Management of Sepsis: Early Resuscitation

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KEYWORDS

• Sepsis • Resuscitation • Early goal-directed therapy
• Fluids • Vasopressor • Inotropes

Abbreviations: ARR, Absolute risk reduction; ALI, Acute lung injury; ARDS, Adult respiratory distress syndrome; APACHE II, Acute physiologic and chronic health evaluation score II; CVP, Central venous pressure; CQI, Continuos quality improvement; ED, Emergency department; EDM, Esophageal doppler monitoring; EGDT, Early goal-directed therapy; ESRD, End stage renal disease; GPU, Inpatient general practice unit (medical-surgical floors); HFH, Henry Ford Hospital; ICU, Intensive care unit; IHI, Institute for Health Improvement; IL-8, Interleukin 8; LOS, Length of stay; MB, Maintainance or 24 hour bundle; mmol/L, millimoles per liter; MODS, Multiple organ dysfunction score; NNT, Number needed to treat; OR, Odds ratio; PAC, Pulmonary artery catheter; PAOP, Pulmonary capillary occlusion pressure; PPV, Pulse pressure variation; RR, Relative risk; RRR, Relative risk reduction; SAPS II, Simplified acute physiologic score; SBP, Systolic blood pressure; $ScvO_2$, Central venous oxygen saturation; SvO_2, Mixed venous oxygen saturation; SD, Standard deviation; SSC, Surviving Sepsis Campaign.

Key links in the chain of survival for the management of severe sepsis and septic shock are early identification and comprehensive resuscitation of high-risk patients.[1] Multiple studies have shown that the first 6 hours of early sepsis management are especially important from a diagnostic, pathogenic, and therapeutic perspective, and that steps taken during this period can have a significant impact on outcome.[2–7] This period applies to the 700,000 cases per year of sepsis presenting to emergency departments and an equal number of patients on general hospital inpatient floors and intensive care units (ICUs)[8] in the United States. The recognition of this critical period and the robust outcome benefit realized in previous studies provides the rationale for adopting early resuscitation as a distinct intervention.[9] Sepsis joins trauma, stroke, and acute myocardial infarction in having ''golden hours,'' representing a critical opportunity early on in the course of disease for actions that offer the most benefit.

THE PHYSIOLOGIC RATIONALE FOR EARLY HEMODYNAMIC OPTIMIZATION

The hemodynamic picture of sepsis represents a continuum from clinically stable disease to circulatory insufficiency resulting from hypovolemia, myocardial depression, increased metabolic rate, vasoregulatory-perfusion abnormalities leading to inflammation, and cytopathic tissue hypoxia.

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These hemodynamic combinations create various degrees of systemic imbalance between tissue oxygen supply and demand ranging from global tissue hypoxia to overt shock and multiorgan failure. Increases in oxygen extraction or decreases in central venous oxygen saturation or mixed venous oxygen saturation signal falling venous oxyhemoglobin saturation. These parameters provide a compensatory mechanism for restoring the balance needed to maintain tissue oxygen. When the limits of this compensatory mechanism are reached, however, lactate production ensues as an indicator of anaerobic metabolism. In this delivery-dependency phase, lactate concentration increases and may be inversely correlated with systemic oxygen delivery and mixed or central venous oxygen saturation.[10] This phase, which is characterized as global tissue hypoxia, is an important transition from sepsis to severe disease. Although this phase is associated with increased morbidity and mortality if unrecognized or left untreated, it can occur with normal vital signs.[11–13] The transition to septic shock can range from a hypodynamic state of oxygen delivery dependency (elevated lactate concentrations and low venous oxygen saturations) to the more commonly recognized hyperdynamic state where oxygen consumption is independent of oxygen delivery (normal to increased lactate concentrations and high venous oxygen saturation), depending on the stage of disease presentation and the extent of hemodynamic optimization (**Table 1**).[10,14–17] Comprehensive resuscitation is a way to optimize systemic oxygen delivery (preload, afterload, arterial oxygen content, contractility), balance oxygen delivery with systemic oxygen demands, optimize the microcirculation, and use metabolic end points to verify efficient cellular oxygen use. Although there is much discussion about the components required to accomplish a comprehensive resuscitation, no single component dictates the overall intent of the resuscitation. These components are interrelated and should be considered as a continuum of care and not as isolated variables.

IDENTIFICATION OF THE HIGH-RISK PATIENT

Although hypotension currently is used to define the transition from severe sepsis to septic shock, it is not sufficiently sensitive as a screening tool for tissue perfusion deficits in early sepsis. A number of studies support the employment of lactate equal to or greater than 4 mmol/L as a marker for severe tissue hypoperfusion and as a univariate predictor of mortality.[18–25] Anion gap or base deficit can be helpful when present. However, a normal bicarbonate or anion gap can be observed in over 20% of patients presenting with a lactate level greater than 4.0 mmol/L.[26,27] Serial lactate levels can be used to assess lactate clearance or changes in lactate over time in as little as the first 6 hours of sepsis presentation. Improved lactate clearance is significantly associated with decreased inflammatory response, improved coagulation parameters (**Fig. 1**), preserved organ function, and improved survival.[5,28]

Patients with severe sepsis and septic shock often have elevated brain natriuretic peptide (BNP) and troponin levels, which are significantly associated with organ and myocardial dysfunction, global tissue hypoxia, and mortality.[29] When adjusted for age, gender, history of heart failure, renal function, organ dysfunction, and mean arterial pressure, a BNP greater than 210 pg/mL at 24 hours is a significant independent indicator of increased mortality.[30] Phau and colleagues[31] have shown that elevated baseline lactate levels offer superior prognostic accuracy to baseline procalcitonin levels, which in turn are superior to N-terminal pro-BNP levels. To improve their prognostic utility beyond those of cytokine measurements and clinical severity scores, serial lactate and procalcitonin measurements may be combined.

HEMODYNAMIC MONITORING

The protocol resuscitation components of early goal-directed therapy (EGDT) were largely derived from the practice parameters for the hemodynamic support of sepsis recommended by the American College of Critical Care Medicine in 1999.[32] The EGDT protocol uses central venous pressure measurements instead of pulmonary capillary wedge pressure to address preload (**Fig. 2**). While tools for hemodynamic optimization may vary, the message is that an early-organized approach to hemodynamic optimization improves outcomes. These various tools are discussed in **Table 2**.

FLUID THERAPY

Aggressive fluid resuscitation is required because of hypovolemia resulting from a decreased oral intake and increased insensible losses from vomiting, diarrhea, or sweating. Venodilation and extravasation of fluid into the interstitial space because of increased capillary endothelial permeability results in decreased cardiac preload, decreased cardiac output, and inadequate systemic oxygen delivery. Rapid restoration of fluid deficits not only modulates inflammation but also decreases the need for vasopressor therapy and