# Early Liberal Fluids for Sepsis Patients Are Harmful

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Our key arguments are as follows: 1) fluid balance and input in randomized controlled trials (RCTs) of therapies in septic shock varies widely; 2) a conservative fluid strategy decreased ventilator and ICU durations compared to liberal fluid strategy in the Fluids and Central Catheters Trial; 3) observational cohort studies show that higher fluid balance is associated with increased mortality; 4) there is a high prevalence of non-fluid responsive patients with severe sepsis and septic shock; 5) mechanisms of increased fluid overload that could lead to death include pulmonary, intra-abdominal, and cerebral edema; 6) well-defined mediators of increased permeability in sepsis increase the risk of tissue edema with even modest increases in transmural hydrostatic pressure; and 7) type of fluid might matter (albumin may have decreased mortality in septic shock).

## FLUID INPUT AND FLUID BALANCE IN SEPSIS AND SEPTIC SHOCK TRIALS

Intravenous fluid resuscitation is the cornerstone of acute resuscitation of sepsis and septic shock, with the overarching goal of improving organ perfusion, often by increasing the mean arterial pressure (MAP). However, at this time, there is no high-level evidence to determine what is the most effective target MAP in septic shock. This was supported in a recent RCT of target MAP 80–85 versus 65–70 mm Hg, which found no difference in mortality (1).

Our first argument to define that early liberal fluids are harmful in septic shock patients is based on a review of fluid balance and input in the rich "Early Goal Directed Therapy" (EGDT) literature. Despite the rigor and very similar inclusion criteria, EGDT RCTs showed a great variability of fluid balance and input. Our previous editorial demonstrated that fluid balance varied from +1,500 to +3,500 mL on the first day of sepsis treatment (2). Also, this fluid balance variability widened considerably over the first 4 days of septic shock, ranging from –2,767 to +11,000 mL (2).

Three important multicenter RCTs (Protocolized Care for Early Septic Shock, Protocolised Management in Sepsis, and Australasian Resuscitation in Sepsis Evaluation) (3–5) were done after the original single centre EGDT RCT (6) to validate the efficacy of EGDT in early septic shock compared to usual care. These RCTs found no differences in mortality between these two different strategies. We highlight that fluid input in RCTs during the first 6 hours varied from about 1,700 (3) to nearly 5,000 mL (6), and was lower compared to the original EGDT RCT (**Table 1**), regardless of treatment group (3–7).

We, therefore, argue that first, even in the rigorous environment of RCTs in sepsis and septic shock, fluid balance and input vary widely across RCTs and second that recent EGDT RCTs had uniformly decreased fluid resuscitation volume compared to the original EGDT. The lack of evidence-based definition of the optimal target MAP in septic shock may explain, in part, this remarkable variablity in fluid input and balance in sepsis and septic shock RCTs.

## COHORT STUDIES OF FLUID INPUT AND BALANCE IN SEPSIS AND SEPTIC SHOCK

Our next evidence from observational cohorts shows overwhelmingly that greater fluid balance is associated with increased mortality (**Table 2**). Although we concede that positive fluid balance in septic patients simply might be a marker of severity of sepsis and septic shock, large multicentre observational cohort studies (8–14) show clearly that higher fluid balance is associated with increased mortality (Table 2). The Sepsis Occurrence in Acutely Ill Patients study demonstrated that each 1 L increment in fluid balance in the first 72 hours of sepsis was associated with a 10% increased mortality rate (15). Similarly, Boyd et al (10) pooled the Vasopressin and Septic Shock Trial RCT to create an observational cohort: the two quartiles with the lowest positive fluid balance at 12 hours (+710 to +2,880 mL) had a significantly

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**TABLE 1. Comparison of Fluid Input in the First 6 Hours in Randomized Controlled Trials of Early Goal Directed Therapy**

| Trial (Publication Year) | Early Goal Directed Therapy (mL) (Mean ± SD) | Mortality Rate (28 D) (%) | Usual Care (mL) (Mean ± SD) | Mortality Rate (28 D) (%) |
|---|---|---|---|---|
| Rivers et al (6) | 4,981 ± 2,984 | 33.3 | 3,499 ± 2,438 | 49.2 |
| Jansen et al (7) | 2,697 ± 1,965 | 30.4 | 2,194 ± 1,669 | 35.6 |
| Protocolized Care for Early Septic Shock (5) | 2,805 ± 1,957 | 21[a,b] | 2,279 ± 1,881 | 18.9[a,b] |
| Australasian Resuscitation in Sepsis Evaluation (3) | 1,964 ± 1,415 | 14.8 | 1,713 ± 1,401 | 15.9 |
| Protocolised Management in Sepsis (4) | 2,226 ± 1,443 | 24.8 | 2,022 ± 1,271 | 24.5 |

[a]Fluid input at first 8 hr and therapy guided by lactate levels.
[b]Mortality rate at 60 d.

**TABLE 2. Comparison of Fluid Balance in Survivors and Nonsurvivors in Observational Studies in Critically Ill Patients**

| Authors | Study Design | *n* Inclusion Criteria | Fluid Balance (L) (Mean ± SD) Time | Survivors | Nonsurvivors |
|---|---|---|---|---|---|
| Alsous et al (9) | Retrospective | 36 Septic shock | Day 1 | +3.30 ± 0.57 | +5.61 ± 0.98 |
| Rosenberg et al (13) | Retrospective (ARDS Network Tidal Volume Study Cohort) | 794 ARDS | Day 4[a] | −3.3 ± 3.1[b] | +9.4 ± 10.3[b] |
| Zhang et al (14) | Prospective | 67 Sepsis | Day 1 | +1.03 (0.55–1.82) | +1.89 (1.43–2.39) |
| | | | Day 3[a] | +2.05 (0.87–3.20) | +3.08 (1.64–4.51) |
| Murphy et al (12) | Retrospective | 212 Septic shock and ARDS | Day 7[a] | +8.06 (2.41–13.83) | +13.69 (7.11–20.24) |
| Micek et al (11) | Retrospective | 325 Septic shock | Day 1 | +2.95 (1.63–4.76) | +4.37 (1.63–7.26) |
| Acheampong and Vincent (8) | Prospective | 173 Sepsis | Day 4[c] | 4.1 mL/kg | 20.9 mL/kg |
| Boyd et al (10) | Retrospective (Vasopressin and Septic Shock Trial Study Cohort) | Septic shock | Day 1[d] | 3.4 (1.8–5.9) | 4.4 (2.5–6.6) |

ARDS = Acute Respiratory Distress Syndrome.
[a]Cumulative fluid balance.
[b]Group of patients with positive fluid balance at day 4 had lower hospital mortality rate compared to the group of patients with negative fluid balance at day 4 (37.1% vs 20.1%).
[c]Fluid balance at day 4.
[d]Fluid balance at 12 hr.

lower risk of mortality (hazard ratio, 0.569 and 0.581 for quartile 1 and 2, respectively) compared with the highest fluid balance quartile (+8,150 mL).

The Fluids and Central Catheters Trial RCT evaluated the causal effects of positive fluid balance on outcomes of patients with acute lung injury, comparing two different fluid strategies (conservative vs liberal). Patients in the conservative fluid therapy group needed fewer days of mechanical ventilation and ICU support and had lower hospital mortality (16).

Taking the previous findings together, we conclude that aggressive fluid resuscitation leading to greater positive fluid balance increases adverse outcomes (longer duration of ventilation [16] and increased mortality) (10, 12, 15) in patients with sepsis and septic shock.

## IDENTIFICATION OF NONRESPONDERS TO FLUID RESUSCITATION

Another important argument is based on the high prevalence of non-fluid responsive patients with severe sepsis and septic shock (17), who often experience more adverse effects of excessive fluid administration. An optimal management approach is to identify which patients benefit from fluid therapy before administering fluids. This can be easily assessed by passive leg raising (PLR) maneuver, a more accurate and clinically robust

method for prediction of fluid-responsiveness compared to the "overused" central venous pressure (18, 19).

## MECHANISMS THAT COULD EXPLAIN WHY EXCESS FLUIDS INCREASE MORTALITY: EFFECTS OF HYPERVOLEMIA AND ENDOTHELIAL DYSFUNCTION

Our next proposal is to show "how" increased fluid balance increases mortality. The Frank-Starling principle states that increased capillary transmural hydrostatic pressure (e.g., due to fluid overload) increases transmural fluid leak into tissue interstitum, causing organ edema and ultimately organ dysfunction. Tissue edema causes pulmonary (20), cerebral (21), cardiac (22), and renal (23) dysfunction in animal models of sepsis. Furthermore, edema impairs oxygen and metabolite diffusion, changes tissue architecture, blocks capillary blood flow and lymphatic drainage, and modifies inter-cellular interaction (24).

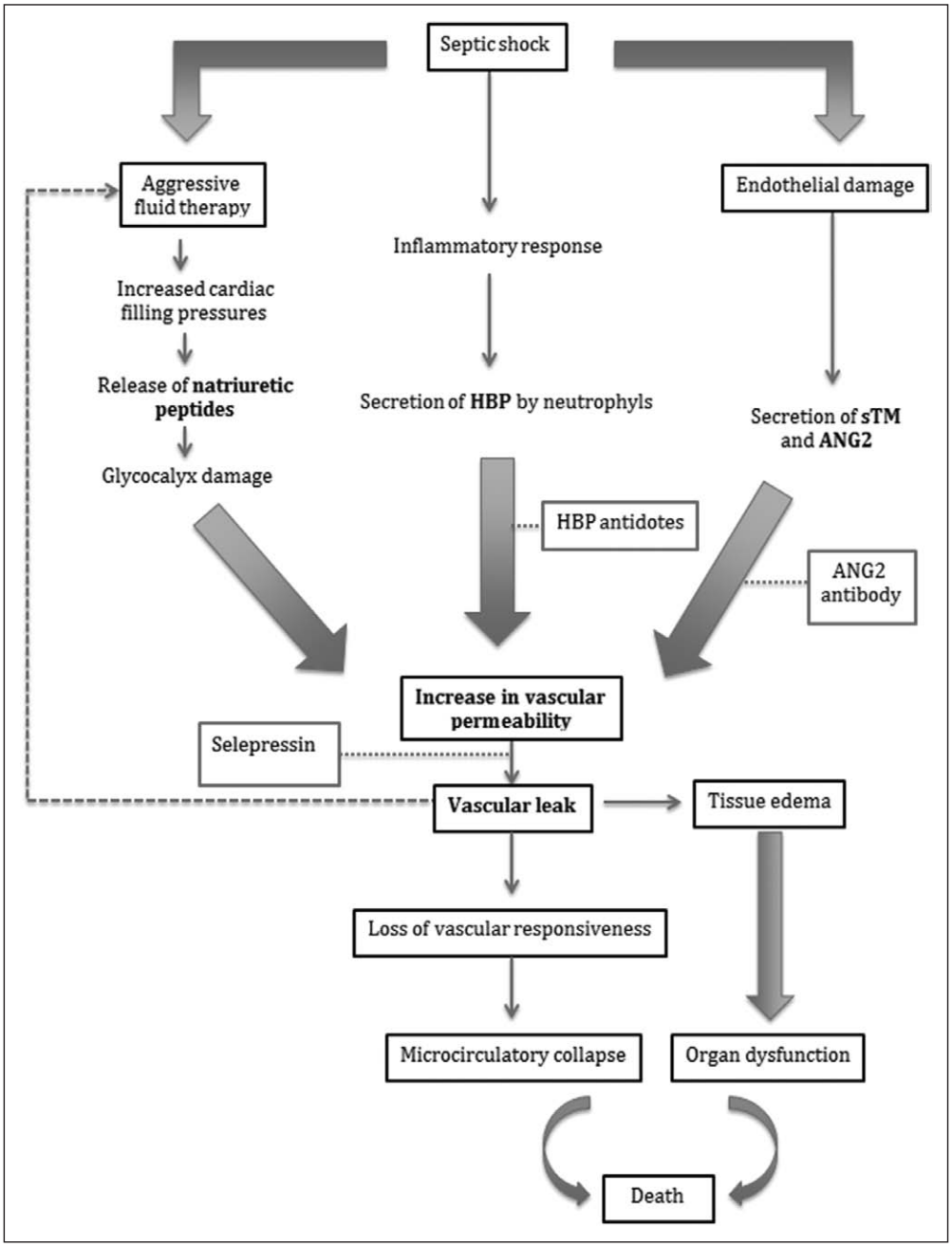


**Figure 1.** Effects of hypervolemia and endothelial dysfunction in septic shock, and potential therapies targeting mediators of increased vascular permeability in sepsis. Endothelial damage and hypervolemia have synergistic effects leading to increase vascular permeability in septic shock. Effects of heparin-binding protein (HBP), soluble thrombomodulin (sTM), angiopoietin-2 (ANG2), and natriuretic peptides are highlighted, culminating in microcirculatory collapse, organ dysfunction, and death. *Blue dotted line* shows the vicious cycle present in sepsis (described in the text). *Red dotted lines* represent therapies that potentially limit the increased vascular permeability present in septic shock.

The association between tissue edema and organ dysfunction may explain why patients with sepsis and high fluid balance have worse outcomes. Increased edema impairs oxygenation and increases work of breathing (due to pulmonary edema); intra-abdominal hypertension contributes to organ—especially renal—hypoperfusion and dysfunction (25); cerebral edema decreases level of consciousness increasing the risk of aspiration and nosocomial pneumonia (26), all of which increase mortality (27).

Sepsis also causes endothelial dysfunction leading to increased vascular permeability (28), thereby exacerbating transmural vascular leak at any given transmural hydrostatic pressure and creating a vicious cycle: 1) sicker patients have greater increases in endothelial permeability; 2) sicker patients have greater third space fluid losses, so they need more fluid input; 3) if fluid input increases transmural hydrostatic pressure even modestly, then sicker patients will have greater fluid leakage into tissues, increasing organ edema, organ dysfunction, and death.

Heparin-binding protein, soluble thrombomodulin, angiopoietin-2, and natriuretic peptides are some of the mediators involved in increased vascular permeability caused by sepsis (29–32). Treatments targeting their effects on

endothelial cells have been investigated (33–36) and might limit fluid requirement, consequently lowering the risks of fluid overload (**Fig. 1**).

## TYPE OF FLUID MIGHT MATTER

We next argue that the type of fluid augments risk of excessive early fluids in sepsis, the age-old colloid/crystalloid controversy, despite recommendations of crystalloids over albumin as the initial fluids of choice by International guidelines (37).

A multicenter open-label RCT (Albumin Italian Outcome Sepsis [ALBIOS]) comparing the use of 20% albumin plus crystalloids to crystalloids alone in 1,810 adult patients with severe sepsis or septic shock showed no difference between groups in 28-day mortality rates. However, in the subgroup of patients with septic shock, there was a significant decrease in 90-day mortality in the albumin compared to crystalloid group (relative risk, 0.88). This is possibly explained by the oncotic, anti-inflammatory, and nitric oxide–scavenging properties of albumin (38). Another hypothesis is that albumin may blunt the early fluid losses caused by increased endothelial permeability. We consider ALBIOS supportive for the concept of limiting fluid balance because albumin could limit permeability, tissue edema, and organ dysfunction.

## CLINICAL RECOMMENDATIONS TO DECREASE RISK OF FLUID OVERLOAD IN SEPSIS

1. Assess fluid-responsiveness using PLR maneuver before initial fluid resuscitation, coupled with real time or intermittent monitoring of cardiac output.
2. Careful early fluid resuscitation with modest fluid challenges (200–500 mL) and titrate according to clinical findings, echocardiography, and noninvasive cardiac output.
3. Start with crystalloids and consider albumin.
4. New treatments to mitigate endothelial injury could be important.

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OPEN

# Early Liberal Fluid Therapy for Sepsis Patients Is Not Harmful: Hydrophobia Is Unwarranted but Drink Responsibly

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## EARLY INTERVENTIONS IMPROVE OUTCOME

Sepsis in the year 2016 remains the most expensive disease treated in hospitals and is the most common cause of in-hospital deaths in the United States (1). However, over the last 15 years, since the introduction of early goal-directed therapy (EGDT) and the Surviving Sepsis Campaign (SSC), there has been a consistent and historic reduction in mortality (2). The reduction from a historic mortality of 46.5% to less than 30% was validated when a trio of multinational trials named Protocolized Care for Early Septic Shock (ProCESS), Australasian Resuscitation in Sepsis Evaluation (ARISE), and Protocolized Management in Sepsis (ProMISe) "compared" various forms of resuscitation strategies (2, 3). This independently obtained historic mortality of 46.5% from an international task force of experts is identical to that of the original EGDT trial (2). Thus, it is absolutely clear that a protocolized approach consisting of early detection (lactate and fluid challenge), antibiotic therapy, source control, prevention of sudden cardiopulmonary events, and early hemodynamic optimization improves outcomes.

Even with unprecedented and replicated mortality benefit, many have proposed to dissemble the original EGDT trial and its components (4). ProCESS, ARISE, and ProMISe attempted to replicate and examine the efficacy of EGDT and have shown all time low mortalities, equal mortality reduction in all arms with no harm of EGDT. For some, these trials have made EGDT synonymous with an early liberal fluid strategy and its negative consequences (5–8). In rebuttal to our distinguished colleagues Genga and Russell (9); we advocate that treating early sepsis is not a time to be hydrophobic. Early fluid therapy in the context of a physiologically based protocol such as EGDT improves mortality for severe sepsis and septic shock.

## THE EBB AND FLOW PHASE OF FLUID MANAGEMENT

In 1942, Cuthbertson (10) described the metabolic response to inflammation, injury, and shock using the concept of the "ebb and flow" phase of critical illness.

> "During the ebb-phase or resuscitation phase, there is low cardiac output, poor tissue perfusion and a cold and clammy patient. During the flow phase which is a staccato affair, the patient struggles to break from the grip of the ebb-phase which last about 3 days. Upon entering the flow-phase, the swollen patient has an increased cardiac output, normal tissue perfusion where diuresis occurs and body weight falls steady."

This eloquent clinical description serves as the framework for the clinical principles of fluid management in early sepsis, **Figures 1** and **2**.

## MECHANISMS FOR THE DEVELOPMENT OF HYPOVOLEMIA IN SEPSIS

Sepsis-induced hypovolemia can be a result of vomiting (poor intake), diarrhea, sweating, edema, peritonitis, or

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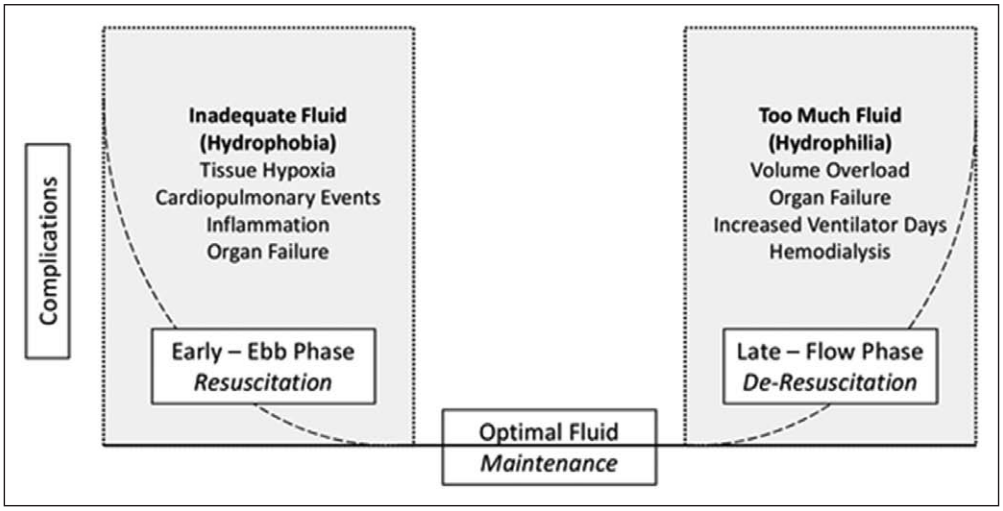


**Figure 1.** Optimal fluid therapy.

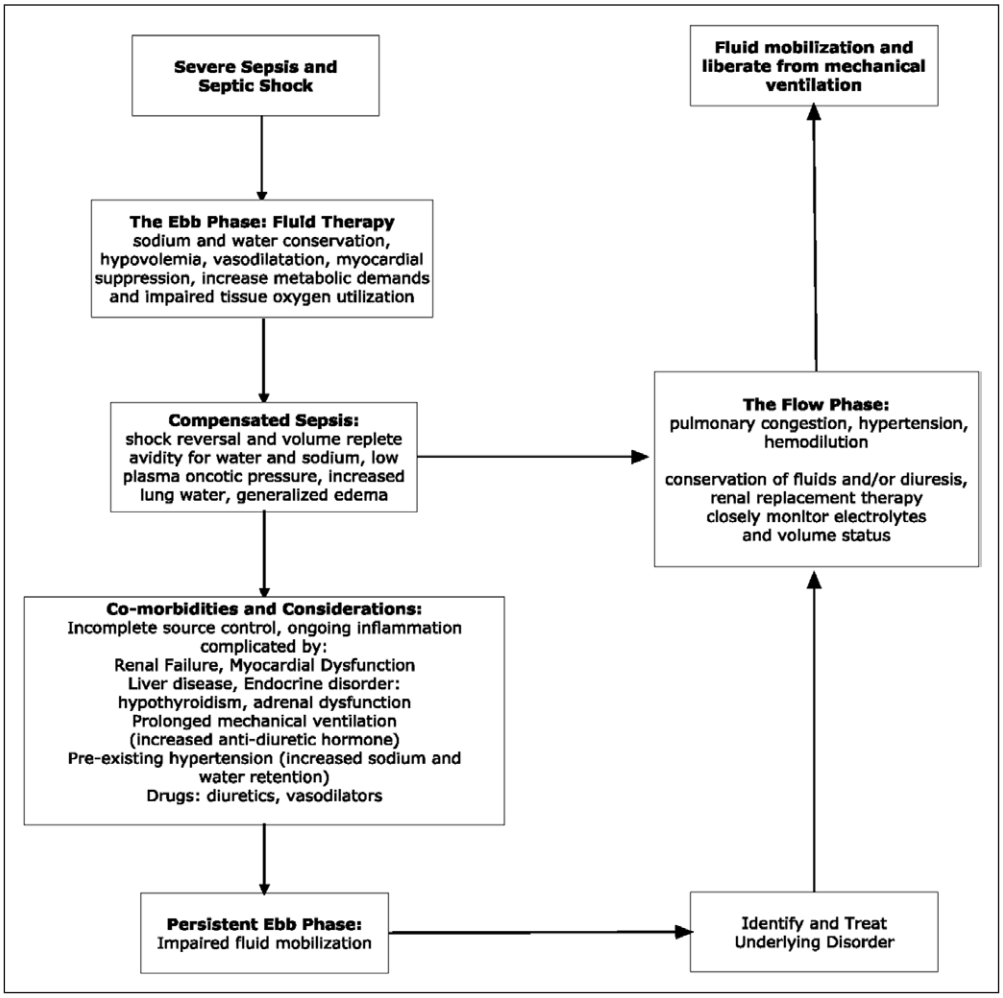


**Figure 2.** The dynamic landscape of fluid management. Reproduced from Schuller et al (11) and Rivers et al (12).

other exogenous losses. Further contributions to hypovolemia may result from vasodilatation, peripheral blood pooling, extravasation of fluid into the interstitial space, and increased capillary endothelial permeability. Hypovolemia and vasodilatation can be exaggerated in patients with comorbidities such as cardiovascular and renal disease where chronic therapy includes diuretics and afterload reduction. All of these mechanisms result in a decrease in intravascular volume which gives rise to a critical reduction in ventricular preload (central venous pressure [CVP]), ventricular diastolic pressure, stroke volume, cardiac output, systemic oxygen delivery, and an increase in systemic oxygen demands (decreased central venous oxygen saturation [$Scvo_2$]) (13).

Compensatory responses as a reaction to decreased circulating blood volume are mediated by the activation of the neuroendocrine system. A redistribution of blood flow away from skeletal muscle beds and the splanchnic viscera supports vital organ blood flow to the heart and brain (14–16), with the augmentation of myocardial contractility leading to increased stroke volume (14). The constriction of arterial and venous capacitance vessels, particularly in the splanchnic bed, augments the venous return (14, 15). The activation of the renin-angiotensin axis releases aldosterone from the adrenal cortex. Changes in serum osmolarity lead to arginine-vasopressin release from the posterior pituitary. Both enhance fluid retention (15, 17–19). Comorbidities, such as congestive heart failure, renal failure, liver disease, and adrenal dysfunction, may modify this salt and water homeostasis and the dynamic "ebb and flow" landscape.

Microcirculatory changes observed in early sepsis such as acidosis, pyrexia, and increased RBC 2,3-diphosphoglycerate

occur, creating a local tissue environment to enhance the unloading of oxygen to tissues. Multiple factors may contribute to microvascular alterations, including driving pressure, alterations in RBC rheology, viscosity (local hematocrit), and leukocyte adhesion to endothelial cells, endothelial dysfunction, and interstitial edema. This is further complicated by the use of vasopressors. The use of techniques evaluating the microcirculation to optimize volume therapy remains to be validated (20, 21).

## EARLY FLUID THERAPY ATTENUATES THE EARLY PATHOGENESIS

The hemodynamic picture of early sepsis is hypotension, decreased CVP, decreased cardiac index, and decreased $Scvo_2$ (13, 22). When the efficacy of antibiotics, cardiovascular support (fluids and dopamine titrated by intravascular monitoring to hemodynamic endpoints), and a combination of these two therapies in dogs with septic shock was compared, survival rates were 0%, 13%, 13%, and 43% in groups receiving no therapy (controls), antibiotics alone, cardiovascular support alone, or combined therapy, respectively (23). Although survivors and nonsurvivors in the combined therapy group required similar quantities of fluid therapy, nonsurvivors gained significantly more weight, suggesting abnormal vascular permeability with extravascular retention of fluids in the nonsurvivors indicating a more pronounced ebb phase. Thus, fluid overload is a result of the method of resuscitation, disease pathogenesis, and underlying comorbidities rather than the clinician's over prescription of fluid administration.

Early fluid therapy modulates initial inflammation. In human models of endotoxemia, isotonic prehydration significantly attenuates concentrations of proinflammatory cytokines (tumor necrosis factor-α, interleukin [IL]-8, and IL-1β), while enhancing concentration of anti-inflammatory cytokines such as IL-10. This effect is associated with a reduction of endotoxin-induced symptoms and fever, while the endotoxin-induced changes in hemodynamic variables remain unchanged. More importantly, the peak activity of the inflammatory response is between 1 and 6 hours after introduction of the insult, which gives rise to the concept of early and late resuscitation as distinct therapeutic entities (24).

## DIAGNOSTIC, THERAPEUTIC, AND OUTCOME IMPLICATIONS OF FLUID THERAPY

Optimizing fluid therapy not only modulates inflammation and increases microvascular perfusion but also decreases the need for vasopressor therapy, steroid use, and more invasive monitoring (20, 24–26). When a clinician is confronted with a profoundly hypotensive patient with an infection, fluid therapy is indicated. However, the clinical assessment of volume status is insensitive, nonspecific, and one of the most challenging clinical assessments. In a post hoc analysis of the Fluids and Catheters Treatment Trial (FACTT) in treatment of acute lung injury (ALI), this hypothesis was examined, which compared physical examination findings of ineffective circulation (capillary refill time > 2 s, skin mottling, and cool extremities) to variables obtained from pulmonary artery catheters. It was found that these physical examination findings are not useful predictors of a low cardiac index or low mixed venous oxygen saturation (27, 28).

## TITRATION OF FLUIDS–A WORK IN PROGRESS

Titration of fluid therapy is performed with numerous methodologies. Frequently, more than one method is required to make an accurate assessment. History, physical examination, dynamic, static and volumetric devices, and ultrasound and metabolic variables can be used, each with certain limitations. Inherent in measuring intravascular pressures is the inference that pressure equals volume. There are many instances for which the pressure within an intracardiac chamber may be elevated and the intravascular volume status may be diminished. The goal is to infuse "adequate" volume to restore perfusion before the onset of irreversible tissue damage without raising cardiac filling pressure to a level that produces hydrostatic pulmonary edema (29, 30). Hemodynamic monitoring used to accomplish these goals can vary and have not been shown to have outcomes superiority (31–33). Although much maligned as a predictor of fluid responsiveness, the general use of CVP in the treatment of severe sepsis and septic shock has been associated with improved outcomes (34–36).

For example, a patient with a CVP of 30 mm Hg, mean arterial pressure (MAP) of 70 mm Hg, heart rate of 80 beats/min, lactate of 5 mM/L, and normal hemoglobin and arterial oxygen saturation and $Scvo_2$ of 44% would get an inotrope. Interestingly, this scenario is associated with increased fluid administration because the CVP is lowered with improved ventricular compliance (37). A patient with a CVP of 4 mm Hg, MAP of 70 mm Hg, heart rate of 80 beats/min, lactate of 5 mM/L, and normal hemoglobin and arterial oxygen saturation and $Scvo_2$ of 44% would get fluid therapy. If CVP was taken in isolation in the first scenario, one would not assume fluid therapy is indicated and some may mistakenly use a diuretic. An elevated CVP has been associated with increased mortality as an interpretation of volume overload when in reality it may be myocardial suppression (38). Thus, using all endpoints in an algorithmic approach is the foundation of a comprehensive resuscitation (39). The discussion regarding CVP is best summarized by Sondergaard et al (35) who stated:

> "Knowledge of the CVP is essential for the measurement of the volume state, the performance of the heart and the SVR. It enters considerations of heart, volume and power efficiency. The CVP provides a floating ground for the differential measurement of intravascular pressures. It does not inherently measure preload or the volume state but its measurement is essential to their calculation. Once the above principles are understood, precise control of the circulation becomes a straightforward mathematically predictable process."

## FLUID THERAPY–EARLY

A hypotensive episode is associated with an increased risk of death, and the response to an adequate fluid challenge improves upon this discriminatory value for risk stratification (40–43). Early fluid therapy targeted to endpoints is associated with a decrease in systemic inflammation, vasopressor use, and mortality and must be distinguished from late aggressive fluid therapy (24, 40, 44–48). Multiple studies have shown that the fluid challenge of 30 mL/kg fluid volume within 3 hours of presentation is associated with increased MAP, normalization of $Scvo_2$, and decreased vasopressor use at 6 hours. There is also a 19% relative reduction in in-hospital 30-day mortality and hospital length of stay (40, 42, 43). This benefit is realized even in patients with a history of renal and heart failure (43). The benefits of fluid administration are maximal when initiated within 30 minutes, making the fluid challenge an important aspect of early sepsis care. Lee et al (40, 49) concluded that "earlier fluid resuscitation may account for the lack of outcome differences between the original EGDT publication and the more recent three trials (ProCESS, ARISE, and ProMISe) and may have contributed to the overall low 60-day in-hospital mortality rate of 19%."

From hospital arrival (prerandomization period) to the end of the 6-hour study period, the total fluid volume was similar and ranged from 3.5 to 5.5 L for the original EGDT publication and ProCESS, ARISE, and ProMISe study groups. Because of the greater lead time prior to enrollment into these trials, between 2 and 2.6 L of fluid was given prior to randomization. There is striking similarity in the amount of fluid given in all trials that approximates the intravascular volume of 5 L. However, the comparative differences in fluid therapy was 1,482 mL (42.4%), 697 mL (16%), 175 mL (4.1%), and 229 mL (4.4%) between the EGDT and usual or control care treatment groups in the EGDT, ProCESS, ARISE, and ProMISe trials, respectively (**Table 1**).

In the EGDT study, this significantly greater volume therapy or treatment effect during the resuscitation (prerandomization and first 6 hr) was associated with a greater reduction (13.8%) in vasopressor therapy, less volume therapy (2 L or 23%), and lower mechanical ventilation rates (14.2%) between the EGDT and control group over the subsequent 6–72-hour time period. These results were observed in the absence of aggressive glucose control, steroid use, protective lung strategies, and conservative fluid management strategies. These were present during the conduction of the ProCESS, ARISE, and ProMISe trials.

## VASOPRESSOR THERAPY

ProCESS, ARISE, and ProMISe trials used vasopressor therapy twice as much compared to the EGDT trial. The more frequent administration of vasopressors in ProCESS, ARISE, and ProMISe may result in a hemodynamic phenotype of "vasodilatory septic shock" which is associated with a lower mortality risk as described by Hernandez et al (50). These findings may further indicate that early vasopressor administration instead of continued fluid therapy may be beneficial once the resuscitation is complete (51). Thus, it seems that ProCESS, ARISE, and ProMISe showed us that 4–6 L of fluid is generally required for early hemodynamic optimization.

The introduction of early vasopressor use is intriguing but challenging (51). Vasodilatory shock after adequate volume resuscitation is the requisite for the physiologic use of corticosteroids. This definition will be altered when vasopressors are introduced at an earlier stage before adequate fluid resuscitation. Waechter et al (52) reports that vasopressor use in the first hour may be associated with increased mortality in patients with greater illness severity. Vasopressor use also increases CVP which may impact volume therapy when this endpoint is artificially elevated (53).

Vasopressor therapy elevates the intensity of patient care because vasopressors require monitoring (i.e., intraarterial pressure monitoring). By placing a patient on vasopressors when adequate volume therapy may have reversed the hypotension, one is placing the patient in a higher level of care and potentially increasing healthcare resource consumption. With EGDT, vasopressor use diminishes by 13.8% over the subsequent 72 hours.

## FLUID THERAPY–LATER

When comparing the original EGDT to ProCESS, ARISE, and ProMISe between 6 and 72 hours, significantly more volume therapy (almost two-fold) was administered in the EGDT study in both treatment groups compared to the three follow-up trials. There was an approximate two-fold increase in vasopressor therapy in ProCESS, ARISE, and ProMISe compared to the EGDT trial during this time period.

ProCESS, ARISE, and ProMISe had mechanical ventilation rates approximately half that of the EGDT and the reference literature (54–56). For example, the SSC database from 2005 to 2008 reports a mechanical ventilation rate of 52.4% (7,877/15,022 of patients), which is almost identical to the EGDT study. Mortality rates in this report were 48.3%, 45.7%, and 33.0% in mechanically ventilated patients with ALI, without ALI, and without mechanical ventilation, respectively. The use of protective lung strategies and conservative fluid management strategies for ALI was not used in the EGDT study as it preceded these trials.

The FACTT trial isolated the manipulation of volume therapy as a controlled intervention which began an average of 43 hours after ICU admission and 24 hours after the establishment of ALI (11). Although there was no difference in 60-day mortality, patients in the conservative strategy group had significantly improved lung and CNS function (decreased need for sedation) along with mechanical ventilation and thus ICU care. There was a statistically significant 0.3-day increase in cardiovascular failure free days in the liberal compared to the conservative fluid group. The increased early volume in the EGDT led to a decreased need for mechanical ventilation over the first 72 hours of hospitalization. This may be due to the modulating effects on IL-8, which has been identified as an ALI culprit within the first 72 hours of presentation (57, 58).

The findings of the FACTT trial brought attention to the negative consequences of the overuse of fluid administration.

**TABLE 1. Comparison of Treatments in Sepsis Trials**

| Therapeutic Intervention | EGDT | | Protocolized Care for Early Septic Shock | | | Australasian Resuscitation in Sepsis Evaluation | | Protocolized Management in Sepsis | |
|---|---|---|---|---|---|---|---|---|---|
| | EGDT | Control | EGDT | Protocol-Based Standard Therapy | UC | EGDT | UC | EGDT | UC |
| Fluid from emergency department arrival to 6 hr[a], mL | 4,981 | 3,499 | 5,059 | 5,511 | 4,362 | 4,479 | 4,304 | 4,216 | 3,987 |
| Difference between groups[b], mL | 1,482 | | | −452 and 667 | | 175 | | 229 | |
| Difference between groups (%) | 42.4 | | | 16 | | 4.1 | | 4.4 | |
| Fluids 6–72 hr, mL | 8,625 | 10,602 | 4,458 | 4,918 | 4,354 | 4,274 | 4,382 | 4,215 | 4,366 |
| Total fluids 0–72 hr, mL | 13,443 | 13,358 | 7,253 | 8,193 | 6,663 | 6,906 | 6,672 | 5,946 | 5,844 |
| Vasopressor 0–6 hr, % | 27.4 | 30.3 | 54.9 | 52.2 | 44.1 | 66.6 | 57.8 | 53.3 | 46.6 |
| Vasopressor 6–72 hr, % | 29.1 | 42.9 | 47.6 | 46.6 | 43.2 | 58.8 | 51.5 | 57.9 | 52.6 |
| Vasopressor 0–72 hr, % | 36.8 | 51.3 | 60.4 | 61.2 | 53.7 | | | 60.5 | 55.0 |
| Inotrope 0–6 hr, % | 13.7 | 0.8 | 8.0 | 1.1 | 0.9 | 15.4 | 2.6 | 18.1 | 3.8 |
| Inotrope 6–72 hr, % | 14.5 | 8.4 | 4.3 | 2.0 | 2.2 | 9.5 | 5.0 | 17.7 | 6.5 |
| Mechanical ventilation 0–6 hr, % | 53.0 | 53.8 | 26.4 | 24.7 | 21.7 | 34.8[c] | 32.9[c] | 20.2 | 19.0 |
| Mechanical ventilation 6–72 hr, % | 2.6 | 16.8 | 33.7 | 31.4 | 27.9 | 38.6[c] | 40.6[c] | 24.4 | 25.4 |
| Any mechanical ventilation, % | 55.6 | 70.6 | 36.2 | 34.1 | 29.6 | 30.0 | 31.5 | 27.4 | 28.5 |
| Steroids prerandomization, % | None | None | 9.3 | 9.4 | 8.3 | | | 5 | 4 |
| Steroids 0–6 hr, % | None | None | 12.3 | 10.8 | 8.1 | | | 11.7 | 11.5 |
| Any steroids 72 hr, % | None | None | | | | 36.9 | 35.9 | 21.9 | 21.1 |

EGDT = early goal-directed therapy, UC = usual care.

[a]The prerandomization period refers to a time frame prior to the time informed consent for study enrollment. Interventions were initiated as indicated.

[b]Difference between groups are early goal-directed therapy minus the treatment group in each trial; Prerandomization and 6 hr of study.

[c]Combined invasive and noninvasive mechanical ventilation.

In order to generalize these results and avoid mitigating the salutary findings, multiple variables must be considered when applying a conservative fluid management approach. The exclusion of patients on hemodialysis, overt renal insufficiency, heart failure, and the relatively young age of the patients studied (age, 50 yr) make the FACTT trial a departure from the reality that many clinicians will face in the treatment of severe sepsis and septic shock.

## FLUID REMOVAL-OPTIMAL TIMING

Although pathogenically well described, the clinical landmark that separates the ebb from flow phase is frequently indistinct and complex. It requires meticulous attention to past medical history (i.e., renal failure and congestive heart failure), cumulative fluid balance, relevant hemodynamic variables, laboratory findings (hemodilution and renal function), and physical examination findings of fluid overload, **Figure 2**. In the absence of early recognition of the flow phase, the complications of pulmonary edema, myocardial complications, respiratory insufficiency, and the continued need for ventilatory support results. Fluid conservation, diuretic therapy, and the institution of renal replacement therapy are clinical decisions made in the flow phase especially in patients with renal insufficiency and cardiac disease (59). When renal replacement therapy is required in the treatment of septic shock, mortality approaches 50%. The optimal timing of initiating renal replacement therapy in the presence of acute kidney injury is not clearly established (60–62).

The body of observational evidence over the last 10 years points towards the deleterious effects of persistently positive

fluid balances in septic shock. Nevertheless, only one large clinical trial has demonstrated the efficacy and safety of fluid removal in ICU patients without cardiovascular dysfunction. The best intervention for active fluid management may be the avoidance of unnecessary fluid loading with the best evidence-based approaches, whereas active fluid withdrawal may have a later role. More evidence from randomized clinical trials is needed to guide physicians in the art and science of late fluid management in septic shock (63).

## HYDROPHOBIA IS UNWARRANTED IN EARLY SEPSIS CARE

- Early titrated fluid administration modulates inflammation, improves microvascular perfusion, organ function, and outcomes.
- Fluid therapy is determined by the method of resuscitation along with various clinically measured variables, disease pathogenesis, and underlying comorbidities rather than the clinician's over prescription of fluid administration.
- Contrary to popular belief, recent EGDT septic shock trials used similar amounts resuscitation fluids in the acute phase when compared to the original EGDT trial. This was associated all time lows in mortality.
- Patients who suffer the negative consequences of fluid overload are already at high risk because of preexisting and acquired comorbidities.
- A comprehensive understanding of "ebb and flow" combined with closely monitored early fluid therapy, accumulation and timely removal is of most importance.
- Fluid therapy should be treated as any drug which involves consideration of the type, dose, duration of treatment, and toxicity (64).
- Hydrophobia may be synonymous with rabies but should not be with early sepsis management.

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