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Fluid Balance in Patients with Acute Kidney Injury: Emerging Concepts

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Abstract

Intensive care unit and surgical populations are at increased risk for acute kidney injury (AKI) and oliguria, which often lead to fluid accumulation. Volume resuscitation is a cornerstone in the treatment of hemodynamic instability in these populations. However, fluid balance evaluation and its management in the critically ill can be challenging. Several clinical and paraclinical tools may aid decision-making regarding fluid management. When fluid therapy is indicated, crystalloids should be the preferred agents. Synthetic colloids have been associated with no survival benefit and increased risk of AKI. There is currently a paradigm shift in which hypervolemia is no longer desirable and is increasingly shown to be detrimental to both renal outcomes and survival. Instead, approaches that aim for neutral and slightly negative fluid balance or 'dry' patients after initial fluid resuscitation are favored. This may be achieved by conservative fluid strategies, diuretics or renal replacement therapy. In this paper, we will review recent findings on the principles of fluid management in AKI, including assessment of fluid need, choice of fluid solutions, influence of fluid overload on outcomes, and some practical issues to achieve fluid balance and minimize complications in patients with AKI.

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Introduction

Acute kidney injury (AKI) is a common pathology in the intensive care unit (ICU) and postoperative setting [1] and is often associated with hemodynamic instability requiring fluid resuscitation with large volumes of fluid. Over the last 5 years there has been increased recognition that fluid accumulation is common in these patients and is exacerbated once AKI and oliguria develop [2–4]. Several studies have shown that fluid accumulation has a significant relationship with adverse outcomes, including increased mortality and reduced renal functional recovery [3, 5]. Oliguria has been shown to be associated with a poorer prognosis [6]. Whether this is a reflection of the severity of the underlying disease or the positive fluid balance that ensues is unclear. These data have prompted several questions regarding the role of fluid administration in AKI, including the amount, type and duration of fluid and its relationship to outcomes. In this article we

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discuss the principles of fluid management in AKI, including assessment of fluid need, choice of fluid solutions, influence of fluid overload (FO) on outcomes, and practical issues to achieve fluid balance and minimize complications in patients with AKI.

Assessment of Fluid Need

Total body water represents approximately 60% of body weight. Two thirds of this total body water is intracellular fluid while the remaining third is in the extracellular fluid. The water is also distributed in different parts of the extracellular fluid: 75% in the interstitium, 20% in the plasma and 5% acting as transcellular fluid. Under normal conditions, water and electrolyte homeostasis is maintained through balanced intake and output. However, different conditions such as sepsis, surgery, dramatic fluid losses or increased intake without adequate compensatory output, such as overzealous fluid administration in AKI, result in unbalanced fluid distribution. Studies have shown that only approximately 50% of hemodynamically unstable patients in the ICU respond to fluid repletion [7] resulting in unnecessary fluid retention in the nonresponders.

Multiple factors contribute to the neurohormonal stimulation controlling fluid balance in the critically ill. Positive pressure ventilation, bleeding, fasting or ileus may all reduce blood pressure through either true reduction of blood volume or diminishing left ventricular filling pressures. Pain and physiological stress not only cause salt retention via the direct effect of catecholamine release and sympathetic activity on proximal tubular reabsorption, but also via stimulation of the renin-angiotensin-aldosterone system. In addition, there may be direct water retention due to antidiuretic hormone stimulation through pain or nonosmotic hypotension stimulus of any shock or sepsis. This hypotensive state will, via reduced renal perfusion, also stimulate the renin-angiotensin-aldosterone system causing further sodium retention. All these factors explain the weak relationship between fluid administration and natriuresis and why additional volume infusions result in salt and water accumulation.

Fluid balance is also influenced by hypoalbuminemia in the severely ill patient. Different mechanisms have been suggested to explain this phenomenon: inflammation, vasodilatation or increased vascular permeability, increased nonspecific catabolism, malnutrition or liver dysfunction leading to reprioritization of synthesis, or increased protein loss. Increased vascular permeability encountered in sepsis leads to loss of albumin in the interstitial space, thereby reducing vascular oncotic pressure and contributing to the altered fluid compartmental distribution and slow vascular refilling. This capillary 'leakiness' may contribute to diuretic resistance or hemodynamic instability during ultrafiltration in renal replacement therapy (RRT).

Different parameters with varied precision levels can be evaluated to estimate a patient's effective volume status and to help therapeutic decision-making (table 1). Oliguria may be an early and accurate biomarker of AKI [6]. Urinary indices may help complement physical examination data. Static measures of cardiac filling pressures such as central venous pressure are often used in the ICU, but multiple studies have shown that they are unable to predict volume responsiveness [8]. Dynamic measures appear to be most valuable in this context.

Choice of Fluid and AKI

The principal of fluid therapy is to maintain or restore effective intravascular volume to assure adequate tissue perfusion. Several fluid types are currently available for fluid resuscitation and repletion. These include colloids such as synthetic hydroxyethyl starches (HES), gelatins or albumin, and crystalloids including saline (i.e. NaCl 0.9, 0.45 or 3%), lactate-based (i.e. Hartmann's solution) or balanced (i.e. Plasma-Lyte 148) solutions. Fluid administration contributes to compartmental shifts depending on the composition of the infused fluid. While colloids mostly remain in the intravascular space, crystalloids distribute across compartments. For example, while giving 1 liter of NaCl 0.9%, approximately 250 ml will remain in the intravascular compartment and the rest will be distributed into the extravascular space. The fraction of fluid remaining in the intravascular space decreases proportionally as the tonicity of the solution used is lowered. Hypotonic solutions are therefore not very effective options for fluid resuscitation.

Over the last decade there has been considerable controversy concerning the influence of fluid composition on organ function, particularly the kidney. Many studies have been conducted to evaluate the superiority and safety of solutions available for volume resuscitation. Mortality, AKI and other adverse effects associated with the use of synthetic colloids have been evaluated in multiple studies, with conflicting results. The discrepancy in outcomes in these studies may be explained by the great heterogeneity in patient populations evaluated, type and volume of

Table 1. Useful parameters for fluid status evaluation

Clinical parameters	Paraclinical parameters	Static measures	Dynamic measures
Body weight changes	Urinary indices (i.e. UNa, FeNa, FeUrea, specific gravity and osmolality)	Central venous pressure IVC diameter	Stroke volume variation and pulse pressure variation
Input/output balance	Hematologic changes	Pulmonary artery occlusion pressure	Aortic flow velocity and stroke volume
Blood pressure, heart rate and orthostasis	Bioelectrical impedance	RV end-diastolic volume	Positive pressure ventilation induced changes in IVC diameter
Urine volume	Lactates, SVO_2	LV end-diastolic area	Microcirculation evaluation
Capillary refill, skin turgor	Extravascular lung water index	Intra-aortic blood volume index	
Organomegaly		Global end-diastolic volume index	
Pulmonary edema			

UNa = Urinary sodium; FeNa = fractional excretion of sodium; FeUrea = fractional excretion of urea; SVO_2 = venous saturation in oxygen; IVC = inferior vena cava; LV = left ventricular; RV = right ventricular.

HES used, and the safety profile of the solution it was being compared to. Pharmacokinetic profiles of HES vary accordingly to their molecular weight, degree of substitution and C_2/C_6 ratio. Hyperoncotic HES are known to be associated with AKI [9, 10], and HES have been shown to deposit in different organs and tissues including the kidneys [11]. Two recent randomized controlled trials using newer HES with lower molecular weights and less substitution showed a neutral or negative effect on mortality and an increased need for RRT [12, 13]. In 2012, the CHEST trial compared fluid resuscitation with 6% HES 130/0.4 versus 0.9% saline. This randomized controlled trial showed no significant mortality difference at 90 days between the two groups, but did demonstrate an increased need for RRT in the HES group as well as treatment-related adverse events. Starch administration was not associated with a substantive volume-sparing effect [13]. A meta-analysis published in 2013 indicated the same tendencies of increased RRT with absence of survival benefit [14]. Synthetic colloids should therefore be avoided in patients with AKI or at risk of developing AKI, which represents most patients in the ICU and operative settings.

The use of hypooncotic albumin has been studied in the SAFE trial and two subsequent subanalyses. No differences in mortality, duration of RRT or new organ dysfunction were noted when compared to saline. The subgroup analysis of patients with severe sepsis demonstrated decreased mortality in the albumin-treated group (OR: 0.71, 95% CI: 0.52–0.97). No differences were found regarding renal outcomes. Another subgroup analysis of the SAFE trial showed decreased survival in patients with traumatic brain injuries treated with albumin [15–17]. Conflicting data exist regarding the renal safety of hyperoncotic albumin [18].

Although crystalloids remain the first choice for fluid therapy, there may be differences in renal outcomes amongst them. Animals studies suggest that hyperchloremia resulting from 0.9% saline infusion may affect renal hemodynamics causing arteriolar vasoconstriction and decreased glomerular filtration rate [19]. A recent study demonstrated decreased renal artery flow and cortical perfusion in subjects who received 0.9% saline compared to a balanced solution (Plasma-Lyte 148) [20]. An Australian prospective study subsequently found lower increases in creatinine, lower incidence of RIFLE 'injury' and need for RRT in ICU patients treated with a chloride-restrictive approach as opposed to a chloride-liberal strategy [21]. Based on the available evidence at this time, it appears that balanced salt solutions may be preferable for managing patients at risk of and with AKI. However, recent studies comparing the use of sodium bicarbonate to saline for preventing cardiac surgery-induced AKI failed to show any benefit from bicarbonate-containing fluids [22].

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Fluid Overload and Outcomes

Maintaining fluid balance is a major goal for ICU patients; however, there is considerable variation in how fluid balance is recorded and calculated. Accurate records of all intakes and outputs rarely correlate with scale weights, partially because they do not include insensible losses. However, chart fluid input and output seem to be more accurate to quantify fluid balance than measuring body weight changes with a scale [23]. A positive fluid balance results in fluid accumulation; however, the magnitude of change may be missed unless one calculates and follows cumulative fluid balance. This has been simplified with the availability of electronic medical records and can be represented graphically. Cumulative fluid accumulation is common in hospital settings, especially in the ICU or postsurgical population, largely due to aggressive strategies for fluid resuscitation. For instance, in a secondary analysis of the VASST trial, fluid accumulation over the first 12 h ranged from 8 to 30 liters in the lowest and highest quartile of septic patients, respectively, and was associated with an incremental risk for mortality [24].

Fluid overload (FO), defined as the total input minus total output divided by initial body weight, is associated with adverse outcomes when reaching more than 10% [3]. Patients with FO have an increased number of ventilation and ICU days and decreased oxygenation index [25]. In multiple observational studies from different populations (pediatric, sepsis, surgical), FO has been associated with increased mortality [24, 26, 27]. The SOAP study found that FO in septic patients with AKI was associated with a higher mortality at 60 days [2]. In a study from the PICARD group, the adjusted OR for mortality was 2.07 in patients with FO at initiation of RRT. In this population, survivors who were taken off RRT had significantly less FO than patients who remained on RRT [3]. A pediatric study also found a 3% increase in mortality for every 1% increase in FO. Children with more than 20% FO had an OR for mortality of 8.5 compared to children with less than 20% [28]. Amongst patients who developed AKI within 2 days in the FACTT trial, positive fluid balance was associated with lower 60-day survival in a post hoc analysis [29]. The RENAL study also demonstrated that a negative fluid balance in patients requiring RRT was associated with increased survival and shorter ICU and hospital stay [30]. In patients with AKI, FO at initiation of RRT has been associated with lack of renal recovery at 1 year [5]. In the PICARD study, FO at peak serum creatinine was also associated with a lower rate of renal recovery [3]. In the RENAL study, a negative mean daily fluid balance was associated with increased RRT-free days [30].

The relationship of fluid accumulation and AKI is complex. Significant fluid accumulation may take several weeks for the patient to eliminate, especially when renal function is altered. Consequently, FO may be a marker of the severity of AKI and may contribute to a missed diagnosis or may mask its underlying severity [31]. Importantly, when corrected for FO, 'unmasked AKI' seems to have an increased mortality compared to patients who never met AKI criteria [32]. Alternatively, FO could be a mediator of the adverse outcomes either through a direct effect via the type of fluid infused (i.e. HES) or due to its accumulation. Fluid accumulation results in interstitial edema, visceromegaly and eventually organ dysfunction. FO increases intra-abdominal pressure which results in renal venous congestion and decreased glomerular filtration rate and AKI which further exacerbates FO through decreased salt and water excretion [33]. Encapsulated organs such as the kidneys have limited accommodation capacity, which results in increased hydrostatic interstitial pressure and eventually decreases organ perfusion pressures and glomerular filtration rate without elevation of intra-abdominal pressure per se. Interestingly, Stone and Fulenwider [34] published a study in 1977 on the protective effect of renal decapsulation on AKI in patients with hemorrhagic shock requiring massive fluid therapy and transfusions. Other factors in FO contribute to organ dysfunction such as altered cell-to-cell interactions resulting in cell separation, dysfunctional glycocalyx function, abnormal oxygen consumption, decreased lymphatic drainage and distortion of normal tissue architecture.

Practical Issues

Fluid therapy is the cornerstone of treatment of hemodynamically unstable patients, and several guidelines are available for initial fluid resuscitation and maintenance, particularly for septic patients. For instance, the Surviving Sepsis Campaign recommends initial fluid challenge with 30 ml/kg of crystalloids using an early goal-directed therapy (EGDT) approach [35]. However, none of the existing guidelines have been designed to evaluate renal outcomes. Optimal fluid parameters and hemodynamic targets have not been established for AKI management. The recent KDIGO guidelines on AKI suggest that fluid repletion should be adequate without

mentioning specific parameters on the quantity and type of fluid to be given and the duration of fluid administration [36]. It is helpful to consider the goals for fluid administration in two contexts: patients who are at risk for AKI from a specific timed insult, e.g. radiological contrast, and patients who present with features of AKI (oliguria, elevated serum creatinine). In the former, several prospective trials, which are now considered the standard of care for managing these patients, have shown that fluid is needed before and should be continued for some hours after the procedure [36–38]. One recent study showed a positive effect of enhanced urine flow with aggressive fluid repletion coupled with diuretic administration in reducing the incidence of contrast-induced nephropathy [39]. Thus, for primary prevention of AKI, it appears reasonable to utilize fluids for a short period encompassing the timed insult. For patients presenting with AKI, the field is much murkier as the primary goal is to ensure that volume depletion and the reduced cardiac 'preload' is not a limiting factor for renal function and that hydration is adequate to maintain tissue perfusion. Fluid administration in this setting should thus be targeted to an improvement in cardiac stroke volume, tissue perfusion and renal function.

As mentioned earlier, static measurements such as central venous pressure are unreliable tools to predict which patients will be responsive to volume repletion. Fluid challenges predict a patient's response to hydration and are indicative of preload dependency. However, 'nonresponders' will have nonetheless received an amount of fluid. Volume responsiveness may be anticipated using different techniques such as passive leg raising or mechanical ventilation tests such as the end-expiratory occlusion test and evaluation of the magnitude of respiratory changes on left ventricular stroke volume. The predictive values of the measures used to evaluate fluid responsiveness vary greatly. The best correlation is seen with the pulse pressure variation and stroke volume variation greater than 13% (AUC: 0.94 and 0.84, respectively) [7, 40]. Certain factors may limit pulse pressure variation or stroke volume variation interpretation, such as increased abdominal pressure, arrhythmias, low tidal volumes (<8 ml/kg), right ventricular failure or vasopressors. Lanspa et al. [41] showed that SSV (>17%) and vena cava collapsibility index (<15%) were predictive of fluid responsiveness in nonventilated patients with septic shock.

From a renal standpoint, unless there is clinically evident dehydration, there is no clear evidence that aggressive hydration can change renal outcome, except in contrast-induced AKI. Animal studies in sepsis models have not shown any improvement in renal blood flow or oxygen delivery after normal saline or hypertonic saline administration [42]. Patients with AKI and apparently normal hemodynamics receiving IV fluid and high doses of diuretics did not show improved renal function [43]. The focus should be to aim at maintaining organ perfusion pressure through a minimal mean arterial pressure. Whether this is achieved with fluid therapy or vasopressors depends on the patient's intravascular volume evaluation. Fluid administration may help to correct cardiac output by restoring filling pressures, but it will not correct the vasodilatation encountered in sepsis. The Surviving Sepsis Campaign recommends aiming for 65 mm Hg mean arterial pressure [35], but targets should be individualized in accordance with patient comorbidities (e.g. renovascular disease or heart failure). It has been suggested that targeting 70–80 mm Hg mean arterial pressure would be necessary to decrease AKI in septic shock [44]. In a recent systematic review by Prowle et al. [45], perioperative patients managed by EGDT had less AKI (OR: 0.47, 95% CI: 0.29–0.76) even though they had received the same quantity of fluid as the non-EGDT group. This may be explained by the increased use of inotropic agents in the EGDT group. The data obtained suggests that EGDT decreases postoperative AKI mainly due to vasopressor use.

Interest has recently been shifting from macrohemodynamic organ perfusion to microcirculation evaluation through direct bedside imaging techniques evaluating microvascular flow index (MFI) and fluid responsiveness before organ dysfunction develops. Pranskunas et al. [46] recently demonstrated that in patients with MFI <2.6, fluid challenge was associated with a reduction of the number of 'clinical signs of impaired organ perfusion' and an increase in MFI. These results were not limited to patients with stroke volume variation ≥10%. No benefit was noted when fluid challenge was administered to patients with MFI >2.6. Ongoing studies such as ProCESS and ARISE are reassessing EGDT, and will evaluate renal outcomes to optimize fluid parameters and hemodynamic targets.

In light of the results regarding FO and outcomes in AKI and ICU patients, it is preferable to avoid liberal fluid maintenance strategies while aiming for neutral or slightly negative daily balances. Critically ill patients rarely require additional maintenance fluids, considering the quantity of water and sodium administered in drugs and nutrition. Once oliguria develops in spite of therapeutic measures to maintain renal perfusion pressure, manage-

ment of fluid balance may become challenging. In the ICU, oliguric patients with or without an increase in creatinine have an increased mortality even after adjustment for fluid accumulation [47, 48]. It remains unclear if the decreased survival is a factor of the severity of the disease or the associated positive fluid balance.

In severe AKI, correcting FO and restoring fluid balance are important goals since the duration of FO correlates with worse outcomes and its correction is associated with improved survival [3]. In this regard, diuretics may have a role in enhancing urine volume; however, most studies examining the effect of diuretics in AKI have found no significant differences on mortality or renal recovery [29, 49–51]. On the other hand, in the ARDS trial, a decreased need for RRT was noted in the conservative fluid group where all patients were given diuretics, compared to the liberal fluid group in which some patients were given diuretics (p = 0.06). The role of diuretics is also being studied in the SPARK study to evaluate their effect of progression and severity of AKI. In patients with oliguria and AKI, RRT is often initiated to treat hypervolemia that is unresponsive to diuretics. Bouchard et al. [3] demonstrated that patients treated with continuous RRT are more likely to reduce their percentage of FO compared with those treated with intermittent dialysis, and mortality was lower when FO was corrected by RRT. Other observational and retrospective studies suggest that the magnitude of FO at RRT initiation is associated with poorer outcome [5, 26]. These data provide a strong case to utilize RRT to correct FO and achieve fluid balance as well as to support organ function.

Conclusion

FO is associated with worse outcomes, including the possibility of decreased renal recovery in critical care patients. It is therefore important to understand that fluid therapy in the critical care unit is a dynamic process. Efforts should be made to find a balance between giving sufficient fluid therapy to maintain hemodynamic stability and organ perfusion while avoiding overzealous volume administration. This may be achieved by initial goal-directed resuscitation during acute presentation and thereafter aiming for a neutral or slightly negative fluid balance. If fluid therapy is indicated, as in true hypovolemia, crystalloids should be favored. Synthetic colloids should be avoided, considering the extensive data regarding their safety profile and lack of clear clinical benefits. Diuretics should be used as adjunctive therapy in AKI to treat FO and possibly to prevent it; however, they should not be continued if there is no an adequate response. Patients with significant fluid accumulation and who are unresponsive to diuretics should be considered for early initiation of RRT to correct FO.

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