Does fluid management affect the occurrence of acute kidney injury?

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**Purpose of review**
To describe the potential impact of different fluid management strategies on renal outcomes in critically ill and postoperative patients.

**Recent findings**
Uncritical fluid administration may induce renal compartment syndrome and renal venous congestion, which contribute to kidney dysfunction. In more than 5000 randomized surgical or septic patients, goal-directed therapy did not reduce fluid accumulation, acute kidney injury (AKI) development or need for renal replacement therapy. In contrast to synthetic colloids, which increase the risk of AKI, albumin solutions and balanced crystalloids appear well tolerated from a renal standpoint in medical and surgical patients requiring intensive care. However, any clinical benefits compared with 0.9% sodium chloride have not yet been demonstrated.

**Summary**
Although synthetic colloids should be avoided in patients with or at risk of AKI, the renal efficacy of using albumin solutions and/or balanced crystalloids as alternatives to 0.9% sodium chloride in high-risk patients is yet to be confirmed or refuted. Improved goal-directed protocols, which minimize unnecessary fluid administration and reduce potentially harmful effects of fluid overload, need to be developed and tested.

**Keywords**
acute kidney injury, fluid management, goal-directed therapy, sepsis, surgery

**INTRODUCTION**
Acute kidney injury (AKI) is a major complication following trauma [1], major surgery [2,3], and sepsis [4] and is associated with a marked increase in mortality and with progression to chronic kidney disease [5,6].

As no specific AKI-treatment exists, hemodynamic support remains the cornerstone of the management of patients with or at risk of AKI. Such hemodynamic support typically includes the administration of intravenous fluids aiming to maintain or improve renal blood flow (RBF), renal tissue oxygenation and glomerular filtration rate (GFR). On the contrary, these indices cannot be reliably measured, and clinicians are forced to rely on imperfect surrogate markers such as systemic blood pressure (BP), lactate blood levels, central or mixed venous saturation, urine output and changes in serum creatinine.

Fluid management in critically ill and postoperative patients varies substantially within and between countries. A recent point-prevalence study, the Fluid Challenges in Intensive Care study [7\textsuperscript{ix}], including 2213 patients from 46 countries, reported large variability in type, volume and rate of fluid administration between centers. In addition, indications for fluid therapy and the assessment of the response to fluid administration were highly inconsistent.

Furthermore, in a survey of more than 3000 intensivists from 30 countries, the Global Observational Evaluations in the ICU investigators...
Experimental studies have demonstrated that a sudden increase in intrarenal volume results in an exponential increase in intrarenal pressure and, consequently, impair both renal perfusion pressure and venous return. The additional finding that decapsulated kidneys demonstrate a linear pressure–volume relationship confirms the key role of the renal capsule in the RCS [12].

Intrarenal volume changes can be induced both by inflammatory edema and by fluid administration. For example, interstitial kidney edema and an almost eight-fold increase in subcapsular pressure was observed following 45 min of warm ischemia in a murine model [13]. Such changes were associated with impaired kidney perfusion, reduced GFR, loss of tubular excretory function and histological evidence of tissue damage. Significantly, early capsulotomy attenuated both functional and structural injuries.

Even in healthy volunteers expected to have an intact endothelial barrier, a significant increase in renal volume was observed after a 2-l crystalloid infusion over 1 h [14]. However, in clinical reality, intravenous fluids are typically administered during states of endothelial ‘leakiness’ in patients at particular risk of developing AKI. Hence, in such patients, uncritical fluid administration may counteract its purpose to improve renal hemodynamics and may instead worsen renal perfusion and excretory function.

Renal venous congestion

Reduced forward flow (cardiac output, CO) leading to decreased RBF and GFR was previously regarded a key mechanism behind AKI. However, the role of central and renal venous pressures in renal physiology and pathophysiology has been increasingly appreciated.

RBF is dictated by the transrenal pressure difference, that is, the difference between renal arterial pressure and renal venous pressure [15*]. Hence, systemic hypotension and impaired CO typically reduce RBF and the hydraulic driving pressure in the glomerular capillaries required to maintain GFR. Yet, AKI is commonly seen despite prompt restoration of CO and mean arterial pressure (MAP) with inotropes, intravenous fluids and vasopressors. Under such circumstances, the effect of central venous pressure, which translates into renal venous pressure, on glomerular hemodynamics requires attention.

Increased central venous pressure (CVP) is associated with AKI progression in different subgroups of patients. In 137 septic patients, CVP but not CO or MAP was independently associated with new or persistent AKI [16]. Importantly, a linear

**KEY POINTS**

- Fluid volume overload may contribute to acute kidney injury development by inducing renal compartment syndrome, renal venous congestion and impaired renal tissue oxygenation.
- According to recent high-level evidence, the use of goal-directed fluid therapy does not attenuate the risk of acute kidney injury.
- Fluid resuscitation with albumin solutions is well tolerated in patients at risk of acute kidney injury due to sepsis or after major surgery.
- Among crystalloids, balanced solutions do not improve renal outcomes in low-to-intermediate risk patients compared with 0.9% sodium chloride.
- The effect of balanced crystalloids vs. 0.9% sodium chloride on renal outcomes in high-risk patients is currently under investigation.

**Does fluid volume overload affect the occurrence of acute kidney injury?**

Excessive fluid administration causing fluid overload has been associated with AKI development in large observational studies [9,10*]. We suggest three potential mechanisms by which excess fluid may lead to renal injury and dysfunction: renal compartment syndrome (RCS), renal venous congestion, and a negative impact on renal oxygenation.

**Renal compartment syndrome**

Major surgery, trauma and sepsis are associated with endothelial dysfunction, glycocalyx breakdown and leakage of plasma water into interstitial compartments causing tissue edema [11]. As the kidneys are enclosed in a semi-rigid fascia (Gerota’s fascia) with minimal ability to accommodate volume changes, intrarenal volume expansion will ultimately lead to raised interstitial tissue pressure and, in severe cases, RCS.
relationship between CVP greater than 12 mmHg and the probability of new or persistent AKI was observed. Similarly, in 107 patients with septic shock and a low prevalence of chronic cardiac diseases (<10%), greater mean CVP during the initial 24 h in ICU was associated with worsening AKI independent of MAP, vasopressor dose and illness severity [17**]. Moreover, in patients with chronic cardiac disease undergoing right heart catheterization, CVP greater than 12 mmHg was associated with progressively lower estimated GFR independent of cardiac index (CI) [18]. Finally, CVP rather than systemic BP or CI was associated with worsening renal function in patients with acute decompensated heart failure [19]. In their aggregate, these studies suggest that venous congestion is a major risk factor for AKI across a wide spectrum of diseases and CO states. Hence, the transrenal pressure difference should be considered when assessing patients with or at risk of AKI. Accordingly, we suggest that fluid removal rather than continuing fluid resuscitation should be considered when CVP exceeds 12 mmHg in patients with worsening kidney function.

**Fluid administration and renal oxygenation**

Renal tissue oxygenation depends on the relationship between oxygen delivery (RBF) and oxygen consumption. Most oxygen is consumed during active tubular reabsorption of filtered sodium via Na/K ATPase. Hence, if RBF and GFR increase so will sodium filtration and, to a similar extent, oxygen consumption. Consequently, oxygen extraction will be kept constant over a wide range of RBF and GFR.

Although fluid therapy may enhance RBF and GFR, its effect on renal oxygen delivery, consumption and tissue oxygenation are difficult to predict for several reasons. First, fluid administration may attenuate or even decrease oxygen delivery due to hemodilution. Second, with increased sodium filtration, reabsorptive work and oxygen consumption will increase. Finally, stressed tubular cells consume more than twice the amount of oxygen than the healthy kidney to reabsorb the same amount of sodium [20].

The idea that fluid administration compromises renal tissue oxygenation is supported by animal data showing impaired tissue oxygenation following hemorrhagic shock despite restoration of CO, RBF and hematocrit using fluid administration and red blood cell transfusion [21–23]. In keeping with such experimental data, plasma volume expansion with crystalloids or colloids failed to improve renal oxygenation following uncomplicated cardiac surgery. In fact, hemodilution in the setting of increased GFR and sodium reabsorption significantly increased oxygen extraction after crystalloid therapy suggesting oxygen supply-demand mismatch [24**].

**Fluid overload and renal outcomes**

Progressive fluid accumulation is frequently observed in critically ill and postoperative patients during the first days of intensive care management. In such patients, greater fluid accumulation is associated with higher AKI prevalence [9,10]. However, sicker patients receive more fluids and are also more likely to develop AKI from the underlying acute illness. Hence, a causal relationship between fluid accumulation and AKI cannot be established from such observational data. On the contrary, the impact of restrictive vs. liberal fluid management on AKI development has not been systematically explored in an RCT.

The best available evidence comes from the Fluid and Catheter Treatment Trial (FACTT) comparing two different fluid management strategies in 1000 patients with acute lung injury [25]. A marked difference in mean cumulative fluid balance was achieved after 1 week in that study: 136 ml in the conservative-strategy group and 6992 ml in the liberal-strategy group (Fig. 1). However, despite significant fluid accumulation in the liberal group patients, their mortality (primary outcome) and the number of renal failure-free days or need for renal replacement therapy (RRT) were not significantly different from the conservative group patients. On the contrary, serum creatinine normalized more rapidly in the liberal group and, consequently, more liberal group patients developed AKI defined as an absolute rise in creatinine of more than 0.3 mg/dl or a relative change of more than 50% over 48 h [26] (Fig. 1).

However, as serum creatinine is distributed throughout the total body water (TBW), its performance as a marker of AKI is limited during progressive fluid balance changes. For example, creatinine will be diluted when TBW expands during fluid accumulation. Consequently, unless the serum creatinine level is adjusted for changes in TBW, AKI will be misdiagnosed. In fact, in a secondary analysis of the FACTT trial, the fluid balance-adjusted AKI prevalence was higher in the liberal group (Fig. 1). Significantly, such adjusted AKI was more strongly associated with RRT and mortality than unadjusted AKI [26].

**DOES GOAL-DIRECTED FLUID RESUSCITATION AFFECT THE OCCURRENCE OF ACUTE KIDNEY INJURY?**

The rationale for goal-directed hemodynamic therapy is to achieve optimal organ perfusion and
oxygen delivery as soon as possible using the best combination of vasopressors, inotropes and fluids. When effective, such therapy should reduce unnecessary fluid administration both in the short and in the longer term.

Since the publication of Rivers’ landmark article in 2001 [27], three large multicenter randomized controlled trials have assessed the utility of early goal-directed therapy (GDT) in patients with septic shock admitted to emergency departments (EDs) in Australasia [the Australasian Resuscitation in Sepsis Evaluation (ARISE) trial [28]], USA [the Protocolized Care for Early Septic Shock (ProCESS) trial [29]] and the UK [the Protocolised Management in Sepsis (ProMISe) trial [30]].

The ARISE, ProCESS and ProMISe trials all failed to demonstrate that early GDT improves survival compared with nonprotocolized standard resuscitation. Furthermore, early GDT did not affect the need for RRT in any of the trials. The lack of effect of fluid resuscitation in sepsis is further supported by recent studies that highlight the lack of a sustained independent hemodynamic effect [31,32].

Two recent RCTs assessed the impact of GDT on renal outcomes following major noncardiac surgery. The largest study, the Optimisation of Cardiovascular Management to Improve Surgical Outcome trial, randomized 734 patients undergoing major gastrointestinal surgery to a CO-guided algorithm (GDT group) during and 6 h following surgery or to usual care [33]. During the intervention period, the administered volumes of intravenous fluids were similar in the two groups (median 4190 ml in the GDT group vs. 4024 ml in the usual care group). AKI, which was defined as a doubling of serum creatinine or sustained oliguria less than 0.5 ml/kg/h for 12 h, occurred in 17 (approximately 5%) patients in each group.

In the more recent single-center Goal Directed Hemodynamic Management and Renal Outcome After Major Noncardiac Surgery (IROM) trial [34*], changes in creatinine after major abdominal surgery were assessed in 180 patients randomized to PICCO-guided GDT or usual care. Since PICCO measurements were done in the usual care group (but results blinded to the treating doctor), it was possible to compare the hemodynamic effects of the GDT-algorithm vs. usual care. Significantly, the time in hemodynamic target range (global end-diastolic index >640 ml/m², mean arterial pressure >70 mmHg,

FIGURE 1. Mean cumulative fluid balance (top left), serum creatinine (top right), unadjusted AKI prevalence (bottom left) and AKI prevalence adjusted for fluid balance (bottom right) in the FACTT trial. Adapted with permission from [25].
CI > 2.51/min/m², and extravascular lung water index \( \leq 10\) ml/kg) showed minimal differences between the two groups. Furthermore, the total amount of perioperative fluid [Ringer’s acetate and/or hydroxyethyl starch (HES)] administered did not differ significantly (Table 1). Therefore, as could be expected, the IROM trial failed to demonstrate a difference in AKI prevalence between the two groups. Such findings also call into question the value or meaning of so-called maintenance fluid therapy in patients who have no evidence of or trigger for volume depletion [35].

### DOES THE CHOICE OF RESUSCITATION FLUID AFFECT THE OCCURRENCE OF ACUTE KIDNEY INJURY?

In addition to the timing and volume of fluid resuscitation, the choice of resuscitation fluid may have important consequences for renal outcomes.

#### Synthetic colloids and acute kidney injury

All synthetic colloids can potentially cause nephrotoxic injuries. Although the mechanism is not fully understood, tubular uptake of colloid particles causing vacuolization, swelling of the cytoplasm (so-called osmotic nephrosis) and tubular dysfunction have been associated with the administration of synthetic colloids [36].

The use of HES has decreased dramatically [7,8] since the publication of two large RCTs, the Crystalloid vs. Hydroxyethyl Starch Trial and the Scandinavian Starch for Severe Sepsis/Septic Shock trial, showing higher need for RRT with HES than with crystalloid solutions (Table 2) [37,38].

Furthermore, observational data suggest that administration of gelatin and dextran solutions contributes to osmotic nephrosis-induced AKI in critically ill patients and following major surgery [39,40].

Given their established side-effect profile including renal injuries, their lack of clinically relevant advantages, the absence of patient-centered benefits and their greater cost, we suggest that fluid resuscitation with artificial colloids should be avoided in patients with AKI or risk thereof.

#### Chloride-rich solutions and acute kidney injury

‘Normal’ 0.9% sodium chloride used to be the dominant resuscitation fluid worldwide. However, due to emerging evidence suggesting that chloride-rich solutions may cause harm, the use of ‘balanced’ salt solutions has increased over the last few years [41,42].
In some recent observational studies, infusion of chloride-rich solutions was associated with a higher occurrence rate of AKI and need for RRT than infusion of balanced solutions [43,44]. Additional experimental studies suggest that chloride-rich solutions decrease RBF and GFR via tubule-glomerular feedback-activation [14]. Yet, the evidence is not consistent, and other observational studies have failed to confirm such associations [45].

Faced with such uncertainty, the Saline vs. Plasma-Lyte 148 for ICU Fluid Therapy (SPLIT) investigators allocated 2278 ICU patients requiring crystalloid fluid therapy to a buffered crystalloid (Plasma-Lyte-148) or 0.9% sodium chloride in a randomized-crossover trial [46,47]. In that trial, a similar proportion of patients in the two groups developed moderate-to-severe AKI (approximately 9%), and only about 3% in each group required RRT. It should, however, be noted that the average ICU length of stay in SPLIT was less than two days. In addition, illness severity was relatively low (mean APACHE II score 14). Finally, only a median of 2 litres of study fluid was administered during the intervention period. Therefore, the question whether 0.9% sodium chloride or balanced crystalloid should be preferred in sicker patients being exposed to greater fluid volumes during an extended period of time in ICU remains unanswered.

A sequel to SPLIT and following a pilot preparation program [48], The Plasma-Lyte-148 vs. Saline (PLUS) trial, will hopefully provide a definite answer to the question. The PLUS trial is a prospective, multicenter, parallel group, blinded, RCT aiming to enroll 8800 critically ill patients requiring fluid resuscitation. In addition to investigate whether Plasma-Lyte-148 decreases 90-day mortality (primary outcome) compared with 0.9% sodium chloride, the effect on kidney function and RRT requirement will be assessed (ClinicalTrials.gov identifier: NCT02721654). Until the results of the PLUS trial have been published, we suggest that chloride-rich solutions should be used with caution in patients with a reduced renal reserve.

### Albumin solutions and acute kidney injury

Hypoalbuminemia (here defined as a serum albumin concentration below 30 g/l) has been associated with AKI in various patient populations [49]. This is unsurprising given that hypoalbuminemia is marker of illness severity and that albumin has anti-inflammatory properties, anticoagulant effects, scavenge reactive oxygen species and contributes to the integrity of the endothelial surface layer.

Albumin is also responsible for maintaining the plasma colloid osmotic pressure. Therefore,
administration of albumin solutions to maintain normal or near normal serum albumin levels in critically ill and surgical patients appears to be a logical therapeutic approach.

Yet the clinical benefits of resuscitation with albumin solutions have not been confirmed. For example, in the Saline vs. Albumin Fluid Evaluation study, resuscitation with 4% albumin did not reduce mortality or duration of RRT compared with 0.9% sodium chloride despite lower cumulative fluid balance in the albumin group (Table 2) [50].

Small-volume resuscitation with concentrated (20–25%) albumin solutions may provide benefits. A theoretical advantage includes a greater volume-expanding effect per volume infused due to restoration of the plasma colloid oncotic pressure and recruitment of interstitial fluid back into the circulation [51]. However, although this approach could potentially reduce organ edema and appears well tolerated [52*], the effect-duration is unknown. In septic patients, daily administration of 20% albumin to maintain serum albumin at least 30 g/l reduced cumulative fluid balance compared with the use of crystalloids. However, such albumin replacement did not reduce mortality, AKI or the need for RRT [53**].

In contrast, in patients with a serum albumin level less than 40 g/l before undergoing off-pump coronary artery bypass surgery, preoperative administration of 20% albumin markedly reduced postoperative AKI (17.6 vs. 31.7% in patients not receiving albumin) [54*].

CONCLUSION

To date, several large RCTs have assessed the impact of different fluid management strategies on patient-centered outcomes including the development of AKI. In response to high-level evidence demonstrating nephrotoxic effects of artificial colloids, the consumption of such fluids has declined in recent years. The optimal fluid choice for resuscitation of patients at risk of AKI remains, however, uncertain. Balanced solutions are not superior to 0.9% sodium chloride in patients at low-to-moderate risk. In contrast, 20% albumin may attenuate cardiac surgery-associated AKI if administered preoperatively in patients with an albumin concentration below 40 g/l. This utility of small-volume resuscitation with concentrated albumin needs, however, to be confirmed in RCTs.

Acknowledgements

None.
Cardiovascular anesthesia


This randomized controlled trial assessed renal oxygenation indices following a fluid bolus of Ringers-acetate or Venofundin after cardiac surgery in 30 patients. Due to hemodilution, both fluids failed to improve renal oxygen delivery despite increased renal blood flow. Increased glomerular filtration rate following Ringers-acetate bolus was associated with impaired renal oxygenation.


29. This trial compared early goal-directed resuscitation vs. usual care in 1260 septic patients requiring crystalloid fluid therapy. No significant differences in mortality or duration of renal replacement therapy were found.


This trial compared three resuscitation strategies in patients admitted to the ED in the United States: protocol-based early goal-directed therapy, protocol-based standard therapy and usual care. No significant differences in mortality or need for organ support were found.


This trial compared early goal-directed therapy with usual care in 1260 septic shock patients admitted to the ED in England. Early goal-directed therapy group patients had greater Sequential Organ Failure Assessment score at 6 and 72 h, were more likely to receive advanced cardiovascular support, and stayed longer in the ICU. No significant differences in mortality or renal replacement therapy were found.


This trial found similar postoperative changes in serum creatinine in patients undergoing major abdominal surgery randomized to goal-directed therapy or standard care. No significant differences in mortality or need for organ support were found.


This point-prevalence study conducted in 49 ICUs in Australia and New Zealand found that 62% of patients received maintenance fluid on the study day and that such maintenance fluid accounted for one-third of total daily fluid input.


This double-blind, cluster randomized, double-crossover trial compared 0.9% sodium chloride with Plasma-Lyte 148 in patients requiring crystalloid fluid therapy in the ICU. No difference in Risk, Injury, Failure, Loss of function and End-stage kidney disease (RIFLE) AKI incidence or use of renal replacement therapy was found.


This is the largest randomized controlled trial exploring the efficacy of 20% albumin infusion to maintain a serum albumin level of at least 30 g/l in patients with severe sepsis. This intervention did not improve survival or renal outcomes.


This randomized trial demonstrated that postoperative AKI incidence in hypoalbuminemic patients receiving a 20% albumin solution before coronary artery bypass graft surgery.