Sepsis and Coronavirus Disease 2019: Common Features and Anti-Inflammatory Therapeutic Approaches

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Abstract: Great efforts are being made worldwide to identify the specific clinical characteristics of infected critically ill patients that mediate the associated pathogenesis, including vascular dysfunction, thrombosis, dysregulated inflammation, and respiratory complications. Recently, coronavirus disease 2019 has been closely related to sepsis, which suggests that most deaths in ICUs in infected patients are produced by viral sepsis. Understanding the physiopathology of the disease that lead to sepsis after severe acute respiratory syndrome coronavirus 2 infection is a current clinical need to improve intensive care–applied therapies applied to critically ill patients. Although the whole representative data characterizing the immune and inflammatory status in coronavirus disease 2019 patients are not completely known, it is clear that hyperinflammation and coagulopathy contribute to disease severity. Here, we present some common features shared by severe coronavirus disease 2019 patients and sepsis and describe proposed anti-inflammatory therapies for coronavirus disease 2019 which have been previously evaluated in sepsis.

Key Words: anti-inflammatory therapy; cytokine storm; sepsis; severe acute respiratory syndrome coronavirus 2

SEVERE CORONAVIRUS DISEASE 2019 MAINTAINS COMMON FEATURES TO SEPSIS

During coronavirus disease 2019 (COVID-19) outbreak, the surge in patients requiring ICU admission has been overwhelming and jeopardized most critical care capacity in several hospitals worldwide (1). Clinically, most patients infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) present no severe symptomatology, but almost 5% of patients show severe lung injury or even Multiple Organ Dysfunction Score (MODS), with mortality at the ICUs between 8% and 38% depending on the country (2). Interestingly, most SARS-CoV-2–infected patients admitted to ICU showed a dysregulated host response characterized by hyperinflammation, alterations in the coagulation, and dysregulation in the immune response (3) that further contribute to MODS, like occurs in sepsis (4, 5).

In particular, some COVID-19 patients show metabolic acidosis, high levels of lactate, and abnormal coagulation variables (i.e. D-dimer, abnormal fibrin degradation products levels) (6), which are indicative of microcirculation dysfunction (7, 8). In fact, these patients suffer from coagulopathy (9), and about 2.5% of COVID-19 patients showed evidence of disseminated intravascular coagulation (DIC) (10–12). It seems that the challenge in recognizing disease complications in COVID-19 patients remains in the heterogeneity manifested in these patients as occurs also in sepsis.

Due to virus infection and to MODS in some cases, many patients with severe COVID-19 meet the Third International Consensus Definitions for Sepsis (Sepsis-3) (13), which define sepsis as "a life-threatening condition that arises when the body's response to infection damages the host's own tissues" (13). It is noteworthy that after Sepsis-3 consensus, both pro- and anti-inflammatory responses were considered to occur simultaneously during sepsis (14).

In this scenario, most deaths in critically ill COVID-19 patients are caused by sepsis (15, 16). In fact, the clinical characteristics shown by these patients meet the typically associated features of septic patients (17, 18). Interestingly, when performing specimen cultures in septic patients from a COVID-19 cohort, about 80% of patients had no bacterial or fungal infection. So viral infection would seem to be the only reason for sepsis (18, 19). Therefore, sepsis is expected to worsen the clinical phenotypes of these critically ill COVID-19 patients (19).

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This Viewpoint provides a summary of how SARS-CoV-2 severe patients met criteria of sepsis and septic shock and explores the clinical care for these patients with special attention to anti-inflammatory therapy.

SARS-CoV-2 can induce the cytokine storm in a subgroup of patients (3, 20), producing high levels of inflammatory mediators in COVID-19 patients (21–25), which was associated with severity and death (21–25).

Severe COVID-19 patients also share some common characteristics with sepsis of respiratory origin, such as dense mucus secretions in airways, diffuse alveolar damage, increased pulmonary inflammation, and high levels of systemic proinflammatory cytokines and microthrombosis (20), probably as consequence of the increase in angiotensin II caused by SARS-CoV-2 and angiotensin-converting enzyme 2 interaction and high levels of interleukin (IL)–6 and other proinflammatory cytokines identified in COVID-19 patients, contributing to coagulopathy (26–28).

COVID-19 patients who suffer sepsis present an altered mental state, dyspnea, reduced urine output, faster heart rate, a weak pulse, and cold extremities, features which are also found in septic shock patients. The aforementioned symptoms are likely brought on by low blood pressure and a hypercoagulation state by the direct and indirect action of SARS-CoV-2. In addition, thrombocytopenia and high lactate (serum lactate levels > 2 mmol/L) have also been observed in most of these patients, which are clinical manifestation of septic shock (29). It is noteworthy that vasoconstriction and DIC are typical characteristics of septic patients (12).

What seems clear is the high complexity and heterogeneity of COVID-19 patients who require multilevel treatment which has been mainly focused to avoid: 1) viral replication (remdesivir has shown beneficial effects) (30), 2) to control the inflammatory cascade (cytokine blockade, among others), and 3) to reduce thrombi formation (anticoagulant therapies). Here, because the potential use of anti-inflammatory therapies in the treatment of COVID-19 patients, we revisited the previous use of these therapies in sepsis settings.

THE ANTI-INFLAMMATORY THERAPY IN SEPSIS REVISITED AND ITS APPLICATION IN COVID-19 PATIENTS

Although the whole representative data characterizing the immune and inflammatory status in COVID-19 patients are not completely known, it is clear that hyperinflammation and coagulopathy contribute to disease severity and death in patients infected by SARS-CoV-2.

Therapeutic options proposed for COVID-19 include among others, cytokine storm blockade by using the IL-1 receptor antagonist anakinra or the use of IL-6 receptor inhibitor tocilizumab. More than 19 clinical trials are currently active worldwide to evaluate the effects of the use of anakinra on hyperinflammation, acute respiratory distress syndrome (ARDS), and respiratory failure in COVID-19 patients (ClinicalTrials.gov). In this regard, reanalysis of data from a phase 3 randomized controlled trial consisting on the use of the anakinra in sepsis showed positive effects on the outcome among the most severe patients with hyperinflammation caused by the cytokine storm and improving the 28-day survival rate of patients with severe sepsis (31).

Notably, IL-1β contributes to the cytokine storm and induces IL-6 expression (32), which has emerged as a promising target for COVID-19 treatment (3). In this regard, a multicenter randomized controlled trial of tocilizumab which can be used previously against cytokine release syndrome has been approved in patients with a phase II trial in Italy (ClinicalTrials.gov; NCT04317092) and a phase III trial approved by the U.S. Food and Drug Administration (ClinicalTrials.gov; NCT04320615) to assess its effect on severe COVID-19. However, both positive (33) and negative results (34) have been obtained in regard to the use of IL-6 blockers to treat COVID-19. These resemble to that previously occurring in sepsis, in which several clinical trials targeting inflammation failed (5), probably conditioned by the heterogeneous and complexity of sepsis (4, 5) and contributed by the simultaneous effects produced by the release of hundreds of signaling factors involved in the inflammation response in sepsis (4, 5).

Corticosteroids have been proposed as drugs to combat cytokine storm by their anti-inflammatory potential (35), and their use has again become a dilemma for clinicians during COVID-19. In fact, it has been described that SARS-CoV-2 expresses a viral amino acid sequence that mimics the host's adrenocorticotropic hormone (ACTH). This sequence allows the virus to escape from the patient's immune response, due to when the immune system releases specific antibodies, they bind to the host's own ACTH. This process prevents the inflammatory suppression characteristic of corticosteroids, thus allowing the virus to induce the inflammatory cascade, which ends up disrupting the patient's immune system and ultimately cause multiple organ failure, including ARDS. Corticosteroid treatment increases the levels of these hormones and is capable of blocking the inflammatory response of SARS-CoV-2. In critically ill patients with sepsis, corticosteroids possibly result in a small reduction in mortality (36). In this regard, a meta-analysis and systemic reviews comparing the use of different corticosteroids, including dexamethasone, suggest their capacity in reducing the 28-day mortality in ICU patients with sepsis (36) and septic shock (37). Interestingly, a recent Bayesian network meta-analysis performed by Zhang et al (38) showed that dexamethasone might be more effective in reducing short-term mortality in sepsis than placebo and suggest a superior capacity in reducing the short-term mortality of sepsis compared with other steroids.

Dexamethasone has recently demonstrated that it may help to blunt the severity of inflammation and prevent a severe hyperinflammatory phase in COVID-19 patients. The Randomized evaluation of COVID-19 therapy (RECOVERY) Collaborative Group has recently demonstrated that mortality at 28 days was lower in the dexamethasone treated group than in the usual care group, most significantly in patients requiring invasive mechanical ventilation or in those receiving oxygen support without invasive mechanical ventilation. However, no benefits were reported among patients who did not require respiratory support (39). Importantly, the risk of progression

to invasive mechanical ventilation was lower in the dexamethasone treated patients (39). Dexamethasone has been recently approved for the treatment of severe COVID-19 patients, and it is currently being evaluated in several clinical trials (ClinicalTrials.gov; NCT04381936; NCT04325061; NCT04347980).

Furthermore, Leisman et al (40) proposed that there is no evidence of cytokine storm in COVID-19 patients and suggest that the use of cytokine-blockade agents should meet with skepticism in the absence of randomized evidence. However, the author propose that anticoagulation should be a key priority for further investigations.

Understanding the underlying molecular and clinical mechanisms that cause the sepsis in COVID-19 patients, specifically those related with hyperinflammation and coagulation is still a primary need to explore in order to improve prognosis and to identify new therapeutic targets with the challenge to reduce mortality and in survivors the length of stay of patients at the hospital, ICU admissions and ICU stays, and in turn healthcare costs.

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