

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 administration⁶⁻⁸ and emerging observational data associating positive fluid balance with higher mortality⁹⁻¹⁵ 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 al²² 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 al²⁶ 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

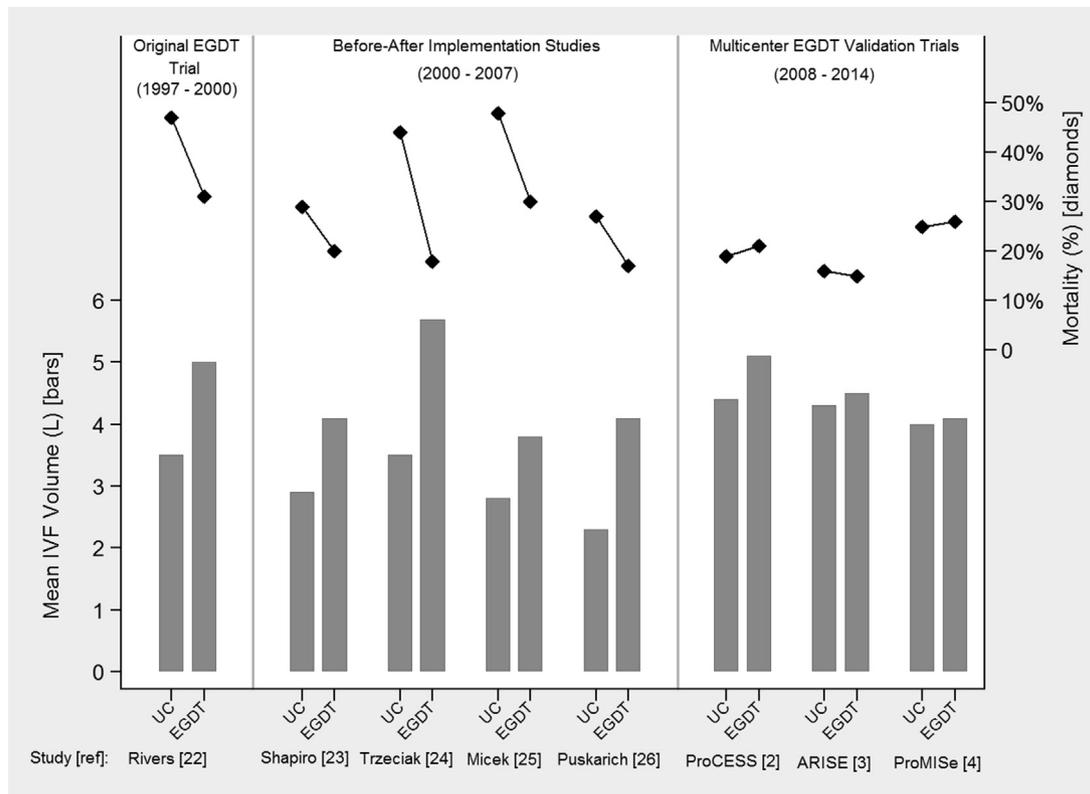


Figure 1. Volume* of early intravenous fluid administration (bars; left axis) and mortality[†] (diamonds; right axis) in severe sepsis and septic shock studies comparing UC to EGDT. Bars show the volume of fluid administered in liters for the UC and EGDT groups in each study. The connected dots demonstrate the percentage of patients who died in UC and EGDT groups in each study. Patients in the UC group of later studies tended to receive more fluid than those in the UC group of earlier studies and similar to patients in the EGDT groups. Mortality was higher in the UC group of studies in which UC patients received less fluid than EGDT patients, but similar in the later studies in which the UC and EGDT groups received similar volumes of fluid. *IVF*, Intravenous fluid; *EGDT*, early goal-directed therapy; *UC*, usual care. *Window for reported mean fluid volumes: first 6 hours after ED presentation: Rivers,²² Shapiro,²³ Puskarich²⁶; total volume during ED stay: Trzeciak,²⁴ Micek²⁵; prandomization period plus 6 hours postrandomization: ProCESS,² ARISE,³ ProMiSe.⁴ [†]Window for reported mortality: in-hospital: Rivers,²² Trzeciak,²⁴ Puskarich,²⁶ ProMiSe⁴; 28-day in-hospital: Shapiro²³; 28-day: Micek²⁵; 60-day in-hospital: ProCESS,² ARISE.³

changes to administrative coding for sepsis.^{29,32,33} Nonetheless, a concurrent decline in sepsis mortality during the same period in which usual care shifted toward larger-volume fluid resuscitation suggests that adoption of a liberal fluid strategy may have contributed to a decrease in sepsis mortality during the past 2 decades.

RESTRICTIVE FLUIDS APPROACH

A “restrictive” fluids approach to septic shock management is characterized by the administration of smaller fluid volumes (often ≤ 30 mL/kg) and earlier use of vasopressors to reduce vasodilation and improve tissue perfusion.¹⁷ With a restrictive fluids approach, the primary method of maintaining blood pressure and systemic perfusion is through vasopressor titration, with fluid boluses added when there is evidence of extreme hypovolemia or when tissue hypoperfusion is suspected despite high vasopressor infusion rates. Historically, the

common practice of requiring central venous access for vasopressor infusion hampered early use of vasopressors.^{34,35} However, current data suggest that norepinephrine administration through large peripheral intravenous catheters for short intervals (hours to days) with appropriate monitoring is safe,^{36,37} facilitating early vasopressor use for sepsis resuscitation.

The physiologic rationale for a restrictive fluids strategy includes data suggesting that intravenous fluid boluses only transiently increase intravascular volume, but subsequently lead to pathologic extravascular fluid leakage (edema), which interferes with cellular function in several organs, including the kidneys, liver, heart, and lungs.⁶⁻⁹ Several days of diuresis after shock resolution is often necessary to remove this excess fluid generated by an initial liberal fluids strategy.¹⁴ By decreasing venous capacitance (thereby converting unstressed volume to stressed volume without a change in overall volume), vasopressors can increase venous

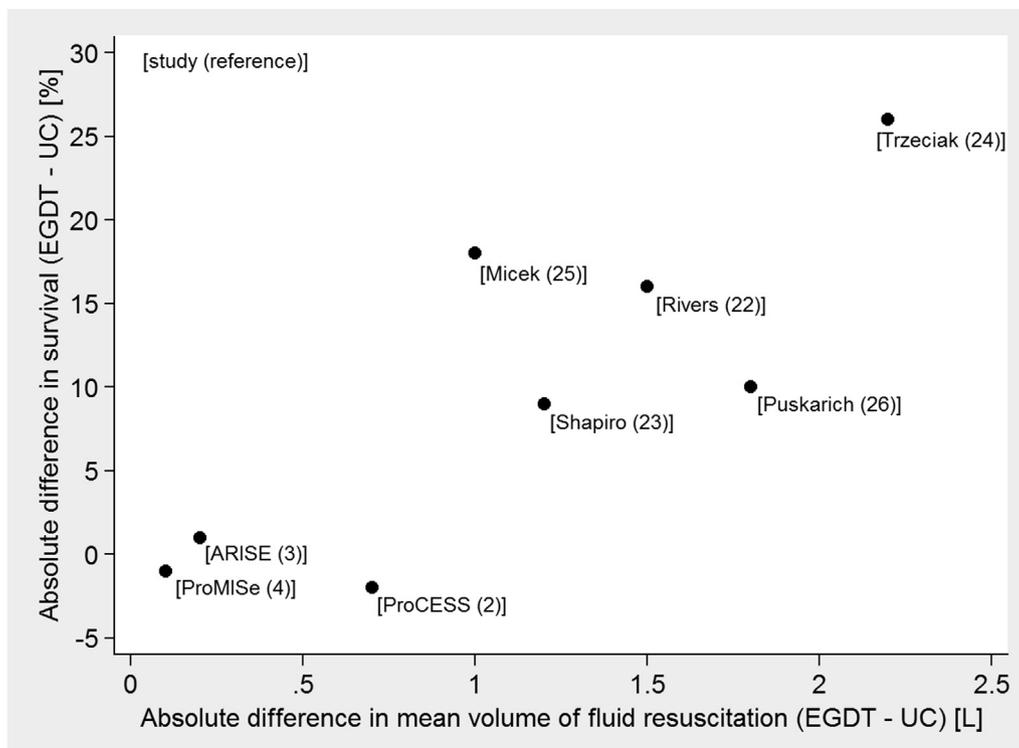


Figure 2. Scatter plot demonstrating the relationship between the difference in mean volume of fluid resuscitation* in the EGDT group and UC group (x axis) versus difference in survival[†] in the EGDT group and UC group (y axis) among 8 studies comparing EGDT and UC for early sepsis treatment. Studies with a larger difference in fluid volumes between groups tended to have a larger difference in survival. The reference for each study is listed in brackets. *Window for reported mean fluid volumes: first 6 hours after ED presentation: Rivers,²² Shapiro,²³ Puskarich²⁶; total volume during ED stay: Trzeciak,²⁴ Micek²⁵; prerandomization period plus 6 hours postrandomization: ProCESS,² ARISE,³ ProMISe.⁴ [†]Window for reported survival: in-hospital: Rivers,²² Trzeciak,²⁴ Puskarich,²⁶ ProMISe⁴; 28-day inhospital: Shapiro²³; 28-day: Micek²⁵; 60-day inhospital: ProCESS,² ARISE.³

return and cardiac output in a fashion similar to that of an intravenous fluid bolus without burdening tissues with excess extravascular fluid.³⁸

Increasing central venous pressure with intravenous fluid boluses may decrease tissue perfusion by narrowing the gradient between arterial pressure and venous pressure, which drives tissue perfusion.³⁹ Some hypothesize that the peripheral vasoconstrictive response to shock is beneficial by selectively providing perfusion to essential organs at the expense of nonvital tissues; rapid reversal of this adaptive physiologic response with intravenous fluid boluses may be harmful.⁴⁰

Physiology studies suggest that between one third and one half of septic shock patients never experience an increase in cardiac output with fluid boluses, and when cardiac output does increase, it typically does so for only 30 to 60 minutes.^{6,7,41-44} Thus, many septic patients treated with intravenous fluid potentially experience limited benefit in terms of increased cardiac output, but are exposed to the negative consequences of tissue edema.

Recommendations for resuscitation of hemorrhagic shock after trauma have evolved during the past 2 decades and now emphasize the avoidance of large-volume crystalloid administration in favor of blood product transfusion and selective use of permissive hypotension.⁴⁵⁻⁴⁷ A shift in sepsis resuscitation from a liberal to restrictive fluids strategy would parallel this recent change in hemorrhagic shock resuscitation.

Observational Clinical Studies Evaluating Early Fluid Administration and Mortality

Seymour et al⁴⁸ analyzed the New York State Department of Health administrative databases to evaluate associations between the timing of several individual components of early sepsis treatment and inpatient mortality. They found that earlier antibiotics, earlier blood cultures, and earlier lactate measurement were all associated with lower mortality. However, earlier administration of an intravenous fluid bolus of 30 mL/kg was not associated with improved mortality; a lapse of each subsequent hour until bolus completion had no association with mortality (odds

Table. Representative observational clinical studies published between 2010 and 2017 evaluating the association between early net fluid balance and mortality in adults with sepsis.

Publication	Study Design [Centers]	Population [Sample Size]	Exposure (Predictor) Variable(s)	Primary Outcome	Main Findings
Boyd et al, ⁹ <i>Crit Care Med</i> , 2011	Secondary analysis of a multicenter RCT [27 centers in Canada, Australia, US]	Adults in ICU with septic shock, receiving norepinephrine ≥ 5 $\mu\text{g}/\text{min}$ [n=778]	Net fluid balance at 12 h after initiation of resuscitation; patients classified according to quartile of net fluid balance	28-day mortality	Compared with patients in the highest quartile of fluid balance (median 8.2 L), those in the lower quartiles of fluid balance (quartile 1: 0.7 L; quartile 2: 2.9 L) had lower risk of mortality in adjusted proportional hazard models (quartile 1 vs quartile 4: aHR 0.57; 95% CI 0.41–0.80); quartile 2 vs quartile 4: aHR 0.58; 95% CI 0.41–0.82). A fluid balance of +3 L at 12 h correlated with optimal survival.
Micek et al, ¹⁰ <i>Crit Care</i> , 2013	Retrospective cohort study [1 center in US]	Adults in ICU with septic shock (vasopressor use >12 h) [n=163]	Net fluid balance at 24 h after shock recognition; patients classified according to quartile of net fluid balance	Inhospital mortality	In an adjusted proportional hazards model, patients in the highest quartile of positive fluid balance at 24 h had increased inhospital mortality compared with those in the first quartile ($P=.001$) and second quartile ($P=.03$).
Sadaka et al, ¹¹ <i>J Intensive Care Med</i> , 2014	Retrospective cohort study [1 center in US]	Adults in ICU with septic shock [n=350]	Net fluid balance at 24 h after ICU admission; patients classified into 4 categories according to net fluid balance: <6, 6–12, 12–18, and 18–24 L	In-hospital mortality	In an adjusted proportional hazards model, compared with patients with <6 L fluid balance, those with 6–12, 12–18, and 18–24 L positive fluid balance had higher mortality risk (aHR 1.52, 95% CI 1.35–1.69; 1.74, 95% CI 1.47–2.01; 1.62, 95% CI 1.20–2.04, respectively)
Acheampong and Vincent, ¹² <i>Crit Care</i> , 2015	Prospective cohort study [1 center in Belgium]	Adults in ICU >48 h with sepsis (infection and ≥ 1 organ failure) [n=173]	Net daily fluid balance for first 7 days of ICU stay; daily fluid balance analyzed on a continuous scale	ICU mortality	On a continuous scale, more positive daily fluid balance was associated with increased ICU mortality in an adjusted proportional hazards model (aHR 1.014/mL per kilogram increase; 95% CI 1.007–1.022)
de Oliveira et al, ¹³ <i>J Crit Care</i> , 2015	Retrospective cohort study [1 center in Brazil]	Adults in ICU with sepsis (infection and ≥ 1 organ failure) [n=116]	Net fluid balance between 24 and 48 h after first recognition of organ dysfunction	Inhospital mortality	A net positive fluid balance >3 L was associated with increased hospital mortality in an adjusted logistic regression model (aOR 3.19; 95% CI 1.19–8.54).
Kelm et al, ¹⁴ <i>Shock</i> , 2015	Retrospective cohort study [1 center in US]	Adults in ICU with sepsis (infection and ≥ 1 organ failure) [n=405]	Signs of fluid overload on day 1 (new pitting edema, crackles, anasarca on examination or new vascular congestion, pulmonary edema or pleural effusion on CXR)	Inhospital mortality	Patients with at least one sign of fluid overload on ICU day 1 had higher risk of inhospital mortality in an adjusted logistic regression model (aOR 2.27; 95% CI 1.31–4.09)
Sakr et al, ¹⁵ <i>Crit Care Med</i> , 2017	Prospective cohort study [multicenter, multinational audit during 10 days]	Adults in ICU with sepsis (infection and ≥ 1 organ failure) [n=1,808]	Net fluid balance at 24 and 72 h after ICU admission; patients classified according to quartile of net fluid balance	28-day inhospital mortality	Fluid balance at 24 h was not associated with mortality; however, higher fluid balance at 72 h was associated with increased mortality. Compared with patients in the lowest quartile of fluid balance at 72 h, aHRs for quartiles 2, 3, and 4 were 1.36 (95% CI 1.03–1.80), 1.47 (95% CI 1.12–1.92), and 1.63 (95% CI 1.25–2.12), respectively.

RCT, Randomized controlled trial; US, United States; aHR, adjusted hazard ratio; L, liter

ratio 1.01 per hour; 95% confidence interval [CI] 0.99 to 1.02). Although confounding is likely in this observational study, these data suggest that early fluid boluses may not be a key component for optimizing sepsis survival.

Furthermore, a growing body of observational literature suggests that larger volumes of intravenous fluid and larger positive net fluid balances are associated with increased mortality in sepsis.^{9-15,49-54} For example, in a recent severity-adjusted multivariable analysis of 23,513 septic adults, each additional liter of intravenous fluid up to 5 L on the first day of treatment was associated with a small decrease in mortality (−0.7% absolute change per liter; 95% CI −1.0% to −0.4%); however, each additional liter beyond 5 L was associated with an increase in mortality (2.3% absolute change per liter of intravenous fluid; 95% CI 2.0% to 2.5%).⁵⁴

The Table summarizes data from 7 recent studies evaluating the association between early net fluid balance and mortality. Cumulatively, these studies included more than 3,500 septic patients from 5 continents, managed according to local usual care. Patients with higher net positive fluid balances consistently experienced higher mortality.⁹⁻¹⁵ Although these results provide rationale for questioning the safety of large-volume fluid boluses and pursuing interventional trials, the high risk of confounding in these observational studies precludes a causality assessment or defining an optimal clinical approach.^{55,56} Severity of illness is a strong potential confounder in the association between volume of fluid administration (and net fluid balance) and mortality because more severely ill septic patients tend to receive more intravenous fluid during routine clinical care.⁵⁴ Although each of these studies used multivariable modeling to adjust for illness severity, potential residual confounding and reverse causality remain concerns.^{55,56}

Clinical Trials Supporting a Restrictive Fluids Approach

Previous trials evaluating a liberal versus restrictive approach largely focused on the postresuscitation period after the resolution of shock.^{52,57,58} In the largest of these trials, the Fluid and Catheter Treatment Trial,⁵⁷ the ARDS Network investigators randomized 1,000 patients to a liberal versus conservative (restrictive) fluids strategy for up to 7 days after the diagnosis of acute respiratory distress syndrome; 85% of these patients had sepsis, pneumonia, or aspiration as the primary cause of acute respiratory distress syndrome, and the mean time from ICU admission to initiation of the fluid management protocol (governed largely by shock resolution) was approximately 40 hours. Compared with patients in the liberal fluids group, those in the restrictive group had lower net fluid balances (mean

cumulative fluid balance after 7 days: −136 mL vs 6,992 mL; $P < .01$), similar 60-day mortality (25.5% versus 28.4%; $P = .30$), and more days alive and free from mechanical ventilation (14.6 versus 12.1; $P < .01$). A post hoc analysis of the subgroup with an initial central venous pressure less than or equal to 8 mm Hg demonstrated substantially greater volumes of fluid administration and higher mortality in patients randomized to the liberal arm compared with the restrictive arm; in the subgroup with initial central venous pressure greater than 8 mm Hg, volume of fluid administered and mortality did not substantially differ between the randomized arms, suggesting that lower fluid volumes administered in the restrictive arm may have been a primary contributor to improved outcomes.⁵⁹ This and other similar trials^{52,58} established the safety of restrictive fluid management in the postresuscitative phase of critical illness and have led investigators to question the practice of large-volume fluid resuscitation during the initial, acute phase of sepsis treatment as well.

To our knowledge, no large clinical trials powered for mortality and conducted in developed countries with advanced critical care capabilities have compared the liberal and restrictive fluid approaches for adults with septic shock during the acute resuscitative phase of management. However, 2 trials in Africa (Fluid Expansion as Supportive Therapy [FEAST]⁴⁰ and the Simplified Severe Sepsis Protocol Trial⁶⁰) and a recent small pilot trial in Northern Europe (Conservative Versus Liberal Approach to Fluid Therapy of Septic Shock in Intensive Care [CLASSIC]¹⁷) suggested potential benefit from an early restrictive approach. Each of these 3 trials is described below.

FEAST Trial

FEAST was an unblinded randomized trial evaluating early intravenous fluid boluses versus usual care without fluid boluses in 3,141 septic children in sub-Saharan East African hospitals.⁴⁰ During the first 8 hours of treatment, children in the bolus group received a median fluid volume of 40 mL/kg, whereas those in the usual care group received a median of 10 mL/kg. Children in the bolus therapy group had higher mortality at 48 hours compared with those in the usual care control group (10.5% versus 7.3%; relative risk 1.45; 95% CI 1.13 to 1.86). Higher mortality for the bolus therapy group was observed across a broad range of subpopulations, including those with respiratory illnesses, neurologic illness, severe anemia, and acidosis.^{8,40} The pathway toward death was more commonly cardiovascular collapse than syndromes characterized by overt fluid overload, such as pulmonary or cerebral edema.⁸ Several characteristics of the FEAST trial limit its generalizability to adults with septic shock in

developed countries, including a study population of children, malaria as the most common infection, and the absence of advanced critical care capabilities (patients were managed on pediatric wards without the availability of mechanical ventilation). Nonetheless, these data suggest that early large-volume fluid boluses are not universally beneficial in early sepsis management.

Simplified Severe Sepsis Protocol Trial

Andrews et al⁶⁰ conducted a randomized trial among 212 adults with septic shock in Zambia to evaluate the effectiveness of the Simplified Severe Sepsis Protocol, which is a quantitative resuscitation protocol similar to early goal-directed therapy, modified for hospitals in developing countries. The study excluded patients with signs of respiratory failure (arterial oxygen saturation <90% and respiratory rate >40 breaths/min) according to previous work in the same setting that suggested the sepsis protocol was harmful for patients with respiratory failure.⁶¹ Patients were randomized to fluid management according to the sepsis protocol versus usual care. The sepsis protocol consisted of an initial 2-L intravenous fluid bolus within 1 hour of sepsis recognition, then an additional 2 L during the subsequent 4 hours. Fluids were stopped if the patient

experienced any of the following: decrease in oxygen saturation by 3%, increase in respiratory rate by 5 breaths/min, or increase in jugular venous pressure to 3 cm above the sternal angle. Usual care in this setting did not include routine large-volume fluid boluses. Patients in the sepsis protocol group received more intravenous fluid than those in the usual care group (median 3.5 L versus 2.0 L; $P<.01$). In-hospital death was more common in the sepsis protocol group than the usual care group (48% versus 33%; $P=.03$). Mechanical ventilation and ICU care were generally not available in this study; therefore, results are not directly generalizable to sepsis management in hospitals with advanced critical care capabilities. However, these results suggest that larger initial fluid boluses may be detrimental in resource-limited settings.

CLASSIC Trial

Hjortrup et al¹⁷ recently published CLASSIC. This was an unblinded pilot trial of 151 adults with septic shock, conducted in 9 Northern European ICUs, to test whether separation in fluid volumes could be achieved between an intervention group (restrictive fluids approach) and usual care group (liberal fluids approach). After ICU admission and initial fluid administration of at least 30 mL/kg,

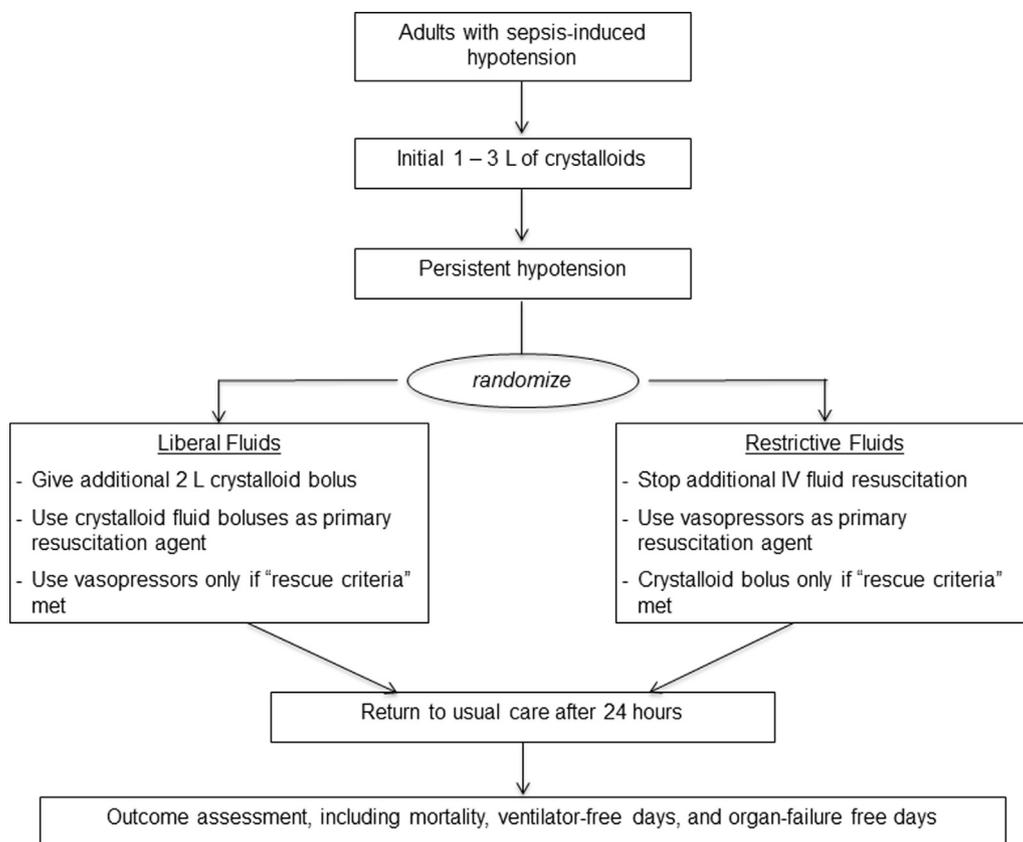


Figure 3. Trial design summary for the CLOVERS trial.

patients were randomized to (1) restrictive fluids, in which additional fluid could be administered only for overt signs of severe hypoperfusion, such as mean arterial pressure less than 50 mm Hg despite norepinephrine infusion, plasma lactate level greater than 4 mmol/L, skin mottling proximal to the knee, or urine output less than 0.1 mL/kg per hour; versus (2) usual care, in which additional fluid was allowable as long as fluid challenges were thought by the treating clinicians to improve hemodynamics. Patients randomized to the restrictive fluids group received less resuscitation fluid during 5 days than those in the usual care group (absolute difference -1.2 L; 95% CI -2.0 to -0.4 L). Although this trial was not powered to detect differences in clinical outcomes, patients in the restrictive fluid group were less likely to have worsening kidney injury (odds ratio 0.46; 95% CI 0.23 to 0.93) and had a non-significant point estimate favoring lower 90-day mortality (odds ratio 0.71; 95% CI 0.36 to 1.40).

CLOVERS: AN UPCOMING TRIAL

Recognizing the equipoise around intravenous fluid management during early sepsis resuscitation and the critical importance of high-quality data in this area to promote continued improvement in sepsis outcomes, the National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury Clinical Trials Network (<http://www.petalnet.org>) developed the CLOVERS trial. The network consists of emergency medicine and critical care researchers at more than 40 enrolling centers dedicated to conducting randomized controlled trials for improving the care of critically ill ED and ICU patients with or at risk for acute respiratory distress syndrome.

CLOVERS will be a multicenter, unblinded clinical trial comparing liberal and restrictive fluid resuscitation strategies for the first 24 hours of septic shock management among adults in the United States (Figure 3). The liberal strategy will consist of intravenous fluid management similar to that of the usual care groups in ProCESS,² ARISE,³ and ProMiSe,⁴ in which fluid administration is encouraged as first-line treatment for signs of hypoperfusion without overt fluid overload. The restrictive strategy will consist of early vasopressor initiation after an initial modest fluid bolus (≤ 3 L), with additional fluids administered only for signs of extreme intravascular volume depletion. This will enable direct comparison between liberal and restrictive fluid strategies for early sepsis resuscitation. Unlike the CLASSIC trial,¹⁷ in which enrolled patients received a median of 4 to 5 L of intravenous fluid before randomization, enrollment for CLOVERS will be in the ED, with patients randomized as soon as possible (but no more than 4 hours) after receiving 1 L of fluid. Patients randomized to the restrictive

strategy will begin receiving a vasopressor infusion to support mean arterial pressure, whereas those randomized to the liberal strategy will receive an additional 2 L of intravenous fluid before vasopressors are considered (except in patients with extreme hypotension necessitating simultaneous fluid and vasopressor resuscitation). The primary outcome will be inhospital mortality to day 90, with key secondary outcomes including ventilator-free days and organ-failure-free days to day 28.

In conclusion, despite significant progress during the past 2 decades, morbidity and mortality from septic shock remain unacceptably high and additional improvement is needed. Intravenous fluid resuscitation is considered an important initial step in sepsis management, but the optimal dosing for intravenous fluid and timing for vasopressors are unknown. Although large-volume fluid boluses of 4 to 5 L within the first 6 hours of treatment are common, this practice is based on low-quality evidence. A growing body of literature has highlighted potential adverse effects from rapid, large-volume fluid boluses. Shifting toward earlier vasopressors and less intravenous fluid during initial resuscitation for septic shock is a potential avenue to improve outcomes; however, current evidence for this approach on patient-centered outcomes is lacking. The upcoming CLOVERS trial will directly compare a liberal and restrictive fluids strategy for early septic shock management in EDs and ICUs in the United States, with the goal of providing patient outcome data needed to inform and guide clinical practice.

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