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Choice of fluid therapy in the initial management of sepsis, severe sepsis, and septic shock

Ronald Chang, MD^{a,b,c} and John B. Holcomb, MD^{a,b}

^aCenter for Translational Injury Research, University of Texas Health Science Center, Houston, TX

^bDepartment of Surgery, University of Texas Health Science Center, Houston, TX

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Abstract

Sepsis results in disruption of the endothelial glycocalyx layer and damage to the microvasculature, resulting in interstitial accumulation of fluid and subsequently edema. Fluid resuscitation is a mainstay in the initial treatment of sepsis, but the choice of fluid is unclear. The ideal resuscitative fluid is one which restores intravascular volume while minimizing edema; unfortunately, edema and edema-related complications are common consequences of current resuscitation strategies. Crystalloids are recommended as first-line therapy, but the type of crystalloid is not specified. There is increasing evidence that normal saline is associated with increased mortality and kidney injury; balanced crystalloids may be a safer alternative. Albumin is similar to crystalloids in terms of outcomes in the septic population but is costlier. Hydroxyethyl starches appear to increase mortality and kidney injury in the critically ill and are no longer indicated in these patients. In the trauma population, the shift to plasma-based resuscitation with decreased use of crystalloid and colloid in the treatment of hemorrhagic shock has led to decreased inflammatory and edema-mediated complications. Studies are needed to determine if these benefits also occur with a similar resuscitation strategy in the setting of sepsis.

Keywords

sepsis; resuscitation; albumin; hydroxyethyl starch; balanced crystalloids; glycocalyx

Introduction

Sepsis is the number one cause of death in non-cardiac intensive care units (1,2) and continues to be a growing problem in the United States and worldwide. The incidence of sepsis more than doubled in the United States from the year 2000 to 2008 (3). Although the mortality rate for sepsis has decreased over the last several years, the number of patients

Corresponding author / reprint requests: Ronald Chang, MD, 6410 Fannin St., Suite 1100, Houston, TX 77030, t: 713-500-6247, f: 713-500-0683, ronald.chang@uth.tmc.edu.

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dying due to severe sepsis and septic shock has increased due to the outpaced growth in incidence of the disease (4,5). The cost of sepsis in the United States now exceeds \$15 billion per year and is increasing by more than 10% annually (6).

Sepsis is a detrimental inflammatory response to infection and has been defined as presumed infection with at least two out of four Systemic Inflammatory Response Syndrome (SIRS) criteria (7). Sepsis can lead to severe sepsis (sepsis plus acute organ dysfunction) and septic shock (severe sepsis plus hypotension not responsive to fluid therapy). Three components are vital in the successful management of life-threatening sepsis: timely and appropriate antibiotic therapy, hemodynamic support, and adequate source control. Hemodynamic support of the severely septic and septic shock patient was revolutionized by the early goal-directed therapy protocol first proposed by Rivers et al in 2001 (8). Since 2002, the Surviving Sepsis Campaign has spearheaded a highly successful international effort to decrease sepsis mortality by adoption of bundled treatment elements (9).

Fluid resuscitation is one of the mainstays in the acute management of sepsis. However, the optimal fluid regimen, including the type and volume of fluid to be given, is unclear. Over the past decade, there have been a multitude of randomized controlled trials and meta-analyses to address this conundrum with no clear consensus or recommendations on a specific therapy. The most recent Surviving Sepsis Campaign guidelines recommend 30 cc/kg of crystalloid within the first 3 hours for any hypovolemic septic patient but do not specify the type of crystalloid to be used (10). Indeed, the current practice of fluid therapy for the critically ill seems to depend more on regional norms and tradition than on evidence-based medicine (11). The objective of this article is to review the evidence regarding the choice of fluid therapy in the initial management of sepsis, severe sepsis, and septic shock in adults. We defer discussion regarding the volume of fluid and resuscitation endpoints to elsewhere in the literature. This article begins with a discussion regarding the basic science and physiology of fluid resuscitation to provide scientific background. Then, the evidence for the use of various fluid therapies in the setting of sepsis, focusing on balanced versus unbalanced crystalloids as well as crystalloids versus colloids, is presented.

Theory of fluid resuscitation: Revised Starling principle and the glycocalyx model

Until relatively recently, the paradigm of fluid resuscitation was dominated by the original Starling principle, which described intravascular and interstitial fluid spaces separated by a semi-permeable membrane and movement of fluid between compartments dependent on the hydrostatic and oncotic pressure gradient between them (12). In mathematical terms, this was described by

$$J_v = K_{f,c} ([P_c - P_i] - \sigma_d [\pi_p - \pi_i])$$

where J_v is the net flow of fluid from the intravascular space to the interstitial space across the capillary wall, $K_{f,c}$ is the filtration coefficient of the capillary wall, P_c is the capillary hydrostatic pressure, P_i is the interstitial hydrostatic pressure, σ_d is the reflection coefficient

of plasma proteins, π_p is the plasma oncotic pressure, and π_i is the interstitial oncotic pressure (13,14).

This model predicted that a high hydrostatic pressure gradient would drive fluid into the interstitium at the arteriolar end of the capillary. With net loss of fluid from the capillary, the plasma oncotic pressure would therefore increase. Near the venule end, this would result in net fluid shift from the interstitium back into the capillary, driven by the oncotic pressure gradient. This circulation of fluid between the capillary and the interstitium would mean very little fluid entering the lymphatics (15). In terms of fluid therapy, this model predicted that raising the plasma oncotic pressure could reverse J_v and induce fluid shift from the interstitium to the plasma (16). Clinical observations, however, are not congruent with these predictions. Lymph flow is much greater than predicted because there is no absorption of fluid at the distal ends of capillaries. In fact, capillaries were found to filter fluid into the interstitium across their entire length, even as they become venules (17). Additionally, infusion of hyperoncotic colloid solution was found to have no effect on pulmonary edema (18).

Revision of the Starling principle explains the above incongruences by incorporation of the endothelial glycocalyx layer (EGL). The EGL is a matrix of membrane-bound glycoproteins and proteoglycans projecting from the luminal surface of endothelial cells (19), serving as the direct interface between blood and the blood vessel. The EGL is as thin as 0.2 μm in the microvasculature, as thick as 8 μm in the large arteries, and estimated to retain as much as 700 cc of intravascular volume (14) much like a sponge. The sub-glycocalyx space is normally separate from the plasma and nearly protein-free; its oncotic pressure replaces that of the interstitium as the primary determinant of transcapillary fluid flow (14). Importantly, the revised Starling principle and EGL model predict that increased plasma oncotic pressure will oppose, but not reverse, filtration of fluid from the intravascular to the interstitial space (14,15).

In sepsis, lipopolysaccharide appears to disrupt the EGL through an oxidative stress mechanism (20), while tumor necrosis factor- α seems to cause endothelial injury by activation of nuclear factor- κB (21). Besides sepsis, the glycocalyx is disrupted in several other acute and chronic inflammatory conditions including diabetes (22), trauma (23), and ischemia-reperfusion (24). Disruption of the EGL results in the extravascular leakage of protein and fluid, resulting in interstitial edema which can be exacerbated by volume overloading and improper resuscitation technique. The consequences can be severe: pulmonary edema may lead to prolonged ventilator dependence and increased risk of ventilator associated pneumonia, while splanchnic edema may lead to ileus necessitating total parental nutrition (25) or to the dreaded abdominal compartment syndrome (26). Edema in patients after abdominal surgery has been shown to delay return of gastrointestinal function (27) as well as increase cardiopulmonary and wound healing complications (28). Furthermore, intracellular edema results in the disruption of many biochemical processes including cardiac myocyte contractility, glucose metabolism, and the inflammatory cascade (29). Increased levels of serum EGL components is associated with increased severity of illness and mortality in septic patients and also appears to inhibit the endogenous anti-microbial activity of plasma in vitro (30). The ideal resuscitation fluid for sepsis would

therefore restore intravascular volume while minimizing edema. In theory, this could be accomplished by a fluid which could restore EGL and endothelial integrity (Figure 1). However, therapies aimed at restoring the EGL in septic patients such as corticosteroids, activated protein C, and antithrombin have not been shown to improve outcomes in the past (31). Although a detailed discussion of the mechanisms underlying the “endotheliopathy” of sepsis is outside the scope of this review, this is an exciting area of investigation where more research is needed.

Crystalloids

Normal saline

0.9% sodium chloride, or normal saline, is the most commonly used intravenous fluid worldwide with hundreds of millions of liters used annually in the United States alone (32,33). It is considered “unbalanced” because it has a strong ion difference of zero, as opposed to plasma and “balanced” fluids which have a strong ion difference of about 24 meq/L (34). Normal saline is the most commonly prescribed fluid therapy for sepsis in the United States, yet its origin is unclear and certainly not the result of rigorous scientific inquiry. Clinicians experimented with intravenous saline therapy during the European cholera epidemic of the 1830s, but there is no recorded use of any fluid resembling 0.9% sodium chloride from that era. Hartog Jakob Hamburger, a Dutch physiologist, incorrectly concluded the physiologic concentration of sodium chloride in blood to be 0.9% based on red blood cell lysis studies in the 1880s, but it is unclear if he intended for his findings to be the basis for an intravenous salt solution (32).

Recently, controversy has increased regarding its use. Resuscitation with normal saline is known to cause a hyperchloremic metabolic acidosis and is associated with increased inflammatory markers (35,36). It has also been shown to induce coagulopathy with increased need for blood products in patients undergoing aortic surgery (37) and in animal models of hemorrhage (38) compared to lactated Ringer's. The hyperchloremia itself appears to alter renal blood flow and thereby renal function. An animal study found that increased serum chloride concentration (but not increased sodium concentration) resulted in constriction of the renal afferent arteriole and reductions in renal blood flow and glomerular filtration rate (39). In a randomized, double-blind crossover study, healthy human volunteers received a 2 liter bolus of normal saline and a 2 liter bolus of Hartmann's solution on separate occasions. Investigators found that sodium and water excretion was slower after the normal saline bolus versus the Hartmann's solution bolus (40), consistent with a hyperchloremic decrease in glomerular filtration rate. A second randomized, double-blind crossover study demonstrated reduced renal cortical perfusion and renal blood flow on magnetic resonance imaging in healthy volunteers after a 2 liter normal saline bolus and no change in renal perfusion after a 2 liter Plasma-Lyte bolus (41). A retrospective analysis of 1,940 ICU patients found that hyperchloremia 72 hours after ICU admission was significantly associated with increased mortality and that every 5 meq increase of serum chloride concentration was associated with a further increase in mortality (adjusted odds ratio [OR] 1.37, 95% confidence interval [CI] 1.11 – 1.69) (42). Because of these findings, the role of normal saline in the treatment of severely septic and other critically ill patients is

undergoing reevaluation. As discussed below, “balanced” crystalloids may offer a safer alternative in these patients.

Balanced crystalloids

Lactated Ringer's and Hartmann's solution are two similar and closely related solutions derived from Sydney Ringer's experiments on explanted frog hearts in the 1880s. Ringer's original solution was modified by Alexis Hartmann in the 1930s when he replaced the bicarbonate with lactate, hence lactated Ringer's (used in the United States) and Hartmann's solution (used in Europe). Plasma-lyte is a relatively new crystalloid which gained FDA approval in the United States in 1979 for intravenous use. Unlike previous fluids, Plasma-lyte was designed as a physiologic fluid (43). Collectively, these and similar formulations are known as “balanced crystalloids.” They have an electrolyte content more closely resembling that of plasma including a much lower chloride concentration than normal saline (Table 1). One major difference is that lactated Ringer's and Hartmann's solution both contain calcium ion while Plasma-lyte does not; this allows Plasma-lyte to be given concurrently with blood products while lactated Ringer's and Hartmann's solution have the theoretical risk of causing a blood clot in the transfusion line. The cost for these solutions are comparable with that of normal saline, and one study even found decreased cost associated with the use of Plasma-lyte in the critically ill when the decreased need for magnesium repletion was taken into account (44).

Because of heightened concerns regarding the use of normal saline, there has been increased interest in the use of balanced crystalloids for the critically ill. In 2008 to 2009, an open-label, prospective sequential-period pilot study was performed at a single ICU in which implementation of a chloride-restricted fluid policy was associated with a significant decrease in acute kidney injury (adjusted OR 0.52, 95% CI 0.37 – 0.75) and need for renal replacement therapy (adjusted OR 0.52, 95% CI 0.33 – 0.81), although mortality was unchanged (45). In 2013, the British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients (GIFTASUP) recommended a balanced crystalloid and not normal saline as the first line resuscitative fluid in surgical patients (46). In 2014, a retrospective study compared patients resuscitated with normal saline and Plasma-lyte during and after major abdominal surgery and found that Plasma-lyte was associated with decreased mortality and morbidity including renal failure requiring dialysis, acidosis requiring intervention, blood transfusions, and post-operative infections (33).

In the sepsis literature, data comparing normal saline to balanced crystalloids are lacking. An animal study investigated normal saline versus Plasma-Lyte resuscitation in a rat model of sepsis and found reduced short-term mortality and decreased acute kidney injury in the Plasma-Lyte group (47). Raghunathan et al performed a large, retrospective, propensity-matched study in 50,000 septic ICU patients across 360 hospitals and found decreased mortality (relative risk [RR] 0.86, 95% confidence interval [CI] 0.78 – 0.94) in patients who received any balanced crystalloid versus those who received exclusively unbalanced crystalloid (48). Furthermore, there appeared to be a dose-dependent relationship with a 7.5% decrease in the odds of mortality for every 10% increase in the proportion of balanced fluid used. The same investigators recently published another retrospective analysis of

60,000 severely septic patients split into four groups depending on fluids received: exclusively normal saline, normal saline and balanced crystalloid, normal saline and colloids, or normal saline with balanced crystalloid and colloids (49). After adjustment, receipt of balanced crystalloids was associated with lower mortality (RR 0.84, 95% CI 0.76 – 0.92) regardless of colloid administration, while co-administration of colloids was not associated with improved outcomes.

Recently, Young et al published a double-blind, cluster randomized, double-crossover trial conducted in 4 ICUs in New Zealand over a 7 month period which randomized 2,278 ICU patients to receive normal saline or Plasma-lyte (50). Fluids were administered at the physician's discretion. The majority of the patients were post-operative after elective surgery, and only 4% were admitted to the ICU for sepsis. The investigators found no difference in acute kidney injury or use of renal replacement therapy between the two groups. Although the protocol was well executed, a significant limitation of this study were the relatively small (median 2000 cc) resuscitation volumes received by patients in both groups as well as the lesser disease severity in these patients (mean Acute Physiology and Chronic Health Evaluation [APACHE] II score 14, overall mortality 8%) compared to patients in other trials. As mentioned in editorial comments, the small fluid volume and lower patient acuity probably precluded the ability to detect any differences in outcomes between the two treatment groups (51).

Rochwerg et al performed a network meta-analysis investigating the effect of different fluid therapies on mortality in septic patients. A 6-node network analysis incorporating balanced crystalloids was performed which suggested that balanced crystalloids was associated with increased survival in septic patients compared to normal saline (52). However, the association was rated “low confidence” due to indirectness of comparison.

Hypertonic saline

The 1990s and early 2000s saw increased interest in the use of hypertonic saline in sepsis resuscitation. “Small volume” resuscitation with hypertonic saline was postulated to achieve hemodynamic normalization by recruitment of fluid from the intracellular space, thereby limiting interstitial edema. Additional proposed benefits include reduced endothelial cell edema leading to improved microcirculatory flow, increased myocardial contractility, and favorable immunomodulatory effects such as decreased neutrophil infiltration and inflammatory damage in the lungs (53). Small clinical studies performed in septic patients who were *already hemodynamically stabilized* demonstrated improved hemodynamics such as increased cardiac output after resuscitation with hypertonic saline versus normal saline (54,55). However, enthusiasm for hypertonic saline in the management of sepsis has waned. Hypertonic saline has been shown to worsen coagulation parameters in vitro (56), and hemorrhagic trauma patients who received pre-hospital resuscitation with hypertonic solutions were found to have increased coagulopathy compared to resuscitation with normal saline (57). Since the advent of early goal directed therapy, there have been two clinical trials investigating the use of hypertonic saline in adult septic patients, both performed in China. One study randomized 60 patients to four treatment groups (normal saline, hydroxyethyl starch [HES], 4% hypertonic saline, and HES in hypertonic saline) (58), while

the second study randomized 135 patients to two treatment groups (7.5% hypertonic saline and 6% HES [130/0.4]) (59). Neither study found a significant mortality difference between the treatment groups.

Colloids

Albumin

Albumin is the most abundant plasma protein, accounting for 50-60% of the protein content in plasma by mass. About 40% of the body's albumin is in the intravascular space in the healthy individual, and it is the primary determinant of the plasma oncotic pressure (14). Albumin is semi-permeable across the EGL and normally has a transcapillary escape rate of 5%, which can increase to over 20% in septic shock (60), accounting for the interstitial edema seen in this condition.

A Cochrane Review from the late 1990s suggested increased mortality in critically ill patients resuscitated with albumin compared to crystalloid (61). Subsequently, a large multinational randomized controlled trial (the SAFE study) was performed in the early 2000s which randomized nearly 7,000 critically ill patients to receive either 4% albumin or normal saline (62). In this heterogeneous patient population, there was no difference in 28 day outcomes between the two groups overall. However, a predefined subgroup analysis of severely septic patients detected a modest mortality benefit favoring 4% albumin after adjustment for baseline covariates (63). More recently, two additional, large, randomized controlled trials (ALBIOS and EARSS) have been completed. ALBIOS randomized 1,818 critically ill septic patients to receive resuscitation with 20% albumin or crystalloid (64). The type of crystalloid used was not specified in the study. There was no difference in 28-day or 90-day mortality or in rates of organ failure between the two groups. The albumin group did have faster time to suspension of vasopressor and inotropic therapy, but the volume of fluid used in 7 days between the two groups were similar. Additionally, post-hoc subgroup analysis did detect a statistically significant lower risk of mortality in patients with septic shock who received albumin (RR 0.87, 95% CI 0.77 – 0.99). EARSS (abstract available only) randomized 798 patients in septic shock to receive resuscitation with 20% albumin or normal saline (65). There was no difference in 28-day mortality or in rates of organ failure. Finally, Patel et al completed a meta-analysis which included 16 clinical trials published between 1982 and 2012 investigating the use of albumin as a resuscitative fluid in septic patients. The authors included a mixture of randomized trials which compared albumin to several different fluids including normal saline, lactated Ringer's, and HES solutions. The study found no statistical difference in mortality in septic, severely septic, or septic shock patients resuscitated with albumin compared to the other fluids (66). Finally, although hypoalbuminemia is associated with poor outcome in severe sepsis (67), correction of hypoalbuminemia in these patients does not appear to improve outcome (66).

Hydroxyethyl starch

Hydroxyethyl starch (HES) is a semi-synthetic colloid solution derived from chemically-modified plant starch. There are different HES solutions that vary in the average molecular weight of the starch molecule, the degree of hydroxyethyl substitution of the starch

molecule, and the concentration of the solution. Hydroxyethylation of glucose moieties prolongs the intravascular presence of the colloid solution by inhibiting enzymatic degradation by plasma amylases, but potentiates the accumulation of HES molecules in tissues and organs (68). Table 2 compares several different HES formulations to albumin solutions and human plasma.

Concern regarding the effect of HES solutions on kidney function began surfacing in the early 2000s. In 2001, Schortgen et al published a study comparing resuscitation with 6% HES (200/0.60-0.66) versus 3% fluid-modified gelatin solution in 129 patients with severe sepsis or septic shock and found that resuscitation with HES was an independent predictor of acute kidney injury (OR 2.57, 95% CI 1.13 – 5.83) (69). In 2008, Brunkorst et al published the results of the VISEP trial, which compared fluid resuscitation with 10% HES (200/0.5) versus lactated Ringer's in patients with severe sepsis or septic shock (70). The study was stopped early due to predefined safety criteria, and data from 537 patients were evaluated. The investigators found no difference in mortality but did find that HES was associated with increased acute kidney injury (22.8% vs 34.9%, $p=0.002$) and need for renal replacement therapy (18.8% vs 31.0%, $p=0.001$). However, one criticism of VISEP was that the majority of patients in the HES group received more HES than the allowed maximum daily dose (71).

New HES solutions were soon developed with lower molecular weights, lower degree of hydroxyethyl substitution, and lower concentration; it was hypothesized that these solutions would result in less tissue and organ accumulation of HES and subsequent kidney impairment than the previous HES solutions. Multiple studies have since been performed investigating their use in severely septic and critically ill patient populations. In 2012, Guidet et al published the results of the CRYSTMAS trial, a double blinded randomized controlled trial which randomized 196 severely septic patients to receive 6% HES (130/0.4) or normal saline for four days after enrollment (71). The study found that a statistically significant smaller fluid volume in the HES group was required to achieve hemodynamic stability compared to the crystalloid group, although the volumes of fluid used over the four day study period were similar. There were no differences in 28 or 90 day mortality, nor were there any differences in organ failure including renal failure.

In 2012, Myburgh et al published the results of CHEST, a large, multinational, double-blinded, randomized controlled trial which randomized 7,000 heterogeneous critically ill patients to receive normal saline or 6% HES (130/0.4) until ICU discharge, death, or 90 days after enrollment (72). The study found no mortality difference between the two groups and no mortality difference in a pre-defined analysis of septic patients. However, the study did find that the use of HES was associated with a 21% increased relative risk (95% CI 1.00 – 1.45) of need for renal replacement therapy compared to normal saline. One limitation of this study which was acknowledged by the authors is that enrollment occurred after patients were already admitted to the ICU, possibly resulting in fewer acutely hypovolemic patients.

In 2012, Perner et al published the results of 6S, a multinational double-blinded, randomized controlled trial which randomized 798 critically ill septic patients to receive Ringer's acetate or 6% HES (130/0.4) (73). The study found that patients who had received HES had a 17%

increased relative risk of mortality (95% CI 1.01 – 1.36) at 90 days compared to the Ringer's acetate group. On the survival curve, the two groups diverged at 21 days, a finding that was also present in the VISEP trial, but which was not statistically significant presumably because of smaller sample size and lack of statistical power in VISEP (70). 6S also reported 35% increased relative risk of renal replacement therapy (95% CI 1.01 – 1.80) in the HES group compared to the Ringer's acetate group, although only one patient in each group still required renal replacement therapy at 90 days. Pre-specified long term follow-up was completed for all patients; the results were published in 2014. At long-term follow-up, there was no difference in mortality between the HES group and the Ringer's acetate group at 6 months or 1 year after enrollment (74).

Finally, Annane et al in 2013 published the results of the CRISTAL trial, an open-label, randomized controlled trial which randomized 2,857 critically ill patients to a crystalloid group or a colloid group (75). This study differed from previous studies because physicians were not limited to a single fluid in either treatment arm and could use whichever fluids were available at their institution. However, the majority of patients in the crystalloid arm received normal saline, while the majority of patients in the colloid arm received HES 6% (130, 0.4). The study found no difference in 28 day mortality between the two groups overall or when examining the predefined sepsis sub-group. The study did find a modest mortality benefit favoring the colloids group at 90 days, but this was not a primary outcome. There was no difference in need for renal replacement therapy in the two groups.

An interesting aside in the story of HES solutions which also showcases the dark side of scientific inquiry is that of Joachim Boldt, a German anesthesiologist and once prominent leader in the world of fluid therapy until he was found to have falsified data, conducted medical research without ethical approval, and is now the subject of an on-going criminal investigation (76). Of concern was that many of his studies reported the use of HES to be favorable, and these studies had been included in meta-analyses of the day (77). In 2013, Zarychanski et al published a new study in which he performed a meta-analysis with and without 7 of Boldt's discredited studies (78). When these studies were included, there were no significant findings; after excluding the 7 studies, the authors found that HES was significantly associated with increased mortality (RR 1.09, 95% CI 1.02 – 1.17), increased acute kidney injury (RR 1.27, 95% CI 1.09 – 1.47), and increased use of dialysis (RR 1.32, 95% CI 1.15 – 1.50). Due to the mounting evidence, the Food and Drug Administration in the United States and the European Medicines Agency both suspended the use of hydroxyethyl starch solutions in the treatment of critically ill patients including those with sepsis in 2013.

Rochwerg et al performed a network meta-analysis investigating the effect of different fluid therapies on mortality in septic patients (52). The study included all of the aforementioned studies in this review as well as several others for a total of 14 randomized controlled trials (Boldt's studies were excluded). A 4-node network analysis comparing crystalloid, HES, gelatin, and albumin solutions demonstrated lower mortality with crystalloids than starches at high confidence, and lower mortality with albumin than crystalloid or starches at moderate confidence. The 6-node network meta-analysis found that balanced crystalloids were superior to saline at low confidence, albumin is superior to saline at moderate

confidence, and balanced crystalloid appears comparable to albumin at very low confidence. The authors concluded that resuscitation using balanced crystalloid or albumin compared to normal saline or HES solutions was associated with reduced mortality in septic patients.

Plasma

As mentioned previously, the ideal resuscitative fluid in the setting of sepsis would achieve euvolemia without causing edema, potentially by rebuilding the damaged EGL and repairing the injured endothelium. Although unstudied in the setting of sepsis, plasma could be such a fluid. Plasma is the component of blood after erythrocytes, leukocytes, and platelets have been removed. This fluid is protein rich and can be thought of as a “super-colloid.” In the last ten years, resuscitation of hemorrhagic shock after trauma has undergone a paradigm shift with the advent of “damage control resuscitation”: decreased utilization of crystalloids and colloids in favor of resuscitation with a balanced ratio of blood products using plasma as the primary volume expander (79). Much of what we know about plasma-based resuscitation comes from studies performed in the setting of trauma and hemorrhagic shock. Adoption of damage control resuscitation principles, especially using plasma as the primary volume expander instead of crystalloid or colloid, has been associated with decreased mortality (80,81), decreased edema-mediated complications such as abdominal compartment syndrome (82), and decreased incidence of inflammatory-mediated complications (83,84) such as acute respiratory distress syndrome, venous thromboembolism, and multiple organ failure.

There is sufficient evidence to suggest that the effects on the EGL are similar between trauma and sepsis: both produce similar changes on the EGL itself (14), serum levels of EGL components such as syndecan-1 are elevated in both trauma (23) and septic (30) patients compared to healthy controls, and increasing levels of serum EGL components correlate with increased morbidity and mortality in trauma (85) and sepsis (86). In animal models of hemorrhagic shock, plasma resuscitation has been shown to repair the EGL (87) and reduce pulmonary endothelial permeability (88,89). Recently, plasma has been shown to reduce gut injury and inflammation in an animal model of hemorrhagic shock, possibly by action on the gut *epithelium*, which also contains glycocalyx (90). Although provocative, there is currently no definitive data in human subjects that plasma mitigates endothelial injury in trauma or in sepsis. However, we do believe there is sufficient evidence based on the in vitro and animal data to theorize that improved outcomes with plasma resuscitation in trauma is (at least partially) due to its actions on the EGL. That similar benefits could occur in the setting of sepsis is an intriguing hypothesis deserving of investigation. Such a hypothesis could be easily tested in an animal model.

Discussion

Beginning with the Rivers study over ten years ago, one of the most important lessons we have learned in the treatment of sepsis is that of time. Delays in the initiation of treatment which includes appropriate antibiotic therapy, acquisition of source control, and hemodynamic resuscitation uniformly increase mortality in the setting of sepsis. The first Surviving Sepsis Campaign guidelines recommended starting fluid therapy “as soon as

possible” and a benchmark of six hours to achieve the initial resuscitation goals, whereas the newest guidelines now specify a volume of fluid (30cc/kg of crystalloid) to be given within a specified time window (3 hours). Indeed, a greater proportion of fluid given early (in the first three hours) rather than late (after the 3-hour mark) was associated with decreased mortality in a retrospective analysis (91). Much like the resuscitation of a patient in hemorrhagic shock, it is plausible that not only the amount, but the type, of fluid administered in the first few “golden” hours can make a substantial difference in outcome.

Although many basic science studies and multiple clinical trials have given us some insight vis-à-vis the optimal choice of fluid therapy for the septic patient, our knowledge in this area is still lacking. Normal saline has been a standard fluid therapy for decades, but new data demonstrating hyperchloremia-induced impairment in renal blood flow and glomerular filtration rate should give us pause. Its use appears to be based more on regional norms and tradition than on evidence based medicine. In this regard, balanced crystalloids such as Plasma-lyte may show promise as an effective, inexpensive, and safer alternative in the septic population. However, besides a small sub-group in the recent study by Young et al, there is no other prospective data comparing balanced crystalloids to normal saline in septic patients. Clinical data regarding the use of hypertonic saline in septic patients is lacking, and the hypothetical benefits of small volume resuscitation need to be weighed against the hyperchloremic effects on kidney function.

Multiple large studies and meta-analyses have investigated the use of colloids in the resuscitation of septic patients. Some studies such as VISEP and 6S included exclusively septic patients while others such as ALBIOS, CHEST, CRYSTMAS, and CRISTAL enrolled a heterogeneous mixture of critically ill patients and performed pre-defined sub-group analyses on the septic cohort. Since nearly all of these studies were performed after patients were already admitted to the ICU, a major limitation is therefore the often substantial amount of fluid these patients had already received by the time of study enrollment. For example, 42% of patients in both treatment arms in the 6s study received 500-1000 cc of HES prior to enrollment (92). In the VISEP study, 83% of all enrollees received a median of 2000 cc of crystalloid and 59% of all enrollees received a median of 850cc of colloid prior to enrollment (93). In order to truly answer the question, “Which fluid is best in the *initial* management of severe sepsis and septic shock?” a study would require randomization to occur as early as possible (ideally in the pre-hospital phase), utilizing the exemption from informed consent mechanism. Although this would be a substantial undertaking, it is not insurmountable – similar prospective studies investigating the optimal fluid resuscitation for trauma patients have been performed previously (81,84,94).

As others have already noted (95), we should be thinking about intravenous fluids as drugs and ought to be putting as much thought and consideration into the prescription of intravenous fluid therapy as we would for the prescription of any other drug. After all, we do not haphazardly order “antibiotics” from the pharmacy to treat a septic patient; instead, we consider the likely source of infection and what potential organisms need to be covered, and thereby come to a rational decision on the type and route of antibiotics required. Prescription of fluid therapy for sepsis mandates the same level of consideration. Frankel et al have recently suggested reevaluation of sepsis resuscitation guidelines through the lens of trauma

resuscitation, suggesting a greater emphasis on rapid source control while “minimizing collateral damage, including the administration of excess fluids,” (96). Indeed, the same benefits of plasma-based resuscitation in the treatment of patients with hemorrhagic shock – decreased inflammatory and edema-mediated complications as well as decreased mortality – are possibilities in the treatment of patients with severe sepsis and septic shock.

Conclusion

The optimal fluid in the initial resuscitation of sepsis is unclear. In the literature, there appears to be more high-quality data on the volume of fluid resuscitation and resuscitation endpoints than regarding the specific type of fluid to give. Enrollees in most randomized trials comparing different fluids received large and confounding amounts of pre-trial fluid. Balanced crystalloids such as Plasma-Lyte are probably superior to normal saline, but further prospective studies are warranted. Albumin appears to be equivalent to crystalloids in terms of outcomes, but should be second-line due to higher cost. Hydroxyethyl starches appear to increase mortality and acute kidney injury in critically ill septic patients and are no longer indicated in the treatment of this patient population after the FDA and EMA issued warnings in 2013. There is very limited clinical data regarding the use of hypertonic saline and no data regarding the use of plasma in sepsis. However, theoretical benefits of resuscitation with plasma in the septic patient including repair of the endothelial glycocalyx layer, restoration of microvasculature integrity, and subsequent limitation of interstitial edema should prompt investigation.

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Responses to reviewers

Reviewer #3: Thank you for reviewing this manuscript and for your excellent comments. We wrote this review for a wide audience and intended for it to focus more heavily on the clinical data with some mechanistic data included as background information– a heavy emphasis on the underlying biochemical mechanisms would be outside of the intended scope of the review. However, we do believe the EGL/endothelial injury story as it pertains to sepsis is an interesting one. We want clinicians to be more cognizant of the consequences of their choices in fluid therapy and believe that the figure allows those not familiar with the endothelial/EGL story as it relates to sepsis to start thinking about the ramifications of their choices of fluid therapy on endotheliopathy and edema. We hope that this review will inspire others to increase investigation into this area. I have added such a statement to the manuscript.

Figure 1.

Effects of severe sepsis, septic shock, and resuscitation strategy on the microvasculature.

Panel A. Homeostasis prior to infection. *Panel B.* Infection products (LPS) and the immune response ($\text{TNF-}\alpha$ and reactive oxygen species) cause shedding of the EGL and vascular permeability. *Panel C.* Normal saline, a commonly used fluid, increases inflammation. Other fluids increase hydrostatic pressure without mitigating endothelial injury, generating edema.

Panel D. An ideal resuscitative fluid which repairs the EGL and normalizes the endothelium would mitigate endothelial permeability and edema. $\text{TNF-}\alpha$, tumor necrosis factor- α ; ROS, reactive oxygen species; LPS, lipopolysaccharide; NS, normal saline. Adapted from *J Trauma* 2010;69(Suppl 1):S55-63. Used with permission.

Table 1
Composition of selected crystalloids compared to human plasma

	Human Plasma	0.9% sodium chloride	Compounded sodium lactate		Compounded sodium acetate		Calcium-free balanced crystalloid
Trade or common name		Normal Saline	Lactated Ringers	Hartmann's solution	Ringer's acetate (Baxter, Deerfield, IL, USA)	Sterofundin (B. Braun, Melsungen, Germany)	Plasma-Lyte 148 (Baxter)
Osmolarity (mOsm/L)	291	308	273	279	277	309	294
Sodium (mmol/L)	140	154	130	131	130	145	140
Chloride (mmol/L)	100	154	109	111	110	127	98
Potassium (mmol/L)	4		4	5	4	4	5
Calcium (mmol/L)	2.4		1.5	2	2	2.5	
Magnesium (mmol/L)	1				1	1	1.5
Lactate (mmol/L)	2		28	29			
Acetate (mmol/L)					30	24	27
Gluconate (mmol/L)							23
Malate (mmol/L)						5	
Bicarbonate (mmol/L)	24						

Table 2

Composition of selected colloids

	Human Plasma	Albumin 5%	Albumin 25%	HES 6%	HES 6%	HES 6%	HES 6%	HES 6% HES 10%	HES 6% HES 10%
Trade or common name				Hespan (B. Braun)	Hextend (BioTime, Berkeley, CA, USA)	Voluven (Fresenius Kabi Norge A.S., Halden, Norway)	Hemohe (B. Braun)		Tetraspan (B. Braun)
Molecular weight (kDa)		66	66	600	670	130	200	130	
Molar substitution				0.75	0.75	0.40	0.50	0.42	
Osmolarity (mOsm/L)	291	309	312	309	307	308	310	297	
Sodium (mmol/L)	140	130-160	130-160	154	143	154	154	140	
Chloride (mmol/L)	100	130-160	130-160	154	124	154	154	118	
Potassium (mmol/L)	4				3			4	
Calcium (mmol/L)	2.4				2.5			2.5	
Magnesium (mmol/L)	1				0.45			1	
Lactate (mmol/L)	2				28				
Acetate (mmol/L)								24	
Malate (mmol/L)								5	
Bicarbonate (mmol/L)	24								