



Fluid resuscitation for acute kidney injury: an empty promise

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Purpose of review

The past decade has seen more advances in our understanding of fluid therapy than the preceding decades combined. What was once thought to be a relatively benign panacea is increasingly being recognized as a potent pharmacological and physiological intervention that may pose as much harm as benefit.

Recent findings

Recent studies have clearly indicated that the amount, type, and timing of fluid administration have profound effects on patient morbidity and outcomes. The practice of aggressive volume resuscitation for 'renal protection' and 'hemodynamic support' may in fact be contributing to end organ dysfunction. The practice of early goal-directed therapy for patients suffering from critical illness or undergoing surgery appears to offer no benefit over conventional therapy and may in fact be harmful. A new conceptual model for fluid resuscitation of critically ill patients has recently been developed and is explored here.

Summary

The practice of giving more fluid early and often is being replaced with new conceptual models of fluid resuscitation that suggest fluid therapy be 'personalized' to individual patient pathophysiology.

Keywords

acute kidney injury, fluid overload, fluid resuscitation, goal-directed fluid therapy, early goal-directed fluid therapy

INTRODUCTION

Acute kidney injury (AKI) is a common and serious complication affecting more than half of the patients admitted to the intensive care unit (ICU) as well as hospitalized and postsurgical patients [1[•],2]. The mainstay of prevention and treatment of AKI has been intravenous fluid therapy with the rationale being that fluid therapy augments cardiac output (CO), maintains urine flow, and dilutes nephrotoxic substances, thus minimizing ischemic and toxic insults to the kidney [3]. Fluid therapy has been the first step in the management of hemodynamic compromise, low urine output, and AKI since the use of an alkalized salt solution for the treatment of cholera was described in 1832 [3,4]. Over the last few years, this decade-old practice has been increasingly called into question with many recognizing the deleterious effects of excess volume administration [3,5,6]. Relatively small positive fluid balances of 5–10% of body weight have been associated with organ dysfunction and poor clinical outcomes in the critically ill and after routine surgery [7–9]. Benefits of fluid resuscitation are

short-lived and limited to the early stage of select disease states such as sepsis, whereas fluid restrictive strategies appear to pose no increased risk of AKI. In addition to the harm posed by excess fluid, certain types of fluid appear to impair renal function independent of the quantity administered [10[•],11,12]. This review seeks to shed new light on recent advances involving fluid therapy and kidney function that stand to change a practice that has seen little change in decades.

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KEY POINTS

- Evidence is mounting that the practice of **aggressive fluid** therapy with the intent of improving end organ perfusion and function is **misguided** and in fact may lead to fluid overload and **further end organ injury**.
- After the **initial acute phase of illness**, **additional fluids** are **unlikely** to **augment CO** and tissue perfusion and may in fact contribute to **worsening** organ dysfunction.
- **GDT** or protocol-based fluid therapy offers **no benefit** over conventional fluid therapy that maintains organ perfusion and avoids fluid overload.
- The composition, quantity, and timing of fluid therapy should be **personalized** to each patient based on the patient's unique physiological response to fluids.

REVIEW

Fluid therapy for acute kidney injury

There is increasing recognition that intravenous fluids are not inert substances but potent drugs with complex pharmaco-therapeutic actions [4,13]. The hemodynamic 'half-life' of intravenous fluids is short-lived, with **only ~20% of intravenous fluids remaining in the intravascular compartment after 90 min** under **normal physiological conditions**, and as little as **5% in disease states** such as sepsis [14,15]. Despite the absence of data supporting its benefit and increasing evidence suggesting harm, fluid therapy remains a key component of the prevention and treatment of AKI [3,16,17]. The belief that infusions of large volumes of intravenous fluids can improve organ perfusion and prevent or treat AKI is not supported by data and does not reflect the complex nature of AKI [3,16,17]. Over the last decade, numerous clinical studies [3,18–27] have demonstrated harm from **excess fluids and benefit from removal** of excess fluids in outcomes in patients with AKI. Evidence is mounting that the practice of aggressive fluid therapy with the intent of improving end organ perfusion and function is misguided and in fact may lead to fluid overload and further end organ injury.

Fluid volume and acute kidney injury

Clinical dogma has long dictated that fluids were the treatment of choice for maintaining adequate renal perfusion and ensuring urine output in patients with or at risk of AKI [28[•]]. This traditional **dogma** is **challenged** by increasing evidence that leaves little doubt that **fluid overload is associated with AKI**, prolonged ICU stay, development or

worsening of organ dysfunction, and excess mortality [7,8,29–35,36[•],37,38]. The causality link between fluid overload and AKI remains less clear, in part because the effects of both AKI and fluid overload are similar and the fact that fluid overload frequently accompanies AKI regardless of cause [6]. **Endothelial dysfunction** appears to be the **underlying nephrotoxic effect** of fluid overload. **Alteration and breakdown** of the endothelial **glycocalyx** causes an increase in vascular fluid capacitance, capillary leak, and interstitial edema, creating a vicious cycle in which intravascular depletion leads to the need for intravascular volume expansion, but fluid replacement leads to worsening edema and volume overload [3]. **Disruption** of the endothelial **glycocalyx** has been demonstrated in **numerous disease processes** including **sepsis, surgery, trauma, and postischemic states** [39^{••},40–44]. Increasing interstitial edema and fluid overload impair renal perfusion by **increasing renal venous pressure, extra-renal compression, and renal interstitial pressure**, which ultimately **decrease** the **glomerular ultrafiltration gradient** [3]. Fluid overload may lead to visceral edema and intra-abdominal hypertension (**IAH**), which has been linked to AKI [45,46]. Intra-abdominal pressures are **transmitted** to the **encapsulated** kidney, causing an elevation in **intra-capsular pressure** and a **decrease** in renal blood flow and glomerular filtration rate [46]. In addition to the evidence linking fluid overload to AKI, there is evidence that **avoidance of fluid overload** may be associated with **lower** need for **renal replacement** therapy, a lower incidence of AKI, increased survival from septic shock, and AKI treated with renal replacement therapy [30,32,47]. The evidence would suggest that fluid overload might be a preventable source of renal morbidity and patient mortality [28[•]].

Fluid type and acute kidney injury

In addition to the volume of intravenous fluid administered, the **type of fluid** appears to impact renal function and may contribute to AKI. The **most common intravenous fluid** administered to patients worldwide is isotonic **saline** (0.9% salt solution) [4,5]. Isotonic saline's popularity remains despite increasing **evidence** linking it to a **greater risk of AKI, morbidity, and death** when compared with other **balanced** electrolyte solutions [48,49[•]]. A recent meta-analysis of 21 studies found a significantly higher risk of AKI, renal failure, metabolic acidosis, blood transfusion, and duration of mechanical ventilation in patients receiving **high-chloride** fluid resuscitation [10^{••}]. Two recent propensity matched studies [50,51], one involving

adult cardiac surgery patients and another involving adults with sepsis, demonstrated an increased risk of mortality associated with hyperchloremic fluids. The mechanism of harm from isotonic saline appears to result from its ability to cause hyperchloremia and metabolic acidosis [52–54]. The increased chloride load results in constriction of the afferent renal arteries, a reduction in renal arterial flow, and a reduction in renal cortical tissue perfusion, even when administered to healthy volunteers [55,56]. Isotonic saline is not the only fluid type linked to patient morbidity and mortality. Results from several large studies [11,57–61] using 6% hydroxyethyl starch for resuscitation of septic and critically ill patients demonstrated an increase in AKI and/or use of renal replacement therapy leading to restriction in its use. Conversely, evidence suggests that fluid resuscitation with 4% albumin solution is safe, except for patients with traumatic brain injury, and poses no increased risk of AKI or nephrotoxicity [12].

The false promise of early goal-directed therapy

In 2001, a single-center, randomized control trial (RCT) of protocol-based resuscitation for patients with septic shock led to the widespread adoption of ‘early goal-directed therapy’ (EGDT) for the management of sepsis [62]. Despite the inability of follow-up studies to reproduce and validate EGDT, it was incorporated into the Surviving Sepsis Campaign (SSC) guidelines in 2004 [63]. Recently, the SSC revised their guidelines and removed recommendations for aggressive fluid administration based in part on the results of several large RCTs demonstrating no outcome benefit to aggressive fluid administration [64,65,66,67]. The SSC guidelines had previously recommended aggressive fluid administration targeting a central venous pressure (CVP) of greater than 8 mmHg, but that level of CVP may decrease renal blood flow and has been associated with an increased risk of AKI and mortality [68–70]. In addition, up to half of septic patients have been found to be ‘nonresponders’ to fluid therapy and thus receive no benefit from fluid administration [5]. Recently, another systematic review and meta-analysis [71**] found no benefit in outcomes with EGDT for patients in septic shock.

The reported benefits of EGDT in septic patients have led numerous groups to extrapolate goal-directed hemodynamic therapy to other patient populations, most notably surgical patients. In a meta-analysis of 24 studies of GDT during surgery, Prowle *et al.* [72] found that GDT was associated with lower incidence of AKI, but only in studies in

which the amount of fluid administered in the GDT group did not exceed the control group and the GDT group incorporated inotropic medications. The authors concluded that the observed reduction in AKI was a function of maintenance of CO, that is, renal perfusion, and avoidance of fluid overload, that is, renal injury [72].

New strategies for fluid therapy

Recognizing that a large percentage of patients are subjected to inappropriate fluid therapy, the Acute Dialysis Quality Initiative (ADQI) recently sought to establish a new model for evidence-based fluid therapy [73]. The ADQI used expert consensus to develop a new model for the resuscitation of critically ill patients consisting of four distinct phases: Rescue, Optimization, Stabilization, and De-escalation [73] (see Fig. 1 and Table 1). During the Rescue phase, fluid is administered as boluses to support acute life-threatening hemodynamic instability, for example, uncompensated shock. Once the patient is no longer at risk for acute decompensation, for example, compensated shock, additional fluid is titrated carefully using fluid challenges to Optimize end organ perfusion and CO. Once the patient has Stabilized, that is, no longer in state of compensated or uncompensated shock, fluids are minimized to achieve a fluid steady state. The final phase, De-escalation, aims to remove excess fluid and minimize additional harm. The Rescue, Optimization, Stabilization, and De-escalation fluid model reflects the current understanding that beyond the initial acute phase of illness, additional fluids are unlikely to augment CO and tissue perfusion and may in fact contribute to worsening organ dysfunction [73].

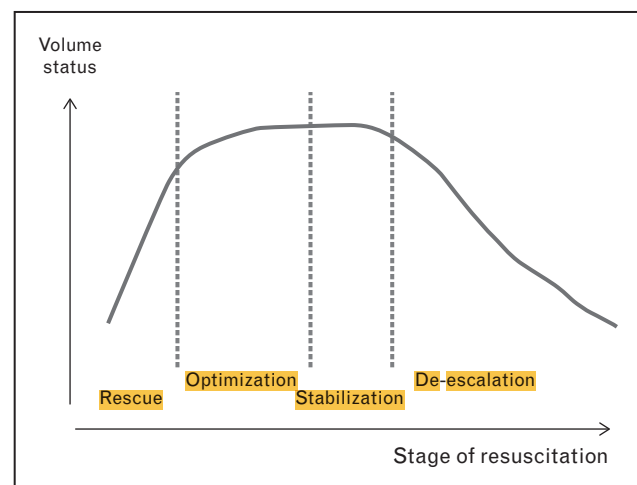


FIGURE 1. Volume status at different stages of resuscitation. Reproduced with permission from ADQI (www.ADQI.org).

Table 1. Clinical characteristics of the four stages of resuscitation

	Rescue	Optimization	Stabilization	De-escalation
Strategy	Patient rescue	Organ rescue	Organ support	Organ recovery
Therapeutic goals	Correct shock	Tissue perfusion	Zero or negative fluid balance	Mobilization of accumulated fluid
Time	Minutes	Hours	Days	Days to weeks
Patient condition	Extremis	Unstable	Stable	Recovering
Fluid therapy	Rapid boluses	Careful titration and fluid challenges	Minimal and maintenance fluids	Avoidance

Reproduced from Hoste *et al.* [73].

Although it is increasingly clear that aggressive fluid administration is not beneficial, determining what constitutes the optimal fluid resuscitation strategy for each patient is less clear and a ‘one size fits all’ strategy is unlikely to be found. In the future, fluid therapy may need to be ‘personalized’ for each patient using a host of patient-specific targets and physiological values to determine the optimal volume, type, and timing of fluid to administer or restrict [74[■]].

CONCLUSION

Intravenous fluids are routinely administered with the clinical intent to increase mean arterial pressure and CO in an effort to improve renal perfusion pressure and renal blood flow, respectively. Unfortunately, the tools needed to guide appropriate fluid resuscitation are unreliable at best or simply not available [3,75]. Without tools to guide fluid titration, fluid accumulation (fluid overload) will occur as frequent boluses and/or continuous infusions are administered to achieve short-lived hemodynamic effects [76–78]. With increasing evidence linking fluid overload to end organ dysfunction, the focus of fluid resuscitation will likely shift from aggressive fluid replacement to one of aggressive prevention of fluid overload. Future research is needed to determine the best strategies for personalizing fluid therapy to patient and disease processes.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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