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Resuscitation Fluids

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Abstract

Purpose of the Review: Intravenous fluid administration is a fundamental therapy in critical care, yet key questions remain unanswered regarding optimal fluid composition and dose. This review evaluates recent evidence regarding the effects of fluid resuscitation on pathophysiology, organ function, and clinical outcomes for critically ill patients.

Recent findings: Recent findings suggest that intravenous fluid composition affects risk of kidney injury and death for critically ill adults. Generally, the risk of kidney injury and death appears to be greater with semisynthetic colloids compared to crystalloids, and with saline compared to balanced crystalloids. Whether a liberal, restrictive, or hemodynamic responsiveness-guided approach to fluid dosing improves outcomes during sepsis or major surgery remains uncertain.

Summary: As evidence on fluid resuscitation evolves, a reasonable approach would be to use primarily balanced crystalloids, consider 2–3 liters for initial fluid resuscitation of hypovolemic or distributive shock, and use measures of anticipated hemodynamic response to guide further fluid administration.

Keywords

Intravenous fluid; resuscitation; saline; balanced crystalloids; colloids

INTRODUCTION

In 1832, Dr. Thomas Latta infused a solution of water, sodium, chloride, and bicarbonate through a metal tube into the veins of patients dying from cholera [1]. In the intervening 186 years, intravenous fluid administration has become a nearly ubiquitous therapy in critical care [2]. Each year more than 30 million patients receive intravenous fluid [3], and fluid therapy is fundamental to the care of patients with sepsis, hemorrhagic shock, and other life-threatening illnesses.

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The potential negative effects of fluid administration have only more recently come into focus. Recent clinical trials indicate that the composition of each intravenous solution may affect organ function and patient outcomes. Starling's model of semi-permeable capillaries subject to hydrostatic and oncotic pressure gradients has increasingly been replaced by a more nuanced understanding of how fluid therapy relates to the endothelial glycocalyx layer [4*], the endothelial basement membrane, and the extracellular matrix [5]. Dynamic measures of fluid responsiveness have been shown to outperform static measures in identifying patients for whom a fluid bolus will increase cardiac output. Fluid overload has been associated with impaired organ function and decreased survival for critically ill patients across a range of diseases and settings.

This article reviews the recent evidence relating to intravenous fluid resuscitation in emergency and critical care settings, to help clinicians select the appropriate composition and dose of intravenous fluid for their critically ill patients.

WHICH FLUID TO GIVE

Intravenous solutions may be divided into two classes: (i) crystalloids, which are solutions of electrolytes in water that cross freely from the vascular space into the interstitium, and (ii) colloids, which contain large molecules that cannot permeate healthy capillary membranes.

Crystalloids

Because they are inexpensive, widely available, and (in most contexts) produce equivalent outcomes to colloid preparations, crystalloids are the most commonly administered intravenous fluid. More than 200 million liters of crystalloid are administered each year in the United States alone [2], and crystalloids are recommended as “first-line” for fluid resuscitation in such common critical illnesses as sepsis, hemorrhagic shock, and cardiac arrest.

“Isotonic” Crystalloids

There are two basic classes of “isotonic” crystalloid solution: saline (0.9% sodium chloride) and balanced crystalloids (e.g., lactated Ringer's, Hartmann's solution, Plasma-Lyte, Normosol, Isolyte). Saline contains 154 mmol/L of sodium and chloride – a chloride concentration approximately 50% greater than that of human extracellular fluid. In contrast, balanced crystalloids contain a sodium, potassium, chloride, and acid-base composition more similar to that of extracellular fluid. Balanced crystalloids achieve this by replacing chloride anions with buffers that are rapidly metabolized into bicarbonate (e.g., lactate and acetate) or excreted (e.g., gluconate). Historically, saline has been the most commonly administered intravenous crystalloid, especially in North America [6]. New data from randomized trials, however, challenge the safety of saline as the primary fluid therapy for acutely ill adults.

A recent, double-blind, randomized trial comparing balanced crystalloids to saline among patients undergoing major abdominal surgery was terminated after the enrollment of 60 patients because 97% percent of patients in the saline group required catecholamine infusion, compared to 67% in the balanced crystalloid group ($P = 0.03$) [7*].

Two recent cluster-randomized, cluster-crossover trials compared balanced crystalloids to saline among nearly 30,000 acutely ill adults in the emergency department and intensive care units at a single center [8**,9**]. Both trials found that the incidence of death, new renal replacement therapy, and persistent renal dysfunction was lower with balanced crystalloids. For every 100 patients treated with intravenous fluid, using balanced crystalloids rather than saline appeared to spare one patient from death, new renal replacement therapy, or persistent kidney dysfunction. The difference between balanced crystalloids and saline appeared to be greatest for the most severely ill patients [10], patients who received the largest volumes of fluid, and patients with sepsis or septic shock.

Additional research is needed to determine (i) the mechanism by which crystalloid composition may affect clinical outcomes and (ii) the patient characteristics (comorbidities, acute conditions, hemodynamic and laboratory values, and markers of organ function) that identify patients most likely to benefit from balanced crystalloids versus saline [11–13]. Until further data are available, clinicians should consider using balanced crystalloids as “first-line” for fluid resuscitation.

Bicarbonate

The lower rates of metabolic acidosis, death, dialysis, and persistent renal dysfunction with crystalloid solutions containing a buffer raise the question of whether intravenous bicarbonate or bicarbonate-containing fluids may improve outcomes for some critically ill adults. A recent randomized trial examined the effect of intravenously administering 4.2% sodium bicarbonate to maintain arterial pH above 7.3 among critically ill adults with severe acidemia [14**]. Bicarbonate therapy did not significantly reduce death or organ failure. The bicarbonate group, however, did experience a 16.7% absolute reduction in receipt of renal replacement therapy. Among the subgroup of patients with acute kidney injury, bicarbonate appeared to prevent the need for dialysis and decrease 28-day mortality. For critically ill adults with severe metabolic acidemia, especially those with non-anion gap acidosis or acute kidney injury, clinicians may choose to consider administration of sodium bicarbonate or an intravenous fluid containing bicarbonate as part of initial fluid resuscitation.

Hypertonic Saline

Concern about sodium and water overload from “isotonic” crystalloid resuscitation has generated interest in using small volumes of hypertonic saline solutions for resuscitation. Interest in hypertonic saline began during World War I [15] and resurged recently based on pre-clinical studies of hypertonic saline for traumatic brain injury and hemorrhagic or non-hemorrhagic shock [16,17]. Among patients with elevated intracranial pressure, bolus administration of hypertonic saline temporarily lowers intracranial pressure, but does not appear to affect survival or cognitive outcomes [18–20]. Preclinical data suggest that, in septic shock, hypertonic saline infusion may exert beneficial effects on tissue hypoperfusion, oxygen consumption, endothelial dysfunction, and inflammation [21,22]. However, a recent randomized trial comparing 3.0% sodium chloride to 0.9% sodium chloride for fluid resuscitation among 442 patients with septic shock was stopped after 42% of patients died in the hypertonic saline group compared with 37% in the isotonic saline group ($P=0.12$) [23*].

Currently, hypertonic saline represents a “first-line” treatment to temporarily reduce elevated intracranial pressure, but should not be used as the primary resuscitation fluid for hemorrhagic or non-hemorrhagic shock.

Colloids

Commonly administered colloids include derivatives of human plasma (albumin) and semisynthetic colloids (starches, gelatins, and dextrans). Compared with crystalloids, the theoretical benefit of colloid solutions is improved volume expansion, due to retention in the intravascular space. Recent evidence suggests, however, that the “volume-sparing” effect of colloids compared to crystalloids is less than anticipated for critically ill adults [24,25].

Albumin

Human serum albumin, a small protein synthesized by the liver, provides 75% of plasma colloid oncotic pressure, binds nitric oxide, and regulates inflammation [26]. A randomized trial comparing use of 4% albumin versus 0.9% sodium chloride among nearly 7,000 critically ill adults found that the albumin group received slightly less fluid but experienced no difference in 28-day mortality [24]. Subgroup analysis suggested a possible beneficial effect from albumin in patients with sepsis and a potential harmful effect in patients with traumatic brain injury [27]. A subsequent trial involving 1,818 patients with sepsis compared crystalloid solutions alone to crystalloid solutions plus daily administration of 20% albumin targeting a serum albumin level of 3 g/L [28]. Mortality was identical in the two groups overall, but albumin appeared to reduce mortality among patients with shock at enrollment. Meta-analyses have suggested reduced mortality with albumin administration in patients with sepsis [29].

The high cost of albumin relative to crystalloid solutions suggests that, while albumin may be appropriate therapy for select subgroups, such as those with cirrhosis [30] and those undergoing liver transplantation, more research is needed before clinicians can consider albumin as a “first-line” fluid for resuscitation.

Semisynthetic Colloids

The expense and limited supply of human albumin solution led to the development of semisynthetic colloid solutions, which contain hydrolyzed bovine collagen (gelatins), glucose polymers (dextrans), or the maize-derived d-glucose polymer amylopectin (hydroxyethyl starches). Hydroxyethyl starch is the only semisynthetic colloid to have been evaluated in multiple large, randomized trials among critically ill adults. Several blinded trials comparing hydroxyethyl starch to crystalloid among critically ill adults found that the volume of fluid required for resuscitation was only slightly different between the colloid and crystalloid groups [25,31], perhaps because damage to the endothelial glycocalyx layer during critical illness prevented the hydroxyethyl starch from remaining in the vascular space. Moreover, the VISEP [31], CRYSTMAS [32], 6S [33], and CHEST [25] trials suggested that use of hydroxyethyl starch might increase the risk of acute kidney injury, need for renal replacement therapy, or mortality [34]. Pending further research, the cost and potential risks for increased acute kidney injury and mortality suggest clinicians should avoid semisynthetic colloids during fluid resuscitation of most critically ill patients.

HOW MUCH FLUID TO GIVE

Once an intravenous solution has been selected, the next challenge faced by clinicians is to determine the “dose” to administer. The negative effects of fluid overload have been increasingly recognized [35–38]. To determine the point at which the potential benefits of further fluid administration are outweighed by the potential risks, clinicians must evaluate not only the patient’s illness and underlying comorbidities, phase of fluid therapy [39], and anticipated hemodynamic response, but also the accumulating evidence from fluid management trials.

Dose of Fluid

Many of the clinical trials examining volume of intravenous fluid resuscitation have focused on adults with sepsis. In a landmark trial in 2001, sepsis patients treated with intravenous fluids, vasopressors, dobutamine, and blood transfusions to achieve physiologic targets experienced a lower mortality than the control group [40]. Patients in the intervention group received an average of 5.0 liters of intravenous fluid in the first six hours, compared to 3.5 liters in the control group. On the basis of this trial and subsequent studies, international guidelines for sepsis management recommend that patients with sepsis receive a rapid infusion of 30 ml/kg of crystalloid fluids in the first three hours after presentation [41], with ongoing fluid administration for patients who continue to exhibit a hemodynamic response [42]. Patients with sepsis or septic shock in the usual care groups in recent randomized clinical trials have received an average of 4.0 – 4.5 liters of intravenous fluid in the first six hours [43–45].

Recent trials of fluid resuscitation in resource-limited settings, however, suggest potential negative effects from fluid bolus administration as a part of sepsis resuscitation. A randomized trial comparing a bolus of 5% albumin, a bolus of saline, and no fluid bolus among more than 3,000 children with severe febrile illness and impaired perfusion in Africa found that fluid boluses significantly increased 48-hour mortality [46]. A pilot trial of adults with sepsis in Zambia was stopped early due to excess mortality among patients with respiratory failure at baseline randomized to the protocolized fluid and vasopressor administration group [47]. Most recently, a trial among 212 patients in Zambia with sepsis-induced hypotension without respiratory failure found that administration of an average of 3.5 liters of fluid in the 6 hours after presentation increased 28-day mortality, compared to administration of an average of 2.0 liters [48*]. A recent pilot trial found that restricting resuscitation fluid after initial sepsis resuscitation was feasible, and might decrease the risk for acute kidney injury [49]. Limiting fluid resuscitation and permissive hypotension appear to increase survival in other causes of shock, such as traumatic and non-traumatic hemorrhagic shock [50,51]. The optimal initial approach to fluid management in sepsis and septic shock remains uncertain [52*,53], and is the subject of ongoing clinical trials [54].

The optimal “dose” of intravenous fluid during invasive major surgery has also been the focus of recent study. Early trials comparing liberal intraoperative fluid management to a restrictive (zero-balanced) strategy reported decreased rates of post-operative cardiopulmonary and surgical-site complications with a restrictive approach [55]. In contrast, a recent multi-center trial comparing a restrictive versus liberal intravenous fluid

regimen among 3,000 patients undergoing major abdominal surgery found that the restrictive approach increased the risk of acute kidney injury, without improving disability-free survival [56**]. The effects of a liberal, restrictive, or goal-directed approach to fluid management on outcomes of major abdominal surgery remains unclear, and further research is required.

Fluid Responsiveness

A primary goal of fluid resuscitation is to increase cardiac output and improve organ perfusion. Only half of hemodynamically unstable patients, however, experience an improvement in stroke volume with fluid administration [57]. Thus, researchers and clinicians are increasingly interested in techniques to predict which patients will experience hemodynamic improvement after fluid administration (“fluid responsiveness”). Early static measures such as central venous pressure and mixed venous oxygen saturation poorly predicted fluid responsiveness, and are no longer recommended for routine use [58,59]. Patient characteristics such as heart failure, hypothermia, and immunocompromise have some predictive ability [60]. Most recent research, however, has focused on “dynamic variables” that quantify changes in hemodynamic measurements or vascular structures following interventions to change ventricular pre-load, such as passive leg raise, changes during the respiratory cycle, mechanical ventilation maneuvers, or small fluid boluses.

Variation in pulse pressure and stroke volume with the respiratory cycle predict fluid responsiveness among non-spontaneously breathing mechanically ventilated patients in sinus rhythm [61]. A recent study found that measuring changes in pulse pressure variation or stroke volume variation that occur when increasing tidal volume from 6 mL/kg predicted body weight to 8 mL/kg may add value in predicting fluid responsiveness [62]. Ultrasound measurements that predict fluid responsiveness include global end-diastolic volume index [63], velocity time integral of the Doppler signal across the left ventricular outflow tract [64,65], and carotid artery flow [66]. Respiratory variation in inferior vena cava diameter is a commonly used measurement, but a recent meta-analysis suggested limited ability to predict fluid responsiveness, particularly in spontaneously breathing patients [67].

Studies of fluid responsiveness have generally focused on short-term physiology rather than patient-centered outcomes. A recent meta-analysis of 1,652 patients enrolled in trials using a range of dynamic variables to guide fluid therapy suggested that the use of such techniques was associated with reduced duration of mechanical ventilation, length of stay, and mortality [68*]. A recent randomized trial comparing cardiac output-guided hemodynamic therapy during and after surgery to usual care among 734 patients undergoing major gastrointestinal surgery reported an absolute risk reduction in 30-day morbidity and mortality of 6.8% [95% CI, -0.3% to 13.9%] [69]. Conversely, a recent study using arterial waveform monitoring to guide fluid resuscitation in patients with septic shock or acute respiratory distress syndrome was stopped early for futility [70]. Additional research will be required to identify the optimal techniques for assessing fluid responsiveness for specific subgroups of patients, and to determine whether guiding fluid management using measures of fluid responsiveness improves clinical outcomes.

CONCLUSIONS

Balanced crystalloids may decrease death and kidney dysfunction compared to saline among adults in the emergency department and intensive care unit. Albumin increases mortality in traumatic brain injury, but may eventually have a role as therapy for septic shock. Semisynthetic colloids appear to increase the risk of acute kidney injury, and should not be used for fluid resuscitation of most critically ill patients.

Determining the amount of fluid to administer during and after resuscitation requires a complex balancing of benefits and risks for each patient. Whether using dynamic measures of fluid responsiveness to guide therapy will improve patient outcomes remains unknown.

A reasonable approach for most emergency and critical care patients requiring fluid resuscitation is to use primarily balanced crystalloids, limit initial fluid boluses to 2–3 liters, and use available hemodynamic monitoring to guide further fluid administration.

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with saline. This was the first large trial to compare balanced crystalloids to saline during critical illness, and the highest quality evidence to date to suggest that balanced crystalloids might result in better clinical outcomes than saline.

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KEY POINTS

- For most critically ill adults, crystalloids remain the “first-line” for fluid resuscitation.
- Balanced crystalloids may decrease the risk of death, renal replacement therapy, or persistent renal dysfunction compared with saline.
- Semisynthetic colloids may increase the risk of acute kidney injury or death compared with crystalloid solutions.
- Whether using measures of fluid responsiveness to guide fluid administration improves clinical outcomes for critically ill adults requires further research.
- A reasonable approach to fluid resuscitation for most acutely ill patients is to use primarily balanced crystalloids, giving 2–3 liters for initial resuscitation and dosing further fluid based on measures of anticipated hemodynamic response.