Scientific Session of the General Meeting of the RAS Members  
“The Role of Science in Overcoming Pandemics and Postcrisis Development of Society”

**Intensive Care of Patients with COVID-19**

S. S. Petrikov*, K. A. Popugaev**, and S. V. Zhuravel’a,***

*aSklifosovskii Research Institute for Emergency Medicine, Moscow, Russia

* e-mail: PetrikovSS@zdrav.mos.ru

** e-mail: stan.popugaev@yahoo.com

*** e-mail: sjuravel@rambler.ru

Received February 1, 2022; revised February 11, 2022; accepted March 17, 2022

**Abstract**—The severe course of COVID-19 requires treatment in emergency and intensive care units. Acute respiratory failure due to the development of pneumonia and acute respiratory distress syndrome is the most common and life-threatening manifestation of the new coronavirus infection. Treatment of patients with severe and extremely severe COVID-19; the use of modern schemes and protocols for drug therapy, mechanical ventilation, and extracorporeal membrane oxygenation; sorption techniques; the use of thermal helium; hemostasis correction; and rehabilitation problems are discussed.

**Keywords:** coronavirus infection, treatment protocols, respiratory support, extracorporeal membrane oxygenation

**DOI:** 10.1134/S1019331622040086

The COVID-19 pandemic has become a major challenge to the healthcare system. A large burden fell on both the outpatient link of medical care and hospitals. The main manifestation of the new coronavirus infection, which determines the severity of the condition of patients, is respiratory failure due to the development of pneumonia and acute respiratory distress syndrome. Such patients require treatment in resuscitation and intensive care units, creating an additional burden on the anesthesiology and intensive care services of hospitals.

**Organization of the treatment process.** When planning resuscitation and intensive care units, one should take into account that 30–50% of patients with coronavirus infection admitted to the hospital will require observation in the intensive care unit. Hence, the resuscitation hospital bed fund needs to be increased from the usual 10% of the total bed capacity to 35–50%. When opening a block for patients with COVID-19 at the Sklifosovskii Research Institute for Emergency Medicine, a ratio of 22/78% (22 resuscitation beds for 80 inpatients) was planned, then it amounted to 36/64% (37 for 65), and in a little while the number of resuscitation beds reached 70%.

An important aspect is the equipping of beds (preferably each one) with artificial ventilation. At least half of the beds should be equipped with high-flow oxygen devices. It should be borne in mind that many modern ventilators have the function of high-flow oxygen supply and can be used for dual purposes. When performing invasive mechanical ventilation in patients with pneumonia caused by COVID-19, humidification of the respiratory mixture is of great importance. Practice has shown that for these purposes it is better to use not HME filters but standard humidifiers.

Infectious blocks required an increase in the staff of doctors and nurses. Thus, the Sklifosovskii Research Institute for Emergency Medicine involved second-year residents in work in infectious diseases units as trainee doctors and block administrators were introduced. This role was entrusted to the heads of the departments of anesthesiology and resuscitation and the heads of the institute’s emergency services. Round-the-clock duty in the command zone was provided by five paired teams of administrators. To improve the quality and effectiveness of treatment, rounds of the units were carried out at least two times a day, involving the management of the institute.

**Treatment schemes and protocols.** Although the fight against the new coronavirus infection has been going on for more than a year and a half, clear evidence-
based intensive care protocols for this category of patients have not been formed thus far. The most important aspect of the treatment of patients with COVID-19 admitted to intensive care units is measures to stop the “cytokine storm.” The introduction of interleukin-6 blockers makes it possible to stop the progression of the pathological process in most cases.

Anticytokine therapy. A cytokine storm develops, as a rule, on days 5–7 of the disease and is manifested by a significant increase in the levels of IL-1, IL-6, IL-2R, and IL-10 [1]. Uncontrolled release of cytokines leads to wide damage to the vascular endothelium and hyperactivation of platelets and the plasma link of hemostasis, which is accompanied by both venous and arterial thrombosis and thromboembolic complications [2]. The key role in the development of the cytokine storm belongs to IL-6 and IL-1 [3]. An increase in the level of IL-6 activates the complement system and hyperproduction of fibrinogen, thrombopoietin, tissue factor, and, accordingly, thrombin. IL-6 increases the level of vascular endothelial growth factor [4], which causes pathological permeability of the vascular wall, primarily the lung parenchyma.

To suppress or reduce the severity of the cytokine storm, biological therapy began to use monoclonal antibodies that block IL-6. They should be divided according to the point of application of pharmacodynamic action (IL-6 receptors, free and bound, or IL-6, freely circulating in plasma) and the route of administration (intravenous or subcutaneous). Tocilizumab, levilimab, and sarilumab block free and bound IL-6 receptors, while olokizumab blocks only IL-6. Tocilizumab is available in both intravenous and subcutaneous forms. Other IL-6 blockers are administered exclusively subcutaneously.

The use of IL-6 blockers is indicated in the presence of pathological changes in the lungs (CT ≥ 1) in combination with two or more of the following signs [5]: \(\text{SpO}_2 < 95\%\), shortness of breath on exertion, C-reactive protein > 60 ng/ml, body temperature ≥38°C for 3–5 days, leukocyte count ≤3.0 × 10^9 L\(^{-1}\), and absolute lymphocyte count ≤1.5 × 10^9 L\(^{-1}\).

The Sklifosovskii Research Institute for Emergency Medicine has formed approaches to the use of various IL-6 blockers. Patients in moderate condition receive olokizumab; those in severe and extremely serious condition, tocilizumab or levilimab. In the case of an extremely severe course of the cytokine storm, as well as in the presence of risk factors (age over 65 years, diabetes mellitus, chronic obstructive pulmonary disease, etc.), we prefer the intravenous form of tocilizumab at a dose of 8 mg/kg but not more than 800 mg. A day after the injection, we perform a control CT scan of the chest. Approximately a quarter of patients require repeated administration of IL-6 blockers. The decision on this is made 24–72 h after the first injection, provided that the typical clinical and laboratory picture of the cytokine storm persists:

- fever above 37.5–38.3°C;
- elevated levels of the C-reactive protein, D-dimer, fibrinogen, ferritin, and lactate dehydrogenase;
- leukopenia; lymphopenia; moderate thrombocytopenia; and the appearance of or an increase in areas of damage to the lung parenchyma in the “ground-glass” form [5].

Another area of therapy focused on stopping the cytokine storm is the use of Janus kinase inhibitors. In this capacity, baricitinib is the most effective and best studied medication. The results of studies show that in a severe and extremely severe course of the disease, its effectiveness is low, while in a moderately severe condition it can be effective [6].

Plasma technologies. Nonspecific removal of chemokines, cytokines, immunoglobulins, immune complexes, cell debris, various pathogenicity factors, complement fragments, and viral RNA, aimed at correcting the cytokine storm, endothelial dysfunction, and coagulopathy, is the basis for the use of plasma exchange in patients with severe forms of COVID-19 [7]. Note that for effective elimination of pathogenicity factors, it is necessary to remove at least one volume of circulating plasma, which, in turn, leads to a significant loss of blood coagulation factors, albumin, and immunoglobulins and requires adequate replacement with fresh frozen plasma and albumin solutions. The risk of infection with viruses and other posttransfusion complications increases.

Practice has shown that the main indication for plasma exchange in patients with COVID-19 is the simultaneous presence of a severe cytokine storm and markers of bacterial inflammation (leukocytosis with left shift and an increased level of procalcitonin). In such patients, IL-6 blockers cannot be used.

The use of glucocorticoids. As is known, glucocorticoid hormones (GCHs) can simultaneously block both cytokines and the complement system [7]. The positive GCH effects in community-acquired pneumonia, including of viral origin, as well as in respiratory distress syndrome, were well known even before the COVID-19 pandemic [8, 9], but at its beginning, their use was not a universally accepted tactic. This approach can be explained by insufficient understanding of the pathogenesis of COVID-19 at that time and the fear of excessive immunosuppression in such patients. With the accumulation of data, attitudes towards GCHs changed. The final period was put by the World Health Organization proceeding from the results of the REACT meta-analysis based on 7 studies, including large-scale ones such as RECOVERY, REMAP-CAP, CoDEX, and CAPE COVID [10]. Glucocorticoid hormones are indicated for severe and extremely severe COVID-19 since they reduce mortality and improve treatment outcomes, but are contraindicated in mild and moderate disease. In medical practice, dexamethasone, methylprednisolone, prednisolone, or hydrocortisone can be used. The latter penetrates the lung parenchyma worse than the others.
listed [11]. Low and medium doses of GCHs should be used, avoiding long courses whenever possible.

**Hemostasis correction.** Hemostasis system control is a routine practice in the management of patients with COVID-19. According to various authors, the frequency of thrombosis in such patients is extremely high. Thus, venous thrombotic and thromboembolic complications develop in 25–27%, and arterial thromboses (acute coronary syndrome, ischemic stroke, peripheral arterial thrombosis), in 3.7–5.7% of patients [12–14]. Hence, anticoagulant therapy is indicated for all hospitalized patients [15, 16]. In the absence of thrombosis at the time of initiation of therapy, prophylactic doses of low-molecular-weight or unfractionated heparins are recommended—the choice is with the treating team [15]. Warfarin and the newer oral anticoagulants are not recommended for use in hospitalized patients with COVID-19 [17].

In our experience, unfractionated heparins may have certain advantages compared to low-molecular-weight heparins because they block more coagulation factors, providing a more reliable anticoagulant effect [18–20]; in addition, they are much easier to titrate and select an effective dose under the control of a special medical test. One should begin the introduction of unfractionated heparin in patients weighing 85–90 kg with 25000–35000 units/day. The recommended doses of low-molecular-weight heparins are as follows: enoxaparin, 1.2 mL/day; fraxiparine, 0.9–1.2 mL/day. Then the dose should be selected with account for the dynamics of laboratory parameters and the presence of thrombotic complications in the patient.

Importantly, some studies have demonstrated the effectiveness of antiplatelet therapy in severe patients with COVID-19 [21, 22]. Our experience confirms the safety of aspirin treatment. We resort to dual antiplatelet therapy only when patients develop thrombocytosis or pronounced activation of the platelet link of hemostasis. Thromboelastography makes it possible to assess adequately and control not only the state of platelet hemostasis but also the efficacy and safety of antiplatelet therapy [23].

**The use of anti-Covid plasma.** With the accumulation of experience in the use of the plasma of convalescents, that is, those who have recovered, the indications for its prescription have undergone some changes. Thus, although many publications discuss the use of such plasma in critically ill patients, our experience casts doubt on the advisability of transfusion to those who have a severe secondary bacterial infection or multiple organ failure, as well as to patients on extracorporeal membrane oxygenation.

It is optimal to use convalescent plasma on the 3–10th day of the disease. At a later date, a transfusion can be considered as a therapeutic intervention when the patient’s own immune response is insufficient. The criteria for such deficiency are lymphopenia (the absolute number of lymphocytes is less than $1.0 \times 10^9 \text{L}^{-1}$), as well as the absence of specific antibodies to SARS-CoV-2 in the patient’s plasma [24]. By now, it has become possible to determine the image of the “optimal patient” for anti-COVID plasma transfusion: days 5–7 of illness, spontaneous breathing with oxygen support, progression of respiratory failure, absence of antibodies to SARS-CoV-2, lymphopenia (less than $1.0 \times 10^9 \text{L}^{-1}$), and persistent fever.

Note that the recommended volumes of transfusion of plasma from convalescents and fresh frozen plasma from healthy donors differ. The analysis of the literature and our own experience have led us to a recommended range of 3–5 mL/kg of anti-COVID plasma for a single transfusion. The expediency of its repeated introduction remains a subject of discussion [25]. In some cases, it is possible to transfuse two or more times with an interval between the injections of no more than 72 h; note that plasma from another donor is preferable. The prescription of convalescent plasma against the background of developed multiple organ failure with the addition of a secondary bacterial infection in the presence of antibodies to SARS-CoV-2 or against the background of lymphocytosis is inappropriate.

**Antibacterial therapy.** When bacterial pneumonia occurs in patients with COVID-19, rational antibiotic therapy is indicated with account for the likely spectrum of pathogens and their stratification considering the risk of multiresistance. Such therapy is prescribed in the presence of convincing signs of a bacterial infection (an increase in the level of procalcitonin more than 0.5 ng/mL, leukocytosis $>10 \times 10^9 \text{L}^{-1}$, left shift (presence of young, immature forms of neutrophils), the appearance of purulent sputum, and the need to increase the oxygen fraction in the inhaled gas mixture) [26]. Antibiotics and the administration route are selected based on the severity of the patient’s condition, analysis of risk factors for the presence of resistant microorganisms (previous antibiotic use, comorbidities, history of hospitalization), and microbiological findings.

According to our data, the need to prescribe antibacterial drugs increases in proportion to the severity of lung damage. Thus, 15% of patients admitted with lung damage of less than 25% (CT 1) and 70% of patients with lung damage CT 3 (50–75%) and CT 4 (more than 75%) required antibiotic therapy during their stay in the hospital.

**Artificial nutrition.** Artificial enteral and parenteral nutrition is an important component of the complex treatment of patients with COVID-19 at all stages. It is necessary to consider the severity of the infectious process, the severity of malnutrition and comorbidity, and respiratory and intensive care [27]. The systemic inflammatory response leads to metabolic disorders of protein, carbohydrate, and lipid metabolism with the development of hypermetabolism—hypercatabolism syndrome. This is a nonspecific systemic response of
the body to damage, characterized by an increase in the need for energy sources and plastic material and the development of pathological tolerance of the body to “ordinary” nutrients (a decrease in the rate of glucose oxidation, an increase in the rate of lipid oxidation, etc.). In this situation, the coverage of energy and plastic needs occurs due to the destruction of the body’s own tissues (autocannibalism). Muscular dystrophy leads to a decrease in the contractility of not only skeletal muscles but also the muscles of the respiratory system and myocardium, which increases the manifestations of their failure [28–31].

Risk factors for the development of malnutrition in patients with COVID-19 are the following: the presence of nutritional deficiencies upon admission to the hospital, prolonged stay in the intensive care unit, prolonged artificial ventilation, elderly and senile age, and chronic diseases (obesity, diabetes, pathologies of the respiratory and cardiovascular systems, oncological pathology, and lesions of the hematopoietic and immune systems). Artificial nutrition should be carried out according to the recommendations for patients in critical condition suffering from respiratory failure, acute respiratory distress syndrome, and sepsis, considering the characteristics of intensive care and recommendations for the main contingent of patients at risk—elderly and senile patients, as well as polymorbid ones [32–34].

Respiratory support. Differences in the manifestations of pulmonary failure in COVID-19 and acute respiratory distress syndrome are being investigated by scientists around the world. While acute respiratory distress syndrome primarily damages the alveoli, which is accompanied by their collapse (compression), accumulation of fluid, and exclusion from ventilation, in viral pneumonia caused by COVID-19, damage to the endothelium of the pulmonary capillaries becomes the central link in the pathogenesis. The capillaries form intravascular microthrombi as a result of an imbalance between procoagulant and fibrinolytic activity in the presence of acute inflammation and endothelial damage. Thus, the ventilation of the alveoli in pneumonia caused by the new coronavirus infection is not disturbed at the initial stage of the disease, and the normal compliance of the lung tissue is also preserved. However, oxygen transport from the alveoli to the capillary bed is sharply reduced due to impaired perfusion. As a result of a decrease in blood flow through the pulmonary capillaries, the physiological dead space increases—the alveoli are ventilated, but their perfusion is absent [35, 36]. Another mechanism of hypoxemia in COVID-19 is presumably a violation of the mechanisms of hypoxic pulmonary vasoconstriction, which further aggravates the ventilation/perfusion ratio (V/Q) and increases the intrapulmonary shunt [37].

Intubation is avoided in many patients by a combination of high-flow oxygen therapy and noninvasive ventilation (NIV), which is confirmed by our experience. However, it should be recognized that in some patients it is impossible to limit oneself to NIV alone. Predicting the effectiveness of NIV and developing objective criteria for the need for intubation are the key problems of respiratory therapy in patients with COVID-19 [38]. Potentially possible criteria include the \( \text{PaO}_2/\text{FiO}_2 \) or \( \text{SpO}_2/\text{FiO}_2 \) index, the CT picture, lung compliance, and clinical criteria (participation of accessory muscles in breathing).

In our opinion, the \( \text{SpO}_2/\text{FiO}_2 \) index is the most important for assessing the dynamics of the lung condition in patients who receive respiratory support using high-flow oxygenation equipment and NIV. According to our data, in patients with successful noninvasive ventilation, the \( \text{SpO}_2/\text{FiO}_2 \) index averaged 153 (122 : 184), the minimum value at which intubation was avoided being 115. In patients with unsuccessful NIV, the same index averaged 121 (97 : 134). Thus, a quantitative value of \( \text{SpO}_2/\text{FiO}_2 \) of 120 or less can be considered a threshold criterion for the failure of NIV and an indication for the transition to invasive ventilation. The principles of its safety are the following: tidal volume of no more than 6 mL/kg of the ideal body weight, positive end-expiratory pressure, and recruitment maneuvers.

Indications for the use of extracorporeal membrane oxygenation (ECMO). According to the current guidelines, indications for the use of venovenous (VV) ECMO in patients with COVID-19 should generally not differ from the standard ones. The decision to use it should be made only after an ineffective use of the entire arsenal of standard therapy, including mechanical ventilation and prone positioning [39, 40]. The experience of using ECMO in patients with COVID-19 at the Sklifosovskii Research Institute for Emergency Medicine has made it possible to form the criteria for making such a decision: 2–3 days of mechanical ventilation; “hard modes” of ventilation (tidal volume \( >6 \) mL/kg, peak airway pressure \( >32 \) cm H\(_2\)O); a result of three points or more when summing up the following indicators: CT 3–4, polysegmental pneumonia (one point), \( \text{PaO}_2/\text{FiO}_2 \) < 100 for more than 12 hours (one point), \( \text{PaO}_2/\text{FiO}_2 \) < 80 for 6 h (two points), \( \text{PaCO}_2 \) > 50 mm Hg (one point), arterial blood pH < 7.32 (one point), peak airway pressure > 32 cm H\(_2\)O (one point); with positive pressure at the end of expiration > 10 cm H\(_2\)O, respiratory volume of 4–6 mL/kg, and \( \text{FiO}_2 > 80\% \), prone positioning was used [41].

COVID-19 can cause severe heart failure. Echocardiography plays a leading diagnostic role in its evaluation. The combination of acute respiratory failure and refractory heart failure in the presence of signs of cardiogenic shock (inadequate tissue perfusion; arterial hypotension in conditions of normovolemia; persistence of signs of shock despite intensive therapy, including inotropic/vasopressor support; infusion
The use of inhalation of a high-temperature mixture of patients with the new coronavirus infection based on cine has developed an innovative method for treating Sklifosovskii Research Institute for Emergency Medicine. Thus, according to our observations, increases the effectiveness of the treatment of patients with COVID-19. The respiratory volume and the comfort of the procedure are monitored. 3–4 procedures depending on the patient’s condition. They breathe easily since there is practically no resistance to breathing in the respiratory circuit of the device.

The Sklifosovskii Research Institute developed the following criteria for including HBO in the complex therapy of patients with COVID-19, based on the experience of treating 160 patients (640 sessions): breathing through the natural respiratory tract (no invasive mechanical ventilation); lung involvement 25–75% (CT 2–4); stable hemodynamics; and the absence of standard contraindications to HBO.

Medical rehabilitation of patients. The pandemic has highlighted the importance of medical rehabilitation as an integral part of the treatment process [48]. Its main goals are to improve respiratory function, prevent the consequences of intensive care exposure, and prevent infectious and thrombotic complications. The range of rehabilitation tasks in the intensive care unit includes the following: creating conditions for the restoration of spontaneous breathing and minimizing respiratory support, postural correction, early mobilization, and early adaptation to everyday living conditions (meals, hygiene) [49].

Our experience in the medical rehabilitation of patients with COVID-19 has shown the need to increase the staff of exercise physiologists working in intensive care units for infectious patients and the importance of expanding the range of rehabilitation activities—increasing the volume of passive cycling, passive joint gymnastics, and assisted breathing exercises. Among the medical rehabilitation procedures, 89% were breathing exercises, which in one-third of the patients were performed on an assistive basis, without their active participation; 40% of patients needed passive kinesitherapy; 62% received cycling kinetics training; and 42% received physiotherapy treatment. All activities were aimed at early recovery of patients. Rehabilitation service specialists resorted to manipulations that helped improve blood oxygenation and ventilation of the respiratory tract and accelerated the process of weaning the patient from mechanical ventilation.

The Sklifosovskii Research Institute developed the following criteria for using the technique is largely determined by effective pathogenetic therapy that contributes to the restoration of lung function, the prevention and treatment of bacterial and/or fungal complications, the assessment of the prospects for the restoration of lung function, and the determination of contraindications (most of them are not absolute). ECMO in a patient, even in critical condition with some contraindications, eliminates hypoxia and gives a chance for recovery. As the experience of various centers shows, the identification of contraindications determines the success of therapy in general and the achievement of a result with a survival rate of 60–70%.

The concentration of He and O₂ is selected individually in the range from 79 to 50% (He) and from 21 to 50% (O₂) to achieve SpO₂ in the range of 95–99% at a temperature of 75 to 96°C and is effective in various concentrations of inert gas [43]. Inhalation procedures should be performed daily for 60 min, divided into 3–4 procedures depending on the patient’s condition. The respiratory volume and the comfort of the procedure are monitored.

The inclusion of inhalations of a thermal gas mixture of helium and oxygen in standard therapy increases the effectiveness of the treatment of patients with COVID-19. Thus, according to our observations, a positive impact on several key indicators was noted.

- During the t-He/O₂ procedure, the oxygenation of organs and tissues improves significantly, and the achieved effect positively stabilizes the patients’ condition. They breathe easily since there is practically no resistance to breathing in the respiratory circuit of the device.
- There is an improved dynamics in oxygenation beyond the procedure, as well as resolution of respiratory failure.

- During the procedure, an indirect anti-inflammatory effect is observed.
- All patients note that, after the procedure with heliox, it becomes much easier to breathe and they feel better.
- During treatment with thermal heliox, a rapid decrease in the vital load is observed [44].

The use of a thermal helium—oxygen mixture. The Sklifosovskii Research Institute for Emergency Medicine has developed an innovative method for treating patients with the new coronavirus infection based on the use of inhalation of a high-temperature mixture of helium and oxygen (t-He/O₂). The new respiratory support technology has been used as a component of complex therapy in patients with moderate and severe COVID-19 since April 2020.

The studies conducted and the experience accumulated at the institute made it possible to formulate the criteria for the use of t-He/O₂: confirmed viral infection with SARS-CoV-2 by PCR, CT signs of lung damage of the ground-glass type, the presence of areas of consolidation and signs of acute respiratory failure, the volume of lung lesions CT 1–3, SOFA score <6 points, and the oxygenation index ≥150.

The inclusion of inhalations of a thermal gas mixture of helium and oxygen in standard therapy is an indication for the use of venoartrial (VA) ECMO. Timely echocardiographic examination is indicated in the presence of any clinical suspicion of cardiovascular dysfunction or signs of circulatory disorders.

It is noteworthy that success in using the technique is largely determined by effective pathogenetic therapy that contributes to the restoration of lung function, the prevention and treatment of bacterial and/or fungal complications, the assessment of the prospects for the restoration of lung function, and the determination of contraindications (most of them are not absolute). ECMO in a patient, even in critical condition with some contraindications, eliminates hypoxia and gives a chance for recovery. As the experience of various centers shows, the identification of contraindications determines the success of therapy in general and the achievement of a result with a survival rate of 60–70%.

Hyperbaric oxygen therapy. Since the very beginning of the pandemic, scientific research has focused on finding therapeutic methods aimed not only at eliminating hypoxia and hypoxemia but also at reducing the risk of transferring the patient to invasive mechanical ventilation. Hyperbaric oxygenation (HBO), which is based on pure oxygen breathing under high pressure, has a combination of these characteristics, making it possible to eliminate any form of oxygen debt by delivering O₂ to organs and tissues by dissolving it in body fluids [45–47].
In conclusion, it should be noted that the success of intensive care for patients with COVID-19 depends not only on the effective use of resuscitation methods but, in the first place, on the presence of a well-coordinated multidisciplinary team of specialists capable of effectively solving difficult problems in an ever-changing clinical picture and severity of the course of the new coronavirus infection.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. G. Chen, D. Wu, W. Guo, et al., “Clinical and immunological features of severe and moderate coronavirus disease 2019,” J. Clin. Invest. 130 (5), 2620–2629 (2020).
2. J. Cohen, “The immunopathogenesis of sepsis,” Nature 420 (6917), 885–891 (2002).
3. Y. Gao, T. Li, M. Han, et al., “Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19,” J. Med. Virol. 92 (7), 791–796 (2020).
4. T. Tanaka, M. Narazaki, T. Kishimoto, “Immunotherapeutic implications of IL-6 blockade for cytokine storm,” Immunotherapy 8 (8), 959–970 (2016).
5. Interim Guidelines: Prevention, Diagnosis, and Treatment of Novel Coronavirus Infection (COVID-19), Version 14 (Dec. 27, 2021) (Ministry of Health of the Russian Federation, 2021). https://static-0.minzdrav.ru/system/attachments/attaches/000/059/041/original/BMP_COVID-19_V14_27-12-2021.pdf
6. E. L. Simpson, J. P. Lacour, L. Spelman, et al., “Baricitinib in patients with moderate-severe atopic dermatitis and inadequate response to topical corticosteroids: Results from two randomized monotherapy phase III trials,” Br. J. Dermatol. 183 (2), 242–255 (2020).
7. P. Keith, M. Day, L. Perkins, et al., “A novel treatment approach to the novel coronavirus: An argument for the use of therapeutic plasma exchange for fulminant COVID-19,” Crit. Care 24 (1), Article no. 128 (2020).
8. M. Ramanan, J. Cohen, and B. Venkatesh, “Steroids and sepsis: The debate continues,” Int. Anesthesiol. Clin. 57 (2), 17–30 (2019).
9. D. G. Ashbaugh, D. B. Bigelow, T. L. Petty, and B. E. Levine, “Acute respiratory distress in adults,” Lancet 2 (7511), 319–323 (1967).
10. Z. Ye, Y. Wang, L. E. Colunga-Lozano, et al., “Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia, and acute respiratory distress syndrome: A systematic review and meta-analysis,” CMAJ 192 (27), E756–E767 (2020).
11. J. A. C. Sterne et al., REACT Collab., “Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: A meta-analysis,” JAMA 324 (13), 1330–1341 (2020).
12. L. Mao, H. Jin, M. Wang, et al., “Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China,” JAMA Neurol. 77 (6), 683–690 (2020).
13. S. Cui, S. Chen, X. Li, et al., “Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia,” J. Thromb. Haemost. 18 (6), 1421–1424 (2020).
14. F. A. Klok, M. Kruij, N. J. M. van der Meer, et al., “Incidence of thrombotic complications in critically ill ICU patients with COVID-19,” Thromb. Res. 191, 145–147 (2020).
15. A. Flaczyk, R. P. Rosovsky, C. T. Reed, et al., “Comparison of published guidelines for management of coagulopathy and thrombosis in critically ill patients with COVID-19: Implications for clinical practice and future investigations,” Crit. Care 24 (1), Article no. 559 (2020).
16. V. Carfora, G. Spiniello, R. Ricciolino, et al., “Anticoagulant treatment in COVID-19: A narrative review,” J. Thromb. Thrombolysis. 51 (3), 642–648 (2021).
17. M. Cattaneo, E. M. Bertinato, S. Birocchi, et al., “Pulmonary embolism or pulmonary thrombosis in COVID-19? Is the recommendation to use high-dose heparin for thromboprophylaxis justified?,” Thromb. Haemost. 120 (8), 1230–1232 (2020).
18. B. L. Davidson, W. H. Geerts, and A. W. Lensing, “Low-dose heparin for severe sepsis,” New Engl J. Med. 347 (13), 1036–1037 (2002).
19. D. Hoppensteadt, J. Fareed, A. L. Klein, et al., “Comparison of anticoagulant and anti-inflammatory responses using enoxaparin versus unfractionated heparin for transesophageal echocardiography-guided cardioversion of atrial fibrillation,” Am. J. Cardiol. 102 (7), 842–846 (2008).
20. J. Thachil, “The versatile heparin in COVID-19,” J. Thromb. Haemost. 18 (5), 1020–1022 (2020).
21. W. C. Song and G. A. FitzGerald, “COVID-19, microangiopathy, hemostatic activation, and complement,” J. Clin. Invest. 130, 3930–3953 (2020).
22. M. VIECC, D. RADOVANOVIC, G. B. FORLEO, and P. SANTOS, “Enhanced platelet inhibition treatment improves hypoxemia in patients with severe COVID-19 and hypercoagulability: A case control, proof of concept study,” Pharmacol. Res. 158, 104950 (2020).
23. M. Ranucci, U. di Dedda, and E. Baryshnikova, “Platelet contribution to clot strength in thromboelastometry: Count, function, or both,” Platelets 31 (1), 88–93 (2020).
24. A. Yu. Bulanov, A. I. Kostin, S. S. Petrikov, et al., “Clinical use of convalescent plasma in the treatment of a new coronavirus infection: Moscow experience,” Anesteziol. Reanimatol., No. 6-2, 33–39 (2020).
25. L. Li, W. Zhang, Y. Hu, et al., “Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: A randomized clinical trial,” JAMA 324 (5), 460–470 (2020).
26. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: Interim guidance, March 13, 2020. https://apps.who.int/iris/bitstream/handle/10665/331446/WHO-
27. Nutritional Support for Patients with COVID-19: Guidelines (Triada, Moscow, 2020) [in Russian].
28. Parenteral and Enteral Nutrition: National Guidelines, Ed. by M. Sh. Khubutia, T. S. Popova, and A. I. Saltanov (GEOTAR-Media, Moscow, 2014) [in Russian].
29. W. Alhazzani, M. H. Moller, T. M. Arabi, et al., “Surviving sepsis campaign: Guidelines of the management of critically ill. Adults with coronavirus disease 2019 (COVID-19),” Intensive Care Med. 46 (5), 854–887 (2020).
30. R. Barazzoni, S. C. Bischoff, Z. Krznaric, et al., “ESPEN expert statements and practical guidance for nutritional management of individuals with Sars-Cov-2 infection,” Clin. Nutr. 39 (6), 1631–1638 (2020). https://doi.org/10.1016/j.clnu.2020.03.022
31. N. Chen, M. Zhou, X. Dong, et al., “Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study,” Lancet. 395 (10223), 507–513 (2020).
32. R. G. Martindale, J. J. Patel, B. Taylor, et al., “Nutrition therapy in patient with COVID-19 disease requiring ICU Care: Updated May 26, 2020,” https://www.nutritioncare.org/uploadedFiles/Documents/Guidelines_and_Clinical_Resources/COVID19/Nutrition20Therapy%20in%20the%20Patient%20with%20COVID-19%20Disease%20Requiring%20ICU%20Care_Updated%20May%202020.pdf. Cited February 1, 2022.
33. D. Volkert, A. M. Beck, T. Cederholm, et al., “ESPEN guideline on clinical nutrition and hydration in geriatrics,” Clin. Nutr. 38 (1), 10–47 (2019).
34. J. Whittle, J. Molinger, D. MacLeod, et al., “Persistent hypermetabolism and longitudinal energy expenditure in critically ill patients with COVID-19,” Crit. Care 24, Article no. 581 (2020).
35. P. K. Bhattrju, B. J. Ghassemieh, M. Nichols, et al., “Covid-19 in critically ill patients in the Seattle Region—case series,” New Engl. J. Med. 382 (21), 2012–2022 (2020).
36. D. R. Ziehr, J. Alladina, C. R. Petri, et al., “Respiratory pathophysiology of mechanically ventilated patients with COVID-19: A cohort study,” Am. J. Respir. Crit. Care Med. 201 (12), 1560–1564 (2020).
37. L. D. Bos, F. Paulus, A. P. J. Vlaar, et al., “Subphenotyping ARDS in COVID-19 patients: Consequences for ventilator management,” Ann. Am. Thorac. Soc. 17 (9), 1161–1163 (2020).
38. M. J. Cummings, M. R. Baldwin, D. Abrams, et al., “Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: A prospective cohort study,” Lancet 395 (10239), 1763–1770 (2020).
39. S. V. Zhurav’el’, D. A. Kosolapov, and M. V. Ketskalo, “Organization of an extracorporeal membrane oxygenation program in adult patients in a multifield hospital: Experience of Regensburg (Germany),” Transplantology, No. 4, 28–32 (2014).
40. A. Combes, D. Hajage, G. Capellier, et al., “Extracorporeal membrane oxygenation for severe acute respiratory distress-syndrome,” New Engl. Med. 378 (21), 1965–1975 (2018).
41. S. V. Zhurav’el’, A. K. Evseev, A. D. Kolokol’tsev, et al., “Historical development and perspectives of extracorporeal membrane oxygenation in clinical practice,” Vysokotehn. Med., No. 1, 51–58 (2020).
42. S. S. Petrikov, S. V. Zhurav’el’, L. V. Shogonova, et al., “Thermal helium–oxygen mixture in the treatment algorithm for patients with COVID-19,” Vestn. Ross. Akad. Med. Nauk 75 (5S), 353–362 (2020).
43. S. D. Varfolomeev, A. A. Panin, V. I. Bykov, et al., “Thermovaccination—thermoheliox as a stimulator of the immune response: Kinetics of the synthesis of antibodies and C-reactive protein in coronavirus infection,” Chem. Biol. Interact. 334, Article no. 109339 (2021).
44. L. V. Shogonova, S. D. Varfolomeev, V. I. Bykov, et al., “Effect of thermal helium–oxygen mixture on viral load in COVID-19,” Pul’monologiya 30 (5), 533–543 (2020).
45. P. N. Savilov, “On the possibilities of hyperbaric oxygen therapy in the treatment of SARS-COV-2-infected patients,” Znanstvena misel 42 (2), 55–60 (2020).
46. P. G. Harch, “Hyperbaric oxygen treatment of novel coronavirus (COVID-19) respiratory failure,” Med. Gas. Res. 10 (2), 61–62 (2020).
47. A. De Maio and L. E. Hightower, “COVID-19, acute respiratory distress syndrome (ARDS) and hyperbaric oxygen therapy (HBOT): What is the link?,” Cell Stress Chaperones 25 (5), 717–720 (2020).
48. S. Iannaccone, P. Castellazzi, A. Tettamanti, et al., “Role of rehabilitation department for adult individuals with COVID-19: The experience of the San Raffaele Hospital of Milan,” Arch. Phys. Med. Rehabil. 101 (9), 1656–1661 (2020).
49. F. Negrini, A. De Sire, E. Andreuelli, et al., “The International Multiprofessional Steering Committee of Cochrane Rehabilitation REH-COVER action. Rehabilitation and COVID-19: The Cochrane Rehabilitation 2020 rapid living systematic review. Update as of July 31, 2020,” Eur. J. Phys. Rehabil. Med. 56 (5), 652–657 (2020).