Does Severe Acute Respiratory Syndrome Coronavirus 2 Cause Sepsis?

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Coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), poses an unprecedented threat to human health, healthcare systems, and our global economy. Since its emergence, clinicians have attempted to extrapolate the pathophysiology and management strategies for more well-known disease processes such as acute respiratory distress syndrome and other respiratory viruses. One important disease paradigm that has been variably applied to COVID-19, however, is sepsis. Although some experts have unequivocally asserted that multiple organ failure arising from COVID-19 is sepsis (1), other case series of severe COVID-19 infections have not labeled the disease as sepsis despite the fact that patients have proven infection and organ dysfunction and therefore meet the formal definition of sepsis (2, 3). We believe it is worth exploring why this is the case, and whether or not it truly serves our patients to think about severe COVID-19 infections as sepsis.

According to the Third International Consensus Definitions of Sepsis and Septic Shock (Sepsis-3), sepsis is a dysregulated host response to infection that causes life-threatening organ dysfunction (4). Many clinicians associate sepsis with severe bacterial infection, but this has never been a requirement of any consensus sepsis definition. Sepsis-3 criteria are agnostic on the source of infection but emphasize instead that organ damage in sepsis is due to the secondary consequences of complex molecular cascades rather than direct invasion by pathogens.

Although our understanding of the mechanisms of COVID-associated organ dysfunction remains incomplete, severe COVID-19 does appear to include inflammatory-mediated organ dysfunction both inside and outside the lungs that is consistent with "viral sepsis" (5, 6). Investigators have documented markedly elevated levels of proinflammatory cytokines, including tumor necrosis factor alpha, interleukin (IL)-1 beta, and IL-6, observations consistent with a "cytokine storm." (7, 8) Anti-inflammatory signals are present as well. These biochemical cascades appear capable of causing organ dysfunction throughout the body, including diffuse alveolar damage in the lungs, coagulopathy and microvascular dysfunction, acute cardiac injury, cytopenias, acute kidney injury, and hepatitis. The roles of hypotension and impaired tissue oxygenation are less clear in COVID-19 than in bacterial sepsis; however, the dysregulated endothelium and microvascular thrombosis typically associated with sepsis are commonly seen in severe cases of COVID-19 (9). Direct viral invasion of the kidneys, heart, and endothelial system has also been reported, but this is not uniformly the case, and thus, the constellation of data suggest that at least some part of COVID-19 organ dysfunction is immune-mediated (10–13).

The observation that nonbacterial organisms can cause sepsis is certainly not novel. Fungi are well-known to cause sepsis and septic shock, and fungal infections have often been included in epidemiologic studies of sepsis. Viral sepsis, however, tends to be under-reported in large sepsis series. A recent international point prevalence study, for example, only attributed 3.7% of infections in critically ill patients to viruses (14). However, this is almost certainly an underestimate due to undertesting given that pneumonia is one of the most common causes of sepsis and a third or more of pneumonias in critically ill patients are caused by viruses (15, 16). Notably, a causative organism is not identified in up to a third of critically ill patients with suspected sepsis; some fraction of these may be due to undiagnosed viral infections (17, 18).

The potential advantages of labeling severe COVID-19 associated with organ dysfunction as sepsis are that it emphasizes the severity of the disorder, the imminent threat of death if it is left untreated, and the necessity of close observation

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and intensive care. Mortality in COVID-19 patients meeting Sepsis-3 criteria in one Chinese cohort was 48% (3). This is far higher than the 15% mortality rate associated with non-COVID sepsis (19). If labeling the condition as sepsis helps to convey the severity of the presentation and the need for aggressive care, then this is likely beneficial.

The question of whether severe viral infections can lead to sepsis or septic shock in the absence of secondary bacterial infection echoes a similar discussion during the 2014 Ebola viral disease (EVD) epidemic. Members of the Global Sepsis Alliance asserted that the multiple organ dysfunction described with EVD should be called sepsis and that failing to do so could detract from resuscitation efforts and damage international efforts to highlight sepsis as a major unrecognized cause of death (20). Other experts argued, however, that "lumping" EVD patients into the broader category of sepsis "could have detrimental implications for the treatment and prognosis of patients with EVD" by encouraging early treatment for bacterial sepsis and protocolized care that might not be appropriate for this disease (21).

This debate highlights what we consider the most compelling argument against labeling severe COVID-19 as sepsis—that many of the treatments that are reflexively applied to patients with sepsis may, in fact, be harmful to patients with COVID-19. Aggressive fluid resuscitation may exacerbate borderline pulmonary function. Empiric antibacterials will expose patients to the risks of antibiotics without clear promise of benefit given that bacterial superinfection in COVID-19 appears to be rare. Applying the label sepsis may also impart subtle pressure to treat patients aggressively in all aspects, including early intubation, even though this may be harmful for some patients.

More broadly, these concerns about labeling severe COVID-19 as sepsis expose a larger issue about sepsis in general. Why is it that sepsis has come to be associated with a uniform set of narrowly prescribed treatments (blood cultures, serial lactates, aggressive fluid resuscitation, and broad-spectrum antibiotics)? Even outside of COVID-19, the essence of sepsis is heterogeneity. Sepsis encompasses a mosaic of sites of infection, causative pathogens, antimicrobial susceptibilities, organ dysfunctions, host susceptibilities, and responses to treatment. The optimal treatment of meningococcal meningitis is radically different from the appropriate treatment for a bowel perforation with polymicrobial spillage into the abdomen, which in turn is different from acute *Legionella pneumophila* pneumonia leading to rapid atrial fibrillation and acute exacerbation of congestive heart failure. The best treatment plan for each of these disorders further depends upon patients' severity of illness, underlying heart, lung, and kidney function, their history of recent antibiotic exposures, allergies, the presence or absence of indwelling devices, and patients' values and preferences. Applying a single, common label to all these conditions risks driving clinicians to shortcut their critical analysis of each patient in favor of treating all in a uniform fashion. One warning sign of premature closure in a patient may be when the diagnosis is listed as sepsis alone rather than sepsis due to organism X in body site Y causing organ dysfunction Z.

The downsides of labeling a condition as sepsis can thus be obviated by being clear that sepsis is a multifactorial disorder, that its management must be customized to each patient, and that it is vital to explicitly name the suspected pathogen, site of infection, and organ dysfunctions associated with sepsis. Once one accepts these preconditions, we believe there is substantial value in labeling severe infections associated with organ dysfunction, including those due to SARS-CoV-2, as sepsis even though they do not all fall under one common treatment pathway. These include drawing clinicians' attention to their patients' vulnerability and the necessity of close care, highlighting the prognostic implications of a sepsis diagnosis, and providing a more accurate accounting of the epidemiology and burden of sepsis. We contend that based upon these considerations, there should be no debate that SARS-CoV-2 is an important cause of sepsis and that labeling it as such is beneficial and appropriate.

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