ± 2.8 days from onset of the disease) was the only sign that was strongly correlated with the severity

Table 3
Typical dynamics of pulmonary X-Ray and Computed tomography changes COVID-19 pneumonia [33]
Таблица 3
Типичные изменения рентгенографической и томографической картины легких в динамике развития пневмонии, обусловленной COVID-19 [33]

Evolution of changes	Radiographic and CT features
Early signs observed in the first few days	Multiple bilateral peripheral (subpleural) ground-glass opacities, including those accompanied by consolidation
	and/or
	the crazy paving sign
	Multiple bilateral rounded ground-glass opacities deep in the lung parenchyma, including those accompanied by consolidation and/or the crazy paving sign
	Areas of increased density (ground-glass opacities combined with consolidation) and the reversed halo sign
Improvement of changes (stable disease)	Development of ground-opacities into consolidation (an increase in density of the affected lung tissue) without evident increase in total lung involvement (extent of disease)
	Emerging signs of organising pneumonia
	Reduction in size of lung opacities
Progression of changes (worsening)	Progressive changes (Figure 1):
	• expansion of ground-glass opacities (extent and volume of lung involvement)
	• appearance of new ground-glass lesions
	• fusion of some ground-glass opacities into larger lesions and progression to subtotal lung involvement in the most severe cases
	• ground-glass opacities are still more extensive than consolidations
	• Development of new signs of other pathologies:
	• left ventricular failure (cardiogenic/hydrostatic pulmonary oedema, bilateral pleural effusion)
	• respiratory distress syndrome (pulmonary oedema)
	• bacterial pneumonia
	• lung abscess and multiple septic emboli
	• pneumothorax and pneumomediastinum
	• other
Respiratory distress syndrome	Common features include:
	• Bilateral subtotal opacities (consolidations and ground-glass opacities)
	• Involvement of the upper and middle lung zones
	• Hyperinflation of basal segments
	• Gradients in lung density, depending on the patient's position (supine, prone)
	• The air bronchogram sign
	The following signs are usually absent (in the absence of circulatory failure):
	• Kerley lines, peribronchial cuffs
	• Enlargement of the left heart and increased vascular pedicle width
	• Pleural effusion
Resolution	Radiographic signs include:
	• Reduction in size of consolidations and ground-glass opacities (the signs of organising pneumonia may not be present)
	• Appearance of typical CT signs of organising pneumonia and changes in the size and configuration of ground-glass opacities and consolidations
	Additional signs:
	• Radiographic signs of resolution should correlate with the evolution of clinical manifestations
	• Radiographic features of lung damage may persist significantly longer than clinical manifestations of the infection
	• The presence of residual lung opacities cannot guide the duration of treatment for this infection and do not constitute an indication for continued treatment if not accompanied by clinical signs of acute inflammation

Table 4
Lung Severity Score scale [42]
Таблица 4
Шкала степени поражения легких [42]

Degree of lung involvement, %	Score
0	0
1 – 25	1
26 – 50	2
51 – 75	3
76 – 100	4

Table 5
Chest computed tomography severity score scale [43]
Таблица 5
Шкала тяжести поражения легких по данным компьютерной томографии [43]

Findings	Score
Normal attenuation	0
Ground-glass attenuation	1
Consolidation	2
20 segments (modified classification: 19 lung segments, with one segment being divided into two)	
Maximum total score: 40 points (20 × 2)	
Interpretation:	
The total score of 19.5 or above was predictive of a severe course with a 83.3% sensitivity and a 94% specificity	

Table 6
CO-RADS scale [47, 48]
Таблица 6
Шкала категориальной схемы компьютерной томографии для пациентов с подозрением на COVID-19 [47, 48]

CO-RADS score	Level of suspicion of COVID-19 infection	CT findings
1	Very low	Normal or non-infectious abnormalities
2	Low	Abnormalities consistent with infections other than COVID-19
3	Indeterminate	Unclear whether COVID-19 is present
4	High	Abnormalities suspicious for COVID-19
5	Very high	Typical COVID-19
6	PCR*	

of COVID-19 ($p < 0.001$), worsening of clinical status ($p < 0.001$), and an increase in the extent of pulmonary involvement ($p < 0.001$). Other CT findings revealed at initial examination (ground-glass opacity, consolidation, and crazy paving sign) did not show any correlation with the severity of clinical status and had no prognostic value for predicting the worsening of the clinical status. This is indirectly confirmed by some clinical observations of patients with radiographic patterns of similar nature and extent showed different clinical course of COVID-19.

In literature, there is no consensus regarding the prognostic value of separate CT findings. *P.Lyu et al.* showed that the volume of areas with consolidation and the extent of the crazy-paving pattern were significantly greater in severe cases than in mild cases of COVID-19 [50]. The study by *F.Liu et al.* demonstrated the prognostic value of the extent of ground-glass opacities for predicting the worsening of clinical status. The most common sign reported in this study was a combined pattern (any combinations of ground-glass opacities and consolidation) [51].

Correlation between polymerase chain reaction results and chest computed tomography findings

In most studies, CT findings were generally correlated with PCR results [1, 4–6, 52]. There have been, however, some publications reporting positive CT findings despite the negative result of the initial screening PCR test. In the study by *X.Xie et al.* [52], five out of 167 patients with negative initial PCR tests had typical CT features of COVID-19 pneumonia. In all these five patients PRC became positive 2 – 8 days after CT examination. In contrast, seven out of the 167 patients had a normal initial CT, despite a positive initial PCR. Within five days after the initial CT, imaging signs of viral pneumonia were observed in one of these patients, while the follow-up data of the other six patients were not reported. Similarly, *M.Chung et al.* [40] reported that in their study three of 21 patients with a confirmed diagnosis did not have ground-glass opacities or consolidation on their initial CT scans but at the time of re-examination two of them demonstrated positive CT findings. No information was reported about the results of their confirmatory laboratory tests.

H.Kim et al. [53] performed a meta-analysis to evaluate diagnostic values of chest CT and PCR. For chest CT scans, the positive predictive value (PPV) ranged from 1.5 to 30.7%, and the negative predictive value (NPV) ranged from 95.4 to 99.8%. For PCR, the PPV ranged from 47.3 to 96.4%, whereas the NPV ranged from 96.8 to 99.9%. The authors reported that the pooled sensitivity was 94% for chest CT and 89% PCR. The pooled specificity for chest CT was only 37% (95% CI: 26, 50%). The authors suggested that considering a low specificity of CT there is a large gap between PPV levels of chest CT and PCR in low-prevalence regions, especially in areas with a prevalence less than 10%.

These data suggest a high probability of false positive CT findings. This obviously dictates the need for fol-

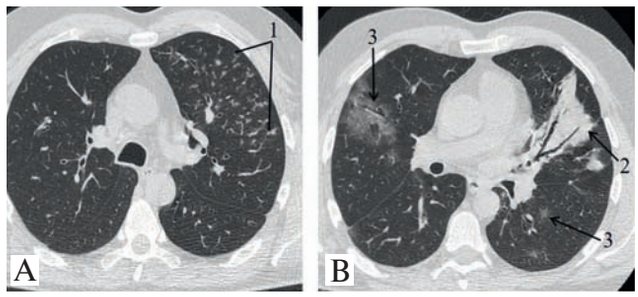

Figure 5. Patient A. 48 years. Moderate COVID-19, complicated by bacterial superinfection. Computed tomography, axial slices, 14th day of the disease. Bronchopneumonia features: tree-in-bud sign (1) in the upper left lobe, segmental consolidation with air bronchogram (2). COVID-19 features: bilateral round-shaped foci of ground glass (3)

Рис. 5. Пациент А., 48 лет. Среднетяжелое течение COVID-19, осложнившееся присоединением бактериальной инфекции. Компьютерная томограмма, аксиальные срезы, 14-е сутки заболевания: признаки бронхопневмонии – симптом «дерево в почках» (1) в верхней доле левого легкого; участок консолидации с воздушной бронхограммой (2). Признаки COVID-19 – билатеральные участки «матового стекла» округлой формы (3)

low-up examinations of people with confirmed disease, resulting in higher healthcare costs and an increasing burden on the healthcare system, as well as growing anxiety on the part of each individual patient and the general population. Moreover, patients with chest CT findings that are only suspicious of COVID-19 could be placed in quarantine, which may cause household problems, difficulties arranging care for children, disabled individuals, or elderly people, or delays in scheduled medical appointments and procedures.

Imaging and etiological diagnosis

Imagining modalities have a high sensitivity for lung involvement in cases suspected for COVID-19. Nevertheless, all of them, including CT, show a low specificity because the same findings can be observed in different lung infections. Certain radiographic findings and their combinations (Table 2) suggest the presence of COVID-19 with a certain probability [33]. The differential diagnosis should primarily include other types of viral pneumonia caused by other coronaviruses (SARS and MERS) and adenoviruses [2, 54, 55].

Pneumonia caused by influenza viruses, adenoviruses, and pneumoviruses (respiratory syncytial virus and human metapneumovirus) may have CT features similar to those of COVID-19. However, they rarely manifest by subpleural lesions. In addition, due to certain pathogenetic factors ground-glass opacities or consolidations can develop in the centrilobular regions [55].

Complications of the novel coronavirus infection (COVID-19)

The following complications of COVID-19 that should be kept in mind while interpreting chest CT findings include: pulmonary embolism (PE), in situ thrombosis of pulmonary vessels, acute heart failure with cardiogenic pulmonary oedema, bacterial superinfection (Figure 5), exacerbation or worsening of chronic lung disease, and treatment complications (pneumothorax, pneumomediastinum, and hematomas) (Figure 6).

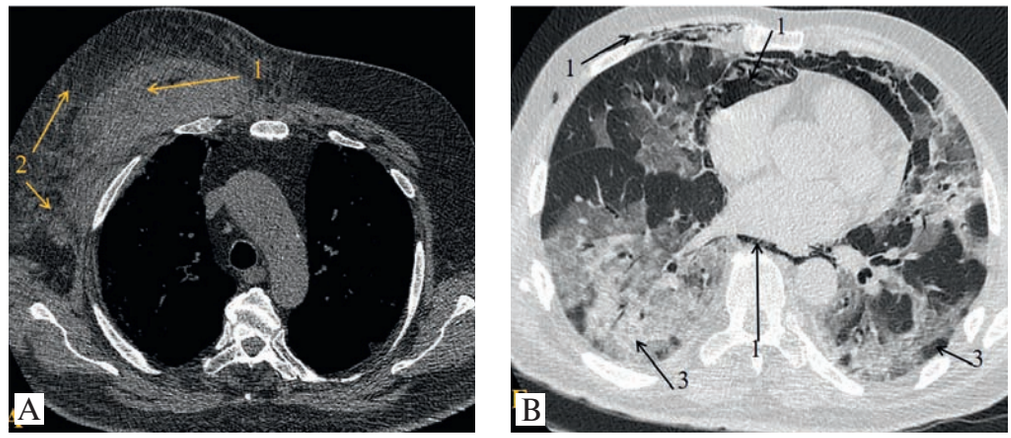

Figure 6. Consequences of the therapy in several patients with severe COVID-19: A, patient T. 74 years, in the intensive care unit department, mechanical ventilation in prone-position. Clinically there is a hematoma at the anterior wall of the right hemithorax. CT, axial slices, 9th day of the disease. Right thoracic muscles are increased in volume (1); stranding and oedema of the anteriolateral subcutaneous fat tissue (2); B, patient K. 74 years, in the intensive care unit department on the mechanical ventilation. CT, axial slices, 2nd day of the disease. Pneumomediastium (1), subcutaneous emphysema (2). Subtotal increased attenuation of the lung parenchyma (3)

Рис. 6. Последствия проводимой терапии у некоторых пациентов с тяжелым течением COVID-19: А – пациент Т., 74 лет, находится в отделении реанимации и интенсивной терапии, проводится искусственная вентиляция легких в прональной позиции. Объективно у пациента определяется обширная гематома правой половины грудной клетки. Компьютерная томограмма, аксиальный срез, 9-е сутки от начала заболевания: правые грудные мышцы увеличены в объеме (1); подкожно-жировая клетчатка переднелатеральной поверхности правой половины грудной клетки отечна, тяжиста (2); В – пациент К., 74 лет, находится в отделении реанимации и интенсивной терапии, проводится искусственная вентиляция легких. Компьютерная томограмма, аксиальный срез, 2-е сутки от начала заболевания. Пневмомедиастинум (1), эмфизема мягких тканей (2). Субтотальное уплотнение легочной паренхимы (3) по типу «матового стекла» и консолидации

Pulmonary embolism and in situ thrombosis are associated with endothelial damage, systemic inflammatory reaction, and, as a consequence, hypercoagulation [24, 56]. Suspected PE is an absolute indication for CT angiography. It is, however, rather difficult to suspect thromboembolism in the absence of its typical clinical signs because markers of clot formation are elevated due to COVID-19.

Conclusion

Cardiogenic oedema is another complication of COVID-19. Its manifestation can be associated both with a direct cytotoxic effect of the virus on the myocardium and vascular endothelium and exacerbation of chronic heart failure [57–59]. CT findings include bilateral subtotal consolidations and ground-glass opacities with air bronchogram located in the middle and upper lung zones and intralobular, interlobular, and peribronchovascular interstitial thickening. There are also gradients in lung density, depending on the patient's position (supine, prone) and hyperinflation of basal segments. As circulatory failure progresses, pulmonary abnormalities also become more prominent, patients develop plural effusion (unilateral or bilateral), and enlargement of the left heart becomes visible by imaging modalities [33, 60].

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Ultrasound of the lungs as an actual research method in the conditions of a new coronavirus infection SARS-CoV-2

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Abstract

A literature review of the main issues of ultrasound diagnosis during the period of the SARS-CoV-2 coronavirus infection pandemic. The review shows the key aspects of ultrasound, the experience of foreign colleagues, reflecting the basic principles of ultrasound diagnostics when working with infected patients, the methodology of the distribution of people into the streams with their increased admission to hospitals in a pandemic.

Key words: ultrasound diagnostics, coronavirus infection, ultrasound of the lungs, COVID-19, pneumonia, pandemic.

Conflict of interests. The authors declare the absence of conflict of interests.

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Ультразвуковое исследование легких: актуальный метод в условиях новой коронавирусной инфекции SARS-CoV-2

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Резюме

Представлен обзор литературы по основным аспектам проведения ультразвукового исследования легких у больных в период пандемии коронавирусной инфекции SARS-CoV-2, основанным на опыте ведущих научных центров разных стран. Продемонстрирована перспективность применения данного метода у больных с патологией легких, особенно в условиях подобной пандемии.

Ключевые слова: ультразвуковая диагностика, коронавирусная инфекция, ультразвуковое исследование легких, COVID-19, пневмония, пандемия.

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

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It is hard to imagine current real-life clinical practice without a wide use of imaging diagnostic techniques, particularly ultrasonography (U/S). In recent years, suspected pulmonary abnormalities have been considered as indications for this examination. This method has a whole range of attractive features, such as availability, non-invasive nature, painfulness, absence of direct contraindications, relative easy to use, lack of need for patient preparation, safety, and harmlessness due to its free-radiation nature, demonstrated in a number of studies. These features make it possible to use lung U/S in a wide range of patients, including pregnant and lactating women, adults, children, and patients with implanted pacemakers, metal implants, and other foreign bodies. This modality has become especially popular in these days, when the world is being affected by a "novel" infection and the number of hospitalised patients has risen dramatically.

It is well known that multiple cases of pneumonia of unknown etiology were first reported in workers of the Huanan Seafood Market selling meat and fish, in the Chinese city of Wuhan, in December 2019. On 1 December 2019 the Chinese authorities reported the spread of pneumonia of unknown etiology to the World Health Organisation (WHO). On 30 January 2020 WHO declared multiple cases of coronavirus infection as a public health emergency of international concern. On 11 February 2020 the disease was named COVID-19, which states for coronavirus disease-2019. The International Committee on Taxonomy of

Viruses (ICTV) announced "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)" as the name of the virus causing this infection [1].

Coronavirus infection is an acute viral disease with a primary lesion of the upper respiratory tract caused by single-stranded, positive-sense RNA virus, belonging to *Betacoronavirus* of the family *Coronaviridae*. It has been spreading around the world in 2019 and 2020, and has been responsible for a huge number of deaths and enormous economic losses [2].

Of note, the identified pathogen was first described as early as the middle of the 20th century. By January 2020, *Coronaviridae* was already viewed as a separate family of viruses including 40 species of enveloped RNA viruses. This family is organised in two sub-families of viruses which infect humans and animals. These viruses are named for the large club-like spikes protruding from their envelope like the spikes of a crown. The latter mediates coronavirus entry through the cell membrane by mimicking molecules to which transmembrane cell receptors bind [1, 2].

At present, there are four known coronaviruses circulating in the human population (HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1), which are always reported among pathogens causing acute respiratory viral infections (ARVI) and are often responsible for mild or moderate respiratory disease. This virus has been classified as a hazard group (HG) 3 pathogen (which corresponds to HG2 in the Russian classification). The virus enters the human body through epithelium in the upper respiratory tract, stomach and intestine. The pathophysiology involves an increased permeability of cell membranes and enhanced outflow of albumin-rich fluid into alveoli caused by the virus. This leads to degradation of surfactant, resulting to alveolar collapse and acute respiratory distress syndrome. Concomitant immunosuppression contributes to the development of opportunistic bacterial and fungal respiratory infections [2].

Computed tomography (CT) is the most informative and highly accurate imaging modality that produces the most detailed images possible of thoracic organs and allows for staging of the disease (classifying it into one of the five stages). It is used in the second step of the diagnostic pathway to confirm the diagnosis after an initial chest radiography has been performed [3].

The high number of infected people in the Russian Federation (as of 8 June 2020 there were 476,658 documented cases) [4] and the resulting enormous burden on the healthcare system suggest the need for the development of additional optimal diagnostic algorithms for pneumonia. The list of mandatory diagnostic examinations. provided in the 2019 Russian Clinical Treatment Guidelines for Pneumonia, does not include ultrasonography (U/S). The provision related to performing lung ultrasonography in 2020 during the COVID-19 pandemic has, however, been modified by including a provisional guidance allowing specialists to use ultrasound to detect pneumonia in the COVID-19 environment [5]. The greatest advantages of this technique involve the following:

- it can be used as a bedside method and in resuscitation divisions;
- it is radiation-free;
- ultrasound devices are easy to disinfect.

There is general agreement that U/S is not acceptable for assessment of lung parenchyma because of a high volume of air in the alveoli and the fact that ultrasound waves are largely scattered in air media. This is, however, true for normal lung tissue, but pathological processes, for example pulmonary oedema, are associated with changes in pulmonary resistance, leading to the appearance of typical structures visualised by ultrasound [6].

The first reports about visualization of lung tissue in pneumonia were made by the Russian scientist *Y.Bogin* as early as fifty years ago [7]. At that time, visualisation of the chest was possible by applying transducers along the standard lines. On ultrasound images pneumonia appeared as inhomogeneous opacities in lung parenchyma [7]. At present, ultrasonography easily differentiates tissues from fluid-filled structures, which appear as diffuse opacities on radiographic images.

Diagnostic ultrasonography can be helpful in obtaining the following clinically important information:

- to detect pleural effusion, to determine the amount of fluid and its relationship to the chest wall, and to choose the optimal puncture point for thoracentesis;
- to detect pleural empyema (its location and extent);
- to detect pneumonia (determine the location, extent, and patterns of pneumonic lesions, identify potential complications, and assess residual abnormalities in the lungs and pleura after achievement of clinical cure);
- to carry out dynamic follow-up of pulmonary and pleural disorders and evaluate the efficacy of treatment;
- to perform differential diagnosis between malignant and benign tumours of the lungs and pleura;
- to monitor the status of the pleural cavity, the degree of lung expansion, and the development of fibrothorax following surgical procedures on the lungs and pleura; and to assess the outcomes of surgical treatment [8].

Ultrasound diagnosis of pneumonia is mainly based on the use of the BLUE (Bedside Lung Ultrasound in Emergency) protocol. In fact, it is a bedside lung ultrasound protocol for emergency situations, which was proposed by *D.A.Lichtenstein* in 2008. This protocol was developed as a 3-minute screening tool to identify the causes of acute respiratory failure in intensive care unit patients. It allows for the differentiation between some pathologies, such as pneumothorax, pulmonary oedema, pulmonary embolism, pneumonia, chronic obstructive pulmonary disease, and asthma [6].

To be able to detect abnormal lung parenchyma on ultrasound scans, it is necessary to have a good understanding of the normal ultrasound lung pattern. In Russia, ultrasound diagnostic procedures are allowed to be performed by doctors specialising in ultrasound diagnostics [9], anaesthesiology and resuscitation [10], emergency medicine [11], or cardiology [12]. The accuracy of the examination depends on the correct choice of a transducer for a particular area of interest. There are three types of transducers: linear with a frequency range of 5 – 15 MHz and the maximum depth of penetration of 10 cm, standard convex with a frequency range of 2 – 7.5 MHz and the maximum depth of penetration of 25 cm, and sector

with a frequency range of 1.5 – 5 MHz. These types have different ratios of the frequency and depth of penetration. Convex and sector transducers can be used to visualise deep structures, while linear transducers are suitable for visualisation of the pleura [13].

Ultrasound examination is most often performed in supine position, but can also be done in semi-recumbent or lateral positions. Each lung is divided into three zones (anterior, lateral, and posterior) delineated by the parasternal, anterior axillary, posterior axillary, and paravertebral lines.

The ultrasound transducer is placed longitudinally over a lung intercostal space (LIS). Scanning begins anteriorly cranially and progress down to the diaphragm along the parasternal line, with each LIS being scanned. The anterior axillary, posterior axillary, and paravertebral areas are examined in the same way. If any abnormalities are detected in any LIS, this space should be examined more thoroughly.

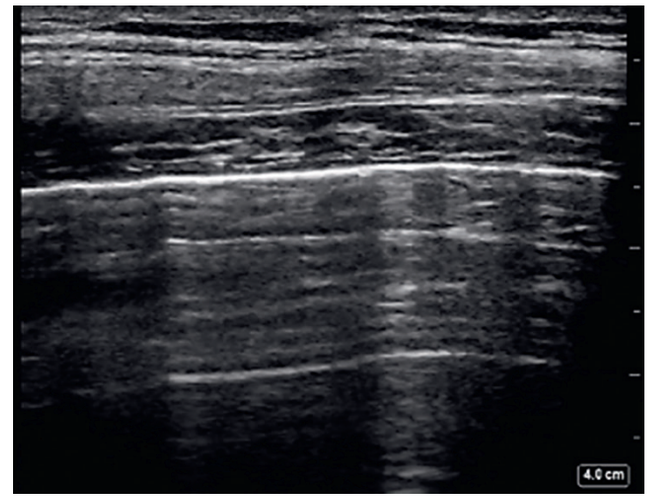

Figure 2. Symptom of pneumothorax of the lung [14]

Рис. 2. Признак пневмоторакса легкого [14]

Key landmarks

The *pleural line*: a thin line representing the pleura, which is seen as a hyperechoic line below the ribs and moves with breathing (Figure 1).

A-lines: repetitive, horizontal, linear arterfacts located at regular intervals behind the pleural line and accompanied by lung sliding; these are signs of the normal lung pattern. A-lines not accompanied by lung sliding are indicative of pneumothorax. *Lung sliding* (demonstrated in B-mode) represents motion of the visceral pleura. This sign is indicative of the normal lung pattern and the absence of pneumothorax (Figure 2).

B-lines: single (⩽ 3 in one LIS) hyperechoic vertical artefacts that originate from the pleural line and appear as a comet tail. They move in synchrony with lung sliding and look like a laser beam. B-lines are indicative of normal lung (Figure 3); however, an increased number of B-lines (> 3 in one LIS) is a marker of pulmonary oedema (interstitial syndrome) (Figures 4, 5). Of note, the detection of B-lines is not 100% specific to COVID-19-associated pneumonia [5].

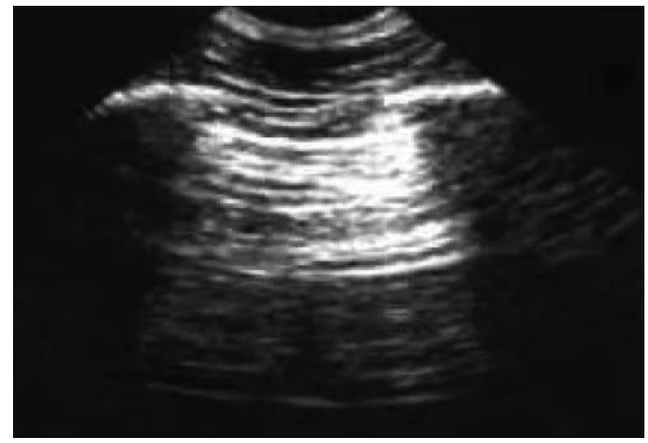

Figure 3. Normal lung [14]

Рис. 3. Нормальное легкое [14]

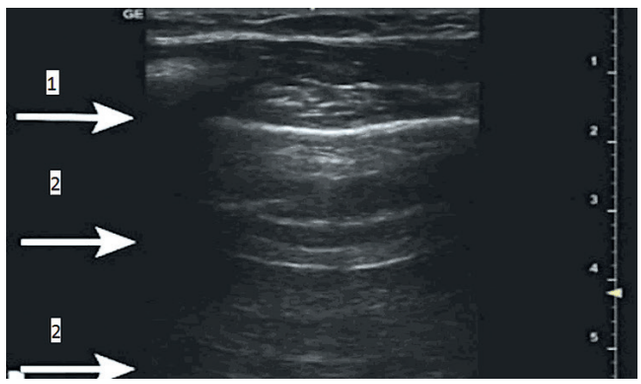

Figure 1. Pleural and A-lines: 1, pleural line; 2, A-line (changes, [14])

Рис. 1. Плевральная и А-линии: 1 – плевральная, 2 – А-линии (с изм., [14])

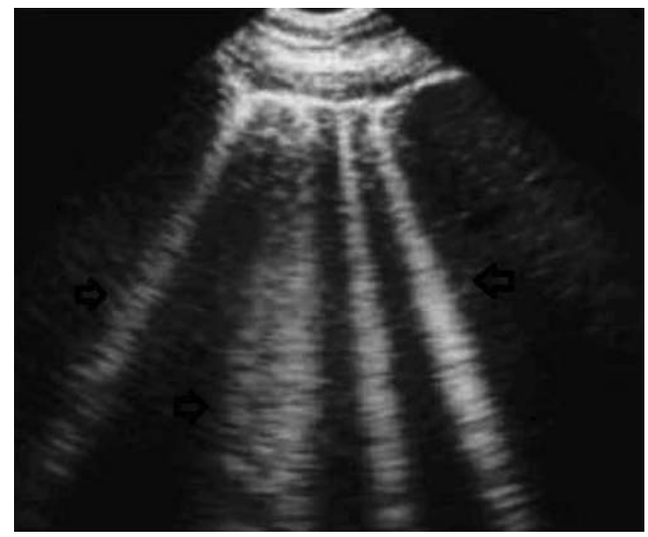

Figure 4. A sign of interstitial pulmonary edema. The arrows indicate B-lines [14]

Рис. 4. Признак интерстициального отека легкого. Стрелками указаны В-линии [14]

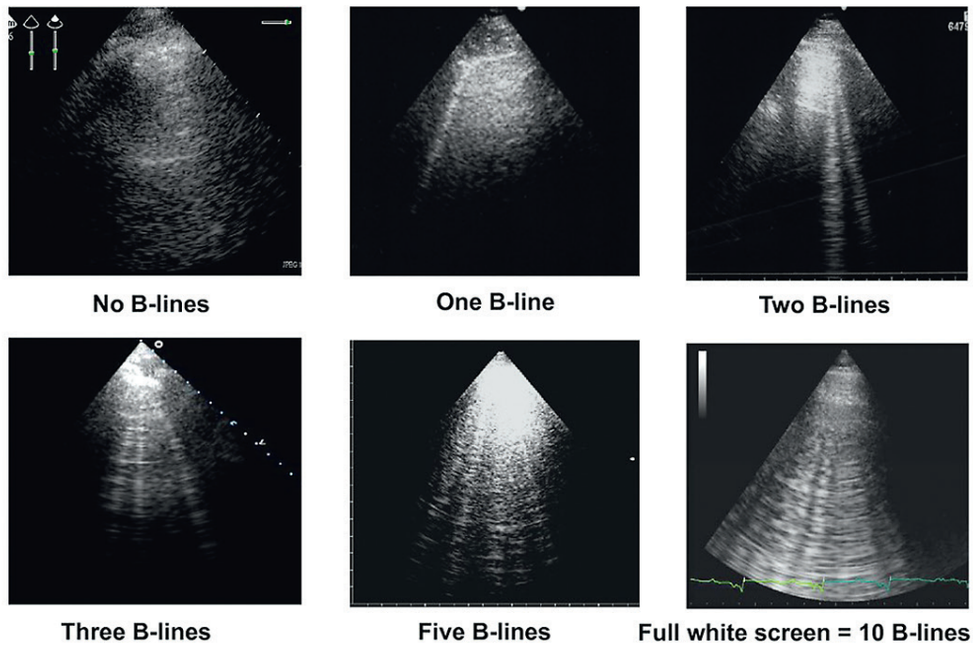

Figure 5. Single and multiple presence of B-lines in the ultrasound picture of the lung [14]
Рис. 5. Единичные и множественные В-линии при ультразвуковом исследовании легкого [14]

The «sea coast» (*Seashore Sign*) (demonstrated in M-mode) is indicative of normal lung sliding and rules out pneumothorax (Figure 6).

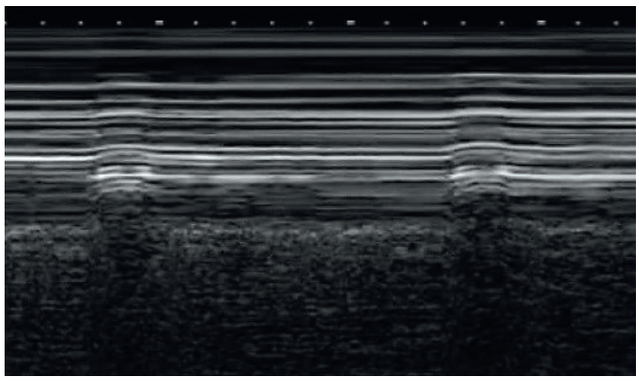

Figure 6. Sign of the “sea coast” in M-mode [14]
Рис. 6. Признак «морского берега» в М-режиме [14]

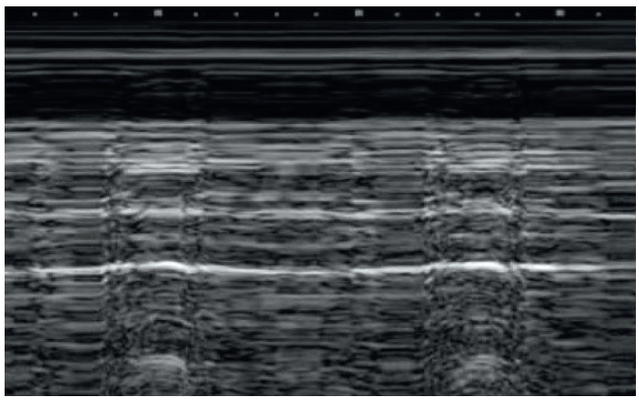

Figure 7. Barcode sign in M-mode [14]
Рис. 7. Признак «штрихкода» в М-режиме [14]

The *barcode sign* (demonstrated in M-mode) indicates the absence of lung sliding and the presence of pneumothorax (Figure 7).

The *quad sign* (*The Quad Sing*) (demonstrated in B-mode) is indicative of pleural effusion. It consists of lines representing the parietal pleura (pleural line), visceral pleura (lung line), and ribs on both sides (Figure 8).

The *sinusoid sign* (*a sign of pleural effusion demonstrated in M-mode*) indicates the movement of the lung line toward the pleural line on inspiration (Figure 9).

The *tissue-like sign*, also known as *lung hepatisation*, indicates lung consolidation (Figure 10). On ultrasound scans, lung tissue takes the appearance of liver tissue.

The *shred sign*, also known as the *fractal sign*, consists of an irregular (shredded) deep border (fractal line) of an area of consolidation. It appears as a hyperechoic border between the consolidated and normal lung tissue (Figure 11).

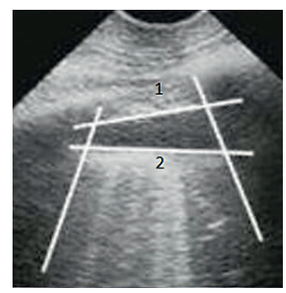

Figure 8. Pleural effusion in B-mode: 1, pleural line; 2, line of the lung (changes, [14])
Рис. 8. Плевральный выпот в В-режиме: 1 – плевральная линия, 2 – линия легкого (с изм., [14])

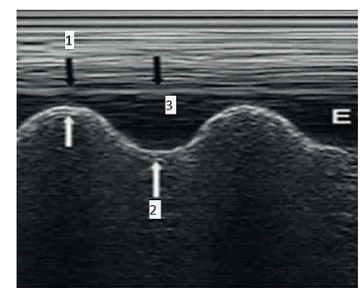

Figure 9. Pleural effusion in M-mode: 1, pleural line; 2, line of the lung; 3, fluid (changes, [14])
Рис. 9. Плевральный выпот в М-режиме: 1 – плевральная линия, 2 – линия легкого, 3 – жидкость (с изм., [14])

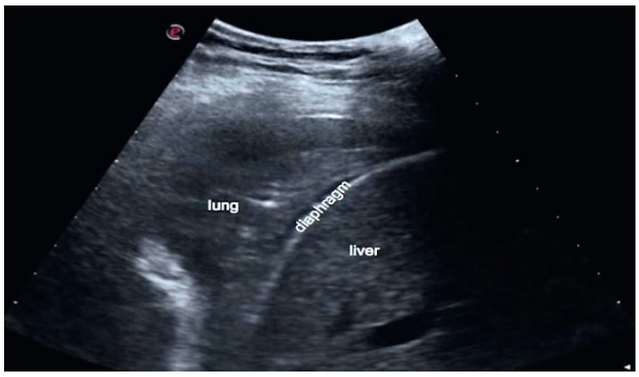

Figure 10. Lung consolidation [14]
Рис. 10. Консолидация легкого [14]

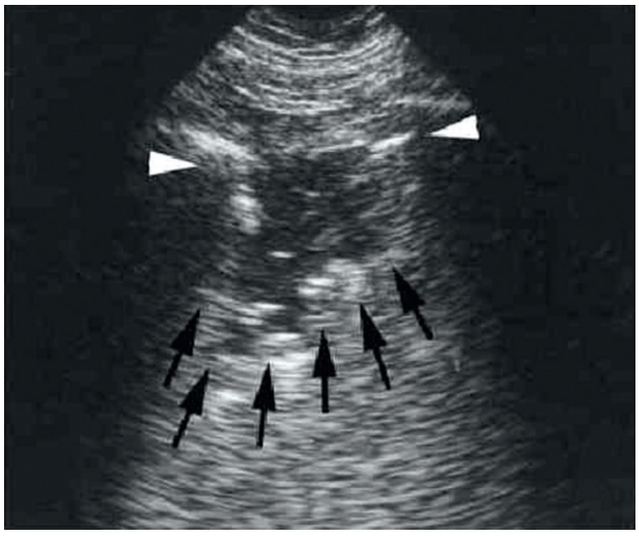

Figure 11. The arrows indicate an uneven, torn line (changes, [14])
Рис. 11. Стрелками указана неровная, рваная линия (с изм., [14])

The key ultrasound signs of COVID-19-associated pneumonia include:

- Irregularity, thickening, and fragmentation of the pleural line and absence of the pleural line along the border of consolidation;
- Appearance of B-lines in a variety of patterns (single, multiple, confluent, i.e. white lung appearance);
- Appearance of A-lines during recovery phase;
- Pleural effusion: uncommon and usually not abundant. It can be of various shape and size, which depends on the amount and distribution of fluid in the pleural cavity;
- Various types of consolidation lesions: local cortical, extended cortical, segmental or lobar [15].

The ultrasonographic features of SARS-CoV-2 pneumonia are related to the stage of disease, the severity of lung injury, and comorbidities. The predominant pattern is varying degrees of interstitial syndrome and alveolar consolidation, the degree of which is correlated with the severity of the lung damage. A recognized limitation of lung ultrasonography is that it cannot detect lesions that are deep within the lung, despite the potential of modern transducers, i.e., the abnormality must extend to the pleural surface to be visible with on ultrasonography examination. Chest CT is required to detect pneumonia that does not extend to the pleural surface [15].

International experience with lung ultrasound

Italian specialists developed a primary assessment protocol to evaluate the health status of people with suspected coronavirus infection. They recommended scanning 14 areas in each patient for 10 s [16], making these scans covering the widest possible surface area. Each area was scored on a 0 – 3 scale, as follows: A score of 0 is given when the pleural line is continuous and regular, with the presence of horizontal artefacts, usually referred to as A-lines. A score of 1 is given when the pleural line is indented, with vertical areas of white visible below. A score of 2 is given when the pleural line is broken and there are small to large areas of consolidation (darker areas) under the broken site with associated areas of white below (white lung pattern). An area is given a score of 3 when the scan shows dense and largely extended white lung tissue, with or without bigger consolidations.

Bedside ultrasound allowed for faster examination, which helped timely assess the need for hospitalisation. This examination was performed in more than 60.000 patients with signs of inflammation (fever and cough) to rule out pneumonia. One of such studies included twelve patients with flu-like symptoms and suspected COVID-19 (nine men and three women; mean age ± standard deviation, 63 ± 13 years old, who were admitted to the Guglielmo da Saliceto Hospital over a period of 4 – 10 days. In two patients ultrasonography detected pulmonary emphysema without concomitant respiratory failure, and three patients had posterior subpleural consolidations. Chest CT scan was performed in all patients and showed a strong correlation with U/S: Five of 12 patients had a crazy-paving pattern, i.e. a combination of ground-glass opacity and interlobular septal thickening. Organizing pneumonia was confirmed in four patients. Lung ultrasound was done by two physicians: one was responsible for the technical procedure, and the other interpreted the images obtained, which also contributed to faster detection of abnormalities [17].

A similar procedure was introduced in a paediatrics department for the evaluation of children with suspected COVID-19, based on the use of lung ultrasound by one paediatrician and another assistant. The paediatrician prepared the ultrasound pocket device, which comprised a wireless probe and a tablet. The probe and tablet were placed in two separate single-use plastic covers. The paediatrician used the probe and did the lung ultrasound, the assistant held the tablet and froze and stored the images, touching neither the patient nor the surrounding materials. The stethoscope was not used because there was a probability to mistakenly touch the patient's mucous membranes with it. This ultrasound procedure was therefore substituted for lung auscultation and significantly reduced doctors' risk of exposure [18].

The National Health Service in England did not even mention lung ultrasound in its clinical guidelines on triage of patients with COVID-19, specifying instead chest X-ray

and CT as the first-line diagnostic imaging tools for equivocal cases [16].

Experts of the People's Republic of China (PRC) have recommended performing early chest CT before clinical manifestations for screening suspected patients. However, the high contagiousness of SARS-CoV-2 and the risk of transporting unstable patients with hypoxemia and hemodynamic failure made chest CT a limited option for the patient with suspected or established COVID-19. This explained the introduction of lung ultrasound, which is still an important diagnostic tool even if it has not yet been fully evaluated [15].

Chinese specialists reported that lung ultrasonography gives the results that are similar to those of chest CT and superior to standard chest radiography for evaluation of pneumonia and/or adult respiratory distress syndrome with the added advantage of ease of use at point of care, repeatability, absence of radiation exposure, and low cost. It is useful for rapid assessment of the severity of SARS-CoV-2 pneumonia, detecting the signs of disease progression, and assessing the need for extracorporeal membrane therapy and ventilatory support.

A comparative study of lung U/S and chest CT on a group of 20 patients with COVID-19 demonstrated specific features that can be detected by each of these imaging modalities (see Table) [15].

Table
Computed tomography and ultrasonographic features of COVID-19 pneumonia [15]
Таблица
Особенности пневмонии COVID-19 при компьютерной томографии и ультразвуковом исследовании легких [15]

Lung CT	Lung ultrasound
Thickened pleura	Thickened pleural line (can be observed in interstitial syndrome due to the appearance of artefacts in the initial stage of pneumonia)
Ground-glass shadow (loss of lung aeration and partial collapse of the alveoli) and effusion	B-lines (multifocal or confluent)
Pulmonary infiltrates (lung consolidation due to accumulation of fluid)	Confluent B-lines (in case of the development and progression of alveolar oedema)
Subpleural consolidation	Small consolidation
Translobar consolidation	Both non-translobar and translobar consolidation
Pleural effusion is rare	Pleural effusion is rare
More than two lobes affected	Multilobar distribution of abnormalities
Atypical in lung CT images in the early stage, then diffuse scattered with the progress of the disease, further lung consolidation	B-lines are the main feature in the early stage, mild infection, and in convalescence period; alveolar interstitial syndrome is the main feature in the progressive stage and in critically ill patients; pleural line thickening with uneven B-lines can be seen in patients with pulmonary fibrosis

Conclusion

To summarize, accumulated clinical experience with lung ultrasonography suggests that it is quite a promising and informative method, allowing for a rapid detection of structural lung abnormalities. Expertise of specialists from different countries demonstrates that the results of completed studies made it possible to view lung ultrasound as an important component of primary diagnostic workup for lung damage in patients with COVID-19 infection. It is explained by a number of its advantages, including its availability, ease of use, and high informative value. In addition, it makes it possible to reduce the number of healthcare professionals working in the COVID-19 environment and limit direct contact with patients. However, there is no doubt that further clinical trials are required to evaluate the potential of this technique in different clinical settings.

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Non-invasive ventilation in patients with novel coronavirus infection COVID-19

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Abstract

In the early stages of the COVID-19 pandemic, many guidelines for the management of patients with new coronavirus infection did not include recommendations for the use of non-invasive ventilation (NIV) due to the concerns that NIV could be accompanied by high tidal volumes that could cause lung damage. In addition, there was an opinion that NIV increases the risk of spreading bioaerosol containing the SARS-CoV-2 virus. At the same time, NIV was widely used in real clinical practice in the management of severe patients with COVID-19 (in some countries, up to 60% of all respiratory support methods). The accumulated experience demonstrates that when applying NIV, the risk of contamination with viral infections is minimized with adequate use of personal protective equipment. To date, the results of a limited number of studies about effectiveness of NIV in hypoxemic acute respiratory failure (ARF) in patients with COVID-19 are available. In most studies, the need for tracheal intubation and hospital mortality, were on average, 20 – 30%, that suggests a fairly high effectiveness of NIV in ARF in patients with COVID-19.

Key words: coronavirus infection SARS-CoV-2, COVID-19, acute respiratory failure, non-invasive ventilation, continuous positive airway pressure.
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Неинвазивная вентиляция легких при новой коронавирусной инфекции COVID-19

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Резюме

На начальных этапах пандемии COVID-19 во многих руководствах по ведению пациентов с новой коронавирусной инфекцией отсутствовали рекомендации по использованию неинвазивной вентиляции легких (НВЛ) из опасений, что последняя может сопровождаться высокими дыхательными объемами, способными вызвать повреждение легких. Кроме того, существовало мнение, что при НВЛ повышается риск распространения биоаэрозоля, содержащего вирус SARS-CoV-2. В то же время НВЛ достаточно широко используется в реальной клинической практике при ведении тяжелых пациентов с COVID-19 (в некоторых странах – до 60 % всех методов респираторной поддержки). Накопленный опыт показывает, что при работе с НВЛ риск контаминации вирусными инфекциями сводится к минимуму при адекватном использовании средств индивидуальной защиты. К настоящему времени доступны результаты небольшого числа исследований, посвященных эффективности НВЛ при гипоксемической острой дыхательной недостаточности у пациентов с COVID-19. По результатам большинства исследований показано, что потребность в интубации трахеи и госпитальная летальность в среднем составляют 20–30 %. Это позволяет сделать вывод о достаточно высокой эффективности НВЛ при острой дыхательной недостаточности у пациентов с COVID-19.

Ключевые слова: коронавирусная инфекция SARS-CoV-2, COVID-19, острая дыхательная недостаточность, неинвазивная вентиляция легких, постоянное положительное давление в дыхательных путях.
Конфликт интересов. Автор заявляет об отсутствии конфликта интересов.

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Viral pneumonia and acute respiratory distress syndrome (ARDS) are the most common complications of the new SARS-CoV-2 coronavirus infection (COVID-19), leading to hypoxemic acute respiratory failure (ARF), in most cases requiring oxygen therapy and respiratory support [1–3]. Hypoxemic ARF is the leading cause of death in patients with severe COVID-19 referred to intensive care units (ICU). Thus, study by *Ruan et al.*, showed that ARF was the leading cause of mortality in 88% of patients suffering COVID-19 [4].

Traditionally, early intubation and mechanical ventilation (MV) were considered to improve survival in patients with ARDS [5]. However, recently published studies from UK, USA, and China, including COVID-19 patients, showed an extremely high mortality rate (65 – 92%) among patients receiving mechanical ventilation [6–8].

Currently, there is increasing interest in non-invasive respiratory modalities, e.g., high-flow nasal oxygen therapy (HFNO) and non-invasive ventilation (NIV).

NIV is a respiratory support method where the main interfaces (mask or helmet) can be easily applied and thereafter easily disconnected from the patient airways [9]. NIV has significant advantages over traditional mechanical ventilation, as the application of artificial airways (endotracheal tube, tracheostomy) is not required, thus increasing patient comfort, reducing the need for sedatives, preserving eating and swallowing functions, and most importantly, significantly reducing the risk of respiratory tract direct injuries and the risk of nosocomial infections [10, 11].

Most often in patients with ARF, the following NIV modes are used: Continuous Positive Airway Pressure (CPAP) and pressure support (PS) or a close similar mode – Bilevel Positive Airway Pressure (BiPAP) [11, 12]. CPAP provides a constant flow of oxygen at a given pressure, which remains constant during inspiration and expiration [11, 12]. PS mode is an assissted mode-in response to the patient's inspiratory effort, the ventilator creates a predetermined level of positive pressure in the airways during the inspiration phase [11, 12].

The role of NIV in COVID-19 patients with hypoxemic ARF is a subject for discussion and debate. Consensus guidelines issued by the Intensive Care Society, the Association of Anesthesiologists and the Royal College of Anesthesiologists states that the use of non-invasive modalities "should be avoided", and also states "There is no survival benefit compared to conventional oxygen therapy, and the risk of environmental viral contamination may be higher" [13]. The guideline "Surviving Sepsis Campaign" recommends attempting NIV only in cases where "high-flow oxygen therapy is not available and there is no urgent indication for tracheal intubation", and under the close monitoring and frequent assessment for progression of respiratory failure [14]. The World Health Organization (WHO) recommends to use NIV only in selected patients with hypoxemic respiratory failure, under close monitoring by experienced medical staff who can perform tracheal intubation in case of rapid deterioration or no improvement after a short trial period [15]. The National Health Service (UK) recommendations consider NIV as the first line respiratory support for COVID-19 patients with hypoxemic ARF [16]. A similar approach was also adopted in the recommendations from Italy, Spain and Russia [17–20].

On the other hand, in real clinical practice NIV for severe COVID-19 is widely used almost everywhere. The proportion of patients requiring non-invasive respiratory support in published studies varies greatly, from 11% to 96%, with higher rate in China (62% on average) and lower in North America (20%) [21]. According to a survey including 1,215 Italian doctors, most of the responders (62%) used NIV (CPAP and BiPAP) as a first-line therapy for patients with hypoxemic ARF associated with COVID-19; 60% of doctors considered indications for endotracheal intubation (EI) and mechanical ventilation only 1 – 8 h after no response to NIV therapy [22]. A summary of non-invasive respiratory modalities use is presented in Table 1 [21].

Bioaerosols and protection of healthcare professionals

It is generally accepted that SARS-CoV-2 spreads mainly through airborne droplets or through direct contact, and nosocomial virus transmission from the patient to medical professionals can be a serious challenge [23]. Biologically hazardous aerosols are usually formed as a result of so-called aerosol-generating procedures, such as nebulizer therapy, oxygen therapy, including HFNC, NIV, tracheotomy [24], and these procedures can expose health care workers (HCWs) to viral pathogens that cause acute respiratory infections. According to published data,

Table 1
Respiratory support in cohort studies of SARS-CoV-2 infection
Таблица 1
Респираторная поддержка в когортных исследованиях по инфекции SARS-CoV-2

Study		Country	Design	Patient population (N)	Respiratory support, *n* (%)	Non-invasive support methods, *n* (%)		
Author	Edition, year					HFOT	NIV	NIRS
Wang D.	*JAMA*, 2020	China	Retrospective SC	138	36 (26)	4 (11)	15 (42)	–
Arentz M.	*JAMA Netw. Open*, 2020	USA	Retrospective SC	21	20 (95)	1 (5)	4 (20)	–
Grasselli G.	*JAMA*, 2020	Italy	Retrospective MC	1,591	1,287 (99)	–	137 (11)	–
Huang C.	*Lancet*, 2020	China	Prospective	41	14 (34)	–	–	10 (71)
Wang K.	*Ann. Intensive Care*, 2020	China	Retrospective	318	27 (8)	17 (63)	9 (3)	
Zhou F.	*Lancet*, 2020	China	Retrospective MC	191	99 (52)	41 (41)	26 (26)	
Guan W.	*NEJM*, 2020	China	Retrospective MC	1,099	67 (6.1)	–	56 (83)	
Liao X.	*MedRixv*, 2020	China	Retrospective MC	81	63 (77)	31 (49)	22 (35)	
Zheng Y.	*MedRixv*, 2020	China	Retrospective SC	34	34 (100)	18 (53)	1 (3)	
Xu Yang	*MedRixv*, 2020	China	Retrospective MC	69	5 (7)	–	3 (60)	
Xu Yonghao	*MedRixv*, 2020	China	Retrospective MC	45	39 (86)	13 (33)	6 (15)	

Note: SC, single-center; MC, multi-center; HFOT, high-flow oxygen therapy; NIV, non-invasive ventilation; NIRS, non-invasive respiratory support methods

3.8% of Chinese HCWs were infected with SARS-CoV-2 virus [25]. 63% of these cases occurred in Wuhan city; Italian data are even worse – 14% of HCWs were infected [26]. How can we reduce the exposure of bioaerosols on HCWs? The basic protective measure is the wearing of effective personal protective equipment (PPE) such as FPP_2/N95 respirators, medical suits, gloves, and eye and face shields [27].

As it was reported by *K.E.Remy et al.*, the risk of virus spreading in living patients (and not in surrogate inanimate body models) on NIV has not been studied [28]. In fact, a number of studies was carried out in healthy volunteers, using smoke laser lighting techniques on patient simulators, showing changes and increase of droplet dispersion along with increasing NIV flow rate [29]. Droplets are particles > 5 μm in diameter that quickly fall to the ground due to gravity; therefore, they are only transmitted over a limited distance (e.g. ⩽ 1 meter). On the other hand, airborne transmission refers to the presence of microbes in droplet cores, which are particles less than 5 μm in diameter that can remain in the air for a long time and can be transmitted to other people over distances of more than 1 m [30].

D.S.Hui et al. [31] measured airflow using smoke as a marker, and confirmed the difference between ventilated and non-ventilated masks by measuring maximum exhaled air distances using various oxygen therapy devices: nasal cannula, Venturi mask, and reservoir mask. The helmet has been demonstrated to be the preferred NIV interface in reducing patient aerosol leakage (with dual circuit NIV configuration) [32]. These authors also demonstrated that exhaled air dispersion during NIV using various interfaces, including the oronasal mask, is also significantly limited, provided that the mask fits well to the patient face [33]. In a real human model (control group of healthy volunteers, patients with catarrhal symptoms and patients with an acute infectious exacerbation of chronic obstructive pulmonary disease) *A.K.Simonds et al.* demonstrated that NIV using a vented mask produced large fraction droplets (> 10 μm) compared to baseline amount of droplets (without any intervention) [34]. Such an increase in the number of large drops was not observed in case of NIV when using unvented mask and in-line filter in the circuit.

The maximum distance values of exhaled air spreading for different procedures and devices are presented in Table 2.

A more prominent diffusion and contamination by the exhaled air is likely in units not equipped with negative pressure rooms. If negative pressure rooms are not available, it is recommended to use rooms with natural ventilation with an air flow of at least 160 L/s per patient, as well as High Energy Particulate Arresting (HEPA) filters [35].

In an observational study by *M.Oranger et al.*, the proportion of HCWs infected with SARS-CoV-2 was similar before and after the introduction of CPAP therapy in the COVID-19 department (6% *vs* 10%) [36]. In a Wuhan study investigating ingress of infection in HCWs, the SARS-CoV-2 infection rate was only 1.1% of the total hospital staff [23], where with most healthcare worker infections occurring in the early stages of the COVID-19 outbreak, resulting from the absent awareness of the high contagiousness of coronavirus infection, and, therefore, not sufficient use of individual protection at that time. Infections in HCWs can be avoided with appropriate personal protection, even when working with patients on NIV. As evidenced by only a few cases of infection of healthcare workers in the later period of the pandemic [37].

Table 2
Maximum distance of spread of exhaled air when using various procedures and devices
Таблица 2
Максимальная дистанция распространения выдыхаемого воздуха при различных процедурах и использовании тех или иных устройств

Method	Maximum distance of exhaled air spread, cm
Nasal cannula oxygen 5 L/min	100
Face mask oxygen 4 L/min	40
Venturi mask oxygen FiO_2 40%	33
Oxygen through mask with reservoir 12 L/min	< 10
CPAP using oronasal mask 20 cm H_2O	Minimal
CPAP through nose cones	33
HFOT 60 L/min	17
NIV through full face mask: IPAP 18 cm H_2O, EPAP 5 cm H_2O	92
NIV through a helmet without a tight fit: IPAP 20 cm H_2O, EPAP 10 cm H_2O	27
NIV through a tight-fitting helmet: IPAP 20 cm H_2O, EPAP 10 cm H_2O	Minimal

Note: NIV, non-invasive ventilation; HFOT, high-flow oxygen therapy; CPAP, continuous positive airway pressure; IPAP, inspiratory positive airway pressure; EPAP, expiratory positive airway pressure.

Thus, even when using NIV in patients, the risk of contamination with viral infections is minimized in case of adequate use of PPE.

Benefits of non-invasive ventilation in hypoxemic acute respiratory failure patients

Despite controversial recommendations, NIV is regularly used in hypoxemic ARF patients [38]. Study by *G.Bellani et al.*, showed that NIV was used in 14.4% of patients with ARDS (436 of 3,022), and 69% of them (300 of 436) were treated only using exclusively NIV [39].

In hypoxemic ARF, the main goals are to improve oxygenation, reduce the work of breathing, and reduce dyspnea [40]. The first goal can usually be achieved by using higher levels of positive end-expiratory pressure (PEEP) to recruit non-ventilated or poorly ventilated alveoli [41]. Increased PEEP may help to keep the alveoli open, leading to increased functional residual capacity, to decreased ventilation-perfusion imbalance and shunt, and hence to an improved oxygenation [40]. In addition, PEEP stabilizes the airway and reduces the heterogeneity of lung volumes distribution [42]. NIV also decreases respiratory muscles load. The main component reducing the work of breathing in NIV is a positive pressure on inspiration (pressure support) [40, 43].

Recently, a physiological randomized crossover study concluded that patients with PaO_2/FiO_2 < 200 mm Hg the use of NIV with a helmet is preferable to HFCN in terms of optimizing oxygenation and reducing inspiratory effort, especially in patients with more severe hypoxemia and a higher work of breathing [44].

In patients with severe community-acquired pneumonia, NIV significantly improved arterial blood oxygenation compared to standard oxygen therapy [45]. In addition, it was shown that the use of CPAP therapy in patients with pneumonia and severe hypoxemic ARF, compared to oxygen therapy, leads to a decreased risk of endotracheal intubation and invasive mechanical ventilation [46].

The use of NIV in patients with some types of ARF, including ARDS, reduces the need for EI and mechanical ventilation. Meta-analysis by *R.Agarwal et al.*, showed that NIV can improve oxygenation and reduce the risk of EI in patients with mild ARDS ($PaO_2/FiO_2 \geqslant 150$ mm Hg) [47]. In a recent meta-analysis by *B.L.Ferreyro et al.*, including 25 studies with 3,804 hypoxemic ARF patients, it was shown that NIV using helmets (risk ratio [RR] 0.26) and face masks (RR 0.76) was associated with a lower risk of EI compared to standard oxygen therapy [48]. NIV using both helmets (RR 0.40) and face masks (RR 0.83) was also associated with a lower risk of hospital mortality.

Limitations of non-invasive ventilation in hypoxemic acute respiratory failure patients

In contrast to patients with invasive mechanical ventilation, for whom there are established protective ventilation protocols, there are currently no ventilation protocols for NIV aimed at reducing the risk of ventilator-associated lung injury. This is possibly one of the main challenges using NIV in hypoxemic ARF patients. Consequently, unsafe settings are usually used. For example, in the recent European cohort of hypoxemic ARF patients in more than half of cases tidal volumes greater than 10 ml/kg of ideal body weight were used [49]. In this study, tidal volumes greater than 9.5 ml/kg were a strong predictor of NIV failure, indicating that close monitoring of tidal volume is necessary. In patients with persistently high tidal volumes, early invasive ventilation may be a reasonable option to reduce the risk of ventilator-induced lung injury.

Often too high inspiratory pressures are used for NIV in severe ARDS patients, leading to an increased transpulmonary pressure (the difference between end-inspiratory pressure and intrathoracic pressure). Increased transpulmonary pressure, on the one hand, can lead to excessive overdistension of alveoli in non-gravity-dependent areas of the lungs, and on the other hand, it can cause a significant increase in dead space. Excessive pressure support can lead to barotrauma and lung biotrauma [50]. A recently published study by *R.Tonelli et al.*, showed that hypoxemic ARF patients with NIV failure had higher transpulmonary pressure levels (39.5 cm H_2O *vs* 30.5 cm H_2O), and decreased esophageal pressure fluctuations (ΔPes) during NIV were a clear indicator of NIV success and improvement of lung X-ray pattern [51].

The main risk of using NIV in hypoxemic ARF may be associated with the delayed intubation despite indications present [52]. Early signs of NIV failure include a higher score when assessing condition severity using scales (e.g., APACHE or SAPS II), and also the absence of improvement in patient condition 1 hour after starting NIV [53]. Studies have shown that the NIV failure is an independent risk factor for death in this patient population. But this risk possibly may be decreased via careful selection of patients for NIV [54].

First data on the use of non-invasive ventilation in COVID-19

To date, only a small number of studies are available on NIV efficacy in hypoxemic ARF patients with COVID-19 [36, 55–61] (Table 3).

All the published studies were open-label, observational. And until today there are no randomized controlled clinical trial. And this can be explained by only a short period of time that NIV was used in COVID-19 clinical practice.

It should be pointed out, that only one of the studies presented included patients from the intensive care unit (ICU) [61], and all the other studies were conducted not in ICU, but in emergency department, pulmonology department, specialized departments for patients with COVID-19 and in intermediate care units (non-invasive respiratory support department).

This practice reflects modern tendencies, according to which, as experience accumulates, the use of NIV is possible not only in the ICU, but also at a "lower level" units, i.e. in units with less monitoring capacity and a lower nurse-to-patient ratio [62]. In addition, today the use of NIV in acute cases is not limited only to in patient departments, but is successfully applied at earlier stages, for example, in the emergency department [63].

In published studies, in the majority of COVID-19 cases, the CPAP mode was used (average pressure about 10 cm H_2O), which is explained by its high efficiency in hypoxemic ARF, and, by the fact that this mode can be implemented using simpler equipment-flow generators (and not necessarily ventilators). An example of such a flow generator is the UCL – Ventura Breathing Aid, developed by Mercedes AMG High Performance Powertrains, specifically for CPAP therapy in critically ill patients with COVID-19 [64].

Either face masks (oronasal masks) or helmets were used as the main interfaces in the abovementioned studies. Potential advantages of the helmet are the possibility of airtight fastening of this interface in patients with virtually any facial shape, exclusion of any damage to the facial skin, and greater comfort for patient [65]. In a study by *B.K.Patel et al.* helmet use in patients with ARDS compared to facial masks was associated with a lower need for EI (18.2% *vs* 61.5%) [66]. Another helmet advantage when working with COVID-19 is the minimal bioaerosol spreading [27, 32]. Given the fact that helmets are still rarely used in our medical institutions, it should be emphasized that non-vented facial masks are also effective interfaces for NIV in severe COVID-19 patients.

Table 3
Studies on the effectiveness of non-invasive ventilation in COVID-19
Таблица 3
Исследования по эффективности неинвазивной вентиляции легких при COVID-19

Study	Design	Patients	Department	PaO_2/FiO_2	Respirators	Interfaces	Regimens	Duration	Outcomes
Oranger et al.	Observational, historical control	38 (NIV)	Pulmonology department	?	Portable NIV respirators	Facial masks	CPAP: 10 cm H_2O	5 (2 – 7.5) days	EI – 23%
		14 (control)							Died – 0%
Duca et al.	Observational, retrospective	78	Emergency department	131 mm Hg (CPAP)	NA	Helmets	CPAP (*n* = 71)	NA	Failure – 88%
				87 mm Hg (NIV)			NIV (*n* = 7)		EI – 33%
									Died – 74%
Pagano et al.	Observational, prospective	18	COVID-19 department	153 mm Hg	NA	Helmets	CPAP: 10 cm H_2O	NA	Died – 61%
Burns et al.	Observational, retrospective	28	COVID-19 department	NA	NA	Masks	CPAP (*n* = 23): 12.7 ± 2.1 cm H_2O	5 days	Died – 50%
							BiPAP (*n* = 5): IPAP 22.4 ± 6.0 cm H_2O/ PEEP 10.2 ± 2.9 cm H_2O		
Nightingale et al.	Observational, retrospective	24	COVID-19 department	122 mm Hg	portable NIV respirators	Non-vented masks	CPAP 8.75 (7.5 – 10) cm H_2O	4.5 days	EI – 38%
									Died – 21%
Aliberti et al.	Observational, prospective	157	HDU	142 mm Hg	Flow generators,	Helmets	CPAP 10.8 ± 2.3 cm H_2O	6 (3 – 10) days	Failure – 44.6%
									EI – 21.7%
									Died – 22.9%
Franco et al.	Observational, retrospective	330 (CPAP)	Respiratory Disease Units	151 mm Hg (CPAP)	Flow generators, portable NIV respirators	Helmets, masks	CPAP 10.2 ± 1.6 cm H_2O	NA	EI – 24.8% (CPAP)
									27.7% (NIV)
		177 (NIV)		138 mm Hg (NIV)			NIV: IPAP 17.3 ± 3.0 cm H2O/ PEEP 9.5 ± 2.2 cm H_2O		Died – 30.3% (CPAP)
Mukhtar et al.	Observational, retrospective	39	ICU	170 mm Hg	NA	NA	NA	2 (2 – 5) дней	EI – 23%
									Died – 26%
Собственные данные	Observational, retrospective	61	COVID-19 department	164 mm Hg	NIV respirators	Non-vented masks	CPAP (*n* = 55): 10.0 (10.0 – 12.2) cm H_2O	8.0 (6.3 – 11.0) days	EI – 27.9%
							NIV (*n* = 6): PS 10.0 (8.0 – 12.1) cm H_2O / PEEP 10.0 (10.0 – 10.3) cm H_2O		Died – 24.6%

Note: NIV, Non-invasive Ventilation; ICU, intensive care unit; HDU, high dependency unit; CPAP, continuous positive airway pressure; IPAP, inspiratory positive airway pressure; PS, pressure support; PEEP, positive end-expiratory pressure; EI, endotracheal intubation; NA, not available.

All of these studies included COVID-19 patients with severe hypoxemic ARF, who met Berlin classification criteria for moderate-to-severe ARDS [67]: the mean baseline PaO_2/FiO_2 ratios ranged from 87 to 170 mm Hg, i.e., according to the classical canons, these patients had indications for invasive mechanical ventilation. The efficacy of NIV in hypoxemic ARF patients with COVID-19 can be assessed using data on the proportion of intubated and deceased patients. Of course, the results presented are rather heterogeneous – patient mortality ranged 0 to 74%, and the need for EI ranged from 22 to 38%. The highest mortality rate (74%) was observed in emergency department patients with severe hypoxemia (PaO_2/FiO_2 87 mm Hg) in Bergamo (Italy). But these results are explained by the extreme shortage of hospital beds in the Italian ICUs during the explosive increase of COVID-19 incidence [55]. In general, in most studies, the need for EI and hospital mortality rates, on average, were 20 – 30%, thus suggesting a fairly high NIV efficacy in ARF patients with COVID-19.

Interestingly, previous experience with NIV in hypoxemic ARF patients with severe community-acquired pneumonia and ARDS is difficult to transfer to patients with COVID-19. For example, according to generally-accepted concepts, the PaO_2/FiO_2 ratio below 150 mm Hg is regarded as a reliable predictor of NIV failure, i.e., it is a direct indication for immediate EI [47, 53]. On the other hand, it is most likely that baseline PaO_2/FiO_2 ratio in COVID-19 patients, is not a predictor of NIV success or failure. For example, in a study by *S.Aliberti et al.*, including 157 patients, baseline PaO_2/FiO_2 values in the success group were even lower than in the failure group (136 *vs* 152 mm Hg) [59]. And in the study by *C.Franco et al.*, including 507 COVID-19 patients, there was also no difference in mortality among patients with baseline PaO_2/FiO_2 rations of 201 – 250, 151 – 200 and 101 – 150 mm Hg (20.3, 25.2 and 24.2%, respectively); mortality was higher (45.5%) only at PaO_2/FiO_2 below 50 mm Hg [60].

Experience gained in managing COVID-19 patients showed that NIV may not be a sufficient universal respiratory support method for absolutely all patients with severe COVID-19. In some patients, NIV can temporarily improve oxygenation and respiratory work, but has no influence on natural disease progression, and ultimately does not prevent the need for EI and invasive ventilation. Unfortunately, today we don't have yet any reliable markers of disease progression in NIV patients. In a study by *W.Wang et al.*, including a nationwide cohort of critically ill COVID-19 patients from China, an elevated D-dimer level (> 1.5 mg/L) on admission was an indicator of a high probability of a ventilator requirement [37]. These results are consistent with evidence that increased D-dimer levels in COVID-19 patients are associated with disease progression [68].

Large randomized controlled trials are currently in progress to assess the NIV efficacy in critically ill COVID-19 patients [69–70]. And results of these studies will help to improve our knowledge of optimal respiratory support in new coronavirus infection patients.

Conclusion

In the early stages of the COVID-19 pandemic, most of guidelines for the management of patients with new coronavirus infection did not contain recommendations for the use of non-invasive ventilation, due to concerns that NIV may require high tidal volumes that could cause lung damage. And also there was an opinion that NIV increases the risk of bioaerosol spreading, containing the SARS-CoV-2 virus. At the same time, NIV is widely used in real clinical practice for the management of severe COVID-19 patients (up to 60% of all respiratory support methods in some countries). The accumulated experience showed that when working with NIV, the risk of contamination with viral infections is minimized with adequate use of personal protective equipment. To date, there are available results of a limited number of studies on NIV efficacy in hypoxemic ARF patients with COVID-19. In most studies, the need for endotracheal intubation and hospital mortality rates, on average, were 20 – 30%, thus suggesting a fairly high NIV efficacy in ARF patients with COVID-19.

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COVID-19 and cardiovascular diseases: from epidemiology to rehabilitation

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Abstract

The article is devoted to a review of data on the prevalence and impact of cardiovascular diseases on the course and outcomes of the new coronavirus infection COVID-19. The review examines the relationship between COVID-19 and the functioning of the renin-angiotensin-aldosterone system, the pathophysiological mechanisms of their mutual influence. The analysis of the latest literature data on the safety of taking angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers is presented. The causes and pathophysiological mechanisms of the development of acute myocardial damage in COVID-19 are discussed. The issue of organizing rehabilitation assistance for patients who have undergone COVID-19 is being considered. The main components and features of the COVID-19 rehabilitation program are presented.

Key words: coronavirus, COVID-19, SARS-CoV-2, cardiovascular diseases, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, arterial hypertension, acute myocardial injury, rehabilitation.

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COVID-19 и сердечно-сосудистые заболевания: от эпидемиологии до реабилитации

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Резюме

Статья посвящена обзору данных о распространенности и влиянии сердечно-сосудистых заболеваний на течение и исходы новой коронавирусной инфекции COVID-19. В обзоре разбирается связь между COVID-19 и функционированием ренин-ангиотензин-альдостероновой системы, патофизиологические механизмы их взаимного влияния. Приведены результаты анализа последних данных литературы о безопасности приема ингибиторов ангиотензинпревращающего фермента и блокаторов рецепторов к ангиотензину II. Обсуждаются причины и патофизиологические механизмы развития острого миокардиального повреждения при COVID-19. Рассматривается вопрос организации реабилитационной помощи больным, перенесшим COVID-19. Представлены основные компоненты и особенности программы реабилитации при COVID-19.

Ключевые слова: коронавирус, COVID-19, SARS-CoV-2, сердечно-сосудистые заболевания, ингибиторы ангиотензинпревращающего фермента, антагонисты рецепторов ангиотензина, артериальная гипертензия, острое миокардиальное повреждение, реабилитация.

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Coronavirus infection COVID-19 (COronaVIrus Disease 2019) caused by novel coronavirus species – SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) has led to high morbidity and mortality all over the globe [1]. Despite SARS-CoV-2 tropism in lungs, COVID-19 results in a high risk of multiple organ failure, including due to cardiovascular system (CVS) involvement.

Epidemiological aspects

Approximately 50% of SARS-CoV-2 patients have multiple morbidity and its rate rises to 72% in severe COVID-19 [2, 3]. Very often COVID-19 patients have cardiovascular diseases (CVD) and cardiovascular risk factors e.g. obesity and diabetes mellitus (DM).

According to one retrospective analysis (n = 1,590 from 575 Chinese hospitals), 25% of COVID-19 patients had comorbidities [4]. Arterial hypertension (AH) was recorded in 16.9%, other CVS – in 53.7%, and DM – in 8.2%. In an Italian cohort of COVID-19 patients (n = 22,512, including 355 lethal cases) comorbid ischemic heart disease (IHD) was recorded in 30%, atrial fibrilation – in 24.5%, a history of stroke – in 9.6%, and DM – in 35.5% [5]. An analysis of the database of 5,700 COVID-19 patients hospitalised to 12 New York hospitals showed AH in 56.6%, IHD in 11.1%, obesity in 41.7%, and DM in 33.8% [6].

A retrospective analysis of clinical and demographic parameters of 1,007 COVID-19 patients hospitalised to in-patient clinics (resuscitation and intensive care unit, ICU) in the Russian Federation with acute respiratory distress syndrome (ARDS) demonstrated that 61.4% of patients had CVD [7]. Most common were AH (56.3% of patients) and IHD (16.3%), followed by a history of stroke (7.1%) and atrial fibrillation (9.3%). Obesity and type 2 diabetes were recorded in 26.1% and 25% of patients, respectively. The incidence of CVD was age-dependant, reaching 80% in the group of patients > 60 years old.

Impact of comorbid CVD on the course and outcome of COVID-19

Patients with CVD and/or standard cardiovascular risk factors (elderly age, men, AH, DM, obesity) are the most vulnerable cohort; they usually have severe COVID-19 and high hospital mortality [8, 9]. A meta-analysis of 6 trials (n = 1,558) allowed identifying independent predictors of severe COVID-19 (with ARDS) [9]. These are the following comorbid diseases: AH (hazard ratio (HR) 2.29, $p < 0.001$), other CVD (HR 2.93, $p < 0.001$), cerebrovascular disease (HR 3.89, $p = 0.002$), DM (HR 2.47, $p < 0.001$), and chronic obstructive pulmonary disease (HR 5.97, $p < 0.001$). With IHD the probability of severe COVID-19 rises 2.5-fold [10].

S.Tai et al. studied the impact of CVD on the risk of severe COVID-19 in patients (n = 332, mean age: 51 years) with mild infection [11]. Comparison of two groups of patients "with CVD" (n = 48, 14.5%) and "without CVD" (n = 284, 85.5%) demonstrated that patients with CVD were older (mean age: 56 years *vs* 50 years, $p = 0.007$), they complained of fatigue (28.3% *vs* 11.1%, $p = 0.002$), chest tightness (40.0% *vs* 6.0%, $p < 0.001$) and myalgia (13.0% *vs* 2.6%, $p = 0.001$) more often; they had DM (8.3% *vs* 2.5%, $p < 0.05$) and pulmonary diseases (8.3% *vs* 1.1%, $p < 0.05$), and were hospitalised to ICU more often (47.9% *vs* 12.4%, $p < 0.001$). Intensive care was required for patients with AH (44.7% *vs* 13.9% with other CVD, $p < 0.001$) and IHD (90.9% *vs* 15.0%, $p < 0.001$, respectively). A multivariate analysis demonstrated that comorbid CVD are an independent risk factor for severe COVID-19 (odd ratio (OR) 2.652, 95% confidence interval (CI) 1.019 – 6.899) [11].

A viral infection can de-stabilise the heart condition, significantly increasing the risk of comorbid CVD. In the trial [12] the risk of death with CVD was 2.4-fold higher ($p = 0.019$). An analysis of 44,672 cases with confirmed COVID-19 from the Chinese Centre for Disease Control and Prevention showed high mortality in patients with CVD (10.5%), AH (6.0%), and DM (7.3%), whereas the overall mortality was 2.3% [13].

A multivariate Cox regression analysis of 1,590 patients hospitalised with COVID-19 showed the following predictors of death: patient age > 75 years (HR 7.86; 95% CI 2.44 – 25.35) and 65 – 74 years (HR 3.43; 95% CI 1.24 – 9.5), coronary artery disease (HR 4.28; 95% CI 1.14 – 16.13), cerebrovascular diseases (HR 3.1; 95% CI 1.07 – 8.94), dyspnea (HR 3.96; 95% CI 1.42 – 11.0), procalcitonin level > 0.5 ng/mL (HR 8.72; 95% CI 3.42 – 22.28), and aspartate transaminase activity > 40 U/L (HR 2.2; 95% CI 1.1 – 6.73) [14].

Thus, very often concomitant CVDs are associated with severe COVID-19 with patient hospitalisation to ICU and worse prognosis. Therefore, all patients, even with moderate and even mild COVID-19 should be subject to a cardiac examination and follow-up.

COVID-19, arterial hypertension and renin-angiotensin-aldosterone system

According to various studies, AH is recorded in 15 – 40% of COVID-19 patients [15, 16]. AH is prevailing in patients with severe COVID-19; e.g. in the study by *W.J.Guan et al.* 23.7% of patients had AH (*vs* 13.4% with mild disease) [17]. It is reported that COVID-19 mortality in patients with AH is 2.6 times higher [10]. Possible mechanisms of AH correlation with poorer COVID-19 outcome can relate to the role of type 2 angiotensin converting enzyme (ACE2) [18].

ACE2 is an essential component of the renin-angiotensin-aldosterone system (RAAS) participating in pathogenesis of AH and other CVDs. It is known that ACE2 is a type I transmembrane protein expressed in lungs (high ACE2 expression is seen on the surface of type II alveolar cells), heart, kidneys, vascular endothelium, liver, testicles, and intestine [19]. ACE2 can be present in a free form as well (in blood).

The physiological role of ACE2 is primarily related to angiotensin I (ATI) cleavage to inactive AT 1 – 9 peptide, which then turns into AT 1 – 7 with the help of ACE or other peptidases, and to ATII degradation to AT 1 – 7 binding to Mas receptors (Figure 1). AT 1 – 7 ensures vaso- and cardioprotection, antiproliferative, antiinflammatory and natriuretic effect. When cleaving ATII, ACE2 mitigates negative effect of the latter (vasoconstriction, cytokine-like activity, sodium retention and development of fibrosis).

SARS-CoV-2 virus binds to ACE2 receptors on target cell surfaces with the help of glycoprotein (peplomer), known as a spike protein (S-protein) [20]. S-protein of SARS-CoV-2 virus mimics ACE2. Then the virus and ACE2 transmembrane domain penetrate cells (endocytosis). SARS-CoV-2 virus causes imbalance in the ACE2 system associated with reduction in AT 1 – 7 levels together with increase in ATII and ACE-ATII-AT_1-receptor path activation. As a result, acute damages to lungs, myocardium, vessels and other organs initially caused by SARS-CoV-2 can worsen.

Another possible mechanism of AH association with severe COVID-19 is related to synergistic immune response [16]. Poor blood pressure (BP) control promotes overactivation of the immune system causing chronic inflammation in the vessel walls and tissues of kidneys. In a study with "mendelian randomization", patients with AH had a correlation between AH and circulating lymphocytes and monocytes [21]. Experimental, prospective and intervention studies demonstrated interaction of some cytokines with AH regulating systems (RAAS, sympathic nervous system) and AH develop-

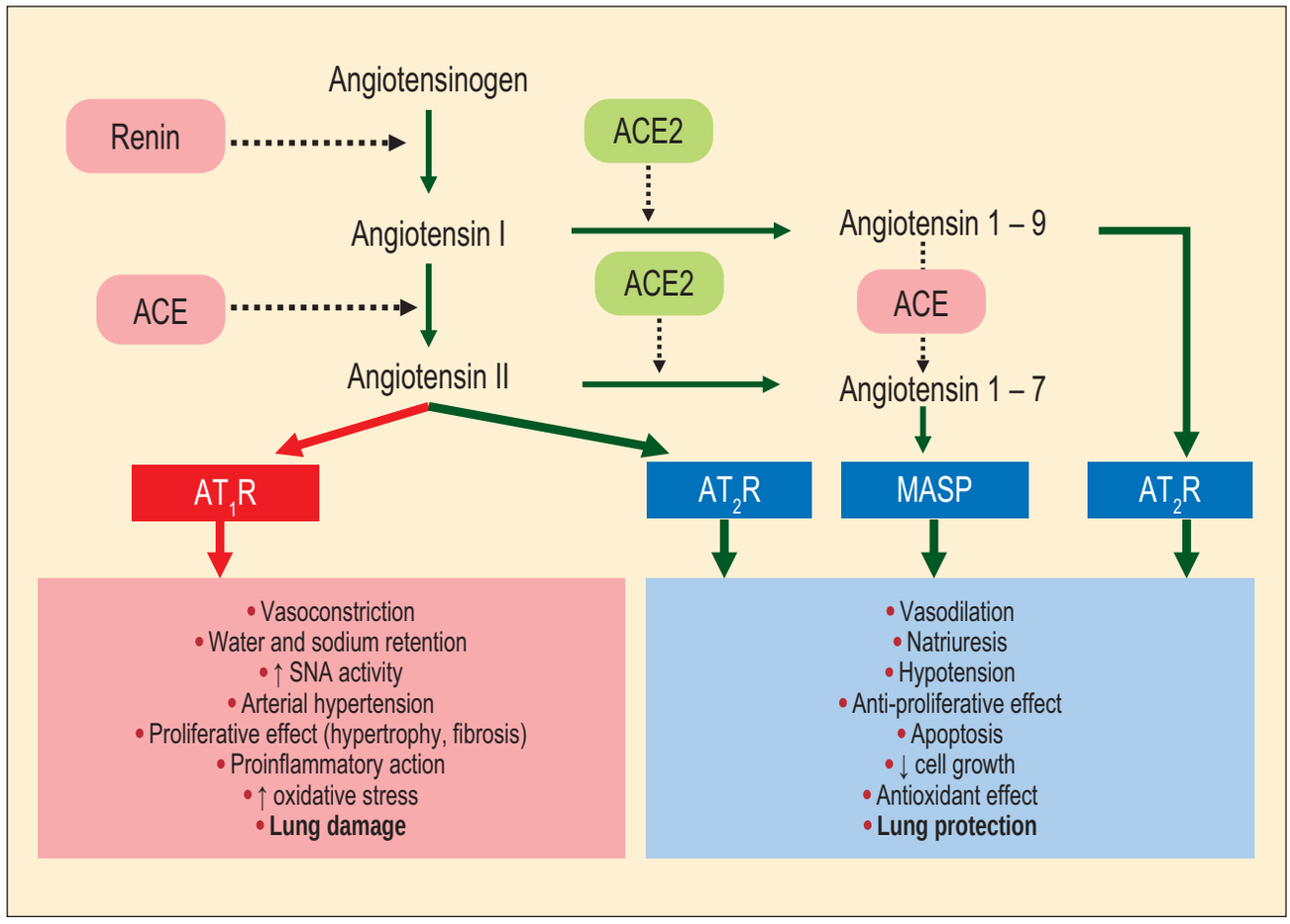

Figure 1. The role of angiotensin-converting enzyme 2 (ACE2) in the rennin-angiotensin-aldosterone system
Note: ACE, angiotensin-converting enzyme; ATR, angiotensin receptors; MASP, Mas protection; ↓ – decrease; ↑ – increase.

Рис. 1. Роль ангиотензинпревращающего фермента-2 в ренин-ангиотензин-альдостероновой системе
Примечание: ↓ – снижение; ↑ – повышение.

ment. For instance, interleukin-6, a predictor of poor COVID-19 outcome, is one of the key cytokines in initiation of inflammatory immune response in AH [18]. In another study on animal models, the relation between AH and circulating $CD8^+$ T-cells was identified [22]. In SARS-CoV-2 infection, a high rate of circulating cytotoxic $CD8^+$ T-cells facilitates hyperproduction of proinflammatory cytokines [18].

It can be believed that, while ensuring better AH control, RAAS inhibitors can mitigate immune system imbalance in AH [16]. During a virus infection, patients with AH should have their AH and cardiovascular risk monitored.

COVID-19 and RAAS inhibitors

The main activity of ACE inhibitors (ACEi) is related to reduction in ATII formation, while ATII receptor inhibitors (ARI) inhibit the interaction between ATII and type 1 angiotensin receptors (AT_1 receptors). ACE2 is not the target for RAAS inhibitors, despite the fact that an experiment on animals demonstrated that administration of RAAS inhibitors can increase ACE2 expression on cell surface [23, 24]. Therefore, there appeared a hypothesis: administration of RAAS inhibitors will promote SARS-CoV-2 internalization to lungs, heart, etc., thus increasing the risk of COVID-19 infection and severity [25]. It provoked a hot discussion.

Unlike experimental studies, COVID-19 patients did not demonstrate sound evidence of increase in ACE2 expression on target cell surface, therefore no increase in the viral load with ACEi/ARI administration [26]. It is obvious that increase in ACE2 activity with RAAS inhibitor therapy does not necessarily cause an increase in patient's susceptibility to infection [18, 27]. To penetrate the host cell, SARS-CoV-2 uses other receptors as well, e.g. transmembrane glycoprotein CD147, transmembrane protease serine 2 (TMPRSS2), acting as a co-factor of S-protein activation for efficient cell invasion by the virus [28]. After virus internalization in the cell and virus RNA release in the cell cytoplasm, ACE2 expression on the cell surface reduces (including alveolar cells). Loss of functional ACE2 (and reduced AT 1 – 7) associated with excessive ATII accumulation promotes lung damage [29]. Studies demonstrated a direct correlation between ATII blood level, viral load and lung damage severity [30]. The protective action of ACE2 in acute lung and myocardium damages has been proven on animal models [31].

It can be assumed that increase in ACE2 expression together with inhibition of proinflammatory ACE2 activ-

ity and "ACE2/AT1 – 7-Mas-receptor" signalling associated with administration of RAAS inhibitors will have a protective effect in SARS-CoV-2 infection [32].

In their study of 1,178 patients hospitalised with COVID-19 in China, *J.Li et al.* demonstrated the lack of correlation between ACEi/ ARI administration and severe infection and mortality [33]. *G.Mancia et al.*, who conducted a case-control analysis on an Italian cohort of COVID-19 patients (n = 6,272, mean age: 68 ± 13 years), did not find any negative impact of ACEi/ARI on the risk of complications, including severe cases [34].

There are first evidences of declining hospital mortality when using RAAS inhibitors in COVID-19 patients [35, 36]. According to a retrospective analysis [36], 2,877 (29.5%) patients with AH hospitalised with COVID-19 had higher mortality rates than patients without AH (4.0% *vs* 1.1%, HR 2.12, 95% CI 1.17 – 3.82, p = 0.013) and needed invasive lung ventilation (4.6% vs 1.3%, $p < 0.001$). Hospital mortality in patients with AH who did not take any antihypertensive medications was 2.17 times higher than in those who took medications (95% CI 1.03 – 4.57, p = 0.041). There are no differences between hospital mortality with administration of RAAS inhibitors and other medications (betablockers, calcium antagonists and diuretics).

Currently, global communities are unanimous: withdrawal from ACE inhibitors or ARI in COVID-19 patients can increase the risk of cardiovascular complications, especially in patients with AH, chronic cardiac failure (CF) and/or a history of myocardial infraction (MI) [37, 38]. Further studies will allow clarifying some mechanisms of RAAS activation and inhibition in COVID-19.

Cardiological manifestations of COVID-19

We have an evidence that COVID-19 negatively impacts de novo cardiovascular pathology development [12]. *N.S.Hendren at el.* proposed a new term to describe cardiological manifestations of COVID-19: **acute COVID-19-associated cardiovascular syndrome** (ACovCS), describing a wide range of cardiovascular and thrombotic complications from coronavirus infection [39]. Acute COVID-19-associated cardiovascular syndrome includes arrythmia (atrial fibrillation, ventricular tachycardia and ventricular fibrillation), acute myocardial injury, fulminant myocarditis (a risk factor for cardiac failure), pericarditis with effusion, cardiac tamponade, arterial and venous thrombotic disorders – acute coronary syndrome (ACS), stroke, pulmonary artery thromboembolia (PATE), deep venous thrombosis (Table). A majority of patients have signs of pulmonary hypertension.

Cardiac manifestations can be a primary phenomenon in COVID-19 (according to some researchers, this is a "cardiac phenotype" of the disease); however, they can be secondary to pulmonary damages (mixed pulmonary and cardiac phenotype) [41]. Of note, symptoms of CVD can be diagnosed at any stage of patient hospitalisation, but usually the risk increases from day 15 after fever initiation (or manifestation of other symptoms of a viral infection). Cardiovascular complications often appear after stabilisation and/or improvements in patient's respiratory status [41].

There are no clear explanations of the variability of cardiological manifestations of COVID-19 and it is unknown why some patients have their cardiovascular system affected. Possible mechanisms of SARS-CoV-2-induced myocardium damages are associated with increased ACE2 expression in heart and vascular endothelium (Figure 2) [20]. Various pathophysiologic mechanisms of cardiovascular complications in COVID-19 [8, 39] have been discussed:

- direct noci-influence of SARS-CoV-2 virus on pericapillary cells (high ACE2 expression on their surface), cardiomyocytes and fibroblasts [42];
- indirect influence of SARS-CoV-2 virus on myocardium during a "cytokine storm" (release of excessive inflammatory mediators and cytokins/chemokines) [42, 43];
- direct noci-influence of SARS-CoV-2 virus on vascular endothelium causing its dysfunction [44, 45];
- hypercoagulation resulting from endothelial dysfunction, increased activity of platelets and von Willebrand factor, increased expression of type 1 antioxidant tissue-type plasminogen activator inhibitor, and reduced tissue-type plasminogen activator production which causes thrombolysis, blood flow disturbances and micro- and macrothrombosis [44];
- marked hypoxaemia resulting in anaerobic processes activation, intracellular acidosis and oxidative stress (direct influence of virus on hematoglobulin causing reduction in blood oxygen capacity) [44];
- imbalance between myocardium oxygen demand and oxygen supply caused by virus-induced inflammation, hypoxia, oxidative stress, endothelial involvement and hypercoagulation, resulting in acute myocardium damage, atheroma instability and rupture associated with coronary artery thrombosis [16];
- sympathic nervous system activation and stress-induced release of catecholamines into the blood flow, causing vasospasm, myocardium hypoperfusion/ischemia and life-threatening arrythmias [46];
- electrolyte imbalance (in severe COVID-19) promoting tachyarrythmia; hypokalaemia is a result of SARS-CoV-2 impact for RAAS [44].

However the exact mechanism of acute myocardium damage in COVID-19 needs further elaboration. Therefore, COVID-19 can provoke acute myocardium damage with poor prognosis for the patient. Prompt myocardium damage identification upon patient admission into hospital and inpatient management is of great importance. Autopsy results demonstrated that cardiotropic viruses, like SARS-CoV-1, can remain in myocardium tissue for several weeks and even months [47]. The information on previous infection caused by SARS-CoV-1 virus makes it possible to assume that COVID-19 survivors may have more cardiovascular complications in future.

COVID-19 and myocardial/cardial damages. Acute myocardial damage in COVID-19 can be associated with a non-ischemic cause (myocarditis, cytokine- or stress-induced cardiomyopathy, etc.) or with myocardial ischemia resulting from coronary artery atherothrombosis [40].

Table
Cardiac manifestations in COVID-19 (acute COVID-19 cardiovascular syndrome) and possible mechanisms (ad. [39, 40])
Таблица
Кардиальные проявления COVID-19 (острый COVID-19-ассоциированный сердечно-сосудистый синдром) и возможные механизмы развития (адапт. из [39, 40])

Pathology	Symptoms	Mechanisms/Comments
Acute myocardial injury (without intracoronary thrombosis)	Increased cardiac troponin I, including additional clinical symptoms and instrumental test results	Mechanisms:
		• direct viral damage to myocardium
		• systemic inflammation
		• imbalance between myocardium oxygen demand and supply
		Possesses prognostic value
Acute coronary syndrome (STEMI and non-STEMI)	Precordialgia, increased troponin, typical ECG changes	Mechanisms:
		• atheromatosis plaque rupture (bursting) (also resulting from inflammation)
		• intracoronary thrombosis; intramural hematoma in damaged atheroma
		• attack of previous IHD
Cardiac failure	De novo left ventricular systolic dysfunction, myocarditis or pericarditis, cytokine-/stress-induced cardiomyopathy	Mechanisms:
		• hypoxaemia, dehydration, hypoperfusion
		• abnormal response to a cytokine storm
		• direct effect of virus
		Any cause of myocardium dysfunction causing acute cardiac failure
		Chronic cardiac failure decompensation resulting from increased metabolic needs
Arrythmia	Supraventricular arrhythmia, ventricular tachycardia or conduction trouble	Mechanisms:
		• hypoxia
		• hypokalaemia
		• disturbed metabolism
		• sympathic nervous system activation and increased blood catecholamines

Note: STEMI, *ST* elevation myocardial infarction; Non-STEMI, non-*ST* elevation myocardial infarction; IHD, ischemic heart disease, ECG, electrocardiography; CF, cardiac failure.

Manifestations of acute myocardial damage are increase in specific cardiobiomarkers, typical abnormal ECG changes or instrumental test results. T- and I-troponins are known risk factors of poor outcomes in acute cardiovascular pathology. Highly-specific cardiac troponin I levels of over 99th percentile of the upper reference limit are an evidence of acute myocardium damage in COVID-19 [8, 40].

In a series of COVID-19 patients from China, acute myocardium damage was recorded in 10 – 30% [2, 10, 48]. In 20 – 40% of cases, symptoms of acute myocardium damage are chest pain (myocardial ischemia), CF augmentation (also caused by myocarditis), arrythmia, and cardiac death [16, 49]. Increased myocardial damage markers in COVID-19 are a sign of severe disease and poor outcome [2]. A meta-analysis of 6 trials (n = 1,527) demonstrated a high probability of severe COVID-19 (with ARDS) associated with acute myocardial injury (risk ratio (RR) 13.48, 95% CI 3.60 – 50.47, p = 0.0001) [50].

In a study of 187 COVID-19 patients by *T.Guo et al.*, 35% had concomitant CVD (AH, IHD or cardiomyopathy), 28% were diagnosed with acute miocardial damage (troponin T > 99th percentile of the upper limit) after contact with the virus [51]. Hospital mortality with normal troponin T in patients without CVD was 7,62%, while where patients had concomitant CVD, hospital mortality was 13.33%; with increased troponin T, the value was 37.50% and 69.44%, respectively (the highest value in this group).

In a study by *S.Shi et al.* (n = 671), 75.8% of casualties had acute myocardium damage (*vs* 9.7% in COVID-19 survivors, p < 0.001) [52]. Where troponin I was > 0.026 mg/mL (a cut-off point), the risk of hospital mortality was 4.56 higher (95% CI, 1.28 – 16.28, p = 0.019). A multivariate analysis demonstrated that the risk of acute myocardial damage in COVID-19 increased: a 10-year increase in the age – 1.64-fold (95% CI 1.28 – 2.10, p < 0.001), concomitant AH – 3.3-fold (95% CI 1.77 – 6.14, p < 0.001), chronic IHD – 2.92-fold (95% CI 1.32 – 6.48, p = 0.008), and chronic obstructive pulmonary disease – 4.01-fold (95% CI 1.28 – 12.61, p = 0.018).

In a series of studies of COVID-19 patients, acute myocardial damage was associated with high levels of

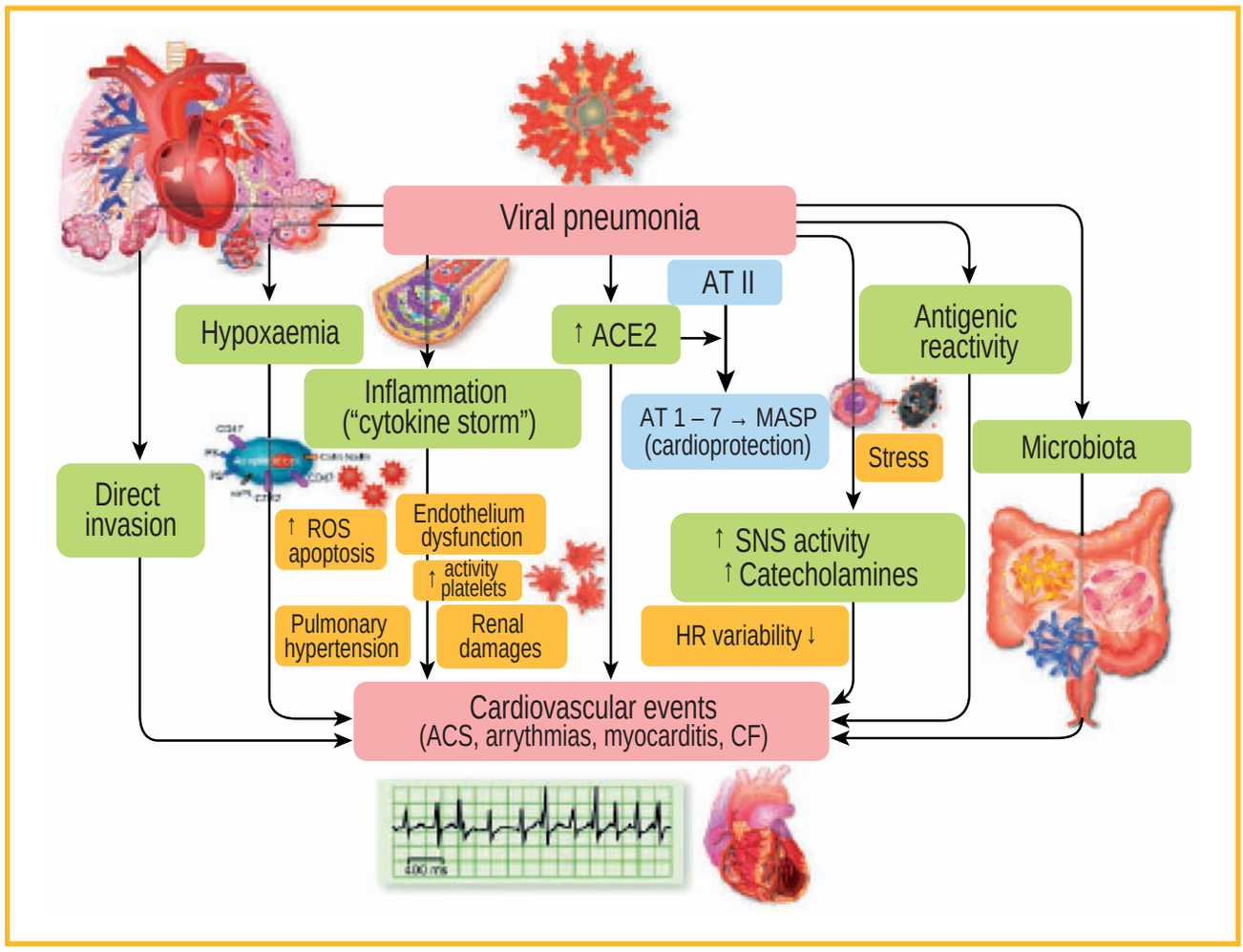

Figure 2. Possible mechanisms for the effect COVID-19 disease on the cardiovascular system (ad. [20])
Note: AT, angiotensin; ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; SNS, sympathetic nervous system; HR, heart rate; ROS, oxygen free radicals; MASP, MAS protection; CF, cardiac failure; ↓, decrease; ↑, increase.

Рис. 2. Возможные механизмы воздействия COVID-19 на сердечно-сосудистую систему (адапт. из [20])
Примечание: ↓ – понижение; ↑ – повышение.

D-dimer, N-thermal pro-B-type natriuretic peptide (NT-pro-BNP), C-reactive protein and interleukin-6 [42, 48, 51, 52]. It proves the association between acute myocardial injury in COVID-19 and marked inflammation and cardiac dysfunction.

COVID-19 and cardiac failure. Viral infection can provoke decompensation of chronic CF, if the patient has comorbidies, and a shock. The incidence of CF in patients who died of COVID-19 was 52%, while in survivors this value was 12% ($p < 0.0001$) [10]. The incidence of new CF cases in COVID-19 patients was aprox. 23% [10].

Acute CF associated with viral infection seems to be a consequence of a prior systolic dysfunction, ARDS and cardiovascular pathology *de novo* (acute myocardial ischemia, MI, tachyarrythmia, myocarditis or cardiomyopathy). First COVID-19 cases in the USA described cardiomyopathy in 33% cases [49]. *E.Argulian et al.* found that right ventricle dilatation seen at echocardiography is associated with a high risk of hospital mortality in COVID-19 patients [53]. COVID-19-associated pulmonary hypertension caused by lung damage and hypoxia or PATE leads to increased right ventricle load and cardiomyocyte damage.

Daily diuresis monitoring, reasonable water schedule, continued scheduled base therapy, including ACEi and ARI, are all very important for COVID-19 patients with chronic CF decompensation [8].

COVID-19 and myocarditis. The incidence of myocarditis in COVID-19 patients is about 8 – 12% [16]. In a high viral load, cases of fulminant myocarditis were recorded (approx 7% of patients) [54]. Myocarditis patients can complain of moderate chest discomfort and palpitations; clinical manifestations are systolic cardiac dysfunction, conduction trouble and tachyarrythmia [16]. Clinically, miocarditis is diagnosed 2 weeks after coronavirus symptoms appear.

COVID-19, acute and chronic coronary syndrome. COVID-19 can trigger atheromatosis plaque instability and cause MI [39, 51], significantly increasing the risk of mortality among infected patients. Acute MI mortality is 40% of the overall COVID-19 mortality rates [2].

Patients with COVID-19-associated pneumonia can have acute type 1 MI (resulting from coronary atherothrombosis associated with atheroma rupture (bursting), epicardial coronary artery occlusion); but usually they have type 2 acute MI (because of imbalance between

myocardium oxygen need and oxygen supply, metabolic stress) [39, 40]. Acute myocardial damage interpreted as acute type 2 MI is recorded in 7 – 30% COVID-19 patients [2].

In pathogenic terms, ACS in SARS-CoV-2 is associated with marked microvascular inflammation, endothelial dysfunction, thrombothic disorders, and haemodynamic changes [39]. It is known that circulating interleukin-6, a biomarker of high COVID-19 mortality, is one of the key inflammatory factors of atherothrombosis [16]. ACS can be promoted by inadequate control of associated cardiovascular risk factors. To verify the diagnosis of ACS in COVID-19 patients, a thorough examination is required [8].

In patients with chronic IHD, SARS-CoV-2 aggravates the disease because of atheroma destabilisation and high risk of atheroma rupture [8, 39, 51]. COVID-19 patients who underwent invasive cardiovascular procedures or surgery are at higher risk of stent or bypass thrombosis.

L.N.Fovino et al. conducted a retrospective analysis of clinical COVID-19 outcomes (a combined endpoint was hospital mortality and need in intensive care) (n = 45, mean age: 65.3 ± 14.6 years) with subclinical coronary artery disease. They assessed coronary calcium score (CCS) levels using chest high-resolution computed tomography (HRCT) [55]. The combined endpoint was recorded in 75% of patients with marked atherosclerosis (CCS ⩾ 400 Agatston units) *vs* 20% of patients (p = 0.004) with minimal/moderate signs of atherosclerosis (CCS < 400 Agatston units); hospital mortality was 50% *vs* 8.9%, respectively (p = 0.003). CCS ⩾ 400 units was a marker of poorer outcomes in patients hospitalised with COVID-19: OR was 7.86 (95% CI 1.16 – 53.01, p = 0.034) in an age- and gender-adjusted model, OR 10.7 (95% CI 1.19 – 68.01, p = 0.035) in a model with age and oxygenation.

In pandemic settings, an exact routing and transportation of patients with suspected ACS should be strictly followed. In general, a widely accepted strategy for management of such patients should be adhered to [8]. In severe COVID-19 and lung damage, when the patient is hospitalised to with respiratory support, conservative strategy is preferable, including in MI1 cases (if an invasive procedure is contraindicated).

COVID-19 and arrythmia. In a series of observations of COVID-19 patients (n = 138) in China, supraventricular and ventricular arrythmia was diagnosed in 16.7% [2]. In severe COVID-19, arrythmia was recorded ≈ 5 times more often than in mild cases. Recurrent paroxysmal atrial fibrillation was found in 23 – 33% of patients with severe COVID-19 (sepsis or ARDS), newly diagnosed paroxysm were diagnosed in 10% [2]. In a recent report from Italy, atrial fibrillation was recorded in 24.5% of 355 deaths (mean age: 79.5 years, including 30% of women) [56].

Prognosis depends on the type of heart rhythm disorder and COVID-19 severity (more favourable prognosis with mild or moderate infection) [8]. There have been reports of arrythmia in COVID-19 patients resulting from proarrhythmic effect of medications (prolonged QT interval and a higher risk of torsade de pointes) [8]. Therefore, standard 12-lead ECG, transthoracic echocardiography, and blood potassium level measurement are mandatory.

ECG monitoring should be started next day after antiviral therapy initiation. In initially congenital or acquired long QT-syndrome, brachycardia (< 50 bpm), ECG monitoring is required 4 hours after first antiviral medication administration. Prior to antiviral medication prescription, plasma potassium should not be < 3.5 mmol/L. In patients with atrial fibrillation, heart rhythm and ventricular contraction rate should be monitored and thromboembolic disorders should be prevented with anticoagulants, taking into account possible interaction of oral anticoagulants with antiviral therapy.

Cardiopulmonary rehabilitation in COVID-19 patients

COVID-19 survivors with cardiovascular complications, especially in moderate and severe cases, need medical rehabilitation. Currently rehabilitation programs are being prepared for such patients. Then these programs will be tested in randomised clinical trials. As COVID-19 is a multi-system disease, rehabilitation programs should be based on syndromic-pathogenetic approach. It will ensure that an adequate number of rehabilitation methods/techniques will be used to correct pathological changes in a specific patient.

Rehabilitation of COVID-19 survivors aims at recovery of functions of external respiration, oxygen transport and utilization by functioning tissues/organs; reduction in dyspnea; cardiovascular system support and minimisation of the risk of cardiovascular complications; improved quality of life; psychological status normalisation; daily activities recovery, and active life.

Key principles of medical rehabilitation of COVID-19 patients: staggered and personalised approach, early initiation (when acute COVID-19 is over and after patient's clinical condition has stabilised), multidisciplinarity, continuous monitoring of patient's condition during rehabilitation (first of all, respiratory and cardiovascular parameters), comprehensive approach to the rehabilitation program.

Any rehabilitation intervention should take into account disease severity, rate of cardiorespiratory decompensation and other organs involvement (kidneys, neurocognitive, psychiatric, musculoskeletal systems), fatigue, asthenia, risk of thromboembolic disorders, and comorbidities. For patients who had severe COVID-19, rehabilitation should consider nutrition status, total body weight and muscle mass. Most promising for pulmonary rehabilitation are first two months after acute coronavirus infection; this is a therapeutic window [57]. During physical rehabilitation COVID-19 patients should have access to oxygen therapy (as required), especially patients with clinical indications or those patients who did not have any respiratory support.

In the novel coronavirus infection, rehabilitation starts in and continues in a specialised inpatient unit – **this is stage 1 of early rehabilitation**. This is an important stage because it allows preventing or minimising com-

plications of a viral disease and detrimental effect from immobilisation; ensuring prevention of critical conditions, joint stiffness and contractions, thrombotic complications; and, if possible, recovery of physical and psychological state of the patient. For patients with severe COVID-19 early rehabilitation is not recommended; it can be considered only after the acute stage, vital functions stabilisation, with positive dynamics evidenced by computer-aided tomography or ultrasound examination [58].

Attention should be paid to exercises of weakest and most important muscles involved in verticalization and locomotion of the patient. Methods of physical rehabilitation comprise: patient positioning ("positioning" rehabilitation, also with the help of the prone position), early mobilisation (passive, partially passive and active motions in all joints with more and more physical activity), verticalization, respiratory manoeuvres, neuromuscular electrical stimulation of lower limbs (for certain groups of patients), dynamic physical activities with low-intensity, low amplitude and slow pace (a bedside stationary bike can be used), moderate resistance exercises (to reduce muscle mass losses and to strengthen the muscles), physical exercises for imbalance correction (if any) [59].

In one therapeutic exercise session (either passive, or passive-active mode) should last for 5 to 15 minutes 3 and more times daily (with the overall duration of at least 30 minutes a day). Once the patient is moved to inpatient setting, therapeutic exercises should last for 10 – 15 minutes 2 – 3 times daily.

Stage 2 of rehabilitation (early inpatient rehabilitation in a specialised inpatient rehabilitation unit) should be arranged in accordance with the antiepidemic provisions. It includes in-ward patient isolation, no group therapy, minimum staff involved into rehabilitation, remote communication between the patient and multidisciplinary team members, use of video, booklets and other telerehabilitation techniques for patient education [60]. At stage II, rehabilitation procedures should last for at least 3 hours 5 times a week.

Physical rehabilitation at stage II means early activation of patient's physical activity, use of various methods of pulmonary and cardiological rehabilitation: diaphragm breathing, exercises for inhale muscles (inspiratory training devices can be used), vibration and compression therapy and acoustic exercises together with drain-activating exercises (where indicated), exercises for general strength, dynamic physical exercises with low intensity (including aerobic exercises on a statutory bike), low-intensity resistance loads (to train main groups of muscles).

Physical exercises in COVID-19 patients with CVD has some features:

- they start with low-intensity loads (exercise stress intensity ⩽ 3 points on modified Borg Dyspnoea Scale or laboured breathing ⩽ 3 on Borg Dyspnoea Scale);
- intensity increases gradually, initially at the account of exposition (duration), then at the account of more intensive exercises (with adequate response to exercises);
- strict state monitoring during exercises.
- power loads in COVID-19 should be based on MRC, UK Medical Research Council.

Special attention should be paid when prescribing physical exercises to patients, whose coronavirus infection was complicated with acute myocarditis, cardiomyopathy, postinfectious cardiac failure [61]. In such cases, rehabilitation should be started after acute period (taking into account contraindications), when the clinical condition is stable and CT, ECG and ultrasonic cardiography results demonstrate positive dynamics.

Stage 3 of rehabilitation is late outpatient rehabilitation (in outpatient settings). Physical rehabilitation of COVID-19 survivors with CVD involves continuation of exercise therapy in order to recover respiratory and cardiovascular system, and transition to more lengthy exercises (statutory bike and/or step exercises). Physical exercises are supervised by medical professionals (also via telerehabilitation). Then patients are recommended to do exercises at home. At home, patients can walk on a flat surface, step up, etc. At this stage it is very important to teach the patient to self-control the condition and ensure safe exercises.

A significant aspect of rehabilitation of COVID-19 patients at all three stages is awareness of the healthy life style (no bad habits, anti-atherosclerotic diet and stress tolerance), explanation why it is important to follow doctor's recommendations, take medications and participate in rehabilitation. Psychological support should be offered almost to all patients with coronavirus infection [62]. Anxiodepressive disorders are managed as required.

Three-stage cardiorehabilitation of COVID-19 patients complicated with ACS (myocardial infraction) or coronary artery bypass grafting should be based on the recommendations of the Russian Society of Cardiosomatic Rehabilitation and Secondary Prevention [63, 64].

Conclusion

The impact from SARS-CoV-2 and other pathogens with toxic, proinflammatory and procoagulation effects can cause decompensation of concomitant CVD and increase hospital mortality rates. The new role of ACE2 as a receptor for SARS-CoV-2 can partially explain the pathophysiological association between the viral infection, immune system and CVD. The novel coronavirus infection can provoke acute myocardial damage and other cardiological complications. As some medications used to treat COVID-19 have cardiotoxic effect, continuous haemodynamic monitoring, ECG and ultrasonic cardiography (as indicated) are mandatory.

As the association between administration of RAAS inhibitors (ACEi and ARI) and a higher risk of infection with more severe COVID-19 has not been yet proven, patients with CVD should keep on taking these medications. COVID-19 survivors should take part in rehabilitation programs for faster and better recovery of their functions (first of all, of respiratory and cardiovascular systems), better quality of life and lower risk of disability.

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Immune mechanisms of SARS-CoV-2 and potential drugs in the prevention and treatment of COVID-19

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Abstract

The lack of specific vaccines against SARS-CoV-2, as well as chemotherapy, significantly affected the spread of infection and the number of adverse outcomes of COVID-19. With the discovery of the pathogenesis of coronavirus infection, especially immune mechanisms, the important role of the innate immunity system in interacting with the virus is obvious. The presence of comorbid conditions, as well as the aging of the body, lead to disturbances in the immune response mechanism, low interferon induction, depletion of $CD8^+$-lymphocytes and natural killers and suppression of the effectiveness of both innate and adaptive immunity. The review discusses various mechanisms of antiviral activity associated with the induction of interferon (IFN) production, the use of direct IFN therapy, the use of antiviral drugs, and immunotropic therapy (synthetic immunomodulators), as promising in the prevention and treatment of COVID-19.

Key words: SARS-CoV-2, pathogenesis, COVID-19, innate immunity, adaptive immunity, interferon therapy.

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Иммунные механизмы SARS-CoV-2 и потенциальные препараты для профилактики и лечения COVID-19

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Резюме

Отсутствие специфических вакцин против SARS-CoV-2, как и химиопрепаратов, в значительной степени сказалось на распространении инфекции и количестве неблагоприятных исходов COVID-19. С раскрытием патогенеза коронавирусной инфекции, особенно иммунных механизмов, очевидна важная роль системы врожденного иммунитета при взаимодействии с вирусом. Коморбидные состояния, так же как и старение организма, приводят к нарушениям механизмов иммунного ответа, снижению интерфероноиндукции, истощению $CD8^+$-лимфоцитов и естественных киллеров и подавлению эффективности как врожденного, так и адаптивного иммунитета. В обзоре рассматриваются различные механизмы противовирусного действия, связанные с индукцией выработки интерферона (IFN), использованием прямой IFN-терапии, применением противовирусных препаратов, а также иммунотропной терапии (синтетических иммуномодуляторов) как перспективных средств для профилактики и лечения COVID-19.

Ключевые слова: SARS-CoV-2, патогенез, COVID-19, врожденный иммунитет, приобретенный иммунитет, интерферонотерапия.

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Due to epidemiological and clinical characteristics of the new coronavirus infection COVID-19, we have to continuously analyze the information on the pathogenesis of this infection. This is also important due to the absence of aetiotropic therapy and due to that the only option is a pathogenetic treatment.

Interaction of the virus and the human immune system includes the following two stages: internalization of the virus into the cell, virus multiplication with concurrent suppression of interferons (IFN) synthesis, induction of a systemic inflammatory response and "cytokine storm".

Each stage is characterized by its own distinctive key mechanisms that determine disease progression. The clinical aspect of COVID-19 disease is determined not only by a direct viral effect, but also depends on the individual response of the human body, thus determining broad disease variety in the population – varying from asymptomatic course of the disease or asymptomatic carrier state to severe course with a high probability of death.

The aim of our work was to analyze current understanding of new coronavirus infection COVID-19 pathogenesis in order to assess the perspectives for use of immune therapy in non-specific prevention and treatment of patients with COVID-19.

Like other respiratory coronaviruses, the primary route of COVID-19 transmission is airborne, but also the fecal-oral route cannot be excluded. In order to enter the cell the virus interacts with angiotensin-converting enzyme 2 (ACE2) receptor and membrane-bound serine protease 2 (TMPRSS2) required for protein S priming.

After binding of protein S to ACE2, direct fusion of the viral and cell membranes takes place, after which the protein undergoes partial cleavage and becomes active. The viral RNA enters the cell cytoplasm, where after its translation the active replication of the viral genome begins. Its interaction with the Golgi complex allows viral particles to be released into the blood plasma, thus continuing the cycle of the virus spreading throughout the body [1].

Considering the decreased ACE2 expression during COVID-19 infection, we can expect renin-angiotensin system failure, with subsequent dysregulation of blood pressure and water-electrolyte balance. At the same time, we cannot exclude that the observed change in ACE2 receptors expression can play an important role in COVID-19 pathogenesis itself [2]. Analysis of statistic data for COVID-19 cases among people living in highland areas showed a milder disease compared to residents of flat land areas. According to the authors' opinion [3], this may be due to both a decreased virus viability under low atmospheric pressure conditions, and due to decreased ACE2 expression in hypoxic environmental conditions.

Researchers demonstrate a lack of consensus on the role of ACE2 receptors in the disease pathogenesis. Experimental data showed a decreased viral load and replication in ACE2-mutant mice [2]. On the other hand, based on the similarity of lung damage observed in COVID-19 and in H5N1 avian influenza virus infection, one can assume a protective effect of exogenous ACE2 administration preventing acute respiratory distress syndrome (ARDS) development.

Mortality gender difference in COVID-19 was also attributed to ACE2, which is lower in women. It is presumably due to either genetic dimorphism, because the ACE2 gene is located on the X-chromosome, or due to different immunoregulatory effects of estrogens compared to testosterone [4].

At the stage of virus penetration into the cell, the viral antigen is presented to antigen-presenting cells (APC) and the virus is recognized by the innate immunity receptors. In the case of SARS-CoV-2 virus, like for all RNA-viruses, pathogen-associated molecular patterns (PAMP) are recognized by endosomal RNA-receptors, Toll-like receptors (TLR3 and TLR7), as well as by cytoplasmic receptors of RIG-I family (Retinoic-Acid-Inducible Gene I) and cytoplasmic helicase MDA-5 (Melanoma-Differentiation-Associated Protein 5, protein 5 associated with melanoma differentiation) [5]. Receptor activation should lead to a cascade response through the NF-kB transcription factor and IRF3 (regulatory IFN transcription factor), followed by the expression type I IFN and other pro-inflammatory cytokines. In addition to PAMP, damage-associated molecular patterns (DAMP), which respond to fragments of damaged cells produced as a result from the intense pyroptosis – characteristic manifestation of COVID-19, also play an important role.

A different response of pulmonary endothelial cells to damage is also linked to the role of DAMP [2]. Mice experiments demonstrated a different response to a protein belonging to a group of nuclear non-histone proteins HMGB1 (high-mobility group protein B1), which is a damage marker that can activate RAGE receptor (receptor for advanced glycation end products) actively expressed in the lung tissue. Researchers found *in vitro* necrosis of cells obtained from male animals, and apoptosis of cells from female animals. Results of experimental studies have already been presented on the efficacy of HMGB1/RAGE antagonists and TLR4 antagonists (also a functional HMGB1 receptor) in the treatment of severe lung damage-associated diseases [6].

Successful activation of interferon-producing cascade should limit the viral replication and suppress SARS-CoV-2 dissemination during the stage of disease onset [7]. However, given the inhibitory effect of the viral NSP1 (nonstructural RNA-binding protein) and rp6 (ribosomal protein S6) proteins, a low efficiency of interferon induction can be assumed, especially at the stage of active viral replication, while direct IFN therapy should demonstrate an adequate therapeutic effect. [8]. The work [9] presents a hypothesis of IFN production activation, associated with the level of intracellular ATP (adenosine triphosphate), the decrease of which, according to the authors opinion, plays one of the key roles in COVID-19 pathogenesis.

One of the most probable reasons for insufficient and tardy innate immunity response in COVID-19 disease is the possible immune evasion (escape) that is characteristic of this virus. Virus replication within cellular organelles prevents the virus from being recognized by cytoplasmic receptors. There is also evidence of a long "lag-period" (microorganisms growth initial phase), which leads to the retarded activation of the IFN cascade, that is too late to prevent viral dissemination. At the same time, a late increase of type I IFN level can potentiate the development of a "cytokine storm", thus prompting us to investigate the role of other IFNs with antiviral activity, e.g., IFN-λ. There is a variety of opinions regarding their role. On the one hand, there are published data [3] that a mutation of the *IFNL4* gene (TT-type), leading to the absence of this subtype, results in a faster and more complete viral load elimination. The authors suggest that this phenomenon results from deactivation of desensitization mechanism, which in other circumstances reduces IFN-α activity. On the other hand, IFN-λ, due to its organ-specificity effects, does not cause such a pronounced pro-inflamma-

tory response as type I IFN, and its presence in the early stages of the disease is able to suppress viral replication without the development of IFN-α lag-syndrome and without induction of "cytokine storm" [10]. In the case of innate immunity mechanisms failure, elements of the adaptive immune system are recruited as a defense, with the development of antibodies and a specific cellular immune response.

Hyperactivation of the innate immune response without a concomitant transition to an adaptive immune response is the important part of this infection pathogenesis. Patients with a severe course of the disease demonstrate a predominance of neutrophils, in contrast to the expected lymphocytes increase. This may be due to the ability of the virus to increase the expression of the membrane receptor of type 2 NK-cells (NKG2A), thus leading to functional depletion of $CD8^+$ lymphocytes and natural killer cells and leading to a suppression of both innate and adaptive immunity effectiveness [1]. The age-related dimorphism of symptoms may be associated with a change in the functional activity of the immune system. Aging-related T-cell lymphopenia, a decreased neutrophil and macrophage activity, a shift in the cytokine balance towards a pro-inflammatory response – all these factors aggravate the course of coronavirus infection. In addition, the phenomenon of antibody-dependent infection enhancement (ADE) suggests that in case of retarded period of antibody titer rise, which is typical for older people, the viral genetic shift can happen changing its antigenic structure, which leads to the accumulation of non-protective antibodies facilitating the viral penetration into cells. These data suggest that the virus, leading to a decrease in the number of ACE2 receptors, continues to spread via other mechanisms and pathways independent of the initial main entrance receptor [11].

In the case of adequate T-cell response, T-cells recruited to the site of infection exert a protective effect and limit the replication and spread of the virus. However, in the case of immune evasion, this accumulation of T-lymphocytes in the tissue leads to a hyperactive reaction, mainly type 1 reaction, with subsequent damage of organ tissues and the possible development of a "cytokine storm" [4], which is characterized by overproduction of pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β. The increased levels of chemokines CXCL10, CCL7, an antagonist of the IL-1 receptor, are associated with increased viral load and loss of lung function [12]. Given the fact that the "cytokine storm" is probably the primary cause of body damage and death, a number of therapeutic strategies associated with inhibition of this process was proposed. The high-priority agents are probably monoclonal antibodies. However, other factors such as adequate vitamin D levels may also be important in achieving the control of this infection [6].

Haemodynamic disorders associated with both systemic inflammatory response and hypoxia are essential in the pathogenesis of COVID-19. Concurrently with the decrease in the level of functioning ACE2 responsible for vasodilation, vasoconstriction develops in the lungs with the resulting hypoxia. Hypoxia, in turn, affects the endothelium and provokes a pro-inflammatory response. In the setting of these processes, hypercoagulation is triggered, related to the release of the von Willebrand factor and to a high expression of tissue factor (TF). As a result, together with the activation of NETosis (the formation of extracellular neutrophil traps – that is a powerful neutrophil function, which is supposed to contribute to the development of multiple organ failure and lead to death), coagulation is initiated and the TF/VIIa pathway is activated. Subsequent microthrombosis in the lungs, which develops in the setting of hypercoagulation state, endothelial damage, and slowed blood perfusion, becomes a pathophysiological substrate for the development of ARDS [13]. Results of autopsies of patients who died from COVID-19 also confirm the presence of coagulation disorder: more than 70% of these cases were diagnosed with disseminated intravascular coagulation syndrome [6].

Consequently, in the pathogenesis of COVID-19, activation of innate immunity mechanisms, a cascade of interferon-producing reactions can facilitate the control of viral replication and suppression of SARS-CoV-2 dissemination during the onset of the disease and promote the involvement of the adaptive immune system with the formation of antibodies. Despite the different opinions regarding the spectrum of therapeutic strategies available, the immunotropic strategy among others is considered as promising for the prevention and treatment of COVID-19.

Synthetic immunomodulators

The synthetic immunomodulator azoximer bromide is one of the potential agents to be used at the early stages of COVID-19 infection development. It is characterizes by the complex mechanism of action – immunomodulatory, detoxifying and anti-inflammatory. Based on clinical studies results, we can discriminate three main roles of this agent in the immunopathogenesis of inflammatory diseases: it increases the effectiveness of innate immunity; it acts as an adjuvant in the development of a humoral immune response; it provides a pronounced pathogenetic and clinical effect in patients with severe inflammatory diseases.

The results of the study showed that incubation of cells with azoximer bromide increased the expression of innate immunity receptors, including MDA-5 [14–17]. High expression of MDA-5 ensures recognition of the virus at an early stage of infection – this is a prevention strategy; at a later stage, a strategy for activating a specific immune response is implemented. It is known that circulating plasmacytoid dendritic cells (pDCs) significantly prevent the spread of the virus in the body, and in particular viremia. These cells, when activated, produce type 1 IFN, thus blocking viral replication. It was found that an azoximer bromide-containing vaccine was significantly superior to nonadjuvant vaccines in increasing the number of pDC in blood plasma [18]. In addition, the drug increased the activity of NK-cells and CTLs – the main cells that provide the killing of virus-infected cells.

Azoximer bromide induces DC maturation, also increasing the expression of co-stimulating molecules $CD80^+/86^+$, ICOSL, required for the subsequent activation of T-follicular cells. These in turn are the key link

for the production of specific high-affinity antibodies by B-cells [19, 20]. Therefore, azoximer bromide provides a phase transition from innate to adaptive immune response – a step that is impaired in patients with severe COVID-19. The incorporation of this agent into a complex therapeutic strategy for patients with severe infectious pathological conditions (pneumonia, acute pancreatic necrosis, sepsis, etc.) was associated with a decrease of disease severity and a decrease in mortality; it provided a decrease of IL-6 concentration, an increase of lymphocytes count, and an increase in phagocytosis activity [1, 2] [21–25]. Decreased disease severity observed in the studies described above may also be due to the ability of azoxymer bromide to suppress NETosis, thus localizing the focus of inflammation and preventing the development of hemodynamic disorders, associated with blood clot formation and damage to the vascular endothelium. Thus, there is a rationale to consider azoximer bromide an effective component for therapeutic strategies in COVID-19 patients, that is effective both at the initial stage of infection and at the stage of systemic inflammation development. Currently, the drug has already been clinically tested in the setting of a new coronavirus infection and is included in the clinical guidelines in Slovakia for the treatment of COVID-19 patients aged ⩾ 65 years [26]. Elderly patients are at high risk of COVID-19 infection with a poor outcome. The physiological aging process also affects the immune system functioning. Aging slows down the timely response of nonspecific body defense mechanisms responsible for the recognition and removal of foreign agents. Studies in elderly and senile people have shown that the inclusion of azoxymer bromide into the treatment scheme for these categories of patients increased the relative and absolute content of T-lymphocytes with the $CD3^+$ and $CD4^+$ phenotypes, increased the ratio of $CD4^+/CD8^+$ lymphocytes, increased serum levels of immunoglobulins A and G, and normalized white blood cell counts [27–30]. This means that the drug can reduce the clinical manifestations of secondary immune deficiency by modulating immune mechanisms, which are essential in avoiding lymphopenia, suppression of type 1 INF, “cytokine storm”, and systemic inflammatory response.

Interferons

Currently, nine types of interferons were isolated in human, and according to their ability to interact with three types of receptors, they are grouped into three families:

- I – IFN-α, IFN-β, IFN-ε, IFN-ϰ, IFN-ω;
- II – IFN-γ;
- III – IFN-λ1, IFN-λ2, IFN-λ3.

IFN-α is widely used in medicine due to its pronounced antiviral, immunomodulatory and indirect antibacterial affect. IFN-α as a regulatory protein, enhances the synthesis of major histocompatibility complex molecules by antigen-presenting cells, securing the proper process of antigen presentation to immunocompeten T-cells. Interferon provides the expression of $CD4^+/CD8^+$ molecules on T-cells, which enables them to recognize the antigen and participate in the immune response. IFN-α, is the factor that enhances the expression of not only MHC molecules, but also other surface molecules. It increases the number of Fc receptors on the surface of immunocompeten T-cells, enabling the normal process of phagocytosis [31–33]. In Russia, a lot of IFN-α medicinal products are used in clinical practice [34–40]. The appropriateness of using IFN-β injectable forms in combination with antiviral drugs is also currently being discussed. However, the results of these studies have not yet been published [41]. In addition to IFN-α, the possibility of using IFN-λ is also discussed, as it has an antiviral effect distinct from that of type I IFNs. Unlike type I IFNs, IFN-λ exerts more organ-specific effects and participates in the maintenance of epithelial cells protective function, particularly in the respiratory tract [42]. Given the low rate of side effects associated with this therapy compared to type I and II interferons, the use of this therapy is potentially appropriate for the prevention of COVID-19.

Interferon inducers are substances of natural or synthetic origin that can induce type I and II IFNs synthesis in the body; they are characterized by immunomodulatory, antiviral, and anti-inflammatory activity [43, 44]. The main producers of IFN in response to the administration of IFN inducers are epithelial intestinal cells, hepatocytes, T-lymphocytes, neutrophils, and granulocytes. The mechanism of antiviral action is due to induction of IFN synthesis and, as a result, due to inhibition of virus-specific proteins translation in infected cells. Ultimately this results in virus reproduction suppression. Natural and synthetic IFN inducers are also able to induce the production of other cytokines: TNF-α, IL-1, IL-6, IL-8, IL-10, and colony stimulating factors. They are indicated in various infectious diseases, primarily viral diseases [45, 46].

Immunomodulatory drugs (for example, containing a polysaccharide complex obtained from a purified *Solanum tuberosum* shoots extract) may have a potential in COVID-19 prevention. An experimental animal study showed its activity against coronavirus, both in terms of clinical improvement and in reducing the estimated viral load. Panavir immunomodulatory activity is due to its effect on macrophage system, and due to induction of IFN synthesis, thus reducing viral infective activity and increasing the viability of the affected cells [47–49]. We are looking forward to clinical trials evidence.

Antiviral medicinal products. Imidazolyl ethanamide pentandioic acid (IEPA) is an original antiviral drug used in Russia, for treatment and prevention of influenza and other acute respiratory viral diseases. It was found that IEPA, being not an interferonogenic agent, increases IFN receptor (IFNAR) synthesis and enhances cell sensitivity to IFN signaling, which are initially suppressed by the

[1] Reshetnikov D.I. [Diagnostics and treatment of liver failure in acute destructive pancreatitis]: Thesis for a candidate degree in medical sciences. Jakutsk; 2009. Available at: *http://medical-diss.com/medicina/diagnostika-i-lechenie-pechenochnoy-nedostatochnosti-pri-ostrom-destruktivnompankreatite#ixzz6JWFU68RU* (in Russian).

[2] Borovkova N.V. [Secondary immunodeficiency in case of purulent-septic complications of surgical diseases]: Thesis for a candidate degree in medical sciences. Moscow; 2011 (in Russian).

influenza virus pathogenicity factor (non-structural protein NS1). The drug is able to stimulate the synthesis of antiviral effector proteins PKR and Mxa in infected cells, thus offsetting the suppressive effect of influenza virus on the IFN system. Theoretical assumptions of IEPA clinical efficacy were confirmed by the data regarding the effect on the innate immunity system under viral infection conditions [50, 51]. Clinical trials are needed to assess its efficacy in terms of new coronavirus infection treatment. Theoretical rationale is not sufficient in this setting.

Numerous studies, carried out both in the Russian Federation and in foreign laboratories, have shown that the medicinal product Umifenovir acts in the early stages of viral reproduction by inhibiting the fusion of the viral lipid envelope with intracellular membranes, thus preventing virus penetration into the cell. But the medicinal product does not affect viral transcription and translation, and it has no effect on neuraminidase (NA) activity and virus adsorption [52–54]. Umifenovir virus-specific mode of action differs from that of other anti-influenza drugs used: Amantadine and Remantadine are ion channel blockers, and Zanamivir and Oseltamivir are NA inhibitors. Umifenovir antiviral activity was confirmed in numerous *in vitro* and *in vivo* studies carried out in Russian core research centers and in independent laboratories in the USA, Great Britain, Australia, France, China, and other countries [55, 56]. In early February 2020, Chinese experts reported the possible efficacy of this medicinal product against coronavirus, but so far there is no confirmation from clinical studies.

Another antiviral and immunomodulatory agent is the sodium salt of the copolymer (1→4)-6-0-carboxymethyl-β-D-glucose, (1→4)-β-D-glucose and (21→24)-2.3,14,15,21,24,29,32-octahydroxy-23-(carboxymethoxymethyl)-7,10-dimethyl-4,13-di(2-propyl)-19,22,26,30,31-pentaoxaheptacyclo[23.3.2.216.20.05.28.08.27.09.18.012.17]dotriaconta-1,3,5(28),6.8(27),9 (18),10.12 (17),13,15-decaene. The primary mode of action of the drug is to induce IFN synthesis. In addition, it induces in the human body the synthesis of the so-called late IFN, which is a mixture of IFN-α and IFN-β, which possesses high antiviral activity. The drug induces IFN synthesis in almost all cells populations involved in the antiviral response of the body: T- and B-lymphocytes, macrophages, granulocytes, fibroblasts, and endothelial cells [57, 58]. There is still no confirmation of this drug effectiveness from clinical trials with COVID-19 patients.

Boceprevir is another potentially effective medicinal product. It is an inhibitor of 3CL protease (the main protease M^{pro}), which is important for the viability of the virus. Like other antiviral drugs with a similar effect (GC-376, calpain II and XII inhibitors), this drug suppressed viral replication in experimental studies. However, the clinical use of these agents is currently a subject of discussion [59].

The use of janus kinase inhibitors (JAKi) is also an issue in question.

The efficacy of these drugs in the treatment of patients with severe COVID-19 was confirmed in a number of randomized clinical studies. However, due to the possibility of further deterioration of coagulation disorders specific to COVID-19 patients, these drugs should be used with caution, after careful risk assessment for adverse effects of such a therapy [60, 61].

However, not only JAKi are able to block the virus internalization, but also inhibitors of CD147 receptor, which is, like JAK, the gateway for COVID-19. This mechanism among others is a target for azithromycin action. The antiviral effect of azithromycin was previously described in a series of scientific works. At the same time, cyclosporine capable of interaction with CD147 can also be used, or its analogs lacking immunosuppressive activity, such as cyclophilin A [62, 63].

Conclusion

The SARS CoV-2 pandemic has prompted researchers and medical practitioners to urgent search for drug therapies suitable for non-specific prevention and treatment aiming to reduce the incidence of adverse disease outcomes. The accumulated knowledge on SARS-CoV-2 immunopathogenesis, data from studies by our scientists searching the effective immunotropic drugs and investigating their mode of action, can serve as a theoretical background for experimental and clinical studies ultimately yielding treatment programs for patients suffering from COVID-19.

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An unusual course of COVID-19 infection with late increase in C-reactive protein (clinical case reports)

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Abstract

Clinical signs of COVID-19 infection are non-specific and diagnosis is typically based on comprehensive evaluation of the patient's history, clinical status, radiological and laboratory findings. A common finding in COVID-19 patients is increased C-reactive protein (CRP), though in some patients, CRP remains within normal range notwithstanding the presence of other criteria of severe disease. We describe two clinical cases of COVID-19 with severe bilateral pneumonia and late increase in CRP. Similar cases re quite challenging for making the diagnosis and indicating the antiinflammatory therapy.

Key words: COVID-19, C-reactive protein, "cytokine storm", coronavirus infection.

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Нетипичное течение новой коронавирусной инфекции COVID-19 с поздним повышением уровня С-реактивного белка (клинические наблюдения)

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Резюме

Клинические проявления COVID-19 неспецифичны, при этом основу диагностики составляет комплексная оценка данных. Одним из характерных лабораторных признаков, отражающих тяжесть течения COVID-19, является повышение уровня С-реактивного белка (СРБ). Однако в некоторых случаях уровень СРБ в течение длительного времени может оставаться в пределах нормальных значений, несмотря на присутствие других признаков тяжелого течения заболевания. В статье представлены два клинических наблюдения тяжелого течения двусторонней пневмонии, ассоциированной с COVID-19, у пациентов с поздним повышением уровня СРБ. Такие больные могут представлять определенные трудности при оценке тяжести течения и подборе патогенетической терапии.

Ключевые слова: COVID-19, С-реактивный белок, «цитокиновый шторм», коронавирусная инфекция.

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The novel coronavirus infection COVID-19 has been investigated worldwide since December 2019. The disease is caused by SARS-CoV-2 virus. Clinical signs of COVID-19 infection are non-specific and the diagnosis is typically based on the comprehensive evaluation of clinical, laboratory, and CT findings. One of the most typical laboratory signs of COVID-19 is increased level of C-reactive protein (CRP). According to international data, CRP strongly correlates with severity of the disease, the extension of lung injury based on CT findings, prognosis and progression of COVID-19 [1–4]. CRP is produced by the liver and, according to *G.Ponti et al.*, CRP can be associated with systemic angiitis in COVID-19 patients [1]. Other laboratory markers of the disease are lymphopenia [5, 6] that can reflect immune defense abnormalities [6]; thrombocytopenia associated with disseminated intravascular coagulation [5, 6]; increased D-dimer related to coagulation activation [5, 6]; and increased serum interleukin-6 (IL-6) and ferritin reflecting the severity of systemic inflammation. Excessive release of various cytokines, such as IL-6, IL-1β, IL-18, interferon gamma, and tumour necrosis factor-alpha, is called as "cytokine storm". The key markers of "cytokine storm" in real clinical practice are CRP and ferritin [1, 7]. CRP is increased in 75 – 93% of COVID-19 patients in the first days of the disease [8] and is used by physicians as one of the most significant markers of the disease severity [9]. Nevertheless, CRP can grow more slowly in some COVID-19 patients and remains within the normal range for a long time despite the presence of other signs of severe course of COVID-19. Thus, physicians could be chal-

lenged while assessing the disease severity and choosing the therapy for such patients. We describe two clinical cases of COVID-19 with late CRP increase.

Case 1

32-year old male who lived in Moscow was admitted to a hospital on the 4th of May, 2020, with fever for past 5 days, diarrhea and vomiting for past 3 days. At home, the patient took paracetamol and aspirin. Previously, he had a history of gastroesophageal reflux disease, pollinosis (allergic rhinitis and allergic conjunctivitis during birch pollution) and angioedema after eating nuts. The patient is a current smoker of hookan quite daily during past 3 or 4 years; he was not exposed to other hazards. He did not have the history of drug intolerance. The patient did not have a close contact to anyone infected by SARS-CoV-2 virus during the previous two weeks.

At presentation, he was febrile to 38.3 °C. Vital signs at the time of presentation revealed normal respiratory rate (RR, 18/min), mild tachycardia (heart rate, 90/min), normal blood pressure (BP, 130/80 mm Hg), normal oxygen saturation (SpO_2, 95%) at the room air; no peripheral oedema, no cyanosis. Lung auscultation was not performed.

Initial laboratory data showed lymphopenia (0.92×10^9/L) with normal white cell (WBC) count (5.79×10^9/L); moderately increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) to 62 and 84 U/L, respectively; and moderately increased creatinine (133 μmol/L). The baseline CRP was 2 mg/L. Chest computed tomography (CT) demonstrated bilateral multifocal, mostly bronchocentric ground glass opacities; an overall right lung involvement score was < 25 %; an overall left lung involvement score was 25 to 50% (CT-2 [9]) (Figure 1A). Nasal and oropharyngeal smears for SARS-CoV-2 virus were positive.

The initial therapy included mefloquine (7 days, the standard regimen), oral azithromycin 500 mg daily, oral lopinavir/ritonavir 400/100 mg daily, paracetamol, fraxiparine 0.4 mg daily. The fever remained at 38.5 °C. On day 3 of admission, the diarrhoea worsened and a sharp increase in hepatic transaminases (AST, 233 U/L; ALT, 234 U/L; gamma-glutamyl transpeptidase (GGT), 112 U/L) and lactate dehydrogenase (LDH) (up to 1,069 U/L) was revealed. By this reason, azithromycin, mefloquine, and ritonavir/lopinavir were withdrawn. From day 5 of admission (day 10 from disease onset), the temperature decreased to 37.5 °C, but hypoxia occurred with the decrease in SpO_2 to 94 – 91% at room air. Supplemental oxygen therapy was initiated via nasal prongs followed by a face mask because the oxygen flow gradually increased to 8 – 10 L/min. Dexamethasone 24 mg/day i.v. was added. Repeated chest CT (day 10 after disease onset) showed further extension of ground glass opacities and the appearance of consolidation areas in both lungs. The total lung involvement increased to 50 – 75% for each lung (Figure 1B).

CRP remained low during first 12 days of the disease (1.9 – 5.27 mg/L) and increased to 42.7 mg/L by day 13. Serum ferritin remained normal as well (127 – 166 μg/L; normal value is > 200 μg/L). IL-6 was measured on day 13 and was 2.5 times higher than normal (15.4 pg/mL; normal value is > 6 pg/mL).

On day 13 of admission, the low-grade fever remains; the patient had mild respiratory failure (SpO_2 80 – 84% at room air with the increase to 96% when using supplemental oxygen 6 L/min via a face mask).

Considering the respiratory failure, slow but progressive increase in CRP level and the liver damage with unsuccessful treatment with previous drugs including systemic steroids, sarilumab (human anti-IL-6R monoclonal IgG1 antibody) 200 mg was administered. This was followed by a rapid decrease in CRP to 10 – 16 mg/L and in the body temperature to 36.4 °C. SpO_2 improved until after the physical rehabilitation was started. To day 21 of the disease, SpO_2 reached 92% at room air and the supplemental oxygen flow was reduced to 3 L/min via nasal prongs. The changes in key markers of systemic inflammation, such as CRP, fibrinogen, IL-6, and lymphocytes, were shown in Figure 2. AST, ALT, GGT and LDH reduced gradually, but were still increased at the patient's discharge from the hospital.

The patient was discharged on day 20 of hospitalisation (day 25 from disease onset) with normal body temperature and SpO_2 of 95% at room air. Chest CT follow-up in a month after the discharge showed mild ground glass opacities and no consolidation (Figure 1C).

Case 2

39-year old male who lived in Moscow was admitted to a hospital on the 30th of April, 2020, on day 6 of disease onset with fever (39 °C), diarrhea, and sore throat. The initial treatment before admission with hydroxychloroquine 200 mg b.i.d. and azithro-

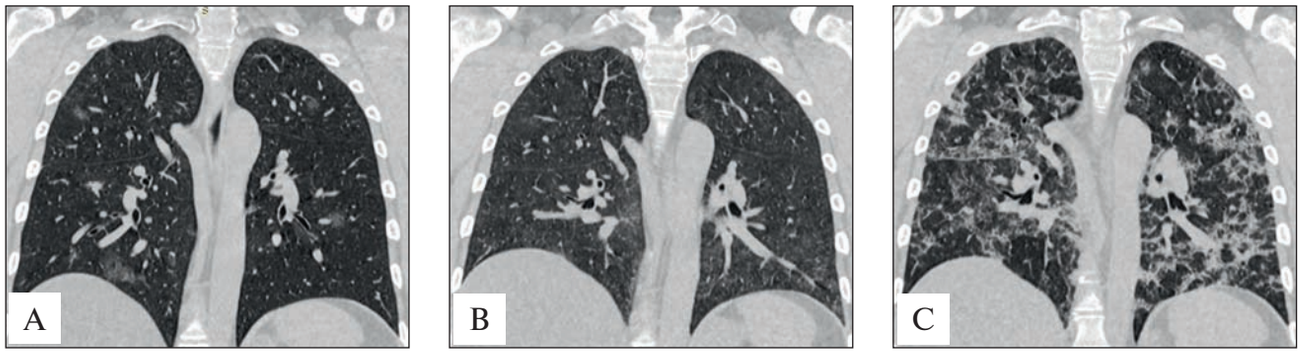

Figure 1. Computer tomogram of the patient's lungs (clinical observation No.1): A, on the 5th day from the onset of the disease (upon admission to the hospital); B, on the 22nd day from the onset of the disease (upon discharge from the hospital); C, 1 month after discharge from hospital

Рис. 1. Компьютерная томограмма легких больного (клиническое наблюдение № 1): А – на 5-е сутки от начала заболевания (при поступлении в стационар); В – на 22-е сутки от начала заболевания (при выписке из стационара); С – через 1 мес. после выписки из стационара

mycin 500 mg q.d. was unsuccessful. The patient did not have previous chronic diseases or hazardous exposure. No history of allergic reactions or drug intolerance.

At admission, the patient was febrile to 38.7 °C. He was overweight with body mass index of 30.9 kg/m^2. Vital signs at the time of admission revealed normal RR (19/min), moderate tachycardia (heart rate, 101 beats/min) and slightly decreased BP (108/66 mm Hg). SpO_2 was 96% at room air at rest. No peripheral oedema and no cyanosis were found. Lung auscultation was not performed.

Laboratory data at baseline showed low WBC (3.1 × 10^9/L), lymphopenia 0.7 × 10^9/L, and mild thrombocytopenia (118 × 10^9/L). CRP was increased to 32 mg/L. Liver transaminases were within normal ranges. Chest CT at baseline showed multiple bilateral diffusive ground glass opacities with reticular changes. The overall lung involvement was 25 to 50% in both lungs (CT-2 [9]). Nasal and oropharyngeal smears for SARS-CoV-2 were positive.

Therapy with lopinavir/ritonavir 800/200 mg/day, interferon-β-1b, and enoxaparin was started at admission. Hydroxychloroquine 400 mg/day was continued. On day 4 after admission, the patient was still febrile with the body temperature of 39 °C and SpO_2 fell to 92% at room air. CRP grew from 32 to 48 mg/L. Supplemental oxygen 6 L/min was initiated via nasal prongs resulting in the SpO_2 improvement to 96%.

On day 5 of hospitalisation (day 11 of disease), the fever became low-grade, but dyspnea worsened. SpO_2 reduced to 87 – 88% at room air. This required to increase the oxygen flow up to 10 L/min with improvement in SpO_2 to 91 – 92%. CRP continued growing to 82 – 113 mg/L. Leukopenia and lymphopenia worsened to 2.9 × 10^9/L and 0.34 × 10^9/L, respectively. There was an increase in LDH to 1,253 U/L, AST to 244 U/L, ALT to 552 U/L, total bilirubin to 21.8 μmol/L, and fibrinogen to 5.73 g/L (the normal value is < 4.00 g/L). Chest CT demonstrated further extension of ground glass opacities to 50 – 75% in each lung corresponding to CT-3.

The patient was transferred to intensive care unit (ICU) on day 5 of hospitalisation (day 11 of disease onset) for non-invasive ventilation (NIV) with CPAP mode (10 cm H_2O, FiO_2 50%). Given the growing CRP, progressive respiratory failure and liver damage, tocilizumab 480 mg was administered i.v.; the dose of enoxaparin was increased to 0.8 mL b.i.d.; lopinavir/ritonavir and hydroxychloroquine were withdrawn.

The temperature dropped to 37.4 °C several hours after tocilizumab infusion and became normal a day later. CRP reduced to 47 mg/L in the next day after tocilizumab infusion with further decrease to 8 – 5 – 2 mg/L. NIV allowed to keep SpO_2 at 95 – 96%. Liver transaminases also reduced, but had not reached the normal level to the time of the patient's discharge from the hospital (Figure 2).

On day 8 of hospitalisation, the patient was weaned from NIV to supplemental oxygen 10 L/min via a face mask and was transferred from ICU to a general ward. The patient was discharged on day 19 of hospitalisation after clinical and laboratory stability was achieved. Chest CT at the end of hospitalisation showed linear and patchy consolidation; the overall right lung involvement reduced to 25% and the overall left lung involvement reduced to 25 – 50% compared to the baseline; this corresponded to CT-2 [9].

Discussion

Clinical cases of COVID-19 with severe bilateral pneumonia were described in this article. A particular feature of these cases was late increase in CRP. The respiratory failure worsened together with CRP growth.

Development of "cytokine storm" requires administration of monoclonal antibodies against ILs or IL receptors. Clinically, these drugs should be used in patients with significant lung injury (50 – 75%) and at least two of the following signs: low SpO_2, CRP as high as > 60 mg/L or 3-fold growth in CRP on days 8 – 14 of disease; fever of > 38 °C during 5 days, WBC < 3.0 × 10^9/L, blood lymphocyte count < 1 × 10^9 /L and/or < 15% [9]. However, physicians are often guided by CRP level and underestimate these clinical criteria.

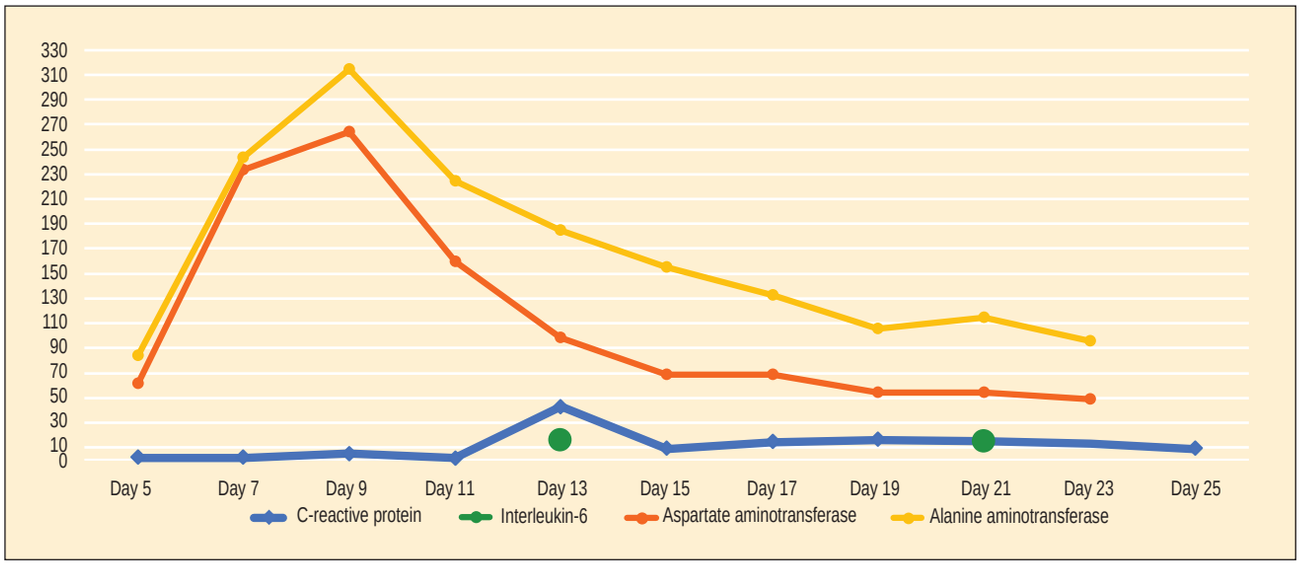

Figure 2. Dynamics of the main laboratory parameters (clinical observation No.1)

Рис. 2. Основные лабораторные показатели в динамике (клиническое наблюдение № 1)

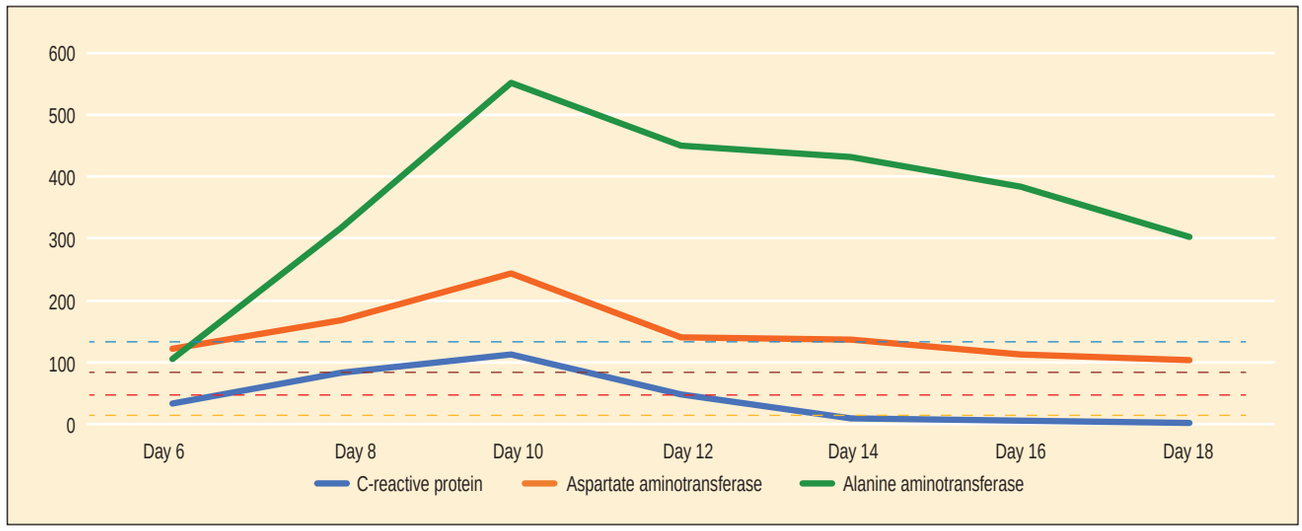

Figure 3. Dynamics of the main laboratory parameters (clinical observation No.2)
Рис. 3. Основные лабораторные показатели в динамике (клиническое наблюдение № 2)

Both patients described were febrile and had low blood lymphocyte count. The patient 2 had also low WBC count. However, the lung involvement in both patients was not extensive enough to suspect the "cytokine storm". When the lung involvement enlarged, the fever, another important clinical sign of "cytokine storm", surprisingly reduced to low-grade level.

In patient 1, CRP has not reached the threshold of 60 mg/L during all the course of the disease and 3-fold growth was found on day 13 only (from 5.27 to 42.7 mg/L). Dexamethasone did not impact significantly on the clinical presentation. In patient 2, CRP exceeded 60 mg/L to day 11 of disease only and 3-fold increase in CRP level occurred much more later (Figure 3).

Therefore, "cytokine storm" is not always associated with contemporary CRP growth to high values in real clinical practice. The measurement of another marker of "cytokine storm", IL-6, is not available everywhere.

Of note, both patients had significantly increased liver transaminases. A rise of liver transaminases could be seen in 20 – 35% of COVID-19 patients; this could reflect acute liver injury associated with COVID-19 [10–12]. Liver damage can be caused by SARS-CoV-2 virus itself that binds to angiotension-converting enzyme (ACE II) receptor in order to enter an epithelial cell. ACE II receptors are expressed on epithelial cells of bile ducts in hepatic tissue and, to a lesser extent, on hepatocytes [10, 11]. An increase in liver transaminases was demonstrated to correlate directly with COVID-19 severity [10, 12]. On the other hand the majority of drugs used to treat the novel coronavirus infection COVID-19, such as ritonavir/lopinavir and hydroxychloroquine, can damage the liver. Both patients received aminoquinolines (mefloquine or hydroxychloroquine) and lopinavir/ritonavir from day 1 of admission. Therefore, it is hard to say whether the increase in transaminases level was associated with COVID-19 severity (in this case, high AST and ALT, similarly to CRP, are features of disease severity) or with drug-induced liver injury. The former thesis is supported by the fact that the liver transaminases begun rising three days after the therapy was started and remained at a high level for 2 – 3 weeks after drugs had been withdrawn.

CRP is produced in the liver [1], therefore, It could be assumed that virus-induced liver damage could dysregulate synthetic liver function followed by lowering CRP level. However, some authors report that an increase in liver transaminases was associated with more severe systemic inflammation in COVID-19 [13, 14]. *Q.Cai et al.* found that hospitalized COVID-19 patients are at higher risk of drug-induced liver injury, primarily due to use of lopinavir/ritonavir which increases this risk in 4 times [15]. Many authors describe a direct association between the increase in liver transaminases and the severity of COVID-19 [13, 15, 16].

Conclusion

In conclusion, COVID-19 patients with higher liver transaminase level should be considered as patients with potentially severe course of COVID-19, even if CRP is normal or slightly increased. We suppose that increased liver transaminases in a patient with chest CT typical for COVID-19 and long-lasting fever should be considered as an indication for administration of anti-IL monoclonal antibodies.

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Pulmonary rehabilitation of patients with coronavirus infection COVID-19, clinical examples

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Abstract

At the end of 2019, an outbreak of a new coronavirus infection was identified in the People's Republic of China centerd in the city of Wuhan. The official name COVID-19 (COronaVIrus Disease 2019) was assigned to the infection caused by the novel coronavirus by the World Health Organization on February 11, 2020. The International Committee on Taxonomy of Viruses assigned the name to the causative agent of the infection – SARS-CoV-2 on February 11, 2020. The bilateral pneumonia is currently known to be the most common clinical manifestation of the variant of coronavirus infection. The development of acute respiratory distress syndrome was found in 3 – 4% of patients. As a result of pneumonia, patients develop ventilation and perfusion disorders, weakness of skeletal muscles. To recover patients after viral pneumonia, methods of pulmonary rehabilitation should be applied. This article represents the methods of pulmonary rehabilitation aimed to improve the blood circulation in the lungs, the ventilation-perfusion ratios, and to the restoration of the skeletal muscles.

Key words: new coronavirus infection COVID-19, SARS-CoV-2 infection, community-acquired pneumonia, pulmonary rehabilitation.

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Легочная реабилитация пациентов, перенесших коронавирусную инфекцию COVID-19 (клинические примеры)

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Резюме

В конце 2019 года в Китайской Народной Республике произошла вспышка новой коронавирусной инфекции с эпицентром в городе Ухань. Всемирная организация здравоохранения 11.02.20 присвоила официальное название инфекции, вызванной новым коронавирусом, COVID-19 (*COronaVIrus Disease-2019*). Международный комитет по таксономии вирусов 11.02.20 присвоил название возбудителю инфекции SARS-CoV-2. В настоящее время известно, что наиболее распространенным клиническим проявлением варианта коронавирусной инфекции является двусторонняя пневмония, у 3–4 % пациентов зарегистрировано развитие острого респираторного дистресс-синдрома. При пневмонии у пациентов развиваются вентиляционно-перфузионные нарушения, слабость скелетной мускулатуры. Для восстановления пациентов после вирусной пневмонии необходима легочная реабилитация. В данной статье приведены методы легочной реабилитации, направленные на улучшение кровообращения в легких, вентиляционно-перфузионных отношений, восстановление работы скелетной мускулатуры.

Ключевые слова: новая коронавирусная инфекция COVID-19, инфекция SARS-CoV-2, внебольничная пневмония, легочная реабилитация.

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At the end of 2019, an outbreak of a new coronavirus infection occurred in the People's Republic of China with an epicenter in the city of Wuhan.

On February 11, 2020, the World Health Organization assigned the official name to the infection caused by the new coronavirus, COVID-19 (Coronavirus Disease 2019). On 11 February 2020 the International Virus Taxonomy Committee assigned the name to the causative agent of the infection, SARS-CoV-2 [1].

It is now known that bilateral pneumonia is the most common clinical manifestation of the coronavirus infection variant; in 3 – 4% of patients the development of Acute Respiratory Distress Syndrome (ARDS) was recorded [1].

The epithelium of the upper respiratory tract and intestinal epithelial cells are the entrance gates of the pathogen. The initial stage of infection is the penetration of SARS-CoV-2 into target cells that have Type II Antiotensin

Converting Enzyme receptors (ACE2). ACE2 receptors are found on the cells of the respiratory tract, kidneys, esophagus, urinary bladder, ileum, heart, and central nervous system. However, the alveolar cells of type II (ACE2) of the lungs constitute the main and rapidly attainable target that determines the development of pneumonia. In the lungs in the early stage of the disease, the prevailing signs are acute bronchiolitis, the alveolo-hemorrhagic syndrome (inside alveolar hemorrhage); edema is an integral part of diffuse alveolar damage. A histological examination of this pathological process reveals the intra-alveolar edema; hyaline membranes line the contours of the alveolar passages and alveoli; the layers of cells of the alveolar epithelium are desquamated; accumulated fibrin can be found in part of the cavities of the alveoli; in a significant part of the cavities of the alveoli there is accumulation of red blood cells and there are signs of inflammation in interstitial cells the form of lymphocytic infiltration. Starting from Day 7 from the onset of the disease, at a later stage, single hyaline membranes, and fibrin and polypoid fibroblastic tissue in the lumens of the alveoli can be observed; the same can be observed in the part of the respiratory and terminal bronchioles (bronchiolitis obliterans organizing pneumonia, BOOP), squamous cell metaplasia alveolar epithelium; in the lumens of the alveoli there are accumulations of siderophages. Atelectasis and sometimes fibroatelectasis may occur [2, 3].

The interalveolar septa are characteristically thickened due to lymphoid infiltration and proliferation of type II alveolocytes. This causes further lung pathologies [4].

The formation of thrombus and changes in the rheological properties of blood leading to pathology of the cardiovascular system play an important part in the development of the disease. This is an essential aspect in the treatment and development of rehabilitation measures for patients. In addition, patients develop adynamia as they hardly ever move in hospital, and many patients have to be in a prone position to improve breathing. Prone positioning is necessary for patients to increase the surface of the lungs engaged in breathing. In this position, the lungs expand, and oxygen enters the parts of the lungs that were previously poorly ventilated. However, this position of the body causes even greater adynamia, damage to the skeletal muscles and (very importantly), the respiratory muscles [5, 6]. Pulmonary rehabilitation methods adopted according to clinical guidelines [7] can resolve the patients' problems.

The concept of pulmonary rehabilitation

Patients who have undergone a new coronavirus (COVID-19), community-acquired pneumonia, need rehabilitation measures in order to recover the consequences of the disease [8].

In recent years, pulmonary rehabilitation methods have become a standard addition to drug therapy in patients with lung disease. The use of pulmonary rehabilitation methods improves the functioning of patients, reduces shortness of breath, improves the quality of life (QOL) of patients and reduces the number of hospitalizations and length of stay (the level of evidence A); the methods also improve exercise tolerance and patient survival, and increase the bronchodilatory effect (the level of evidence B). Initially, pulmonary rehabilitation methods were developed for patients with chronic obstructive pulmonary disease. Further study of pulmonary rehabilitation methods has shown that the same principles apply to patients with other lung conditions. At present, it is impossible to provide full-fledged medical care for patients with lung diseases without the use of methods of pulmonary rehabilitation [9, 10].

The definition of pulmonary rehabilitation by the American Thoracic Society (ATS) Board of Directors given in December 2005 and the European Respiratory Society (ERS) Executive Committee in November 2005 is fundamental: pulmonary rehabilitation accompanies the main treatment of patients, and includes education, changes in the patient's lifestyle; it improves the physical and mental state of the patient with chronic respiratory diseases and contributes to long-term health improvement. The pulmonary rehabilitation program includes patient assessment, physical training, patient education, nutritional adjustments and psychological support. In a broader sense, pulmonary rehabilitation is a range of treatment strategies for patients with chronic lung disease throughout the patient's life; it involves active collaboration between the patient, their family and health care workers [11].

Pulmonary rehabilitation for patients with a new coronavirus infection (COVID-19), community-acquired pneumonia

The goal of rehabilitation in patients who have undergone a new coronavirus infection (COVID-19), community-acquired pneumonia, is to improve respiratory function, relieve symptoms, reduce possible anxiety and depression, reduce the likelihood of complications, and normalize the work of the respiratory and skeletal muscles, and nutritional status.

The assessment of the patient's condition before rehabilitation is based on a general clinical assessment, (especially functional evaluation), including respiratory function, cardiac status, and the assessment of physical activity. It is necessary to control the state of the respiratory system, including the assessment of the functional activity of the lungs, and the amplitude of the diaphragm. It is important to evaluate the pathology of the cardiovascular system, the circulatory system and the nutritional status of the patient.

Methods of pulmonary rehabilitation

Inspiratory training

In coronavirus pneumonia, due to damage to the alveoli, it is necessary to influence the inspiratory muscles in order to reduce perfusion disturbances and decrease tidal volumes, in order to improve the ventilation capacity of the lungs. In training exercises, it is most important to influence all mechanisms of the respiratory system. The in-

spiratory muscles are active in the act of breathing and affect all aspects of pulmonary ventilation. By affecting the breathing pattern, the stress on the alveoli can be reduced by reducing the resistance in the bronchi and improving ventilation. This is especially important for patients who have to be prone positioned when the inspiratory muscles suffer. In order to restore the respiratory muscles, exercises can be used aimed at training the diaphragm: diaphragmatic breathing and exercises with training inhalation that should be done long enough (one-two-three) to improve ventilation and exhale with little resistance through closed lips (one-two-three-four) [11–13].

The use of training devices aimed at inspiratory muscles training (IMT), improves and restores lung function, and more intensively affects the restoration of the ventilation capacity of the lungs [14–16].

The use devices providing threshold resistance to the IMT is the most common approach to training the respiratory muscles. The devices used for training inspiratory muscles are Threshold IMT, Respironics (USA), and Powerbreathe Classic and Plus, Gaiam Ltd (UK).

The devices have a spring, a valve and a metered load. The valve opens only when the inspiratory pressure generated by the patient exceeds the resistance of the spring, and the exhalation occurs unimpeded through the expiratory movable valve. Stepped resistance is created in the devices that can be gradually increased during the training. The exercise increases lung capacity and improves lung function [17–19].

Various studies have been conducted to examine the efficacy of IMT, where IMT was used alone or combined with body training. A meta-analysis of IMT studies comparing with placebo or low resistance, showed that less than 30% in patients with COPD demonstrate a significant increase in strength and endurance of their respiratory muscles. In addition, the research showed significant and clinically significant reductions in dyspnea at home and an increase in the peak tidal flow. Improvements have also been shown in the 6 minute step test [20–24].

The use of IMT enables the influence on both the inspiratory muscles and the expiratory muscles that are activated after the inspiratory muscles. In order to enhance the discharge of sputum, (with the development of bronchitis), breathing machines with negative pressure during exhalation can also be applied, such as Flutters, Shakers, and Acapella devices. These devices do not train muscles, but they create additional resistance through the positive expiratory pressure during exhalation to give an impetus for coughing up phlegm, due to the opening of the airways. For example, the Threshold PEP trainer has a spring-loaded valve that creates positive pressure on exhalation, which is overcome by the patient by the expiratory muscles straining. However, the development of pneumonia associated with the coronavirus infection COVID-19 normally does not show any airway obstruction (unless the patient was diagnosed with bronchial asthma or COPD before the disease) and sputum discharge. Cough develops in response to damage to the alveoli, and not to the development of purulent bronchitis. Therefore, the use of these trainers for COVID-19 is not relevant.

Vibration and percussion therapy

Considering the pathological inflammatory process that results from the development of viral pneumonia, and fibrin accumulation in the alveoli, the use of inspiratory training alone is not enough. The pathological process affects a large number of structures in the lungs, and the restoration of the ventilation capacity of the lungs and the reduction of fibrotic changes stipulates the use of high-frequency oscillation of the chest in conjunction with compression. This method combines the mechanical effect of high-frequency vibration and compression on the chest stimulating the restored drainage function of the lungs, and the improved blood supply to the lungs [25, 26]. The device providing this effect both affects the improvement of sputum discharge through the vibration exposure and is capable of affecting the functional and volume parameters of the lungs due to the compression effect of positive pressure, and of improving ventilation in the alveoli (as was shown in the studies of *A.Nicoloni et al.* and *R.Gloeck et al.* [27, 28]). In Russia there are two devices applied that have such characteristics: Hill-Rom Vest/Vest Airway Inc., USA, and Ventum Vest Vibration YK-800, China. Several international studies have demonstrated positive results regarding the effect of the device on the drainage function of the lungs by improving the MCC and functional changes in the lungs; the safety of this device was assessed in patients with RD. The vibration-compression apparatus consists of a vest connected by two tubes to an air pressure generator. The air pressure generator quickly builds and deflates the vest. A violent movement of the chest is created by compression and relaxation. The frequency of vibration and pressure is created by the individual adjustment of the device, but patients with coronavirus pneumonia need sufficiently significant compression and vibration (although the maximum indicators in the devices are quite safe); however, for patients with other lung pathology, vibration is primarily important. The use of vibration and compression therapy is counter-indicated in patients with suspected thromboembolism and bullous emphysema of the lungs; therefore, computed tomography of the lungs is mandatory before the rehabilitation program. In addition, when selecting modes of the procedure, a patient's comfort is essential as they experience discomfort during breathing and shortness of breath. The setting options vary in different devices. In some devices, the frequency is adjustable in the range from 1 to 20 Hz, the compression can be adjusted from 1 to 12 bar, and the time can be altered from 1 to 30 minutes. In other devices, the vibration frequency is 1 – 20 Hz, and the compression varies from 1 to 30 bar, the procedure can last from 1 to 99 minutes.

Training for the upper and lower muscle groups

The restoration of the motor activity of the skeletal muscles (especially the upper muscle group) comprises an important stage of rehabilitation, since the muscles interact with the respiratory muscles. In addition, in severe pneumonia or with a considerable length of stay (more than 10 days), it becomes necessary to re-

store the strength of skeletal muscles [29, 30]. Patients rapidly lose muscle strength. For this, skeletal muscle training is used. Hand weights, weights, steppers, bicycle ergometers and treadmills can be used. During training, it is necessary to focus on the breathing pattern; all exercises should be perfored slowly with a long inhalation and exhalation with resistance. For example, steppers are used depending on the patient's tolerance, but it is important to breathe correctly during exercise (a long inhale through the nose, and exhale through closed lips).

At the "IntegraMed" Respiratory Clinic, we have used all the presented rehabilitation methods with a positive effect. From March, 2020, 62 patients have undergone pulmonary rehabilitation under the program of patients who have had COVID-19 with pneumonia. All patients have been given a full course of rehabilitation during at least 10 sessions and continued further training of the upper and lower muscle groups and inspiratory training. After they were discharged from hospital, the patients began the course of therapy at different periods due to the different periods of quarantine, the patients' own wish to get out of the disease, as in addition to three patients (two with obesity syndrome ad hypoventilation and one patient with hyperventilation syndrome), there were no issues with the respiratory organs and cardiovascular system. All patients, regardless of the quarantine timing, had similar complaints of chest congestion and difficulty in breathing, dry cough, migratory chest and back pains, pain in the trachea, and fear of death. After they completed the rehabilitation course, their complaints regressed. There is no doubt that pulmonary rehabilitation should be started already in the hospital; the earlier rehabilitation measures are commenced, the less manifestations of disturbances from the bronchopulmonary system and the faster the recovery of patients. According to the study of the function of external breathing, obstructive type of bronchial patency was not revealed in these patients; however, 53 patients showed a decrease in forced vital capacity (FVC). It was impossible to conduct bodyplethysmography and diffusion examination of the lungs at that time. These studies started only in July. In this paper we present the data of two clinical cases of patients with different types of pulmonary rehabilitation.

Case 1

Patient K., 39 years old, got acutely ill on February 28, 2020, after returning from Italy (February 20, 2020). The patient' s temperature rose to 37.4 – 38 °C; it decreased after taking paracetamol. On Day 4 of the disease, the temperature rose to 39 °C. From March 03, 2020, as prescribed by the therapist, the patient started taking amoxicillin. On March 04, due to a sharp deterioration in the patient's condition (the temperature was up to 39 °C, dry heavy cough, shortness of breath, and weakness), the patient turned to a private clinic, where they performed computed tomography (CT) of the lungs, and diagnosed bilateral polysegmental pneumonia.

The patient was immediately taken by an ambulance to be admitted to a hospital in Moscow. The patient was tested for RNA 2019-SARS-CoV-2 as of March 04, 2020, the result was positive.

After a course of therapy, with a positive trend in the clinical state, two negative results for RNA 2019-SARS-CoV-2, (the last of which was dated March 13, 2020), the patient was discharged with recommendations for rehabilitation measures. According to the blood tests, the patient showed a sharp decrease in leukocytes and lymphocytes. The patient was discharged on March 24, 2020.

According to the CT scan of the chest organs dated March 10, 2020, there is a picture of bilateral polysegmental pneumonia of viral genesis. The lung damage was 65%.

The CT of the chest organs as of March 13, 2020, showed positive dynamics in the form of a decrease in the affected areas up to 50% (Figure 1).

The ultrasound of the pleural cavities as of March 09, 2020, showed minimal hydrothorax on the left, with a local decrease in the airiness of the lower lobe of the left lung.

The patient's history shows active sports (playing tennis 5 times a week). The patient does not smoke. There was an allergic reaction in the form of Quincke's edema to phenobarbital; no other allergy is noted.

According to the spirometry data as of March 25, 2020, no impairment of bronchial patency was revealed. Forced expiratory volume in 1 sec (FEV_1) – 99%, FVC – 103%, FEV_1/FVC – 78%, mean forced expiratory flow during the 25% of FVC $(MEF)_{25}$ – 86%, MEF_{50} – 109%, MEF_{75} – 47%, MEF_{25-75} – 86%.

The ultrasound of the pleural cavity as of March 25, 2020, showed no signs of fluid in the pleural cavities.

After the patient was discharge from the hospital, there were complaints of dry cough, and tightness in the chest that greatly disturbed the patient.

The clinical blood test as of March 28, 2020, showed an increase in platelets up to 397 g/l, an increase in lymphocytes up to 43%, and the absolute indicators 2,24 thousand/μl.

From March 25, 2020, the patient was recommended therapy with Azithromycin (Sumamed) 250 mg one pill once a day, three times a week (Monday, Wednesday, Friday) during a month; Fluimucil 600 mg 2 times daily was prescribed as an antioxidant therapy.

Rehabilitation activities began on April 01, 2020, as since then the patient was able to visit the clinic.

The patient was prescribed training of the inspiratory muscles using a breathing device with an initial resistance of 40 mm H_20, 20 breathing movements 3 times daily.

High-frequency chest oscillation was performed using vibration-compression therapy with a 10 bar compression and a frequency of 13 Hz, for 30 minutes.

Results

After three sessions of high-frequency oscillation of the chest, the patient stopped coughing, and the feeling of chest congestion disappeared. However, when the patient was unable to attend the therapy sessions for two days for family reasons, and the cough and tightness in the chest returned. The patient resumed therapy sessions. There were 10 sessions in total.

After ten therapy sessions using high-frequency oscillation of the chest, and an inspiratory trainer, inhalation of Fluimucil, and taking Sumamed, the patient's condition stabilized. The cough was stopped, the feeling of tightness in the chest does not resume.

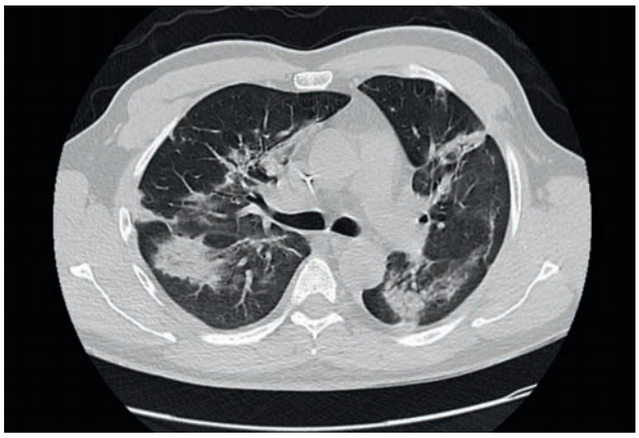

Figure 1. Computer tomogram, patient K. 39 years old, 13.03.20
Рис. 1. Компьютерная томограмма пациента К. 39 лет от 13.03.20

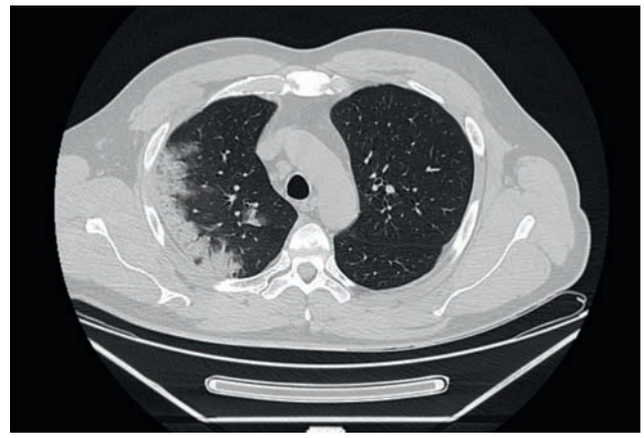

Figure 3. Computer tomogram, patient A. 52 years old, 01.05.20
Рис. 3. Компьютерная томограмма пациента А. 52 лет от 01.05.20

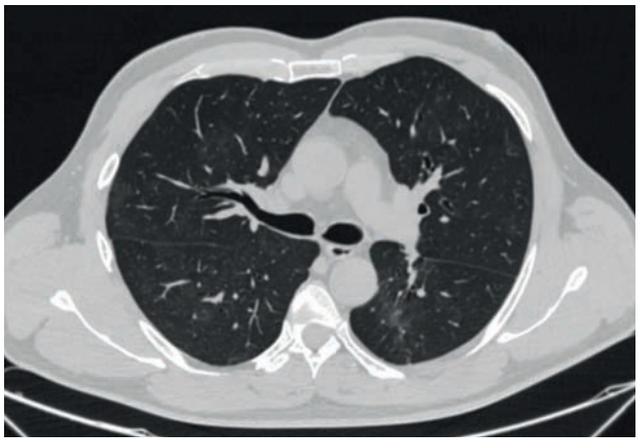

Figure 2. Computer tomogram, patient K. 39 years old, 15.04.20
Рис. 2. Компьютерная томограмма пациента К. 39 лет от 15.04.20

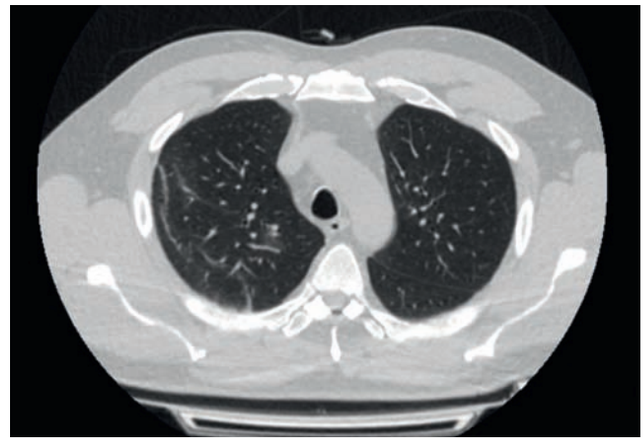

Figure 4. Computer tomogram, patient A. 52 years old, 10.06.20
Рис. 4. Компьютерная томограмма пациента А. 52 лет от 10.06.20

According to the CT scan of the chest organs as of April 15, 2020, there was a drastic positive trend in the form of a significant decrease in the size and intensity of the foci of inflammation and ground glass opacities (Figure 2).

According to the spirometry data as of April 16, 2020, there was no improvement in bronchial patency. FEV_1 – 103%, FVC – 98%, FEV_1/FVC – 85%, MEF_{25} – 111%, MEF_{50} – 101%, MEF_{75} – 92%, MEF_{25-75} – 107%.

The clinical blood test as of April 23, 2020, showed all indicators completely normalized, including the leukocyte formula.

As a result of the rehabilitation measures, there was a significant improvement in the patient's condition, the improvement of the drainage and ventilation functions of the lungs.

Case 2

Patient A., 52 years old, on April 27, 2020, signs of ARVI appeared (myalgia, chills, body temperature increased to 38.2 °C, general weakness). On the third day, a dry cough appeared.

On May 30, the patient turned to a private clinic, where a CT scan of the chest organs was performed and upper lobe pneumonia was diagnosed.

According to the CT scan of the chest organs as of May 01, 2020, there were infiltrative changes and areas of ground glass in the upper lobe of the right lung. On the visual scale, it corresponds to the CT-3 (Figure 3).

The blood tests as of May 03, 2020, showed CRP – 19.3 mg/L, ferritin – 886 ng/mL; leukocytes – 3.6 × 10^9/L; fibrinogen – 4.7 g/L.

The CT scan was regarded as pneumonia caused by the viral infection COVID-19. The prescriptions were Azithromycin 500 mg per day, 7 days, hydroxychloroquine 200 mg, the first day 400 mg twice a day, then 200 mg twice a day, 7 days. Fluimucil was prescribed at a dose of 1,800 mg per day. During the treatment, the patient's body temperature varied in the range from 36.8 to 38 °C for 5 days. Then it returned to normal. Dry cough and fatigue persisted.

On May 09, 2020, high-quality IgM/IgG tests for SARS-CoV-2 were carried out, and turned out to be positive. The patient continued treatment with Fluimucil at a dose of 1,800 mg per day for 3 weeks.

According to the spirometry data as of May 28, 2020, no impairment of bronchial patency was revealed. FEV_1 – 120%, FVC – 116%, FEV_1/FVC – 83%, MEF_{25} – 114%, MEF_{50} – 114%, MEF_{75} – 98%, MEF_{25-75} – 115%.

Rehabilitation started on May 28, 2020.

The patient was prescribed inspiratory muscles training using a breathing trainer with an initial resistance of 50 mm H_2O, 30 respiratory movements twice a day.

High-frequency chest oscillation was performed using vibration-compression therapy with 11 bar compression and a frequency of 13 Hz, for 30 minutes.

Results

After five sessions of high-frequency chest oscillation, the patient noted ease in breathing, decreased fatigue; coughing ceased. The exercises were daily, with a break on Saturday and Sunday. A total of 10 sessions were performed.

After 10 sessions of the complex therapy, the general state of health corresponded to the previous quality, in the patient's opinion.

According to the CT scan of the chest organs as of June 10, 2020, there was a positive trend, interstitially infiltrative changes in the upper lobe of the right lung, with a predominance of severe fibrotic changes. The positive dynamics was compared to that of May 01, 2020 (Figure 4).

The blood tests as of June 04, 2020 showed the complete normalization of all previously changed parameters.

As a result of the rehabilitation measures, the quality of life and general physical condition improved significantly, coughing ceased.

Conclusion

The use of pulmonary rehabilitation methods aimed at improving blood circulation, ventilation-perfusion relations and restoring skeletal muscle function is extremely important for patients who have undergone pneumonia associated with SARS-CoV-2 coronavirus infection. Moreover, the earlier rehabilitation measures are commenced, the less the consequences for the patient [31, 32]. Complaints such as migrating chest and back pain, burning feeling, and shortness of breath with normal parameters of respiratory function can be demonstrated in the patients for quite a long time. Pulmonary rehabilitation methods that improve the ventilation and perfusion capacity of the lungs lead to the relief of these complaints. However, given the various pathological processes both in the lungs and in other organs and systems, the patient should be followed up during a year to prevent complications of the disease [31–33].

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