Critical Care

Key Controversies in Colloid and Crystalloid Fluid Utilization

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Nearly 2 centuries have passed since the use of intravenous fluid became a foundational component of clinical practice. Despite a steady stream of published investigations on the topic, questions surrounding the choice, dose, timing, targets, and cost-effectiveness of various fluid options remain insufficiently answered. In recent years, 2 of the most debated topics reference the role of albumin in acute care and the safety of normal saline. Although albumin has a place in therapy for specific patient populations, its high cost relative to other fluids makes it a less desirable option for hospitals and health systems with escalating formulary scrutiny. Pharmacists bear responsibility for reconciling this disparity and supporting the rational use of albumin in acute care through a careful evaluation of recently published literature. In parallel, it has become clear that crystalloids should no longer be considered a homogenous class of fluids. The past reliance on normal saline has been questioned due to recent findings of renal dysfunction attributable to the solution's supraphysiologic chloride concentration. These safety concerns with 0.9% sodium chloride may result in a practice shift toward more routine use of "balanced crystalloids," such as lactated Ringer's or Plasma-Lyte, that mimic the composition of extracellular fluid. The purpose of this review is to summarize the evidence regarding these 2 important fluid controversies that are likely to affect hospital pharmacists in the coming decades — the evidence-based use of human albumin and the rising role of balanced salt solutions in clinical practice.

Over 30 million patients receive intravenous (IV) fluid each year in the United States.^{1,2} This practice is utilized most commonly in the intensive care unit (ICU), where more than one-third of all critically ill patients are resuscitated with IV fluid.³ The ubiquitous use of fluids in acute care is perpetuated by the need to replace volume loss, maintain organ perfusion, and achieve hemodynamic goals. Furthermore, early and aggressive IV fluid administration improves patient outcomes in many syndromes and is emphasized in consensus recommendations for sepsis, cirrhosis, hypovolemia, burns, and hemorrhage.⁴⁻¹¹ However, after the initial resuscitation phase, a balancing act between "adequate" hydration and "over" hydration ensues to avoid the harmful sequelae associated with volume overload such as respiratory failure, peripheral edema, increased cardiac demand, and acute kidney injury (AKI).¹²

Nearly 2 centuries have passed since IV fluid became a foundational component of the hemodynamic

resuscitation strategy.¹³ Despite a steady stream of literature on the subject, questions surrounding the choice of fluid, dose, timing, targets, and cost-effectiveness remain insufficiently answered. Ambiguity in the literature is due to a lack of rigorous head-to-head trials, questionable selection of primary outcomes, and faint signals of efficacy or safety in study subgroups.

As the controversial topic of IV fluid utilization is expansive,¹³⁻¹⁵ we sought to summarize 2 key issues with recent updates to the literature. The 2 topics discussed in this review are of great importance to pharmacists now and will continue to be in the coming years: the evidence-based use of human albumin and the rising role of balanced salt solutions in clinical practice.

HUMAN ALBUMIN: GUIDE TO CURRENT EVIDENCE

Globally, colloids remain the most common ICU resuscitation fluid, attributed largely to starch

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and gelatin utilization in China, Canada, New Zealand, and several European countries. In the United States, human albumin remains the colloid of choice.³ Unfortunately, the high acquisition cost of albumin and its limited availability make it less attractive to hospitals and health systems facing formulary scrutiny. Indeed, albumin has become a common target of medication use evaluations and cost transformation strategies.¹⁶⁻¹⁸ It is for these reasons that pharmacists must have an intimate knowledge of the evidence surrounding albumin's use to ensure cost-effective implementation of this therapy.

In healthy adults, endogenous albumin, which is synthesized exclusively by the liver, comprises about 80% of intravascular colloid oncotic pressure.^{19,20} In theory, use of albumin to restore oncotic pressure during resuscitation of acutely ill patients seems favorable given the widespread inflammation and third-spacing of intravascular fluid that occurs. The pressure gradient induced by exogenous albumin administration is often considered volume-sparing due to its potential to draw this third-spaced fluid back into the vasculature. However, high-level clinical data suggest that albumin is only slightly more volume-sparing than crystalloids. Whereas conventional estimates predicted 1 L of colloid would produce comparable volume expansion to 3 to 4 L crystalloid, the actual ratio in critically ill patients may be closer to 1 L colloid for every 1.4 L crystalloid.²¹

Albumin also possesses several non-colligative properties of unknown clinical relevance. Endogenous albumin serves as an antioxidant and modulator of the inflammatory response. It may also enhance microcirculatory and mesenteric blood flow, bind toxic substances (eg, free fatty acids), and scavenge free radicals.^{22,23} Although these mechanisms show promise, only select patient populations benefit from supplementation with hyperoncotic, commercially available albumin products.¹⁹ These 2 distinct approaches, albumin-based fluid resuscitation with the 4% to 5% concentration product and albumin supplementation with the 20% to 25% solution, deserve independent focus in this review as their purported mechanisms, desired targets, and possible benefits may differ.

Comparison Between Albumin and Crystalloid Resuscitation

In 1998, the Cochrane Injuries Group released a meta-analysis that indicated albumin-based resuscitation afforded no survival advantage over crystalloid.

In fact, the group found that albumin was associated with increased mortality in patients with hypovolemia, burns, and hypoalbuminemia.²⁴ These findings were met with great concern and skepticism as they reflected a pooled analysis of small trials with variable scientific rigor. In response, the Saline versus Albumin Fluid Evaluation (SAFE) trial was conducted and, to date, serves as the pivotal clinical trial for volume expansion in critical illness. This landmark study demonstrated comparable efficacy and safety of 4% albumin and 0.9% sodium chloride when used for routine resuscitation in ICU patients.²¹ A subsequent meta-analysis inclusive of these data reinforced these findings and demonstrated no difference in outcomes between routine crystalloid-based therapy and resuscitation with albumin (relative risk [RR] 1.01; 95% CI, 0.93-1.10).²⁵

Although albumin seems to exhibit comparable efficacy and safety to crystalloids in the general population, certain subpopulations may experience differential effects. Albumin should be avoided for routine resuscitation in traumatic brain injuries since a post hoc analysis of the SAFE study identified a heightened risk of death with albumin, perhaps attributable to coagulation abnormalities.¹³ In contrast, among patients with severe sepsis and septic shock, there have been intermittent signals of benefit with albumin when used as the primary resuscitation fluid. In the SAFE trial, patients with severe sepsis or septic shock randomized to albumin experienced a reduced risk of mortality relative to those in the normal saline group after adjustment for potential confounders (RR 0.71; 95% CI, 0.52-0.97).²⁶ Unfortunately, large meta-analyses have been unable to consistently reproduce these results^{27,28}; the most recent iteration of the Surviving Sepsis Campaign guidelines recommends the use of albumin only "...in patients who continue to require substantial amounts of crystalloid to maintain adequate mean arterial pressure."^{4(p596)} Lastly, although crystalloids are the preferred IV resuscitation fluid in burn patients, data from animal studies have alluded to a benefit of colloids for reduction of edema in nonburned soft tissue.²⁹⁻³¹ Based largely on expert opinion, the American Burn Association guidelines suggest that albumin may be administered after the initial 12 hours for burns that involve more than 40% of the body surface area.⁸ Albumin 4% to 5% replacement is also warranted after plasma exchanges of greater than 20 mL/kg in one session or greater than 20 mL/kg per week over multiple sessions.^{32,33}

Role of Supplementation of 20% to 25% Albumin

Critical Illness and Severe Sepsis

Whereas volume expansion with 4% to 5% albumin has been studied extensively, less is known about the role for albumin supplementation in the ICU. A small trial randomized 100 critically ill patients with hypoalbuminemia (≤ 3 g/dL) to either no albumin or 60 g of albumin (20%) on day 1 followed by 40 g each day if serum albumin was less than 3.1 g/dL. Patients in the albumin supplementation group demonstrated a greater improvement in organ dysfunction than patients in the nonsupplemented group.³⁴ However, valid concerns about the clinical utility of the primary endpoint and the external validity of these findings make the study, at best, difficult to interpret.^{35,36} The recently conducted ALBIOS trial assessed a similar albumin replacement strategy exclusively in patients with severe sepsis and septic shock. All patients underwent guideline-concordant early goal-directed fluid resuscitation with crystalloid and were then randomized to receive either no supplementation or up to 60 g per day of 20% albumin to reach a serum concentration greater than 3 g/dL. All-cause mortality at day 28 was not statistically different between groups; but in the subgroup with septic shock, patients supplemented with albumin experienced a lower risk of 90-day mortality that narrowly achieved statistical significance (RR 0.87; 95% CI, 0.77-0.99).³⁷ These data for albumin supplementation seem to be characterized by either questionable study methodology or negative primary outcome findings, with hypothesized benefit found only in isolated study subgroups. Although these investigations are provocative, the practice of albumin supplementation in critical illness or the use of serum albumin as a therapeutic target cannot be routinely recommended.

Other Acute Care Indications

There are several other clinical situations where a benefit of albumin supplementation has been demonstrated. The American Association for the Study of Liver Diseases (AASLD) recommends albumin supplementation after any large volume paracentesis (>5 L) to reduce the risk for hemodynamic compromise.^{5,6,38-40} In spontaneous bacterial peritonitis, albumin supplementation on days 1 and 3 may decrease the incidence of renal failure and mortality, particularly in patients at high risk of death (defined as urea ≥ 30 mg/dL or bilirubin ≥ 4 mg/dL).^{41,42} Other

appropriate indications for albumin supplementation include the diagnosis, prevention, and treatment of hepatorenal syndrome.^{41,43,44} There is no role for albumin replacement in malnutrition, improving drug transport capacity, or nephrotic syndrome.^{19,45} **Table 1** summarizes the currently recommended indications and doses of albumin.

Summary of the Place in Therapy for Albumin

Given the comparable efficacy and safety between albumin- and crystalloid-based resuscitation approaches and the considerable increase in cost associated with the former, it is prudent to reserve albumin for only specific situations. In fluid resuscitation, one could follow the Surviving Sepsis Campaign approach and administer 250 mL to 1 L of 5% albumin if 3 to 4 L of crystalloid fails to achieve hemodynamic targets. Albumin should be considered after hour 12 for burns that involve more than 40% of body surface area. Albumin supplementation for the sole purposes of normalizing plasma albumin concentrations or providing antioxidant or anti-inflammatory properties cannot be recommended. The best data for albumin supplementation are in the setting of large volume paracentesis, spontaneous bacterial peritonitis, hepatorenal syndrome, and therapeutic plasmapheresis.

CRYSTALLOIDS: PAST, PRESENT, AND FUTURE

In general, the debate about crystalloid selection for resuscitation of hospitalized patients is in its infancy. Whereas the focus of fluid selection literature in the last few decades and the first half of this review article compared colloid-based resuscitation to crystalloid-based therapy, the future will likely emphasize careful comparisons between the myriad of isotonic crystalloid options. Based on the most recent ICU data, 0.9% sodium chloride is the primary crystalloid fluid selected for resuscitation, but the use of “balanced” or “physiologic” solutions such as lactated Ringer’s or Plasma-Lyte is gaining popularity (**Table 2**).^{3,46} A practice shift from normal saline to balanced crystalloids will surely affect the hospital pharmacist. There will be greater risk for IV incompatibility between calcium-containing balanced solutions (eg, lactated Ringer’s) and other medications or blood products.^{47,48} Also, pharmacists will need to help the care team navigate issues with the reduced availability of these agents, patient selection nuances, and cost.⁴⁹

Table 1. Summary of albumin indications for use and doses

Indication	Dose	Considerations
Severe sepsis and septic shock (volume resuscitation)		
<i>Albumin</i> 4%-5%	250-1000 mL boluses	Limit to use when 3-4 L of crystalloid fails to achieve hemodynamic targets
Burns		
<i>Albumin</i> 4%-5%	Dependent on fluid requirement calculation, severity of burn, and resuscitation targets (eg, urine output)	Limit to use in patients with >40% BSA affected, after the initial 12 hours post burn
Complications of liver disease		
Hepatorenal syndrome <i>Albumin</i> 20%-25%	1 g/kg (maximum of 100 g/day) for 2 days followed by 20-40 g/day	Use in combination with a systemic vasoconstrictor
Paracentesis <i>Albumin</i> 20%-25%	6-8 g per 1 L fluid removed	May not be necessary for single paracentesis of <4-5 L
Spontaneous bacterial peritonitis <i>Albumin</i> 20%-25%	1.5 g/kg on day 1 and 1 g/kg on day 3	Consider limiting use to high risk patients, defined as urea $\geq$ 30 mg/dL or bilirubin $\geq$ 4 mg/dL
Therapeutic plasma exchange		
<i>Albumin</i> 4%-5%	Dependent on volume exchanged and institutional protocols	Limit to exchanges of > 20 mL/kg in one session or > 20 mL/kg/week over multiple sessions

Note: BSA = body surface area.

Table 2. Composition of commonly used intravenous fluids

	Plasma	0.9% Sodium chloride	Plasma-Lyte 148 ^a	Lactated Ringer's	Albumin 5%
Sodium (mmol/L)	140	154	140	131	130-160
Potassium (mmol/L)	5	—	5	5.4	$\leq$ 2
Chloride (mmol/L)	100	154	98	111	— ^b
Calcium (mmol/L)	2.2	—	—	2	—
Magnesium (mmol/L)	1	—	1.5	1	—
Bicarbonate (mmol/L)	24	—	—	—	— ^b
Lactate (mmol/L)	1	—	—	29	—
Acetate (mmol/L)	—	—	27	—	—
Gluconate (mmol/L)	—	—	23	—	—
pH	7.4	5.4	5.5	6.5	7.4
[Na ⁺]:[Cl ⁻] ratio	1.4:1	1:1	1.43:1	1.18:1	—

^aPlasma-Lyte A has the same composition with the exception of a pH of 7.4.

^bBuffering salt differs according to manufacturer, but may include sodium bicarbonate or sodium chloride.

We briefly summarize the history of crystalloid-based resuscitation, discuss pathophysiologic concerns associated with indiscriminant use of normal saline, and outline the limited primary literature evidence that compares the isotonic crystalloids.

History of Resuscitation Fluids

The cholera pandemic that reached England in 1831 represents the first published literature describing the use of salt-based fluid resuscitation for restoration of intravascular volume.⁵⁰ An 1832 landmark publication by Robert Lewins characterized the positive experiences of one of his contemporaries, Thomas Latta, with treating 6 cholera patients with a solution comprised of sodium chloride and sodium bicarbonate salts. He is quoted as suggesting that a weak saline solution when injected into cholera patients can “restore the natural current in the veins and arteries, improve the colour of the blood, and recover the functions of the lungs.”^{51(p243)} Over the next century, authors published reports of their successes and failures with a variety of salt-based solutions for resuscitation of what we would refer to as hypovolemic, distributive, or hemorrhagic shock. Awad and colleagues⁵⁰ elegantly summarize the composition of these primitive resuscitation solutions, none of which resemble what we now refer to as “normal saline” or 0.9% sodium chloride. Hartog Jakob Hambruger is credited with coining this term, although it is an obvious misnomer in that the solution of 154 mmol/L of sodium and 154 mmol/L of chloride in no way resembles the composition of extracellular fluid.^{52,53} In addition to lacking many of the components of extracellular fluid such as potassium, bicarbonate, calcium, magnesium, phosphorous, and dextrose, saline also contains a supraphysiologic concentration of chloride relative to the 97 to 107 mmol/L considered normal in humans.^{50,54}

Concerns About Chloride

Excess exogenous chloride administration induces many adverse physiologic effects including renal artery vasoconstriction, AKI, hyperchloremic metabolic acidosis, gastrointestinal dysfunction, and stimulation of inflammatory cytokines.⁵⁴⁻⁵⁶ In some of the earliest preclinical work in this field, Wilcox exposed 48 canines to intrarenal infusions of 1 of 6 hypertonic solutions, 2 of which contained chloride (NaCl and NH₄Cl) and 4 of which did not (NaHCO₃, Na Acetate, Dextrose, NH₄Acetate). After 30 minutes of infusing chloride-containing fluids,

renal blood flow, glomerular filtration rate, and urine output significantly declined. In contrast, during infusion of chloride-free solutions into the renal artery, renal blood flow increased and GFR and urine output remained unaffected.⁵⁷ A crossover study in healthy human volunteers reproduced these findings and demonstrated a reduction in renal artery blood flow velocity and renal cortical tissue perfusion during administration of normal saline, but not during the infusion of Plasma-Lyte 148 (a low chloride solution).⁵⁸ Moreover, in specific models of sepsis and hemorrhagic shock, balanced fluids resulted in decreased incidences of hyperchloremia, metabolic acidosis, serum and histologic evidence of AKI, and inflammation versus normal saline.⁵⁹⁻⁶¹

Clinical Comparisons Between Crystalloids

Although preclinical models and healthy volunteer studies would favor preferential use of balanced crystalloid solutions over 0.9% sodium chloride for resuscitation, there is a paucity of high-caliber literature vetting this practice in the context of routine clinical care.

Two large propensity-matched observational studies evaluated crystalloid choice using a hospital claims database.^{62,63} In 3,704 cases of open abdominal surgery, patients who received Plasma-Lyte experienced a significant decrease in the incidence of major complications relative to normal saline recipients, but no difference in mortality or hospital length of stay.⁶³ A subsequent study evaluated 6,730 medical cases of septic shock. Included individuals were grouped according to use of either 0.9% sodium chloride monotherapy during the first 2 days of sepsis or the use of any amount of balanced fluids with or without saline. The authors found a significant reduction in adjusted in-hospital mortality among patients who received balanced crystalloids. When mortality was stratified by the proportion of balanced fluids used, there was a dose-response relationship, wherein those who received the highest proportion of balanced crystalloids experienced the lowest mortality. One ICU described their experience with limiting the routine use of chloride-liberal IV fluids (eg, normal saline) and establishing a chloride-restrictive IV fluid practice (eg, lactated Ringer's). After the practice change, reductions occurred in the magnitude of creatinine rise, the incidence of AKI, and the use of renal replacement therapy.^{64,65}

Comparative randomized trial data in this field have been limited in size and scope. Small studies

of fewer than 100 participants in acute pancreatitis, hepatobiliary and pancreatic surgery, abdominal aortic aneurysm repair, and trauma found reduced hyperchloremia and improved acid-base status with balanced crystalloids compared to saline, but the analyses were insufficiently powered to evaluate clinical outcomes.⁶⁶⁻⁶⁹ In brain injury, where the slight hypotonicity of lactated Ringer's may be unfavorable in large volumes, an alternative balanced solution (Isofundine; 304 mOsmol/L) again resulted in less acid-base disturbances than normal saline.⁷⁰ Fluid selection in kidney transplantation is of particular interest, because both balanced solutions and normal saline could pose meaningful risks. A 2002 survey of kidney transplant centers found 0.9% sodium chloride was the most commonly selected perioperative IV fluid; this was attributed to apprehension about the use of potassium-containing solutions in patients with renal failure.⁷¹ Yet the recent evidence linking normal saline to a heightened risk for renal dysfunction heralds an equal and opposite concern. Comparative literature has failed to validate either of these considerations. In several studies, there has been no association between perioperative hyperkalemia in kidney transplant recipients and choice of IV crystalloid; however, patients with preoperative potassium concentrations greater than 5.5 mmol/L were often excluded from these studies. Also, fluid choice did not influence postoperative serum creatinine, urine output, or dialysis dependence.⁷²⁻⁷⁵

Crystalloid Selection: Summary

Normal saline has been the primary resuscitation fluid used in the hospital setting for nearly 100 years, but its nonphysiologic profile may have deleterious effects. Balanced crystalloids more closely parallel the composition of extracellular fluid and consequently may be the preferred fluid choice. Although the comparative literature at present is of low to moderate quality, there is a consistent signal from these studies that indicates balanced solutions are associated with reduced hyperchloremia, improved acid-base status, and improved clinical outcomes, specifically at the level of the kidney. These efficacy benefits likely offset the marginal increase in acquisition costs associated with balanced salt solutions.⁴⁹ There are insufficient data at this point to suggest which balanced salt solution is most preferred.

CONCLUSION

Recently published literature and the heightened emphasis on evidence-based resource utilization have

refocused the hospital pharmacist's attention toward the challenges of fluid selection. Resuscitation with iso-oncotic albumin exhibits comparable efficacy and safety to crystalloid-based resuscitation, and the associated cost elicits a need to conserve use to well-defined circumstances. The best data for supplementation of hyperoncotic albumin are in the setting of liver disease and therapeutic plasmapheresis. Balanced crystalloids, such as lactated Ringer's or Plasma-Lyte, should be considered as first-line fluid therapies. These agents may supplant the use of normal saline in the future because of concerns about its association with adverse patient outcomes.

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