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PERSPECTIVE ARTICLE

Sepsis During COVID-19: Mechanisms and Implications for The Treatment

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ABSTRACT
Currently about 5 million people are infected with novel SARS-CoV-2. In 5% of cases these patients were critically ill and they were admitted for treatment in ICU departments. Sepsis is a common reason of this critical conditions and although proper mechanism of its development is not known, it had been proposed hypothesis, that SARS-CoV-2 has ability of direct damage of cells and organs. Except this secondary bacterial infection has a role in sepsis development. The role of phenotype, genotype, race, ethnic, and social properties in COVID-19 sepsis development is not known. Treatment options for COVID-19 sepsis is not specific and recommendations of Surviving Sepsis Campaign (SSC) must be followed with caution of infection preventive measures
Key words: *Sepsis, SARS-CoV-2, COVID-19, mechanisms, treatment, shock.*

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INTRODUCTION

Disease, induced by novel coronavirus SARS-CoV-2 and named as COVID-19 affected about 5 million people globally and is related with enormous medical, social and economic problems. In 5% of cases patient condition is critical, they are admitted to ICU departments, where frequently is diagnosing severe sepsis, which is related with mortality rate about 30% (). Understanding the mechanism of viral sepsis in COVID-19 is necessary for better treatment of patients and improving outcome. In this review we are concerning on the possible mechanisms of SARS-CoV-2 viral sepsis and characters of its treatment.

SARS-CoV-2 VIRAL SEPSIS

Third international consensus defined sepsis as a life-threatening organ dysfunction caused by dysregulated host response to infection. [1-4]. Critically ill COVID-19 patients to whom we can see multiple organ failure including, kidney, liver and lungs, manifestation of shock with cold extremities and weak peripheral pulse, acidosis, impairment of peripheral microcirculation with or without of hypotension met with this criteria of sepsis [1, 2, 3]. In most cases these septic patients have no other infection source except SARS-CoV-2. Chinese authors, Li H et al proposed interesting hypothesis about the developing of sepsis during COVID-19 (5). At first, they are focusing on the spread of virus in the organs of patient. Virus can damage respiratory tract, it can cause spleen atrophy, lymph node necrosis, renal hemorrhage, liver enlargement, degeneration of the neurons in the brain [9]. Virus particles can be detected in respiratory, fecal and urine samples (8). This broad dissemination might be the result of direct attack of virus to the target organs, which are expressing angiotensin-converting enzyme 2 (ACE2). Interestingly, that high expression of ACE2 in the circulatory system after infection of SARS-CoV-2 might partially contribute to septic hypotension (6, 11).
Like the influenza infection, COVID-19 is characterized with cytokine storm. Particularly, it had been shown that tumor necrosis factor (TNF) α, interleukin 1β (IL-1β), IL-6, granulocyte-colony stimulating factor, interferon gamma-induced protein-10, monocyte chemo attractant protein-1, and macrophage

inflammatory proteins 1-α are elevated when clinical signs of infection are manifested [7]. Mechanisms of this elevation are not yet known. It is questionable, whether direct virus-induced tissue damage, systemic cytokine storm, or the synergistic effects of both, contributes to the multiple organ dysfunction of severe COVID-19 patients. Like of influenza infection proinflammatory phase and cytokine storm is following by lymphopenia, especially the number of CD4 and CD8 T-cell subpopulations are decreasing which increases the risk of bacterial infection in COVID-19 patients (10). Particles of SARS-CoV-2 had been detected in blood samples and T lymphocytes and it can serve as an explanation of lymphopenia during COVID-19. [10]. According to these findings Li H et al hypothesized, that in asymptomatic patients initially alveolar macrophages are involving in immune surveillance and then innate and adaptive immune response establishes, which leads to patients recover. In severe cases alveolar capillary barrier is damaging, cytokine storm and uncontrolled inflammation developing and adaptive immune response is not forming. Schematically this hypothesis is presenting on the Fig. 1.

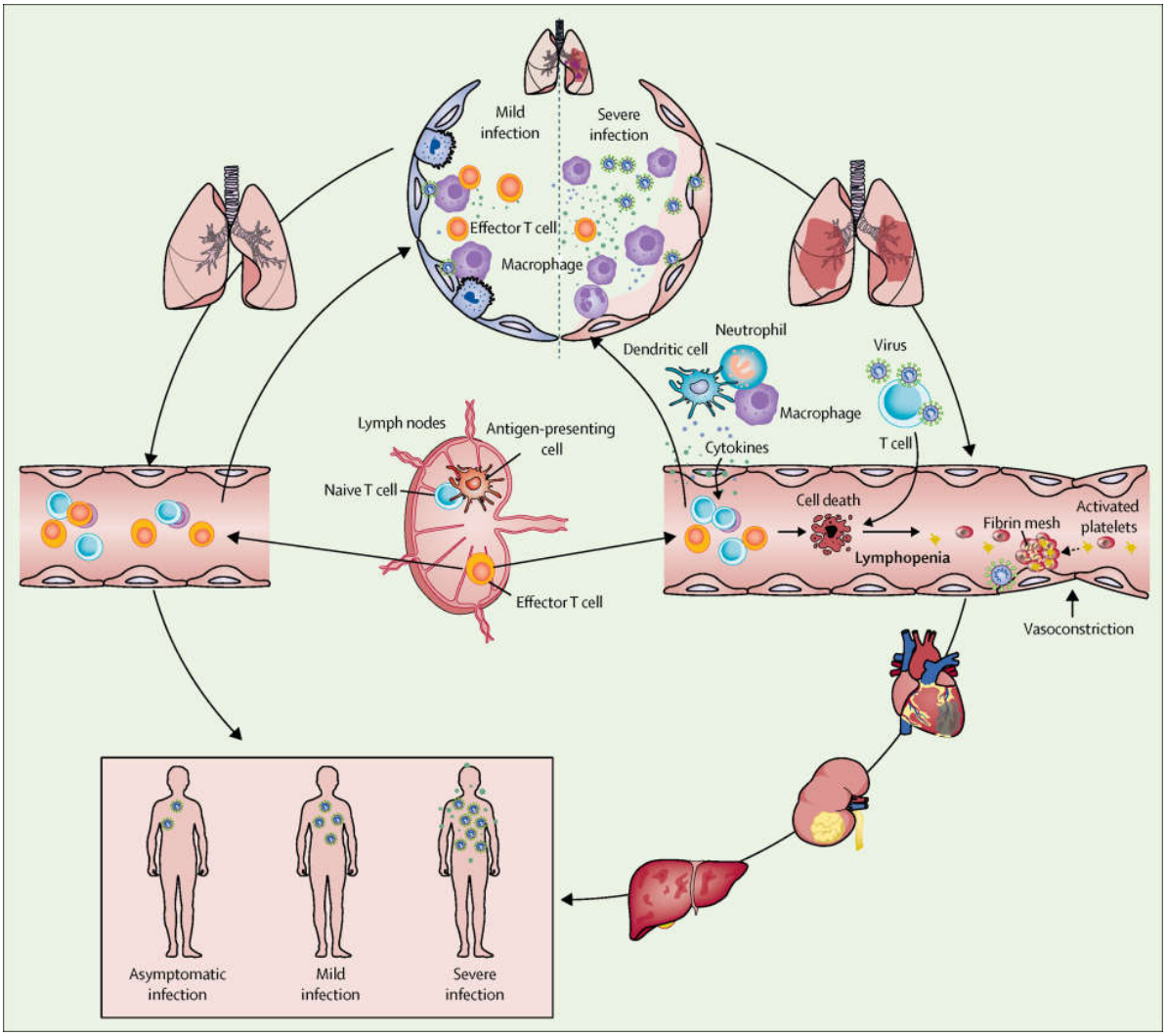

Fig. 1. Occurrence and outcome of severe acute respiratory syndrome coronavirus 2 viral sepsis (Li H, Liu L, Zhang D et al).

According to this hypothesis is possible to divide COVID-19 sepsis patients into 4 novel phenotypes, presented by C Seymour *et al.* [4]. It seems that asymptomatic patients are belonging to alpha phenotype with the fewest abnormal laboratory tests, least organ dysfunction and lowest in-hospital mortality rate. Mild infection will be in patients with beta phenotype who were older and had the most chronic illnesses and renal dysfunction or gamma phenotype, characterized with elevated measures of inflammation and primarily pulmonary dysfunction. Severe infection will be in delta phenotype patients with more liver dysfunction and shock and the highest in-hospital mortality rate. As an argue of this hypothesis serve the fact, that in non COVID-19 septic patients inflammatory cytokines IL-6, IL-10,

and TNF measured at baseline were greater in the γ phenotype and δ phenotype compared with the α phenotype, suggesting a predominantly hyperinflammatory response [6, 12, 13, 14]. The 4 sepsis phenotypes strongly correlated with patterns of the host immune response, mortality, and other clinical outcomes but is this postulate true or not for COVID-19 patients remains unclear. As sepsis is the common, heterogenous clinical syndrome, for better understanding ofits development mechanisms during COVID-19 establishment of the roles of multiple factors are needed. Among these factors are gender, smoking, ethnic, race, social and economic properties, immunophenotypes [9, 12, 15, 17, 25], blood genomic endotypes [16], presence of nosocomial infection [17, 18] inflammatory pathobiology and neutrophil phenotypes [14, 19, 20] ,metabolic profile of patient [21].

TREATMENT OF COVID-19 SEPSIS

SARS-CoV-2 outbreak and septic complications of COVID-19 are the subject on which is concentrating the all forces of ICU-s worldwide during last months. General principles of sepsis treatment are non-specific. There are nine well-known principles recommended by Surviving Sepsis Campaign (SSC), including: 1) use crystalloids over colloids for volume resuscitation; 2) avoid hydroxyethyl starch; 3) avoid dopamine if norepinephrine is available; 4) starting supplemental oxygen if peripheral oxygen saturation ($Sp0_2$) is less than 92%; 5) $Sp0_2$ be maintained no higher than 96%; 6) low tidal volume ventilation; 7) targeting plateau pressures of less than 30 cm H_2O; 8) avoid the routine use of inhaled nitric oxide; and 9) avoid staircase, or incremental positive end-expiratory pressure (PEEP), recruitment maneuvers [22, 23].

Specific problems of COVID-19 sepsis treatment include preventive measures of infection spread among the healthcare personnel and patients (23, 26).For this purposes N-95 mask is needed. Aerosol-generating procedures must be performed in negative-pressure rooms. Nonemergent procedures should be canceled to increase ICU bed availability. Patient visitation should be very limited and education on proper infection control measures should be strictly enforced. With the increasing demand for ICU supplies, critical care providers should be aware of their inventory, including personal protective equipment, respirator masks, and oxygen support including mechanical ventilators. Isolation of ventilated or nonventilated patients are needed when nonaerosol-generating procedures are performed. Cleaning and waste disposal should be made with caution for avoiding the generation or reaerosolization of infectious material. Endotracheal aspiration is preferable than bronchoalveolar lavage, bronchial wash, or sputum induction. For achieving of SpO2 between 92-96% use of high-flow nasal canula is better and safer, than noninvasive positive pressure ventilation [22, 23].

Results of clinical trials are needing to answer of many questions regarding the treatment of sepsis. This is about the use of: 1) corticosteroids in adults with ARDS; 2) antiviral agents; 3) recombinant interferon; 4) chloroquine or hydroxychloroquine; 5) tocilizumab; or 6) helmet noninvasive positive pressure ventilation (NIPPV) rather than mask NIPPV [22, 24, 27, 28].

Treatment options are depending under presence of comorbidities (e.g. diabetes, hypertension), type of shock and generally is not differ from treating of severe sepsis and septic shock in nonCOVID-19 patients (29).Cause of shock can be multiple and can include myocardial dysfunction, secondary bacterial infection (16-20% of non-survivors), cytokine storm. Shock will be diagnosed if there is a clinical criteria - acute onset of new and sustained hypotension (MAP < 65 or SBP < 90) with signs of hypoperfusion requiring intravenous fluid (IVF) or vasopressors to maintain adequate blood pressure [22, 23]. First goal of treatment is to differentiate shock and maintain hemodynamic parameters, especially mean arterial pressure (MAP) and systolic blood pressure (SBP) in ranges not <65 mm. Hg. and <95 mmHg .respectively. Initiallyearly empiric antibiotic and standard treatment of distributive shock is needed with conservative fluid management and norepinephrine. Point of care ultrasound (POCUS) is indicated for assessment of fluid response, cardiovascular system and lung anatomic and physiologic state (30). For keeping infection preventive measures, standard chest X-ray is preferable and if possible, computed tomography should be avoided [22, 23]. Cardiogenic shock occurring in 23-33%of ICU COVID-19 patients, mostly in non-survivors, which are in older ages, with comorbidities and concomitant respiratory failure [31]. Cardiogenic shock may present late, with acute decline of left ventricular ejection fraction (LVEF) even after improvement of respiratory failure. For treatment of these patients cardiovascular medicine consultation service is recommended, in selective cases mechanical circulation support is needed. Prognostic factors of death are heart failure and myocardial damage [23, 31].

Patients with COVID-19 sepsis can have cytokine activation syndrome. They are developing rapid progression to ARDS, shock, and multiorgan failure [5, 7]. It had been shown, that COVID-19 confirmed patients with ARDS have higher neutrophil counts [7, 10]. Therefore, neutrophil activation likely contributes to the pathogenesis of cytokine storm and ARDS. Definition of this neutrophil phenotype, as

well as liver, inflammatory and protein metabolism markers are crucial for proper diagnosis and treatment. For management of these patients cytokine blockade, particularly IL-6 and IL-1 is needed [7, 10, 28]. Although steroids can worse lung injury, they may be helpful in the hyperinflammatory state [27]. Cytokine storm (activity of pro-inflammatory cytokines IL-2, IL6, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A and TNF-α) is associated with the classical syndrome named disseminated intravascular coagulation (DIC) and the subsequent consumption coagulopathy [32, 33].Therefore, the use of LMWH, UFH, or fondaparinux at prophylactic doses is strongly advised forseptic, as well as for all COVID-19 hospitalized patients; patients with anticoagulant contraindications should be treated with limb compression [32, 33].

CONCLUSION

According to current knowledge about novel SARS-CoV-2, this virus can directly damage organs and cells, including blood cells and particularly lymphocytes and this phenomenon can serve as an underling mechanism of sepsis. Development of sepsis can be related to virus spread and/or secondary bacterial infection. Novel septic phenotypes are not clearly understood regarding to COVID-19 sepsis. Development and prognosis of sepsis can be related not only to SARS-CoV-2 but phenotypic, genotypic, ethnic, social, aging and gender factors as it is seen earlier in non-COVID-19 sepsis. Generally treatment of COVID-19 sepsis is same, as it is recommended by SSC for non-COVID-19 sepsis.

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SUMMARY

Currently around the world, about 5 million people are infected with the new SARS-CoV-2 coronavirus. In 5% of cases, the disease is severe, and patients are admitted to the intensive care unit for treatment. The cause of a critical condition is often sepsis. The mechanism of its development is unknown, but a hypothesis has been put forward that SARS-CoV-2 can cause direct damage to cells and organs. In addition, a secondary bacterial infection may be involved in the development of sepsis. The role of other factors, such as racial and ethnic origin, socio-economic, genotypic and phenotypic factors, is unknown. There is no special approach to treatment, and it is advisable to follow the company's recommendations for rescue from sepsis, taking into account measures of protection against infection.

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