Open Forum Infectious Diseases
PERSPECTIVES

Meeting the Challenges of Sepsis in Severe Coronavirus Disease 2019: A Call to Arms

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Sepsis is a life-threatening organ dysfunction that is caused by a dysregulated host response to infection. Sepsis may be caused by bacterial, fungal, or viral pathogens. The clinical manifestations exhibited by patients with severe coronavirus disease 2019 (COVID-19)-related sepsis overlap with those exhibited by patients with sepsis from secondary bacterial or fungal infections and can include an altered mental status, dyspnea, reduced urine output, tachycardia, and hypotension. Critically ill patients hospitalized with severe acute respiratory syndrome coronavirus 2 infections have increased risk for secondary bacterial and fungal infections. The same risk factors that may predispose to sepsis and poor outcome from bloodstream infections (BSIs) converge in patients with severe COVID-19. Current diagnostic standards for distinguishing between (1) patients who are critically ill, septic, and have COVID-19 and (2) patients with sepsis from other causes leave healthcare providers with 2 suboptimal choices. The first choice is to empirically administer broad-spectrum, antimicrobial therapy for what may or may not be sepsis. Such treatment may not only be ineffective and inappropriate, but it also has the potential to cause harm. The development of better methods to identify and characterize antimicrobial susceptibility will guide more accurate therapeutic interventions and reduce the evolution of new antibiotic-resistant strains. The ideal diagnostic test should (1) be rapid and reliable, (2) have a lower limit of detection than blood culture, and (3) be able to detect a specific organism and drug sensitivity directly from a clinical specimen. Rapid direct detection of antimicrobial-resistant pathogens would allow targeted therapy and result in improved outcomes in patients with severe COVID-19 and sepsis.

In this Perspective paper, we identify unmet needs in the management of sepsis in critically ill patients with COVID-19 and present strategies to improve patient outcome. A discussion of the burden of sepsis from an epidemiologic and personal perspective is followed by a review of the pathophysiology of sepsis and the rationale for early detection and therapeutic intervention especially in patients at high risk of becoming septic. People most at risk include individuals living in disadvantaged and underserved minority communities. The most immediate measures that may improve patient outcome are the implementation of molecular detection systems that rapidly identify viral, bacterial, and fungal pathogens in the bloodstream.

THE NATIONAL AND GLOBAL BURDEN OF SEPSIS

Sepsis is a life-threatening organ dysfunction that is caused by a dysregulated host response to infection and is responsible for at least 1 in 3 hospital deaths. When an infection progresses to sepsis, organ dysfunction ensues. Sepsis kills approximately 350 000 Americans annually (270 000 hospital deaths and an additional 80 000 to 100 000 deaths of patients discharged to inpatient hospice) [1–3] and claims more lives than the top 3 cancers combined (lung, colorectal, breast) [4]. In a study of Medicare beneficiaries, sepsis was recognized to be the costliest hospital inpatient condition [5].

Sepsis is a leading cause of death that imposes a heavy financial burden on all countries. For example, there are an estimated 4 million annual cases in Europe resulting in 680 000 deaths per year. The United States spends an estimated $62 billion annually on sepsis treatment, making it the most expensive in-hospital therapeutic cost [6]. The global burden of sepsis, from any cause, is estimated to be 50 million cases per year and is the cause of 1 in 5 deaths, with a disproportionate number being from low- to middle-income countries [7].

Septic shock in patients is a subset of sepsis in which underlying abnormalities in hemodynamics and cellular metabolism are profound enough to substantially increase mortality [8]. For each hour of delay in providing appropriate therapy, survival decreases by 7.6% [9]. Sepsis is a severe health hazard requiring timely and appropriate therapy.

SEPSIS IS PERSONAL

Sepsis in a patient is more than a statistic; for those affected, it is life changing. The

Received 28 July 2022; editorial decision 22 November 2022; accepted 29 November 2022; published online 1 December 2022

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https://doi.org/10.1093/ofid/ofac645

personal experience in 2018 of one of the authors (RAB) illustrates this point. After sustaining a thumb puncture wound from a rose thorn while working in his garden, he did what most would do—he ignored it and attributed it to the cost of being a gardener. That changed quickly as his thumb and hand began to swell and become painful. A trip to a free-standing emergency center resulted in the administration of an oral broad-spectrum antibiotic. His situation soon worsened and a trip to the Emergency Room ensued. After an infectious disease consultation, more broad-spectrum antibiotics were administered intravenously, and he was admitted for monitoring. Deterioration continued even as the antibiotics flowed. Although he was being treated, the treatment regimen proved to be inappropriate and ineffective because the causative organism was not correctly identified, nor was its susceptibility to antimicrobials accurately determined in a timely fashion.

The delay in diagnosis led to the development of life-threating sepsis because accurate microbial identification and susceptibility determination required days. Ultimately, a regimen of intravenously administered vancomycin followed by a step down of 21 days of oral clindamycin proved to be effective and lifesaving.

PATHOPHYSIOLOGY OF SEPSIS AND SEVERE CORONAVIRUS DISEASE 2019

A brief review of the pathophysiology of sepsis underscores the rapidity of potentially lethal multisystem organ damage and the need for rapid initiation of antimicrobial therapy guided by accurate microbiological diagnosis. The immune system of septic patients responds to pathogen-associated molecular patterns, which activate innate host defenses to destroy intruding pathogens. When responding to overwhelming sepsis, the immune system may become hyperactivated, contributing to tissue injury, multisystem failure, and death.

Microbial pathogens also inflict direct injury to host cells by eliciting inflammation that compromises local circulation and produces organ damage. Both organism-mediated injury and host inflammatory damage contribute to the release of host molecules, known as danger-associated-molecular-patterns. Danger-associated-molecular-patterns, such as fibronectin, heat shock proteins, uric acid, and ATP, are molecules within cells that are released from damaged host cells that paralyze immune response to microbial pathogens [10].

At the intracellular level, both Gram-negative and Gram-positive bacterial pathogens, as well as *Candida* spp, trigger the release of nuclear factor-kappa B (NF-κB). The NF-κB proteins are dimeric, sequence-specific, transcription factors involved in the activation of an exceptionally large number of genes in response to inflammation, viral and bacterial infections, as well as other physiologically stressful events [11]. Once transferred to the nucleus, NF-κB proteins initiate transcription of immunomodulatory cytokines including interleukin (IL)-1β, IL-10, and tumor necrosis factor (TNF)α.

Release of these proinflammatory and immunomodulatory cytokines leads to the increased production of prostaglandins, proteases, leukotrienes, and oxidative metabolites from phagocytic cells. These inflammatory mediators lead to microvascular coagulopathy and multisystem tissue injury. Sepsis-related pulmonary injury results from a combination of cytokine release, interstitial and intra-alveolar fluid accumulation, as well as extravasation of neutrophils into the interstitial and alveolar spaces.

The symptoms exhibited by COVID-19 sepsis in patients overlap with those experienced by those with sepsis from secondary bacterial or fungal infections and can include altered mental status, dyspnea, reduced urine output, tachycardia, hypotension [12], and multisystem failure [13]. The development and implementation of rapid diagnostics is imperative for distinguishing the overlapping clinical manifestations sepsis and of COVID-19.

Beltrán-García et al [12] underscored the parallels in patients between sepsis and severe COVID-19; these include fever, leukopenia, hypotension, thrombocytopenia, coagulopathy, microthrombosis, and hemolytic anemia. Both conditions are characterized by increased proinflammatory cytokine production, including IL-6, IL-1β, IL-2, IL-8, IL-17, and TNFα. Sepsis and COVID-19 inflammatory response also may result in respiratory failure, multiorgan dysfunction syndrome, hyperbilirubinemia, decreased glomerular filtration rate, hypoalbuminemia, immune dysregulation, and predisposition to opportunistic infections.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-triggered hyperactivation of the lectin pathway of complement has been reported to cause hypocomplementemia and a dysfunctional adaptive immune response, greatly diminishing both microbial killing via the membrane attack complex and clearance by opsonization [14]. In recent studies of patients suffering from acute severe COVID-19, researchers found that secondary hypocomplementemia rendering activation of the antibody-dependent classic pathway inactive and significantly decreasing serum bactericidal activity may be a critical mechanism underlying the predilection for bacterial sepsis. Despite the presence of patient serum antibodies against *Klebsiella pneumoniae*, serum bactericidal activity and complement opsonization of *K pneumoniae* were decreased in sera of patients with acute COVID-19 as the result of reduced complement functional activity (CH_{50}). These data support the hypothesis that complement consumption and secondary hypocomplementemia in the early phase of severe COVID-19 is an important risk factor for secondary bacterial infections.

BURDEN OF SEPSIS IN CORONAVIRUS DISEASE 2019

Critically ill patients hospitalized with SARS-CoV-2 infections are at increased

risk for secondary bacterial and fungal infections [14–22]. Little et al [18] reported that patients with COVID-19 suffered a mortality rate of 15.8% compared with the 4.1% of patients hospitalized with influenza. Patients hospitalized with COVID-19 are at a 22% increased risk of developing sepsis and 113% more likely to go on to develop septic shock compared with patients hospitalized with influenza. This cascade of disease progression may be prevented with rapid and accurate diagnostic and therapeutic interventions.

Among the earliest studies of sepsis in patients afflicted with COVID-19, Zhang et al [16] observed that within a cohort of patients with COVID-19 admitted to the ICU in a single university hospital in Wuhan from January 2, 2020 to February 10, 2020, 22 (58%) of 38 patients with severe COVID-19 developed secondary infections, including bloodstream, respiratory, and urinary infections. Gram-negative bacilli constituted 50% of these infections. These secondary infections contributed to a higher mortality rate than among patients who did not have secondary infections. Among the 221 patients studied, 16 (7.2%) had invasive mechanical ventilation (IMV) and 10 (4.5%) had IMV plus extracorporeal membrane oxygenation (ECMO). However, among those patients with severe COVID-19, patients with IMV and IMV plus ECMO constituted 29.1% and 18.2%, respectively.

Puzniak et al [19] conducted a multicenter analysis of the clinical microbiology and antimicrobial usage in patients hospitalized in the United States with or without COVID-19, between March 1 and May 31, 2020, at 241 acute care hospitals in the BD Insights Research Database. There were 17 003 patients (12%) with bloodstream infections (BSIs), 24% of whom were in the intensive care unit (ICU). The most common organisms causing BSI were *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans*, and *Pseudomonas aeruginosa*, *K pneumoniae*, and *Enterococcus faecalis*. Patients with COVID-19 suffered higher rates of hospital-onset infections, antimicrobial usage, as well as increased hospital and ICU length of stays.

Nucci et al [20] found an increased incidence of candidemia in patients admitted to a tertiary care hospital during the height of the COVID-19 pandemic. Two periods were compared: January 2019 to February 2020 (period 1) and March to September 2020 (period 2). Forty-one episodes of candidemia were documented, including 16 in period 1 and 25 in period 2 (9 patients with COVID-19). The incidence of candidemia (per 1000 admissions) was 1.54 in period 1 (pre-COVID-19) versus 7.44 in period 2 (COVID-19) ($P < .001$).

A systematic review and meta-analysis reported by Landsbury et al [21] of coinfections in patients with COVID-19 consisted of 30 studies and 3834 patients. A bacterial coinfection was found in 7% (95% confidence interval [CI], 3%–12%) with a higher proportion of ICU patients having bacterial coinfections than those in mixed ward/ICU settings (14%; 95% CI, 5–26).

In assessing risk factors for secondary BSIs and outcomes in 375 patients hospitalized with severe COVID-19, Bhatt et al [22] conducted a multicenter, case-control study and found that 34% of patients (128) suffered BSIs, including 117 (91.4%) bacterial and 7 (5.5%) fungal, with the most common organisms being *Staphylococcus epidermidis*, *S aureus*, *E faecalis*, *E coli*, *C albicans*, and *Candida glabrata*.

CONVERGENCE OF RISK FACTORS FOR MORTALITY IN SEPSIS AND SEVERE CORONAVIRUS DISEASE 2019

The same risk factors that may predispose to sepsis and poor outcome from BSIs converge in patients with severe COVID-19. Advanced age, diabetes mellitus, obesity, immunocompromised conditions, antineoplastic therapy, hematological malignancies, transplantation, and other immune impaired conditions increase the risk for sepsis in patients hospitalized with severe COVID-19.

SEPSIS, CORONAVIRUS DISEASE 2019, AND HEALTH CARE INEQUITY

By improving the outcome of sepsis, the disparate outcomes from COVID-19 in historically disadvantaged minorities may also be improved. Although the United States spends more per capita on healthcare than any other developed country [23], that care is not distributed equitably [24]. The United States consistently has among the highest disparities across a diverse set of self-reported health and healthcare measures. The people at greatest risk of being underserved often live in areas of geographic isolation with persistent shortages of healthcare providers. Underserved people frequently have lower socioeconomic status, lower levels of educational attainment, cultural and social differences, and lack health insurance [25]. The underserved inhabit remote rural areas as well as inner cities; they include ethnic minorities, prisoners, the poor, elderly, homeless, marginalized, physically challenged, and mentally challenged individuals.

Indigenous Americans, Pacific Island Americans, and Black Americans have the highest mortality rates from COVID-19 infections [26]. Healthcare disparity plays a role in explaining the disproportional burden. Healthcare inequity is most obvious in "healthcare deserts", which is defined as geographic areas where needed medical, behavioral, mental, dental, and/or pharmaceutical healthcare services are extremely limited or altogether unavailable [27]. The key to understanding healthcare deserts is the distinction between "availability" of care and "access" to care. The former without the latter creates a desert. The degree to which these disparities impact upon sepsis in critically ill patients with severe COVID-19 is unknown.

RESPONSE TO SEPSIS IN CORONAVIRUS DISEASE 2019

The European Society of Intensive Medicine, Global Sepsis Alliance, and

the Society of Critical Care Medicine in a recent report proposed that increasing the awareness of sepsis in COVID-19 may be a vehicle by which the global burden of sepsis can be reduced [28]. The standards of care for sepsis management include volume resuscitation, antimicrobial agents, anticoagulation, hemodynamic support, oxygen/ventilatory support, and renal replacement therapy. Timing of initiation of antimicrobial agents is critical in sepsis. As noted above, each hour of delay in appropriate treatment increases mortality at an estimated 7.6%. The duration of hypotension before initiation of effective therapy is a critical determinant of survival in septic shock [9].

Current diagnostic standards for distinguishing between (1) patients who are critically ill, septic, and have COVID-19 and (2) patients with sepsis from other causes leave healthcare providers with 2 suboptimal choices. The first choice is to empirically administer broad-spectrum, antimicrobial therapy for what may, or may not, be sepsis. Such treatment may not only be ineffective and inappropriate, but it also has the potential to cause harm. The harm can take the form of allowing the disease to progress, causing adverse or allergic drug reactions, increasing the risk of *Clostridioides difficile* diarrhea, and/or fostering the development of antimicrobial resistance (AMR) and multiple drug-resistant organisms. The second choice is to wait for an accurate diagnosis from blood cultures and susceptibility profiles. Although this course would ensure more appropriate and targeted therapy, obtaining the "gold standard" blood cultures takes 24–72 hours or longer, depending upon the pathogen. These 2 suboptimal approaches pinpoint the problem and highlight the need to develop better and more rapid diagnostics for patients with sepsis.

ANTIMICROBIAL RESISTANCE

The emergence of AMR is a global problem that, according to the World Health Organization and the World Bank, threatens our ability to successfully treat bacterial infections [29]. The reported incidence of deaths from AMR is 1.27 million/year but the actual number is likely to be much higher. The lives lost and the costs incurred are projected to result in a 3.8% reduction in annual gross domestic product by 2050. Despite this ominous mortality related to AMR, there remains a paucity of new antimicrobial agents with novel targets [30].

A systematic review and meta-analysis of patients with COVID-19 during the first 18 months of the pandemic from November 2019 to June 2021 documented a pooled prevalence of coinfection of 24% ((95% CI, 8%–40%) with AMR in bacterial and fungal pathogens [31]. The development of better testing to identify and characterize AMR will guide more accurate therapeutic interventions and reduce the selection evolution of new antibiotic-resistant strains.

RAPID MICROBIAL DIAGNOSTICS

The need for rapid microbial diagnostics for early sepsis detection and treatment is essential. Such rapid testing ideally would be conducted at the bedside and would offer a significant advantage over current blood culture testing that requires days to complete and frequently delays the administration of appropriate life-saving therapy. In the absence of point-of-care detection of pathogens causing sepsis, rapidly available laboratory-based diagnostic data may guide initial empirical antimicrobial therapy.

The current gold standard for the detection of sepsis-causing pathogens is a blood culture that requires approximately 24–72 hours for completion [32]. Effective treatment of sepsis requires a timelier intervention. There are numerous nonspecific biomarkers that are elevated or prolonged in patients with sepsis, including the white blood cell count, serum lactate level, C-reactive protein level, procalcitonin level, prothrombin time and partial thromboplastin time, platelet count, and d-dimer levels [33–35]. Although these tests are valuable in management of patients with severe COVID-19, they may yield abnormal results in a wide range of inflammatory, infectious, or disease conditions.

The ideal rapid diagnostic test would (1) be rapid and reliable, (2) have a lower limit of detection (LOD) than blood culture, and (3) be able to detect a specific organism directly from a clinical specimen. The LOD is the smallest amount of an analyte that can reliably be detected; LOD is also referred to as analytic sensitivity. In practical terms, LOD is the lowest level of analyte that can be statistically distinguished from a blank sample [36].

Rapid microbial diagnostics are critical to improving the management of patients by providing key working data to distinguish between sepsis caused by bacteria or fungi versus SARS-CoV-2 versus a combination of the 2. There are numerous US Food and Drug Administration (FDA)-approved molecular diagnostic tests for detecting sepsis-causing pathogens; some are culture independent [37–42].

The procalcitonin test detects host response to pathogens and is useful in distinguishing viral from bacterial infection [39]. There are also culture-dependent rapid diagnostic tests that rely on blood culture results before they can be leveraged, such as matrix-assisted laser desorption ionization time-of-flight mass spectrometry, real-time multiplex polymerase chain reaction (PCR), and in situ hybridization [40–42].

Among other culture-independent systems for detection of bacteremia and candidemia that provide rapid detection are magnetic resonance (T2 Biosystems), metagenomic shotgun sequencing, nucleic acid amplification tests (NAATs), and non-NAATs, including assays for detection of (1→3)-β-D-glucan, as well as mannan antigen/antibody. Currently available rapid molecular systems for diagnosis of sepsis include SeptiTest-UMD CE IVD, MicroDx UMD, SeptiFast, Magicplex Sepsis Real-Time test (Seegene), Accelrate Pheno platform, and T2MR.

The T2MR platform is the only FDA-approved, rapid culture-independent molecular system that identifies common bloodborne bacterial and fungal pathogens directly from blood within 3–5 hours. Based upon 2 large pivotal studies, these detectable pathogens include *S aureus, E faecium, E coli, K pneumoniae, and P aeruginosa*, as well as the common medically important *Candida* spp: *C albicans*, *C tropicalis*, *C parapsilosis*, *C glabrata*, and *C krusei* [43, 44].

Several commercial systems have also streamlined and partly automatized the follow-up of antimicrobial susceptibility testing from positive blood cultures. Systems such as the Vitek and Microscan instruments perform automated turbidity measurement for multiwell liquid cultures. The BD Phoenix system applies a redox indicator to enhance the detection of organism growth. These systems have turnaround times as short as 4 hours for identification and 6–8 hours for susceptibility testing [45]. The CE-marked Alfed 60 AST system (Alifax S.r.l., Via F. Petrarca, 2/1,35020 Polverara PD, Italy) uses sensitive laser-light-scattering technology to detect bacterial growth in a liquid culture broth and provides antimicrobial susceptibility results directly from positive blood culture bottles within 4–6 hours.

A REAL-WORLD PERSPECTIVE

This paper began at the bedside with the perspective of one of our authors and now concludes with that of another, MWM. He has cared for more than 2000 patients with COVID-19 and estimates that approximately 20% of patients with severe COVID-19 who are admitted to an intensive care unit will develop sepsis. The challenges are distinguishing the clinical manifestations of sepsis versus those of COVID-19 and often warrant the empirical use of broad-spectrum antimicrobial agents with further adjustment pending results of blood, respiratory secretions, and urine. Hospitalization may result in repeated exposure to antimicrobial agents for suspected sepsis. The development of more point-of-care assays or rapid clinical microbiological assays will greatly improve targeted therapy, reduce unnecessary antimicrobial exposures, reduce adverse events, reduce emergence of resistant pathogens, and strengthen stewardship.

Rapid diagnostic tests have the potential to improve outcomes for patients with sepsis and severe COVID-19. However, having improved diagnostics and technologies available will not solve the problem in and of themselves. Healthcare providers and patients should be educated about their value and that the improved technologies be incorporated into medical practice. The challenges are many, but they can be addressed. The first step is to raise awareness of the ubiquity of sepsis as a cause of morbidity and mortality in hospitalized patients. Next, an empirical approach to therapeutics can evolve to targeted therapy based upon rapidly available and more accurate data. Finally, rapid diagnostics must be deployed for use and be accessible for use across all segments of the healthcare system. Doing so will shorten the lag from time of exposure to appropriate and targeted therapy, reduce the likelihood of administration of unnecessary drugs, and improve outcome. Healthcare costs will be lowered simply by eliminating the administration of unnecessary and ineffective drugs. Shortened hospital length of stay will free up hospital beds and ease staffing shortfalls. Targeted, effective therapy will reduce the probability of developing AMR. The challenges of dealing with sepsis and SARS-CoV-2 are substantial, but the rewards for doing so are much greater.

Early clinical bedside recognition and targeted treatment of potentially infected foci in patients with wounds, peripheral or central venous catheter insertion sites, or secondary onset bacterial pneumonia may prevent a catastrophic septic event.

Ginsburg and Klugman [46], in their prescient essay written in 2020, warned of the potential for emergence of antimicrobial resistance in patients with COVID-19 pneumonia. They further underscored the diagnostic challenges of recognizing secondary bacterial pneumonia and recommend a multitiered COVID-19 diagnostic strategy that incorporates point-of-care tools to identify those at risk. The evidence-based guidelines from the Dutch Working Party on Antibiotic Policy recommended a duration of 5 days of antimicrobial therapy in patients with proven or suspected secondary bacterial pneumonia in hospitalized patients with COVID-19, while monitoring symptoms, signs, and inflammatory biomarkers, thereby minimizing unnecessary antibiotic exposure in this complicated setting [47]. Pickens et al [48] recommended against the guideline-based empirical administration of antimicrobial agents at the time of intubation in patients requiring mechanical intubation for COVID-19, emphasizing that treatment should be determined by laboratory assessment of bronchoalveolar lavage (BAL) fluid.

Rapid microbial diagnostics performed on sputum, tracheal aspirates, and BAL fluid may complement culture-based laboratory methods to afford early targeted treatment of secondary pneumonias and prevent sepsis. For example, the BioFire FilmArray Pneumonia Panel Plus (BFPP), which is a multiplexed PCR system with a turnaround time of approximately 1 hour, detects 27 hospital-associated bacterial and viral respiratory pathogens and 7 antimicrobial resistance genes [49]. The Unyvero Lower Respiratory Tract Panel also uses a rapid multiplexed PCR system with diagnostic yield under 5 hours for detection of 19 common bacterial causes of hospital-acquired pneumonia, 10 antimicrobial resistance genes, and, uniquely, *Pneumocystis jirovecii* [50].

Consistent with these pressing unmet needs in the care of critically ill patients with sepsis and COVID-19, the Centers for Disease Control and Prevention (CDC) [51] recently reported that

antimicrobial-resistant, hospital-related infections increased by 15% from 2019 to 2020. During this period of initial onslaught of the pandemic, infections caused by carbapenem-resistant *Acinetobacter* spp increased by 78%, multidrug-resistant *P aeruginosa* increased by 32%, carbapenem-resistant Enterobacterales increased by 35%, antifungal-resistant *Candida auris* increased by 60%, and other resistant *Candida* spp increased by 26%. The need for new technologies to rapidly detect these pathogens from blood and other specimens as a guide to initial antimicrobial therapy is essential for improved outcome.

CONCLUSIONS

In this Perspective, we reviewed the burden of bacterial and fungal sepsis from epidemiological and personal viewpoints. We highlighted the convergence of risk factors and clinical manifestations of severe COVID-19 and sepsis posing a daunting bedside challenge to accurate diagnosis. Although administration of broad-spectrum antimicrobial therapy in the absence of a microbial diagnosis is the standard of care in the empirical management of sepsis, the strategy is also associated with adverse events and selection of resistant pathogens. In response, we further underscore the CDC's call for adoption and implementation of early and accurate microbial diagnosis to guide targeted, initial, antimicrobial therapy.

Acknowledgments

Financial support. TJW was funded in part by the Henry Schueler Foundation (Chicago, IL) and the Save Our Sick Kids Foundation (Milwaukee, WI). RAM was funded by the American Medical Association Foundation (Chicago, IL) and the WBB Research Institute ([WBBRI] Cranford, NJ). The WBBRI also provided a forum for discussion of the public health implications of coronavirus disease 2019 and bacterial and fungal sepsis and assisted in the sponsorship and funding of this report.

Potential conflicts of interest. TJW has received grants for experimental and clinical antimicrobial pharmacology, therapeutics, immunopharmacology, and microbial diagnostics to his institutions from Allergan, Amplyx, Astellas, Lediant, Merck, Medicines Company, Scynexis, Shionogi, T2 Biosystems, Tetraphase, and Viosera; and he served as consultant to Amplyx, Astellas, Allergan, ContraFect, Gilead, Karyopharm, Leadiant, Medicines Company, Merck, Methylgene, Partner Therapeutics, Pfizer, Scynexis, Shionogi, Statera, and T2 Biosystems. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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