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PRESENTATION AND TREATMENT OF SEVERE COVID PNEUMONIA – Current Knowledge and Experiences of Intensive Care Unit of the Clinic of Pulmonology, Clinical Center of Serbia –

Abstract: Severe COVID infection is most often presented as bilateral pneumonia and, according to current knowledge, can be explained by cytokine storm, hypercoagulability and microvascular thromboses. Patients at risk of poor outcome include obese middle-aged men and persons with cardiovascular and pulmonary comorbidities and diabetes. One of specific traits of COVID 19 pneumonias is frequent discrepancy between clinical presentation, radiographic findings and oxygen saturation. Regular monitoring and use of early warning scores improve survival and decrease rates of emergency admissions to intensive care units. Corner-stone of treatment of critically ill patients include oxygen, anti-inflammatory and anticoagulant therapy. Best results are obtained through administering high flow oxygen and non-invasive mechanical ventilation.

Key words: COVID, pneumonia, ARDS, corticosteroids

Introduction: Severe COVID infection is most frequently presented as bilateral pneumonia and, according to current knowledge, can be explained by cytokine storm, hypercoagulability and microvascular thromboses. Patients at risk of poor outcome include obese middle-aged men and persons with cardiovascular and pulmonary comorbidities and

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diabetes. A significant number of critical patients with negative PCR test have typical clinical picture and radiographic findings of COVID pneumonia, and therefore require to be treated as COVID patients. Serologic testing (IgG and IgM) for presence of SARS-CoV-2 antibodies is not recommended for diagnostics and screening (1). Corner-stone of treatment of critically ill patients include oxygen, anti-inflammatory and anticoagulant therapy. Certain number of patients suffers from physical weakness and severe fatigue for months, particularly after prolonged ventilation.

Clinical presentation

Severe COVID infection is most often presented with bilateral pneumonia with respiratory insufficiency. Systemic form of the infection, apart from pneumonia, includes neurological symptoms, diarrheal syndrome and cardiovascular complications. Most common symptom is high body temperature. Approximately 20% of patients develop severe clinical picture, and 6% of them get critically ill. There is no single parameter that would predict the course of the disease. Clinical deterioration, worsening of radiographic findings and aggravated hypoxia usually occur within 7-12 days from the onset of the disease. Clinical picture of patients with COVID pneumonias hospitalized in intensive-care units (ICU) can be moderately severe, severe and very severe – in case of critically ill. Patients with moderately severe clinical picture (form 3) can also be admitted to semi-intensive-care units (SICU), with permanent monitoring. Severe clinical picture (form 4) include serious dyspnea, high respiratory frequency and SaO2 bellow 90%, while the picture of critically ill is characterized by onset of ARDS, multiple organ dysfunction or septic shock.

Pathophysiology

Severe COVID pathophysiology is primarily attributed to the hyperimmune response of the host due to direct cell damage, release of proinflammatory substances and activation of innate response of activating alveolar macrophages and complement cascades. Strong proinflammatory response causes damage to alveolar epithelial cells and vascular endothelium, as well as microvascular micro-thromboses, which lead to the development of ARDS. Therefore, one of the hypotheses explaining development of ARDS in severe COVID infections points to so-called MicroCLOTS – *microvascular COVID 19 lung vessels obstructive thrombo-inflammatory syndrome* (2). Progressive endothelial thrombo-inflammatory syndrome may also be involved in changes of microvascular bed of the brain, kidneys, and intestines, leading to multiorgan dysfunction and death (2). With such pathogenesis, it is logical that anti-inflammatory and anti-

coagulant therapies are beneficial. Cytokine storm (Cytokine storm syndrome, CSS) is one of the forms of systemic inflammatory response of the host to viral infection, very typical of COVID (3). Such systemic inflammation, resulting from infiltration of lymphocytes and monocytes into lungs and heart, can lead to ARDS and cardiac insufficiency. Therefore all COVID patients with severe clinical picture should, if possible, undergo basic screening related to cytokine storm or hyperinflammation (CRP analysis, LDH, IL 6, D-dimer and ferritin). Interleukin 6 (IL 6) is significant parameter for assessing severity of the disease, and is also one of the predictors of lethal outcome (4).

Imaging

Most common radiographic findings in patients admitted to intensive-care units are combination of reticular changes, *ground glass* opacifications and consolidations, predominantly peripheral and in lower and middle lung lobes. Radiographic deterioration usually develops 6 to 12 days from the onset of symptoms, ranging from progression of reticular changes and peripheral consolidations to ARDS-like findings. Radiographic finding often lag behind clinical improvements, since changes recede slowly, leaving many therapy related dilemmas, as well as those related to the process of extubation, weaning of mechanical ventilation or discharge from the hospital. According to the recommendations of the Radiology Department of the Belgrade Faculty of Medicine, there are no indications for daily radiography of stable intubated COVID patients (5). Thoracic CT in COVID patients hospitalized in ICU was indicated in case of clinical and radiographic deterioration, mostly in cases of suspected pulmonary thromboembolism, pulmonary edema, bacterial superinfections or pneumothorax; also for the purpose of monitoring changes in patients with slow and unsatisfactory radiographic regression. Most patients in ICU had typical CT findings of peripheral *ground glass* changes and/ or consolidations in lower and middle lung lobes.

Experience

One of specific traits of COVID 19 pneumonias is frequent discrepancy between clinical presentation, radiographic findings and oxygen saturation. Cases of rapid clinical deterioration with emergency admissions to intensive-care units led to the understanding of the need for regular monitoring and proper assessment of the severity of condition. Some of the main criteria for admission of COVID patients into ICU was respiratory distress (when oxygen flow of 4 l/min cannot sustain SaO2 at 92%, i.e. PaO2 8,66 Kpa), severe dyspnea, hemodynamic instability and significant comorbidity. Therefore a special emphasis was on early warning scores in patients

with COVID 19. In the Clinic for Pulmonology of Clinical Center of Serbia we used MEWS – Modified Early Warning Score. After objective assessment, a decision was made on further treatment – correction of therapy, more frequent monitoring or admitting/moving patients to ICU or SICU. Crucial thing during COVID epidemic was to the good organization of ICU and forming well-coordinated teams. In the Intensive Care Unit of the Clinic of Pulmonology of CCS at all times we had both pulmonologist and anesthesiologist on the team, organized in seven teams working 4-hour shifts. Joint work, knowledge and experience have resulted in a number of successfully cured and patients separated from mechanical ventilation. Another important thing was to form semi-intensive care unit, also under the supervision of pulmonologists and anesthesiologists, where we accommodated severe COVID patients without mechanical ventilation, but still requiring some form of continual oxygen therapy and permanent monitoring. Forming SICU in other COVID centers in Serbia also resulted in improved survival of patients. Another characteristic of ICU and SICU of Clinic of Pulmonology was daily engagement of physiatrists and physiotherapists in the process of early rehabilitation of patients with the most severe forms of the disease. Treatment of patients in ICU averagely lasted from three to four weeks.

Treatment

At the moment there is no cure for COVID 19 whatsoever, and none of the therapeutic options has been confirmed as efficient in randomized clinical studies. Since there is no vaccine, severe COVID pneumonia is currently treated with combination of existing antiviral, immunosuppressant and immunomodulatory medication, symptomatic-supportive and oxygen therapy. As of July 2020 in Serbia has been used the current 8th version of the treatment protocol for COVID-19 (6). The most significant novelty of this version is more liberal use of corticosteroids and use of new antiviral medication (favipiravir). Poor outcome is due to the severity of inflammatory response, inadequate assessment of the severity of patient's condition, prolonged hypoxia, delayed initiation of mechanical ventilation, obesity and inadequately treated comorbidities. High mortality rate, typical for intensive-care units and mechanically ventilated patients, reaching up to 88% even in developed countries, was not the case in the Intensive Care Unit of the Clinic of Pulmonology, and the reasons were permanent monitoring and timely team work **(7).** Apart from oxygen therapy, the emphasis in our ICU from the very beginning of epidemics has been on immunosuppressive, above all corticosteroid therapy. Doses were 0,5–2 mg/kg of body weight, for 5 to 14 days. Early administration of corticosteroids, in the initial stage of ARDS, has been considered irreplaceable for stopping cytokine storm and further progression of the disease toward mechanical ventilation. According to the latest guidelines, it is recommended to administer corticosteroids to patients having moderate and severe ARDS and patients with ARDS

and shock, in order to stop clinical and radiographic progression of the moderately severe clinical picture and to avoid mechanical ventilation. Recommended dose of methylprednisolone is 1-2 mg/kg of body weight, for 3 to 5 days (6). Its parenteral use is also indicated in case of septic shock and some organ insufficiency. Elevated CRP in COVID infection most often indicates highly active disease and hyper-immune response, and seldom is an indicator of bacterial superinfection. Therefore in indicates introducing corticosteroids, rather than antibiotics. Another option, beside methylprednisolone, is dexamethasone, 6 mg/kg of body weight intravenous for 10 days, in patients with moderately severe or severe clinical picture, depending on different guidelines (6, 8). Corticosteroids (dexamethasone) are the only medications that do decrease mortality in severe COVID pneumonias (9). Tocilizumab, a recombinant monoclonal antibody, IL-6 receptor antagonist, is used in severe COVID pneumonias (forms 3, 4, 5) in case of clinical and radiographic progression and elevation of parameters of inflammation (IL 6, D-dimer, ferritin) (6). According to some studies, tocilizumab can reduce the risk of invasive mechanical ventilation and death in patients with severe COVID – 19 pneumonia (10). Tocilizumab was administered to COVID patients in ICU, but clinical benefit cannot be adequately assessed, since it was used together with corticosteroids. Yet, most recent studies show neither clear benefits, nor influence of tocilizumab on the course and outcome of COVID infection (11, 12). Out of other medications and treatment procedures, some were used for the first time for this indication (lopinavir – ritonavir, favipavir, chloroquine) and drug interactions and their side effects were followed. Among patients treated in ICU most frequents side effects were observed in case of use of chloroquine. Side effects of chloroquine were particularly pronounced in patients with cardiac diseases, and were presented as arrhythmias (bradyarrhythmias) or worsened heart insufficiency, so chloroquine, and later hydroxychloroquine too, were used very selectively, shortly and with no clear benefits. Most serious interactions were observed due to simultaneous use of chloroquine / hydroxychloroquine and azithromycin and levofloxacin. Since June 2020 chloroquine and hydroxychloroquine have not been approved for use against severe COVID infections, because they brought no clinical improvements for COVID patients (13, 14). All patients in ICU of the Clinic of Pulmonology of CCS with severe bilateral pneumonias (forms 3, 4, 5) also received antibiotics, first according to the local guidelines for community-acquired pneumonias, and then in accordance with culture samples and inflammation parameters. Favipavir, the only antiviral drug in 8th version, is recommended for use in patients with initially severe pneumonias (form 3, 4, 5), while Asian guidelines and the most recent findings recommend it for mild forms of the disease. It is effective if used within the first 5–7 days from the onset of symptoms, which substantially narrows the scope of its use in ICU (6,9). When it comes to anticoagulant therapy, due to severity of the disease in all patients in ICU, therapeutic doses of low molecular weight heparin were used, with monitoring of

anti-xa. Therapeutic doses of low molecular weight heparin were adjusted to renal function or BMI (15). MSCT angiography confirmed no lung thromboembolisms with this kind of treatment. Due to possible co-infections with flu virus H1N1, oseltamivir was also used at the beginning of COVID epidemics, but demonstrated no therapeutic efficiency when it comes to COVID 19 (16).

One of crucial elements of the treatment of severely ill COVID patients is proper assessment of the moment of initiation of non-invasive or invasive mechanical ventilation, as well as of separation from it. If the intubation is necessary, lung-protective ventilation was used, avoiding asynchrony. Very important part of the treatment was prone positioning of patients, which reduces adverse effects of ventilation and enables better efficiency and ventilation of all parts of lungs (WHO recommends prone positioning of patients with ARDS for 12-16 hours a day) (17). CPAP (continuous positive airway pressure) was proven to be the most useful method of non-invasive ventilation, and it was used the most in the ICU of Clinic of Pulmonology. High flow oxygen therapy (HFO) in total provided the best results, since it was more extensively used than NIV, because it could be used at other wards too. High flow oxygenation improves gas exchange in acute respiratory insufficiency, decreases work of breathing and respiratory rate, relieves dyspnea and is comfortable for patients. According to experiences of some centers, if high flow oxygen therapy fails, it is indicated to intubate patient right away. Experience of the Clinic of Pulmonology showed positive effect of switching from HFO to NIV, which, together with changing position of patients, with prevailing prone position, helped to avoid higher rate of intubations. In all patients in ICU, except in highly febrile patients, fluid intake was restricted (30 ml/h), along with administration of diuretics, in order to avoid hypervolemia. Their diet consisted of target caloric intake of 20 kCal/kg, including mandatory use of supplements (vitamin C and D, Zinc, probiotics). First choice vasopressor was noradrenaline, then dobutamine, while adrenalin and dopamine were rarely used. Most frequently used anesthetics were midazolam, propofol, rocuronium bromide, fentanyl, remifentanil and dexmedetomidine.

Bacterial superinfections were infrequent, and sepsis and decubital wounds significantly less frequent than in patients with H1N1. Several therapeutic bronchoscopies were performed and endoscopic findings in all patients showed only mucosal hyperemia and vulnerability, without significant quantities of secretions and pus.

Elevated troponin in severe bilateral pneumonias was most usually a marker of acute myopericarditis, while elevation of BNP (NT pro BNP) wasn't treated as absolutely specific marker of heart failure, but as marker of inflammation and cytokine storm. Signs of damage to the cardiovascular system in COVID infection presented mostly as coronary ischemia, myopericarditis or arrhythmias. Most long-lasting are these consequences of damage to the cardiovascular system, persisting even after patients get discharged, more than pulmonary damage and complications. Most accurate methods for assessing severity of COVID infection after the completion of

treatment are thoracic MSCT, diffusion capacity of the lungs for CO, and ultrasound and magnetic resonance of the heart.

Conclusion

There is no effective cure for COVID infection at the moment. Since there is no vaccine, it seems that oxygen therapy, corticosteroids and anticoagulants are the most important therapies leading to favorable outcome. Sufficient number of well-educated medical personnel, proper assessment of timely initiation of adequate therapy, physical rehabilitation, care and psychological support make satisfactory recovery of a large number of severe COVID patients possible.

A few days before the article was sent to the journal, the 9th version of the Protocol for the treatment of COVID infection in Serbia was published. The most significant changes compared to version 8 relate to anticoagulant therapy and the lack of recommendations for chloroquine.

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