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TOXICOLOGIST`S OPINION ON THE MECHANISMS OF VIRUS-INDUCED HEMOGLOBINOPATHIES WITH TOXIC PNEUMONITIS AND SYSTEMIC HYPOXEMIA FROM COVID-19 AND SUBSTANTIATION OF RATIONAL DETOXIFICATION METHODS

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ABSTRACT. *Coronavirus disease COVID-19 is currently a global problem for humanity, becoming a pandemic. From the standpoint of toxicologists, there is a need to summarize the literature on the pathogenetic and pathophysiological mechanisms of the main clinical manifestations about COVID-19 and to justify ways to optimize treatment strategies using detoxification therapy.*
Purpose. *Based on the analysis of literature data to identify pathogenetic mechanisms of the main clinical COVID-19 syndromes, to summarize the results of clinical and laboratory studies, clinical and hematological criteria for predicting severe cases with fatalities and to justify ways to optimize detoxification therapy.*
Material and Methods. *Analytical review of scientific publications was performed using abstract databases of scientific libraries PubMed, Medline and text databases of scientific publishers Elsevier, PubMed Central, BMJ Group and other VIP-databases and covers the period from January 1, 2020 to April 30, 2020. Methods of system, comparative and content analysis are used.*
Results and Conclusions. *Publications on the identification of infection ways with SARS-CoV-19 virus, mechanisms in formation for clinical manifestations of COVID-19 different disease variants to identify the most informative predictors of the severe disease forms that lead to fatalities are analyzed. Literature data on the mechanisms of viremia development of SARS-CoV-19, pathogenetic and pathophysiological mechanisms of virus-induced hemoglobinopathies, toxic pneumonitis, systemic hypoxemia, hyperferritinemia, cytokine "storm", oxidative stress and endotoxicosis are summarized; improvement of detoxification therapy which included efferent treatments, the complexing agents to remove excess levels of iron and ferritin, antioxidants and antihypoxants, oxygen therapy, transfusion of immune plasma convalescents, donor blood components and stem cells, was justified.*
Key Words: *coronavirus disease, COVID-2019, virus-induced hemoglobinopathies, pneumonitis, detoxification therapy.*

The outbreak of coronavirus disease COVID-19, caused by the coronavirus SARS-CoV-2, which appeared in Wuhan, has become a global problem for all mankind and has become a pandemic – more than 6 million people are infected on the planet, and more than 500,000 were killed by it.

It is known that coronaviruses (Lat. Coronaviridae) are a large family of RNA viruses that can infect humans and some animals. In recent decades, four coronaviruses (HCoV-229E, -OC43, -NL63 and HKU1) have been circulating in the population, occupying 15–20% of the structure of the viral acute respiratory illnesses (ARI) and causing in the population lesions of the upper respiratory tract of mild to moderate severity. At the end of 2002, the coronavirus SARS-CoV, belonging to the genus Bettacoronavirus, appeared in China, the causative agent of SARS, which causes the development of Severe Acute Respiratory Syndrome (SARS) in humans. It has been proven that the natural reservoir of SARS-CoV are bats, intermediate hosts – camels and Himalayan civets. During the epidemic period from 2002 to 2003, more than 8,000 cases of SARS were registered in 37 countries, of which 774 (9.7%) were fatal. Since 2004, no new cases of SARS-CoV pneumonia have been reported worldwide.

In 2012, a new coronavirus MERS-CoV (Middle East respiratory sindrome – related) coronavirus appeared in the Arabian Peninsula – the causative agent of the Middle East severe acute respiratory syndrome, which also belongs to the genus Bettacoro-navirus. The main natural reservoir of MERS-CoV are single-humped camels (dromedaries). From 2012 to January 2020, 2,519 cases of coronavirus pathology caused by MERS-CoV virus were registered, of which 866 (34.4%) were fatal; in total, 82% of cases were reported in Saudi Arabia. Currently, MERS-CoV continues to circulate and cause new cases, mainly among the population of the Arabian Peninsula.

Aim. Based on the analysis of literature data to identify pathogenetic mechanisms of the

main clinical COVID-19 syndromes, to summarize the results of clinical and laboratory studies, clinical and hematological criteria for predicting severe cases with fatalities and to justify ways to optimize detoxification therapy.

Material and Methods. Analytical review of scientific publications was performed using abstract databases of scientific libraries PubMed, Medline and text databases of scientific publishers Elsevier, PubMedCentral, BMJ Group and other VIP-databases and covers the period from January 1, 2020 to April 30, 2020. Methods of system, comparative and content analysis are used.

Results. The new SARS-CoV-2 coronavirus is probably a recombinant virus between the bat coronavirus and the unknown origin of the coronavirus, and its genetic sequence is at least 79% similar to the SARS-CoV sequence [1].

The leading transmission route of SARS-CoV-2 is airborne, which is realized by coughing, sneezing and talking at close range and contact routes of transmission. The entrance gate of this virus is the epithelium of the upper respiratory tract, epitheliocytes of the stomach and intestines. The initial stage of infection is the penetration of SARS-CoV-2 into target cells that have receptors for angiotensin-converting enzyme type II (Angiotensin-converting enzyme 2 – ACE2), so this receptor is a functional receptor for SARS-CoV-2 virus responsible for the COVID-19 pandemic. ACE2 receptors are present on the mucous membranes of the mouth, nose, eyes, respiratory tract cells, mainly alveolar pneumocytes type II in lungs, cells of the esophagus, stomach, duodenum, colon, rectum, heart, central nervous system, and on blood cells: neutrophils, plasma cells, lymphocytes, etc. [6, 7, 9, 11]. Type II pneumocytes are small cylindrical alveolar cells located in close proximity to the pulmonary capillaries involved in the synthesis of alveolar surfactant, a surfactant that is known to play an important role in gas exchange [3].

Today, the issue of angiotensin-converting enzyme (ACE) inhibitors – Enalapril, Lisinopril and others – is widely used among the population suffering from hypertension, and aldosterone receptor blockers (ARBs) – Sartans (Losartan, Valsartan, Telmisartan, etc.), which promote the compensatory expression of ACE2 receptors on cells and allegedly increase the gateway for penetration and spread of COVID-19 virus [9, 10]. But experimental data show that ACE inhibitors and ARBs may be useful in infected patients to limit lung damage by inhibiting type II angiotensin receptors [8]. At the same time, some studies have shown the effect of ACE2 on the pathological progression of tissue damage and certain chronic diseases, which suggests that ACE2 may have some significance in the progression of COVID-19 [9]. The authors also note that the question of the potential effect of ACE inhibitors on the course of this viral pathology requires more detailed study. However, it has been shown that COVID-19 virus has a much higher affinity for ACE2 than SARS-CoV virus (SARS virus), so it is more virulent, because it binds easily to receptors and penetrates into body cells [8, 9, 10, 11].

The penetration of the virus is probably through the olfactory bulb (like some chemical compounds, such as dioxins, etc.), as a result of which most patients with COVID-19 at an early stage of the disease develop a change in smell (hyposmia) [4, 5]. However, there are no studies on the presence of ACE2 receptors and other entrance gates for the virus in the nerve cells of the olfactory bulb.

It has been shown that the COVID-19 virus has on its surface a number of structural proteins that bind to the ACE2 receptor: thorn proteins (S), shell proteins (E), membrane proteins (M) and nucleocapsid phosphoprotein [7, 11]. In addition, the virus contains encoded proteins: orf1ab, orf 3a, orf 6, orf 7a, orf 10 and orf 8, etc., of which the proteins orf8 and orf3a of the COVID-19 virus are significantly different from the proteins of other coronaviruses – they are more strongly associated with ACE2, and therefore can cause more serious pathological changes [7]. The mechanisms that cause the high pathogenicity of the new virus COVID-19 have not been studied enough.

COVID-19 viruses with the help of thorn proteins (S), transmembrane glycoproteins and transmembrane proteases bind to the ACE2 receptor and enter the cells of the body, where they create functional domains with different proteins and enzymes, forming duplication complexes [7, 10, 11].

By infecting the human body, the COVID-19 virus causes acute respiratory disease with several variants; 80–85% of the population has a mild course (50–60% of them are almost asymptomatic; 10–20% have a moderate course), 5–10% have a severe course, and in

some cases a rapid course [1-6, 12-22]. The study of clinical signs of COVID-19 revealed [1-6, 12-22] that in the moderate form of COVID-19 patients aged 42–55 years predominate, in severe – over 56 years. In almost all cases, the disease begins with a runny nose, myalgia, headache, fever up to 38–39° C, cough (initially dry, sometimes superficial), and after a few days – with sputum. 2-3 later days joins increased fatigue, then comes weakness. In 10–20% of cases in the first days there may be abdominal pain, diarrhea, chest tightness, in 10–15% of cases – skin lesions rashes or vesicles, in 5–6% – eye lesions. In moderate and especially severe forms in 3-5 days there is shortness of breath, acrocyanosis progressing in the following days. In severe forms of COVID-19 disease in all cases develops hypoxemic syndrome (socalled «altitude sickness») with a decrease in oxyhemoglobin below 90% and with loss of consciousness, up to coma.

Laboratory tests in patients with moderate COVID-19 disease reveal a normal number of leukocytes or moderate leukocytosis, and in severe-leukocytosis from 8 to 11.5x10^9 / l, neutrophilia and lymphocytopenia in the first days with subsequent expression and decreased hemoglobin levels, especially in patients with severe form of the disease [31, 37, 39-41, 56, 57, 78]. At the same time, there is an increase in the level of serum ferritin – in the moderate form of the disease – in 2–3 times, and in severe form – in 4–6 times. There may be a moderate increase of transaminases levels (ALT, AST), a decrease in albumin – up to 38–35 g / l in moderate and up to 33–25 g / l – in a complicated form, due to reduced synthetic liver function, there is also an increase level of lactate dehydrogenase (LDH) – in moderate forms of the disease up to 250-280 U / L, and in severe forms – 2-3 times [31-41, 56, 57, 78]. Studies of the coagulation system reveal the development of coagulopathy in patients with severe forms of the disease with a slight increase in prothrombin time Prothrombin Time (PT) and activated Partial Thromboplastin Time (PTT) with a significant increase in the level of D-dimers less than 0.5 μg / ml in healthy individuals – up to 20.0 μg / ml in patients) and often with thromboembolic disorders (pulmonary embolism, stroke ets.) [22, 23, 37, 39, 42, 49]. In some cases, there is an increase in procalcitonin levels [40, 41, 51, 52]. Sometimes patients with moderate disease and almost all patients with severe form are characterized by a progressive increase of acute inflammatory protein levels (C-protein, tumor necrosis factor – TNFα, interleukins: IL-1β, IL-2, IL- 6, IL-7, IL-8, IL-9, IL-10, IL-17,

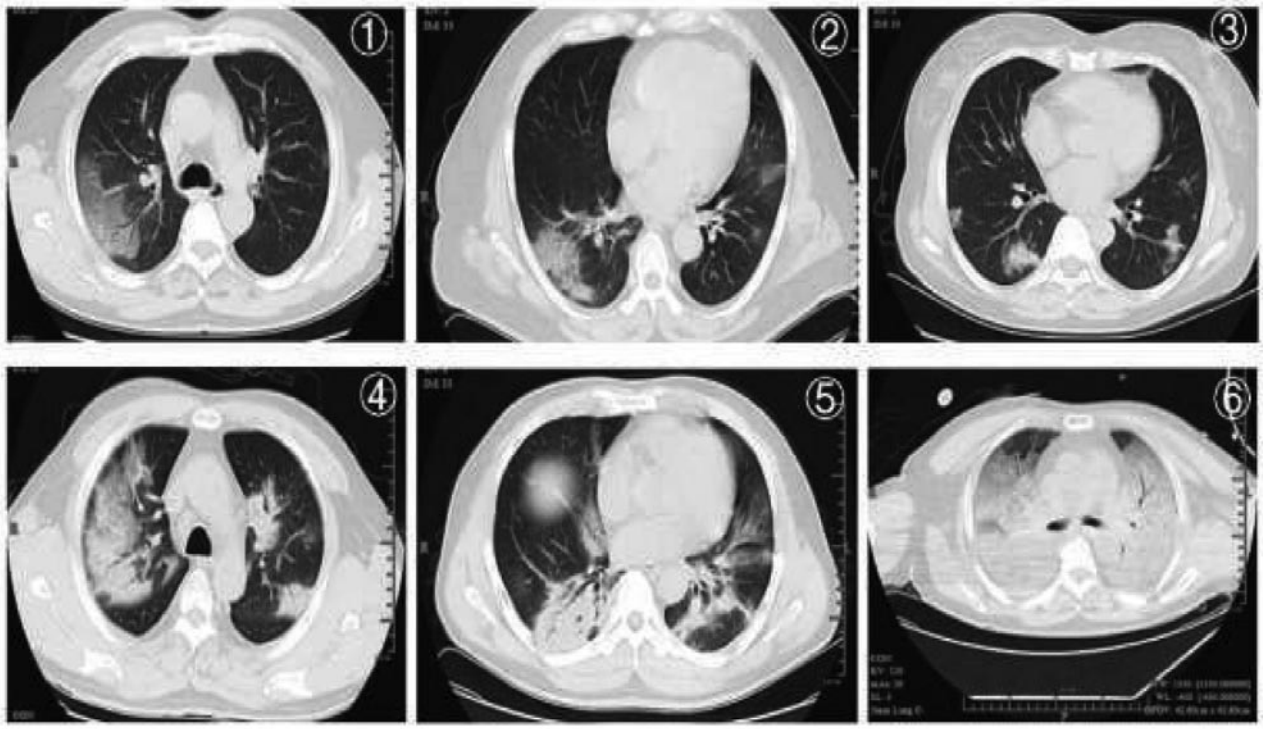

Figure 1. 1, 2 – "frosted glass" syndrome; 3 – nodules and focal exudation; 4, 5 – multiple seals of lung tissue; 6 – diffuse seal, "white lung" [78].

G-CSF, GM-CSF, gamma-interferon – IFNγ, cytokines and chemokines: IP10, MCP1, MIP1A and MIP1B in serum) with the cytokine "storm" syndrome in severe forms of coronavirus disease [15, 16, 21, 24, 40, 41,56, 57, 73, 120]. Particular attention is paid to the formation of complement-associated microvascular damage with thrombosis in the pathogenesis of COVID-19 [23].

The formation of more frequent bilateral pneumonia in moderate and severe forms of COVID-19 is described [2-6, 8-20]. The peculiarity of these virus-induced pneumonias in patients with COVID-19 is a long period when there are no typical signs of inflammation during auscultation of the lungs and X-ray pictures, and a specific computed tomography (CT) picture of the lungs as a polysegmental small focal seals called "ground glass", and in moderate form of disease – large foci, sometimes draining, which later forms a syndrome of "white lungs" – in severe forms of COVID-19 [25-26]. The appearance of such small areas of "frosted glass" in the lungs during CT in some patients with asymptomatic COVID-19 is noteworthy. The decrease in transparency is due to the decrease in the airiness of the alveoli and their gradual filling with a viscous abundant secretion with increased levels of hyaluronic acid (HA) [75, 76], which is released due to damage to the alveoli. CT images allows you to see the characteristic white spots that characterize the presence of fluid in the alveoli [2, 25, 26]. Pathological studies have confirmed that the lungs of COVID-19 victims are filled with a clear viscous jelly that resembles the state of the lungs when drowned in water [74]. Although the nature of clear jelly is still unclear, elevated levels of hyaluronic acid in the alveolar secretion are associated with SARS [75]. In the lungs of patients with COVID-19 is also detected a fairly high level of inflammatory mediators (IL-1, TNFα), which are potent inducers of hyaluronic synthase-2 (HAS2) in endothelial cells (responsible molecule or cluster of differentiation – CD31), alveolar epithelial cells lungs (responsible molecule – EpCAM) and fibroblasts [75-76]. Importantly, hyaluronic acid has the ability to absorb water 1000 times its molecular weight, so reducing the presence or inhibition of hyaluronic acid synthesis may be a component of the pathogenetic treatment of patients with COVID-19 [77, 78].

A retrospective study of CT images in 4121 patients with COVID-19 showed that bilateral lung damage was found in 73.8% of subjects, multilobar lesions had 67.9%, signs of "ground glass" – 68.1%, signs of emphysema – 44.7 %, spotted changes – 40.3%, signs in the form of "cobwebs" – 39.5%, cords – 36.8% and knots – 20.5%. Lymphadeno-pathy was observed in 5.4% and pleural transudate – in 5.0% of patients (Fig. 1) [25].

Another study shows that in the analysis of 33 CT images in patients with COVID-19 bilateral lung damage was detected in 87.9% of cases, in 90.9% – there were subpleural lesions, in 36.4% – interstitial changes, in 75.8% – signs of "frosted glass", 54.5% – thickening of the interlobar septa [26].

The results of postmortem biopsy and histological examination also show all components of diffuse alveolar damage: damage to alveolar epithelial cells, compaction of hyaline membranes, hyperplasia of type II pneumocytes, abundant intraalveolar neutrophilic infiltration and infiltration of siderophages, which indicate the increased level of iron [27].

Histological examination of lung tissue in patients with COVID-19 revealed diffuse pulmonary lesions: the appearance of thickened hyaline membranes and obliteration of small vessels with signs of acute phase components – with infiltration of neutrophils and siderophages, with hyperplasia of type II pneumocytes and thickening of interstitial tissue [28]. In some cases, the alveoli were filled with hemorrhagic exudate, fibrin and inflammatory infiltration cells. Diffuse hyperplasia of type II pneumocytes was combined with fibrinoid necrosis of small vessels. In other patients, intense neutrophilic intra-alveolar infiltration prevailed, which indicates the accession of a bacterial infection (Fig. 2).

Sinusoidal dilatation, nuclear accumulation of glycogen in hepatocytes, signs of focal steatosis of large vessels with infiltration of atypical small lymphocytes of the portal tract were observed in the liver tissues. In some cases, there is a compaction of the liver structure with areas of fibrosis and regenerative nodules with signs of cirrhotic changes. Cardiac biopsy revealed focal edema, interstitial fibrosis and myocardial hypertrophy, ischemic injuries, especially in patients with arterial hypertension [28].

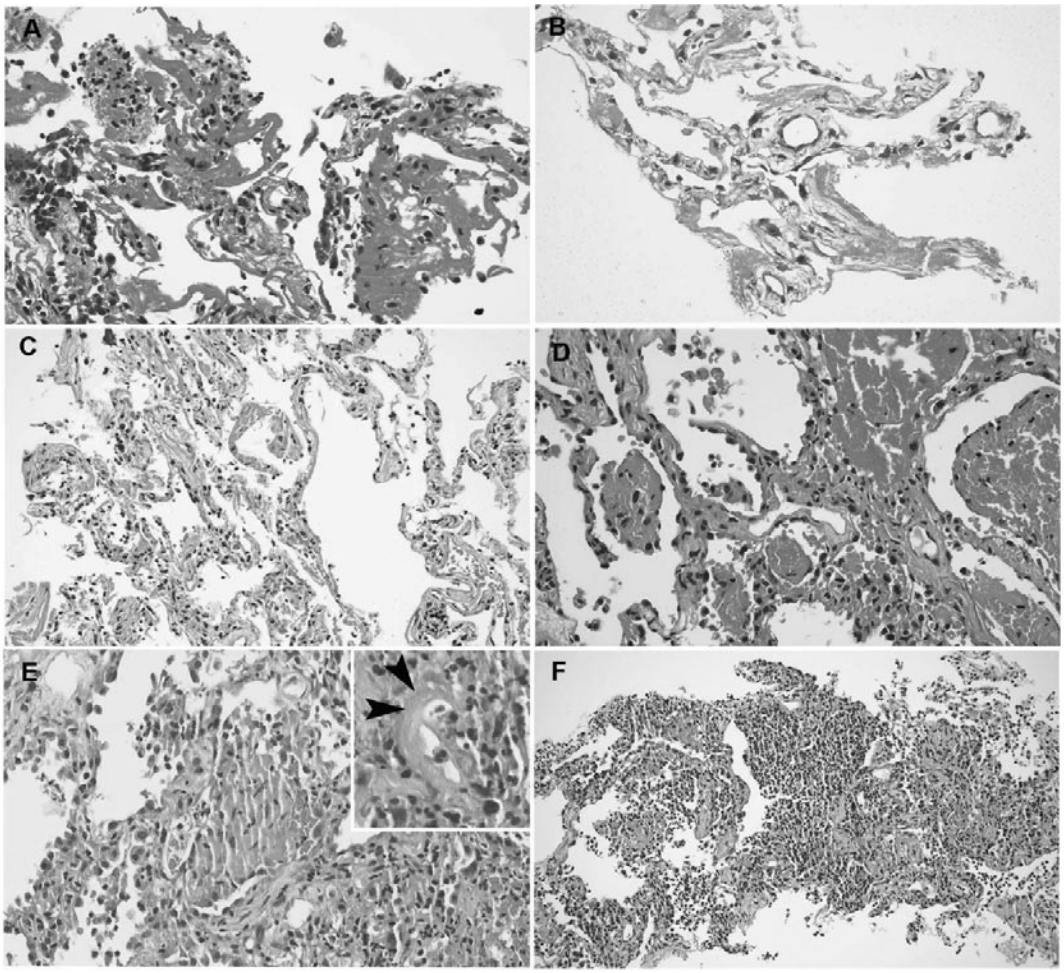

Figure 2. Histological changes in the lungs: a – thickened hyaline membrane mixed with desquamated pneumocytes and mononuclear inflammatory cells; b – thinned hyaline membranes without obvious inflammatory infiltration; c – focal hyaline membrane, hyperplasia of type II pneumocytes and mild interstitial thickening; d – alveolar spaces filled with exudate of erythrocytes and small plugs of fibrin in adjacent alveoli; e – agglomeration with intraalveolar fibroblasts mixed with fibrin and inflammatory cell infiltration, diffuse hyperplasia of type II pneumocytes in the background (insert: fibrinoid vascular necrosis); f – the phenomenon of bronchopneumonia with pronounced neutrophilic infiltration and filling of the alveolar spaces (Tian S. et al.) [27].

It was determined that in most patients with moderate COVID-19 and in all patients with severe disease one of the main syndromes was increasing shortness of breath with a decrease in hemoglobin and high levels of ferritin in the blood and signs of cytokine "storm", which indicated the formation severe hypoxemic syndrome [31-37, 40, 41, 56, 57]. But the genesis of systemic hypoxemic syndrome and high levels of ferritin have not yet been clearly explained.

Molecular genetic analysis of COVID-19 [1, 7, 10] and computer homologous modeling of the structure of SARS-Cov-19 proteins with estimation of binding energy with heme porphyrin [7] revealed that one of the main targets of the new virus is porphyrins hemoproteins. Porphyrins are probably the main life form of coronaviruses that is required for their replication. It is known that the group of hemoproteins includes hemoglobin and its derivatives, myoglobin and respiratory enzymes (the whole system of cytochromes, catalase, peroxidase). All of them contain as a non-protein component— structural-like hemoporphyrins and different in composition and structure of the protein, which provides a variety of their biological functions. Hemoglobin contains globin as a protein component, and heme as a non-protein component. Species differences in hemoglobin are due to globin, while heme in all types of hemoglobin is the same. The basis of the structure of the prosthetic group of most hemoproteins is the porphyrin ring, which is a

derivative of the tetrapyrrole compound – porphyrin. Unsubstituted porphyrin is called porphin. In the heme molecule, porphin is represented as protoporphyrin IX. Protoporphyrin, attaching iron, is converted into heme. Iron in heme is covalently linked to two atoms of the protoporphyrin molecule, and to two – by coordination. Heme in the form of hemoporphyrin is a prosthetic group not only for hemoglobin and its derivatives, but also for myoglobin, catalase, peroxidase, cyto-chrome oxidase. Iron with the help of four bonds forms a complex with porphyrin, its 5th coordination bond connects with the nitrogen atom of the protein molecule, and the 6th bond is designed to attach oxygen (with the formation of oxyhemoglobin and oxymyoglobin) or other ligands. An iron atom located in the center of the heme pigment. One divalent iron atom can bind four oxygen molecules. Thus, in addition to the main hemoglobin – HbA1 in the blood, the existence of HbA2 (2.5%) in the blood, which also consists of two α-chains and two β-chains, has been proved in adults. Fetal hemoglobin (neonatal hemoglobin, HbF) is also known, which is converted to HbA by the end of the year. Fetal hemoglobin contains almost no β_1 chains, which is probably why children under 1 year of age do not often get COVID-19. It could be assumed that in people with altered hemoglobin (with a small number of β-chains) coronavirus disease may have a different course. However, recent reports from the WHO and the International Thalassemia Federation advise against drawing premature conclusions due to insufficient evidence on this issue [77]. The main role in gas exchange is played by oxyhemoglobin (HbO_2) – a compound of molecular oxygen with hemoglobin. Oxygen is attached to each heme of the hemoglobin molecule by means of coordination lines of iron, and the addition of one molecule of oxygen to the tetramer facilitates the attachment of the second molecule, then the third, and so on. The peculiarity of oxygen binding provides not only the binding of its maximum amount, but also its release in peripheral tissues. This is also facilitated by the presence of H^+ ions and CO_2 molecules in tissues with intensive metabolism. In lung tissue, oxygen accelerates the release of CO_2 and H^+.

It has been shown that non-structural proteins of COVID-19 virus (orf1ab, orf3a, orf8) attack β1-chains of hemoproteins, in particular hemoglobin, capturing porphyrin and inhibiting heme metabolism [7, 29]. These proteins and surface glycoproteins bind tightly to heme porphyrin. At the same time, iron atoms dissociate, which accumulate in cells, causing toxic oxidative stress and destroying them and get into the surrounding tissues, where they are captured by siderophages [27, 28]. In addition, excessive amounts of iron enter the bloodstream, in connection with which hyperferritinemia develops.

It is known that the authors noted hyperferritinemia in COVID-19 [1-7, 12-21] is not only a marker of inflammation [29], but also an indicator of elevated iron level, because ferritin is the main depot of iron, linking it in the body to 25 –30% and ensuring its participation in homeostasis. So, low levels of ferritin indicate iron deficiency, and high – reflects excess levels of iron in the body. In addition, iron, redox processes and inflammation are inextricably linked [29, 30, 31]. Thus, high levels of ferritin (especially elevated in patients with severe COVID-19 – an increase of 4–6 times) are likely to have both protective and destructive effects [119]. The role of ferritin in inflammatory processes is still insufficiently studied.

In the process of destruction of hemoglobin by COVID-19 virus and its non-structural proteins by immune hemolysis of erythrocytes and heme leakage from damaged erythrocytes [7] and other hemoproteins containing porphyrin, iron levels increase in serum and show toxic effects with oxide formation.

It is known that one molecule of ferritin can deposit more than 4500 molecules of iron, thereby protecting cells from oxidative damage. Iron in excessive amounts is highly toxic, generates toxic free radicals that directly damage cellular proteins, lipids and nucleic acids [30].

It is also known that ferritin induces the expression of proinflammatory cytokines. However, in turn, cytokines and paracrine signaling molecules, such as nitric oxide (NO), also induce ferritin synthesis. At the cellular level, macrophages play an important role in iron homeostasis, forming siderophages, directly carrying out phagocytosis of virus-damaged erythrocytes and structures of iron-containing heme. That is why histologists detect accumulations of siderophages in the alveoli of patients who died of COVID-19 disease [27, 28]. COVID-19 creates an acute need for

macrophage-mediated metabolism of erythrocytes and hemoglobin due to impaired gas exchange, which causes the development of tissue hypoxia and systemic hypoxemia. Macropha- ges are able to release iron through ferroportin as a substrate for cellular recirculation in erythrocytosis. However, an excessive number of damaged erythrocytes, heme molecules, elevated levels of iron, ferritin and many pro-inflammatory proteins (cytokines, C-protein, etc.) cause microcirculation disorders, vascular obliteration, thrombus formation, which lead to the formation of focal necrosis [22, 31], and in the lung tissue – hypoxic foci, which are visualized on CT as "frosted glass".

It is demonstrated that porphyrin of glycosylated hemoglobin, the level of which is higher in patients with diabetes mellitus, obesity, cardiovascular pathology, metabolic disorders, in particular older age groups, is most susceptible to viral infection. Obviously, this is associated with higher mortality from coronavirus disease among patients with a history of these diseases [2-7, 12-21].

It was shown [7] that the proteins of the virus – orf1ab, orf10, orf3a with the participation of surface glycoprotein, coordinated by viral RNA, directly bind to the β1-chain of hemoglobin and deoxyhemoglobin molecules, leading to the dissociation of iron. This also explains in some way the pathogenicity of the new virus, which does not enter erythrocytes because they do not have the necessary receptor to bind the S-glycoprotein of the virus. This virus is not capable of endocytosis due to the lack of necessary proteins. It is possible that, in addition to nonstructural proteins, hemoglobin also destroys antibodies of the virus itself, produced by plasma cells that contain ACE2 receptors. Probably fragments of heme come out through the pores of the damaged erythrocyte, and some – due to immune hemolysis.

Levels of deoxyhemoglobin, as well as glycosylated hemoglobin, in patients with cardiovascular disease, obesity and diabetes are higher, so there is more gateway for the virus. These patients are more likely to become infected with large amounts of the virus and are more likely to die from severe forms of COVID-19 [7, 29]. In this group, low hemoglobin levels are more common [37, 40, 41], probably due to virus-induced hemolysis, as well as high levels of ferritin, and postmortem biopsy reveals severe infiltration of alveoli by siderophages [27, 28].

In determining the prognostic markers of severe disease and death in COVID-19 a significant place is occupied by high serum ferritin, which is associated with excessive iron levels, cytokine "storm", the formation of oxidative stress and systemic hypoxemic syndrome [40, 41]. High ferritin content or hyperferritinemic syndrome is associated with fatal consequences in other pathologies – severe sepsis [33, 34] and blood diseases [32, 36]. The authors showed that high levels of ferritin induce the activation of macro-phages – the development of macrophage activation syndrome with the formation of cytokine "storm" and with impaired microcirculation and gas exchange [35].

Cytokine "storm" along with hyperferritinemia contributes to 10-15% of patients with COVID-19 development of SARS [1-7, 21, 25, 26, 39]. The development of cytokine "storm" is facilitated by the activation of neutrophils, which is enhanced powerful function of these cells – the ability to form extracellular traps (Extracellular traps net) (fig. 3) [39].

It is known that neutrophils phagocytose bacteria, fungi, viruses, damaged cells and utilize them with lysosomal enzymes, oxidative reactions and by activating autophagy. In recent years, it has been shown that the killer function of neutrophils is provided in the extracellular space by forming from its own DNA extracellular traps (Neutrophil extracellular traps – NET), including neutrophil elastase, intracellular proteins-triggers of nuclear disintegration, peptidilarginine deiminase – type-4) – PAD 4), histone proteins that are part of the structure of nuclear chromatin and provide DNA packaging, and also play an important role in the regulation of gene expression and chromatin rearrangement. The main function of NET is the lysis of pathogens, but their excessive formation upon activation of neutrophils triggers a cascade of inflammatory reactions, promotes the formation of microthrombosis, increases the viscosity of bronchoalveolar secretion, promotes the formation of SARS (Fig. 4) [39].

The authors believe that these extracellular traps play an important role in the formation of cytokine "storm" in COVID-19 disease, severe forms of which are accompanied by cytokine "storm", characterized by increased plasma concentrations of inflammatory mediators: CRP, IL1β, TNF-α, IL2, IL6, IL7, IL8, IL10,

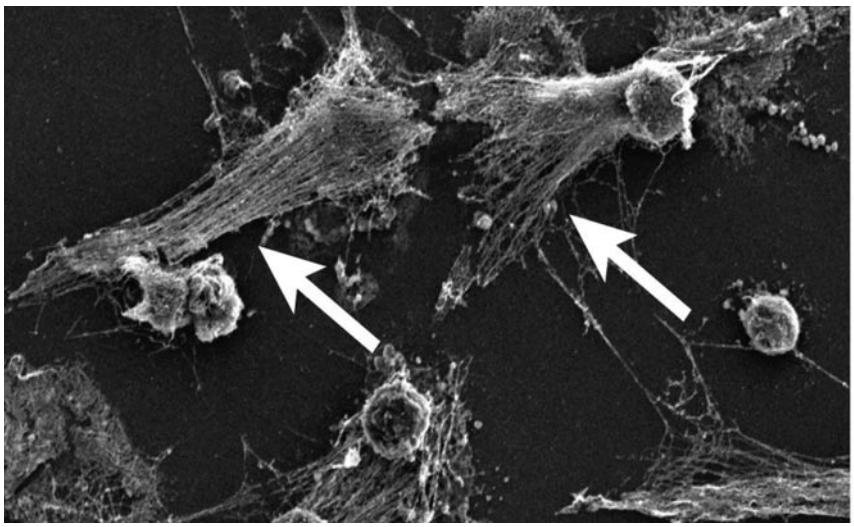

Figure 3. Electronic photograph of extracellular traps (Neutrophyl extracellular traps – NET). As part of the body's immune system, neutrophils detect bacteria and can use their DNA (see arrows) to attack bacteria through a thin network of DNA (NET) containing toxic enzymes (Barnes B.J. et al.) [39].

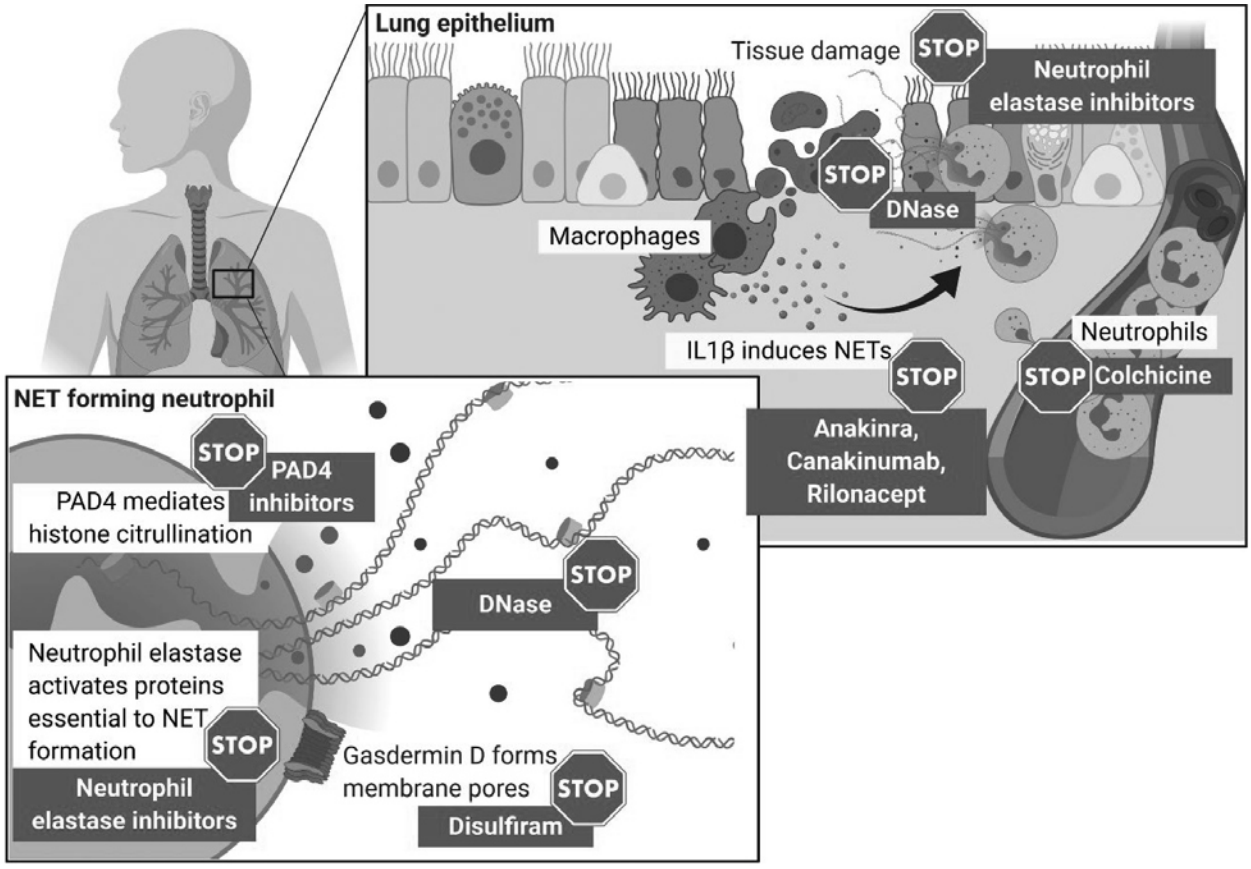

Figure 4. Mechanisms of NET formation (Neutrophil extracellular traps) and mechanisms of inhibition of NET formation by colchicine, which inhibits neutrophil migration and infiltration at sites of inflammation and IL1β blockers (Anakinra), which will prevent the development of inflammation (Barnes B.J. et al.) [39].

IL17, as well as ferritin, procalcitonin and others. [37, 39, 40, 42] and probably contribute to the formation of toxic pneumonitis. Excessive expression of cytokines and ferritin contributes to lung tissue damage, the development of SARS, the formation of microthrombosis and leads to death [31].

Thus, the mechanism of formation of pathological disorders in COVID-19 is characterized by great diversity. Analyzing the data, we can make the following generalizations:

1) viremia SARS-CoV-2 is realized in tissues with a high content of ACE2 receptors – in the lungs, heart, gastrointestinal tract,

mucous membranes of the mouth, nose and eyes, blood cells, especially lymphocytes, which contributes to their lysis and lymphopenia [7-10, 38, 43, 56, 57];

2) non-structural proteins of SARS-CoV-2 virus coordinated by viral RNA (orf1ab, orf10, orf3a), its surface glycoprotein and ORF8 protein have a high tropism to porphyrin hemoproteins (hemoglobin, especially glycosylated hemoglobin, glycosylated hemoglobin, enzymes of the respiratory chain (cytochromes), enzymes of the P450 system, causing the dissociation of iron, increasing its level in blood cells, alveoli and blood plasma reduce the ability of hemoglobin to carry oxygen and form gas exchange disorders and hypoxia; this causes alveolar infiltration by siderophages, which contributes to gas exchange disorders and the development of hypoxia, the formation of hyperferritinemia, oxidative stress and neutrophil activation [31-37, 39 - 41, 56, 57, 78] and may indicate that the coronavirus disease caused by SARS-CoV-2, is more a blood disease than a lung disease that contributes to the development of toxic pneumonitis;
3) activation of neutrophils and the formation of a network of extracellular traps (NET), as well as oxidative stress and hyperferritinemia trigger a cascade of cytokine "storm", contribute to the development of systemic inflammation and the development of SARS, damage to lung tissue, microcirculation, thrombosis activation [37, 39, 40, 42, 49, 63];
4) prognostic biomarkers (predictors) of severe COVID-19, the development of SARS and fatalities are: neutrophilia [41], lymphopenia [15, 16, 38, 40, 41, 44-57], hyperferritinemia [15, 16, 40, 41, 45-50], thrombocytopenia [15, 16, 41, 45, 47, 48], increased levels of C-protein [15, 16, 41], interleukin-6 [41, 40], procalcitonin [40, 41, 51, 52], LDH [15, 16, 40, 41, 56, 57], as well as strengthening the process of lung damage, visualized on CT imagens as a massive focusses of “grapes glass” [40, 41];
5) predictors of hypercoagulable processes, disseminated intravascular coagulopathy and thromboembolism are elevated blood levels of D-dimer, prothrombin time (PT) and activated partial thromboplastin time (PTT) [31, 40, 44, 49, 54-60];
6) risk factors for severe course and fatalities in COVID-19 are old age, high body mass index and obesity, as well as comorbidities: diabetes, chronic pathology of the bronchi and lungs, cardiovascular system, liver, kidneys, cancer and the accession of a bacterial infection [40, 41].

The treatment regimens for patients with COVID-19 often include the following items:

1) antiviral therapy (Remdesivir, Favipiravir, Favilavir and etc.) [7, 53, 116] (Fig. 5);
2) antimalarial drugs – Chloroquine and others that can to some extent delay the attack of heme and porphyrin capture by proteins of the virus COVID-19 orf1ab, orf3a, orf10, as well as inhibit the binding of surface glycoproteins [2, 5, 7, 12];
3) transfusion of immune plasma of persons with COVID-19 (the method was used by Chinese doctors, who estimated its effectiveness at approximately 30%) [78];
4) antibiotics – in cases of joining the bacterial microflora;
5) anticoagulants – recommended to use heparins under the control of platelet count, prothrombin time (PT) and activated partial thromboplastin time (PTT) and other indicators of the hemostasis system [23, 24, 31, 39, 41, 49, 50, 58];
6) corticosteroid therapy – to suppress the cytokine “storm” [78, 80-82], we believe that it is also advisable to use inhaled forms of corticosteroids (Seritide, Beclatate etc.);
7) genetically engineered biological drugs containing monoclonal antibodies: inhibitors of tumor necrosis factor (TNFα) (infliximab (Remicade), adalimumab (Humira), golimumab (Simponi), etc.); interleukin-6 receptor inhibitors (Tocilizumab, Sarilumab); interleukin-1 blockers (Anakinra, Conakinumab, Rilonacept) [39]; blocker of B-lymphocyte activation rituximab (Rituximab); T-lymphocyte activation blocker Abatacept, etc. [24, 42, 52, 53, 67, 70-73, 117] (Fig. 5);
8) stem cell transplantation [70-73]; we consider it appropriate to use injections of fresh placental blood enriched with stem cells;
9) blood oxygenation by non-invasive and invasive artificial lung ventilation (ALV) and Extracorporeal Membrane Oxyge-nation (ECMO) [61-65, 74].

It should be noted that low blood oxygen saturation during artificial lung ventilation is associated with low oxygen capacity of erythrocytes. The US Society for Intensive Care (Society of Critical Care Medicine) has pub-

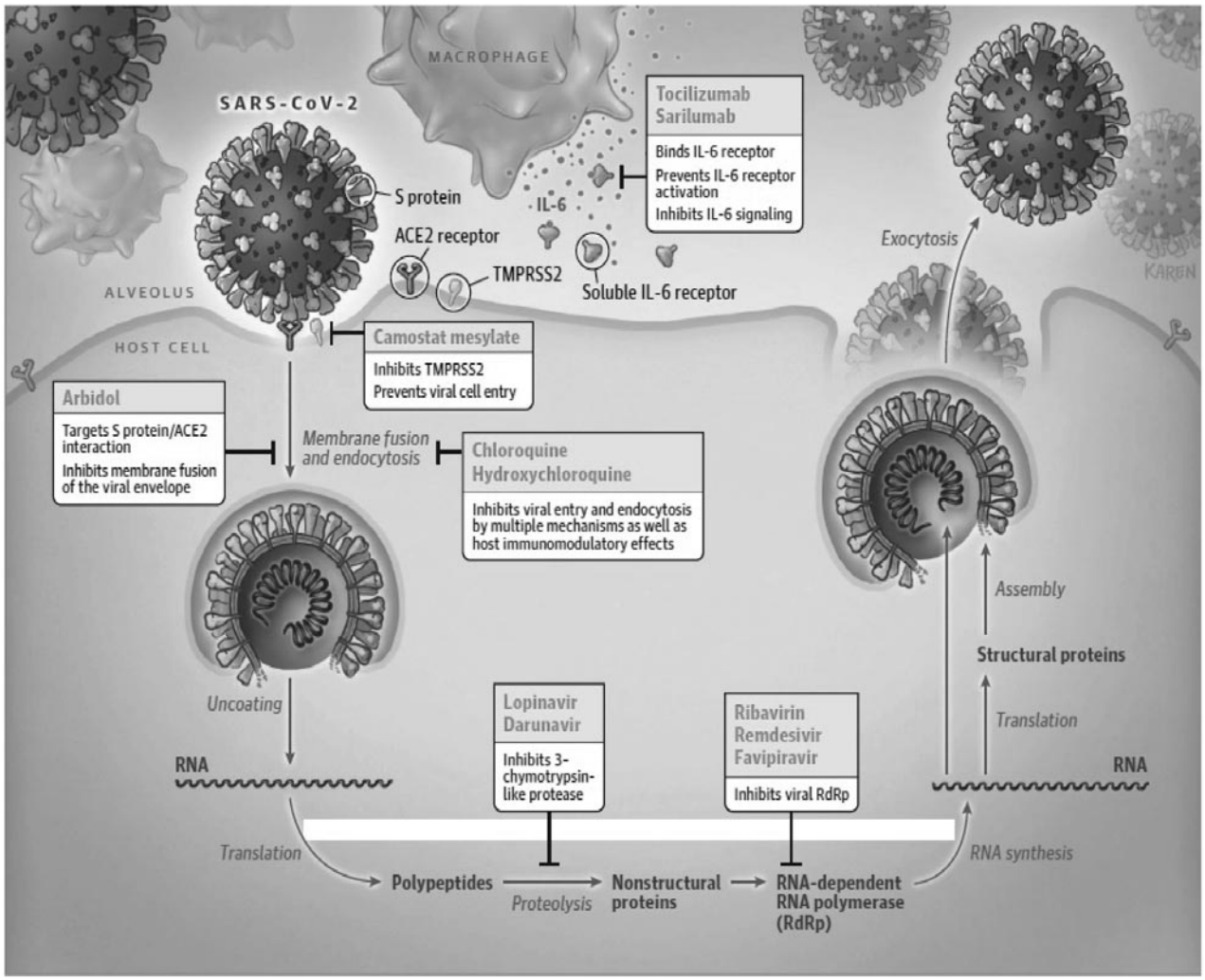

Figure 5. A simplified scheme of severe acute respiratory syndrome in SARS-CoV-2, theViral Lifecycle and Potential Drug Targets. ACE2 – angiotensin-converting enzyme 2; S protein – spike protein; and TMPRSS2 – type 2 transmembrane serine protease (Sanders J.M. et al.) [117].

lished preliminary guidelines [66] proposing venous-venous extracorporeal blood oxygenation (VV ECMO) in the treatment of SARS in patients with persistent refractory hypoxemia despite intensive therapy. The authors proposed an algorithm containing indications for early use of ECMO: paO_2: $Fi0_2$ <80 mm Hg. for> 6 hours; paO_2: $Fi0_2$ <50 mm Hg. for> 3 hours; pH <7.25 with $PaCO_2$> 60 mm Hg for> 6 hours However, such recommendations can be considered indicative due to insufficient evidence. It should be borne in mind that ECMO is an extremely high-tech and high-cost procedure, which in the context of a pandemic can be used only in those patients who have a sufficiently favorable prognosis. The authors note that it is advisable to use the method of ECMO in patients without comorbidities, less than 7 days on mechanical ventilation, do not belong to the group of seriously ill elderly people. In addition, ECMO can be recommended only in centers with sufficient resource support and in premises where the necessary conditions for anti-epidemic safety and unrestricted access of personnel to personal protective equipment are created [62-66].

The use of extracorporeal blood purification (EBP) in treatment of COVID-19 can be quite diverse, due to both hyperferritinemia and cytokine “storm”, and the development of multiple organ lesions, clinically manifested by acute liver and kidney damage syndromes. Some authors suggest that 15–30% of patients with severe COVID-19 are diagnosed acute kidney injury, while 67% of severely ill patients with COVID-19 may have organ dysfunction syndromes caused by high levels of circulating cytokines [84, 85, 108].

The problem of finding effective methods for the correction of hyperferritinemia arose long before the advent of COVID-19. Studies performed in recent decades demonstrate the effectiveness of plasmapheresis (plasma exchange) in the treatment of hyperferritinemia, which can accompany various pathological conditions (autoimmune diseases, viral and bacterial infections, sepsis, metallotoxicosis, etc.) [86-88]. A number fereti of authors point to the positive effect of hemodialysis in the correction of hyperferritinemia [122].

It should be borne in mind that a significant proportion of patients with COVID-19 have severe comorbidities that are accompanied by chronic dysfunction of certain organs and systems and require constant support (hemodialysis, peritoneal dialysis, etc.). COVID-19 is also a real deadly threat to surgical patients with infectious complications, including sepsis. Cytokines play a crucial role in coordinating and enhancing the host's immune response to infection. The nature of localized or systemic release of pro-inflammatory and anti-inflammatory cytokines varies depending on the disease. A dysregulated cytokine response can lead to a hyperinflammatory condition that contributes to the development of sepsis and septic shock, a condition that causes high mortality in critically ill patients. In turn, sepsis is accompanied by further excessive release of cytokines and other inflammatory mediators that cause refractory hypotension, tissue damage, metabolic acidosis, and ultimately multiorgan failure. Saving the lives of such COVID-19 patients requires extraordinary effort and resources.

For decades, extracorporeal detoxification methods (plasmapheresis and partial replacement of blood plasma, peritoneal dialysis, etc.) have been used in the treatment of multiple organ dysfunction syndrome (MODS) in adults and children [89, 90, 91]. In modern conditions, in vitro blood purification is offered as an adjuvant therapy for sepsis and is aimed at combating dysregulation of the immune system, which is known to cause organ dysfunction. The method proved to be effective in a wide range of severe inflammatory processes accompanied by cytokine "storm", endotoxicosis and multiorgan failure [92-96, 123].

Over the years, various treatments have been developed to address the problem of immune dysregulation. Most of the available blood purifiers focus on removing endotoxins that trigger the immune cascade, or a cytokine "storm" with subsequent organ damage. In this context, the reduction of plasma cytokines in patients with COVID-19 is a new concept of blood purification, designed to reduce the levels of pro-inflammatory and anti-inflammatory mediators released in the early phase of systemic inflammation. Therefore, extracorporeal cytokine hemadsorption is a technology used in the treatment of dysregulated inflammatory conditions, not only such as sepsis [97-104, 109].

In April 2020, the US Food and Drug Administration (FDA) approved the use of a number of innovative devices for extracorporeal blood purification (EBP): Spectra Optia Apheresis System with Depuro D2000 adsorption cartridge, Seraph 100 Microbind Affinity Blood device, CytoSorb device and oXiris Set device. The above devices are officially approved for the treatment of patients of the age of 18 years or older with confirmed coronavirus disease 2019 (COVID-19) who are admitted to the intensive care unit with respiratory failure or have a very high risk of developing it. These extracorporeal blood purification (EBP) systems reduce the number of cytokines and other inflammatory mediators that control the immune response by filtering the blood and then returning it to the patient [117, 118, 119]. Also, in May this year, the FDA granted a separate permit for the use of systems: multiFiltrate PRO System and multiBic/multiPlus Solutions for use in continuous renal replacement therapy (CRRT).

Recent publications have demonstrated clinical experience with the use of hemadsorption using CytoSorb membranes, which have provided rapid hemodynamic stabilization and increased survival rate, especially among patients with COVID-19 who were initiated early in the disease [105, 106]. Given this positive clinical experience, randomized follow-up studies are needed to determine the potential benefits of this new treatment. Today, hemadsorption can be used to reduce the level of cytokines in the case of excessive inflammatory response, as well as substances such as myoglobin, free hemoglobin or bilirubin. Inflam-mation control can provide a positive effect on the endothelial glycocalyx, and may be conducive to maintaining vascular barrier function, which plays a key role in the development of

tissue edema, provides oxygen balance and lactate levels [111, 112].

Membranes with high adsorption capacity are also used during ECMO. During ECMO therapy, many oxygen transport systems are activated, which in itself may provoke the release of cytokines, so the regulation of excessive plasma cytokine levels can be considered a valuable component of treatment. The authors note that a rapid and significant decrease in procalcitonin (PCT) and C-reactive protein (CRP) levels was observed after CytoSorb therapy compared to the control group [107].

Other authors have demonstrated the effectiveness of a highly adsorption membrane oXiris®, which combines cytokine and endotoxin removal, renal replacement, and antithrombogenic properties [110]. Currently, oXiris is used in all countries of Europe and Asia and has been used for more than 10 years to treat thousands of patients. oXiris has been validated for use in leading PrisMax and Prismaflex systems by leading Baxter companies. PrisMax, which was launched in the United States in 2019, is a new generation blood purification platform.

Our experience in the use of extracorporeal detoxication methods in the treatment of chemical poisonings and a wide range of diseases in patients of different ages suggests that modern extracorporeal detoxication (including hemadsorption therapy) can be considered as a new promising option for treating patients with pronounced inflammatory reaction,providing rapid stabilization of hemodynamics and metabolism, which will finally ensure the preservation of organ functions [111-115].

Removal of cytokines and endotoxins from the blood is a promising approach to treating conditions where the patient's blood contains excessive levels of these inflammatory mediators, however, in vitro blood purification is an area where little reliable research is being published and where is little scientific consensus on many issues, therefore, research in this direction is promising and timely.

Taking into consideration the processes that cause the formation of virus-induced toxic pneumonitis in COVID-19, due to excess iron and high levels of ferritin, lipid peroxidation products, proinflammatory cytokines, metabolic endotoxicosis products, we consider it appropriate to consider the following methods as perspectives:

1. The use of the Artificial Liver Support System (ALSS); in patients with COVID-19 it can provide plasma metabolism, adsorption, perfusion and filtration of inflammatory mediators such as endotoxins and harmful metabolites of small or medium molecular weight; maintain the required range of serum albumin, coagulation factors, ensure optimal balance of fluid volume, electrolytes, correct acid-base status of blood, which will reduce the manifestations of cytokine "storm", shock, pneumonia and severe pathological disorders of homeostasis in patients with COVID-19 [67, 78, 83];

2. The use of extracorporeal detoxication (plasmapheresis and plasma substitution, hemadsorption, hemodialysis, ultrafiltration, hemodiafiltration, etc.) in the treatment of patients with coronavirus pneumonitis, which may reduce the activity of the cytokine "storm", increase the level of and provide organoprotective effects, which has already been confirmed by a number of authors [66, 97-104, 109];

3. The use of chelators of excess iron and ferritin, a complex of forming agents (Desferal, etc.) for the formation of complexes with trivalent iron ions (to a lesser extent with divalent) and the formation of stable complexes with iron, which will prevent its participation in further reactions; complexing agents bind iron, ferritin and hemosiderin, do not interact with iron cytochromes, myoglobin and hemoglobin, are easily excreted by the kidneys and intestinal contents, do not cause an increase in the excretion of erythrocytes and trace elements;

4. The use of antioxidants for the correction of oxidative stress (Tocopherol, Vitamin C, alpha-lipoic acid, Quercetin, drugs based on deoxycholic acid, etc.);

5. The use of antihypoxants of substrate action (ATP, Solcoseril, Actovegin), regulatory action (Mildronate, Trimeta-zidine, Mexidol, Cytoflavin), systemic drugs (multivitamins, Wobenzym) and plastic regulators (Inosine, Bemityl), etc.;

6. The spread of preventive measures to increase the body's tolerance to hypoxia, such as the use of respiratory training system according to the method of K.P. Buteyko, as well as training with a delay of breathing up to 1.5-2 minutes. with rest intervals – 2–3 minutes. for healthy and asymptomatic COVID-19 to increase tolerance to hypoxia.

Undoubtedly, the main means of preventing coronavirus disease COVID-19 is vaccination of the population. Scientists from different countries are working to create an effective vaccine. In addition, time works for us – the most favorable factor for the natural spontaneous weakening of the aggression of the virus.

The autors declare that there are no conflicts of interest.

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ПОГЛЯД ТОКСИКОЛОГІВ НА МЕХАНІЗМИ ФОРМУВАННЯ ВІРУСІНДУКОВАНИХ ГЕМОГЛОБІНОПАТІЙ І ТОКСИЧНОГО ПНЕВМОНІТУ ЗІ СИСТЕМНОЮ ГІПОКСЕМІЄЮ ПРИ COVID-19 ТА ОБГРУНТУВАННЯ РАЦІОНАЛЬНИХ МЕТОДІВ ДЕТОКСИКАЦІЇ

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РЕЗЮМЕ. *Коронавірусна хвороба COVID-19 у даний час є глобальною проблемою для людства, набувши характеру пандемії. З позиції токсикологів назріла необхідність узагальнити літературні дані про патогенетичні та патофізіологічні механізми формування основних клінічних проявів COVID-19 і обгрунтувати шляхи оптимізації лікувальних стратегій, використовуючи детоксикаційну терапію.*

Мета роботи. *На підставі аналізу літературних даних виділити патогенетичні механізми формування основних клінічних синдромів COVID-19, узагальнити результати клініко-лабораторних досліджень, клінічні та гематологічні критерії прогнозування тяжкого перебігу зі смертельними наслідками при даній патології та обгрунтувати шляхи оптимізації детоксикаційної терапії.*

Матеріал і методи. *Аналітичний огляд наукових публікацій виконаний з використанням реферативних баз даних наукових бібліотек PubMed, Medline і текстових баз даних наукових видавництв Elsevier, PubMed Central, BMJ Group та інших VIP-баз даних та охоплює період з 1 січня 2020 по 30 квітня 2020 року. Використано методи системного, порівняльного і контент-аналізу.*

Результати та висновки. *Проаналізовано публікації щодо виявлення шляхів інфікування вірусом SARS-CoV-19, механізмів формування клінічних проявів різних варіантів перебігу хвороби COVID-19 для виділення найбільш інформативних предикторів розвитку тяжких форм захворювання, що призводять до летальних наслідків. Узагальнено літературні дані про механізми розвитку віремії SARS-CoV-19, виділені патогенетичні і патофізіологічні механізми формування вірусіндукованих гемоглобінопатій, токсичного пневмоніту, системної гіпоксемії, гіперферитинемії, цитокінової «бурі», окисного стресу і ендотоксикозу при COVID-19 і обгрунтовано шляхи оптимізації детоксикаційної терапії з включенням еферентних*

методів лікування, комплексутворюючих засобів для виведення надлишкових рівнів заліза та феритину, антиоксидантів і антигіпоксантів, кисневої терапії та трансфузії імунної плазми реконвалесцентів, компонентів донорської крові та стовбурових клітин.

Ключові слова: *коронавірусна хвороба, COVID-2019, вірусіндуковані гемоглобінопатії, пневмоніт, детоксикаційна терапія.*

ВЗГЛЯД ТОКСИКОЛОГОВ НА МЕХАНИЗМЫ ФОРМИРОВАНИЯ ВИРУСИНДУЦИРОВАННЫХ ГЕМОГЛОБИНОПАТИЙ И ТОКСИЧЕСКОГО ПНЕВМОНИТА С СИСТЕМНОЙ ГИПОКСЕМИЕЙ ПРИ COVID-19 И ОБОСНОВАНИЕ РАЦИОНАЛЬНЫХ МЕТОДОВ ДЕТОКСИКАЦИИ

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РЕЗЮМЕ*. Коронавирусная болезнь COVID-19 в настоящее время является глобальной проблемой для человечества, приобретя характер пандемии. С позиции токсикологов назрела необходимость обобщить литературные данные о патогенетических и патофизиологических механизмах формирования основных клинических проявлений COVID-19 и обосновать пути оптимизации лечебных стратегий с использованием детоксикационной терапии.*

Цель работы. *На основании анализа литературных данных выделить патогенетические механизмы формирования основных клинических синдромов COVID-19, обобщить результаты клинико-лабораторных исследований, клинические и гематологические критерии прогнозирования тяжелого течения со смертельным исходом при данной патологии и обосновать пути оптимизации детоксикационной терапии.*

Материал и методы. *Аналитический обзор научных публикаций выполнен с использованием реферативных баз данных научных библиотек PubMed, Medline и текстовых баз данных научных издательств Elsevier, PubMed Central, BMJ Group и других VIP-баз данных и охватывает период с 1 января 2020 по 30 апреля 2020. Использованы методы системного, сравнительного и контент-анализа.*

Результаты и выводы. *Осуществлен анализ публикаций по выявлению путей инфицирования вирусом SARS-CoV-19, механизмов формирования клинических проявлений различных вариантов течения COVID-19 для выделения наиболее информативных предикторов развития тяжелых форм заболевания, приводящих к летальному исходу. Обобщены литературные данные о механизмах развития виремии SARS-CoV-19, определены патогенетические и патофизиологические механизмы формирования вирусиндуцированных гемоглобинопатий, токсического пневмонита, системной гипоксемии, гиперферритинемии, цитокиновой «бури», окислительного стресса и эндотоксикоза при COVID-19 и обоснованы пути оптимизации детоксикационной терапии с включением эфферентных методов лечения, комплексобразующих средств для вывода избыточных уровней железа и ферритина, антиоксидантов и антигипоксантов, кислородной терапии и трансфузии иммунной плазмы реконвалесцентов, компонентов донорской крови и стволовых клеток.*

Ключевые слова: *коронавирусная болезнь; COVID-2019; вирусиндуцированные гемоглобинопатии, пневмонит, детоксикационная терапия.*

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