

Chapter 2

Fluids in Septic Shock: Crystalloid, Colloids, or Blood?

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Crystalloids

Crystalloid fluids are true solutions, those whose particles are dissolved into their ionic forms and able to pass through a semipermeable membrane. For the purpose of this chapter, they are isotonic solutions, namely 0.9 % saline and lactated Ringers. Crystalloids have long been the “work horse” intravenous fluids of medicine. They are relatively inexpensive, readily available, have a long shelf life, and require no special preparation other than warming.

The origin of intravenous crystalloid therapy can be traced to the landmark observations of William O’Shaughnessy in the early nineteenth century. While combating the Indian cholera pandemic that devastated the former British Empire in the 1830s, O’Shaughnessy observed that blood samples of cholera patients had lost large amounts of water, salt, and alkaline content. Additionally, he wrote “Urea exists in those cases where suppression of urine has been a marked symptom.” Despite his accurate description of the fluid depleted state of his patients, O’Shaughnessy never applied this knowledge to treatment in humans.

Drawing upon these observations, Thomas Latta, a contemporary of O’Shaughnessy, pioneered the development of fluid resuscitation. Frustrated by his initial failures with rectal and oral hydration, Latta published the first known report of intravenous resuscitation when he infused six pints of a salt-containing solution

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into an elderly woman dying of cholera in May of 1832. Though he described an appropriate clinical response, the patient expired due to continued fluid losses. Latta continued his efforts with three additional cholera patients, one of whom survived the disease and recovered.

Though their work laid the foundation for modern intravenous fluid therapy, as the cholera pandemic subsided, so did the early interest in fluid therapy, and their contribution was largely forgotten by history. Though early efforts in fluid resuscitation held promise, it would take another 50 years for a resurgence of interest. With Jennings report of intravenous resuscitation in shock due to obstetrical hemorrhage in the 1880s, interest re-emerged. By the turn of the century, saline solutions appear to have become standard practice in hospital-based medicine [1].

Albumin

In the human body, albumin exists as the most common plasma protein, making up about 50 % of all plasma protein content and accounting for 80 % of intravascular oncotic pressure. The liver synthesizes 10–12 g of albumin daily, which is not stored, and is degraded continuously. Intravascular oncotic pressure, based on albumin content, is one of the many mechanisms by which the body maintains a state of homeostatic organ perfusion, but likely the simplest.

Clinical use of albumin as a volume expander was first reported during the Second World War, where it was widely used in its freeze-dried form. Since that time, albumin has been widely used to expand intravascular volume and increase plasma oncotic pressure. Albumin usage has also been championed as a resuscitative fluid due to its ability to serve as a carrier of pharmacologic compounds, scavenge reactive oxygen species, and serve as an acid-base buffer. The clinical efficacy and safety, especially compared to crystalloid fluids, have been the subject of much interest in the medical literature in recent years.

Albumin Versus Crystalloids in Sepsis

The ideal choice of fluid for resuscitation in sepsis and septic shock has been the subject of much debate over the last decade. While there is little doubt that effective fluid resuscitation is paramount to the care of the septic patient, the studies published in recent years have attempted to determine whether the choice of fluid influences patient outcomes. The first large study published regarding this was the SAFE study in 2004. Nearly 7000 ICU patients requiring intravenous fluid resuscitation were randomized to receive either 0.9 % saline or 4 % albumin. The authors reported no difference in a 28-day mortality in the study population as a whole (20.9 % vs. 21.1 %, $p = 0.87$). Additionally, there were no differences in

mechanical ventilation days, renal replacement therapy, and ICU length of stay. In their subgroup analysis, patients with severe sepsis showed a trend toward decreased mortality in the albumin group (30.7 %) when compared to those receiving saline only (35.3 %), but the study was underpowered to determine any true benefit to albumin [2].

In the 2013 CRISTAL study, Annane et al. looked at 28-day mortality in ICU patients requiring fluid resuscitation for hypovolemia. Unlike the SAFE trial, the CRISTAL trial focused on patients who presented to the ICU with hypotension and lactic acidosis. Nearly 3000 patients were randomized to either colloids (4 or 20 % albumin or HES) versus crystalloids. The primary endpoint of 28-day mortality (25.4 % vs. 27 %, $p = 0.26$) did not reveal a difference between colloids and crystalloids. When analyzed for 90-day mortality, the colloid group exhibited increased survival (30.7 % vs. 34.2 %, $p = 0.03$). The authors felt this result was “exploratory” and should spur further study, and did not conclude that there is a definitively lower mortality at 90 days. The study shows that colloid and crystalloid resuscitation are likely equivalent in terms of overall mortality. However, when interpreting the results of the CRISTAL trial in the context sepsis, it should be noted that the majority of colloid solutions administered were hydroxyethyl starches (70 %), which have been shown to have deleterious effects [3].

The previous studies clearly demonstrated the need for a study to evaluate the potential difference in albumin and crystalloid in patients with severe sepsis and septic shock. To address this population, the ALBIOS trial was conducted as a large open-label study of more than 1800 patients at 100 different ICU's across Italy. Patients were randomized to receive both crystalloids and albumin boluses to maintain a serum albumin level >30 g/L versus crystalloid alone. As in the previous studies, 28-day mortality was chosen as the primary outcome and the two arms failed to show a significant difference in survival (31.8 % vs. 32 %, $p = 0.94$). Secondary outcomes of 90-day mortality, organ dysfunction, and length of stay were also equivalent [4].

Albumin and crystalloid have also been evaluated with respect to lung injury, pulmonary edema, and organ injury. Differences have not been shown definitively. Interestingly, albumin was shown to increase cardiac index in a more linear fashion than crystalloid, but the clinical significance of this remains unclear.

What can be inferred from these studies? In the authors' opinions, while albumin is a safe and effective resuscitative fluid in severe sepsis and septic shock, it has not shown any clear superiority over crystalloid. However, the endpoint of mortality may be the wrong endpoint to research. Few interventions have an effect of such magnitude that it carries through to mortality. It may be enough that clinical endpoints can be achieved with lower volumes. It is unlikely that there will ever be a study powered to detect a difference in PF ratio, compartment syndromes, or ventilator days as a primary outcome. Therefore, given the increased cost associated with albumin usage, crystalloid should be the primary resuscitative fluid in sepsis. When additional or adjunctive fluids are needed, albumin still appears to be safe.

Starches

Hydroxyethyl starch is a commonly used fluid for volume expansion in the ICU worldwide. Several recent randomized controlled trials have been published evaluating 6 % hydroxyethyl starch (HES) solutions in septic patients. In 2012, the CRYSTMAS study was published, evaluating the safety and efficacy of HES versus 0.9 % saline. The study reported no difference in mortality (31 % vs. 25.3 %, $p = 0.37$) or acute renal failure (24.5 % vs. 20 %, $p = 0.454$). The primary outcome of this trial was resuscitative volume infused, not mortality or renal failure, and was underpowered to detect the 6 % observed nominal difference in mortality. The CHEST trial in 2012 evaluated the 90-day mortality in a mixed population of 7000 ICU patients randomized to either HES or 0.9 % saline. Although no difference in 90-day mortality was detected (18 % vs. 17 %, $p = 0.26$), a significant risk of kidney injury requiring renal replacement therapy was detected (7 % vs. 5.8 %, $p = 0.04$). The 6S group from Scandinavia also provides additional evidence for caution in their study of HES versus Ringer's acetate in severe sepsis. The study of 798 patients revealed an increased risk of 90-day mortality, renal failure, and bleeding complications associated with HES. Interestingly, while their long-term follow-up data at 6 months and one year did not show a significant increase in mortality risk, post hoc analysis did suggest that the increased risk of death was closely linked to bleeding complications. Due to concerns of increased mortality, bleeding, and renal dysfunction, the use of HES as a resuscitative fluid in sepsis is not recommended [5, 6].

Blood

The transfusion of blood products is a common adjunctive therapy in patients with septic shock. Clearly, patients with ongoing hemorrhage in the setting of septic shock usually require transfusion, but other patients are transfused for anemia without the presence of hemorrhage as well. In the past, patients were routinely transfused to a hematocrit of 30 %, with the belief that increased red cell mass would improve tissue oxygenation and decrease myocardial ischemia. In Rivers Early Goal Directed Therapy (EGDT) study, transfusions were used to target goal-mixed superior vena cava oxygen saturation ($ScVO_2$), regardless of hematocrit. As early as 1999, the Transfusion Requirements in Critical Care (TRICC) study showed no risk in allowing hemoglobin to fall below 7 g/dL before transfusion. These findings were corroborated by the Transfusion Requirements in Septic Shock (TRISS) study, which found that in patients admitted to the ICU with septic shock, there was no benefit in transfusing above hemoglobin of 7 g/dL. The authors do not transfuse unless the hemoglobin falls below 7 g/dL. Given her recent emergent operation and ongoing fluid resuscitation, it would be prudent to follow serial hemoglobin levels to assess for hemodilution or hemorrhage. With the

increased recognition of adverse events related to blood transfusion, such as ABO mismatch, increased risk for infection, transfusion-related lung injury (TRALI), and transfusion-associated circulatory overload (TACO), the risk/benefit ratio must be thoroughly assessed by the treating physician prior to initiating transfusion [7].

Fluids and Protocol-Based Care

EGDT is a concept of targeting therapy in the early hours of septic shock to reach certain physiologic endpoints for resuscitation. In his single center trial reported in 2001, Rivers randomized patients to a protocol aimed at using fluids, vasopressors, invasive hemodynamic monitoring, and transfusion to resuscitate to CVP of 8–12, MAP >65, ScVO₂ >70 %, and a urine output of greater than 0.5 ml/kg/h, and demonstrated a 16 % reduction in mortality when compared to usual care. The findings of this study caused a dramatic shift in the critical care management of septic shock and heavily lent to the Surviving Sepsis Campaign Guidelines. However, Rivers study was not without criticism. His method of EGDT mandates invasive hemodynamic monitoring with central venous catheters and advocates for resuscitation to supraphysiologic endpoints. What is also unclear is which elements of EGDT were responsible for the dramatic improvement in outcomes [8].

Two recent studies have aimed at comparing EGDT and/or protocol-based resuscitation with usual care at the discretion of the attending critical care physician in patients with severe sepsis and septic shock. The ProCESS study was a multi-center randomized controlled trial with 1341 patients with septic shock, randomized to protocol-based care (that did not require invasive hemodynamic monitoring, inotropes, or transfusions), EGDT, or usual care. The study showed essentially no difference in mortality across all groups at 60 days, 90 days, and 1 year [9].

ARISE 2014 was a similar multicenter international randomized control trial that compared EGDT to usual care in over 1600 patients with severe sepsis or septic shock. Like the Process trial, the ARISE investigators were unable to show any difference in early or late mortality between the two groups. In addition, the subjects randomized to EGDT received a higher volume of IV fluids, more inotropic and vasopressor support, and were more likely to receive transfusions [10].

These two studies have shed new light on numerous aspects of the care of patient with severe sepsis and septic shock. First, invasive hemodynamic monitoring for resuscitation in the septic patient does not appear to improve outcomes. Second, transfusion of packed red blood cells should be used judiciously and only in the setting of symptomatic anemia. Most importantly, the individual judgment of the seasoned critical care physician cannot be replaced by a standardized protocol. In a recent retrospective cohort study of patients undergoing EGDT, 67 % of patients exhibited signs of fluid overload on the first clinical day and 48 % had persistent overload on day three. This fluid overload was linked to an increased number of interventions (thoracentesis, diuresis, mechanical ventilation, etc.) and was associated with an increased risk of in-hospital mortality.

Individualized Approach to Resuscitation in Septic Shock

Septic patients present to the ICU with a unique physiology based on their underlying medical condition and degree and response to critical illness. We recommend an initial fluid challenge and continued resuscitation with crystalloid in most patients. Albumin can safely be used as a resuscitative adjunct at the discretion of the bedside physician, with the understanding that the cost is greater than crystalloid. Hydroxyethyl starches should be abandoned in the treatment of sepsis. Lack of physiologic improvement demands further investigation for the cardiovascular status with echocardiography and/or pulmonary artery catheterization. Other commercially available systems for monitoring hemodynamic parameters from arterial line waveforms may be useful, but like the traditional methods, are limited by a set of suppositions which are difficult to achieve in the real world. In practice, life-threatening hypotension is temporized with norepinephrine while proceeding with hemodynamic investigations. For patients presenting with anemia, red cell transfusion should be reserved for patients with a hemoglobin level less than 7 g/dL. Ultimately the resuscitation of the septic patient in the intensive care unit should be guided not by absolute number and guidelines, but based of the clinician's judgment and titrated to the appropriate clinical response.

Clinical Scenario

A 64 year-old woman is status post emergent subtotal colectomy for *Clostridium difficile* colitis and toxic megacolon that developed one week after coronary artery bypass graft and mitral valve replacement. Her ejection fraction is 45 % at baseline. Upon return from the operating room to the surgical intensive care unit, she is oliguric, febrile to 39 °C, and has a hemoglobin of 7.5 gms/dL.

Beyond a shadow of a doubt, the above patient provides a picture of surgical sepsis, the management of which is complicated by her underlying comorbidities. Though this presentation paints a picture of the organ system dysfunction associated with severe sepsis, the astute clinician must also quickly evaluate for other potential underlying causes, such as cardiac failure, injury to the ureters during colectomy, or ongoing hemorrhage. The keys to managing the septic patient are immediate recognition, fluid and vasopressor resuscitation, early broad-spectrum antibiotic therapy, source control of surgical sepsis, and support of dysfunctional or failed organ systems. For the scope of this chapter, we will focus our efforts on how and why septic patients should be fluid resuscitated.

Supporting end-organ perfusion is critical in combating the deleterious host response to infection. Hypoperfusion from sepsis is multifactorial. Septic shock results in a marked state of vasoplegia, and arterial and venous dilation due to the lack of vascular smooth muscle contractility. This response negatively impacts organ perfusion by two mechanisms: Arterial dilation causes

systemic hypotension, while venodilation in splanchnic and cutaneous beds decreases venous return to the right heart, lowering the effective circulating volume and thus cardiac output. In addition, the inflammatory response in sepsis also leads to diffuse endothelial injury, resulting in abnormalities in microvascular blood flow as well as increased capillary permeability and fluid shifts into the interstitial space. Further, intravascular volume can be further depleted by fluid losses from the gastrointestinal tract (i.e., vomiting associated with bowel obstruction or the diarrhea caused by the above patients C. diff infection), evaporative and blood loss during surgery, general anesthesia, and the patients underlying medical comorbidities.

Intravenous fluid resuscitation is the first-line therapy for improving hypotension and end-organ dysfunction in severe sepsis and septic shock. During the resuscitative phase, ensuring adequate intravascular volume and end-organ perfusion is a top priority. In the absence of known or preceding cardiac dysfunction, the Surviving Sepsis Campaign Guidelines suggest a minimum volume of 30 mL/kg challenge of intravenous crystalloid bolus should be used for initial resuscitation and intravenous fluid administration should continue as long as there is evidence of physiologic improvement in hemodynamic parameters [11].

The aforementioned patient certainly requires intravenous fluid resuscitation. Having undergone an emergent operation for toxic megacolon, she not only exhibits signs of end-organ dysfunction related to sepsis, but also may be under resuscitated due to blood and fluid losses in the operating room. The patient's response to this initial fluid challenge should be closely monitored and additional consideration should be given to her known previous cardiac dysfunction. She has recently undergone coronary bypass grafting and a mitral valve replacement and her baseline echocardiogram showed a slightly decreased ejection fraction of 45 %. Although her initial operation was intended to ensure adequate myocardial blood flow and cardiac chamber function, evaluating her cardiac function early in her ICU course is essential for optimizing her resuscitation.

Cardiac dysfunction complicates fluid resuscitation in septic patients. Based on a recent meta-analysis of echocardiographic data, diastolic dysfunction is present in nearly half of patients with sepsis and is associated with significantly increased risk for mortality. The ability of the ventricle to relax and fill with blood during diastole is an important consideration when giving a fluid challenge to a septic patient. Increasing the intravascular volume in the presence of marked diastolic dysfunction will increase cardiac filling pressures as well as venous and pulmonary hydrostatic pressures, without a concurrent beneficial increase in stroke volume or cardiac output.

There are multiple tools at the disposal of the critical care physician to assess cardiac function. A focused clinical exam will reveal overt signs of

cardiac dysfunction such as jugular venous distension, third and fourth heart sounds, and peripheral edema. Chest radiographs should be obtained to evaluate for cardiomegaly and vascular congestion. However, given the above patient's past medical history, further objective evidence is warranted. A focused bedside echocardiogram looking for both systolic and diastolic dysfunction (as well as prosthetic valve function) should be performed and followed up with a formal bedside transthoracic echocardiogram. In the presence of major cardiac dysfunction, aggressive fluid resuscitation could further exacerbate end-organ dysfunction and early use of vasopressors and inotropes should be considered.

Without evidence of systolic or diastolic function requiring pharmacotherapy to improve cardiac output, fluid resuscitation should begin upon arrival to the intensive care unit. The initial resuscitative fluid in this patient should be intravenous crystalloid. Though it will be discussed in detail below, based on multiple recent clinical trials, resuscitating septic patients with albumin provides no tangible benefit over crystalloids. The use of hydroxyethyl starches in sepsis has been shown to cause harm and should be avoided. Although the patient in the clinical scenario is anemic, in the absence of ongoing hemorrhage, transfusion should be held unless the hemoglobin falls below 7 g/dL.

In addition to intravenous fluid resuscitation, other causes of this patient's oliguria should be investigated. A renal ultrasound would show dilation of the renal pelvis and collecting system if a ureter was inadvertently ligated. Ascites could represent a urinary leak from an injured, but not ligated ureter. Serum and urine chemistries should be obtained to evaluate electrolyte and creatinine clearance and fractional excretion of sodium. Urine output should be monitored via a Foley catheter, which hopefully would have been placed at or before the operation. Adequate monitoring of cardiopulmonary status and sufficient intravenous access are necessary elements of care in this patient.

The patient's response to resuscitation and the results of clinical investigations should further guide the management of this patient. Early goal-directed therapy and standardized, protocol-based care have not been shown to improve outcomes in severe sepsis and septic shock. Invasive hemodynamic monitoring has not been shown to be efficacious when applied to a broad population of septic patients. However, if the patient in the scenario above failed to respond adequately to fluid resuscitation, the authors would consider using a pulmonary artery catheter to guide the use of vasopressors or inotropes. Further therapy and interventions for this patient should be guided by her clinical response and the seasoned judgment of the bedside physician.

Key Questions

1. *Is it any wonder that sepsis is such a difficult disease to treat with fluids? How is one supposed to perfectly fill a leaking system with only inferential endpoints of fullness?*
2. *Are colloids and crystalloids truly no different or are we lacking adequately powered studies in very selected subgroups like the elderly with congestive heart failure?*

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