Sepsis and Septic Shock – Basics of diagnosis, pathophysiology and clinical decision making

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INTRODUCTION

As of 2017, the World Health Organization has made the recognition, prevention, and management of sepsis a global health priority.1 Hippocrates considered the term

KEYWORDS

- Critical care
- Sepsis
- Septic shock
- SIRS
- qSOFA
- Vasopressors

KEY POINTS

- The definition of sepsis has evolved over time. Most recently, the term “sepsis” has been defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
- There are several screening tools available to identify sepsis, including the SIRS (Systemic Inflammatory Response Syndrome) criteria and the qSOFA (quick Sequential Organ Failure Assessment) score. These tools have imperfect sensitivity and specificity and should be used carefully.
- The septic state affects nearly every organ system and can lead to profound derangements in physiology and laboratory findings.
- Management of sepsis relies on early identification and empiric antimicrobial therapy, adequate but not excessive fluid resuscitation, and support of hemodynamic goals with vasopressors.
- Several classes of vasopressors are available, including catecholamines, vasopressin, and renin-angiotensin-aldosterone agonists. Norepinephrine has been suggested as the initial vasopressor of choice; however, multimodal vasopressor therapy may be useful to avoid deleterious effects of high-dose monotherapy.

INTRODUCTION

As of 2017, the World Health Organization has made the recognition, prevention, and management of sepsis a global health priority.1 Hippocrates considered the term
“sepsis” as a process of rotting flesh, and recently, it has been defined as life-threatening organ dysfunction resulting from infection.1 Despite best efforts at protocol-based care pathways, mortality from septic shock remains high at nearly 35% to 40%.2

**Sepsis-1: Systemic Inflammatory Response Syndrome Criteria**

The term “sepsis” had been used broadly for decades; however, it had been associated with multiple definitions, and the term had been loosely applied to many syndromes. In an effort to improve the ability to study sepsis, a convention of experts met in 1992 and formalized the definition of the term.3 At that time, the term “sepsis” was defined as an inflammatory response to infection. The clinical diagnosis was defined by 2 or more Systemic Inflammatory Response Syndrome (SIRS) criteria paired with a suspected or confirmed source of infection.4 Septic shock was defined at this time as persistent hypotension or hyperlactatemia despite fluid resuscitation.

**Sepsis 2.0 and “Severe Sepsis”**

Many criticisms arose regarding the Sepsis-1 definitions, most notably that the SIRS criteria merely reflected an appropriate response to infection. A new term had emerged, “severe sepsis,” which implied organ dysfunction as a result of the sepsis state. In 2001, a second expert group convened to update the Sepsis-1 definitions.5 The definitions were left largely unchanged, with the exception of the introduction of the Sequential Organ Failure Assessment (SOFA) criteria to identify organ dysfunction, which was indicative of severe sepsis (Table 1).

**2016 Update: Sepsis 3.0**

The initial definition specified in the Sepsis-1 criteria was widely used for almost 2 decades; however, it was hindered by poor sensitivity and specificity. A main criticism is that the physiology implied by the SIRS criteria (tachycardia, fever, leukocytosis, and hypotension) are focused on the inflammatory response, which is common to many critical illnesses (trauma, pancreatitis, postsurgical inflammation).6 To illustrate, more than 90% of patients admitted to an intensive care unit (ICU) met the criteria for sepsis.7 Another criticism is that the SIRS criteria failed to identify 13% of patients with similar profiles of infection, organ failure, and substantially increased mortality.8

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<td><strong>Comparison of older and new definitions for the spectrum of sepsis and septic shock</strong></td>
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Because the inflammatory response is an expected and useful response in many cases of infection, a challenge for a new definition of sepsis was to differentiate the life-threatening, dysregulated response present with sepsis from the normal inflammatory response of uncomplicated infection. In 2016, the Sepsis Task Force again updated the definition to be the pattern of life-threatening organ dysfunction caused by a dysregulated host response to infection.\(^9\)

Clinically, this was characterized by an acute change of 2 or more points in the SOFA score in the setting of suspicion for infection.\(^9,10\) The baseline score is assumed to be 0 in patients not known to have preexisting organ dysfunction. The SOFA score had a good predictive validity for mortality of patients in the ICU. For patients with suspected infection, the area under the receiver operating characteristic (AUROC) is 0.74. This number is superior to the SIRS criteria, which has an AUROC of 0.66.\(^9\)

Under this new definition, the term “severe sepsis” is redundant. Accordingly, this term was dropped from the updated definition. Septic shock was defined as the subset of sepsis with profound circulatory, cellular, and metabolic dysregulation, and associated with a much higher mortality of \(\sim 40\%\), compared with the 10% mortality observed with sepsis.\(^9,11\) Septic shock is clinically identified as a persistent hypotension requiring vasopressors to keep mean arterial pressure (MAP) greater than 65 mm Hg and elevated serum lactate greater than 2 mmol/L, \(\text{despite}\) adequate fluid resuscitation.

**Quick Sequential Organ Failure Assessment Screening Tool**

Although the change in SOFA score is a robust mortality stratification tool, it is cumbersome to calculate and requires laboratory values that are not readily available for quick screening of patients outside of the ICU. For example, a serum lactate level that is routinely analyzed from a blood gas sample in the ICU may be difficult to do on a ward patient and on a serial basis. The task force set out to identify readily accessible screening measures and arrived at 3 criteria, termed the qSOFA (quick Sequential Organ Failure Assessment). For patients outside of the ICU who had 2 or more of the following criteria: Glasgow score less than 13, systolic blood pressure less than 100 or respiratory rate (RR) \(\geq 22\), mortality was similar to those patients identified using the full SOFA score.\(^9\)

**Performance of Quick Sequential Organ Failure Assessment Versus Sequential Organ Failure Assessment Versus Systemic Inflammatory Response Syndrome for Screening**

Subsequent studies have highlighted the need for careful use of the tools for different patient populations. As a screening tool for emergency department (ED) patients, multiple studies have shown worse performance of qSOFA compared with SIRS for early identification of sepsis.\(^12–14\) As a prognostic risk stratification tool of ICU patients, the SOFA score better predicted mortality.\(^14\) A systematic review found similar results; the SIRS criteria had better sensitivity but worsened specificity for the detection of sepsis among ED, ICU, and hospital wards patients.\(^15\)

**EPIDEMIOLOGY**

In the United States, there are currently \(\sim 1.7\) million cases of sepsis per year, a trend that has been increasing annually. There are almost 250,000 deaths per year owing to sepsis, and it is the leading cause of death in noncardiac ICUs.\(^16,17\)

Of septic patients admitted to ICUs worldwide, the most common source of infection is the lungs (64%), abdomen (20%), bloodstream (15%), and urinary tract (14%).
Of isolated organisms, 62% were gram-negative bacteria; 47% were gram-positive bacteria, and 19% were fungi. The most common gram-positive organism is *Staphylococcus aureus* (20%), and the most common gram-negative isolates are *Pseudomonas* (20%) and *Escherichia coli* (16%).

Many factors are associated with increased risk of mortality in patients with sepsis and septic shock: emergency surgery (odds ratio [OR] 1.56), trauma (OR 1.01), transfer from hospital floor (OR 1.37), presence of chronic obstructive pulmonary disease (OR 1.21), cancer (OR 1.33), heart failure (OR 1.45), immunosuppression (OR 1.81), cirrhosis (OR 2.14), previous mechanical ventilation (OR 1.90), or hemodialysis (OR 1.58).

**PATHOPHYSIOLOGY**

The pathophysiology underlying the septic state is complex. It is unclear why some patients mount a productive immune response to fight infection, whereas others deteriorate into a dysregulated state. The role of several cellular mediators has been investigated, especially tumor necrosis factor-α and interleukin-1, which can reproduce the sepsis symptoms when administered exogenously. It was previously thought that sepsis was the result of a “cytokine storm” of these mediators; however, it has since been shown that release of proinflammatory mediators is also accompanied by anti-inflammatory mediators.

It is also known that exogenous administration of lipopolysaccharide (LPS) leads to endothelial damage and shedding of the endothelial glycocalyx. This mechanism leads to the hyperpermeability and edema formation that are seen with sepsis. LPS also causes the release of nitric oxide (NO) from damaged endothelial cells, which leads to pathologic arteriodilation and hypoperfusion. Conversely, exogenous inducible nitric oxide synthase inhibitors appear to reverse the pathologic vasodilation in animal models.

**CLINICAL MANIFESTATIONS BY ORGAN SYSTEM**

The presenting signs and symptoms of sepsis often involve multiple organ systems. Profound release of various inflammatory mediators during sepsis leads to multiorgan system failure (Fig. 1). Hence, sepsis needs to be managed as a systemic disorder.

**Cardiovascular**

Pathologic arterial and venodilation leads to hypotension, which can be profound. In addition, myocardial depression is observed in up to 60% of septic patients. The exact mechanism of this septic cardiomyopathy is unclear. Mildly elevated troponin levels are commonly observed and can be linked to severity of sepsis.

**Pulmonary**

Cytokine-mediated lung injury results in increased permeability of alveolar and capillary endothelium, causing noncardiogenic pulmonary edema, which impairs oxygenation and ventilation. Development of hypoxia and metabolic acidosis results in significant tachypnea. The incidence of acute respiratory distress syndrome (ARDS) in patients with sepsis is 7%. Careful monitoring of respiratory parameters is key in identifying patients who will require intubation and mechanical ventilation because of respiratory muscle fatigue.

**Renal**

Sepsis-related acute kidney injury (AKI) contributes significantly to morbidity and mortality of sepsis. Risk factors for the development of AKI are advanced age,
chronic kidney disease, and cardiovascular disease. The pathophysiology is multifactorial, including hemodynamic changes, endothelial dysfunction, inflammation of the renal parenchyma, and obstruction of tubules with necrotic cells and debris. Prompt volume resuscitation, preventing hypotension and avoiding the use of nephrotoxic agents, such as intravenous contrast, can help mitigate the risks of developing AKI. Once AKI has developed, appropriate dosing of medications, avoiding volume overload by the use of diuretics, and careful management of electrolytes are required. In patients requiring renal replacement therapy, there appears to be benefit to early initiation over delayed initiation.

**Hematological**

The primary hematological manifestations are anemia, leukocytosis, neutropenia, thrombocytopenia, and disseminated intravascular coagulation (DIC). Inhibition of thrombopoiesis and immunologic platelet damage are responsible for the thrombocytopenia observed without DIC. Anemia is secondary to inflammation, shortened red blood cell survival, and hemolysis in the setting of DIC. DIC is diagnosed by thrombocytopenia, and prolongation of prothrombin time or activated partial thromboplastin time. DIC in sepsis can present as bleeding from multiple sites or thrombosis of small
and medium blood vessels. In the absence of bleeding, coagulopathy can be monitored along with treatment of underlying disorder. In patients with bleeding from multiple sites, platelet and coagulation factor replacement should be considered.33

**Gastrointestinal**

Liver failure is an uncommon but significant complication of septic shock, occurring in less than 2% of septic patients, with a marked impact on morbidity and mortality.35 Septic hepatic dysfunction is diagnosed by an increase in bilirubin concentration greater than 2 mg/dL and coagulopathy with international normalized ratio greater than 1.5.36 The pathophysiology is attributed to hemodynamic, cellular, molecular, and immunologic changes leading to parenchymal hypoxia. Clinical manifestations include hypoxic hepatitis, sepsis-induced cholestasis, coagulopathies, and hyperammonemia, causing hepatic encephalopathy.37

**Endocrine**

Hyperglycemia is common in septic patients and is attributed to stress-induced elevation of glucagon, catecholamines, cortisol, and growth hormone–combined insulin resistance induced by the release of cytokines.38 Glucose should be frequently monitored in septic shock, with the goal of keeping blood glucose less than 180 mg/dL, while avoiding overaggressive control and associated hypoglycemic episodes.36 In addition to metabolic dysregulation, 8% to 9% of patients with severe sepsis have evidence of adrenal insufficiency, which can further contribute to catecholamine insensitivity.39 Management with exogenous steroids is discussed separately. Septic patients also have vasopressor deficiency due to depletion of stores, increased vasopressinase activity, and nitric oxide–mediated inhibition of vasopressin production.40 The hypothalamic-pituitary-thyroid axis can also be affected during sepsis, leading to apparent clinical hypothyroidism; however, there is no evidence favoring the treatment of septic hypothyroidism.38,41

**Neurologic**

Septic encephalopathy is a common manifestation of severe sepsis and septic shock. Symptoms can include changes in mental status, alteration in sleep/wake cycle, disorientation, agitation, and hallucinations. Altered mental status may be the only presenting sign in geriatric patients. Focal deficits are not typical of septic encephalopathy and should be evaluated with neuroimaging and stroke workup. Seizure is a rare complication of septic encephalopathy and may be diagnosed with electroencephalographic monitoring.42 In the event of significant alterations in mental status, some patients may require endotracheal intubation for airway protection. Other reversible causes of encephalopathy, such as hypoxemia, hypercapnia, hypoglycemia, hyponatremia or hypernatremia, drug toxicity, hyperammonemia, and thyroid insufficiency, should be rapidly assessed and ruled out.25

**MANAGEMENT OF SEPSIS AND SEPTIC SHOCK**

**Era of Early Goal-Directed Therapy**

In 2001, a landmark trial was published that demonstrated mortality benefit to “early goal-directed therapy” (EGDT), which used an algorithm of fluid resuscitation, blood transfusion, vasopressors, and inotropes to targeted specific hemodynamic goals of MAP, central venous pressure, and mixed venous oxygen saturation.43 This trial ushered in an era of sepsis care in which pulmonary artery catheters were routinely placed in most septic patients to monitor these parameters.
More recent trials have failed to replicate the results of EGDT, and the practice of algorithmic resuscitation has mostly fallen out of favor. However, many of the principles of fluid resuscitation and hemodynamic goals still remain in place and are reflected in the Surviving Sepsis Campaign guidelines.

**Screening and Diagnosis**

If concern for sepsis is elevated based on screening criteria (qSOFA or SIRS) and clinical picture, initial management should not be delayed while awaiting further diagnostic studies. Blood cultures should be drawn promptly, and urine cultures should be collected if there is suspicion for urinary tract infection. Imaging should usually include a chest X-ray to rule out developing pneumonia, and further imaging, such as abdominal computed tomographic scan if there is suspicion for intraabdominal process (eg, diverticulitis, abscess). Procalcitonin levels may be drawn early in the process, not to act as a diagnostic criterion, but to later guide antibiotic cessation for certain infections.

**Antibiotics and Source Control**

Observational studies have suggested that early initiation of antibiotic therapy may be associated with better outcomes, and this idea has been incorporated into the Surviving Sepsis Guidelines as a goal of initiation of antibiotics within 1 hour of presentation. There is concern that these data are not robust, and that this guideline will lead to widespread inappropriate utilization of antibiotics. When there is adequate suspicion for sepsis, cultures should be obtained and broad-spectrum antibiotic therapy should be initiated to empirically cover a range of likely pathogens, dependent on the patient’s comorbidities and presentation. In most patients, antibiotics should be directed toward gram-positive and gram-negative bacteria. In patients with an intraabdominal process, anaerobic coverage is indicated. In patients with immunodeficiencies or immunosuppression, antifungal and/or antiviral therapies may be indicated.

The antimicrobial therapy should be narrowed based on the results of cultures, as able. Serial procalcitonin measurements have been shown to successfully guide cessation of antibiotic therapy to reduce cumulative exposure.

The source of the infection should be addressed if possible. The patient should be closely examined for a localized source, such as infected pressure ulcer or erythematous vascular catheter site. Management may include removal of invasive devices (eg, dialysis catheters, infected orthopedic hardware, or pacemakers) or surgical evacuation of intraabdominal abscess.

**Fluid Resuscitation**

Observational studies have demonstrated that reducing the duration of hypotension in sepsis is associated with decreased mortality in septic shock. The premise of fluid resuscitation is to increase cardiac output and MAP to combat pathologic vasodilation. The Surviving Sepsis Campaign recommends an initial fluid bolus of 30 mL/kg. For most patients, this amount is probably adequate. However, concern has been raised that this volume is probably excessive for many patients. Observational studies have shown that excess volume administration is associated with worsened mortality, which may be due to associated pulmonary edema requiring prolonged mechanical ventilation and worsened kidney injury.

In an effort to avoid overresuscitation, several measures have been used to predict volume-responsiveness, defined as the augmentation of a patient’s cardiac output with additional fluid. Bedside echocardiography and ultrasonography have emerged...
as the most reliable tools, with an increase in the carbon monoxide before and after a “minibolus” of 100 to 250 mL functioning as a reliable indicator.\textsuperscript{52,53} The variation of inferior vena cava diameter with inspiration is an accurate predictor of volume responsiveness in mechanically ventilated patients, although there is conflicting evidence in spontaneously breathing patients.\textsuperscript{54} Likewise, pulse-pressure variation (PPV) on arterial line tracing can be used under specific conditions with mechanically ventilated patients. For patients who are in sinus rhythm and mechanically ventilated with tidal volumes of greater than 8 mL/kg (ideal body weight), PPV of $\geq 12\%$ is predictive of fluid responsiveness.\textsuperscript{55}

**Target Blood Pressure**

Retrospective data have suggested an association of MAPs less than 85 with progressively increasing risk for mortality and kidney injury.\textsuperscript{56,57} The only large randomized trial of 2 blood pressure targets in patients with septic shock attempted to compare the effect of lower MAP target (65–70) compared with higher target (80–85) and did not demonstrate a mortality benefit of one versus the other.\textsuperscript{56} However, a prespecified post hoc analysis of the same trial demonstrated significantly increased renal injury in those with preexisting chronic hypertension and maintained at the lower MAP target. On the other hand, there were more cardiac arrhythmias in the higher MAP group, largely because of the likely use of high-dose catecholamines in that arm.\textsuperscript{58} Therefore, it may be prudent to maintain relatively higher MAP targets in patients with septic shock, although we are limited by retrospective observational data and cannot recommend a specific threshold that fits all patients.\textsuperscript{59,60} Further randomized trials addressing this topic are urgently needed. Of note, the surviving sepsis guidelines recommend a target MAP of at least 65 mm Hg for titrating vasopressor support.\textsuperscript{36}

**Vasopressor Choice**

Vasopressors should be used in septic shock to support the patient’s blood pressure during and after fluid resuscitation. Historically, dopamine was recommended as the initial blood pressure agent of choice in septic shock. However, randomized trials comparing the use of dopamine versus norepinephrine as an initial agent showed higher incidences of tachyarrhythmia and worsened mortality with dopamine compared with norepinephrine.\textsuperscript{61} Hence, the recommendation from the Surviving Sepsis Campaign that norepinephrine be used as a first-line agent.\textsuperscript{62} Epinephrine has been compared with norepinephrine as an initial agent and did not reveal a mortality difference; however, epinephrine was associated with greater tachycardia and lactic acidosis.\textsuperscript{63} Specifically, in a septic patient with hypotension and with evidence of cardiomyopathy and associated right heart dysfunction, epinephrine may be added for inotropic benefit and if cardiac output is insufficient to maintain perfusion.\textsuperscript{64} Vasopressin is a non–catecholamine molecule that directly acts on V1 and V2 receptors. Vasopressin has also been compared with norepinephrine and showed no mortality benefit overall; however, the subgroup patients with “less severe” septic shock appeared to have slightly lower mortality.\textsuperscript{65} In addition to the catecholamine and vasopressin pathways, modulation of the renin-angiotensin-aldosterone pathway has been studied as a means to synergistically augment blood pressure and reduce catecholamine requirements. Exogenous angiotensin II has been shown to increase MAPs and decrease catecholamine requirements in patients with septic shock on high-dose vasopressors and demonstrated a good safety profile.\textsuperscript{66} Considering all available current data, norepinephrine remains the first-line agent for initial blood pressure management in septic shock. However, high-dose vasopressors, especially
catecholamines at norepinephrine equivalents of 0.8 μg/kg/min or higher, have been associated with a 50% 30-day and almost 80% 90-day mortality. Hence, there is a much-needed push to the early use of multimodal catecholamine-sparing adjunct vaspressors (both vasopressin and angiotensin II) in this regard.

**Adjunct Therapies: Steroids, Vitamin C, and Thiamine**

Several adjunct therapies have been investigated as mechanisms to combat the body’s dysregulated response to sepsis. Systemic steroids have been evaluated in several randomized trials; however, the results of these trials have not consistently demonstrated mortality benefit. Most recently, the ADRENAL trial evaluated the effect of continuous infusion of hydrocortisone on patients with septic shock and did not demonstrate a benefit compared with placebo. The APROCCHSS trial showed modest mortality benefit with the administration of bolus-dose hydrocortisone every 6 hours along with a daily administration of oral fludrocortisone.

Ascorbic acid (vitamin C) has gained attention as an antioxidant that may ameliorate the dysregulated response to sepsis. A small retrospective before-and-after study evaluated the effect of a cocktail of ascorbic acid along with thiamine and hydrocortisone and found promising results. A prospective randomized trial demonstrated decreased vasopressor requirements and decreased mortality in patients receiving bolus-dose ascorbic acid. The CITRIS-ALI trial investigated the role of ascorbic acid on organ dysfunction scores in patients with sepsis and ARDS and showed no significant difference.

**SUMMARY**

Sepsis and septic shock are leading causes of in-hospital mortality. Sepsis is currently understood as the pattern of life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is the subset of these patients with persistent hypotension and persistently elevated lactate, which is associated with much higher mortality. The SIRS and qSOFA scores can be used to screen patients for sepsis; however, the SIRS tool is associated with poor specificity and the qSOFA score is associated with decreased sensitivity. Initial management of sepsis includes broad-spectrum antimicrobial therapy directed toward likely pathogens, fluid resuscitation guided by measurements of fluid responsiveness, and support of MAP with vasopressors. The initial vasopressor of choice in septic patients is often norepinephrine; however, a multimodal vasopressor regimen using different classes of vasopressors may be required in cases of severe hypotension to avoid the deleterious side effects of escalating 1 vasopressor alone. Adjunct therapies continue to be evaluated for their role in sepsis therapy, including corticosteroids and vitamin supplementation.

**DISCLOSURE**

Departmental resources supported this work. The authors have nothing to disclose.

**REFERENCES**


