Fluid and Hyponatremia Management

By Craig B. Whitman, Pharm.D., BCPS, BCCCP

Reviewed by Serena A. Harris, Pharm.D., BCPS, BCCCP; Ohoud A. Aljuhani, Pharm.D., BCCCP; and Abigail D. Antigua, Pharm.D., BCCCP

LEARNING OBJECTIVES

1. Evaluate intravascular volume status and administer intravenous fluids (IVFs) to a critically ill patient.
2. Develop a plan to administer the appropriate IVF choice in a critically ill patient according to evidence from the literature.
3. Justify the use of peripheral administration of hypertonic saline and vasopressin antagonists to correct hyponatremia in a critically ill patient.
4. Demonstrate the role of desmopressin in preventing sodium overcorrection when treating hyponatremia.

ABBREVIATIONS IN THIS CHAPTER

AKI	Acute kidney injury
IVC	Inferior vena cava
IVF	Intravenous fluid
LOS	Length of stay
RRT	Renal replacement therapy
SIADH	Syndrome of inappropriate antidiuretic hormone
TBI	Traumatic brain injury

Table of other common abbreviations.

INTRAVENOUS FLUID THERAPY

Introduction

Intravenous fluid (IVF) therapy has been used in clinical medicine since the 1830s during the European cholera epidemic (Severs 2015). Many indications exist for IVF therapy in the critically ill population. Intravascular volume replacement is the most common reason for using large volumes of IVF in the ICU, with sepsis, trauma, burn, and perioperative volume loss requiring replacement. Hypovolemia occurs with reduction of extracellular volume and requires replacement with IVF. Electrolyte repletion, management of acidosis, and prevention and management of drug-induced toxicities are other examples of common indications for IVF (Severs 2015). Many IVFs have been developed to optimize composition and administration in patients requiring treatment. These solutions are classified as crystalloids and colloids. Crystalloid solutions contain small solutes with various amounts of water. The prototypical crystalloid solution is 0.9% sodium chloride (normal saline), with lactated Ringer solution and other various "balanced crystalloid" solutions available for IVF therapy. Intravascular volume expansion from normal saline is maintained for up to 6 hours, with close to one-half of the infusate located in the interstitium (Severs 2015). Colloid solutions contain large molecules that more effectively maintain intravascular volume by exerting an oncotic pressure. Available colloids include iso-oncotic (4%–5%) and hyperoncotic (20%–25%) albumin solutions, semisynthetic colloids like hydroxyethyl starch, dextrans, gelatins, and blood products.

Despite the longstanding use of available IVFs, considerable debate exists regarding the optimal fluid choice, dose, and method of administration in the critically ill population. This chapter aims to discuss recent advances in knowledge of IVF therapy and provide insight into optimal use of various fluid choices in this population.

Assessment of Volume Status in the Critically Ill Patient

Assessing intravascular volume status and fluid responsiveness in critically ill patients is one of the more challenging aspects of managing IVF therapy in this population. Appropriate assessment is important because it may mitigate a positive fluid balance, which may be associated with increased mortality (Malbrain 2014). A variety of methods including physical examination, chest radiography, laboratory values, and invasive monitoring can be used to assess volume status. There is no universally accepted method to assess intravascular volume in critically ill patients. Physical examination findings should be used during the initial evaluation of intravascular volume status and combined with dynamic measurements of blood volume. The Surviving Sepsis Campaign guidelines recommend using dynamic variables to assess fluid responsiveness, including passive leg raises, pulse pressure variation, and stroke volume variation (Rhodes 2017). Esophageal Doppler monitoring and ultrasound measurement of the inferior vena cava (IVC) can also be considered if the equipment is available and the operator has expertise in its use. Esophageal Doppler monitoring may be limited because it requires the patient to be sedated (Kalantari 2013). The accuracy of IVC ultrasonography may be affected by elevated intra-abdominal pressure (e.g., post-laparotomy) or large body habitus. In general, static measurements of intravascular blood volume (e.g., central venous or pulmonary artery occlusion pressure) should be avoided as the sole assessment method (Rhodes 2017; Kalantari 2013). To optimize therapy, intravascular volume should continually be assessed and reassessed in patients who receive IVF.

IVF Administration in Critically Ill Patients

Fluid may be administered in a variety of ways in critically ill patients. The 12th Acute Dialysis Quality Initiative Conference workgroup has proposed definitions pertinent to fluid administration (Hoste 2014). Fluid bolus is a rapid infusion to correct intravascular volume status in shock states that consists of at least 500 mL over a maximum of 15 minutes. A fluid challenge is a rapid infusion to correct hemodynamic instability, administering 100–200 mL over 5–10 minutes followed by reassessment (Hoste 2014). The Surviving Sepsis Campaign recommends 30 mL/kg as the initial fluid challenge in patients with sepsis (Rhodes 2017). Fluid infusion is the continuous delivery of IVF to maintain homeostasis, replace losses, or prevent organ injury. Maintenance infusion is administration to provide fluids for patients who cannot maintain their needs by the oral or enteral route. For individuals without ongoing losses, a maximum rate of 1–2 mL/kg/hour is recommended (Hoste 2014).

Four distinct phases of fluid therapy in resuscitation have been proposed: rescue, optimization, stabilization, and de-escalation (Rewa 2015). The rescue phase occurs with hemodynamic instability and associated impaired organ perfusion, resulting in life-threatening shock. Intravenous fluids are administered using boluses in the rescue phase. Optimization is when the patient is no longer at imminent risk of life-threatening shock but requires fluid therapy to optimize cardiac function, sustain tissue perfusion, mitigate organ dysfunction, and achieve physiologic end points. Methods of fluid administration in this phase vary between bolus, fluid challenge, and continuous infusion. During the stabilization phase, the goals of fluid therapy are to provide ongoing organ support, prevent worsening organ dysfunction, and avoid further complications. The need for fluid during this phase is directed toward maintaining intravascular volume homeostasis and replacing ongoing losses. Fluid challenge and continuous infusion are the methods of IVF administration during stabilization. The de-escalation phase occurs with mobilization and removal of accumulated fluid. With recovery and decreasing illness severity, a negative fluid balance is typically targeted and may be achieved by spontaneous or active diuresis of the patient (Rewa 2015).

CONTROVERSIES IN FLUID RESUSCITATION

Crystalloids vs. Colloids

Theoretical advantages exist for using one type of IVF versus another. Colloids may more effectively maintain intravascular volume status, leading to potentially less total volume

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Understanding of intravascular fluid composition, mechanism of action, and toxicities
- Understanding of sodium and water physiology and homeostasis
- General knowledge of pathophysiology and differentiation of sodium disorders
- Knowledge of modes of renal replacement therapy used in critically ill patients
- Knowledge of standard treatment approaches for sodium abnormalities

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med 2017;45:486-552.
- Verbalis JG, Goldsmith SR, Greenberg A, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med 2013;126:s1-s42.

administered, which may reduce significant edema (Rewa 2015). However, albumin costs as much as 30 times more than normal saline or lactated Ringer solution (Severs 2015). Meta-analyses of small studies evaluating the difference between crystalloid and colloid solutions have had mixed results, leading to questionable effects of colloids on mortality (Finfer 2004).

The Saline versus Albumin Fluid Evaluation (SAFE) study was the first large, multicenter, double-blind, controlled trial to evaluate differences in clinical outcomes between crystalloid and colloid solutions (Finfer 2004). The SAFE study randomized 3499 subjects to 4% albumin and 3501 subjects to normal saline. Over the first 2 days, subjects in the albumin group received less mean volume than normal saline (1183.9 ± 973.6 mL on day 1, 602.7 ± 892.7 mL on day 2 vs. 1565.3 ± 1536.1 mL on day 1, 954 ± 1484.4 mL on day 2; p<0.001). No significant difference occurred in the primary outcome of 28-day mortality (20.9% albumin vs. 21.1% normal saline, p=0.87). Hospital and ICU length of stay (LOS), duration of mechanical ventilation, need for dialysis, and new organ failure were similar. The adjusted OR for death with albumin was 0.71 (95% CI, 0.52–0.97; p=0.03), suggesting its superiority to normal saline. However, those who had a traumatic injury and received albumin were at higher risk of death than those who received normal saline (13.6% vs. 10%, RR 1.36 [95% CI, 0.99–1.86]). Those with traumatic brain injury (TBI) were at higher risk of death if they received albumin (24.5% vs. 15.1%, p=0.009). A post hoc analysis of the SAFE study, the SAFE-TBI study, corroborated these results, especially in patients with severe brain injury (Glasgow Coma Scale scores 3–8) (Myburgh 2007). Data from the SAFE study suggests that for overall volume resuscitation in critically ill patients, normal saline and albumin are essentially equivalent in efficacy and safety. However, albumin solutions should be avoided in patients with trauma or TBI. In addition, the findings from the subgroup analysis are limited because the study was not designed to evaluate these results.

The CRISTAL study was an open-label, multicenter trial that evaluated outcomes related to the use of crystalloids versus colloids in patients with hypovolemic shock (Annane 2013). A total of 1414 subjects were in the colloid group, with 1443 in the crystalloid group. Subjects in the crystalloid group could receive normal saline or lactated Ringer solution, and those in the colloid group could receive albumin (4%, 5%, 20%, or 25%), dextrans, starches, or gelatin solutions. All-cause mortality at 28 days was 25.4% in the colloid group compared with 27% in the crystalloid group (RR 0.96 [95% CI, 0.88–1.04]; p=0.26). At 90 days, the crystalloid group had better mortality (number needed to treat 29), but the colloid group had more subjects alive not receiving mechanical ventilation or vasopressors. Other secondary outcomes, including dialysis requirement, ICU and hospital LOS, and duration of resuscitation therapy, did not differ between the groups. Subjects in the colloid group received significantly lower median cumulative volumes in the first ICU week: 2 L (interquartile range [IQR] 1–3.5) compared with 3 L (IQR 0.5–3.2) (p<0.001). Despite equivalent outcomes, this study had many significant limitations. About 25% of subjects received open-label fluid administration. The study duration extended over 9 years, which may also reflect inconsistencies in practice over that time and changes in guideline recommendations. Finally, the study allowed a variety of fluids to be chosen at the clinician's discretion, making it extremely difficult to ascertain any difference between the specific fluids used. Despite this limitation, the study design may make the data somewhat more generalizable because, reflecting the reality of clinical practice.

Normalizing serum albumin may help maintain oncotic pressure differences that retain volume in the vasculature more effectively. This was tested in the Albumin Italian Outcome Sepsis (ALBIOS) study, a multicenter, open-label, randomized controlled trial (Caironi 2014). Patients were randomized to receive crystalloid (n=907) or crystalloid with 20% albumin (n=903) to maintain serum albumin concentrations of 3 g/dL. No differences in 28-day mortality occurred between the groups (31.8% albumin vs. 32% crystalloid; p=0.94), nor were secondary outcomes such as 90-day mortality, ICU/hospital LOS, acute kidney injury (AKI), need for dialysis, and duration of mechanical ventilation any different. However, the albumin group discontinued vasopressors more quickly than the crystalloid group with a median of 3 days (IQR 1–6) compared with 4 days (IQR 2–7) (p=0.007). Post hoc analysis showed a lower 90-day mortality rate in patients with septic shock who received albumin (43.6% vs. 49.9%; p=0.03). Overall, the ALBIOS trial has strengths, including a multicenter design, as well as limitations, including differences in albumin concentration compared with the SAFE study and the open-label design. Mortality was less than expected and may have caused the study to be underpowered to find differences. However, the data analyses suggest that normalization of albumin using exogenous administration does not result in improved mortality but affects hemodynamic recovery in patients with sepsis. The potential for improved mortality in septic shock requires further study to confirm these findings.

In addition to albumin, hydroxyethyl starch has been compared with crystalloid solutions for resuscitation in critically ill patients. Three large, well-designed studies have shown an increased risk of AKI and the need for renal replacement therapy (RRT) using hydroxyethyl starch (Myburgh 2012; Perner 2012; Brunkhorst 2008). In addition, 90-day mortality has been higher in subjects receiving hydroxyethyl starch than in those receiving Ringer acetate (Perner 2012). Hydroxyethyl starch has also been associated with an increased risk of coagulopathy, mainly due to its reduction of factor VIII and von Willebrand factor (Severs 2015). Because of an increased risk of renal injury and mortality, hydroxyethyl starch is not recommended for critically ill patients requiring fluid resuscitation (Rhodes 2017).

Meta-analyses comparing outcomes between the use of crystalloids and colloids have shown mixed results. A 2011 Cochrane review (Roberts 2011) showed that the RR of death with colloids was 1.02 (95% CI, 0.92–1.13). The SAFE study clearly influenced the results of this meta-analysis because it composed 75% of the data. Another 2011 meta-analysis showed that using albumin in patients with sepsis reduced mortality (OR 0.82 [95% CI, 0.67–1], p=0.047) (Delaney 2011). A 2013 Cochrane review that included the use of semisynthetic colloids had a 0.99 RR of death (95% CI, 0.71–1.06) (Perel 2013).

Variability in outcomes, patient populations, and products used in these clinical trials limits the generalizability of the available data. However, colloid solutions have no clear advantage over crystalloids for standard fluid resuscitation in critically ill patients, and fluid choice should be patient-specific. These data do not apply to trauma and burn patients, in whom specific approaches to fluid management have been developed and will not be covered in this chapter. Several guidelines, including those of the Surviving Sepsis Campaign and the National Institute for Health Care Excellence, recommend crystalloid solutions over colloids for resuscitating critically ill patients (NICE 2017; Rhodes 2017). This is based on the limited quality of data analyses that suggest positive outcomes associated with colloid solutions, a lack of clear benefit with use of albumin, and the significant difference in cost between the two fluid types. A combination of crystalloids and colloids may be used for certain patients when large-volume resuscitation is required or to expedite weaning of vasopressor drugs in the setting of shock. Another takeaway from the data analyses is that hydroxyethyl starch should be avoided in the critically ill population because of the increased risk of renal dysfunction, coagulopathy, and mortality.

Balanced Crystalloid Solutions vs. Normal Saline Solutions

The most commonly used crystalloids include normal saline and several balanced crystalloid solutions, including lactated Ringer solution, Plasma-Lyte 148, and Normosol. Table 1 details the different composition of some of these IVFs compared with human plasma. Relative to human plasma, normal saline has a significantly higher sodium and chloride content and contains no additional electrolytes or buffers.

Balanced crystalloid solutions include bicarbonate, lactate, acetate, and a variety of electrolytes. Many of these solutions were developed to be more physiologically compatible with human plasma. Despite having compositions more similar to plasma, the balanced crystalloid solutions have their own set of potential disadvantages. Lactated Ringer solution is hypotonic compared with plasma and may lead to complications related to cerebral edema in patients with neurologic emergencies (Ince 2014). Incompatibilities of calcium exist with other intravenous medications and blood products, making coadministration with lactated Ringer solution difficult. Newer balanced crystalloids like Plasma-Lyte 148 were developed to overcome some of these negative effects. Plasma-Lyte 148 and Normosol are both isotonic and may not have the same deleterious effects in patients at risk for development or worsening of cerebral edema. The absence

Table 1. Components of Human Plasma and Common Crystalloid Solutions

	Human Plasma	Normal Saline	Lactated Ringer Solution	Normosol-R pH 7.4	Plasma-Lyte 148
Osmolarity (mOsm/L)	275–295	308	273	294	294
pH	7.35–7.45	4.5–7	6–7.5	4–8	7.4
Na (mEq/L)	135–145	154	130	140	140
Cl (mEq/L)	94–111	154	109	98	98
K (mEq/L)	3.5–5.3	0	4	5	5
Calcium (mEq/L)	2.2–2.6	0	2.7	0	0
Magnesium (mEq/L)	0.8–1	0	0	3	1.5
HCO_3 (mEq/L)	24–32	0	0	0	0
Acetate (mEq/L)	1	0	0	27	27
Gluconate (mEq/L)	0	0	0	23	23
Lactate (mEq/L)	1–2	0	28	0	0

Information from: Severs D, Hoorn E, Rookmaaker M. A critical appraisal of intravenous fluids: from the physiological basis to clinical evidence. Nephrol Dial Transplant 2015;30:178-87.

of calcium and lactate may alleviate some of the concerns of compatibility and metabolic derangements associated with lactated Ringer solution.

A concern of using normal saline in critically ill patients that has garnered significant attention is its association with hyperchloremic acidosis. Classically, the dilutional acidosis theory and the Stewart hypothesis have been used to explain hyperchloremic acidosis as a consequence of saline administration. Dilutional acidosis occurs with a reduction in pH, bicarbonate, and anion gap with an increase in chloride concentrations (Doberer 2009). Hyperchloremia has been associated with the development of AKI from sustained renal vasoconstriction through A_1-receptor-mediated afferent arteriole constriction and increased renal intracapsular pressure, resulting in decreased tissue perfusion, reduced microvascular flow, and impaired renal function (Ren 2004). In a retrospective study of 1940 patients with sepsis and septic shock, increases in serum chloride from baseline were associated with significantly increased mortality (adjusted OR 1.27; 95% CI, 1.02–1.59; p=0.03) (Neyra 2015). Use of balanced crystalloid solutions has reduced hyperchloremic acidosis in patients undergoing renal transplantation, abdominal aortic aneurysm repair, and trauma resuscitation (Potura 2015; Shaw 2012; O'Malley 2005; Waters 2001). A propensity-matched sample of over 30,000 patients requiring open abdominal surgery in a retrospective analysis showed significant decreases in postoperative infection, need for dialysis, need for blood transfusion, and electrolyte disturbances in those who received Plasma-Lyte 148 compared with normal saline (Shaw 2012).

In critically ill patients, some retrospective analyses have shown an association between worse outcomes and use of normal saline. In a sample of 109,836 patients who met systemic inflammatory response syndrome criteria and received crystalloids, mortality was higher (adjusted OR 1.09; 95% CI, 1.06–1.12) with increasing volume-adjusted chloride load (105 mEq/L or more) (Shaw 2014). Another retrospective study showed that, in a propensity-matched cohort of 6730 patients, use of balanced crystalloids was associated with lower in-hospital mortality than normal saline (RR 0.86; 95% CI, 0.78–0.94) (Raghunathan 2014).

Despite the associations between normal saline and worse clinical outcomes, including mortality, these studies had small sample sizes or were retrospective and had populations with significant heterogeneity. The first prospective study to evaluate the effects of various crystalloid solutions in critically ill patients was conducted in a single center in Australia (Yunos 2012). This was an open-label, before-after study in a 22-bed ICU. The study allowed use of normal saline, 4% succinylated gelatin solution, and 4% albumin in the control period (chloride-liberal), followed by a phase-out period, and then the intervention period (chloride-restrictive), in which clinicians could choose between lactated Ringer solution, Plasma-Lyte 148, and 20% albumin. The study population included 760 subjects in the control period and 773 in the intervention period. Significantly fewer subjects in the intervention period developed the primary outcome of AKI, as defined by "injury" and "injury and failure" (6.3% vs. 3%, p=0.002; 14% vs. 8.4%, p<0.001), and fewer subjects required RRT. The two groups did not differ in mortality, LOS, or requirement for long-term dialysis. Study limitations include the single-center, before-after design, which eliminates any direct comparison between IVFs studied and limits the applicability to the ICU that served as the study site. In addition, this was a bundle-of-care study, making it difficult to ascertain which individual IVF may have caused a difference in the incidence of AKI.

The first well-designed prospective study to compare the effects of normal saline with Plasma-Lyte 148 was the 0.9% saline versus Plasma-Lyte 148 for ICU fluid therapy (SPLIT) trial, a prospective, multicenter, randomized, blinded, double-crossover controlled trial (Young 2015). A total of 1152 subjects received Plasma-Lyte 148, and 1110 subjects received normal saline. Acute kidney injury did not differ in subjects receiving Plasma-Lyte 148 (RR 1.04 [95% CI, 0.80–1.36; p=0.77]). Secondary outcomes did not differ significantly between the two groups, including RRT, ICU/hospital LOS, duration of mechanical ventilation, and mortality. Despite showing no risk of adverse outcomes with normal saline, this study had several limitations. The mean Acute Physiology and Chronic Health Evaluation II (APACHE II) score was 14.1, and about 70% of subjects were surgical, with 50% having elective procedures. This may account for the population's relatively low mortality rate (6.6% ICU mortality in Plasma-Lyte 148 vs. 7.2% ICU mortality in normal saline and 7.6% hospital mortality in Plasma-Lyte 148 vs. 8.6% hospital mortality in normal saline). In addition, AKI was defined as subjects meeting any level of the risk, injury, failure, loss, and end-stage kidney disease (RIFLE) criteria. Therefore, severity of kidney injury is difficult to elucidate. Chloride concentrations were not collected, so no correlations were possible between hyperchloremia, fluid choice, and AKI. The median total amount of study fluid administered to each group was 2 L, making it difficult to extrapolate the findings to large-volume resuscitation. The study is also limited because, despite blinding of the investigators to study fluid, two-thirds of the investigators were able to accurately identify the Plasma-Lyte 148 administered. That open-label Plasma-Lyte 148 was allowed according to the protocol introduces potential for bias.

The Isotonic Solutions and Major Adverse Renal Events Trial (SMART) was a single-center, unblinded, cluster-randomized, multiple-crossover trial that compared normal saline with balanced crystalloid solutions (Semler 2018). A total of 7942 subjects were randomized to receive balanced crystalloids, with 7860 to receive normal saline. One major difference of the SMART trial compared with the SPLIT trial is that in the SMART trial, the balanced crystalloid group could receive

either Plasma-Lyte 148 or lactated Ringer solution. A significant difference in the primary outcome of major adverse kidney events in 30 days was found between the two groups (14.3% in balanced crystalloid group vs. 15.4% normal saline group; adjusted OR 0.9 [95% CI, 0.82–0.99], p=0.04). In addition, subjects who received balanced crystalloids had a higher mean number of RRT-free days (25 ± 8.6 vs. 24.8 ± 8.9, OR 1.11 [95% CI, 1.02–1.2]). Although mortality did not differ significantly, in-hospital death before 30 days trended in favor of the balanced crystalloid group (10.3% vs. 11.1%, OR 0.9 [95% CI, 0.8–1.01], p=0.06). Subgroup analysis revealed significant decreases in the composite outcome of death, new RRT, or persistent renal dysfunction in subjects in the medical and neurologic ICUs, subjects with sepsis, subjects without TBI, and those who were receiving RRT before study enrollment. Chloride concentrations were collected and were similar at baseline (median 103 mEq/L [IQR 100–106]) in the balanced crystalloid group compared with 103 mEq/L (IQR 100–106 in the normal saline group). However, significantly more subjects had a Cl concentration greater than 110 mEq/L in the normal saline group (24.5% vs. 35.6%, p<0.001) and an HCO_3 less than 20 mEq/L (35.2% vs. 42.1%, p<0.001). Ventilator-free, ICU-free, and vasopressor-free days were not significantly different between the two groups. The SMART trial has many strengths and limitations. Overall, the trial was well designed and had a large sample size. Chloride concentrations were collected and correlated with the fluid type used. The study population differed from that in the SPLIT trial, with 21.4% being surgical admissions and 14.8% having a diagnosis of sepsis or septic shock (3.4% of subjects had sepsis in the SPLIT trial). The mean cumulative volume of study fluid administered from ICU admission to hospital discharge or 30 days was 2.3 plus or minus 3.6 L in the balanced crystalloid group and 2.6 plus or minus 4.5 L in the normal saline group. Similar to the SPLIT trial, this makes it difficult to extrapolate the SMART study's findings to large-volume resuscitation. The estimated in-hospital mortality was 9.4% (95% CI, 9–9.9) in the balanced crystalloid group compared with 9.6% (95% CI, 9.2–10) in the normal saline group. This is difficult to compare with the SPLIT trial because the predicted mortality was estimated using the Vizient database and cannot reliably be related to use of the APACHE II score. Other limitations include the study's single-center and unblinded design. Finally, the risk of AKI between use of lactated Ringer solution and Plasma-Lyte 148 cannot be distinguished in this study because the balanced crystalloid group could receive either fluid.

Recent data analyses have had similar findings in the non-critically ill population when comparing normal saline with balanced crystalloid solutions. The Saline against Lactated Ringer's or Plasma-Lyte 148 in the Emergency Department (SALT-ED) trial was a single-center, unblinded, multiple-crossover trial that included 6708 subjects receiving Plasma-Lyte 148 or lactated Ringer solution and 6639 receiving normal saline (Self 2018). The median volume of study fluid administered in each group was 1 L (IQR 1–2). Although hospital-free days did not differ significantly (up to 28 days), subjects receiving balanced crystalloids had a lower frequency of an adverse kidney event (4.7% vs. 5.6%, OR 0.82 [95% CI, 0.7–0.95], p=0.01). Although the SALT-ED trial was specifically of non-critically ill patients, the findings are consistent because the risk of AKI appears to be increased using normal saline compared with balanced crystalloids.

According to the available data, normal saline may increase the risk of hyperchloremic metabolic acidosis and AKI, even at the low cumulative volumes administered. The association between normal saline use and increased mortality deserves further study because several retrospective analyses have indicated such a relationship. Data from the SMART trial showing a potential mortality benefit of using balanced crystalloid solutions are merely speculative because the study was not designed to find a difference in that outcome. Currently, clinical practice guidelines do not recommend use of balanced crystalloid solutions over normal saline, aside from avoidance of hyperchloremia (NICE 2017; Rhodes 2017). Recent publication of the SMART and SALT-ED studies may alter these guideline recommendations in the future. However, additional data are required in critically ill patients at high risk of death and those who receive large volumes of IVF, greater than 60 mL/kg in a 24-hour period (Sen 2017). In addition, it is unclear whether Plasma-Lyte 148 is superior to lactated Ringer solution, which is more readily available and less costly. The average wholesale cost of Plasma-Lyte 148 is about 5 times that of normal saline (Smith 2014). Currently, it seems prudent to carefully select a crystalloid fluid on the basis of patient characteristics and institutional availability. Although data analyses suggest increased risk in harm with normal saline, further study is required to confirm these findings. In the meantime, lactated Ringer solution may be considered an optimal fluid choice in most critically ill patients requiring fluid administration, with Plasma-Lyte 148 and Normosol as alternative options because of their high cost. According to the available data, balanced crystalloid solutions are preferred in patients who receive large-volume resuscitation, have or develop hyperchloremia, or are receiving RRT.

UPDATES IN MANAGING HYPONATREMIA IN THE ICU

Introduction

Hyponatremia may cause complications in critically ill patients, including neurologic deficits, muscle weakness and cramps, hyperventilation, impairment in gluconeogenesis, and decreased left ventricular function (Verbalis 2013). The presence of hyponatremia in the ICU is associated with mortality rates as high as 37.7%. Management of hyponatremia depends on its underlying

Patient Care Scenario

A 63-year-old woman (weight 63 kg) with a history of chronic obstructive pulmonary disease and heart failure (ejection fraction of around 35%) was admitted for septic shock secondary to a UTI. She has received 2 L of normal saline (bolus) and is receiving a norepinephrine infusion for shock at 30 mcg/minute. She is intubated on mechanical ventilation and sedated. Laboratory values are within normal limits, except for Cl 108 mEq/L. Given the patient's presentation, develop a plan to assess for fluid responsiveness, what type of fluid to administer, and how to monitor therapy.

ANSWER

Fluid responsiveness should be reassessed often because the patient is now receiving vasopressor therapy. Evaluation of the patient's intravascular volume should begin with a physical examination, including capillary refill, skin turgor, extremity temperature, mucus membranes, urine color, and urinary output. Laboratory tests such as SCr, BUN, and lactate may also indicate fluid status. Dynamic assessments should be used over static measurements because dynamic assessments tend to be more reliable measurements of intravascular volume responsiveness. Passive leg raises and pulse pressure variation are noninvasive and easily done to assess fluid responsiveness. If the equipment is available, the clinician may do esophageal Doppler monitoring or ultrasound assessment of the IVC.

Regarding selecting the best fluid for this patient, no clear evidence shows that colloid solutions are superior to crystalloids across the board. Albumin may result in less total volume administered and has clinical outcomes similar to saline. This may be consequential in the patient because she is at higher risk of developing pulmonary edema, given her underlying heart failure. Additional crystalloid resuscitation may exacerbate this negative effect. Therefore, it may be reasonable to administer 5% albumin 250–500 mL instead of saline, followed by reassessment of intravascular volume status. Use of albumin has been associated with faster resolution of hemodynamic instability when combined with crystalloids. Because this patient is taking relatively high norepinephrine doses, albumin in addition to crystalloid resuscitation may be of benefit.

Hyperchloremic metabolic acidosis has been associated with 0.9% sodium chloride, and data analyses suggest increased risk of renal dysfunction using this fluid. Because the patient has already developed hyperchloremia, lactated Ringer solution would be optimal if crystalloid resuscitation were desired. In addition, no data suggest a benefit of Plasma-Lyte or Normosol over lactated Ringer solution; thus, the cost of these agents would not make them first line. Additional monitoring of chloride and renal function is recommended.

1. Annane D, Siami S, Jaber S, et al. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. JAMA 2013;310:1809-17.
2. Semler MW, Self WH, Wanderer JP, et al. Balanced crystalloids versus saline in critically ill adults. N Engl J Med 2018;378:829-39.

cause and may include infusion of normal saline, hypertonic saline, and water restriction (for syndrome of inappropriate antidiuretic hormone [SIADH]). Several limitations to widely accepted treatment modalities exist, including unpredictable and rapid changes in sodium and administration-related complications of hypertonic saline.

Peripheral Administration of Hypertonic Saline Solutions for Hyponatremia

Hypertonic saline is typically reserved for patients with severe hyponatremia (Na less than 120 mEq/L or with associated symptoms). Hypertonic saline is also commonly used in patients with intracranial hypertension secondary to TBI or other causes of cerebral edema. One of the main concerns regarding use of hypertonic saline is the need for appropriate administration to minimize complications related to infusion of the fluid. Historically, 3% sodium chloride solutions are administered through a central venous catheter because of the risk of phlebitis and extravasation-related injuries from its hyperosmolarity (Dillon 2018). Central venous catheters are associated with an increased risk of infection, pneumothorax, and thrombosis. In addition, significant delays in effective therapy may occur because of the time required to place a central venous catheter. This may be unacceptable in patients with severe TBI or hyponatremia who require urgent administration of hypertonic saline. At least three retrospective studies have evaluated the safety of peripheral administration of 3% sodium chloride (Table 2).

All three studies suggest that peripheral administration of 3% saline is a safe alternative in managing hyponatremia, especially in patients for whom timely placement of central venous access is not achievable. The frequency of infusion-related reactions such as phlebitis and extravasation was low across all the studies. One subject developed brachial vein thrombosis without further complications. In the largest study, phlebitis or extravasation occurred in about 7% of the population. Of note, this study included two separate centers, where one institution had a maximum rate of 3% sodium chloride of 30 mL/hour and the other, 75 mL/hour. On further analysis, 8 of the 15 subjects who developed an infusion-related adverse event had their infusion changed to an alternative peripheral site, 5 had their infusion changed to central administration, and 2 had their infusion completely stopped. No additional complications were noted in the patients who had peripheral administration continued through an alternative site. Of note, most subjects had at least a 20-gauge catheter in place, and

Table 2. Studies Evaluating Peripheral Administration of 3% NaCl

	Dillon RC 2018	Perez CA 2017	Jones GM 2016
Sample size	66	28	213
Indication			
Hyponatremia	42 (64%)	0 (0%)	0 (0%)
Neurologic injury	19 (29%)	28 (100%)	213 (100%)
Catheter gauge			
≤ 20	101 (60%)	28 (100%)	208 (97.7%)
≥ 22	67 (40%)	0 (0%)	5 (2.3%)
Infusion rate (mL/hr)			
Initial	30 (IQR 25–43)	Not described	30 (IQR 20–30)
Median/mean	34 (IQR 30–42)	39 ± 10	30 (IQR 24.4–34.7)
Maximum	50 (IQR 8–75)	50	30 (IQR 25–40)
Range		30–50	
Median/mean infusion duration (hr)	14 (IQR 4–30)	36 (range 1–124)	0.85 (IQR 0.44–1.36)
Infusion-related adverse events			
• Phlebitis	2	1	9
• Extravasation	0	0	6
• Venous thrombosis	0	1	0

NaCl = sodium chloride.

Information from: Dillon RC, Merchan C, Altshuler D, et al. Incidence of adverse events during peripheral administration of sodium chloride 3%. J Intensive Care Med 2018;33:48-53; Perez CA, Figueroa SA. Complication rates of 3% hypertonic saline infusion through peripheral intravenous access. J Neurosci Nurs 2017;49:191-5; and Jones GM, Bode L, Riha H, et al. Safety of continuous peripheral infusion of 3% sodium chloride solution in neurocritical care patients. Am J Crit Care 2016;26:37-42.

the infusion rates were mainly 30–40 mL/hour. Therefore, it seems prudent to ensure that larger catheters are used and to maintain low infusion rates if the peripheral route is chosen. Data from the largest study are limited because of the short infusion duration. However, the other two studies suggest that infusions beyond 1 hour (up to 24–36 hours) can safely be administered through a peripheral line. Despite promising results from these three studies, small sample size and retrospective design significantly limit their impact on practice, and additional larger, prospective studies are required to confirm these findings before peripheral administration of hypertonic saline can routinely be recommended.

Another study compared the efficacy and safety of 5% and 23.4% sodium chloride in subjects with intracranial hypertension (Carter 2017). The study was conducted retrospectively at a single institution and included data from 11 patients who received 5% sodium chloride administered peripherally. The infusion according to institutional protocol was administered over 15 minutes. No infusion-related adverse events were documented. Data analyses from this study suggest that in patients who require rapid lowering of intracranial pressure, peripheral administration of 5% sodium chloride is an alternative to 23.4% solutions, especially in patients who have delays in establishing central venous access. However, additional data from larger and/or well-designed controlled trials are required to ensure the safety of this treatment approach.

Adjunctive Desmopressin to Prevent Sodium Overcorrection in Hyponatremia

Sodium overcorrection may lead to devastating neurologic consequences. Current expert panel recommendations include limiting the increase in sodium to 8 mEq/L in 24 hours for patients at high risk of osmotic demyelination and to 10–12 mEq/L in 24 hours and 18 mEq/L in 48 hours in those at normal risk (Verbalis 2013). Those at high risk of osmotic demyelination include patients with Na less than 105 mEq/L, hypokalemia, alcoholism or advanced liver disease, and malnutrition. Hypertonic saline solutions may increase the risk of osmotic demyelination because they can replete sodium more rapidly. One strategy to limit sodium overcorrection is using desmopressin in patients at high risk. Desmopressin is a synthetic analog of antidiuretic hormone that binds to vasopressin 2 (V_2) receptors in the kidney, increasing free water reabsorption through aquaporin channel translocation (Rafat 2014). Theoretically, desmopressin can decrease the

rapid rise in serum sodium as patients are actively treated for hyponatremia. Three retrospective studies have evaluated desmopressin to prevent overcorrection in patients with severe hyponatremia (Na less than 120 mEq/L). One study of 25 subjects evaluated the effects of desmopressin 1–2 mcg intravenously or subcutaneously every 6–8 hours (Sood 2013). No subjects had an increase greater than 12 mEq/L in 24 hours or greater than 18 mEq/L in 48 hours. No subject was identified as having neurologic complications or a complication related to desmopressin administration.

Another study reported the effects of desmopressin in patients who had a sodium correction greater than 12 mEq/L in 24 hours (n=6) or those at risk (n=14) (Perianayagam 2008). Five subjects received hypertonic saline, three of whom received 1- to 2-mcg doses of desmopressin in the study. In subjects who had overcorrection in the first 48 hours, only one had a sodium increase greater than 18 mEq/L in 48 hours. None of the subjects at risk had sodium increases beyond these limitations at 24 and 48 hours. Similar to the previous study, none of the subjects had significant neurologic complications.

The third study was another retrospective analysis in two ICUs including 20 subjects (Rafat 2014). Subjects in this study received doses of 2–4 mcg intravenously of desmopressin. The sodium correction rate was significantly decreased after receiving desmopressin (-0.02 mEq/L/hour vs. 0.81 mEq/L/hour; p=0.001). Eleven subjects required a re-lowering of sodium. So many cases requiring re-lowering indicates that the general approach to management was flawed in the study sites. Of note, only three subjects were treated using hypertonic saline, and several patients received hypotonic fluids. Because of its retrospective nature and incomplete reporting of how the study sites managed hyponatremia, these findings are difficult to interpret. None of the patients receiving desmopressin had seizures; however, one patient developed central pontine myelinosis. This patient's sodium increased by 10 and 16 mEq/L at 24 and 48 hours, respectively. Of interest, this patient did not receive hypertonic saline. He presented with hypokalemia and had a history of alcoholism, placing him at high risk of osmotic demyelination.

The main limitations to these data include retrospective designs, small sample sizes, and lack of ability to effectively measure effects on neurologic outcomes. Because of these limitations, it is unclear whether desmopressin alone was responsible for the changes in sodium versus careful initiation and close monitoring of hypertonic saline administration. However, this strategy appears safe and effective in the absence of well-designed studies. Expert panel recommendations include the adjunctive use of 2- to 4-mcg doses of desmopressin to prevent sodium overcorrection in patients with severe hyponatremia (Verbalis 2013). Despite the recommended doses by the expert panel, two of the studies previously described used 1- to 2-mcg doses. Therefore, the exact dose used to prevent overcorrection remains unclear. This strategy should be combined with replacing free water losses with 5% dextrose or oral water. Once the sodium reaches 128 mEq/L, desmopressin should be discontinued. In patients requiring re-lowering of sodium in the setting of overcorrection, desmopressin can be administered with free water replacement at 3 mL/kg/hour (Verbalis 2013).

Vasopressin Antagonists for Hyponatremia in Critically Ill Patients

Another drug class that has been used for hyponatremia in critically ill patients is vasopressin antagonists ("vaptans"). These agents are high-affinity nonpeptide antagonists of arginine vasopressin V_2 and V_{1A} receptors. Vaptans produce renal excretion of solute-free water, sparing sodium (Lehrich 2012). The available agents are conivaptan and tolvaptan. According to the labeling, conivaptan is administered intravenously with a loading dose of 20 mg over 30 minutes, followed by 20 mg as a continuous infusion over 24 hours, which can be continued up to 4 days. Tolvaptan is an oral agent with a starting dose of 15 mg/day that can be titrated to 60 mg daily, depending on serum sodium response (Lehrich 2012). Both conivaptan and tolvaptan are substrates of CYP3A4 and are contraindicated in the setting of using strong CYP3A4 inhibitors. Tolvaptan is preferred in patients with cirrhosis because it is more selective to V_2 receptors. Conivaptan is a nonselective vasopressin antagonist that may lead to decreased renal perfusion and hepatorenal syndrome. The vaptans are relatively well tolerated, with infusion-site reactions being the most common adverse effect with conivaptan, together with hypokalemia, orthostatic hypotension, and fever (Lehrich 2012). These agents are labeled to treat euvolemic or hypervolemic hyponatremia and can correct sodium in patients with heart failure. However, vaptans should not be used to treat hypovolemic hyponatremia. In addition, free water restrictions should be discontinued when vaptans are used to prevent significant volume losses (Lehrich 2012). Compared with other methods of treating hyponatremia such as hypertonic saline and desmopressin, vaptans are significantly more costly. Nevertheless, vaptans may be an attractive alternative in treating patients with hyponatremia for a variety of reasons. For example, conventional therapies like hypertonic saline do not always produce a predictable change in sodium and may increase the risk of osmotic demyelination (Murphy 2009). As discussed earlier, evidence showing that desmopressin may prevent sodium overcorrection is derived entirely from retrospective analyses. In addition, the debate of using central versus peripheral access with hypertonic saline is ongoing. Finally, using volume restriction in patients with SIADH may result in intravascular depletion and decreased cerebral perfusion (Murphy 2009).

Two prospective studies have compared conivaptan and hypertonic saline for treating SIADH in critically ill patients. The first was a prospective, single-center study that included patients with SIADH without head injury or neurosurgery

Table 3. Change in Sodium and Daily Fluid Balance Comparison

	Time	Conivaptan	3% NaCl	p Value
Sodium (mEq/L)	12 hr	129.4 ± 2.8	127.7 ± 1.1	0.006
	24 hr	131.5 ± 2.1	127.3 ± 2.8	< 0.001
	48 hr	130.5 ± 2.6	126.5 ± 1.9	< 0.001
	72 hr	129.4 ± 2.5	127.5 ± 3.8	0.159
Daily fluid balance (mL)	Day 1	−1094.3 ± 286.7	−425 ± 165	< 0.001
	Day 2	−579 ± 375.8	−260.5 ± 282.5	0.005
	Day 3	−370 ± 219.9	+263.5 ± 546	< 0.001

Information from: Reddy SN, Rangappa P, Jacob I, et al. Efficacy of conivaptan and hypertonic (3%) saline in treating hyponatremia due to syndrome of inappropriate antidiuretic hormone in a tertiary intensive care unit. Indian J Crit Care Med 2016;20:714-8.

(Reddy 2016). Eighty subjects were included, with 40 receiving conivaptan and 40 receiving 3% sodium chloride. Each treatment was administered until serum sodium reached 130 mEq/L or up to 72 hours, whichever came first. Most subjects were older than 75 and had idiopathic etiology of SIADH. The average (SD) baseline sodium was 112.8 plus or minus 4 mEq/L in the 3% sodium chloride group compared with 114 plus or minus 6.4 mEq/L in the conivaptan group. Baseline characteristics did not differ significantly, and the predicted mortality in each group was 26%. No significant differences between groups occurred in sodium at 6, 12, and 24 hours. However, at 48 and 72 hours, the conivaptan group had significantly higher average (SD) serum sodium (128.9 ± 2.6 mEq/L vs. 133 ± 3.8 mEq/L, p<0.001, and 133.7 ± 1.2 mEq/L vs. 135.9 ± 1.4 mEq/L, p<0.001, respectively). The average time to achieve an Na concentration greater than 130 mEq/L was significantly shorter in subjects receiving conivaptan than in those receiving 3% sodium chloride (54.60 ± 13.30 hours vs. 66.15 ± 13.29 hours, p<0.001). The LOS values in the ICU and hospital were also longer in patients who received 3% sodium chloride (ICU 4.61 ± 0.91 days vs. 3.35 ± 0.89 days; p<0.001; hospital 6.41 ± 1.41 days vs. 5.65 ± 1.45 days; p<0.001). The finding of shorter stays in the ICU and hospital is intriguing because this may offset the higher cost of using conivaptan to treat SIADH. The study is limited because of its small sample size and unblinded design. Therefore, these findings require further study before any definitive conclusions can be made regarding conivaptan use over traditional methods such as hypertonic saline solutions.

The second study was a prospective, randomized trial of patients who developed hyponatremia postoperatively after head and neck surgery (Rajan 2015). The two treatment arms consisted of 20 subjects who received a single 20-mg intravenous bolus of conivaptan and 20 subjects who received a 3% sodium chloride infusion at 20–30 mL/hour. The intervention is notable because the use of a single-bolus dose of conivaptan differs from how it is typically administered. Baseline characteristics were similar between the groups, including average (SD) sodium of 125.5 plus or minus 2.4 mEq/L in the conivaptan group and 123.9 plus or minus 2.9 mEq/L in the hypertonic saline group. Table 3 contains the results comparing the two therapies. Conivaptan resulted in statistically significantly higher sodium concentrations for the first 48 hours and a more negative fluid balance during the 3 days postdose than did 3% sodium chloride. Study limitations include small sample size and restricted patient population. Although the study had statistical differences, it is unclear whether the difference in sodium is clinically significant between use of conivaptan and hypertonic saline. However, the difference in fluid balance appears to be clinically significant and may affect clinical outcomes. This study shows that conivaptan as a single bolus may be at least as effective in increasing sodium at a reasonable rate as hypertonic saline while maintaining a greater negative fluid balance.

Additional findings from the neurocritical care literature may support the use of bolus doses of conivaptan. Euvolemic hyponatremia is common in patients with neurologic emergencies and usually develops from SIADH (Marik 2013). Development of hyponatremia in these patients may result in cerebral edema, herniation, and mortality. Historically, hypertonic saline has been used to treat hyponatremia in this patient population. However, several retrospective studies have shown that a single 20-mg intravenous dose of conivaptan raises serum sodium with minimal adverse effects (Marik 2013; Human 2012; Murphy 2009). Some of these studies also had patients who received several conivaptan doses at doses of 10 or 40 mg. Therefore, it is difficult to make a definitive recommendation of whether single or multiple doses of conivaptan are optimal for these patients. However, a single bolus dose may decrease the cost of using conivaptan and could limit the chance for volume overload. In addition, a continuous infusion of conivaptan requires a dedicated catheter,

which may affect administration of other drugs because of compatibility. Of importance, these suggestions have not been validated and serve only as potential outcomes for future research.

Despite the promising results from several studies, current recommendations do not support use of vaptans in treating severe hyponatremia (Na less than 120 mEq/L). Hypertonic saline solutions are still recommended as first line for this indication (Verbalis 2013). However, vaptans can be considered as an alternative to hypertonic saline, especially in patients with hyponatremia/SIADH in the setting of acute neurologic conditions such as intracerebral or subarachnoid hemorrhage, or in those who require limited volume administration.

CONCLUSION

Despite widespread IVF use, the true efficacy and safety of IVFs in the critically ill population remains unknown. Newer data suggest that for most patients, crystalloid solutions such as normal saline or lactated Ringer solution are preferred. However, colloid solutions, specifically albumin, play a role in large-volume resuscitation and in restoring hemodynamic stability in patients with septic shock. Additional data analyses have shown an increased risk of hyperchloremic metabolic acidosis and renal dysfunction associated with the use of the prototypical crystalloid solution, normal saline. Use of balanced crystalloid solutions (e.g., lactated Ringer solution, Plasma-Lyte 148, or Normosol) may reduce the risk of these adverse outcomes. Currently, it is unclear whether major clinical outcomes such as mortality are affected by the use of balanced crystalloids.

Electrolyte disturbances in the critically ill population are common and require astute recognition, prompt treatment, and effective prevention. Traditional methods of managing hyponatremia include the requirement of establishing central venous access to administer hypertonic solutions. Recent data analyses suggest that for short durations, peripheral administration is a reasonable alternative and is helpful for patients in whom establishing invasive vascular access is difficult. Treatment of hyponatremia is also associated with significant CNS abnormalities in the setting of overcorrection. Desmopressin may be a useful adjunctive therapy to prevent the development of sodium overcorrection in those at risk. In addition, vasopressin antagonists have been more specifically studied in the critically ill population with SIADH and may be reasonable alternatives for patients with this electrolyte disorder. Use of bolus conivaptan is intriguing because it may prevent the need for central line placement for use of hypertonic saline, can limit the volume of drug/fluid infused, and may mitigate the cost of therapy using a single dose.

Appropriate selection of fluids or drugs and monitoring for safety and efficacy are important ways for the critical care pharmacist to contribute to the care of patients requiring IVF or management of electrolyte disorders.

Practice Points

Despite several well-designed clinical trials evaluating IVF therapy in critically ill patients, many questions remain. In addition, various treatment approaches have been described for ICU patients with electrolyte disorders:

- **Crystalloid solutions are preferred for most patients who require fluid resuscitation because of their equal efficacy and lower cost compared with colloid solutions. Colloid solutions may be considered in patients who may be limited in total volume administration or to enhance the efficacy of crystalloid resuscitation.**
- **Hydroxyethyl starch should not be used for fluid resuscitation in critically ill patients.**
- **Balanced crystalloids such as lactated Ringer solution, Plasma-Lyte 148, and Normosol may be considered as alternatives to normal saline to prevent hyperchloremic metabolic acidosis. Normal saline may increase the risk of AKI in patients requiring fluid therapy.**
- **Despite historical use of administering 3% sodium chloride through central venous access, peripheral administration may be relatively safe when given for short periods. This method of administration may be considered if timely administration of hypertonic saline is required in patients with severe hyponatremia.**
- **Desmopressin administered with hypertonic saline may limit the rate of sodium increase in patients with severe hyponatremia. This may provide a useful tool to prevent devastating adverse outcomes of sodium overcorrection.**

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Self-Assessment Questions

1. The ICU attending calls for a recommendation on intravenous fluid (IVF) administration for a patient who was admitted for a chronic obstructive pulmonary disease exacerbation and is now hypotensive. The patient's laboratory values are as follows: Na 142 mEq/L, K 3.9 mEq/L, Cl 102 mEq/L, CO_2 24 mEq/L, BUN 8 mg/dL, and glucose 110 mg/dL. The patient has no history of heart failure and has a recent left ventricular ejection fraction of 60%. Which one of the following is the best IVF administration to recommend for this patient?

   A. Hydroxyethyl starch 50-mL/kg bolus
   B. 5% albumin 250-mL bolus
   C. 0.9% sodium chloride 1000-mL bolus
   D. 0.9% sodium chloride 100 mL/hour

2. A 29-year-old man is in the ICU for sepsis secondary to necrotizing fasciitis. After receiving fluid resuscitation of 30 mL/kg of normal saline, his Na is now 152 mEq/L and Cl is 116 mEq/L. The patient remains hypotensive and has been determined to be fluid responsive. Which one of the following IVFs is best to recommend for this patient?

   A. 0.9% sodium chloride
   B. 25% albumin
   C. 5% albumin
   D. Plasma-Lyte 148

Questions 3–5 pertain to the following case.

A.Y., a 48-year-old woman (weight 53.5 kg), was admitted for an emergency bowel resection, in which she had an exploratory laparotomy. Postoperatively, she is in the ICU with septic shock and respiratory failure. A.Y. has received 4 L of 0.9% sodium chloride over the past 3 hours and is currently intubated, on mechanical ventilation, and receiving fentanyl 150 mcg/hour and midazolam 2 mg/hour for analgesia and sedation. A.Y. is also receiving piperacillin/tazobactam 4.5 g intravenously every 6 hours for intra-abdominal sepsis. She is receiving norepinephrine 30 mcg/minute and vasopressin 0.04 unit/minute for shock, and her mean arterial pressure is 50 mm Hg. Laboratory values include Na 141 mEq/L, K 4.2 mEq/L, Cl 104 mEq/L, CO_2 18 mEq/L, BUN 12 mg/dl, SCr 1.1 mg/dL, and glucose 129 mg/dL.

3. Which one of the following would best assess A.Y.'s fluid responsiveness?

   A. Ultrasound monitoring of the inferior vena cava (IVC)
   B. Lactate measurement
   C. Esophageal Doppler monitoring
   D. Central venous pressure

4. Which one of the following fluid therapy strategies would be best to recommend for A.Y.?

   A. 500 mL of 5% albumin over 15 minutes
   B. 0.9% sodium chloride 200 mL/hour continuous infusion
   C. Lactated Ringer solution 100 mL over 5 minutes
   D. Furosemide 40 mg intravenously every 8 hours

5. Two days later, A.Y.'s vasopressors are discontinued, and she remains hemodynamically stable with mean arterial pressures of 70–80 mm Hg. She remains intubated and sedated on fentanyl 100 mcg/hour and propofol 20 mg/kg/minute. Her blood and peritoneal fluid cultures have grown *Enterobacter cloacae*, and her antibiotics were changed to ertapenem 1 g intravenously daily. Her abdominal drain has put out around 200 mL of fluid per day. Currently, A.Y.'s laboratory findings include Na 144 mEq/L, K 4.4 mEq/L, Cl 104 mEq/L, CO_2 24 mEq/L, BUN 33 mg/dL, SCr 2.1 mg/dL, and glucose 144 mg/dL. Her chest radiography reveals no significant changes, and her lungs are clear to auscultation. Further assessment reveals that A.Y. is fluid responsive. Which one of the following is the best fluid management strategy for A.Y.?

   A. Furosemide 10-mg/hour continuous infusion
   B. 0.9% sodium chloride 1500 mL over 60 minutes
   C. Lactated Ringer solution 100-mL/hour continuous infusion
   D. 100 mL of 25% albumin over 30 minutes

6. A 71-year-old man, who was admitted after falling from a ladder, is now in the ICU with several rib fractures and a right femur fracture. His blood pressure is 73/44 mm Hg. On physical examination he appears to be fluid responsive. The patient currently has one peripheral intravenous catheter available for access. He is receiving an infusion of packed RBCs for suspected bleeding with an Hgb of 5.3 g/dL. Other laboratory values include Na 143 mEq/L, K 4.4 mEq/L, Cl 105 mEq/L, CO_2 21 mEq/L, BUN 13 mg/dL, and SCr 1.1 mg/dL. Which one of the following fluids is best to recommend for this patient?

   A. 5% albumin
   B. 3% sodium chloride
   C. 0.9% sodium chloride
   D. Lactated Ringer solution

7. An ICU patient with ascending cholangitis has received 10 L of 0.9% sodium chloride and 2 L of lactated Ringer solution for fluid resuscitation. She remains on vasopressor support and, despite the aggressive fluid administration,

appears to be intravascularly depleted. She also has had increasing oxygen requirements on the ventilator with worsening pulmonary edema on chest radiography. Her Na and Cl are 143 mEq/L and 102 mEq/L, respectively. Which one of the following is best to recommend for this patient?

A. 5% albumin
B. 0.9% sodium chloride
C. 3% sodium chloride
D. Plasma-Lyte 148

8. A 36-year-old woman with a history of type 2 diabetes is in the ICU for diabetic ketoacidosis. She has already received 8 L of 0.9% sodium chloride and requires additional volume. Her Na is 143 mEq/L, K 3.8 mEq/L, Cl 120 mEq/L, HCO_3 17 mEq/L, and pH 7.19. Which one of the following is best to recommend for additional fluid resuscitation in this patient?

A. 0.9% sodium chloride
B. Sodium bicarbonate
C. Plasma-Lyte 148
D. 25% albumin

9. A 36-year-old man was admitted 3 days ago after developing respiratory failure from a heroin overdose. He was hypotensive on admission and received 6 L of lactated Ringer solution for resuscitation. He has since been hemodynamically stable and is being assessed for readiness to extubate. Chest radiography reveals mild pulmonary edema. Which one of the following is best to recommend for this patient?

A. Administer an additional 1-L bolus of 0.9% sodium chloride.
B. Start 0.45% sodium chloride/5% dextrose in water solution at 80 mL/hour for maintenance.
C. Administer 500 mL of 5% albumin solution.
D. Administer 20 mg of intravenous furosemide.

10. A 50-year-old man is in the ICU with septic shock; his multidisciplinary care team is discussing the plan for fluid therapy. The patient is intubated, sedated on fentanyl 150 mcg/hour and propofol 20 mcg/kg/minute, and receiving norepinephrine 20 mcg/minute for shock. Currently, his mean arterial pressure is 68 mm Hg. On examination, the patient is not fluid responsive. He has received 12 L of normal saline during his ICU stay, and chest radiography from this morning reveals significant pulmonary edema. Laboratory analysis shows Na 142 mEq/L, K 4 mEq/L, Cl 111 mEq/L, CO_2 18 mEq/L, BUN 21 mg/dL, SCr 1.4 mg/dL, and albumin 2.4 g/dL. Which one of the following is the best approach for this patient's fluid therapy?

A. 25% albumin 50-mL bolus
B. 0.9% sodium chloride 75 mL/hour
C. Normosol 1000-mL bolus
D. 0.9% sodium chloride bolus

11. For which one of the following patients would peripheral administration of 3% sodium chloride be most appropriate to treat hyponatremia?

A. 53-year-old man with chronic alcohol use disorder who presents with Na 125 mEq/L and is awake, alert, and oriented
B. 40-year-old woman with 22-gauge peripheral intravenous catheter and Na 118 mEq/L
C. 66-year-old man with altered mental status, seizure, Na 112 mEq/L, and significant difficulty inserting central venous access
D. 23-year-old woman who presents with venlafaxine-induced syndrome of inappropriate antidiuretic hormone (SIADH) with Na 118 mEq/L

Questions 12 and 13 pertain to the following case.

L.T. is a 68-year-old man (weight 62 kg) with a history of hypertension. He presents to the ED with severe altered mental status. Medications before admission include hydrochlorothiazide 25 mg orally daily, lisinopril 10 mg orally daily, and spironolactone 100 mg orally daily. L.T.'s laboratory findings are Na 102 mEq/L, K 4.9 mEq/L, Cl 110 mEq/L, CO_2 25 mEq/L, BUN 27 mg/dL, SCr 1.4 mg/dL, and glucose 110 mg/dL. On physical examination, no edema is noted; the patient has dry mucous membranes and poor skin turgor. His blood pressure is 110/66 mm Hg, heart rate 120 beats/minute, respiratory rate 24 breaths/minute, and SaO_2 95%. L.T.'s wife reports he was evaluated by his primary physician about a week ago, who increased his diuretic doses for poorly controlled hypertension.

12. Which one of the following is the optimal recommended rate of change (increase) in L.T.'s sodium?

A. 8 mEq/L in 24 hours
B. 10 mEq/L in 24 hours
C. 12 mEq/L in 24 hours
D. 18 mEq/L in 48 hours

13. L.T. was initially treated with 3% sodium chloride 100 mL/hour with a subsequent increase in Na to 115 mEq/L after 16 hours of receiving the infusion. Which one of the following strategies is best to recommend for L.T.'s hyponatremia?

A. Discontinue 3% sodium chloride; administer conivaptan 20 mg intravenously × 1.
B. Discontinue 3% sodium chloride; administer desmopressin 2 mcg intravenously every 8 hours plus 5% dextrose in water 180 mL/hour.
C. Continue 3% sodium chloride at 100 mL/hour.
D. Continue 3% sodium chloride at 100 mL/hour; add desmopressin 2 mcg intravenously every 8 hours.

14. A 71-year-old man with a history of hyperlipidemia presents to the ED with 2-day history of dizziness and severe diarrhea. On admission, his laboratory findings include Na 122 mEq/L, K 3.1 mEq/L, Cl 94 mEq/L, CO_2 18 mEq/L, BUN 33 mg/dL, and SCr 1.5 mg/dL. The patient reports that he has not felt well for several days and has had limited oral intake with the onset of diarrhea. On physical examination, he has dry mucous membranes and poor skin turgor. The patient was initiated on 0.9% sodium chloride 100 mL/hour through a peripheral intravenous line and desmopressin 2 mcg intravenously every 8 hours on admission. Twenty-four hours later, his Na is 129 mEq/L. Which one of the following is best to recommend for this patient's hyponatremia?

    A. Discontinue 0.9% sodium chloride, start 3% sodium chloride 30 mL/hour, and continue desmopressin.
    B. Continue 0.9% sodium chloride 100 mL/hour, discontinue desmopressin, and administer conivaptan 20 mg intravenously × 1.
    C. Discontinue 0.9% sodium chloride, and continue desmopressin.
    D. Continue 0.9% sodium chloride 100 mL/hour, and discontinue desmopressin.

15. The ICU attending calls you for a recommendation on a patient admitted with acute hyponatremia. She explains that the patient has a peripheral line inserted with Na of 115 mEq/L and has significant peripheral edema, so she would like to limit volume administration. Which one of the following is best to recommend for this patient?

    A. Administer 3% sodium chloride 40 mL/hour for 48 hours.
    B. Administer a 20-mg intravenous bolus of conivaptan and reassess sodium in 4 hours.
    C. Administer a 20-mg intravenous bolus of conivaptan followed by a 20-mg intravenous continuous infusion for 5 days.
    D. Administer 0.9% sodium chloride 100 m/hour for 24 hours.