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Clinical Review

PRACTICAL CONSIDERATIONS IN SEPSIS RESUSCITATION

Brit Long, MD,* Alex Koyfman, MD,† Katharine L. Modisett, MD,‡ and Christian J. Woods, MD, FACP, FIDSA, FCCP§

*Department of Emergency Medicine, San Antonio Military Medical Center, Fort Sam Houston, Texas, †Department of Emergency Medicine, The University of Texas Southwestern Medical Center, Dallas, Texas, ‡Department of Pulmonary and Critical Care Medicine, MedStar Georgetown University/MedStar Washington Hospital Center, Washington, District of Columbia, and §Sections of Infectious Diseases and Pulmonary Critical Care, MedStar Washington Hospital Center, Washington, District of Columbia

Reprint Address: Brit Long, MD, 3551 Roger Brooke Dr, San Antonio, TX 78219

□ **Abstract—Background: Sepsis is a common condition managed in the emergency department, and the majority of patients respond to resuscitation measures, including antibiotics and i.v. fluids. However, a proportion of patients will fail to respond to standard treatment. Objective: This review elucidates practical considerations for management of sepsis in patients who fail to respond to standard treatment. Discussion: Early goal-directed therapy revolutionized sepsis management. However, there is a paucity of literature that provides a well-defined treatment algorithm for patients who fail to improve with therapy. Refractory shock can be defined as continued patient hemodynamic instability (mean arterial pressure, ≤ 65 mm Hg, lactate ≥ 4 mmol/L, altered mental status) after adequate fluid loading (at least 30 mL/kg i.v.), the use of two vasopressors (with one as norepinephrine), and provision of antibiotics. When a lack of improvement is evident in the early stages of resuscitation, systematically considering source control, appropriate volume resuscitation, adequate antimicrobial coverage, vasopressor selection, presence of metabolic pathology, and complications of resuscitation, such as abdominal compartment syndrome and respiratory failure, allow emergency physicians to address the entire clinical scenario. Conclusions: The care of sepsis has experienced many changes in recent years. Care of the patient with sepsis who is not responding appropriately to initial resuscitation is troublesome for emergency physicians. This review provides practical considerations for resuscitation of the patient with septic shock. When a septic patient is refractory to standard therapy, systematically evaluating the patient and clinical course may lead to improved outcomes. Published by Elsevier Inc.**

□ **Keywords—sepsis; resuscitation; vasopressor; antimicrobial; septic shock; metabolic**

INTRODUCTION

Emergency physicians (EPs) are well versed in the care of the septic patient, with nearly 3 million annual visits to the emergency department (ED) related to sepsis (1–3). In response to the rising rates of septic shock and a lack of substantial decrease in mortality, Dr. Emmanuel Rivers and the Early Goal-Directed Therapy (EGDT) Collaborative Group designed a now well-known study randomizing patients presenting to the ED with sepsis to receive EGDT vs. standard therapy. Standard therapy (or usual therapy at that time) was at the discretion of the clinician with defined goals of central venous pressure (CVP) ≥ 8 mm Hg, mean arterial pressure (MAP) ≥ 65 mm Hg, and urine output ≥ 0.5 mL/kg/h. No specific treatment algorithm was utilized in the standard group. Patients in the EGDT groups remained in the ED for 6 h and received protocolized therapy in the ED. Patients received fluid boluses of 500 mL until the CVP was 8–12 mm Hg and vasopressors until MAP was 65–90 mm Hg. If the central venous oxygen saturation ($ScVO_2$) was < 70%, red blood cells were transfused until hematocrit ≥ 30%. If $ScVO_2$ was still < 70% or hematocrit was already > 30%, dobutamine was provided.

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Rivers et al. found a lower hospital mortality rate and improved physiologic markers of shock in those patients who received EGDT rather than standard therapy, with mortality 30.5% vs. 46.5% in the EGDT and standard therapy groups, respectively (4,5). This landmark study was criticized due to concerns about the plausibility of initiating EGDT in a busy ED without a dedicated physician to ensure compliance with the bundle and availability of the invasive technology used in this study to measure $ScVO_2$ (4,5). Additionally, several recent studies evaluating EGDT vs. today's standard (or usual) therapy have demonstrated similar patient outcomes when standard therapy involves fluid resuscitation and early antimicrobial administration (6–8). Improved patient care and physician knowledge of sepsis have resulted in changes in the standard or usual care of sepsis. These recent studies demonstrate patients receive 2–4 L i.v. fluids and rapid antibiotics, which is far different than the standard group in the Rivers et al. study. This raises the question of which components of EGDT actually provide a mortality benefit, and future studies are needed to clarify this (6–8).

SEPSIS PRESENTATION

Sepsis exists as a continuum of disease, and patients may advance or rescind along this continuum during their ED course. While traditionally this spectrum has been divided into systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock (Table 1), others have argued that with the evolving understanding of serious infection and its variable presentations, the clinical entity of sepsis should be redefined due to significant heterogeneity (9,10).

SIRS-Negative Patients

Many have questioned the use of SIRS criteria and definition of sepsis. One of the criticisms of using SIRS criteria to define sepsis is that the criteria miss 1 of 8 patients with diagnosed severe sepsis (3,10). However, the criteria can diagnose 7 of 8 patients with severe sepsis, for a sensitivity of 88% (10). In an intensive care unit (ICU) population, where SIRS criteria were retrospectively applied, mortality was 24.5% in SIRS-positive patients and 16.1% in SIRS-negative patients (10). The SIRS-negative patients also had shorter ICU and hospital stays, as well as higher rates of discharge home (10). This study brings into light the importance of sepsis evaluation in patients who might not mount a SIRS response, such as the elderly, patients on medications affecting adrenergic activity (such as β-blockers), and immunocompromised patients.

With the controversy surrounding the use of SIRS to define sepsis, a new definition has been proposed by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine (11). This updated definition utilizes the Sequential Organ Failure Assessment (SOFA) score, which is a system using respiratory evaluation, coagulation testing, bilirubin, cardiovascular assessment, mental status evaluation, and renal system testing. The quick SOFA (qSOFA) score can be used for rapid assessment. This updated sepsis definition requires the presence of suspected or documented infection and at least two criteria on qSOFA (systolic blood pressure $\leq$ 100 mm Hg, altered mental status [Glasgow Coma Scale $\leq$ 13], or tachypnea [$\geq$ 22 breaths/min]). Severe sepsis is removed from the new definition, and septic shock is defined by sepsis with need for vasopressors to maintain MAP $\geq$ 65 mm Hg and lactate $\geq$ 2 mmol/L after adequate fluid resuscitation (11). This has not been accepted by the American College of Emergency Physicians.

Use of Lactate

The use of lactate in sepsis has been well studied, and serum lactate is recommended as a screen for sepsis, as initial lactate concentration is associated with suspected infection and severity of illness (12–18). Point of care lactate is useful for screening, specifically for lactate levels $\geq$ 2 mmol/L (12–18). With increasing lactate

Table 1. Definitions of Sepsis, Severe Sepsis, and Septic Shock (2,9)

Condition	Definition
Sepsis	Documented/suspected infection plus two of the following: Temperature > 38°C or < 36°C, heart rate > 90 beats/min, respiratory rate > 20 breaths/min or PCO_2 < 32 Torr, WBCs > 12,000/mm^3 or < 4,000/mm^3, or > 10% immature forms
Severe sepsis	Sepsis plus organ dysfunction/tissue hypoperfusion: lactate > 2 mmol/L, altered mental status, respiratory failure, acute renal injury (Cr > 0.5 mg/dL above baseline or oliguria), evidence of disseminated intravascular coagulation, liver failure, troponin elevation, transient hypotension (SBP < 90 mm Hg or MAP < 65 mm Hg), acidosis
Septic shock	Sepsis plus any of the following: Hypotension (SBP < 90 mm Hg, MAP < 70 mm Hg, or > 40 mm Hg SBP decrease from baseline) refractory to i.v. fluids, or lactate > 4 mmol/L

MAP = mean arterial pressure; SBP = systolic blood pressure; WBC = white blood cell.