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Fluid Overload in AKI - Epiphenomenon or Putative Effect on Mortality?

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Abstract

Purpose of review—The incidence of acute kidney injury (AKI) is increasing dramatically, and despite advances in dialytic therapy and critical care, there has been little improvement in associated morbidity and mortality. Recently, several articles have suggested that fluid overload in patients with AKI is associated with an increased risk of death.

Recent findings—Observational studies have demonstrated an association between fluid overload and poor outcomes (including death) in patients with AKI; however, whether this association is causal or due to residual confounding is unknown. A recent study testing the impact of fluid overload and diuretics on outcomes in the context of a randomized controlled trial suggests that the beneficial impact of diuretics in those with AKI is mediated by reducing fluid overload. Finally, potential mechanisms by which fluid overload may contribute to death include failure to recognize AKI due to creatinine dilution, direct tissue edema leading to decreased renal perfusion, and an increased risk of other complications such as sepsis.

Summary—Based on the current literature, the relative contributions of the direct effects of fluid overload versus the association of fluid overload with other patient characteristics associated with adverse outcome (e.g., sepsis) remain unknown. Additional human studies, including randomized controlled trials, are warranted to further clarify these issues.

Keywords

Acute kidney injury; fluid overload; renal replacement therapy; intra-abdominal hypertension

Introduction

When AKI is a complication of systemic illness, fluid administration is often considered essential to prevent hemodynamic and nephrotoxic insults that might further compromise renal function. A long-standing tenet of AKI management has promoted volume resuscitation in response to hypotension and oliguria to augment cardiac output and urine output, respectively. The benefit of this approach is challenged, however, by increasing evidence suggesting that fluid overload is associated with impaired organ function (reviewed in [1]). Organ dysfunction is thought to be at least partially mediated by organ edema, which distorts tissue architecture, impairs oxygen and metabolite diffusion, and obstructs capillary flow and lymphatic drainage. These effects are particularly pronounced in encapsulated

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Conflicts of Interest
There are no relevant conflicts of interest.

organs such as the kidney, which cannot accommodate additional volume without significant increases in interstitial pressure and compromised blood flow. The deleterious effects of organ edema have been best demonstrated in the lung, where restrictive fluid management strategies have been associated with improved oxygenation and shortened duration of mechanical ventilation [2–5]. Subsequently, attention has turned to the impact of fluid overload on outcomes such as mortality and recovery of renal function in patients with AKI; whether or not the association of fluid overload with adverse outcomes is due to direct effects of fluid overload itself or due to indirect associations between fluid overload and other disease states associated with adverse outcomes is unknown and is the subject of this review.

Fluid overload is associated with adverse outcomes in children with AKI

The association between fluid overload and mortality was first observed in critically ill children with AKI requiring renal replacement therapy (RRT) [6–8]. Recently, Sutherland and colleagues reported data from the Prospective Pediatric CRRT Registry, the largest cohort of critically ill children receiving continuous RRT [9]. In the 297 patients studied, percent fluid overload was calculated from ICU admission to RRT initiation using fluid intake and output data and divided into three strata based on percent increase in body weight: <10%, 10–20%, and ≥20%. In univariate analyses, patients with ≥20% fluid overload had higher mortality than patients with either 10–20% fluid overload or < 10% fluid overload ($p<0.001$). In a multivariate logistic regression model controlling for severity of illness, fluid overload remained independently associated with mortality (odds ratio [OR] 1.03 per 1% increase in fluid balance, 95% confidence interval [CI] 1.01–1.05).

Fluid overload is associated with adverse outcomes in adults with AKI

Four recent studies have examined the impact of fluid overload on outcomes in adults with AKI. In the first of these, Payen and colleagues suggested that fluid overload was an independent risk factor for death in critically ill patients with AKI and sepsis [10]. Bouchard and colleagues subsequently examined the association of fluid overload and outcomes in adults using the Program to Improve Care in Acute Renal Disease (PICARD) cohort, a cohort of 618 critically ill patients with AKI requiring nephrology consultation [11]. Fluid balance in the three days preceding nephrology consultation was expressed as a percentage relative to the hospital admission weight, with fluid overload defined as an increase of > 10%. Mortality at 30 days, 60 days, and hospital discharge, as well as APACHE III score, number of failed organ systems, need for mechanical ventilation, and incidence of sepsis, were all significantly higher in patients with fluid overload. In patients requiring RRT, the OR for death associated with fluid overload was 2.07 and 2.52 at dialysis initiation and cessation, respectively, after adjusting for initial dialysis modality and for APACHE III score. In non-dialyzed patients, the adjusted OR for death associated with fluid overload at AKI diagnosis was 3.14 after adjusting for APACHE III score only. Mortality was proportional to both the degree and duration of fluid overload.

The most recent study in the literature is a retrospective analysis of data from subjects enrolled in ANZICS-RENAL, a large, randomized clinical trial of dose of dialysis in patients with AKI [12, 13]. In this study, positive fluid balance during ICU admission was again associated with an increased risk of death, even after adjustment for severity of illness and other clinical factors associated with an increased risk of death (OR 3.14, $p < 0.0001$). Positive fluid balance was also associated with a decreased number of RRT-free days, ICU-free days and hospital-free days. Of note, the mean SOFA cardiovascular score was higher in those with positive fluid balance, suggesting that there may be important hemodynamic differences between patients who are able to achieve negative fluid balance and those patients who remain in positive fluid balance. Furthermore, this finding highlights the

importance of future studies to better characterize the impact of extracorporeal fluid removal on hemodynamics and hemodynamic stability; such studies will be critical for the design of clinical trials to test the impact of fluid removal and fluid balance on patient outcomes.

While most studies examining fluid overload in AKI have focused on mortality as the primary outcome, the association between fluid overload and renal recovery also remains elusive. Episodes of AKI increase the risk for future chronic kidney disease or end stage renal disease, and 10–30% of patients with dialysis-requiring AKI remain dialysis dependent at discharge [14, 15]. Non-modifiable risk factors, such as pre-morbid creatinine, age, and comorbidities have been identified as predictive factors in the recovery of renal function, but studies investigating modifiable risk factors, such as fluid balance, have been lacking.

To address this, Heung and colleagues recently performed a retrospective analysis of 170 patients with AKI presumed due to acute tubular necrosis who required at least one inpatient dialysis treatment [16]. Percent fluid overload was calculated using patient weights at dialysis initiation and at baseline, defined as the average outpatient weight within 3 months of hospitalization, the patient's self-reported weight, or the hospital admission weight. Renal recovery was defined as discontinuation of RRT for at least two consecutive weeks.

Within 1 year of RRT initiation, 35.9% of patients recovered renal function. In multivariate regression analysis, an increase in percent fluid overload at RRT initiation remained a significant negative predictor of renal recovery (hazard ratio [HR] 0.97, CI 0.95–1.0, $p = 0.024$). Consistent with previous studies, in the multivariate analysis for mortality, fluid overload was associated with a lower likelihood of survival (OR 0.96, CI 0.92–0.99, $p = 0.010$). This study contrasts that of Bouchard, in which an association between fluid overload at the time of AKI diagnosis and recovery of renal function was not observed; this might be explained by the significantly longer follow-up period of the current study.

These studies highlight the inherent difficulties in drawing conclusions from observational studies of fluid balance and mortality. For example, in the Bouchard study, fluid overload was associated with both adverse outcomes (e.g., mortality) as well as risk factors for mortality (e.g., APACHE III score, presence of multi-organ failure, and sepsis). Even though the analyses were adjusted for severity of illness and need for RRT, residual confounding likely exists in the association between fluid overload and mortality; that is, adjustment for APACHE III score alone may be insufficient to account for differences between subjects who are fluid overloaded and those who are not. Nonetheless, this study demonstrated that the progression, duration, and correction of fluid overload are important factors associated with mortality and likelihood of renal recovery.

Residual confounding is also an inherent problem with observational studies of therapies to prevent or mitigate fluid overload in critically ill patients with AKI. Although fluid restriction is often impractical given obligate fluid intake from intravenous medications and the provision of adequate nutrition, diuretics are often used in the setting of AKI to enhance urine output and minimize positive fluid balance. However, the literature regarding the use of diuretics to reduce the severity or duration of AKI or to prevent the need for RRT is at best inconsistent [17–22].

Diuretics and fluid management in AKI

The FACTT trial was a multi-center randomized controlled trial evaluating a conservative versus liberal fluid management strategy in patients with acute lung injury along with the use of a pulmonary artery catheter versus central venous catheter for hemodynamic monitoring [2, 23]. The conservative fluid management strategy reduced fluid overload and duration of mechanical ventilation without increasing the need for RRT. Because fluid and

diuretic management were determined by randomization and hemodynamic measures, the FACTT trial offers an opportunity to analyze the relationship between fluid status, diuretics, and outcomes without the usual confounding seen in observational studies. In a secondary analysis, Grams et al. [24] attempted to differentiate the impact of fluid overload from the impact of diuretic administration on mortality in patients who developed AKI within 2 days of study enrollment (N = 306). Over the 7-day study period, patients with AKI in the fluid conservative group received more furosemide than in the fluid liberal group (562 mg/d versus 159 mg/d) and had less cumulative fluid accumulation (3.7L versus 10.2L). In univariate analysis, factors significantly associated with mortality included stage of AKI, mean CVP, mean daily fluid balance, early oliguria, and need for RRT, while a higher mean furosemide dose was negatively associated with mortality. In multivariate analyses, positive fluid balance remained significantly associated with 60-day mortality after adjustment for numerous covariates, and the association was unaffected by adjustment for post-AKI furosemide dose. The post-AKI furosemide dose was also significantly associated with decreased mortality in the full model, but the association was no longer significant after adjustment for post-AKI fluid balance. This suggests that fluid balance is a causal intermediate in the association between diuretics and mortality; i.e., the benefit derived from furosemide is from the reduction in fluid overload (summarized in Table 1). Although these results are less affected by the confounding that is often present in observational studies, this study used a very specific patient population, which may limit its generalizability. Furthermore, in the FACTT trial, patients had to be shock-free for 12 hours prior to the administration of diuretics, so the safety, tolerability and clinical impact of diuresis in patients with shock requiring vasopressors, a common situation in clinical practice, was not clarified by this study.

Impact of fluid overload on AKI ascertainment

Apart from residual confounding, a second indirect mechanism by which fluid overload may be associated with adverse outcomes is by masking the presence, delaying the recognition, or underestimating the severity of AKI. Since minimal increases in creatinine are associated with significant increases in mortality [27–29], failure to recognize AKI because of fluid overload may lead to a relative increase in mortality in those with fluid overload who (by conventional creatinine criteria) do not have AKI, or have mild AKI. Along these lines, Macedo and colleagues used the PICARD cohort to test the hypothesis that fluid overload would both underestimate the severity of renal dysfunction based on serum creatinine and increase the time to AKI detection [25]. Using admission weight to estimate total body water, daily crude serum creatinine values were adjusted for the cumulative daily fluid balance using a simple formula, where adjusted creatinine = serum creatinine*(1+[on study cumulative net fluid balance/total body water]). Creatinine adjusted for fluid balance was significantly higher than the unadjusted creatinine at each time point, and the difference between median crude and adjusted values progressively increased to 0.65 mg/dl on day 7. 64 patients (25%) experienced a delay of at least one day in recognizing a 50% increase from baseline creatinine when crude and adjusted creatinine values were compared. Dialysis was initiated more frequently in patients with late recognition. Although delayed recognition of AKI did not result in mortality differences in this study, an adequate assessment of AKI severity could lead to earlier implementation of preventive and therapeutic strategies (e.g., avoiding contrast, discontinuing nephrotoxic medications, adjusting medication doses) to minimize morbidities associated with AKI.

Liu and colleagues extended the findings of Macedo and colleagues from patients with established AKI to a large group of critically ill patients at risk for AKI in another secondary analysis of the FACTT trial [26]. The incidence of AKI was examined over the first 8 days of the study before and after adjustment of serum creatinine for cumulative fluid balance.

The incidence of AKI before adjustment for fluid balance was greater in those managed with the conservative fluid protocol; after adjustment for fluid balance, the incidence of AKI was greater in those managed with the liberal fluid protocol, highlighting the critical role of fluid balance in AKI ascertainment. Patients who met AKI criteria after adjustment of creatinine for fluid balance (but not before) had a mortality rate (31%) that was significantly greater than those who did not have AKI either before or after adjustment for fluid balance (12%) and those who no longer had AKI after adjustment for fluid balance (11%); their mortality was similar to patients with AKI both before and after adjustment for fluid balance (38%). In multivariate logistic regression analysis, patients who met AKI criteria after adjustment of creatinine for fluid balance (but not before) had a OR for death of 2.09 (95% CI 1.19–3.67, $p = 0.001$) compared to those without AKI; similarly, patients with AKI both before and after adjustment of creatinine for fluid balance had an OR for death of 3.16 (95% CI 2.04–4.87, $p < 0.001$). This study suggests (but does not prove) that positive fluid balance can mask kidney injury. Since even small changes in creatinine are associated with increased mortality, not adjusting serum creatinine for fluid balance may obscure changes in renal function that are associated with risk of death. Further work is needed to determine whether these volume overloaded patients with “hidden” AKI truly have AKI based on sensitive novel biomarkers of kidney dysfunction (reviewed in [30–33]).

Direct consequences of fluid overload on renal function

The direct mechanisms by which fluid overload may be harmful remain poorly characterized in human studies. A mechanism by which fluid overload may contribute directly to renal dysfunction is by leading to intra-abdominal hypertension and the abdominal compartment syndrome, both of which are associated with significant morbidity and mortality in critically ill patients (reviewed in [34] and Table 2). The kidneys are vulnerable to even small increases in intra-abdominal pressure (IAP), and oliguria and renal dysfunction are among the earliest signs of increasing IAP. Elevated IAP leads to compression of intra-abdominal vessels, compromised microvascular blood flow [35], and increased renal venous pressure [36], which in turn results in impaired renal plasma flow, decreased glomerular filtration rate, and oliguria [37]. At higher levels of IAP, decreased cardiac output and elevated levels of catecholamines, renin, angiotensin, and inflammatory cytokines may also contribute to renal dysfunction [38]. Intriguingly, in a recent small study of patients with congestive heart failure, improvements in renal function after administration of diuretics correlated with improvement in IAP, rather than changes in left or right sided filling pressures or in cardiac output [39]. Albeit small, this study is one of the first to suggest that changes in IAP may directly affect renal function.

Another direct mechanism by which fluid overload may contribute to adverse outcomes is by increasing the risk of sepsis after AKI, which was suggested by another observational study based on the PICARD cohort [40]. The authors of this study speculate that fluid overload increases gut edema and impairs barrier function, leading to bacterial translocation. Other possible links between AKI and sepsis include the generalized immunocompromised state associated with AKI, cytokine release, insulin resistance, and oxidative stress [41]. Thus, there are a number of plausible mechanisms through which fluid overload might directly contribute to mortality; however, additional studies in humans are needed to better characterize these mechanisms.

Conclusion

Unfortunately, the current literature provides more questions than answers about the role of fluid overload in AKI. No study to date has shown causal relationship between fluid overload and mortality or recovery of renal function, and it is unclear whether correction of fluid overload will lead to improved survival in critically ill children or adults. The results of

Grams and colleagues suggesting that fluid removal is on the causal pathway by which furosemide has mortality benefit in patients with AKI treated with diuretics suggests that fluid overload may be more than an epiphenomenon in AKI. However, to assess whether fluid overload is an important causal contributor to mortality or non-recovery of kidney function rather than simply a marker of illness severity, prospective randomized controlled trials comparing different fluid administration strategies in patients with AKI are essential. However, we will first need to demonstrate the safety and feasibility of fluid removal in critically ill and potentially hypotensive patients; data from prior randomized clinical trials may be helpful here. Furthermore, while % fluid overload is an intriguing criteria to use for initiation of dialysis or ultrafiltration, a potential concern is that subjects who would not require dialysis for conventional indications may be exposed to the potential risks of dialysis with associated fluid removal, including catheter placement; again, pilot studies may help inform the feasibility of such studies, with regards to both patient safety and practitioner "buy-in."

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Key Points

1. Several studies have suggested an association between fluid overload and mortality in patients with AKI.
2. However, the relative contributions of the direct effects of fluid overload versus the association of fluid overload with other patient characteristics associated with adverse outcomes (e.g., sepsis) remain unknown.
3. A recent study suggested that fluid balance is a causal intermediate in the association between diuretic administration and decreased mortality; i.e., the benefit derived from furosemide is from the reduction in fluid overload.
4. Fluid overload can both underestimate the severity of renal dysfunction based on serum creatinine and increase the time to AKI detection.
5. Direct mechanisms by which fluid overload may have a direct impact on renal function and adverse outcomes include elevations of intrabdominal pressure, which reduces renal plasma flow and decreases the glomerular filtration rate, and increasing the risk of sepsis following AKI.

Table 1

Summary of key findings from the recent literature

Summary of key findings from the recent literature
Post-AKI diuretic therapy is associated with improved mortality in a population of critically ill patients with acute lung injury managed with a conservative fluid management approach. A negative fluid balance is the likely causal intermediate in the association between diuretics and mortality [24]
In critically ill patients, dilution of the serum creatinine by fluid accumulation can lead to underestimation of the severity of AKI and may increase the time needed to identify a 50% increase in the serum creatinine [25]
Patients with “unrecognized” AKI that is revealed after adjusting serum creatinine for positive fluid balance had a mortality rate significantly greater than those who did not have AKI either before or after adjustment for fluid balance or those who no longer had AKI after adjustment for fluid balance [26]

Table 2

Putative mechanisms by which fluid overload leads to worse outcomes

Putative mechanisms by which fluid overload leads to worse outcomes
Organ edema leading to impaired organ function
Distortion of tissue architecture
Impairment of oxygen and metabolite diffusion
Obstruction of capillary flow and lymphatic drainage
Initiation or exacerbation of intra-abdominal hypertension and the abdominal compartment syndrome
Compression of intra-abdominal vessels
Compromised microvascular blood flow
Increased renal venous pressure, leading to oliguria and decreased glomerular filtration rate
Masking the presence, delaying the recognition, or underestimating severity of AKI
Increased risk of sepsis
Increased gut edema with impaired barrier function and bacterial translocation
Generalized immunocompromised state associated with AKI
Cytokine release, insulin resistance, oxidative stress