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 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

Sepsis is a critical, life-threatening condition typically triggered by bacterial infections. [1, 2] It represents a complex response from the body's immune system, leading to potential organ dysfunction or failure. In 2016, the traditional systemic inflammatory response syndrome (SIRS) criteria were supplanted by the quick Sequential Organ Failure Assessment (qSOFA), which facilitates rapid bedside evaluation of organ dysfunction in patients suspected of having an infection. The qSOFA score is determined by three criteria: a respiratory rate of ≥22 breaths/min, a systolic blood pressure (BP) of ≤100 mm Hg, and an altered level of consciousness. A score >2 is linked to unfavorable outcomes. However, due to inconsistent data regarding its diagnostic utility, qSOFA has been deprioritized in the 2021 sepsis guidelines, regarded more as a predictive tool than a definitive diagnostic measure. [3, 4, 5]

For completeness, severe sepsis is characterized as sepsis accompanied by organ dysfunction. [1, 2] The definitions of sepsis and septic shock were updated in 2001 and 2021 by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine. [3, 6] Among the most commonly utilized scoring systems are the qSOFA and the National Early Warning Score (NEWS). The NEWS is calculated based on respiration rate, oxygen saturation, systolic BP, pulse rate, level of consciousness or confusion, and temperature. Scores range from 0-4 (low risk), 5-6 (medium risk), and ≥7 (high risk for sepsis-associated mortality). [3] Early identification scores, including NEWS, Modified Early Warning Score (MEWS), and SIRS, demonstrate greater reliability and predictive capability compared to the qSOFA.

Multiple organ dysfunction syndrome (MODS) is characterized by progressive organ dysfunction in a severely ill patient, with failure to maintain homeostasis without intervention such as pressors or IV fluids. It is the end stage in infectious conditions (sepsis, septic shock) and noninfectious conditions (eg, SIRS due to pancreatitis). The greater the number of organ failures, the higher the mortality risk, with the greatest risk associated with respiratory failure requiring mechanical ventilation.

MODS can be classified as primary or secondary. [7] Primary MODS is the direct result of identifiable injury or insult with early organ dysfunction (eg, renal failure due to a nephrotoxic agent or liver failure due to a hepatotoxic agent).

Secondary MODS is organ failure that has no attributable cause and is a consequence of the host's response (eg, acute respiratory distress syndrome [ARDS] in individuals with pancreatitis).

The following parameters are used to assess individual organ dysfunction:

Respiratory system: Partial pressure of arterial oxygen (PaO2)/fraction of inspired oxygen (FiO2) ratio

Hematology: Platelet count, coagulation panel (prothrombin time and partial thromboplastin time)

Liver: Serum bilirubin

Renal: Serum creatinine (or urine output)

Brain: Glasgow coma score

Cardiovascular: Hypotension and vasopressor requirement

Septic shock is defined as sepsis with hypotension requiring vasopressor therapy to maintain a mean blood pressure of more than 65 mm Hg and a serum lactate level exceeding 2 mmol/L (18 mg/dL) after adequate fluid resuscitation. [4] This has a greater risk for mortality and long-term morbidity.

Pseudosepsis is defined as fever, leukocytosis, and hypotension due to causes other than sepsis. Examples might include the clinical picture seen with salicylate intoxication, methamphetamine overdose, or bilateral adrenal hemorrhage.

Etiology

Sepsis can be caused by an obvious injury or infection or a more complicated etiology such as perforation, compromise, or rupture of an intra-abdominal or pelvic structure. [8] Other

etiologies can include meningitis, head and neck infections, deep neck space infections, pyelonephritis, renal abscess (intrarenal or extrarenal), acute prostatitis/prostatic abscess, severe skin or skin structure infections (eg, necrotizing fasciitis), postsurgical infections, or systemic infections such as rickettsial infection. A more detailed discussion of sepsis etiology in various organ systems is provided in Etiology.

Clinical Presentation

Individuals with sepsis may present with localizing symptoms related to a specific site or source of infection or may present with nonspecific symptoms. Individuals with nonspecific symptoms usually are acutely ill with fever and may present with or without shaking chills. Mental status may be impaired in the setting of fever or hypotension. Patients with bacteremia from any source often display an increased breathing rate resulting in respiratory alkalosis. The skin of patients with sepsis may be warm or cold, depending on the adequacy of organ and skin perfusion. A detailed history and physical examination is essential in determining the likely source of the septic process. This helps the clinician to determine the appropriate treatment and antimicrobial therapy.

See Clinical Presentation, History and Physical Examination, and Treatment for more detail.

Diagnosis

A diagnosis of sepsis is based on a detailed history, physical examination, laboratory and microbiology testing, and imaging studies. [1, 2, 3]

Laboratory studies that may be considered include the following:

Complete blood count (CBC) - May show elevated or low white blood cell count, anemia, and/or thrombocytopenia

Chemistry studies, such as markers of liver or kidney injury - May suggest organ dysfunction

Bacterial cultures - Blood cultures and site-specific cultures based on clinical suspicion (eg, wound culture, sputum culture, or urine culture)

Stained buffy coat smears or Gram staining of peripheral blood - May be helpful in certain infections

Urine studies (urinalysis, microscopy, urine culture)

Certain biomarkers, such as procalcitonin [9, 10, 11] and presepsin [12] - May be useful in diagnosing early sepsis and in determining prognosis

Imaging modalities should be focused on areas of clinical concern, based on the history and physical examination, and may include the following:

Chest radiography (to rule out pneumonia and diagnose other causes of pulmonary infiltrates)

Chest CT scanning (to further evaluate for pneumonia or other lung pathology)

Abdominal ultrasonography (for suspected biliary tract obstruction)

Abdominal CT scanning or MRI (for assessing a suspected non-biliary intra-abdominal source of infection or delineating intrarenal and extrarenal pathology)

Site-specific soft tissue imaging, including ultrasonography, CT scanning, or MRI (to assess for possible abscess, fluid collection, or necrotizing skin infection)

Contrast-enhanced CT scanning or MRI of the brain/neck (to assess for possible masses, abscess, fluid collection, or necrotizing infection)

The following cardiac studies may be useful if cardiac involvement or disease is suspected as a cause or complication of infection:

Electrocardiography (ECG) to evaluate for conduction abnormalities or delays or arrhythmias; pericarditis may be a cause of “pseudosepsis”

Cardiac enzyme levels

Echocardiography to evaluate for structural heart disease

Invasive diagnostic procedures that may be considered include the following:

Thoracentesis (in patients with pleural effusion)

Paracentesis (in patients with ascites)

Drainage of fluid collections/abscesses

Bronchoscopy with washing, lavage, or other invasive sampling (in patients with suspected pneumonia)

See Workup for more detail.

Management

Initial management may include the following [3] :

Inpatient admission or ICU admission for monitoring and treatment

Initiation of empiric antibiotic therapy, to be followed by focused treatment based on culture, laboratory, and imaging data

Supportive therapy as necessary to maintain organ perfusion and respiration; timely intervention with infection source control, hemodynamic stabilization, and ventilatory support

Transfer if requisite facilities are not available at the admitting hospital

Appropriate empiric antimicrobial therapy depends on adequate coverage of the presumed pathogen(s) responsible for the septic process, potential antimicrobial resistance patterns, and patient-specific issues such as drug allergies or chronic medical conditions. Tying sites of infection to specific pathogens should occur, as follows:

Intravenous line infections: Consider broad-spectrum coverage for gram-positive organisms, especially methicillin-resistant Staphylococcus aureus (MRSA) (linezolid, vancomycin, or daptomycin) and gram-negative nosocomial pathogens (especially Pseudomonas species and other Enterobacteriaceae [piperacillin-tazobactam, carbapenems, or cefepime]), and line removal. Some of these may be Candida infections.

Biliary tract infections: Typical bacterial agents include Enterobacteriaceae, gut-associated anaerobes, and Enterococcus. Consider carbapenems, piperacillin-tazobactam,

cephalosporins, or quinolones in combination with an anaerobic agent such as metronidazole.

Intra-abdominal and pelvic infections: Typically Enterobacteriaceae, gut-associated anaerobes, or Enterococcus (carbapenems, piperacillin-tazobactam, or cephalosporins or quinolones in combination with an anaerobic agent such as metronidazole)

Urosepsis: Typically Enterobacteriaceae or Enterococcus (carbapenems, piperacillin-tazobactam, cephalosporins, quinolones, or aminoglycosides)Pneumococcal sepsis: Third-generation cephalosporins, respiratory quinolone (levofloxacin or moxifloxacin), carbapenem, or vancomycin if resistance is suspected

Sepsis of unknown origin: Meropenem, imipenem, piperacillin-tazobactam, or tigecycline; metronidazole plus levofloxacin, cefepime, or ceftriaxone may be alternativesEarly surgical evaluation for presumed intra-abdominal or pelvic sepsis is essential. Procedures that may be warranted depend on the source of the infection, the severity of sepsis, and the patient's clinical status, among other factors.

Once an etiologic pathogen is identified, typically via culture, narrowed antibiotic therapy against the identified pathogen is appropriate (eg, penicillin for penicillin-susceptible Streptococcus pneumoniae).