Received: 24 April 2024 | Revised: 11 July 2024 | Accepted: 16 July 2024

DOI: 10.1002/emp2.13264

JACEP OPEN
JOURNAL OF THE AMERICAN COLLEGE OF EMERGENCY PHYSICIANS OPEN
A GLOBAL JOURNAL OF EMERGENCY MEDICINE
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REVIEW ARTICLE

General Medicine

State of the art of sepsis care for the emergency medicine clinician

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Funding and support: By *JACEP* Open policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist

Abstract

Sepsis impacts 1.7 million Americans annually. It is a life-threatening disruption of organ function because of the body's host response to infection. Sepsis remains a condition frequently encountered in emergency departments (ED) with an estimated 850,000 annual visits affected by sepsis each year in the United States. The pillars of managing sepsis remain timely identification, initiation of antimicrobials while aiming for source control and resuscitation with a goal of restoring tissue perfusion. The focus herein is current evidence and best practice recommendations for state-of-the-art sepsis care that begins in the ED.

KEYWORDS
sepsis, sepsis syndrome, septic shock, severe sepsis, systemic inflammatory response syndrome

1 | INTRODUCTION

Sepsis impacts 1.7 million Americans on an annual basis and at least 350,000 of those inflicted die during their initial hospitalization or are discharged to hospice care.[1] A recent analysis of emergency department (ED) presentations estimated that up to 850,000 annual visits to US ED's are affected by sepsis.[2]

Sepsis is the body's dysregulated host response to infection that is life threatening through the disruption of organ function.[3] The pillars of managing sepsis remain focused on timely identification, initiation of antimicrobials, source control, and resuscitation with a goal of restoring tissue perfusion. Herein, we will focus on current evidence and best practice recommendations for state-of-the-art sepsis care beginning in the ED.

1.1 | Timely identification

Most sepsis cases are diagnosed upon admission to US hospitals following presentation to EDs, but detection of sepsis is challenging. In fact, more than one-third of patients with septic shock can present with vague symptoms such as fatigue and weakness that are not specific to infection as opposed to explicit symptoms such as fever, productive cough, or dysuria. Vague symptoms can lead to delayed antibiotic administration and higher risk of mortality.[4] Early recognition of sepsis promotes the delivery of timely interventions. Systematic screening for sepsis serves to enhance the goal of early recognition; however, we lack a validated gold standard screening tool. Early warning scores such as systemic inflammatory response syndrome (SIRS), national early warning score (NEWS), modified early warning score (MEWS),

Supervising Editor: Robert Levine, MD

sequential organ failure assessment (SOFA) score, and quick SOFA (qSOFA) have been tested, implemented, and compared. In a cohort of >16,000 patients presenting to the ED, the use of SIRS criteria identified patients with possible sepsis 118 min before they met sepsis definitions by use of SOFA criteria.[5] Only 46.4% of the cohort met qSOFA criteria at up to 5 h after SIRS or SOFA criteria were met. In this study, the use of SOFA criteria alone resulted in delayed administration of antibiotics and use of SIRS alone delayed identification of sepsis in those with organ dysfunction.[5] The most recent surviving sepsis guidelines recommend against the use of qSOFA as a single screening tool for sepsis or septic shock compared to SIRS, NEWS, or MEWS.[6] Clinical decision support for early identification of sepsis has leveraged the electronic health record, leading to development of proprietary models. The clinical application of such models is limited without gains over early warning scoring systems such as SIRS or SOFA.[7]

Sepsis is indeed a heterogeneous disease process. In categorizing sepsis clinical phenotypes, broad differences exist for outcomes and distribution of host response biomarkers.[8] While valuable and crucial to our understanding of timely identification and intervention, the translation of sepsis phenotypes to the bedside is not yet mature for implementation.

1.2 | Resuscitation: Restoration of tissue perfusion

The dysregulated host response compounding organ dysfunction in sepsis is life threatening and the art of sepsis resuscitation ultimately targets restoration of tissue perfusion. The goal is to restore the balance of delivery of oxygen and consumption of oxygen and optimize oxygen extraction at a cellular level. Patients who present to the ED with sepsis are frequently in the early phases of the illness. Those especially with septic shock are thus primed for early goal directed therapy focused on restoring hemodynamic stability.

1.3 | Sepsis-induced hypoperfusion

1.3.1 | Fluids

Hypotension is a marker of circulatory failure in sepsis. In the early phases of sepsis, hypotension serves as an early indicator of decreased relative preload, a consequence of the dysregulated host response to infection that enhances capillary permeability. Subsequently, this process leads to vasomotor paralysis clinically manifested as hypotension associated with decreased systemic vascular resistance (decreased preload and afterload).

Delivery of oxygen throughout the body is dependent on two broad components: cardiac output and content of oxygen in the blood (see Figure 1). Cardiac output is essential to circulate the oxygenated blood volume and in turn is influenced by heart rate and stroke volume. Stroke volume is influenced by the effects of pre-load, contractility, and afterload on the heart. Restoring preload through fluid resuscitation aims to enhance oxygen delivery by increasing stroke volume and thus cardiac output. The surviving sepsis campaign guidelines continue to suggest early fluid resuscitation with 30 mL/kg of crystalloid fluid for sepsis-induced hypoperfusion.[9]

The early resuscitation phase of sepsis induced hypoperfusion aims to stabilize and restore oxygen balance. The debate over early fluid resuscitation versus early use of vasoactive support in sepsis-induced hypoperfusion contributes to a degree of hydrophobia. Recent large multicenter trials have evaluated the early conservative versus liberal approaches for fluid resuscitation. The 2022 publication of Conservative versus Liberal Approach to Fluid Therapy in Septic Shock (CLASSIC) trial and the 2023 publication of the Crystalloid Liberal versus Vasopressors Early Resuscitation in Sepsis (CLOVERS) trial showed no differences in mortality.

The CLASSIC trial was an ICU-based trial comparing restrictive and liberal fluid administration for patients who had received at least 1 L of fluid and screened positive for septic shock within the preceding 12 h. A total of 1554 patients were enrolled, 770 to the restrictive fluid group and 784 to the standard fluid group. The restrictive fluid group received a median of 1798 mL (interquartile range [IQR], 500–4366) and the standard fluid group received a median of 3811 mL (IQR, 1861–6762). There was no difference in the primary outcome of death at 90 days, occurring in 42.3% of the restrictive fluid group and 42.1% of the standard fluid group (adjusted absolute difference, 0.1%; 95% confidence interval [CI] −4.7 to 4.9, $p = 0.96$).[10]

The CLOVERS trial aimed to enroll 2320 patients and was terminated early for futility at the second interim analysis with 1563 enrolled. Over 90% of enrolled patients were randomized while in the ED and had received a median amount of 2050 mL of crystalloid prior to randomization. During the first 6 h following randomization, the liberal fluid group had received a further 2.3 L and the restrictive group 500 mL. At end of a 24-h period, the liberal fluid group received 3.4 L and the restrictive group 1267 mL. The results showed no difference in the primary outcome of 90-day mortality: 14% in the restrictive group and 14.9% in the liberal group, difference −0.9% (95% CI: −4.4 to 2.6).[11] A post hoc analysis of the CLOVERS trial did reveal a higher percentage of patients in the restrictive fluid group compared to the liberal fluid group who were admitted to the ICU with early vasopressor use (difference of 8.1%, 95% CI: 3.3–12.8).

In short, the value of fluid resuscitation for sepsis should not be underestimated and fear of fluid administration in favor of vasopressor use increases risk of admission to the ICU and utilization of healthcare resources, without impacting survival. As in both CLASSIC and CLOVERS trials, patients were recruited to each arm after receiving a specified amount of crystalloid fluids, the effect (i.e., benefit or harm) of early administration of 30 mL/kg of crystalloid fluids is not fully addressed. However, an initial resuscitation approach of 30 mL/kg of crystalloid fluids for sepsis-induced hypoperfusion followed by initiation of vasopressors (i.e., norepinephrine) is in line with addressing the pathophysiological changes for sepsis (Figure 2).

Continuous assessment of the patient's condition with appropriate hemodynamic monitoring will determine whether more fluids or more vasopressor is needed. There is a lack of evidence to support a difference in any absolute liberal versus restrictive approach to

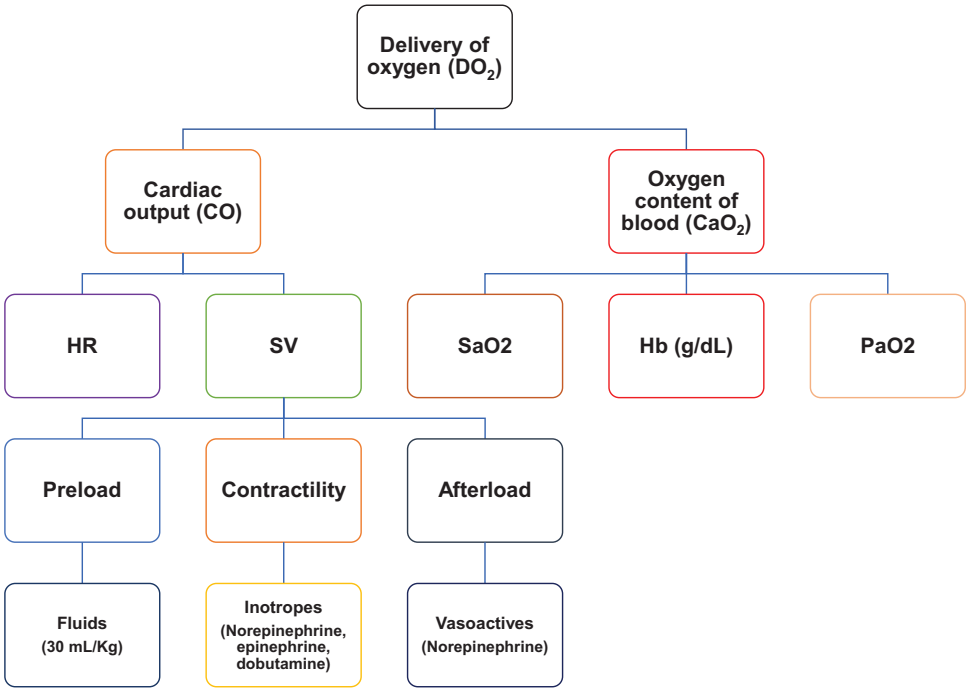

FIGURE 1 Components of delivery of oxygen.

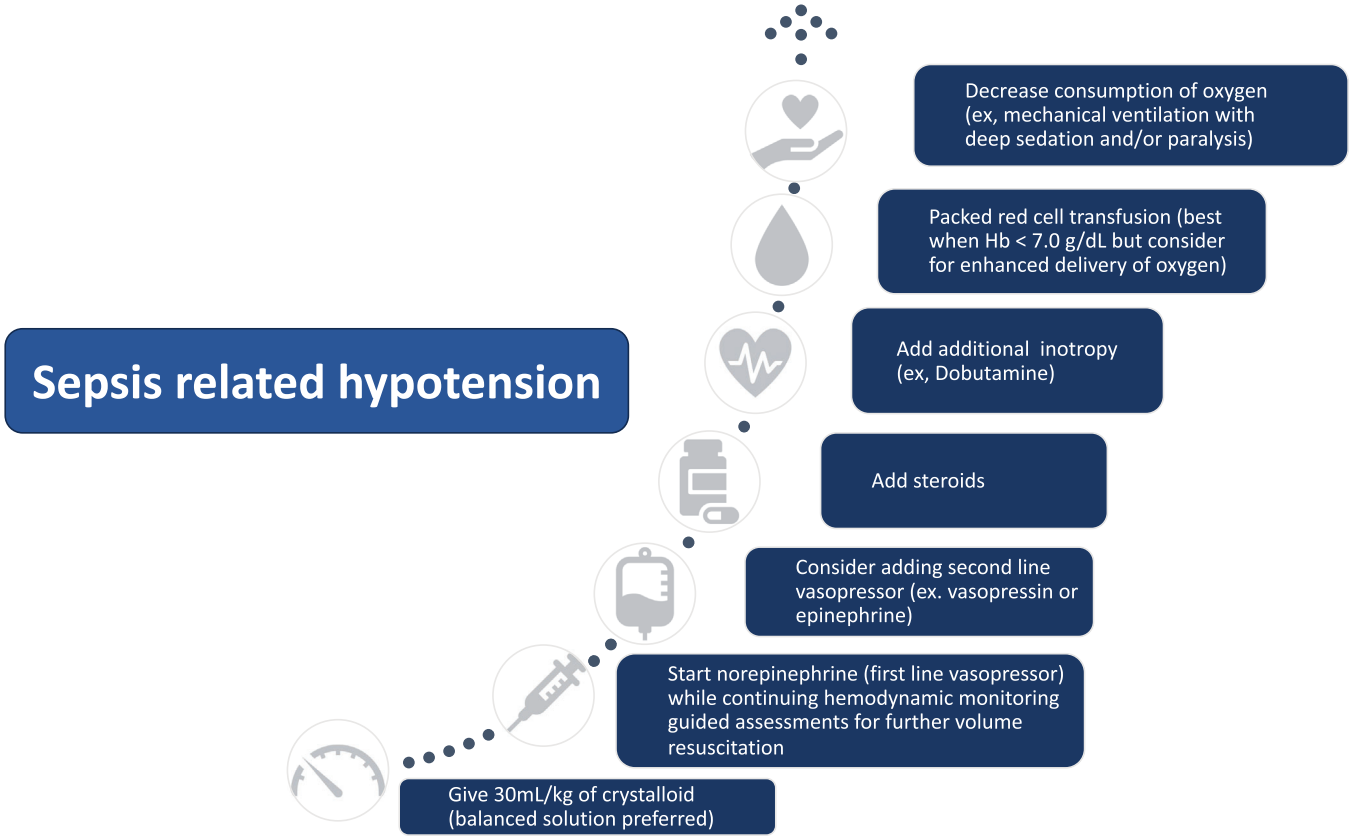

FIGURE 2 Steps for addressing sepsis-induced hypotension.

fluid management in the early phases of sepsis-induced hypoperfusion. Optimization of fluid resuscitation using hemodynamic monitoring, beyond the initial fluid bolus, has the potential added benefit of swift de-escalation of vasopressors and reduced critical care utilization.

1.3.2 | Lactate response

The 2016 third consensus conference definition describes septic shock as a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality. Septic shock is identified when patients require vasopressor to maintain a mean arterial pressure ≥65 mmHg and a lactate level >2.0 mmol/L despite adequate fluid resuscitation.[3] The Center for Medicare and Medicaid Services (CMS), which recently added sepsis bundle compliance to its hospital value-based purchasing (VBP) program, continues to follow SEP-1 definitions that recognize sepsis plus lactate >2.0 mmol/L as severe sepsis and sepsis plus lactate ≥4.0 mmol/L as septic shock.[12,13] Lactate levels serve as a biomarker for evaluating associated mortality risk, not a definition for sepsis per se. Broder and Weil in 1964 noted the correlation of the rise of lactate levels as an indicator of oxygen debt representative of the severity of circulatory failure.[14] A sharp rise in lactate levels >4.0 mmol/L was a strong indicator of mortality and decreased probability of survival. The 2016 secondary analysis of the ARISE study which focused on patients with hyperlactatemia without hypotension also highlighted the risks of higher 90-day mortality, decreased likelihood of being discharged from the ICU or hospital alive, longer ICU and hospital admissions, and increased likelihood of requiring ventilatory or vasopressor support.[15] Thus, measuring a lactate level in patients with suspected sepsis or septic shock will assist in risk stratification. Trends in lactate, or lactate clearance, is a key tool for monitoring the response to therapy.

1.4 | Antimicrobials and source control

Time to antimicrobial delivery and source control remain a key pillar for management of sepsis. Ferrer et al. reported a linear risk of increased mortality for each hour of delay in antibiotic administration from the first through sixth hour among patients with severe sepsis and septic shock.[16] The duration of time between patient arrival to the ED and the delivery of appropriate antimicrobials impacts long-term outcomes. In patients with sepsis as defined by Sepsis-3 definitions, each hour delay in antibiotic administration from ED arrival was associated with a 10% increase in the adjusted odds of death at 1 year.[17]

The balance around early administration of antimicrobials is associated with a fear of adverse outcomes and harms related to antimicrobial overuse. Donnelly et al. simulated a 50% reduction in time to antimicrobials in over 12 hospital scenarios with a cohort of 1,559,523 hospitalizations. While there was variation on impacts, the worst-case scenario resulted in rare occurrences of new antibiotic-associated adverse events.[18] A proposed approach for antimicrobial management for suspected sepsis is to select antimicrobials based on national guidelines and local susceptibilities, patient factors, and suspected sources. Following initial selection, proceed to daily evaluation of antimicrobials with incorporation of clinical signs and symptoms, culture results and molecular diagnostics and combine with analysis of dosing strategies. Finally, de-escalate focusing on narrowing therapy based on culture results with consideration of shorter durations based on responses to therapy.[19]

1.5 | Challenges and dilemmas

The greatest impacts to patient outcomes in sepsis are associated with early identification and intervention. A significant number of patients presenting to the ED have signs and symptoms that may be concerning for sepsis; however, the disease is challenging to diagnose because of the heterogeneity of these presenting signs and symptoms. Advanced biomarkers, such as monocyte distribution width (MDW) that is proprietary to Beckman Coulter's complete blood count (CBC) analyzers and Cytovale's IntelliSep, are promising in early detection of sepsis with a reported area under the receiver operator characteristic curve of 0.82[20] and 0.89,[21] respectively. Given CBC is the most commonly ordered blood test in the United States EDs,[22] MDW is additionally advantageous as it can serve as a broad sepsis screening tool, which can potentially help identify the presence of occult sepsis obviating the need for a pretest probability. The search for clinical decision support tools continues and no single gold standard approach has emerged. The evolution of clinical practice guidelines, policies, and regulations stir controversy in balancing sensitivity and specificity, raising concerns of resource overuse. In 2015, CMS introduced SEP-1 as a core measure with a purpose to promote early identification and intervention. Sep-1 was added to the Safety Domain of Medicare's VBP program with calendar year 2024 as the first performance year.[12] Compliance with SEP-1 is associated with decreased mortality among Medicare beneficiaries with sepsis.[23,24] Using a propensity-based analysis, compliance with SEP-1 was associated with an absolute risk reduction of 5.67% in a standard propensity matched analysis and a reduction of 4.06% reduction in the stringent match.[23] Similar to the SEP-1 approach of sepsis bundles, the introduction of mandated sepsis bundles in New York State have been associated with improved risk adjusted mortality.[25,26]

The challenge of effectively leveraging quality improvement programs to achieve success in clinical quality initiatives surrounding sepsis can seem substantial. However, performance improvement programs for sepsis have value in reducing mortality and enhancing adherence to sepsis bundles.[27] In 2023, the CDC published its report on Hospital Sepsis Program Core elements to support and guide the key elements in designing and implementing these programs. In 2022, 73% of hospitals participating in the CDC's annual National Healthcare Safety Network survey reported having a sepsis program of which 85% reported emergency medicine representation on the committees.[28] Thus, emergency medicine has an important opportunity to lead and influence the enhancement of performance improvement for sepsis clinical quality initiatives across the hospital setting.

1.6 | On the horizon

Novel and emerging approaches for sepsis are a priority for the solving sepsis program, a part of the Division of Research, Innovation and Ventures (DRIVe) established by Biomedical Advanced Research and Development Authority (BARDA), part of the Administration for Strategic Preparedness and Response (ASPR) within the United States Department of Health and Human Services (HHS). Through key partnerships across the government, the program aims to address the continuum of sepsis by seeking out innovative interventions for each step of early identification and clinical management to reduce mortality and improve outcomes.[29]

Modern diagnostic tools for sepsis are shifting the paradigm from detection methods of identifying the pathogens through culture and biochemical techniques to molecular detection using standard and real-time PCR. Further advanced methodologies have focused on point of care testing and species-specific biosensors.[30] Sepsis is a highly challenging condition to diagnose, and ideal treatment must be optimized to each patient's unique immune-inflammatory response.[31] Patient phenotyping based on the current state of their immune system is critical to tailor specific treatments. The dysregulated host response in sepsis is heterogeneous and fluctuates between excessive inflammation and immunosuppression. Biomarker identification of the transcriptomic description of phenotypes has not achieved the necessary sensitivity and specificity to be translated into routine clinical practice. Though there are important strides being made, therapeutic explorations targeting the host response continue in areas of immune checkpoint inhibitors, cytokines, and growth factors.[32]

Expanding our horizons to artificial intelligence and machine learning, research combining numerous biomarkers and machine learning to identify severe underlying infection and immune system overactivation is active. In April 2024, the FDA-granted authorization for the first artificial intelligence/machine learning based software for identifying patients at risk for having or developing sepsis. Specific requirements have been set for software validation and clinical performance testing.

2 | CONCLUSION

Sepsis continues to impact millions of Americans annually. Most sepsis cases in hospitalized patients are recognized upon admission to the hospital through the emergency department. Early recognition and intervention are essential, and the key pillars of sepsis management include a bundled approach of identifying the source, delivering timely antimicrobials, and prioritizing resuscitation. Although further research is necessary for early detection and ideal resuscitation, the CMS SEP-1 guidelines and bundle compliance provide an effective strategy for improving outcomes. Sepsis is a challenging disease to recognize, and the implementation of process improvement programs can enhance bundle adherence while reducing mortality.

AUTHOR CONTRIBUTIONS

All authors contributed to the conceptual design of the manuscript. N. Jayaprakash drafted the manuscript, and all authors contributed equally to the critical review and editing of the manuscript.

CONFLICT OF INTEREST STATEMENT

N. Jayaprakash received Honorarium for CHEST 2023 (travel), Site PI for grants to institution: Abbott laboratories sponsored LANER-HF trial; NIH sponsored AIMS trial; Biocogniv sponsored Sepsis AI marker study. N. Sarani worked for Beckman Coulter Diagnostics: Site PI: Linking Novel Diagnostics with Data-Driven Clinical Decision Support Prenosis: Site PI: Early stratification of septic patients, consulting on clinical utility of monocyte distribution width in the acute care setting.

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How to cite this article: Jayaprakash N, Sarani N, Nguyen HB, Cannon C. State of the art of sepsis care for the emergency medicine clinician. *JACEP Open*. 2024;5:e13264. https://doi.org/10.1002/emp2.13264