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

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Abstract

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 – 75 ml/kg (4–6 liters in an 80 kg adult) over 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 (≤2–3 liters)] 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 (NHLBI) Prevention and Early Treatment of Acute Lung Injury (PETAL) Network, we designed a randomized clinical trial to compare the liberal and restrictive fluids strategies—the *Crystalloid Liberal Or Vasopressor Early Resuscitation in Sepsis* (CLOVERS) trial. The purpose of this manuscript 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.

INTRODUCTION

For the past two decades, clinicians in the emergency department (ED) and intensive care unit (ICU) have routinely administered large volumes of intravenous fluid (IVF) to patients with septic shock, often totaling greater than 5 liters (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.

With inadequate evidence to support a specific IVF strategy for the management of early septic shock, two alternative approaches have emerged: (1) *a liberal fluids approach* that relies on a larger volume of initial IVF administration [often 50 – 75 ml/kg (4–6 liters in an 80 kg adult)]; and (2) *a restrictive fluids approach* consisting of a smaller volume of initial IVF [often ≤30 ml/kg (≤2–3 liters)] 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 IVF resuscitation—the *Crystalloid Liberal Or Vasopressor Early Resuscitation in Sepsis* (CLOVERS) trial. The goal of this manuscript is to describe the current state of the literature regarding IVF resuscitation in early septic shock and the rationale for the upcoming CLOVERS trial.

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LIBERAL FLUIDS APPROACH

A “liberal” fluids approach to septic shock management is characterized by the administration of several liters (typically 50 – 75 ml/kg) of IVF during the first several hours of treatment.[1,16,17] Vasopressor infusions are added immediately if the patient is profoundly hypotensive (e.g., 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 (US), based in part on the initial Surviving Sepsis Campaign recommendations and Early Goal Directed Therapy (EGDT).[1,2,5] A liberal fluids approach is also encouraged by the SEP-1 Core Measure from the Centers for Medicare and Medicaid Services (CMS) and 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 via capillary endothelial dysfunction, both which contribute to hypotension.[5] IVF administration replenishes intravascular fluid lost to the extravascular space and increases volume within dilated vessels, potentially increasing cardiac pre-load, 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 following 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 on vasopressors to be admitted to an ICU, thus preserving ICU bed capacity.

Clinical Evidence Supporting a Liberal Fluids Approach

In the 1990s, in-hospital mortality rates for septic shock were 40%−50% for hospitals in developed countries.[5] In 2001, Rivers et al[22] published results of a trial noting lower in-hospital mortality with EGDT, a protocolized resuscitation strategy targeting CVP, mean arterial pressure (MAP), and central venous oxygen saturation ($ScvO_2$). Patients in the EGDT group received larger fluid volumes during the first 6 hours of treatment than those in the standard therapy group (mean volume of IVF administration: 5.0 L vs 3.5 L), and experienced a lower in-hospital mortality (31% vs 47%).[22]

Following the Rivers et al trial[22], early large volume fluid resuscitation was widely adopted in the US.[1,2,5,16] Observational studies at many institutions during the next 10 years suggested that implementation of EGDT protocols, even with incomplete adherence, were associated with larger volumes of fluid administration and lower mortality (Figure 1–2).[5,23–26] For example, Puskarich et al[26] conducted a before-after analysis of EGDT therapy

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implementation at their institution and found a substantial increase in the volume of IVF administered during the first 6 hours of resuscitation (mean 2.3 L before EGDT vs 4.1 L with EGDT) and decline in in-hospital mortality (27% vs 17%). However, most of these early studies evaluating the impact of EGDT 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 EGDT in observational studies was largely due to earlier and more appropriate antibiotics, not fluid volumes or achievement of hemodynamic goals.[29]

In 2014–2015, results of 3 large multicenter trials evaluating EGDT were published. Each of these trials—ProCESS[2] in the US, ARISE[3] mostly in Australia and New Zealand, and ProMISe[4] in England—demonstrated no incremental mortality benefit between patients initially resuscitated according to EGDT versus usual care. While the timing of fluid administration varied between arms, overall IVF volume between ED presentation and 6 hours post-enrollment was approximately 4 – 5 liters in all groups of all trials. This suggests that early large volume fluid resuscitation was part of usual care (Figure 1–2). 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% – 25%) since the 1990s (approximately 40% - 50%), when early large volume fluid resuscitation was less common.[5,31] Of note, several factors other than fluid resuscitation likely contributed to a decline in reported sepsis mortality over time, including implementation of early sepsis screening, diagnosing less severely ill patients as having sepsis, and changes to administrative coding for sepsis.[29,32,33] Nonetheless, a concurrent decline in sepsis mortality during the same time period in which usual care shifted toward larger volume fluid resuscitation suggests adoption of a liberal fluid strategy may have contributed to a decrease in sepsis mortality during the past two 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 IVF boluses only transiently increase intravascular volume, but subsequently lead to pathologic

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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 are 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 return and cardiac output in a fashion similar to an IVF bolus without burdening tissues with excess extravascular fluid.[38]

Increasing CVP with IVF 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 non-vital tissues; rapid reversal of this adaptive physiologic response with IVF 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 only does so for 30–60 minutes.[6,7,41–44] Thus, many septic patients treated with IVF 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 over the past two 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 al[48] 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 in-patient mortality. They found that earlier antibiotics, earlier blood cultures, and earlier lactate measurement were all associated with lower mortality. However, earlier administration of a 30 ml/kg IVF bolus was not associated with improved mortality; a lapse of each subsequent hour until bolus completion had no association with mortality (odds ratio: 1.01 per hour, 95% 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 larger volumes of IVF 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 IVF 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 IVF, 95% CI: +2.0 to +2.5%).[54]

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Table 1 summarizes data from 7 recent studies evaluating the association between early net fluid balance and mortality. Cumulatively, these studies included over 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] While 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 IVF 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

Prior trials evaluating a liberal versus restrictive approach largely focused on the post-resuscitation period after the resolution of shock.[52,57,58] In the largest of these trials, the Fluid and Catheter Treatment Trial (FACTT),[57] the ARDS Network Investigators randomized 1,000 patients to a liberal versus conservative (restrictive) fluids strategy for up to 7 days following the diagnosis of ARDS; 85% of these patients had sepsis, pneumonia or aspiration as the primary etiology of ARDS, 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 6992 ml, $p < 0.01$), similar 60-day mortality (25.5% vs 28.4%, $p=0.30$), and more days alive and free from mechanical ventilation (14.6 vs. 12.1, $p<0.01$). A post-hoc analysis of the subgroup with an initial CVP ≤8 mm Hg demonstrated substantially greater volumes of fluid administration and higher mortality in patients randomized to the liberal arm compared to the restrictive arm; in the subgroup with initial CVP >8, volume of fluid administered and mortality did not substantially differ between the randomized arms, suggesting 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 post-resuscitative 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.

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, two trials in Africa (FEAST[40] and the Simplified Severe Sepsis Protocol Trial[60]) and a recent small pilot trial in Northern Europe (CLASSIC[17]) suggested potential benefit from an early restrictive approach. Each of these 3 trials is described below.

FEAST Trial

FEAST (Fluid Expansion As Supportive Therapy) was an unblinded randomized trial evaluating early IVF boluses versus usual care without fluid boluses in 3,141 septic children

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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, while 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 to those in the usual care control group (10.5% vs 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 sub-populations, including those with respiratory illnesses, neurologic illness, severe anemia, and acidosis.[8,40] The pathway toward death was more commonly cardiovascular collapse rather 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 al[60] 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 EGDT modified for hospitals in developing countries. The study excluded patients with signs of respiratory failure (arterial oxygen saturation <90% and respiratory rate >40 breaths per minute) based on prior work in the same setting suggesting 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 IVF bolus within 1 hour of sepsis recognition, then an additional 2 L over 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 per minute, 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 IVF than those in the usual care group (median 3.5 L vs 2.0 L, p <0.01). In-hospital death was more common in the sepsis protocol group than the usual care group (48% vs 33%, p=0.03). 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 larger initial fluid boluses may be detrimental in resource-limited settings.

CLASSIC Trial

Hjortrup et al[17] recently published *CLASSIC* (Conservative versus Liberal Approach to fluid therapy of Septic Shock in Intensive Care). This was an unblinded pilot trial of 151 adults in 9 Northern European ICUs with septic shock 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, patients were randomized to: (1) restrictive fluids, in which additional fluid could only be administered for overt signs of severe hypoperfusion, such as MAP <50 mm Hg despite norepinephrine infusion, plasma lactate >4 mml/L, skin

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mottling proximal to the knee, or urine output <0.1 ml/kg/hr; 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 over 5 days than those in the usual care group (absolute difference: −1.2 L, 95% CI: −2.0, −0.4). 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 (OR: 0.46, 95% CI: 0.23, 0.93) and had a non-significant point estimate favoring lower 90-day mortality (OR: 0.71, 95% CI: 0.36, 1.40).

CLOVERS: AN UPCOMING TRIAL

Recognizing the equipoise around IVF 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 (NHLBI) Prevention and Early Treatment of Acute Lung Injury (PETAL) Clinical Trials Network (www.petalnet.org) developed the CLOVERS trial. PETAL 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 (ARDS).

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 US (Figure 3). The liberal strategy will consist of IVF management similar to 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 – 5 L of IVF prior to 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 be started on a vasopressor infusion to support mean arterial pressure, while patients randomized to the liberal strategy will receive an additional 2 L of IV fluid before considering vasopressors. The primary outcome will be in-hospital 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 two decades, morbidity and mortality from septic shock remain unacceptably high and additional improvement is needed. IVF resuscitation is considered an important initial step in sepsis management, but the optimal dosing for IVF and timing for vasopressors are unknown. Although large-volume fluid boluses of 4–5 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 IVF during initial resuscitation for septic shock is a potential avenue to improve outcomes; however, current evidence for this approach on patient-centered outcomes is

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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 US with the goal of providing patient outcome data needed to inform and guide clinical practice.

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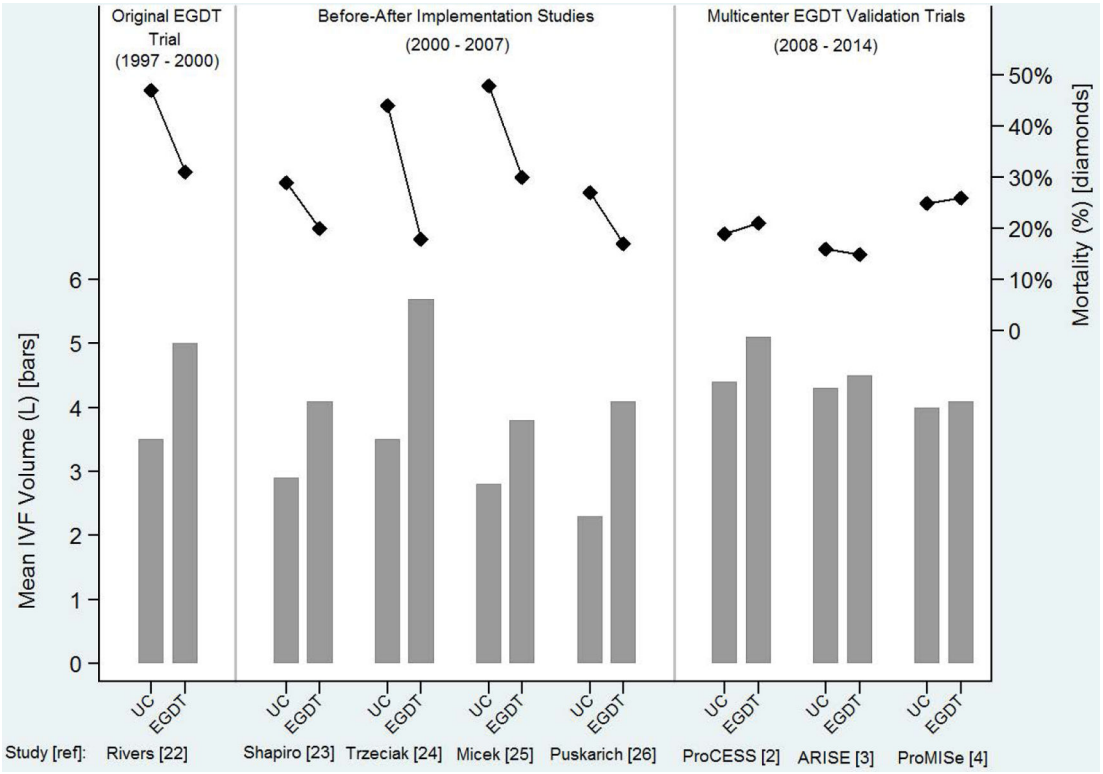

Figure 1.

Volume[a] of early intravenous fluid administration (bars; left axis) and mortality[b] (diamonds; right axis) in severe sepsis and septic shock studies comparing usual care to Early Goal Directed Therapy. Bars show the volume of fluid administered in liters for the usual care and Early Goal Directed Therapy groups in each study. The connected dots demonstrate the percentage of patients who died in usual care and Early Goal Directed Therapy groups in each study. Patients in the usual care group of later studies tended to receive more fluid than those in the usual care group of earlier studies, and similar to patients in the Early Goal Directed Therapy groups. Mortality was higher in the usual care group of studies in which usual care patients received less fluid than Early Goal Directed Therapy patients, but similar in the later studies in which the usual care and Early Goal Directed Therapy groups received similar volumes of fluid. UC: usual care; EGDT: Early Goal Directed Therapy; L: liter

Footnotes:

a. Time window for reported mean fluid volumes: first 6 hours after ED presentation: Rivers[22], Shapiro[23], Puskarich[26]; total volume during ED stay: Trzeciak[24], Micek[25]; pre-randomization period plus 6 hours post-randomization: ProCESS[2], ARISE[3], ProMISe[4].

b. Time window for reported mortality: in-hospital: Rivers[22], Trzeciak[24], Puskarich[26], ProMISe[4]; 28-day in-hospital: Shapiro[23]; 28-day: Micek[25]; 60-day in-hospital: ProCESS[2], ARISE[3].

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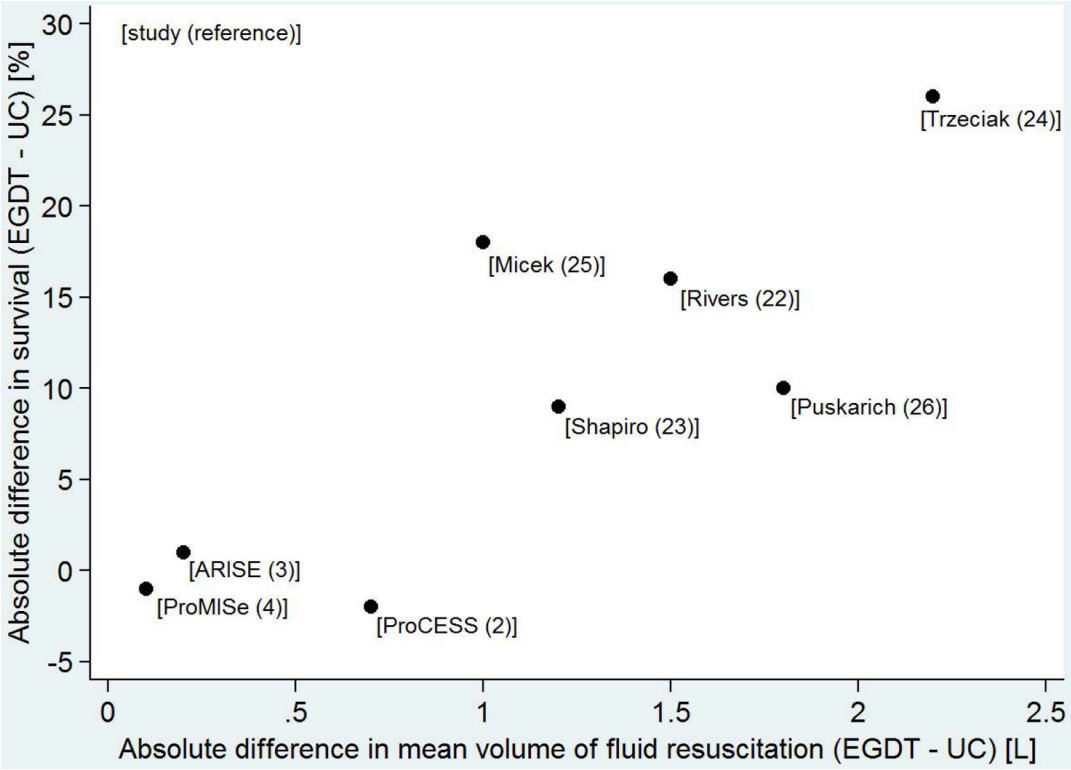

Figure 2.

Scatterplot demonstrating the relationship between the difference in mean volume of fluid resuscitation[a] in the Early Goal Directed Therapy group and usual care group (x-axis) verses difference in survival[b] in the Early Goal Directed Therapy group and usual care group (y-axis) among 8 studies comparing Early Goal Directed Therapy and usual care 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. UC: usual care; EGDT: Early Goal Directed Therapy; L: liter

Footnotes:

a. Time window for reported mean fluid volumes: first 6 hours after ED presentation: Rivers[22], Shapiro[23], Puskarich[26]; total volume during ED stay: Trzeciak[24], Micek[25]; pre-randomization period plus 6 hours post-randomization: ProCESS[2], ARISE[3], ProMISe[4].

b. Time window for reported survival: in-hospital: Rivers[22], Trzeciak[24], Puskarich[26], ProMISe[4]; 28-day in-hospital: Shapiro[23]; 28-day: Micek[25]; 60-day in-hospital: ProCESS[2], ARISE[3].

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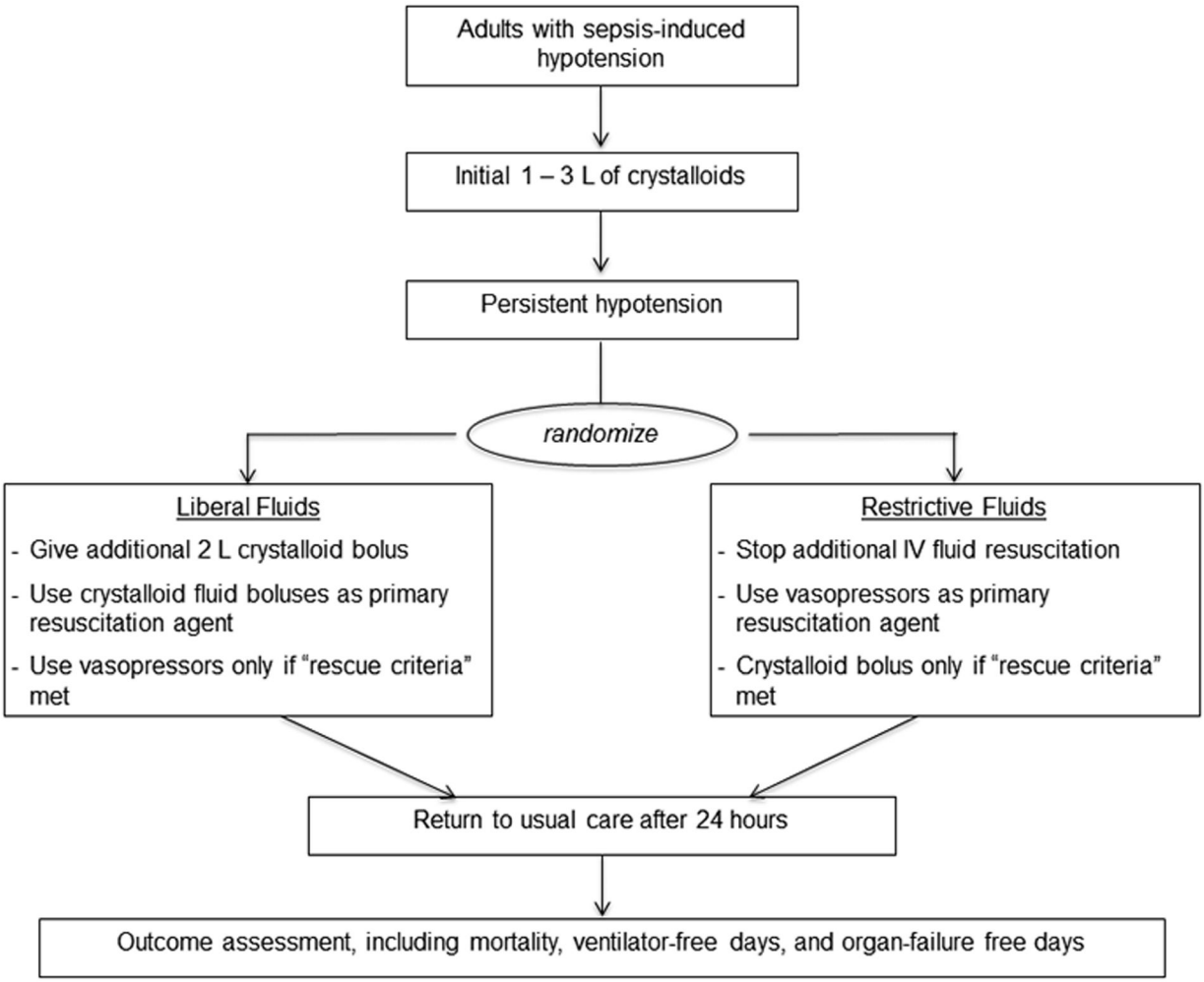

Figure 3.
Trial design summary for the Crystalloid Liberal Or Vasopressor Early Resuscitation in Sepsis (CLOVERS) trial.

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Table.

Representative observational clinical studies published between 2010 and 2017 evaluating the association between early net fluid balance and mortality in adults with sepsis. RCT: randomized controlled trial; ICU: intensive care unit; CI: confidence interval; HR: hazard ratio; OR: odds ratio; US: United States

Publication	Study Design [centers]	Population [sample size]	Exposure (Predictor) Variable(s)	Primary Outcome	Main findings
Boyd et al. Crit Care Med 2011[9]	Secondary analysis of a multicenter RCT [27 centers in Canada, Australia, USA]	Adults in ICU with septic shock on norepinephrine ≥5 mcg/min [n = 778]	Net fluid balance at 12 hours after initiation of resuscitation; patients classified according to quartile of net fluid balance	28-day mortality	Compared to 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 (0.41, 0.82). A fluid balance of +3 L at 12 hours correlated with optimal survival.
Micek et al. Crit Care 2013[10]	Retrospective cohort study [1 center in US]	Adults in ICU with septic shock (vasopressor use >12 hours) [n = 163]	Net fluid balance at 24 hours after shock recognition; patients classified according to quartile of net fluid balance	In-hospital mortality	In an adjusted proportional hazards model, patients in the highest quartile of positive fluid balance at 24 hours had increased in-hospital mortality compared to those in the first quartile (p=0.001) and second quartile (p=0.034).
Sadaka et al. J Intensive Care Med 2014[11]	Retrospective cohort study [1 center in US]	Adults in ICU with septic shock [n = 350]	Net fluid balance at 24 hours after ICU admit; patients classified into 4 categories according to net fluid balance: <6L, 6–12 L, 12–18L, 18–24L.	In-hospital mortality	In an adjusted proportional hazards model, compared to patients with <6 L fluid balance, those with 6–12L, 12–18L, and 18–24 L

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Publication	Study Design [centers]	Population [sample size]	Exposure (Predictor) Variable(s)	Primary Outcome	Main findings
					positive fluid balance had higher mortality risk [aHR: 1.52 (1.35, 1.69), 1.74 (1.47, 2.01), 1.62 (1.20, 2.04), respectively].
Acheampong & Vincent. Crit Care 2015[12]	Prospective cohort study [1 center in Belgium]	Adults in ICU >48 hours with sepsis (infection & ≥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 per ml/kg increase (95% CI: 1.007, 1.022)].
de Oliveira et al. J Crit Care 2015[13]	Retrospective cohort study [1 center in Brazil]	Adults in ICU with sepsis (infection & ≥1 organ failure) [n = 116]	Net fluid balance between 24 and 48 hours after first recognition of organ dysfunction	In-hospital mortality	A net positive fluid balance >3 L was associated with increased hospital mortality in an adjusted logistic regression model [aOR 3.19 (1.19, 8.54)].
Kelm et al. Shock 2015[14]	Retrospective cohort study [1 center in US]	Adults in ICU with sepsis (infection & ≥1 organ failure) [n = 405]	Signs of fluid overload on day 1 (new pitting edema, crackles, anasarca on exam or new vascular congestion, pulmonary edema or pleural effusion on CXR)	In-hospital mortality	Patients with at least one sign of fluid overload on ICU day #1 had higher risk of in-hospital mortality in an adjusted logistic regression model [aOR: 2.27 (95% CI: 1.31, 4.09)].
Sakr et al. Crit Care Med 2017[15]	Prospective cohort study [multicenter, multinational audit over 10 days]	Adults in ICU with sepsis (infection & ≥1 organ failure) [n = 1,808]	Net fluid balance at 24 hours and 72 hours after ICU admission; patients classified according to quartile of net fluid balance	28-day in-hospital mortality	Fluid balance at 24 hours was not associated with mortality; however, higher fluid balance at 72 hrs was associated with increased mortality. Compared with patients in the lowest

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Publication	Study Design [centers]	Population [sample size]	Exposure (Predictor) Variable(s)	Primary Outcome	Main findings
					quartile of fluid balance at 72 hrs, adjusted hazard ratios for quartiles 2, 3, and 4 were 1.36 (1.03, 1.80), 1.47 (1.12, 1.92), and 1.63 (1.25, 2.12), respectively.