

Fluid and electrolyte overload in critically ill patients: An overview

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Abstract

Fluids are considered the cornerstone of therapy for many shock states, particularly states that are associated with relative or absolute hypovolemia. Fluids are also commonly used for many other purposes, such as renal

protection from endogenous and exogenous substances, for the safe dilution of medications and as "maintenance" fluids. However, a large amount of evidence from the last decade has shown that fluids can have deleterious effects on several organ functions, both from excessive amounts of fluids and from their non-physiological electrolyte composition. Additionally, fluid prescription is more common in patients with systemic inflammatory response syndrome whose kidneys may have impaired mechanisms of electrolyte and free water excretion. These processes have been studied as separate entities (hypernatremia, hyperchloremic acidosis and progressive fluid accumulation) leading to worse outcomes in many clinical scenarios, including but not limited to acute kidney injury, worsening respiratory function, higher mortality and higher hospital and intensive care unit length-of-stays. In this review, we synthesize this evidence and describe this phenomenon as fluid and electrolyte overload with potentially deleterious effects. Finally, we propose a strategy to safely use fluids and thereafter wean patients from fluids, along with other caveats to be considered when dealing with fluids in the intensive care unit.

Key words: Fluid therapy; Critically Ill; Oliguria; Water-electrolyte balance; Central venous pressure; Resuscitation; Acute kidney injury; Diuretics; Multiple organ dysfunction syndrome; Systemic inflammatory response syndrome

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Core tip: Fluids are a cornerstone of the management of critically ill patients with systemic inflammatory response syndrome who are at risk of multiple organ dysfunction syndrome. However, as with any therapy, fluids can be associated with harm, such as added or worsening organ dysfunctions. Therefore, patients should be weaned from fluids when possible, sometimes through an active de-resuscitation strategy.

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INTRODUCTION

Fluids have been widely used in critically ill patients to optimize hemodynamics^[1], to enhance renal protection from contrast^[2], globins^[3], and uric acid^[4], to offer caloric intake^[5] and as an adjunct for medication dilution^[6]. During the first hours of shock syndromes, isotonic fluids can stabilize arterial pressure and perfusion and are lifesaving at times. Furthermore, to reach physiological hemodynamic targets, a large amount of intravenous fluids may be required. Some fasting patients receive infusions of one to three liters of dextrose in water with added electrolytes, mainly sodium, chloride and potassium, to avoid hypoglycemia, dehydration and electrolyte deficiency. Renal protection in critically ill patients is of huge importance, and hyperhydration is frequently used to enhance urine output and to avoid renal tubular cell injury by the retention of toxic substances at high concentrations. Finally, many drugs require a large amount of fluids with electrolytes to be safely administered.

Fluids and electrolytes are responsible for a large amount of volume that is infused in critically ill patients and are commonly associated with reduced urine output and renal electrolyte excretion failure, particularly chloride-rich solutions. This combination is even more accentuated in the first hours of critical illness^[1,7] or in the presence of acute kidney injury (AKI)^[8-10]. Ultimately, the inadequate management of fluids and electrolytes in critically ill patients culminates in hydroelectrolytic overload, which causes physiological derangements and worse outcomes^[11]. This manuscript describes the mechanisms, pathophysiology, and potential consequences of fluid and electrolyte overload and provides a combined bedside approach to avoid it.

ELECTROLYTE OVERLOAD

Primary electrolytes in basic human physiology

Sodium and chloride are the main determinants of colloid osmotic forces in human plasma and interstitial space because they account for 80% of the osmolality of these fluids^[12]. Plasma non-permeable proteins attract positively charged ions and repel negatively charged ions, leading to a passive transmembrane distribution of anions to preserve plasma and interstitial space electroneutrality, known as the Gibbs-Donnan effect. A steady-state is achieved when the plasmatic osmolality is 1 mOsm/L greater than the interstitial space, and the capillary hydrostatic pressure opposes the osmotic movement of the water into the intravascular space^[13].

Even at a constant interstitial space osmolality, to maintain cell volume, the transport of osmotically active substances across the cell membrane (mainly sodium and potassium) counterbalances the intracellular osmotic forces imposed by high-molecular-weight anionic proteins (Double-Donnan effect)^[14].

One of the main roles of electrolytes and their homeostasis is the distribution of fluids throughout the human body. Colloid osmotic and hydrostatic pressures are the main forces influencing the fluid distribution between intravascular and interstitial spaces, whereas changes in intra or extracellular osmolality are in general followed by water movement and determine the changes in cell volume^[14].

Sodium overload

Sodium is the main cation of solutions infused into critically ill patients. The 0.9% saline solution has 154 mEq/L of sodium, that is, one liter of 0.9% saline infusion carries 3.4 g of sodium, which represents approximately eight 100 g packages of commercially available potato chips, a huge amount of the electrolyte^[15]. Nevertheless, sodium renal excretion is largely impaired in critically ill patients,^[10] particularly in patients with AKI^[8].

In a sample of septic patients, for instance, the mean isotonic fluid intake was 5000 mL during the first 24 h in the ICU, with a urine output of 2000 mL during the same period and a mean sodium urinary concentration of 55 mEq/L^[16]. In this casuistic, the total amount of sodium infused was 770 mEq in the 24 h period analyzed with a concomitant sodium excretion of 110 mEq, resulting in a positive fluid and sodium balance of 3000 mL and 660 mEq, respectively. Because of the large sodium distribution volume in adults (49 L to 70 kg), the expected effect of the remaining 660 mEq of sodium and 3000 mL of water in patients with a pre-infusion sodium concentration of 145 mEq/L is approximately 4.0 mEq/L^[17]. Notably, patients with established kidney injuries were excluded from the Stelfox *et al.*^[18] study, and consequently the sodium overload effect in patients with AKI is expected to be even more striking. To exemplify this finding, Table 1 shows a water and electrolyte cumulative evolution of a mono-compartment mathematical model of a post-resuscitation phase with low urinary sodium and chloride, similar to the septic patients of Noritomi's study.

Other groups have also described resuscitation fluids as a contributing factor to ICU-acquired hypernatremia with a dose-response effect: the greater the saline infusion, the worse the hypernatremia condition^[19]. However, other sources of saline contribute to sodium loading in critically ill patients and may be a modifiable risk factor, such as normal saline used to dilute parenteral drugs and to keep catheters open^[20]. Finally, in Australia and New Zealand, a point-prevalence study demonstrated that sodium administration in excess

Table 1 Closed mono-compartment mathematical marginal model simulating the body water space of distribution

Variables	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5
Patient's resulting variables						
Na ⁺ (mEq/L)	140	142	148	151	146	144
Cl ⁻ (mEq/L)	100	108	114	117	113	111
Fluid balance (mL)	-	6000	0	800	800	0
Cumulative fluid balance (mL)	-	6000	6000	6800	7600	7600
Distribution water volume and electrolyte data						
Vd (L)	36	42	42	43	44	44
Total mass of Na ⁺ (mEq)	5040	5964	6216	6493	6424	6336
Total mass of Cl ⁻ (mEq)	3600	4536	4788	5031	4972	4884
Fluids output						
Diuresis (mL)	-	2000	1200	1200	1200	2000
Urinary Na ⁺ (mEq/L)	-	30	50	70	90	110
Urinary Cl ⁻ (mEq/L)	-	30	50	70	90	110
Fluids input						
Volume	6000	2000	2000	2000	2000	2000
Na ⁺ (mEq/L)	154	154	154	0	0	0
Cl ⁻ (mEq/L)	154	154	154	0	0	0

The main assumptions of this model are the absence of feces, sudoresis, renal replacement therapy, and the absence of Gibbs-Donnan effect. This patient was resuscitated with 4000 mL of 0.9% saline and received additional 2000 mL of 0.9 fluids during the Day 0. He received an amount of 0.9% saline during day 1 and day 2, afterwards the same 2000 mL of volume was infused without electrolytes due to hypernatremia. Vd: Denotes distribution volume.

of recommended daily requirements (*i.e.*, 1-2 mmol/kg) was fairly common, with the major sources being maintenance fluids (30.9%), fluid boluses (16.3%) and drug boluses (12.3%)^[21].

Hypernatremia is present at hospital admission and at ICU admission in 2% and 7% of patients, respectively^[22,23]. By contrast, up to 27% of patients in the ICU develop hypernatremia during their ICU stay^[18]. In a speculative view, this higher incidence of hypernatremia in critically ill patients might be explained by sodium overload. Critical illness related hypernatremia is associated with disease severity, kidney injury and dysfunction, mechanical ventilation and ICU length-of-stay^[18]. Finally, hypernatremia is associated with higher in-hospital mortality^[18,22,24,25] and it has been considered in several ICUs as a quality-of-care marker^[26,27]. Recently, a group also retrospectively noted that correcting this abnormality ultimately resulted in better survival^[28].

Chloride overload

Chloride is the main anion of fluids used in critical care settings, and its concentration is well correlated to the sodium concentration to maintain the electroneutrality of solutions^[29]. The 0.9% saline solution, Ringer's lactate solution, and Plasmalyte contain 154, 109 and 98 mEq/L of chloride, respectively^[15]. Because the serum chloride concentration is approximately 100 mEq/L, it is expected that a 0.9% saline infusion potentially increases the serum chloride concentration. In septic patients, Park *et al.*^[30] showed that 2000 ± 300 mL of a 0.9% saline infusion promptly resulted in a disproportionate elevation of serum chloride in comparison to the sodium concentration (Figure 1). Of note, this disproportionate elevation occurred in spite of equal chloride and sodium

concentrations in the 0.9% saline solution that was infused^[15,30].

The principle of the unequal chloride and sodium concentration elevations is based on the fact that the initial serum chloride concentration is lower than the initial sodium concentration. Therefore, the same infused amount in mEq/L of sodium and chloride is expected to have a greater effect on the ion with the lower serum concentration - in this case, chloride (Figure 2).

Kellum *et al.*^[31] demonstrated in a canine model of endotoxemia that only one-third of the post-volume infusion of chloride associated acidosis could be explained by exogenous chloride. The authors attributed this fact to an extravascular to intravascular chloride shift that was driven by differences in the transmembrane potential and the Gibbs-Donnan effect secondary to the fluid challenge. This same finding of chloride elevation was observed in humans with severe sepsis and septic shock^[16]. Therefore, one can expect an intrinsic chloride elevation in patients with systemic inflammation, which is amplified by a chloride-rich fluid infusion, such as the many previously described sources of normal saline that are infused in critically ill patients.

In addition to these sources of chloride, the renal excretion of chloride is also impaired, similarly to sodium excretion, during the initial phase of critical illness^[9,10], particularly in patients with AKI^[8]. The net result is a positive balance of chloride (Table 1), and an increased serum chloride concentration results in a hyperchloremic metabolic acidosis^[16,32]. This is also called "SID acidosis" and is not related to outcomes in mixed critically ill patients^[33]. However, specifically in septic patients, initial hyperchloremic acidosis is associated with a higher mortality^[16].

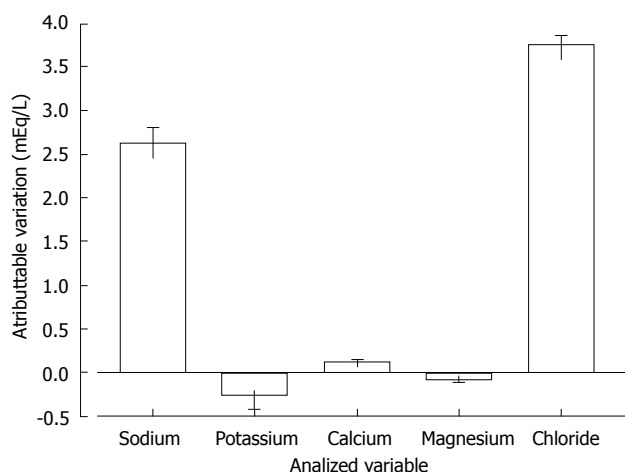


Figure 1 Variation of plasma electrolytes concentration immediately after 2000 ± 300 mL infusion of 0.9% saline in septic patients. Adapted from Park *et al*^[30].

Pathophysiology

Renal consequences: Electrolyte overload may have detrimental effects on renal function, particularly chloride overload. Animal studies suggest that chloride may influence renal blood flow (RBF), which is mediated primarily by its effects on afferent and intrarenal arterial vessels^[34,35]. In canine experiments, the renal infusion of solutions containing chloride, such as 0.9% saline or NH_4Cl , led to reductions in the total RBF and GFR in both denervated and *in situ* kidneys^[34]. In an animal model of sepsis, unbalanced solutions worsened sepsis-induced AKI^[36]. Other experiments confirmed that extracellular chloride is essential for contraction in renal afferent arterioles^[37,38]. In humans, an infusion of 2 L of 0.9% saline over 1 h was associated with a reduction in the RBF velocity and renal cortical tissue perfusion measured by magnetic resonance imaging (MRI); these changes were not observed after a similar infusion of a balanced crystalloid^[39]. Moreover, studies in healthy volunteers have shown a delayed urine output with saline compared to a balanced solution^[40].

An infusion of hypertonic solutions containing chloride into the renal artery causes a biphasic response in renal vascular resistance^[34]. Hyperosmolality leads to an abrupt renal vasodilatation and consequent increase in RBF. After 1-5 min, vasodilatation is reversed, and RBF and GFR decrease below pre-infusion levels. The second phase is absent in hypertonic solutions that do not contain chloride.

In vitro, the entry of chloride from elevated tubular chloride concentrations into epithelial renal cells causes the depolarization of the basolateral membrane^[41]. Increased NaCl concentrations in the macula densa stimulate ATP release, resulting in the extracellular formation of adenosine, which is involved in the signal transmission of the tubule-glomerular feedback response, increasing afferent arteriolar resistance and reducing GFR^[35,42].

Clinically, Yunos *et al*^[43] translated this experimental

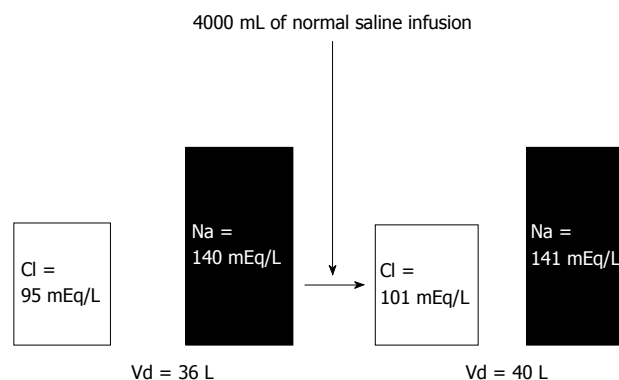


Figure 2 A monocompartmental model of intravascular 0.9% saline infusion, simulating the extracellular volume modification. To the initial distribution volume (V_d) = 36 L (approximately 60% of body mass of 60 kg), the total AMMOUNT of Cl^- and Na^+ were 3420 and 5040 mEq respectively. The infusion of 4000 mL of 0.9% saline results in additional 616 mEq of Cl^- and Na^+ to the total QUANTITY of extracellular electrolytes, that is, 4036 and 5656 mEq of Cl^- and Na^+ respectively. The new total AMMOUNT of electrolytes are distributed in a new V_d of 40 (36 + 4) liters, resulting in the new concentrations, where the chloride elevation was more striking than the sodium elevation.

knowledge to a large population of critically ill patients in a prospective open-label sequential period pilot study. After a control period and a wash-out phase, the use of chloride-rich intravenous fluids was restricted; this resulted in decreased chloride administration (694 to 496 mmol/patient) and led to better renal outcomes even after adjustment for covariates, including less high-severity AKI [OR = 0.52 (95%CI: 0.37-0.75); $P < 0.001$] and the reduced use of renal replacement therapy [OR = 0.52 (95%CI: 0.33-0.81); $P = 0.004$]^[43].

Acid-base consequences: Large volume resuscitation is commonly required in patients with sepsis and trauma. These patients may receive crystalloid infusions of many times their plasma volumes. Because the chloride concentration in 0.9% saline is approximately 50% higher than the plasma values, the chloride load associated with these volumes is significant. As previously described in this review, the chloride load associated with normal saline, which is a solution with a strong ion difference (SID) of 0, may be one of the main determinants of acidosis induced by fluids, along with chloride shifts that may occur in patients with sepsis (and other inflammatory states) and the Gibbs-Donnan effect after fluid challenges. These chloride loads and shifts interact with the patient's renal function, leading to both more AKI and subsequently lower chloride excretion, which might affect the kidney's recovery.

In surgical patients, when 0.9% saline was used as the primary intraoperative solution, significantly more acidosis was observed on completion of the surgery. These patients required larger amounts of bicarbonate to achieve predetermined measurements of base deficit and were associated with the use of larger amounts of blood products^[44]. In another trial, a 0.9% saline infusion was compared to a balanced electrolyte and glucose solution. Two-thirds of the patients in the 0.9% saline

group but none of the patients in the balanced fluid group developed hyperchloremic metabolic acidosis, and the hyperchloremic acidosis was associated with reduced gastric mucosal perfusion on gastric tonometry^[45].

Although the effects of chloride are well studied, little is known about the potential contributions of sodium to the metabolic acid-base state. In a sample of 51 critically ill patients, a rise in serum sodium levels during the development of hypernatremia was accompanied by an increasing pH, serum bicarbonate, and standard base excess, and consequently metabolic alkalosis^[46]. In addition, the development of metabolic alkalosis correlated with the SID but not with the absolute serum sodium concentrations, indicating that the increase in the serum sodium-to-chloride ratio led to the development of metabolic alkalosis^[47].

Inflammatory response: Fluid and electrolyte overload may also influence cytokine production and the inflammatory response. In an animal model of hyperchloremic acidosis induced by dilute HCl infusion, moderate (SBE, - 5 to - 10) and severe (SBE, - 10 to - 15) acidosis significantly increased cytokine expression in a dose-dependent fashion in normotensive septic rats^[48]. These results are consistent with *in vitro* studies showing that HCl influences cytokine production in LPS-stimulated cells^[49], and pH interferes in nitric oxide^[50] and tumor necrosis- α production^[51] by macrophages in cell models. Interestingly, acidosis etiology may determine the inflammatory response pattern. Hyperchloremic acidosis is essentially pro-inflammatory as assessed by the increased NO release and the IL-6-to-IL-10 ratio, whereas lactic acidosis is associated with an anti-inflammatory pattern^[49].

Hemodynamic consequences: Chloride overload and its consequent hyperchloremic acidosis may have direct and independent deleterious effects on hemodynamics and survival. In an endotoxic shock model in rats, moderate and severe acidosis that was generated by HCl infusion induced a significant drop in blood pressure. This change in blood pressure was correlated with increases in plasma chloride concentrations and to a lesser degree with a decrease in pH^[52]. Furthermore, saline solution resuscitation was associated with a significantly shorter survival time compared to a balanced electrolyte solution containing starch in a similar animal model. Survival time was negatively correlated with both the decrease in pH and the increase in serum chloride following the initial resuscitation. The decrease in pH appeared to have been brought on by changes in chloride, lactate, and PaCO₂. However, lactate values were not different between the groups, and the changes in PaCO₂ were not correlated with survival time. Thus, hyperchloremic acidosis, rather than acidosis in general, was strongly and independently associated with early mortality in these animals^[53].

FLUID OVERLOAD

Pathophysiology

The renal compartment syndrome: The human body is composed of different organ systems. Lungs are, perhaps, the most affected organs by fluid overload, followed by encapsulated organs such as the kidneys. Experimental and clinical evidence from more than 30 years ago links the development of renal edema with oliguria and the perpetuation of ischemic AKI^[54]. This could be explained by reduced perfusion pressure through the kidneys as a result of higher central venous pressure, which has been better described in the context of cardiorenal syndromes^[55,56]. In addition to heart failure, patients with systemic inflammatory response syndrome (SIRS) may also develop interstitial edema and subsequently increases in interstitial pressure, leading to lower perfusion pressure, particularly in encapsulated organs such as the kidney^[57].

In animal models, Burnett *et al.*^[58] also demonstrated that an increase in renal venous pressure associated with volume expansion led to higher interstitial pressures and decreased sodium excretion in association with a decreased RBF and glomerular filtration rate. Recently, Cruces *et al.*^[59] experimentally described a model that provided even more support of the existence of a renal compartment. In their work, pressure had a nonlinear dependence on volume in the intact kidney, whereas the decapsulated kidney followed a linear pressure-volume curve, thus corroborating the hypothesis that kidney hypoperfusion might be explained by a reduced perfusion pressure. Clinical evidence supporting the role of interstitial edema to worse kidney outcomes will be discussed later in this review.

Pulmonary consequences: Derangements in the capillary permeability, which occurs in SIRS, combined with an increased hydrostatic pressure, as induced by aggressive fluid resuscitation, results in major interstitial edema that can lead to important clinical consequences.

Fluid overload increases hydrostatic pressure, leading to fluid accumulation in the lungs. Studies in mice have shown that the leakage occurs in the bronchiole, and the backflow of fluids leads to alveolar edema^[60]. There is a reabsorption of fluids in the interstitial space and, because the accumulated fluids are drained across the lymphatic vessels to the thoracic duct and superior vena cava, alterations in systemic venous pressure, which occurs during fluid overload, result in impaired lymphatic drainage and consequently pulmonary edema^[61], leading to a gas exchange impairment.

The high hydrostatic pressure not only causes fluid leakage but also generates mechanical stress injury to capillary walls, leading to the impairment of the mechanisms of fluid reabsorption^[62] and alveolo-capillary barrier damage^[63,64]. This damage causes

ultrastructural changes in the capillary, altering permeability to proteins and activating the inflammatory response^[65], which compromises gas exchange^[66].

Hypoxemia resulting from impaired gas exchange leads to lung regional blood flow redistribution. As demonstrated by Ruff *et al.*^[67], fluid overload leads to an inversion of the pulmonary perfusion pattern, with decreased blood flow to the pulmonary dependent regions and increased blood flow to the non-dependent regions, most likely because of hypoxic vasoconstriction.

The clinical features of pulmonary edema are not restricted to oxygenation but are a result of decreased pulmonary ventilation as well. In 1922, Drinker had described a tidal volume reduction of 40%-70% in an induced pulmonary edema animal model^[68], and a subsequent study has shown that a negative fluid balance strategy improved lung compliance and arterial oxygenation^[69].

Considering Starling's equation in which pulmonary edema is a result of colloid osmotic and hydrostatic forces, one approach to this clinical problem is to lower filling pressures. Despite concerns regarding lowering cardiac output and oxygen delivery, current evidence shows that a conservative fluid strategy improves the oxygenation index and number of ventilation-free days without compromising hemodynamics or other organ functions^[11,70].

Other organ consequences: Other organs might be affected by fluid overload in addition to the lungs and kidneys. Worse outcomes of the skin and the recovery of soft tissue wounds after surgery have been described, and the trial of Brandstrup *et al.*^[71] showed that a more conservative approach on fluids achieved better outcomes, particularly regarding surgical complications.

Gastrointestinal complications, such as ileum and anastomotic leakages, can also be increased because of interstitial edema associated with accumulated fluids during critical illness or major surgeries^[72]. This might lead to delays in the administration of nutritional needs and worsen the possibility of achieving an adequate enteral nutrition intake.

The liver is also an encapsulated organ, and interstitial edema could lead to a sort of compartment syndrome. In shock states, in addition to hypoperfusion, a high central venous pressure is required for the development of ischemic hepatitis^[73]. High venous pressures are usually secondary to a low cardiac output in patients with congestive heart failure, but it can also occur in fluid overloaded patients with SIRS who develop myocardial dysfunction.

From a broader perspective, abdominal compartment syndrome can be seen as another preventable complication of fluid overload. This syndrome would be an extreme situation regarding fluid overload states and can be either primary or secondary. In this case, fluid overload contributes to the development of abdominal compartment syndrome, leading to deleterious effects on many organ systems, including hemodynamic (as a result

of reduced venous return), renal (as a result of increased renal venous pressure) and even respiratory system mechanics (by reducing the thoracic wall compliance)^[74].

Other organ systems have more limited evidence associating fluid overload with worse outcomes. Although the brain could be considered an encapsulated organ, in general ICU patients whose blood-brain barrier is considered intact, fluid overload will most likely not lead to a significant cerebral edema that will develop into intracranial hypertension. However, it might be associated with an increased incidence of delirium^[75], which is associated with worse outcomes.

Acid-base water effect: Despite the effect of electrolytes on acid-base status, water itself might influence the acid-base status. Some experimental evidence from *in vitro* studies suggests that the dilution of plasma with distilled water changes many electrolyte concentrations, but because the ensuing proportions are maintained regarding the SID, PaCO₂ and weak anions, there is no significant difference in the pH^[76]. However, in a mathematical modeling approach validated thereafter with human plasma, Gattinoni *et al.*^[77] demonstrated that water itself, when in an open system, leads to acidosis, mainly because of the reaction of CO₂ with H₂O. The same group later described a possible rule that would regulate pH changes during crystalloid infusion, with interesting results. Mainly, the baseline [HCO₃⁻] values would dictate the pH response to a crystalloid solution whose (SID) would be the main determinant of the direction of the pH change^[78]. As an example, giving a patient both 0.9% saline [(SID) = 0] or dextrose in water [(SID) = 0] can lead to worsened acidemia, depending on the patient's renal function and pulmonary function to counteract these effects. However, 0.9% saline comes with an added cost, which is that of electrolyte overload, as we have discussed.

Observational evidence correlating fluid overload with worse outcomes

Fluid overload or cumulative fluid balances have been associated with worse outcomes in many scenarios, including in patients with sepsis^[79], cancer^[80], and surgical patients^[81], and during weaning from mechanical ventilation^[82] and at discharge from the ICU^[83].

A sub analysis of the VASST trial, which included patients with septic shock who were on vasopressors, reported that a positive fluid balance at both 12 h and 4 d after the onset of shock was associated with worse outcomes. Interestingly, the patients with CVP values below 8 mmHg at 12 h after septic shock onset had improved survival compared to patients with higher values of CVP^[79], which are recommended by the surviving sepsis campaign during the first hours of resuscitation^[84]. More provocative are the findings of Murphy *et al.*^[85], who studied a cohort of patients with septic shock who thereafter developed acute respiratory distress syndrome (ARDS), in which they hypothesized whether an adequate initial

fluid resuscitation strategy and a conservative late fluid management strategy were associated with improved survival^[85]. In this cohort, the patients who achieved both adequate initial fluid resuscitation and conservative late fluid management had the lowest mortality. Interestingly, the patients who achieved a conservative late fluid management but not adequate initial fluid resuscitation had lower mortality rates than those who achieved adequate initial fluid resuscitation but not conservative late fluid management. This appears to provide a lesson regarding this population: trying to optimize hemodynamics later in the course of the disease is most likely deleterious, whereas achieving negative fluid balances, *i.e.*, actively de-resuscitating patients even if the initial resuscitation was not deemed adequate, appears to be successful, particularly for patients with ARDS^[11]. In patients with ARDS, a large observational cohort also demonstrated that more positive fluid balances are associated with worse outcomes^[86].

In patients being weaned from mechanical ventilation, data demonstrate that a 24-h negative fluid balance on the day of the spontaneous breathing trial and a cumulative negative fluid balance were associated with better weaning outcomes^[82]. In another cohort of elderly patients, both negative fluid balances and decreasing values of central venous pressure were associated with better weaning outcomes^[87]. A higher cumulative fluid balance, even after ICU discharge, was also associated with worse outcomes during hospitalization^[83].

In patients with AKI, positive fluid balances have also been associated with worse outcomes. In a sub analysis of a European cohort of general ICU patients who developed AKI, a positive mean fluid balance was an independent risk factor for 60-d mortality^[88]. In a sub analysis of the RENAL study, the authors investigated the effect of fluid balance on the outcomes of patients with many different statistical approaches, and they consistently found an association between negative mean daily fluid balances and improved clinical outcomes^[89].

Many of these conditions in which fluid overload has been shown to be deleterious share a common feature: the presence of SIRS and the risk of multiple organ dysfunction syndrome, which can manifest clinically as shock along with AKI, ARDS and many other possible organ dysfunctions, septic or non-septic in origin^[90]. What remains to be established is whether fluid overload is only a biomarker^[91] that puts patients under an increased risk of death or an iatrogenic condition from critical care that should be considered in daily care and actively treated and avoided. This is a question to be answered with randomized controlled trials.

Randomized controlled trials correlating fluid overload with worse outcomes

Some randomized controlled trials in critically ill patients attempted to address whether a conservative

fluid management approach would result in better outcomes for patients instead of a liberal approach, testing the hypothesis that fluid overload is not only a biomarker but is also a modifiable risk factor for worsening organ dysfunctions and death. In each trial, the fluid-restrictive protocols were different; however, the greatest objective in all of the studies was to withdraw fluids from the patients and/or to avoid giving unnecessary fluids.

In patients admitted to an intensive care unit who required a pulmonary artery catheter, Mitchell *et al.*^[70] compared an extravascular lung-water based strategy against a wedge pressure-based strategy for the treatment of 101 patients. Regardless of the protocol used, in the extravascular lung-water based strategy, the cumulative fluid balance was 142 ± 3632 mL compared to 2239 ± 3695 mL in the other group. The conservative strategy led to better outcomes in this group although mortality was unchanged.

In patients undergoing high-risk colorectal surgery, Brandstrup *et al.*^[71] also tested another conservative strategy for fluid management during the perioperative state and achieved a significantly lower fluid balance in these patients, yielding a lower rate of complications after surgery, many of which included surgical wound repair and cardiopulmonary complications.

In the landmark FACTT trial, which included two different protocols for the fluid management of patients with ARDS, patients in the conservative group achieved a negative fluid balance throughout the course of the disease, whereas patients in the liberal group progressively accumulated more fluids during their ICU stay. The primary outcome (mortality) was not different between the groups. However, the conservative group achieved a higher number of ventilator-free days and ICU-free days but had less vasopressor free-days, along with a slight trend towards a lower dialysis requirement through day 60 ($P = 0.06$)^[11]. This trial demonstrated an interesting point: when using a conservative fluid management strategy, one will likely require vasopressors for a longer period but paradoxically at the benefit of being able to breathe without the ventilator sooner and being discharged from the ICU sooner. The cumulative fluid balance of both arms of the FACTT study is shown in Figure 3, as is the fluid balance of the ALVEOLI^[92] and ARMA^[93] studies about protective mechanical ventilation in ARDS patients.

Finally, during weaning from mechanical ventilation in a mixed ICU population, it has been demonstrated that a brain natriuretic peptide-driven strategy for fluid withdrawal resulted in more negative cumulative fluid balances [median, -180 (-2556; 2832) vs -2320 (-4735 to 738), $P < 0.001$], resulting in more ventilator-free days, although without impact on mortality^[94].

These trials, although conducted in different clinical scenarios, share an interesting feature. In the population of patients at risk of developing new organ failures (such as patients during high-risk surgery) or with ongoing organ failures (such as patients with ARDS) or even

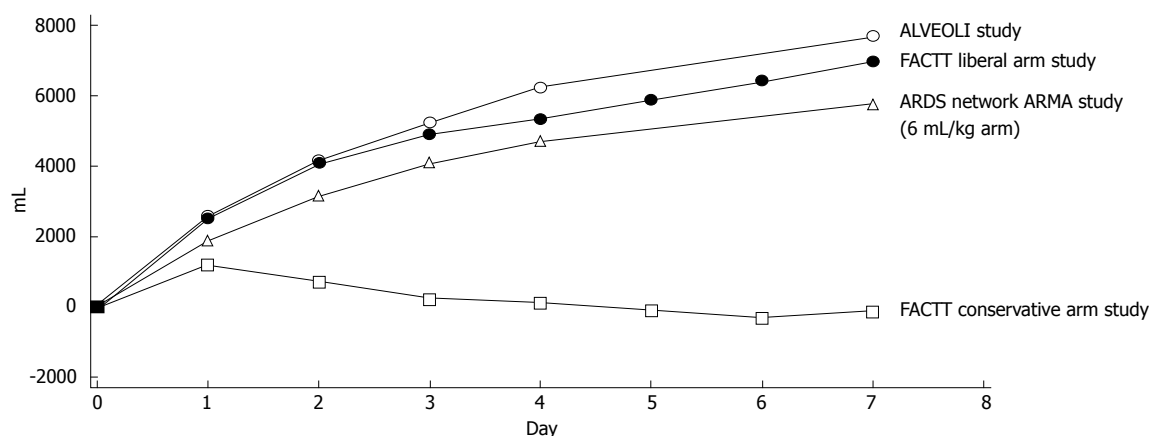


Figure 3 Cumulative fluid balances of the acute respiratory distress syndrome network group studies. The FACTT conservative fluid strategy arm returned to the neutral fluid balance within the first three days after randomization. The former strategy did not result in better survival, however patients were ventilated for less time and spent less time in the ICU in the conservative group. Adapted from Wiedemann *et al*^[11]. ARDS: Acute respiratory distress syndrome; ICU: Intensive care unit.

during recovery of the critical illness, a conservative strategy led to better outcomes. Whether this can be extrapolated to all clinical scenarios remains to be answered.

The kidney paradox (oliguria worsened by fluid challenge)

Oliguria is usually considered a marker of decreased cardiac output, and a fluid challenge is often considered in an attempt to increase the cardiac preload and enhance cardiac output, which would ultimately enhance organ perfusion. However, after the optimization of hemodynamic parameters, some patients will still develop AKI and may have persistent oliguria on the ensuing days. Hence, after the first hours of resuscitation, oliguria should be interpreted as a marker of organ dysfunction but should not be seen as a marker of low cardiac output and does not necessarily indicate the need for volume expansion.

In this context of oliguria and a high risk of fluid overload, an added fluid challenge may worsen urine output and even renal function, as we have discussed previously in this review; most of the time, this will contribute to fluid and electrolyte overload. Clinically, Van Biesen *et al*^[95] demonstrated in a cohort of septic patients with AKI that additional fluid therapy failed to improve renal function, and other studies have shown an association between a positive fluid balance and worse outcomes in patients with AKI^[91], in addition to a decreased likelihood of renal recovery^[88,96]. Another implication of increasing cumulative fluid balances in this context is the potential underestimation of the diagnosis or severity of AKI because of an increased creatinine distribution volume^[97].

Therefore, this kidney paradox should be avoided in which clinicians attempt to enhance urinary output through repeated fluid challenges to avoid worsening kidney injury; these actions may in fact lead to more fluid accumulation and ultimately a worse outcome.

A BEDSIDE PATIENT-TAILORED APPROACH

To avoid potentially deleterious complications associated with fluid and electrolyte overload (Table 2), a patient-tailored approach is necessary to result in better outcomes for the individual patient. This will involve some aspects of fluid resuscitation, maintenance fluids, other sources of electrolytes and water and, ultimately, an active de-resuscitation strategy that may aim at the fluid balance and, if performed adequately will also remove the excessive loads of sodium and chloride. Here we describe how clinicians can address this situation at the bedside.

Judicious resuscitation

During the acute phase of resuscitation, fluids should be used judiciously to achieve an adequate perfusion. This encompasses four distinct aspects of fluid resuscitation: timing, type, amount and avoidance of the kidney paradox^[98].

Resuscitation with fluids should be performed during the appropriate timing for this action, which occurs during the onset of the injury (intra-operative states) or soon after it (first hours after septic shock, major surgery or other acute physiological insults)^[1]. There is no evidence that fluid resuscitation after these first moments will lead to better results. In fact, as we have discussed so far, the evidence points in the opposite direction.

In general, balanced solutions should be the fluids of choice in patients with shock states because they carry a lower chloride load, lead to less acid-base disturbances and most likely to better organ dysfunction outcomes, particularly for the kidneys, as shown in the study by Yunos *et al*^[43].

The proper amount of fluid for acute care resuscitation is another critical component of judicious resuscitation. A recently published cohort of septic patients from

Table 2 Potential complications of fluids and electrolytes overload

Organ system	Complication	Main modifiable risk factor	Pathophysiological mechanism
Central nervous system	Delirium	Hypernatremia	Excessive sodium load Kidneys inability to excrete excess sodium load
Renal/metabolic	Worse recovery of renal function Worsening acute kidney injury Worsening acidemia	Cumulative fluid balance/higher CVP Unbalanced solutions Unbalanced solutions	Renal edema, reduced perfusion pressure Chloride-induced renal vasoconstriction Solution SID relative to plasma SID Kidneys inability to excrete excess chloride load
Respiratory	Impaired gas exchange Altered pulmonar and chest wall mechanics Increased work of breathing	Cumulative fluid balance/higher CVP/higher EVLW	Lung edema
Gastrointestinal	Ileum Hepatic congestion Increased intra-abdominal pressure (may induce by itself more organ dysfunctions)	Cumulative fluid balance Higher CVP Cumulative fluid balance	Bowel edema Hepatic congestion Visceral edema (bowel, renal, <i>etc.</i>), ascites
Hemostasis	Increased bleeding	Unbalanced solutions	Acidemia secondary to chloride load
Wound healing	Impaired wound healing	Cumulative fluid balance	Local edema
Hemodynamics	Worse microcirculatory blood flow	Higher CVP	Reduced perfusion pressure

CVP: Central venous pressure; SID: Strong ion difference; EVLW: Extravascular lung water.

Australia and New Zealand, which yielded impressive mortality outcomes, demonstrated that patients received approximately 3 L of fluids during the first hours of resuscitation^[99]. Furthermore, in the recently published PROCESS trial, in patients who received more fluids (approximately 1 L more) in one of the three study arms, there were more cases of new onset renal failure than the usual care group^[7]. With this in mind, particularly in cases of septic shock, after an initial fluid challenge of 20-30 mL/kg, we favor an earlier use of vasopressors and the avoidance of repeated fluid expansion in patients with vasodilatory states, particularly in those with adequate perfusion parameters who are no longer fluid-responsive^[100].

Another issue to be considered is to avoid the “kidney paradox”. In oliguric patients, one should strongly consider avoiding repeated volume expansions after the first hours of resuscitation because this will most likely lead to higher filling pressures and more fluid accumulation despite a possibly increased urine output. In patients who further develop anuria, fluid challenges might be even more deleterious.

Acid-base monitoring during resuscitation

During the resuscitation phase of critical illness, in addition to usual hemodynamic monitoring, it is important to monitor potentially deleterious effects of fluids and electrolytes on the acid-base status. As previously discussed, both fluid composition and quantity can influence acid-base status^[98]. Through acid-base monitoring, one can identify at an earlier stage metabolic complications occurring during resuscitation. If possible, one should attempt to quantify which component of metabolic acidosis is worse during acute resuscitation because they carry different prognostic significances^[16].

Active de-resuscitation

After a judicious resuscitation strategy, active de-

resuscitation should be considered to avoid the deleterious effects of continuous fluid accumulation when the patient does not passively excrete the excess amount of water and electrolytes. This can be achieved both with diuretics, which have been shown to be safe in the context of AKI, or with an earlier indication of hemodialysis, as defended by some authors, when the former cannot control fluid overload^[101]. To achieve a safe withdrawal of fluids and electrolytes, some factors must be considered:

Fluid removal rate: either with dialysis or diuretics, the fluid removal rate should be titrated to the patient hemodynamic status to avoid underfilling during this phase^[102]. If tolerated, there will likely be no deleterious effects of fluid withdrawal, even in the presence of vasopressors or inotropic drugs.

Intermittent vs continuous infusion of diuretics: in critically ill patients, the continuous infusion of diuretics was not extensively studied. Better evidence from other clinical situations has not demonstrated any consistent advantage of one way of administering diuretics over another, except for higher doses of diuretics in intermittent therapy for the same fluid balance achievement compared to continuous infusion diuretic therapy^[103,104]. As long as a target diuresis is achieved, there will likely be no differences among these treatments.

Association of albumin to furosemide: although albumin was not associated with better outcomes in patients with septic shock^[105] or for fluid resuscitation in general ICU patients^[106], in patients with ARDS, a better hemodynamic tolerance during fluid withdrawal was achieved with the combination of albumin and furosemide^[107] and could be a useful adjunct during the active de-resuscitation phase.

Monitoring and treating metabolic complications: the use of diuretics is associated with more metabolic disturbances, including hypernatremia, hypokalemia and metabolic alkalosis^[11]. To counteract these disturbances,

we favor the use of acetazolamide if the patient develops metabolic alkalosis, thiazide diuretics and increases in free water reposition if hyponatremia ensues and the aggressive reposition of electrolytes to avoid extreme electrolyte disturbances. We refer the reader to the trial by Mekontso Dessap *et al.*^[94], which proposed a method to do this safely with a combination of diuretics.

Consideration for an earlier indication of renal replacement therapy in oliguria should be part of an active de-resuscitation strategy because some patients will develop stage III AKI^[108], will be unresponsive to diuretics and, during this process, will accumulate fluids progressively, which has been consistently shown to be associated with worse outcomes in this specific population^[88,89,96].

Although pulmonary edema is a common trigger for fluid withdrawal, it is a late and potentially deadly consequence of fluid overload. Hence, during this phase of active fluid withdrawal, some very simple monitoring strategies can be used.

Central venous pressure, although recently receiving discredit as a guide to fluid loading^[109], was used in the largest randomized controlled trial on conservative fluid strategies^[11]. In this regard, although there are many physiological states that can influence its isolated value, higher CVP values have been associated with worse outcomes in many conditions, including septic shock^[79], likely not only because of fluid overload but also because of the associated significant effect of heart dysfunction on its values. Therefore, it can be an adjunct for active de-resuscitation strategies, and a goal towards lower CVP values (*e.g.*, down to < 4 mmHg in adequately perfused patients without vasopressors) is a simple way to monitor this strategy.

An even simpler solution is to focus on fluid balance. Although daily weights would potentially be better, these values are also prone to error when measuring patients on ICU beds^[110], and we believe that fluid balance, although imperfect, appears to be a simple bedside target of active de-resuscitation. Therefore, reaching even to negative fluid balances during the first days of critical illness onset and, as soon as possible, aiming at more negative fluid balances until reaching a cumulative fluid balance of approximately zero during the ICU stay appears to be a good approach.

In addition to active fluid withdrawal, one should avoid the unnecessary entrance of fluids and electrolytes in the form of electrolyte reposition, drugs dilution and as caloric intake on a daily basis because as we have previously discussed, these are important sources of sodium, chloride and water. In this regard, we favor using hypertonic glucose solutions if deemed necessary for minimum caloric intake (when the enteral route is not available for feeding) and the avoidance of maintenance fluids when there are no clinically relevant fluid losses (*e.g.*, ileostomy). Finally, electrolytes, antimicrobials and other drugs should be diluted in the minimum necessary amount of fluids and preferentially in 5% dextrose in water^[20].

With all this evidence combined, it appears that a judicious initial fluid resuscitation followed by a conservative fluid management approach will lead to better outcomes in patients in many different shock states, including in patients with sepsis and patients with other causes of non-septic SIRS. As we have discussed, hyponatremia is associated with worse outcomes, along with hyperchloremic acidosis in some scenarios and also progressive cumulative fluid balances. Many of the studies in this regard examined these issues separately, whereas these may be different aspects of the same problem: that of fluid and electrolyte overload.

CONCLUSION

Although there are no adequate prospective experimentally designed studies that have shown that fluids are essential in the treatment of critically ill patients, fluids are used liberally among ICU patients, and fluid accumulation is very common throughout the course of a patient's ICU stay. In this review, we provided evidence of the potentially deleterious effects of fluids and electrolytes on many organ systems, how to monitor for these complications and how to manage this increasingly recognized clinical problem. Currently, we favor a more conservative approach regarding fluid management strategies in general ICU patients, although a randomized controlled trial addressing this issue is mandatory to shed light on this discussion, along with deeper mechanistic studies to understand the relative contributions of each component of fluid therapy.

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