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POSTCOVID SYNDROME: RISK FACTORS, PATHOGENESIS, DIAGNOSIS AND TREATMENT OF PATIENTS WITH RESPIRATORY DAMAGE AFTER COVID-19 (RESEARCH REVIEW)

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Abstract. The purpose of the review: to determine the pathogenetic basis of PCR and tactics of management of patients with respiratory damage after COVID-19 in outpatient settings. The results of studies related to the problem of postcovid syndrome confirm that the pathogenetic mechanisms of postcovid syndrome are multifaceted and require correction. Disorders in the immune system after COVID-19 ensure the maintenance of the inflammatory process in the affected organs with impaired microcirculation and distelectases in the alveolar structures of the lungs and other affected organs, remodeling of the bronchial epithelium with the deposition of hyaluronic acid in the interstitial tissue of the perialveolar and bronchi with the formation of connective tissue.

Keywords: postcovid syndrome, risk factors, pathogenesis, diagnosis, treatment

Introduction. The urgency of the problem of postcovid syndrome (PCS) is associated with the widespread spread of respiratory viral SARS-CoV-2 infection (COVID-19) in Russia and in the world and the lack of awareness of medical workers about its consequences. According to Rospotrebnadzor, as of March 31, 2022, 17,842,925 people with a confirmed diagnosis of COVID-19 were registered in Russia, including 2,757,421 people in Moscow, of whom 368,722 (2.07%) and 43,138 (1.56%) people died, respectively [1]. A mild disease without pneumonia or with pneumonia with a lesion of up to 25% of lung tissue was registered in 81% of cases, and about 19% of patients had a moderate and severe course of infection and needed hospitalization. In mild cases, recovery occurred within 2 to 6 weeks, but in some patients, the duration of the recovery period increased. After hospitalization for severe COVID-19, up to 20% of patients noted the persistence of symptoms of varying severity, among which signs of respiratory and vascular damage prevailed [2].

The purpose of the review: to determine the pathogenetic basis of PCR and tactics of management of patients with respiratory damage after COVID-19 in outpatient settings.

The etiology of COVID-19. COVID-19 is caused by the SARS-CoV-2 virus, which has been in epidemic circulation since 2019 and caused a pandemic in 2020. The SARS-CoV-2 virus is highly variable, and the assumption that it will weaken over time and move into the category of endemic infections, like other respiratory infections, is not confirmed. The emergence of new strains is accompanied by increased morbidity with an increase in the number of hospitalizations and deaths.

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For 2020-2021 . several strains were identified, designated in accordance with the WHO classification system as the "British" strain — alpha (B.1.1.7), "South African" — beta (B.1.351), "Brazilian" — gamma (P.1), 2 subspecies of the "Indian" strain — delta and Kappa (B.1.617.2 and B.1.617.1), on November 26, 2021, the "South African" strain — omicron (B.1.1.529) was detected. In February — March 2022, 2 strains of the virus were detected among the Russian population: delta (B.1.617.2) and omicron (B.1.1.529) [3, 4]. In the latter strains, mutations L452R and F486 provide increased transmissivity (contagiousness), the first of the mutations found in the delta strain makes it easier to bind to the ACE2 receptor through which the virus enters human cells, and F486 weakens the neutralization of antibodies and helps to elude the immunity created by the vaccine. According to WHO, the omicron strain is highly contagious due to the presence of 15 mutations in the S-protein receptor region, in addition to other mutations, which increases the rate of transmission of the virus. If at the beginning of the pandemic, the average number of infected people in the naive population was 1.5–2.5 and the incubation period varied from 1 to 10 days, then for the omicron strain this indicator is 5, and the incubation period was reduced to 2.5–4 days. The number of reproductions of R has also increased dramatically: from 0.8 to 1.4 — so many people on average infect one infected [5].

Pathogenesis and clinical picture of COVID-19 and PCS. COVID-19 is caused by the entry of SARS-CoV-2 into the cell by attaching to APF2 receptors using transmembrane glycoprotein CD147 [6]. Cellular transmembrane serine protease type 2 promotes the binding of the virus to APF2 by activating its S-protein, which is necessary for the penetration of SARS-CoV-2 into the cell. At the same time, the structure of the binding domain of the wedge-shaped glycoprotein on the surface of the SARS-CoV-2 virus is stronger than that of other SARS-like coronaviruses, since it has a site for cleavage by furin-like proteases. APF2 receptors are present on the endothelial and epithelial surfaces of the alveoli, on enterocytes of the mucous membrane of the small intestine, on cells of the adrenal glands, bladder, brain (hypothalamus and pituitary zones), vascular endothelium and macrophages. With COVID-19, the laryngeal epithelium, the atrial fibrillation epithelium of the respiratory tract, alveolocytes of types I and II with the development of diffuse alveolar damage and respiratory distress syndrome are most often affected [7]. In some patients, a specific lesion of the endothelium of the vessels of the lungs, myocardium, kidneys and other organs is detected in the form of endotheliitis and pronounced alveolar hemorrhagic syndrome caused by direct viral invasion or immuno-mediated damage. The defeat of the gastrointestinal tract (gastrointestinal tract) is manifested by symptoms of catarrhal gastroenterocolitis. Damage to immunocompetent organs is accompanied by apoptosis and pyroptosis of lymphocytes, mainly CD4+ T cells, which underlies lymphopenia, macrophage hyperactivity syndrome, hemophagocytic syndrome, neutrophil leukocyte netosis and is one of the causes of disseminated intravascular coagulation syndrome (DIC).

Hemostasis disorders are caused by hypercoagulation and immunothrombosis, including an increase in the level of coagulation factor VIII, Willebrand factor, fibrinogen and D-dimer concentration, as well as endotheliopathy. Dissemination of SARS-CoV-2 from the systemic bloodstream or through the plate of the latticed bone in combination with endotheliopathy can cause brain damage.

The morphological basis of the manifestations of PCS on the part of the respiratory system are exudative-proliferative inflammation and diffuse damage to the alveolar epithelium with its subsequent remodeling, atelectases (distelectases), hemorrhagic infarcts, as well as hemorrhages into the lung tissue in the acute period of the disease [7]. Histological examination of the lung tissue on the 4th-37th day of the disease revealed pronounced intraalveolar edema, hyaline membranes lining the contours of respiratory bronchioles, alveolar passages and alveolar sacs in the form of strips of different thickness. Noted: epithelial damage associated with viral exposure — desquamation of bronchial and bronchiolar epithelium, type I and II alveolocytes, proliferation of type II alveolocytes; fullness of branches of pulmonary arteries and veins, capillaries of interalveolar septa with damage and desquamation of endotheliocytes, erythrocyte sludge, organizing and fibrin thrombi, foci of perivascular hemorrhages, intrabronchiolar and intraalveolar clusters red blood cells. One third of the deceased had focal hemorrhages and/or hemorrhagic infarcts. Pronounced expression of factor VIII was found in the vascular endothelium in patients with COVID-19 [7].

Taking into account the presented data, it can be assumed that the exudative phase of inflammation can be resolved with the complete restoration of the structure of the lungs. The appearance of fibroblastic tissue with compaction of the interalveolar and interlobular septa, desquamation of the alveolar epithelium in the exudative-proliferative phase of inflammation leads to the formation of connective tissue and scarring in the lungs. In addition, in patients with severe forms of the disease, there is a lesion of the pulmonary vessels in the form of endotheliitis and DIC syndrome, which also disrupts tissue repair.

During COVID-19, there are: acute stage, when symptoms are determined no longer than 4 weeks. from the onset of the disease; continuing symptomatic stage for 4-12 weeks. from the onset of the disease; the condition after the disease (PCS), when symptoms persist for longer than 12 weeks. and they cannot be explained by an alternative diagnosis [2]. In accordance with ICD-10, the PCC belongs to the section of medicine "Infectious and parasitic diseases" and is encoded as a personal history of COVID-19 (U08.9) or a condition after COVID-19 (U09.9) indicating the manifestations of the disease. The criterion for the diagnosis of PCS is the presence of a transferred infection confirmed by a positive result of PCR on the RNA of the SARS-CoV-2 virus, or a probable case of COVID-19 infection with the detection of immunoglobulin G (IgG) or total IgM, IgG to the SARS-CoV-2 virus. PCS is not associated with an active viral infection and the risk of infection of others. Example

of the formulation of the diagnosis of PCS: U09 State after COVID-19. Postcovid syndrome (PCR of SARS-CoV-2 nasopharyngeal smear positive, date; CT-4, date): Condition after ventilator. Residual interstitial lung changes with predominance of fibrosis, cavitation of the upper lobes. Respiratory failure of the II degree. Headache. Sleep disturbance. Arthralgia. Skin manifestations (hair loss).

COVID-19 can occur with varying severity of symptoms and severity, from mild to critical, which is determined primarily by the volume of lung tissue damage according to computed tomography of the chest organs (CTCO), the severity of respiratory, cardiovascular and organ failure [2]. The risk group for severe COVID-19 and related health consequences includes patients with blood type A (II), male (odds ratio (OR) 1.59, 95% confidence interval (CI) 1.53–1.65), blacks (OR 1.48, 95% CI 1.30–1.69), South Asian peoples (OR 1.44, 95% CI 1.32–1.58), elderly people (OR 1.59 for 10 years, 95% CI 1.19–2.13), smokers (OR 1.07, 95% CI 0.98–1.18) [4]. The presence of chronic diseases in the patient increases the risk of severe course and death in COVID-19. In ischemic heart disease (CHD), the mortality rate is 5.1 times higher than in its absence (10.4% and 2.2%, respectively; OR 5.16, 95% CI 5.16–8.49, $p<0.0001$), in chronic obstructive pulmonary disease (COPD) — 3.5 times (4.8% and 1.4%, respectively; OR 3.55, 95% CI 1.88–6.79, $p<0.001$), with diabetes mellitus (DM) — 1.9 times (19.3% and 11.1%, respectively; OR 1.92, 95% CI 1.48–2.48, $p<0.001$), with arterial hypertension (AH) — 1.1 times (38.7% and 22.2%, respectively; OR 1.09, 95% CI 1.05–1.14, $p<0.001$). Chronic renal failure increases the incidence of adverse outcome by 3.7 times (OR 3.69, 95% CI 3.09–4.39), obesity with a body mass index of 40 kg/m2 and above — by 1.9 times (OR 1.92, 95% CI 1.72–2.13). The risk of severe course of this infection is also increased in autoimmune diseases, immunosuppressive conditions, hematological malignancies [6].

The analysis of CTCO data of 260 594 patients (male-female ratio 44%/56%, average age 49.5 years), conducted with the help of artificial intelligence, showed that the incidence of lung lesions varied from 64.0% to 79.9%: changes up to 25% (CT-1) lung lesions occurred in 46.2–56.9 in % of cases, up to 50% (CT-2) — in 15.5–22.3%, up to 75% (CT-3) — in 4.3–5.7% and more than 75% (CT-4) — in 0.2–0.5% [8].

The main causes of death in COVID-19 were: acute respiratory distress syndrome - 93.2% of cases, cardiovascular complications — 3.7% and pulmonary embolism (PE) - 1.0%. Mortality among patients undergoing oxygen therapy was 10.1% and increased when transferred to non-invasive (36.8%) or invasive (76.5%) ventilation. The risk of death increased with age, in the presence of coronary heart disease, obesity, type 2 diabetes, and in age groups older than 50 years, it was significantly higher in men than in women [9]. Changes in the lungs after a serious illness can persist for a long time and cause the symptoms of PCS. Previously conducted studies in 54 patients 24 months after COVID-19 revealed that the

indicators of FEV1, FVC, total lung capacity and diffusion capacity <80% of the proper value were available, respectively, in 10 (18,2%), 9 (16,4%), 6 (10,9%) and 29 (52.7%) patients and the distance covered in the 6-minute walking test was less than in the comparison group [10].

At the stage of recovery after moderate and severe COVID-19, a significant part of patients have a wide range of time-varying physical or mental manifestations associated with residual inflammation, immune dysfunction after viral organ damage, as well as with the nonspecific effects of hospitalization and the consequences of intensive care, social isolation and exacerbation of concomitant chronic diseases.

The most common symptoms recorded up to 12 weeks. from the onset of the disease, included fatigue (15-87% of patients), shortness of breath (10-71%), chest pain (12-44%), cough (17-34%), as well as palpitations, heart failure, psychological and cognitive disorders, olfactory disorders and gastrointestinal disorders [2]. At the same time, one third of patients had more than 1 symptom, including such as joint pain, headache, dizziness, runny nose, poor appetite, muscle pain, insomnia, hair loss, excessive sweating, stool disorder and uncontrolled weight change.

Among the symptoms lasting more than 12 weeks. (the actual PCS) were: fatigue — 47% (95% CI 27-68%), shortness of breath — 22.0% (95% CI 12-32%), sleep disturbance — 36% (95% CI 10-74%), depression — 22.0% (95% CI 20-24%), hair loss — 23% (95% CI 21-25%), cognitive impairment — 24.0% (95% CI 18-21%) [11]. Some patients noted a lack of breathing, pain when breathing, chest pain, persistent cough, and a change in heart rhythm. Data analysis showed that women had an increased risk of PCR (OR 1.49, 95% CI 1.24–1.79), as well as people with mental health disorders (OR 1.46, 95% CI 1.17–1.83) and general health (OR 1.62, 95% CI 1.25–2.09), with bronchial asthma (BA) (OR 1.32, 95% CI 1.07–1.62), overweight (OR 1.16, 95% CI 1.12–1.21), obese (OR 1.53, 95% CI 1.47–1.59), smokers (OR 1.35, 95% CI 1.28–1.41) and patients after hospitalization for about COVID-19 (OR 3.46, 95% CI 2.93–4.09) [11].

Researchers [12], having re-examined 81 patients (mean age 51.8±11.7 years) with initial changes in the lungs 90-111 days after COVID-19, tried to identify individuals at risk of developing lung consequences. The absence of symptoms of the disease was noted in 33% of cases and full resolution according to CTCO — in 56.8%. The leading initial signs on CTCO in the groups of full resolution (FR) and residual changes (RC) were: "frosted glass" — 68.6% and 73.9%, respectively, consolidation — 17.1% and 8.7%, mixed pattern — 14.3% and 17.4%. After 3 months. in the RC group, 45.7% of patients had changes in the type of "frosted glass", 25.7% in the type of parenchymal stripes, 17.2% mixed changes in the form of parenchymal stripes and "frosted glass", 17.2% bronchiectasis, 11.4% thickening of the interlobular septa. Compared with those examined with FR viral pneumonia, patients with RC were older in age (59.6±9.3 years and 45.8±13.8 years), 51.8% (28.3%) of smokers among them, 60.0% (63%) of men, had a BMI >25 kg/m2 —

60.0% (26.0%). Concomitant diseases, among which DM, AH and COPD prevailed, were present in 80% with OI and 43.5% with PR, respectively; the duration of inpatient treatment in patients with OI was longer (11.2±4.1 days and 7.6±2.3 days, respectively), and 28.6% of patients were in ICU versus 6.5% of patients with PR. According to the clinical examination, the number of white blood cells, the level of CRP, the severity score of pneumonia in the OI group compared to the FR group were higher, and the initial saturation during hospitalization was lower (88.1±2.2% and 92.3± 3.8%, respectively), steroid therapy was used only in 51.8% of patients (vs. 84.8% in group of FR).

A meta-analysis of data from 7 publications with the results of a study of the respiratory function of patients with chronic respiratory diseases (CRD) and without them after 30 days or more from the beginning of COVID-2019 revealed a violation of the diffusion ability of the lungs (DAL) in 39.0% of patients, a violation of the ventilation function of the lungs (VFL) of restrictive and obstructive type in 15.0% and obstructive like 7.0%. A 6-minute walking test with control of BPD and heart rate, SpO2 before and after walking along a 30-meter corridor revealed a decrease in exercise tolerance (the test is considered positive for desaturation when walking ≥4% of the initial level at rest) [13].

In general, the main pathogenetic mechanisms of PCS that determine the appearance of various symptoms, including pulmonary ones, include the following:

immune disorders in the form of a decrease in the total number of B, T and NK cells in the blood of patients with COVID-19, especially in severe infection, with the preservation of the function of CD4+, CD8+ T cells and NK cells and dysregulation of T-cell reactions, which can cause immunopathology with delayed elimination inflammatory changes in organ tissues [6];

fibrosis of lung tissue under the influence of SARS-CoV-2 virus and as a result of increased activity of transforming growth factor β (TGF-β) [14];

inflammation and production of cytokines IL-1, TNF, CD31+ in the endothelium and adhesion molecules (EpCAM+) in the alveoli, their effect on the synthesis and deposition of hyaluronic acid-2 (HAS-2) and fibroblast division [15];

neutrophil apoptosis and netosis with the formation of a secret in the respiratory tract containing DNA and hyaluronic acid (linear glycosaminoglycan) [16];

lesions of type II alveolocytes with impaired synthesis and reutilization of pulmonary surfactant and its deficiency, contributing to atelectases (distelectases) of alveolar structures [17];

damage to the endothelium of the pulmonary vessels with microthrombs and microcirculation disorders [7].

Thus, the correction of these pathological processes through the appointment of anti—inflammatory and antifibrosis therapy, improvement of microcirculation,

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reduction of thrombosis - all this can contribute, in particular, to the restoration of lung tissue.

Treatment of patients with respiratory damage after COVID-19. Due to the multifactorial pathogenesis of PCS, its clinical manifestations vary in a wide range and can affect various organs and systems. In this regard, the working classification of PCS [2, 18] provides for the isolation of respiratory, cardiac, gastrointestinal, renal, endocrine, neurological, psychopathological, rheumatic, dermatological variants of the course, as well as forms with nutritional insufficiency and damage to blood cells.

At the outpatient stage, when a patient goes to the PC for medical help, the severity of inflammation is assessed based on data from a clinical blood test, levels of CRP, ferritin, transaminases. With signs of heart failure, natriuretic peptide, troponin, D-dimer are determined; with arthralgia and myalgia, antinuclear antibodies and creatine phosphokinase are determined, and with muscle weakness, blood glucose and thyroid hormone levels are determined. To detect kidney damage, urea and blood creatinine are examined. In case of lung damage, chest X-ray is performed after 3 or 6 months. from the onset of the disease, and if small branches are suspected of PE, CTG with angiography, ECG, ultrasound of the heart. Spirometric examination should be carried out after 6 or 12 weeks. from the onset of the disease. At each visit to the therapist, the pulse oximetry indicator is measured at rest and after 40 steps in the office or in the "sit-up" test. The target SpO2 level is 94-98%. At the final stage of treatment, a 6-minute walking test is performed.

Signs of respiratory damage (respiratory symptoms, impaired ventilation or diffusion function of the lungs, residual interstitial changes in the lungs with a predominance of fibrosis / frosted glass, consolidation /cavitation, etc. with respiratory insufficiency, the condition after ventilation, extracorporeal membrane oxygenation) occupy a leading place in the structure of the symptoms of PCS and are most pronounced in chronic AML [2]. Inflammation caused by the products of the metabolism of microorganisms causes local disorders, both tissue and immune. Immune disorders are expressed in a decrease in the functional ability of defense cells, weakening of various links of humoral immunity. The very effect of an infectious agent often causes secondary suppression of immunity. The administration of immunomodulatory drugs can reduce the duration of the inflammatory reaction and the recovery time [14].

For a number of years, the domestic drug azoximer bromide (AzB) (Polyoxidonium®, NPO Petrovax Pharm LLC, Russia), which belongs to the class of water-soluble derivatives of heterocain aliphatic polyamines, has been used to treat patients with pneumonia and exacerbations of chronic AML [19]. This class of compounds has no analogues in the world both in structure and properties. The most pronounced effect of AzB is manifested in an increase in the relative and absolute content of T-lymphocytes with the CD3+, CD4+ phenotype, an increase in the ratio

of CD4+ /CD8+T-lymphocytes, an increase in the content of IdA and IgG in blood serum mainly in individuals with initially reduced values of these indicators. With initially elevated indicators, normalization of the content of blood leukocytes was noted. In vitro experiments have shown that AzB inhibits the ability of neutrophils to netose — the formation of neutrophil extracellular traps [14]. Possessing antioxidant properties and membrane-stabilizing activity, AzB ensures the removal of active oxygen radicals and lipid peroxidation products from the body, inhibits free radical reactions, exhibits pronounced antitoxic activity due to the blocking of soluble substances toxic to living cells and microparticles, which is especially important in the development of respiratory infection. The administration of AzB to patients with SARS-CoV-2 infection is pathogenetically justified [14, 20], and it has demonstrated these properties in the treatment of patients in the acute period of COVID-19 [21] and the recovery period [22]. In the study of S.V. Efimov et al. [21] in 32 people hospitalized with COVID-19, including 22 people with a severe course of the disease, due to the use of AzB in complex standard therapy on the 9th-10th day, it was possible to achieve an improvement in the condition, normalization of blood SpO2, reduction of CRP levels, all patients were discharged. On the 28th-72nd day of the study, there were no cases of secondary infection or delayed mortality. K.V. Kasyanenko et al. [22] in a prospective open comparative non-interventional clinical study in parallel groups, the effect of AzB on the severity and duration of some symptoms persisting for more than 12 weeks after SARS-CoV-2 infection and the level of chronic stress was assessed by a standard survey method. The experimental group consisted of 55 people who took AzB for 10 days, and the comparison group consisted of 35 people who did not receive medications. There was a statistically significant decrease in the frequency of detection of joint and muscle pain, headache, frequency of hyposmia, impaired concentration, dizziness on the 10th day of observation in the experimental group compared with the comparison group.

After COVID-19 of moderate to severe course with signs of respiratory and heart failure against the background of concomitant chronic lung and heart diseases, diabetes and other conditions associated with impaired immunity, the risk of fibrosis in the lungs is increased [2, 12, 13]. Some patients are concerned about shortness of breath, cough, heaviness in the chest and decreased exercise tolerance, there are inflammatory changes in the blood test. To restore lung tissue and reduce the risk of developing pulmonary fibrosis, patients at risk of severe disease, indicated earlier, are recommended to administer the enzyme preparation bovgialuronidase azoximer (BovA). Pronounced antifibrotic properties of the drug are provided by conjugation of hyaluronidase with a carrier of the AzB derivative, which increases the resistance of the enzyme to denaturing effects. The drug has a prolonged hyaluronidase enzymatic activity, chelating, antioxidant and immunomodulatory properties and a moderately pronounced anti-inflammatory effect [23]. The effectiveness of BovA has been proven in comparative studies on the treatment of interstitial lung diseases and

lung damage caused by COVID-19. A decrease in shortness of breath, an improvement in gas exchange, VFL, a decrease in the volume of lung tissue damage according to CTGK data and an improvement in exercise tolerance after course use of BovA were demonstrated [24-26].

In an open comparative multicenter prospective study of DISSOLVE among 160 patients with residual lung changes detected no later than 2 months after discharge from the hospital after COVID-19, the effectiveness of BovA in the prevention and treatment of post-inflammatory pneumofibrosis and interstitial lung changes was confirmed [26]. In the group of patients who received the drug at a dose of 3000 IU 1 time every 5 days intramuscularly, on the 75th day, shortness of breath decreased, VVC increased, blood saturation, the distance of the path in the test with a 6-minute walk. This effect persisted on the 180th day and exceeded that in the basic therapy group.

Some patients with PCS have long-term respiratory symptoms (MS) (cough, sputum, wheezing in the chest) associated with bronchial damage after a viral infection, a violation of the ventilation function of the lungs is recorded. In these cases, inhaled β2-agonists and short-acting m-cholinolytics are used until the disappearance of MS. Nebulizer therapy with a combination of a β2-agonist and an anticholinergic agent can provide a more pronounced bronchodilating effect than each drug individually. In accordance with the recommendations of GINA (2021) and GOLD (2021), during the recovery period after COVID-19, patients with BA and COPD should continue treatment corresponding to the severity of the disease [27, 28]. The basis of basic COPD therapy is long—acting bronchodilators, which increase the patency of the respiratory tract and reduce the severity of the phenomenon of "air trap" and hyperinflation of the lungs, therefore, reduce the symptoms of COPD. The first-line drugs are long-acting β2-agonists and long-acting anticholinergic drugs both in monotherapy and in combination.

After COVID-19, exacerbations of BA and COPD are recorded in some patients, which is associated with an increase in the synthesis of proinflammatory cytokines (IL-1, -6, -11) in epithelial cells of the respiratory tract [29]. Inhaled glucocorticosteroids (iGCS) have an anti-inflammatory effect, reduce the severity of edema of the bronchial mucosa, mucus production, sputum formation and hyperreactivity of the respiratory tract. If a patient with COPD or BA received iGCS before a viral infection, then after an infectious disease, taking iGCS with an exacerbation of the disease should be continued at an increased dose using iGCS using a metered-dose aerosol inhaler and a spacer or nebulizer. The use of iGCS is justified in those who previously received this treatment as a basic therapy, i.e. patients with BA and COPD are not recommended to interrupt basic iGCS therapy in order to avoid exacerbation of diseases. There is still insufficient data on the effect of iGCS on the severity of COVID-19 and the outcomes of the disease, but if there are

indications for iGCS, these drugs are prescribed to patients with a short course of up to 7-10 days if they were not basic therapy [30].

Antibacterial drugs are prescribed to patients with PCOS only when a bacterial infection is attached, with an increase in the amount of viscous purulent bronchial secretions and are used simultaneously with mucolytics and expectorants. It is assumed that the use of the drug hyaluronidase, which destroys hyaluronic acid and reduces the viscosity of bronchial secretions, may be useful in PCS [16, 31, 32].

The most important factor contributing to the manifestations of PCS and systemic microcirculation disorders in various organs is systemic endothelial dysfunction, endotheliitis [33]. The clinical picture is most clearly manifested in the defeat of the microcirculatory link of the lungs, being the basis for performing single-photon emission computed tomography (SPECT) of the lungs in order to detect microcirculation disorders. The SPECT data in 136 patients with proven COVID-19 of varying severity, transferred from May 2020 to June 2021, revealed changes in microcirculation in the lungs in the postcovid period. The degree of severity of these disorders significantly depended on the degree of lesion of the pulmonary parenchyma (correlation coefficient (rs) 0.76, p=0.01) and demonstrated an average correlation dependence on the duration of the disease (rs=0.48, p=0.05) and the degree of residual changes according to CTGK (rs=0.49, p=0.01). At all stages after COVID-19, patients with persistent clinical complaints had changes in microcirculation in the vessels of the lungs, which may indicate the development of vasculitis. Despite the regression of changes by the 3rd-6th month after COVID-19, according to the SPECT data, a fibrosing process in the lungs was recorded in 30-36% of patients. Similar changes after 9 and 11 months were detected in 19.1% of the surveyed. A number of signs may indicate the formation of fibrous changes with subsequent outcome in virus-associated interstitial lung disease, regardless of the severity of pneumonia. Among them, according to the SPECT data: 1) a progressive decrease in microcirculation in the lower parts of the lungs; 2) the appearance of local hypoperfusion zones with critically low accumulation of radiopharmaceutical; 3) long-lasting areas of lung tissue compaction of the "frosted glass" type, reticular changes and the development of traction bronchiectasis; 4) a decrease in DSL and alveolar volume [33]. Well-known drugs for improving microcirculation in damaged tissues (pentoxifylline), antihypoxic action (trimetazidine dihydrochloride) and antiplatelet agents (acetylsalicylic acid) accelerate the recovery processes in patients with PCS [34, 35].

Venous and arterial thrombosis is registered in 31% of hospitalized patients with COVID-19 [36]. Venous thromboembolism was the most frequent (27%) and mainly in the pulmonary artery. Independent predictors of thromboembolism were older age and the presence of coagulopathy (prothrombin time more than 3 seconds above the upper limit of normal values, activated partial thromboplastin time more than 5 seconds, respectively (OR 4.1, 95% CI 1.9–9.1), elevated levels of D-dimer,

fibrinogen and antithrombin. When confirming thrombotic microangiopathy and recurrent PE or venous thrombosis, anticoagulants are used in standard doses. These recommendations remain relevant for PCS with mandatory monitoring of hemostasis system indicators.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs and have a wide range of applications. With pronounced clinical and laboratory signs of inflammation after infection (pleurisy, joint and muscle pain) NSAIDs are prescribed in a short course of up to 7-10 days (ibuprofen, paracetamol, meloxicam, diclofenac) [37].

The duration of rehabilitation after COVID-19 totals 6-8 weeks, but after a serious illness, the terms are lengthened depending on the patient's condition and impaired organ functions. Rehabilitation includes lifestyle modification, medical and physical support. To determine the stage and scope of rehabilitation procedures, criteria corresponding to the patient's state of health and physical activity tolerance are used [38]. Adequate physical activity is determined on the basis of an individual assessment, taking into account age and comorbid conditions. Pulmonary rehabilitation can be carried out both at home and in a rehabilitation center using video programs, the Internet, and a mobile phone. Exercises include breath control, breathing exercises, and a gradual increase in the amount of physical activity as the tolerance increases. In case of respiratory failure and a decrease in blood oxygen saturation below 91%, it is recommended to use a mobile oxygen concentrator at home for long-term oxygen therapy with an oxygen supply rate of 4-5 liters /min until the patient's condition improves.

Nutritional support should be provided to all patients, especially the elderly and with gastrointestinal diseases, whose body weight decreases significantly during the illness. Easily digestible products, well processed and rich in protein are used [39, 40]. Correction of drug therapy for the control of chronic AML, the state of the cardiovascular and endocrine systems, as well as neuropsychiatric rehabilitation is recommended for all patients with PCS.

Conclusion. The results of studies related to the problem of PCS confirm that the pathogenetic mechanisms of PCS are multifaceted and require correction. Disorders in the immune system after COVID-19 ensure the maintenance of the inflammatory process in the affected organs with impaired microcirculation and distelectases in the alveolar structures of the lungs and other affected organs, remodeling of the bronchial epithelium with the deposition of hyaluronic acid in the interstitial tissue of the perialveolar and bronchi with the formation of connective tissue. In the long term after infection, the most persistent changes are noted in the lungs, which leads to a decrease in the tolerance of physical activity and quality of life. Currently, there is a sufficient arsenal of medicines aimed at restoring functions disrupted as a result of the disease and preventing PCR, whose effect has been confirmed by numerous studies: immunomodulators, drugs that improve

microcirculation, antithrombotic agents and antiplatelet agents, drugs with antifibrotic and anti-inflammatory effects. Active dispensary monitoring aimed at early diagnosis and treatment of detected organ dysfunction, taking into account their pathogenetic mechanisms, is a reliable basis for improving the clinical condition of patients after COVID-19, for the treatment and prevention of PCS.

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