UDC 616.98:578.834]-092-036.882-085.273+615.357
DOI: 10.15587/2519-4798.2021.241456

CURRENT CONCEPTION ABOUT THE PATHOGENESIS AND INTENSIVE CARE OF SEVERE COVID-19 (REVIEW)

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The aim of the research. *The aim of this work was to summarize the scientific literature data on the pathogenesis and intensive care of the severe course of coronavirus infection.*
Materials and methods. *Databases such as PubMed, Google Scholar, Scopus and Web Of Science 2020–2021 were used for literary searches.*
Results. *An intense inflammatory response against the SARS-CoV-2 virus in COVID-19 patients causes a cytokine storm and hypercoagulability with the development of acute respiratory distress syndrome (ARDS) and multiple organ failure. Approximately 17 % to 35 % of hospitalized patients with COVID-19 are treated in the intensive care unit, most often due to hypoxemic respiratory failure and the development of ARDS, and between 29 % and 91 % of patients in intensive care units require invasive ventilation.*
In addition to acute respiratory failure, hospitalized patients may have acute renal failure (9 %), liver dysfunction (19 %), coagulation disorders (10–25 %), and septic shock (6 %).
More than 75 % of hospitalized patients require additional oxygen therapy. Respiratory support could vary from the need for oxygen supplementation through a nasal catheter to invasive ventilation or extracorporeal membrane oxygenation in patients with the most severe ARDS.
The uncontrolled inflammation and coagulation seen in COVID-19 patients is similar to multifactorial ARDS, where a plethora of evidence has demonstrated the ability of long-term corticosteroid therapy (CST) to reduce inflammation-coagulation-fibroproliferation and accelerate recovery.
With regard to the assessment of the benefits of therapeutic anticoagulation in patients with elevated D-dimer, the question has not yet been finally resolved, and research devoted to this is still ongoing.
Conclusions. *The approaches to respiratory, anticoagulant, anti-inflammatory therapy in critically ill patients with COVID-19 require further research to determine the optimal treatment tactics*
Keywords*: COVID-19, SARS-CoV-2, acute respiratory failure, acute respiratory distress syndrome, respiratory therapy, corticosteroid therapy*

How to cite:
Georgiyants, M., Korsunov, V., Dubrov, S., Loskutov, O., Bohuslavska, N., Nikonov, V., Cherkashyna, L., Oparin, O., Nartov, P., Holianishchev, M. (2021). Current conception about the pathogenesis and intensive care of severe COVID-19 (review). ScienceRise: Medical Science, 5 (44), 4–9. doi: http://doi.org/10.15587/2519-4798.2021.241456

1. Introduction

The new coronavirus disease 2019 (COVID-19) has spread worldwide, causing thousands of cases of acute respiratory failure with a high mortality rate [1, 2].

On March 14, 2020, the World Health Organization (WHO) declared a coronavirus outbreak with a confirmed pandemic in 127 countries. The incidence of acute respiratory distress syndrome (ARDS) in COVID-19 infection ranged from 17 % to 41 % [3, 4]. That is why the study of the pathogenesis and intensive care of severe coronavirus infection remains relevant for the timely provision of medical care to patients.

The aim of this work was to summarize the data of the scientific literature on the pathogenesis and intensive care of severe coronavirus infection.

2. Materials and methods

Databases such as PubMed, Google Scholar, Scopus and Web Of Science were used to search for literature, where the results of research published in 2020–2021 were found.

3. Results

SARS-CoV-2 virus, the causative agent of COVID-19, belongs to the family coronaviridae, has a diameter of 60 nm to 140 nm and characteristic adhesions in the range from 9 nm to 12 nm, giving virions the appearance of a solar corona. Structurally, it consists of single-stranded RNA. The viral genome lies within the envelope, the glycoproteins of which are crucial for the virus to enter the host cell. The SARS-CoV-2 adhesion protein (SARS) is related to the angiotensin-converting enzyme-2 (ACE-2) receptor, which is used by the virus to enter the cell. Due to genetic recombination and variation, coronaviruses could adapt and infect new hosts [5–8].

At the onset of infection, SARS-CoV-2 targets cells, such as nasal and bronchial epithelial cells and

pneumocytes, through a viral structural adhesion protein (S) that binds to the receptor (ACE-2). Transmembrane serine protease type 2 (TMPRSS-2), present in the host cell, promotes virus uptake by cleavage of ACE-2 and activation of protein S, which mediates the penetration of coronavirus into host cells. ACE-2 and TMPRSS-2 are expressed in host target cells, especially in type II alveolar epithelial cells. Like other respiratory viral diseases, such as influenza, profound lymphopenia can occur in individuals with COVID-19 when SARS-CoV-2 infects and kills T lymphocyte cells. In addition, a viral inflammatory response consisting of both an innate and an adaptive immune response (including humoral and cell-mediated immunity) impairs lymphopoiesis and increases lymphocyte apoptosis [9, 10].

In the later stages of infection, when virus replication is accelerated, the integrity of the epithelial-endothelial barrier is disrupted. In addition to epithelial cells, SARS-CoV-2 infects endothelial cells of the pulmonary capillaries, enhancing the inflammatory response and causing an influx of monocytes and neutrophils. Autopsy studies have shown diffuse thickening of the alveolar wall by mononuclear cells and macrophages that penetrate the airspace in addition to endothelium.

Interstitial mononuclear inflammatory infiltrates and edema develop and appear as "frosted glass" on computed tomography (CT) [11].

Intense inflammatory response against the virus in patients with COVID-19 causes a storm of cytokines and hypercoagulation with the development of acute respiratory distress syndrome and multiorgan failure [12].

Patients have endothelial dysfunction with a thrombo-inflammatory condition. Pulmonary microthrombosis and endothelial damage lead to V/Q mismatch (ventilation / perfusion), hypoxemia, and vasodilation [13].

Cytokine storm is characterized by hyperproduction of pro-inflammatory cytokines and chemokines (tumor necrosis factor alpha, interleukin-6 and interleukin-1β). Lymphocytopenia is one of the characteristic features of the cytokine storm. In critically ill patients, the level of C-reactive protein, pro-calcitonin, D-dimer and ferritin is markedly elevated and is associated with a poor prognosis [14, 15].

Bradykinin-dependent angioneurotic pulmonary edema may contribute to disease progression. In combination, endothelial barrier integrity and alveolar-capillary oxygen diffusion are characteristic features of COVID-19 [16].

The pathophysiology of COVID-19 is complex, and the disease could compromise the lungs, heart, brain, liver, kidneys, and coagulation system. In severe COVID-19 there is a fulminant activation of coagulation and consumption of coagulation factors. A report from Wuhan (China) states that 71 % of the 183 people who died from COVID-19 met the criteria for diffuse intravascular coagulation [17, 18].

COVID-19 could cause myocarditis, cardiomyopathy, ventricular arrhythmias, acute coronary syndrome, and shock [19–21].

Venous and arterial thromboembolic events are observed in 31–59 % of hospitalized patients with COVID-19.

Patients with comorbidities are highly prone to develop cytokine storm. Concomitant diseases, such as hypertension, coronary heart disease and diabetes, are associated with a higher risk of death [22].

Common clinical signs of COVID-19 are cough, shortness of breath and fever [23–25].

Additional symptoms such as weakness, fatigue, myalgia, headache, anosmia and ageusia, nausea, vomiting, and diarrhea have also been reported commonly [26].

Approximately 17 % to 35 % of hospitalized patients with COVID-19 are treated in the intensive care unit, most often due to hypoxemic respiratory failure and the development of ARDS. Among patients in intensive care units with COVID-19, 29 % to 91 % require invasive lung ventilation [25, 27, 28].

ARDS is defined as a form of inflammatory pulmonary edema of noncardiogenic etiology with a decrease in areas of normoventilated lung and, as a consequence, is characterized by a decrease in respiratory compliance and the effect of shunting.

The Berlin definition proposes ARDS categories based on the degree of hypoxemia: mild (200 mm Hg<<PaO_2/FIO_2≤300 mm Hg), moderate (100 mm Hg<<PaO_2/FIO_2≤200 mm Hg) and severe (PaO_2/FIO_2≤ ≤100 mm Hg), and 4 auxiliary variables for severe ARDS: radiographic severity, respiratory compliance (≤40 ml/cm H_2O), positive end-expiratory pressure (PEEP) 10 cm H_2O) and adjusted expiratory volume per minute (≥10 l/min) [29].

Patients with severe COVID-19 usually have tachypnea (respiratory rate ≥30 breaths per minute), decreased saturation (oxygen saturation ≤93 %), and pulmonary infiltrates >50 % (according to CT data) [30].

A group of experts suggests that COVID may have two ARDS phenotypes [31].

In the first phenotype, patients often show normal compliance even with severe hypoxemia, with normal or even increased minute ventilation, and more than half of these patients do not have shortness of breath ("silent hypoxemia"). Radiographically, such patients have tomographic lesions in the form of "frosted glass", which indicate interstitial and non-alveolar edema, and at this stage the infiltrates are relatively limited. These patients are referred to as "type L" ("low elastance"), with the additional main characteristics of high compliance, limited response to changes in PEEP and low lung mass, assessed by chest CT.

In the second phenotype, the patient's condition may improve clinically or, due to individual factors or inadequate treatment, evolve into a more severe form close to classical ARDS. This is called "type H" (from "high elastance, high elasticity"), which also demonstrates low compliance, better sensitivity to changes in PEEP and high lung mass, assessed on chest CT [32].

In addition to acute respiratory failure (ARF), hospitalized patients may develop acute renal failure (9%), liver dysfunction (19%), coagulation disorders (10–25%) and septic shock (6%) [33–35].

Regarding the treatment of patients with COVID-19, more than 75 % of hospitalized patients require additional oxygen therapy. Respiratory support may differ from the need to add oxygen through a nasal catheter to invasive pulmonary ventilation or extracorporeal membrane oxygenation (ECMO) in patients with the most severe form of ARDS. In general, patients should receive

a minimum amount of additional O_2 to achieve a SpO_2 level of 92 to 96 %. Without the analysis of blood gases, the degree of hypoxemia can be assessed by the ratio of SpO_2/FiO_2, the value of which ≤315 indicates ARDS [36].

The COVID-19 pandemic has revealed the continuing uncertainty and implications of discussions about whether patients with significant hypoxemia should use an early intubation strategy or, conversely, a conservative non-invasive approach [33, 37, 38].

Some studies demonstrate the potential beneficial effects of HFNO (high-flow nasal oxygenation) in the context of acute respiratory failure associated with COVID-19, and support recent evidence that HFNO is associated with a reduced risk of intubation in this group of patients [39].

Many hospitals use non-invasive ventilation (NIV) as an attempt to prevent the development of severe respiratory failure, which requires invasive ventilation support. The European Society of Intensive Care Medicine (ESICM) and the National Health Service of England (NHS-England) recommend the use of NIV as an initial measure for respiratory failure in patients with COVID-19. In the vast majority of cases, COVID-19 used the mode of continuous positive airways pressure, CPAP, (average values of about 10 cm H_2O), which is due to its relatively high efficiency in ARF [40].

In some studies, prone-position in non-intubated patients has significantly improved oxygenation [41, 42].

In severe cases of respiratory failure, as seen with COVID-19, hypoxemia may lead to a sustained increase in respiratory effort resulting in self-inflicted lung injury (P-SILI). In addition, other factors, such as fluid overload or myocardial damage caused by SARS-CoV-2, may also play an important role in the deterioration of the condition due to pulmonary congestion [43].

The intubation threshold for respiratory failure associated with COVID-19 is controversial, as many patients have normal respiratory function but severe hypoxemia [44].

As for the strategy of mechanical ventilation, it should take into account the different mechanisms of lung damage and different manifestations of the disease, i.e. the ARDS phenotype.

L-type patients, usually patients with good pulmonary compliance, are recommended to be ventilated with a larger tidal volume (about 7–8 ml / kg of ideal body weight) and a PEEP of 8 to 10 cm H_2O to avoid redirection of blood flow from aerated pulmonary capillaries, which may increase the effect of shunting.

With disease progression and worsening of inflammatory edema, the patient may switch to “type H”. The pathophysiology of this progression is probably the result of a combination of factors: in addition to self-induced lesion (P-SILI), the viral lesion itself leads to uncontrolled inflammation and edema, with local and generalized thrombogenesis, intense cytokine release and right ventricular overload. The formed pulmonary edema is close to the classical representation of ARDS, with collapsed alveoli and large normoperfusion and hypoaerated areas. In these more advanced cases, the mechanical ventilation strategy should be more traditional: elevated PEEP, VT<6 ml/kg, prone position and alveolar recruitment manoeuvres [32].

Regarding the etiotropic therapy of COVID-19, currently the most promising antiviral drug is remdesivir. After several large-scale clinical trials of remdesivir, despite the ambiguity of the available results, on May 1, 2020, the FDA (food and drug administration) granted emergency use of remdesivir for the treatment of COVID-19 in the United States [45].

Remdesivir is an adenosine nucleotide prodrug that is metabolized in body cells to form a pharmacologically active adenosine triphosphate analogue that inhibits viral RNA polymerases. Previous studies have shown that remdesivir has in vitro activity against Ebola and several coronaviruses, demonstrating prophylactic and therapeutic efficacy in non-clinical models [46, 47].

Remdesivir is included in the treatment protocols of COVID-19 in Ukraine, according to which on the first day – a loading dose of 200 mg once a day (iv for 30–120 minutes), on the second day – a maintenance dose of 100 mg once a day (in / for 30–120 minutes) [48].

Of course, the maximum effect of remdesivir is seen in the early stages of the disease [49], whereas in hospitalized patients, anti-inflammatory drugs may be useful to prevent disease progression, and anticoagulants to prevent thromboembolic complications.

The uncontrolled inflammation and coagulation observed in patients with COVID-19 [50] is similar to multifactorial ARDS, where much evidence has demonstrated the ability of long-term corticosteroid therapy (CST) to reduce inflammation-coagulation-fibroproliferation and accelerate recovery [51].

A study by Chinese scientists showed that COVID-19, associated with increased levels of cytokines, resembles secondary hemophagocytic lymphohistiocytosis, a condition that responds to CST [4].

Although some recommendations were against the use of corticosteroids [52, 53], dexamethasone (6 mg/day) in the RECOVERY study reduced mortality among those receiving invasive mechanical ventilation or oxygen alone [54].

Dexamethasone is officially approved for the treatment of COVID-19 in many countries, including Ukraine. It is not specific (antiviral), but it has been tested and is effective in suppressing the patient's hyperimmune response to the virus. Methylprednisolone is also used, including as a pulse therapy for critical patients [48].

A meta-analysis of 60 studies with 31,732 patients was performed. The included trials were classified into trials that included only steroid therapy and those that included steroids in addition to other standard treatments. As for steroid treatment, the most common steroid is methylprednisolone (used in 28 trials) at different doses depending on the age of the patients. The maximum loading dose of methylprednisolone used was 500 mg intravenously for 1 hour in the study (IRCT20080901001165N52). Steroids were given for a minimum of 3 days to a maximum of 21 days. Other steroids used are budesonide, ciclesonide, dexamethasone, formoterol, prednisolone, prednisone and hydrocortisone. Their safety and efficacy in the treatment of COVID-19 symptoms, especially in the pneumonia

stage, have been tested. The trials also included patients of different age groups at different stages of COVID-19.

Corticosteroids can regulate immune-mediated lung damage and reduce its development to respiratory failure and death. Dexamethasone has been reported to reduce the duration of mechanical ventilation. Glucocorticoid therapy has shown a significant improvement in the permeability of the alveolar-capillary membrane and mediators of inflammation and tissue repair. The results of these tests show promising results and recommend the use of methylprednisolone and dexamethasone in severe COVID-19. It is likely that certain corticosteroid treatments may have differences in efficacy depending on the stage of the disease and in different manifestations of the disease [55].

Therefore, based on the above, systemic corticosteroids are the only treatment that reduces mortality in randomized controlled clinical trials in patients with severe COVID-19. Despite these data, there are still many questions about the use of immunosuppressants in these patients. The incidence of secondary infections during corticosteroid therapy in patients with COVID-19 is unknown, although information on this side effect has been reported in the scientific literature on influenza. Observational studies of other immunomodulatory agents, such as tocilizumab, have shown conflicting results and also suggest an increased risk of secondary infections [56].

Further reliable randomized controlled trials of these drugs are expected, but systemic corticosteroids are currently the mainstay of treatment for severe COVID-19 disease to alleviate cytokine storms.

Of course, anticoagulant therapy plays an important role in the treatment of patients with COVID-19. Many studies are devoted to this area, some of them are quite long. In particular, the issue of prescribing appropriate doses of anticoagulants in critically ill patients should be addressed.

Prevention of thromboembolic events by subcutaneous low molecular weight heparin is recommended for all hospitalized patients with COVID-19 [18, 48, 35].

However, the question of evaluating the benefits of therapeutic anticoagulation in certain patients (i.e., those with elevated D-dimer) has not yet been definitively resolved, and studies are still ongoing.

4. Conclusions

Therefore, the range of complications with COVID-19 is very wide, which may be due to hypoxia, coagulopathy, "cytokine storm", as well as the combined effect of these factors, which determines the need for early diagnosis, the use of effective therapy and a multidisciplinary approach for better outcomes in patients with COVID-19.

Approaches to respiratory, anticoagulant, anti-inflammatory therapy in severe patients with COVID-19 require further research to determine the optimal treatment tactics.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Financing

The study was performed without financial support.

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Received date 29.07.2021
Accepted date 07.09.2021
Published date 30.09.2021

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