



Sepsis in patients hospitalized with coronavirus disease 2019: how often and how severe?

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Purpose of review

To discuss why severe COVID-19 should be considered sepsis and how co-infection and secondary infection can aggravate this condition and perpetuate organ dysfunction leading to high mortality rates.

Recent findings

In severe COVID-19, there is both direct viral toxicity and dysregulated host response to infection. Although both coinfection and/or secondary infection are present, the latest is of greater concern mainly in resource-poor settings. Patients with severe COVID-19 present a phenotype of multiorgan dysfunction that leads to death in an unacceptable high percentage of the patients, with wide variability around the world. Similarly to endemic sepsis, the mortality of COVID-19 critically ill patients is higher in low-income and middle-income countries as compared with high-income countries. Disparities, including hospital strain, resources limitations, higher incidence of healthcare-associated infections (HAI), and staffing issues could in part explain this variability.

Summary

The high mortality rates of critically ill patients with severe COVID-19 disease are not only related to the severity of patient disease but also to modifiable factors, such as the ICU strain, HAI incidence, and organizational aspects. Therefore, HAI prevention and the delivery of best evidence-based care for these patients to avoid additional damage is important. Quality improvement interventions might help in improving outcomes mainly in resource-limited settings.

Keywords

acute respiratory distress syndrome, bacterial pneumonia, coronavirus disease 2019, ICU, sepsis, viral pneumonia

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to enormous pressure on health systems around the world with a surge in hospitalizations for pneumonia. Critical disease (i.e. respiratory failure, septic shock, and/or multiple organ dysfunction) has been reported in approximately 5% of the symptomatic patients [1]. These patients meet criteria for sepsis [2,3]. Additionally, bacterial co-infection or secondary infection can aggravate the condition and perpetuate organ dysfunction [4,5]. In this narrative review, we discuss the concept that COVID-19 with organ dysfunction is sepsis, the importance of co-infection and secondary infections, and the severity of sepsis in COVID-19 patients.

SEVERE CORONAVIRUS DISEASE 2019 IS SEPSIS

According to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), sepsis is a 'life-threatening organ dysfunction caused by a dysregulated host response to infection' [6]. Sepsis can be caused by several pathogens, such as bacteria, viruses, fungi, or parasites. In COVID-19 sepsis, the causative agent is the SARS-CoV-2.

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KEY POINTS

- Severe COVID-19 meets the Sepsis-3 criteria and should be considered as viral sepsis.
- The role of co-infection is not yet defined but secondary infection seems to play a major role in morbidity mainly in resource-poor setting.
- COVID-19 mortality is high and disparity are present around the world with initial data showing that, as previously reported for endemic sepsis, mortality in low-income and middle-income countries is higher compared with high-income countries.
- The ICU strain, the incidence of HAI, and organizational aspects are important modifiable factors that determine mortality.

Although there is undoubtedly direct viral toxicity, a dysregulated host response to infection is also present [2]. Although there is controversy about the role of the ‘cytokine storm’ in the pathogenesis of COVID-19, there is clearly an increase in the proinflammatory cytokines and chemokines including tumor necrosis factor (TNF), interleukin 1a (IL-1a), interleukin 6 (IL-6), granulocyte-colony-stimulating factor, interferon gamma-induced protein-10, monocyte chemoattractant protein-1, and macrophage inflammatory proteins-1 [7[■]]. The deregulated inflammatory response together with the direct virus damage lead to endothelial cell activation. Given the pivotal role of these cells in maintaining homeostasis and in the control of vascular permeability and coagulation, the dysregulation of these processes contributes to the generation of thrombotic disorders and further compromise in oxygen delivery leading to organ dysfunction [8[■]]. Although the most concerning clinical feature of COVID-19 is acute respiratory distress syndrome requiring mechanical ventilation [9], it can also result in several extrapulmonary manifestations [10[■]]. Severe cases can progress to organ dysfunction syndrome (MODS) including distributive shock, coagulation abnormalities, renal injury, neurological and cardiac dysfunction may ensue both because of the direct viral toxicity as to the nonhomeostatic host response to viral infection. In fact, MODS accounts for most of the deaths from COVID-19 [11,12].

Sepsis is an umbrella term, which describes a clinical syndrome caused by different infectious agents that share common mechanisms of disease but significant differences exist and contribute to specific clinical manifestations and complications [13[■]]. Thus, patients with COVID-19 share pathophysiological and clinical features already described

in patients with sepsis, including long-term disabilities [14,15]. However, some peculiarities are present, such as lymphopenia or relative lymphopenia, hypoxemia in the presence of almost normal lung compliance and a profound COVID-19-induced coagulopathy affecting not only the microcirculation but also resulting in large vessel thrombosis and major thromboembolic complications [16,17]. Viral sepsis and death in COVID-19 can occur in otherwise healthy individuals of any age but predominantly occurs in adults with advanced age or with underlying medical comorbidities [1]. As with bacterial sepsis, biological and medical heterogeneity of the patients affect the multifaceted host response to infection, leading to different spectrum of disease severity and clinical presentations. Subphenotypes have been described in critically ill patients with COVID-19 [18].

Different from bacterial and fungal sepsis, specific therapy directed to the causative agent is still substantially less effective for COVID-19, being one of the potential explanations for the high mortality in patients with severe forms of the disease [19]. However, whichever the infectious agent is, once established, MODS has high mortality. The best management of COVID-19 sepsis should not be focused only on respiratory failure but supportive care and monitoring [20[■]]. It is important to assure the maintenance of tissue perfusion and infection control to interrupt the pathogenesis of MODS, in addition to prevention of iatrogenic complications including secondary infection until recovery occurs.

CO-INFECTION AND SECONDARY INFECTIONS

Bacterial infections, especially *Streptococcus pneumoniae* and *Staphylococcus aureus*, and even viral or fungal co-infections, have been commonly reported in previous epidemic and pandemic outbreaks of viral respiratory infections, such as influenza. During the H1N1 pandemic influenza in 2009, bacterial co-infection was identified in 30% of cases admitted to ICUs [21]. Bacterial complications are associated with a higher severity of illness and use of healthcare resources, and increased risk of death [22,23].

Mechanisms by which viral infections, including SARS-Co-V-2, may predispose to concomitant and secondary bacterial infections involve the damage of respiratory airways and simultaneously defects in both innate and acquired immune response providing a favorable environment for bacterial growth, adherence, and invasion into healthy sites of the respiratory tract [17,19,24].

Data regarding coinfections and secondary infections in COVID-19 pneumonia are emerging.

There are several published articles, ranging from letters to the editor to systematic reviews and meta-analyses [23,25]. Co-infection and secondary infection are distinct clinical entities, although used interchangeably in medical literature and clinical practice. Although both are present in COVID-19, the issue of secondary infection and multidrug resistance are of greater concern. Langford *et al.* demonstrated in a living meta-analysis and systematic review the presence of co-infection in 3.5% (95% CI 0.4–6.7%) and secondary infection in 14.3% (95% CI 9.6–18.9%) of patients with COVID-19 [23]. When pooling all included studies, the proportion of COVID-19 patients with bacterial infection was 6.9% (95% CI 4.3–9.5%), ranging from 5.9% in hospitalized patients to 8.1% in critically ill patients. Despite an overall low rate of bacterial infections, over 70% of patients received antibiotics, suggesting overuse. Specific species of bacterial co-pathogens were reported in 11 of 24 studies (45.8%), representing a low isolating proportion of less than 14% of the patients with reported infections. The most common organisms reported were *Mycoplasma* spp. ($n = 11$ patients), *Haemophilus influenzae* ($n = 5$ patients), and *Pseudomonas aeruginosa* ($n = 5$ patients) [23].

In a recent preprint systematic review and meta-analysis, including 48 articles, the pooled prevalence of co-infection was 12% (95% CI 6–18%) and of superinfection was 14% (95% CI 9–21%), with the highest prevalence of 17% (95% CI 1–43%) among ICU patients. Among those with co-infections, the three most frequently identified bacteria were *Strep. pneumoniae* (17.9%), *Klebsiella pneumoniae* (16.7%) and *Haemophilus influenzae* (12.4%). The three most frequently identified viruses among co-infected patients were Influenza type A (8.1%), Rhinovirus (6.3%) and non-SARS-CoV-2 coronaviruses (3.7%). For fungi, only *Candida* spp. (0.7%) and *Mucor* spp. (0.7%) were identified. Among those with secondary infections, the three most frequently identified bacteria were *Acinetobacter* spp. (22%), *Escherichia coli* (18%) and *Pseudomonas* (16%). The only reported virus was Human Metapneumovirus (4%) and for fungi only *Candida* spp. (14%) was identified [25].

However, there is conflicting data. Several studies evidenced high incidence of bacterial secondary infection and sepsis because of HAI in COVID-19 patients [5,26^{***},27–29]. A review by Lai *et al.* reported that the prevalence of COVID-19-associated secondary infections could be as high as 50% among nonsurvivors [28]. In a multicenter retrospective analysis of prospectively collected data including 774 adult patients with severe COVID-19 in 8 Italian hub hospitals, 359 (46%) patients

developed 759 hospital-acquired infections (44.7 infections/1000 ICU patient-days) [26^{***}]. The authors reported a high prevalence of multidrug-resistant (MDR) bacteria (35% of all isolated agents). As expected, ventilator-associated pneumonia (VAP) (389, 50%), bloodstream infections (183, 34%), and catheter-associated bloodstream infections (CABSI) (74, 10%) were the most frequent HAIs. Gram-negative bacteria (especially Enterobacteriaceae) and *Staph. aureus* caused 64 and 28% of VAPs. The vast majority of the patients, 534 (69%) received at least one antibiotic at admission, of them 240 (44.9%) were broad-spectrum antibiotics. HAIs prolonged mechanical ventilation and hospitalization, and HAIs complicated by septic-shock almost doubled mortality [26^{***}].

There is no robust data from low-income and middle-income countries (LMICs) regarding HAIs in COVID-19 patients. A systematic review reported 44% of nosocomial infection in these patients in China suggesting that the impact might be greater than in developed countries [29]. Previous data already suggested that the rates for HAI are higher in resource-poor settings. In non-COVID patients, data from the International Nosocomial Infection Control Consortium (INICC) clearly show higher rates for CABSI, VAP and catheter-associated urinary tract infections [30]. These findings suggest that there is a lower infection risk in countries with higher socioeconomic level. Considering the level of ICU strain throughout the pandemic, the situation of LMIC is worrisome. The burden of COVID-19 exposed important healthcare deficits around the world. Over-crowding in ICUs, temporary ICU beds, lack of trained and experienced healthcare workers, low nurse-to-patient staffing ratios, burnout syndrome, insufficient medical equipment and supplies, antibiotics stewardship personnel workload, infection prevention resource diversion may contribute to increased rates of healthcare-associated infections, antibiotic overuse, and increased multidrug resistance.

SEVERITY OF SEPSIS IN CORONAVIRUS DISEASE 2019 PATIENTS

Regardless of the causative agent of sepsis, the virus or a bacterial coinfection or secondary infection, the patients with severe COVID-19 present a phenotype of multiorgan dysfunction that leads to death in an unacceptable high percentage of the patients. A recent systematic review including 32 studies showed the prevalence of several organ dysfunctions and support in COVID-19 patients. As expected, respiratory support was

the main life-sustaining therapy in ICU patients admitted with COVID-19, with high-flow nasal therapy being used by 20% of the patients, noninvasive ventilation by 25.5% and almost 60% of the patients being under invasive mechanical ventilation. Extracorporeal membrane oxygenation was used in only 2.5% of the cases. Nearly 30% of the cases had hemodynamic dysfunction and 16.6% of the patients needed renal replacement therapy [31[■]].

Until now, no specific severity score for ICU patients with COVID-19 was developed and validated; however, almost all studies in critically ill patients reported the SOFA score on admission. Gupta *et al.* [32[■]] showed that the PaO₂/FiO₂ ratio, liver and renal dysfunction as described in SOFA score were associated with mortality. Interestingly, in this study, the authors found that shock and coagulation dysfunction on day 1 were not related to mortality. There was a clear association between respiratory dysfunction and death; however, the concomitant presence of other dysfunctions, such as cardiovascular and acute kidney injury significantly increased the risk of death [31[■],33].

There are conflicting data on the mortality of COVID-19 critical patients [31[■],34]. Early data from China showed mortality rates in critical ill patients ranging from 14 to 61% [32[■]]. In Italy, Grasselli *et al.* [4] reported an ICU mortality around 25%. Data from United States of America showed that almost one in each four patients died after ICU admission [34]. Serafim *et al.* [31[■]] analyzed 65 383 ICU admissions from several countries and reported an ICU mortality of 32%; however, when considering only mechanically ventilated patients, the mortality was 59%. Karagiannidis *et al.* reported an in-hospital mortality in ventilated patients requiring dialysis of 73% in Germany [33]. There is also lack of robust data on the causes of death. Although ARDS has a high mortality rate, death because of refractory hypoxemia is reportedly rare. Even in cohorts of ARDS patients treated in the 1990s, less than 20% of death were because of refractory hypoxemia, being most of the deaths secondary to multiorgan failure [35]. Reported causes of deaths in COVID-19 patients are scarce but differently from non-COVID-19 ARDS respiratory failure seems to play a major role. Small studies reported respiratory failure as cause of death in 53% [36] and 45% [37] of the cases with smaller percentage of the patients dying from shock and multiorgan failure. Ketchum *et al.* evaluated the cause of death from 82 COVID-19 patients. The authors reported that the most common organ dysfunction prior to death were pulmonary (81.7%), neurologic (57.3%), and renal (39%). Interestingly, septic shock was present in 40.2%

cases. However, septic shock was considered the primary cause of death only in 26.8% [38[■]]. Gupta *et al.* [32[■]] analyzed the cause of death from 787 patients and found that 92.7% of them died from respiratory failure; however, almost 40% also had septic shock.

One possible explanation for the inconsistency in the mortality rates and in the causes of death might be the influence of health disparities in the outcomes of COVID-19 patients as previously reported for sepsis. A recent systematic review estimated that the sepsis mortality rate for hospitalized patients is 26.7%, being 41.9% for ICU-treated sepsis [39]. However, as there is a paucity of data coming from LMICs, these numbers might be underestimating the sepsis burden as data from these settings showed higher mortality rates [40–42]. In a recent analysis from the Global Burden of Disease Study based on death certificates, Rudd *et al.* demonstrated that sepsis incidence and mortality varied substantially across regions with higher rates in countries with lower sociodemographic index. The highest burden was found in sub-Saharan Africa, Oceania, south Asia, east Asia, and southeast Asia [43]. In the current pandemic, disparities related to socioeconomic status have also been demonstrated. Ranzani *et al.* in a retrospective study over 250 000 hospital admissions in Brazil evidenced a high incidence of mortality in patients admitted to ICU (55%) and even higher for those submitted to invasive mechanical ventilation (80%). This study also demonstrated that the mortality was influenced by regional disparity in health system [44[■]]. Kurtz *et al.* [45] reported a trend in mortality reduction possibly related with more liberal use of noninvasive respiratory support (e.g. noninvasive ventilation and high nasal flow catheter), resources with variable availability in Brazilian ICUs [46]. Disparities were also reported in developed settings. Recently, Chuperk *et al.* found significant interhospital variation in mortality for critically ill patients with COVID-19 in United States. This variation was mostly explained by hospital-level socioeconomic status, strain, and physiologic differences [47[■]].

Disparities might influence some of the major determinants of mortality in COVID-19 ICU patients. Secondary infections and the consequent bacterial sepsis multiorgan dysfunction syndrome seem to be one of the major causes of death in patients with prolonged ICU stay under mechanical ventilation, at least in resource poor settings. A higher incidence of HAI is expected with a higher ICU strain, characterized by overcrowded ICU, inadequate staffing, lack of supplies, and inadequate antibiotics stewardship leading to a higher

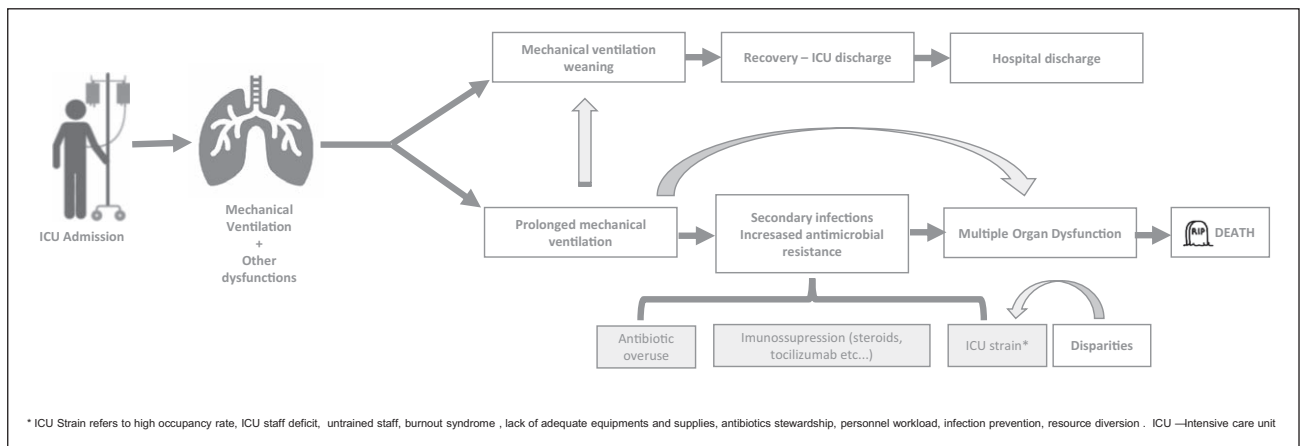


FIGURE 1. Possible trails related to death in mechanically ventilated coronavirus disease 2019 critically ill patients.

incidence of HAI, and these factors are influenced by disparities in healthcare. In addition, COVID-19 patients can have infection complications from treatments, such as immunosuppression from corticosteroids or tocilizumab. Multidrug resistance can arise as a consequence of antibiotics overuse. The current ICU strain also exposes patients to other serious adverse events that might increase the risk of death [48]. Figure 1 presents the possible trails to death in COVID-19 patients. Therefore, it is of utmost importance to deliver the best evidenced-based care for these patients to avoid additional damage [49]. HAI prevention with the use of validated bundles and antimicrobial stewardship, the early diagnosis and proper management of secondary infections are necessary to reduce the impact of sepsis derived from secondary infections. Similarly, quality improvement initiatives aiming to reduce the gap between evidence-based medicine and bedside management should be implemented. Recent studies demonstrate that the use of quality improvement interventions is associated with improved outcomes in LMICs [50].

CONCLUSION

The severe forms of COVID-19 should be considered as viral sepsis. More data about co-infection and secondary bacterial infections is necessary mainly from resource-limited settings. Mortality rates for COVID sepsis either caused by the virus or complicated by secondary infection is high. Notwithstanding the severity of the viral disease, the ICU strain, the incidence of HAI, and organizational aspects are important factors that determine mortality. These factors are influenced by disparities, which can contribute to the variability in outcomes worldwide. HAI prevention, the use of evidenced-based treatment, and the proper management of sepsis

through quality improvement are important initiatives to improve outcomes.

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Conflicts of interest

There are no conflicts of interest.

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