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SUPPLEMENT ARTICLE

Sepsis Perspective 2020

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Sepsis is defined as a dysregulated immune response to infection affecting millions of individuals per year and carries high morbidity and mortality rates even if appropriate care is provided [1, 2]. In the United States, sepsis is considered the most common cause of inpatient death, affecting 1.7 million adults per year and contributing to 270 000 deaths [3]. Globally, there were an estimated 49 million cases of sepsis in 2017 [4]. Sepsis incidence and mortality rates varied significantly by region. Furthermore, sepsis can be difficult to accurately diagnose, is a diverse clinical syndrome, and there is no reference standard for diagnosis. Subjectivity in determining whether an infection is present and whether organ dysfunction is due to infection can be challenging.

After hospitalization, survivors can be too ill to return to their homes or work and may require ongoing care in venues such as skilled nursing facilities. In addition, cognitive impairment and functional disability can be major consequences, adding significantly to societal health care costs and productivity. Iwashyna et al demonstrated that severe sepsis in this older population was independently associated with substantial and persistent new cognitive impairment and functional disability among survivors. The magnitude of these new deficits was significant, likely resulting in a critical downturn in patients' ability to live independently [5]. Rosendahl et al [6] documented the risk of psychological symptoms in not just survivors, but also spouses.

Sepsis also ranks in the top 10 of principal diagnoses leading to readmission. Multiple studies document up to a 26% risk of readmission. These readmissions were frequently due not just to infection but also to other acute conditions and seemed to result in substantially increased morbidity and mortality rates [7, 8].

Sepsis can also be very expensive to treat, with total inpatient hospital and skilled nursing facility admission counts, costs, and mortality rates increasing over time from calendar year 2012 to calendar year 2018 in Medicare beneficiaries [9]. The total cost of inpatient hospital admissions including an explicit sepsis code for those beneficiaries in those calendar years rose from $17 792 657 303 to $22 439 794 212. The total cost of skilled nursing facility care in the 90 days after an inpatient hospital discharge for Medicare Part A/B rose from $3 931 616 160 to $5 623 862 486 over that same interval.

Over the past 2 decades, the Surviving Sepsis Campaign (SSC) has released several guidelines aimed at standardizing and improving the management of patients with severe sepsis and septic shock. These guidelines have helped raise sepsis awareness and triggered numerous quality improvement initiatives around the world [10]. In 2013, the New York State Department of Health began a mandatory state-wide initiative to improve early recognition and treatment of severe sepsis and septic shock [11]. The Centers for Medicare & Medicaid Services' SEP-1 measure has appropriately established sepsis as a national priority for quality improvement. SEP-1 was first implemented in October 2015 and requires hospitals to report their bundled performance rates to Centers for Medicare & Medicaid Services as part of the Inpatient Quality Reporting Program. This is a condition of payment, and results are publicly available.

While the Infectious Diseases Society of America (IDSA) supports SSC and SEP-1 for making sepsis care a national priority, IDSA chose not to endorse the 2016 version of the SSC guidelines. IDSA's reasons included the guidelines' failure to acknowledge the uncertainty and subjectivity that frequently confound a diagnosis of sepsis, the guidelines' conflation of sepsis and septic shock, overly aggressive recommendations for sustained combination therapy for gram-negative septic shock, and unclear guidance on measuring adherence to time-to-antibiotics [12]. Several of these concerns also apply to SEP-1 but are amplified by the powerful influence of national quality measures on clinician prescribing and hospital behavior. IDSA recently published a Position Paper outlining several recommendations aimed at reducing the risk of unintended consequences of SEP-1 while maintaining focus on its evidence-based elements [13]. IDSA's core recommendation is to limit SEP-1 to septic shock, where the evidence supports the benefit of immediate antibiotics. Prompt empiric antibiotics are often appropriate for suspected sepsis without shock, but IDSA believes there is too much heterogeneity and difficulty defining this population, uncertainty about the presence of infection, and insufficient data on the necessity

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of immediate antibiotics to support a mandatory treatment standard for all patients in this category. This position paper is endorsed by the American College of Emergency Physicians, Pediatric Infectious Diseases Society, Society for Healthcare Epidemiology of America, Society of Hospital Medicine, and Society of Infectious Disease Pharmacists.

In this supplement to *The Journal of Infectious Diseases,* we offer 10 articles with the goal of presenting the science and complexity on the diagnosis and treatment of sepsis. Shappell et al [14] summarize the strengths and weaknesses of common approaches to sepsis surveillance. An objective surveillance definition is crucial in making meaningful comparisons, tracking quality improvement efforts and outcomes. Tawfik and colleagues [15] remind us of the complex interplay between various parts of the immune response. These investigators developed an immune profiling panel consisting of 16 biomarkers. These biomarkers can be integrated into a molecular multiplex platform that will enable clinicians in the future to more precisely manage critically ill patients.

Gilbert [16] reviews a commonly available biomarker, procalcitonin (PCT), and discusses PCT biology, interpretation of elevated serum PCT levels, and the advantages of measuring serum PCT in septic patients. He also presents a list of topics that need additional study. Eubank et al. [17] discuss the role of rapid diagnostics in the diagnosis and treatment of patients with sepsis. They conclude that these advances hold tremendous promise in increasing diagnostic yield, decreasing turnaround time, and improving outcomes when integrated into robust antimicrobial stewardship programs. Weinberger et al [18] review published articles assessing the evidence concerning time-to-antibiotics and mortality. As they point out, most of these relate to observational cohort studies that have key limitations and biases. This article helps us understand the true relationship between time-to-antibiotics and mortality for patients with suspected sepsis and septic shock.

Strich and colleagues [19] provide guidance on empiric antimicrobial therapy in an era of increasing antimicrobial resistance. They suggest using local antibiograms, risk for resistant infection including prior colonization or infection with a multidrug-resistant organism, recent antimicrobial therapy, severity of illness, and if infection is community or hospital onset. Once a clinician decides to start antimicrobial therapy for sepsis in critically ill patients, selection and dosing are essential to improve outcomes. Phe et al [20] discuss using pharmacokinetic and pharmacodynamic principles to achieve optimal dosing. They highlight significant physiological alterations that can alter the usual kinetics and variability of antimicrobial agents, including using therapeutic drug monitoring to achieve target goals.

Busch and Kadri [21] review appropriate duration of treatment for patients with serious infections. They highlight the consequences of unnecessary antimicrobial exposure. Guidance regarding duration of therapy in sepsis is surprisingly limited. The challenge is that many published trials on duration exclude critically ill patients. As they point out, potential challenges to shorter duration of therapy in sepsis include source control, treatment of multidrug-resistant organisms, and the alterations in pharmacokinetic and pharmacodynamic discussed by Phe et al [20]. McCreery et al [22] discuss the current knowledge of sepsis in immunocompromised patients, the diagnostic and therapeutic challenges, and the diverse microbial pathogens.

Finally, Winslow and Swenson [23] review unintended consequences of the current sepsis mandates. They highlight that the mandate to rapidly start broad-spectrum antimicrobial agents within a specified time frame, especially for patients who are not in shock, can result in overuse of broad-spectrum antimicrobial therapy. This can lead to increased resistance, increased adverse effects, and increased risk of *Clostridioides difficile.* They correctly point out that unlike guidelines, mandates such as SEP-1 reduce the time clinicians have to review diagnostics and therapeutic strategies appropriate for an individual patient that can lead to overuse and misuse of broad-spectrum antibiotics.

I believe the this supplement will provide a valuable resource to the Infectious Diseases community.

Note

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