Liberal Versus Restrictive Intravenous Fluid Therapy for Early Septic Shock: Rationale for a Randomized Trial

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Prompt intravenous fluid therapy is a fundamental treatment for patients with septic shock. However, the optimal approach for administering intravenous fluid in septic shock resuscitation is unknown. Two competing strategies are emerging: a liberal fluids approach, consisting of a larger volume of initial fluid (50 to 75 mL/kg [4 to 6 L in an 80-kg adult] during the first 6 hours) and later use of vasopressors, versus a restrictive fluids approach, consisting of a smaller volume of initial fluid (≤30 mL/kg [≤2 to 3 L]), with earlier reliance on vasopressor infusions to maintain blood pressure and perfusion. Early fluid therapy may enhance or maintain tissue perfusion by increasing venous return and cardiac output. However, fluid administration may also have deleterious effects by causing edema within vital organs, leading to organ dysfunction and impairment of oxygen delivery. Conversely, a restrictive fluids approach primarily relies on vasopressors to reverse hypotension and maintain perfusion while limiting the administration of fluid. Both strategies have some evidence to support their use but lack robust data to confirm the benefit of one strategy over the other, creating clinical and scientific equipoise. As part of the National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury Network, we designed a randomized clinical trial to compare the liberal and restrictive fluids strategies, the Crystalloid Liberal or Vasopressor Early Resuscitation in Sepsis trial. The purpose of this article is to review the current literature on approaches to early fluid resuscitation in adults with septic shock and outline the rationale for the upcoming trial. [Ann Emerg Med. 2018;■:1-10.]

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INTRODUCTION

For the past 2 decades, clinicians in the emergency department (ED) and ICU have routinely administered large volumes of intravenous fluid to patients with septic shock, often totaling greater than 5 L in the first several hours of resuscitation.[1-5] However, an improved mechanistic understanding of potential harm from excessive fluid administration[6-8] and emerging observational data associating positive fluid balance with higher mortality[9-15] have recently challenged the paradigm of large-volume fluid resuscitation.

Because of inadequate evidence to support a specific intravenous fluid strategy for the management of early septic shock, 2 alternative approaches have emerged: a liberal fluids approach that relies on a larger volume of initial intravenous fluid administration (often 50 to 75 mL/kg [4 to 6 L in an 80-kg adult]); and a restrictive fluids approach consisting of a smaller volume of initial intravenous fluid (often ≤30 mL/kg [≤2 to 3 L]) and earlier use of vasopressors. Because of the equipoise surrounding these competing treatment strategies, we designed a randomized clinical trial to compare a liberal versus restrictive approach to intravenous fluid resuscitation, the Crystalloid Liberal or Vasopressor Early Resuscitation in Sepsis (CLOVERS) trial. The goal of this article is to describe the current state of the literature in regard to intravenous fluid resuscitation in early septic shock and the rationale for the upcoming CLOVERS trial.

LIBERAL FLUIDS APPROACH

A "liberal" fluids approach to septic shock management is characterized by the administration of several liters (typically 50 to 75 mL/kg) of intravenous fluid during the first several hours of treatment.[1,16,17] Vasopressor infusions are

[†]A list of PETAL Network Investigators is included in Appendix E1, available online at http://www.annemergmed.com.

added immediately if the patient is profoundly hypotensive (eg, systolic blood pressure <70 mm Hg) or remains hypotensive despite large-volume fluid resuscitation. This liberal fluids strategy dominates current ED care in the United States, based in part on the initial Surviving Sepsis Campaign recommendations and early goal-directed therapy.[1,2,5] A liberal fluids approach is also encouraged by the SEP-1 Core Measure from the Centers for Medicare & Medicaid Services and The Joint Commission, which recommends an infusion of at least 30 mL/kg of crystalloid fluid within 3 hours of septic shock recognition.[18,19]

Septic shock patients manifest decreased vasomotor tone and intravascular volume depletion from loss of fluid into the extravascular space through capillary endothelial dysfunction, both of which contribute to hypotension.[5] Intravenous fluid administration replenishes intravascular fluid lost to the extravascular space and increases volume within dilated vessels, potentially increasing cardiac preload, stroke volume, and cardiac output, leading to increased tissue perfusion and oxygen delivery. Fluid boluses may also improve microvascular perfusion by increasing the driving pressure across capillary beds. These potential advantages to the microcirculation may be present even when the patient does not exhibit traditional signs of "fluid responsiveness," such as an increase in stroke volume or cardiac output after a fluid challenge.[20]

Reversal of hypotension with fluid boluses may allow clinicians to avoid or limit vasopressors, which have the potential to cause patient harm, including cardiac dysrhythmias; increased myocardial oxygen demand; digital, renal, and mesenteric ischemia; and soft tissue damage from extravasation.[21] Using fluids instead of vasopressors to treat hypotension may also allow clinicians to avoid some ICU admissions in hospitals that require all patients receiving vasopressors to be admitted to an ICU, thus preserving ICU bed capacity.

Clinical Evidence Supporting a Liberal Fluids Approach

In the 1990s, inhospital mortality rates for septic shock were 40% to 50% for hospitals in developed countries.[5] In 2001, Rivers et al[22] published results of a trial noting lower inhospital mortality with early goal-directed therapy, a protocolized resuscitation strategy targeting central venous pressure, mean arterial pressure, and saturation of central venous oxygen. Patients in the early goal-directed therapy group received larger fluid volumes during the first 6 hours of treatment than those in the standard therapy group (mean volume of intravenous fluid administration 5.0 versus 3.5 L) and experienced a lower inhospital mortality (31% versus 47%).[22]

After the trial by Rivers et al,[22] early large-volume fluid resuscitation was widely adopted in the United States.[1,2,5,16] Observational studies at many institutions during the next 10 years suggested that implementation of early goal-directed therapy protocols, even with incomplete adherence, were associated with larger volumes of fluid administration and lower mortality (Figures 1 and 2).[5,23-26] For example, Puskarich et al[26] conducted a before-after analysis of early goal-directed therapy implementation at their institution and found a substantial increase in the volume of intravenous fluid administered during the first 6 hours of resuscitation (mean 2.3 L before early goal-directed therapy versus 4.1 L with early goal-directed therapy) and decline in inhospital mortality (27% versus 17%). However, most of these early studies evaluating the effect of early goal-directed therapy involved implementation of a multifaceted bundle of sepsis care, and the effects of different volumes of fluid resuscitation were not separated from the effects of other bundle components, such as early sepsis recognition, prompt antibiotics, and specialized sepsis response teams.[27,28] A recent meta-analysis suggested that the mortality benefit associated with early goal-directed therapy in observational studies was largely due to earlier and more appropriate antibiotics, not fluid volumes or achievement of hemodynamic goals.[29]

In 2014 to 2015, results of 3 large multicenter trials evaluating early goal-directed therapy were published. Each of these trials—Protocolized Care for Early Septic Shock (ProCESS)[2] in the United States, Australian Resuscitation in Sepsis Evaluation (ARISE)[3] mostly in Australia and New Zealand, and Protocolised Management in Sepsis (ProMISe)[4] in England—demonstrated no incremental mortality benefit between patients initially resuscitated according to early goal-directed therapy versus usual care. Although the timing of fluid administration varied between arms, overall intravenous fluid volume between ED presentation and 6 hours postenrollment was approximately 4 to 5 L in all groups of all trials. This suggests that early large-volume fluid resuscitation was part of usual care (Figures 1 to 2). Therefore, the ProCESS, ARISE, and ProMISe trials cannot provide insight on the comparative effects of a liberal versus restrictive fluid strategy. However, these trials, plus other observational studies,[30] demonstrated a substantial decline in the short-term mortality risk for patients with septic shock (currently 15% to 25%) since the 1990s (approximately 40% to 50%), when early large-volume fluid resuscitation was less common.[5,31] Several factors other than fluid resuscitation likely contributed to a decline in reported sepsis mortality over time, including implementation of early sepsis screening, diagnosing sepsis in less severely ill patients, and