Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHEST

Coronavirus Disease 2019 Sepsis

A Nudge Toward Antibiotic Stewardship

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Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection; such infections can be caused by bacteria, fungi, or in the case of coronavirus disease 2019 (COVID-19), a virus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]). In bacterial sepsis, which is the most common variety, early and appropriate antibiotics are crucial to decrease mortality rates and the progression to more severe forms of disease.[1]

Severe COVID-19 frequently is characterized by multiorgan failure that includes hypotension and shock, acute respiratory failure, acute kidney injury, coagulation abnormalities, and others. Both bacterial sepsis and COVID-19 lead to similar patterns of multiorgan failure. Because SARS-CoV-2 is an infecting organism, it is logical to conclude that severe COVID-19 is indeed sepsis that is caused by SARS-CoV-2.

When bacteria are the causative organism, most patients improve with oral antimicrobials, and only a few patients experience sepsis or more severe forms that require aggressive inpatient care. In the case of COVID-19, some patients are asymptomatic; others experience mild symptoms, and only a small fraction progress to severe COVID-19. A key difference between viral sepsis and either bacterial or fungal sepsis is that, for most viral infections, specific therapies are substantially less effective than antibacterial or antifungal agents. Specific to the current pandemic, remdesivir shortens the duration of illness for survivors but does not improve survival. We believe that this inability to alter the infectious burden exogenously results in the necessity for care that is principally supportive. It potentially explains the high mortality rate of patients with severe COVID-19 who required invasive mechanical ventilation in early reports, a lethality higher than expected for severe ARDS related to sepsis of another cause.

COVID-19 can be said to be sepsis with no highly effective antimicrobial therapy. Although we are unlikely to ever see a trial that will compare antibiotics vs no antibiotics in bacterial sepsis, Kumar et al[2] provided the closest evidence to that scenario. The mortality rate of patients with septic shock who received inappropriate antimicrobials bordered 90%; those patients who received appropriate antibiotics had a fivefold mortality rate reduction. The mortality rate of the inappropriate antibiotic group is similar in magnitude to the 88% mortality rate reported in patients with severe COVID-19 on mechanical ventilation. The patients with COVID-19 could not receive appropriate antimicrobials because such therapy for SARS-CoV-2 did not exist.

No currently active physician has practiced in an era without antibiotics to treat bacterial infections, but the circumstance that we describe brings to mind reports from that era. Before the advent of penicillin, pneumococcal pneumonia conferred an 84% mortality rate in patients ≥70 years old; bacteremic pneumonia in that age group was uniformly fatal.[3] Antibiotics were not the only medical treatment lacking; ICUs, mechanical ventilation, and the ability to assess for VTE or disseminated intravascular coagulation were nonexistent. However, it is highly likely that, without antibiotics, these other technologies could be only partially effective.

Recognizing that there are unique aspects of SARS-CoV-2 infection, just as there are unique aspects of infection

ABBREVIATIONS: COVID-19 = coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

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with many bacteria, it is possible that the current COVID-19 pandemic provides a glimpse of what patient care future could look like if we fail to stem the rising tide of antimicrobial resistance. Given the high number of infections caused by multi-drug resistant organisms (2.8 million cases and >3,500 attributable deaths each year),[4] it is not far-fetched that, in the future, there could be no available drugs to appropriately treat bacterial infections. For instance, in 2019, there were 200,000 cases and >9,000 deaths caused by extended-spectrum β-lactamase organisms; these numbers reflect a 50% increase compared with comparable estimates in 2013. In addition, the need to treat extended-spectrum β-lactamase infections with carbapenems is likely to raise the rates of resistance to this antibiotic class over time.[5] The emergence of *Candida auris*, a highly resistant fungus, represents a threat for patients in ICUs. This pathogen was isolated in >300 patients in 2019, which is a significant and worrisome growth in incidence that has tripled in the few years since it was first reported in the United States in 2013. This organism has demonstrated resistance to all antimicrobial classes that are used to treat fungal infections, and it is associated with a very high mortality rate.

We consider COVID-19 a reminder that reinforces the need for and the practice of antibiotic stewardship by physicians and health systems. Without effective antibiotics, most sepsis care becomes purely supportive. There is, however, a good side to understanding that we are dealing with viral sepsis and subsequent ARDS, which is that supportive care is more effective than it was in the pre-antibiotic era. Intensivists understand more principles of early recognition, mechanical ventilation, renal replacement therapy, nutrition, and VTE prophylaxis. With time and the application of best practices, survival of critically ill patients with COVID-19 is improving.

Regarding antimicrobial resistance, infection control efforts are demonstrably effective, which should promote compliance with these initiatives by ICU clinicians. Over time, the rates of carbapenem-resistant *Acinetobacter baumannii*, multi-drug resistant *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant Enterococcus have all declined.[4,5] The rates of *C difficile* infection, a marker of indiscriminate use of antibiotics, are also declining. These are all reasons to strengthen resolve and to continue to apply the best evidence-based treatments for both COVID-19 and for antimicrobial resistant organisms.

COVID-19 is sepsis caused by SARS-CoV-2, a virus for which there is little in the way of antimicrobial therapy. Because it is sepsis, known tenets of sepsis care and organ support must be our guiding principles. Surprisingly, a key lesson that we must take from the war on this viral sepsis is that we must redouble our efforts to be stewards of antimicrobials and ensure that we have adequate means to control bacterial and fungal infection. Moreover, it is critical that high priority be given to randomized controlled trials that are testing drugs to treat SARS-CoV-2 and the ensuing sepsis. As we face subsequent waves of this plague, patients will do better if we are both able and prepared to provide more than just supportive care.

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