



Fluid Overload

In Critically Ill Patients with Acute Kidney Injury

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Introduction

Several observational studies, mostly performed in the pediatric population (1-5), suggest an association between fluid overload and increased mortality in critically ill patients with acute kidney injury (AKI). Moreover, an adverse effect of fluid overload on outcomes has been reported in other critically ill patients without AKI, including patients with septic shock and acute lung injury (6-12). In these latter patient groups, frequently aggressive fluid resuscitation is provided to treat the common complication of hypotension (13). The potential problem with the general approach of aggressive fluid resuscitation is that a certain percentage of patients are left with significant fluid overload, particularly those patients with compromised renal function.

On this issue, a “chicken and egg” debate has occurred that severe fluid overload is simply an indication of a very sick patient who requires large volumes of fluid to maintain hemodynamic stability – in other words, severe fluid overload is a surrogate for pronounced critical illness. However, there is increasing evidence that fluid overload itself has toxic effects on organ function and contributes

independently to mortality in critically ill patients. In this regard, fluid status can be viewed as an AKI “biomarker” (14, 15). A recent study from the Program to Improve Care in Acute Renal Disease (PICARD) study group in the US is the first evidence of an association between fluid overload and mortality in critically ill adult AKI patients (16). Although the focus of this review is on this recent PICARD study, earlier studies performed in critically ill patients with and without AKI will also be discussed.

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Fluid Balance in Critically Ill Patients: Pre-PICARD Studies

Critically ill patients without AKI

In a landmark randomized controlled trial (RCT) performed by Rivers and colleagues (17), a highly protocolized resuscitative approach (early goal directed therapy; EGDT) was compared to conventional management in 263 emergency department patients admitted with sepsis-induced hemodynamic compromise. The resuscitation protocol was conducted for a period of six hours in the emergency department. The clinical parameters used as targets during the resuscitation protocol included, central venous pressure, mean arterial pressure, and central venous oxygen saturation. Although a major aspect of the protocol included aggressive volume administration, both groups were administered a mean of approximately 14 L of fluid. However, a greater proportion of fluid was administered in the emergency department in the EGDT group compared to the conventionally managed group.

It is noteworthy that the mean serum creatinine in both groups was 2.6 mg/dL at baseline, suggesting a high incidence of AKI even before fluid administration began. However, participation in the trial of end-stage renal disease patients, who were not excluded from enrollment by the protocol, could at least partly explain the elevated mean serum creatinine at baseline. On the other hand, a significant percentage (more than 20%) of patients had pre-existing renal insufficiency, placing them at increased risk for the development of AKI.

Relative to septic patients receiving conventional treatment, those in the protocolized care group had a significantly lower mortality rate at hospital discharge, 30 days, and 60 days. Furthermore, the difference was significant in patients with septic shock and severe sepsis but not significant in those with sepsis syndrome. However, the paper did not specifically report for

the two groups the percentage of patients with AKI at entry and the subsequent development of AKI (including the need for renal replacement therapy) after the treatment interventions. As severe sepsis and septic shock have been demonstrated clearly to be risk factors for AKI (18, 19) and based on the relatively high mean serum creatinine at baseline, a reasonable assumption for the study patient population is that AKI progressed in a significant percentage, with many eventually requiring renal replacement therapy. Moreover, based on the volume of fluid used for resuscitation, a specific concern is the need for dialysis specifically related to fluid overload in the setting of AKI. Based on the clinical implications of fluid overload in sepsis syndromes (see below), questions remain from the EGDT study.

The effect of fluid overload on outcome in the specific setting of septic shock was evaluated retrospectively in 36 patients by Alsous and colleagues (6). Mortality outcomes were adjusted for age, baseline APACHE II score, SOFA score on days 1 and 3, and the need for mechanical ventilation. For patients in whom a net negative fluid balance of at least 500 mL could be achieved within the first three days of ICU hospitalization, survival was 100%. Conversely, survival of patients in whom net negative fluid balance could not be attained was only 20%. Another assessment of the data showed that during the seven-day analysis period, daily fluid balance on average was always more positive in patients who died versus those who survived. From Day 2 to Day 7, surviving patients essentially attained neutral fluid balance on a daily basis while non-surviving patients had mean positive fluid balance values ranging from 1 to 4 L per day. The differences between surviving and non-surviving patients were the greatest (approximately 3.5 – 4 L) on days 2 and 3.

Combining aspects of both the Rivers (17) and Alsous (6) studies, Murphy and colleagues recently performed an observational analysis of 212 patients who developed acute lung injury in the setting of septic shock (7). In this study, the effect of both timing of fluid resuscitation and control of fluid balance on outcome were assessed. Adequate initial fluid resuscitation was defined as the administration of an initial fluid bolus of ≥ 20 mL/kg prior to and achievement of a central venous pressure of ≥ 8 mm Hg within 6 hrs after the onset of therapy with vasopressors. Conservative late fluid management was defined as neutral or negative fluid balance measured on at least two consecutive days during the first seven days after septic shock onset.

Patients who met both the initial resuscitation and fluid balance criteria were reported to have the lowest hospital mortality while patients meeting only one or neither of these criteria had significantly worse outcomes. Specifically, hospital mortality in patients meeting both criteria and those meeting neither criterion was 18.3% and 77.1%, respectively ($P < 0.001$). Consistent with the Alsous study, daily fluid balance in non-surviving patients was significantly greater (and always positive) on days 3 to 7 than in surviving patients, in whom daily fluid balance became non-positive on day 4. On days 3 to 7, daily fluid balance ranged approximately from +2500 to +1000 mL in non-surviving patients and from +1300 mL to -500 mL in surviving patients. Moreover, cumulative fluid balance also differed significantly between non-surviving and surviving patients during the same time period, with day 7 values being +13.7 L and +8.0 L, respectively. Finally, based on multivariate regression analysis, the inability to achieve conservative late fluid management status was found to be an independent risk factor for mortality (adjusted odds ratio 6.13; $P < 0.001$).

In an observational survey of European ICU practices in sepsis management termed the SOAP Trial, Vincent et al. (8) compared clinical parameters in 1,177 septic patients and 1,970 non-septic patients. One of the parameters assessed was fluid balance within the first 72 hours of ICU admission. The mean cumulative fluid balance in the septic group during this period was 1.8 L versus 0.5 L in the non-septic group. Moreover, based on multivariate regression analysis, the authors report that mean fluid balance during this time period was found to be a significant and independent predictor of mortality. Specifically, a 10% increase in mortality risk was associated with each 1 L increase in cumulative fluid balance.

The above three studies (6-8), specifically in septic populations, along with studies performed in other patient populations (9-11) suggest positive fluid balance adversely impacts clinical outcomes. Nevertheless, as observational studies, they can only establish an association rather than a causal relationship. However, a recent RCT involving patients with acute lung injury provides more substantive evidence of the deleterious effect of fluid overload in critically ill patients. In the Fluid and Catheter Treatment Trial (FACTT) performed by the ARDS Clinical Trial Network investigators (12), one intervention in the 2x2 design was the use of a pulmonary artery catheter or a central venous catheter for hemodynamic management. The other intervention was use of a "conservative" or "liberal" fluid management strategy over a one week intervention period. The primary endpoint was 60-day mortality while secondary endpoints included ventilator-free days and organ failure-free days. Fluid administration and the use of vasoactive agents and furosemide were guided by filling pressures and mean arterial pressure with a defined protocol. Approximately 500 patients comprised each of the two fluid management arms.

After a week the average total fluid balance in the conservative group was -136 mL while it was $+6992$ mL in the liberal group ($P<0.001$).

Although survival at 60 days was not significantly different between the two groups, a number of other outcome parameters differed significantly.

- Ventilator-free days and ICU-free days were both significantly higher in the conservative group.
- Cardiovascular failure during the first week occurred at a significantly higher rate in the liberal group than in the conservative group.
- The percentage of patients requiring dialysis in the conservative group was lower than in the liberal group (10 vs 14%; $P=0.06$).

Although not specifically stated, a possible dialysis precipitant in the liberal group was fluid overload, given the large net positive fluid balance that occurred in these patients.

Critically ill patients with AKI

As noted above, an association between fluid overload and increased mortality (1-4) in critically ill pediatric patients with AKI is suggested by several studies. A recent study (5) performed in the adult AKI population provides further support for this association and also elucidates AKI's detrimental impact on fluid balance in general. In this study, Payen et al. utilized the SOAP data base to assess the effect of fluid balance on outcomes in 1,120 septic patients who developed AKI. These investigators reported that mean daily fluid balance was significantly more positive in AKI patients who died versus those who survived (0.98 ± 1.50 vs. 0.15 ± 1.06 L/24 hours; $P<0.001$). In addition, multivariate regression analysis demonstrated that mean daily fluid balance was a significant and independent mortality predictor. Specifically, the authors report that a 1 L positive fluid balance per 24 hours was associated with an approximate 20% increase in mortality risk. Finally, mean daily fluid balance was found to be significantly greater in oliguric patients versus non-oliguric patients (0.62 ± 1.33 vs. 0.27 ± 1.23 L/24 hours; $P<0.01$) and in dialyzed patients versus non-dialyzed patients (0.60 ± 1.50 vs. 0.39 ± 1.21 L/24 hours; $P<0.01$).

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The PICARD Study (16)

Study design

This trial was an observational study in which fluid status was estimated quantitatively in 618 AKI patients. Of these patients, approximately two-thirds (396) required some form of dialysis. Fluid balance was estimated by measuring the sum of all fluid inputs (e.g., intravenous fluids, medications, nutrition, etc.) and the sum of all fluid outputs (e.g., urine, stool, nasogastric fluid, etc.). On a daily basis, “fluid accumulation” was calculated as the difference in these sums divided by the body weight at the time of hospital admission. These measurements were made starting three days before nephrology consultation and continued until hospital discharge. The study defined “fluid overload” as a fluid accumulation value of greater than 10% (i.e., the point at which a patient sustained a fluid-related weight gain of 10% from baseline).

As shown in Table 1, the patients who met the 10% fluid overload criterion at the time of AKI diagnosis were more critically ill than patients with lesser degrees of fluid accumulation. The fluid overload group had significantly higher APACHE III and SOFA scores, higher number of organ failures, and higher percentage of patients with respiratory failure, ventilator dependence, and sepsis or septic shock. It should be noted that the outcomes reported below were adjusted for the greater illness severity in the fluid overload group.

Table 1: Patient Characteristics

	No Fluid Overload	Fluid Overload	P Value
Clinical measures at AKI diagnosis			
Systolic BP (mmHg)	116	111	0.07
Diastolic BP (mmHg)	58	58	0.87
Mean arterial pressure (mmHg)	78	76	0.43
Temperature (°C)	37.0	37.1	0.61
Heart rate	93	101	0.004
Median urine output (mL)	950	738	0.04
Oliguria (<400 ml/day)	26%	30%	0.55
Creatinine (μmol/L)	256	194	<0.0001
Blood urea nitrogen (mmol/L)	20.0	15.7	0.0003
pH	7.36	7.33	0.07
Potassium (mEq/l)	4.6	4.6	0.07
FiO ₂	45%	52%	0.03
Leukocyte count (1000/mm ³)	13.5	14.9	0.20
Hemoglobin (g/l)	106	101	0.09

Severity of illness:			
APACHE III score	79	90	<0.0001
SOFA score	6.7	8.7	<0.0001
Number of organ failures	2.6	3.2	0.0002
Central nervous system failure	19%	20%	0.84
Liver failure	27%	36%	0.09
Hematologic failure	25%	34%	0.12
Cardiovascular failure	50%	52%	0.66
Respiratory failure	55%	86%	<0.0001
On ventilator	32%	65%	<0.0001
Sepsis/septic shock	22%	39%	0.0005

Study results

Figure 1 shows the association between fluid overload and survival both in patients treated with dialysis and patients treated conservatively. For the patients who received dialysis (either IHD or CRRT) (Figure 1A), in whom fluid status was assessed at the time of dialysis initiation, survival was significantly higher in those patients without fluid overload (fluid accumulation < 10%) than in patients with fluid overload (fluid accumulation > 10%). Likewise, in those patients not treated with dialysis (Figure 1B), fluid overload at the time of AKI diagnosis was associated with lower survival.

Figure 1: Relationship Between Fluid Overload and Survival

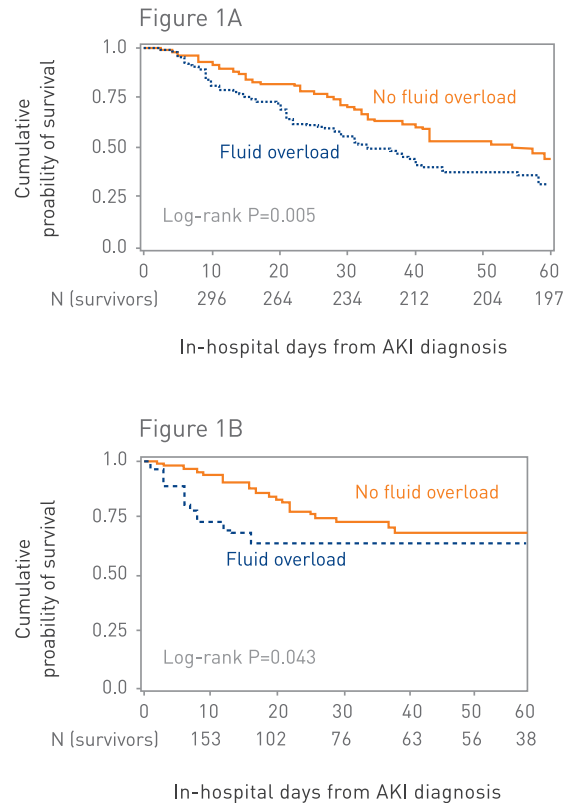
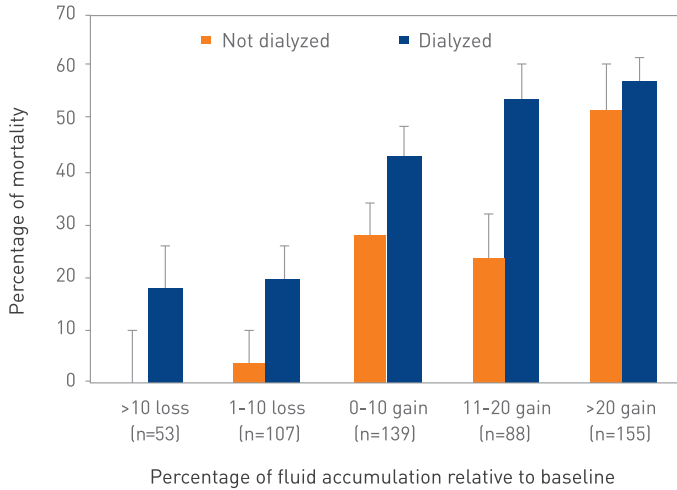


Figure 2: Relationship Between Fluid Accumulation and Mortality



In Figures 2 and 3, additional evidence suggesting an association between fluid overload and mortality is shown. Figure 2 demonstrates that patients achieving negative fluid balance (“loss”) had substantially lower 60-day mortality than patients who had positive fluid balance (“gain”). For each weight change class, the mortality of dialyzed patients was significantly greater than that of non-dialyzed patients, consistent with greater illness severity in the former group. Figure 3 shows the length of time patients remained in a fluid overloaded state while being treated with dialysis also was associated with mortality. There was a stepwise increase in mortality as the percentage of dialysis days in a fluid-overloaded state increases from 0% (mortality, 18%) to 100% (mortality, 62%). One potential interpretation of these data is that duration of fluid overload is a surrogate for the effectiveness of its correction by a particular dialysis modality.

Figure 3: Relationship Between Duration of Fluid Overload and Mortality

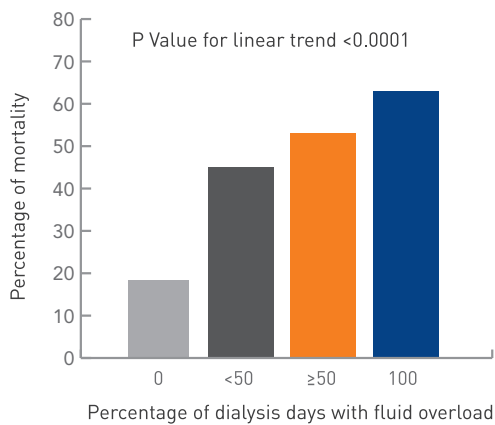
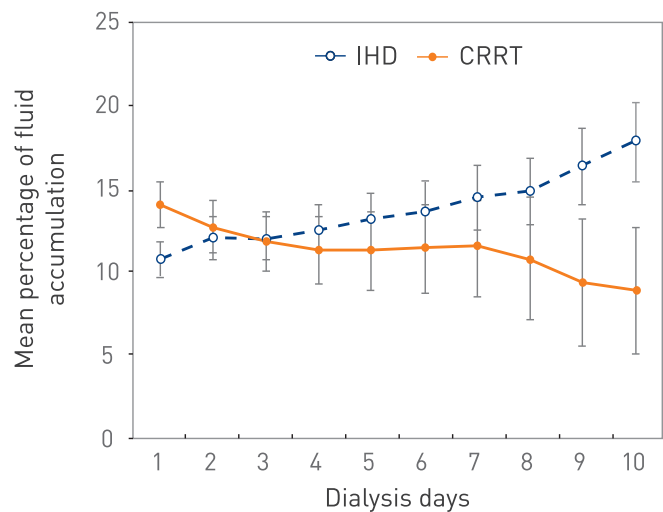


Figure 4 Authors report that consistent with a greater degree of illness severity, fluid overload at the initiation of therapy was higher in the CRRT group (mean value, approximately 14%) compared with the IHD group (approximately 11%). Despite this, net fluid removal with CRRT on a daily basis resulted in a progressive decrease in this mean value to approximately 8% after ten days. On the other hand, this mean value progressively increased over time in the IHD group, reaching approximately 18% after 10 days.

Finally, the study also suggests that patients with fluid overload (>10% fluid accumulation) at the time of their highest serum creatinine were less likely to recover renal function than those patients without fluid overload.

Figure 4: Relationship Between Dialysis Modality and Fluid Accumulation



This study should alert the clinical community that fluid accumulation is not an innocuous process without clinical consequences, but rather a potentially “toxic” phenomenon that influences patient outcomes.

Summary

The PICARD Study provides further evidence of an association between fluid overload and both increased mortality and decreased renal recovery in critically ill adult AKI patients. The study shows that not only does the extent of fluid accumulation influence survival but so does the duration of fluid overload in dialyzed patients. The latter finding suggests the ability of a dialysis modality to achieve net fluid removal may be an indirect determinant of outcome.

More generally, the PICARD Study is important because it reinforces the role of fluid as an AKI “biomarker”, a concept recently proposed by Bagshaw and colleagues [15]. As such, this study should alert the clinical community that fluid accumulation is not an innocuous process without clinical consequences but rather a potentially “toxic” phenomenon that influences patient outcomes. To further clarify the relationship between fluid overload and outcomes in the critically ill, AKI patients additional studies are necessary.

1. Foland JA, Fortenberry JD, Warshaw BL, et al: *Fluid Overload Before Continuous Hemofiltration and Survival in Critically Ill Children: A Retrospective Analysis*. Crit Care Med 2004;32:1771-6.
2. Gillespie RS, Seidel K, Symons JM: *Effect of Fluid Overload and Dose of Replacement Fluid on Survival in Hemofiltration*. Ped Nephrol 2004;19:1394-9.
3. Goldstein SL, Currier H, Graf C, Cosio CC, Brewer ED, Sachdeva R: *Outcome in Children Receiving Continuous Venovenous Hemofiltration*. Pediatrics 2001;107:1309-12.
4. Goldstein SL, Somers MJ, Baum MA, et al: *Pediatric Patients with Multi-Organ Dysfunction Syndrome Receiving Continuous Renal Replacement Therapy*. Kidney Int 2005;67:653-8.
5. Payen D, de Pont AC, Sakr Y, Spies C, Reinhart C, Vincent JL: *A Positive Fluid Balance is Associated with a Worse Outcome in Patients with Acute Renal Failure*. Crit Care 2008;12:R74.
6. Alsous F, Khamiees M, DiGirolamo A, Amoateng-Adjepong Y, Manthous A: *Negative Fluid Balance Predicts Survival in Patients with Septic Shock: A Retrospective Pilot Study*. Chest. 2000;117:1749-54.
7. Murphy CV, Schramm GE, Doherty JA, et al: *The importance of fluid management in acute lung injury secondary to septic shock*. Chest 2009;136:102-109.
8. Vincent JL, Sakr Y, Sprung CL, et al: *Sepsis in European Intensive Care Units: Results of the SOAP Study*. Crit Care Med. 2006;34:344-53.
9. Brandstrup B, Tønnesen H, Beier-Holgersen R, et al, Danish Study Group on Perioperative Fluid Therapy: *Effects of Intravenous Fluid Restriction on Postoperative Complications: Comparison of Two Perioperative Fluid Regimens: A Randomized Assessor-Blinded Multicenter Trial*. Ann Surg. 2003;238:641-8.
10. Lowell JA, Schifferdecker C, Driscoll DF, Benotti PN, Bistrrian BR. *Postoperative Fluid Overload: Not a Benign Problem*. Crit Care Med. 1990;18:728-33.
11. Schuller D, Mitchell JP, Calandrino FS, Schuster DP. *Fluid Balance During Pulmonary Edema. Is Fluid Gain a Marker or a Cause of Poor Outcome?* Chest. 1991;100:1068-75.
12. ARDS Clinical Trial Network: *Comparison of Two Fluid-Management Strategies in Acute Lung Injury*. N Engl J Med. 2006 Jun 15;354:2564-75.
13. Bagshaw SM, Lapinsky S, Dial S, et al: *Acute Kidney Injury in Septic Shock: Clinical Outcomes and Impact of Duration of Hypotension Prior to Initiation of Antimicrobial Therapy*. Intensive Care Med. 2009;35:871-81.
14. Mehta RL: *Fluid Balance and Acute Kidney Injury: The Missing Link for Predicting Adverse Outcomes?* Nat Clin Pract Nephrol. 2009;5:10-1.
15. Bagshaw SM, Brophy PD, Cruz D, Ronco C: *Fluid Balance as a Biomarker: Impact of Fluid Overload on Outcome in Critically Ill Patients with Acute Kidney Injury*. Crit Care. 2008;12:169.
16. Bouchard J, Soroko S, Chertow CM, Himmelfarb J, Ikizler TA, Paganini EP, Mehta RL, *Program to Improve Care in Acute Renal Disease (PICARD) Study Group: Fluid Accumulation, Survival and Recovery of Kidney Function in Critically Ill Patients with Acute Kidney Injury*. Kidney Int 2009;76:422-7.
17. Rivers E, Nguyen B, Havstad S, et al; *Early Goal-Directed Therapy Collaborative Group: Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock*. N Engl J Med. 2001;345:1368-77.
18. Bagshaw SM, Uchino S, Bellomo R, et al: *Septic Acute Kidney Injury in Critically Ill Patients: Clinical Characteristics and Outcomes*. Clin J Am Soc Nephrol. 2007;2:431-9.
19. Wan L, Bagshaw SM, Langenberg C, Saotome T, May C, Bellomo R. *Pathophysiology of Septic Acute Kidney Injury: What Do We Really Know?* Crit Care Med. 2008;36(4 Suppl):S198-203.
20. Augustine JJ, Sandy D, Seifert TH, Paganini EP: *A Randomized Controlled Trial Comparing Intermittent Hemodialysis with Continuous Dialysis in Patients with ARF*. Am J Kidney Dis. 2004;44:1000-7.

About the Author

After training in nephrology at Indiana University, Dr. William Clark has worked actively in the dialysis field for the past 16 years, especially in the area of AKI. He has been an active participant in the Acute Dialysis Quality Initiative and has authored approximately 100 journal articles and book chapters in the areas of nephrology and critical care medicine. He is currently Clinical Assistant Professor of Medicine at Indiana University and Vice President of Medical Strategy and Therapy Development at Gambro.

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