Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury

Josée Bouchard[1], Sharon B. Soroko[1], Glenn M. Chertow[2], Jonathan Himmelfarb[3], T. Alp Ikizler[4], Emil P. Paganini[5] and Ravindra L. Mehta[1], Program to Improve Care in Acute Renal Disease (PICARD) Study Group

[1]Division of Nephrology and Hypertension, Department of Medicine, University of California San Diego, San Diego, California, USA; [2]Division of Nephrology, Department of Medicine, Stanford University School of Medicine, Palo Alto, California, USA; [3]Division of Nephrology, Department of Medicine, University of Washington, Seattle, Washington, USA; [4]Division of Nephrology, Department of Medicine, Vanderbilt University, Nashville, Tennessee, USA and [5]Division of Nephrology, Department of Medicine, Cleveland Clinic Foundation, Cleveland, Ohio, USA

Fluid accumulation is associated with adverse outcomes in critically ill patients. Here, we sought to determine if fluid accumulation is associated with mortality and non-recovery of kidney function in critically ill adults with acute kidney injury. Fluid overload was defined as more than a 10% increase in body weight relative to baseline, measured in 618 patients enrolled in a prospective multicenter observational study. Patients with fluid overload experienced significantly higher mortality within 60 days of enrollment. Among dialyzed patients, survivors had significantly lower fluid accumulation when dialysis was initiated compared to non-survivors after adjustments for dialysis modality and severity score. The adjusted odds ratio for death associated with fluid overload at dialysis initiation was 2.07. In non-dialyzed patients, survivors had significantly less fluid accumulation at the peak of their serum creatinine. Fluid overload at the time of diagnosis of acute kidney injury was not associated with recovery of kidney function. However, patients with fluid overload when their serum creatinine reached its peak were significantly less likely to recover kidney function. Our study shows that in patients with acute kidney injury, fluid overload was independently associated with mortality. Whether the fluid overload was the result of a more severe renal failure or it contributed to its cause will require clinical trials in which the role of fluid administration to such patients is directly tested.

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Correspondence: *Ravindra L. Mehta, 200 W Arbor Drive, Mail Code 8342, San Diego, California 92103, USA. E-mail: rmehta@ucsd.edu*

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Despite progress in the delivery of intensive care and dialytic support, there has been relatively little improvement in the survival of patients suffering from acute kidney injury (AKI) over the last three decades.[1] In critically ill patients with AKI, mortality rates range from 50 to 70% and have usually been attributed to multiple complications related to AKI, such as infections, bleeding, and fluid overload.[2,3]

Ample recent data have highlighted the role of fluid accumulation on adverse outcomes in critically ill patients. Randomized clinical trials have shown that restrictive fluid management strategies are beneficial in acute respiratory distress syndrome and following major surgery in terms of duration of mechanical ventilation and cardiopulmonary complications, respectively.[4,5] Observational studies in pediatric populations undergoing continuous renal replacement therapy (CRRT) have shown an association between fluid accumulation and mortality.[6–9] Fluid accumulation has also been associated with long-term dialysis dependence in one study involving 30 patients at a single center.[10]

The Program to Improve Care in Acute Renal Disease (PICARD) began as an observational study of 618 critically ill patients with AKI from five academic medical centers in North America. PICARD was designed to identify demographic, clinical, and process of care factors associated with favorable and adverse outcomes after AKI.[11] We hypothesized that fluid overload would be associated with mortality and non-recovery of kidney function in critically ill patients with AKI.

RESULTS

Demographics, past medical history, severity of illness scores, and clinical and laboratory values stratified by the presence or absence of fluid overload are included in Table 1. APACHE III scores and the number of failed organ systems, sepsis, and ventilator requirements were significantly higher in patients with fluid overload than in those without.

Table 1 | Patients' characteristics at the time of acute kidney injury diagnosis based on fluid overload status[a]

Variable	AKI diagnosis in absence of fluid overload	AKI diagnosis with fluid overload	*P*-value
Demographics:			
Age (years)	59.9	58.2	0.34
Male	59%	61%	0.83
Dry weight (kg)	82.4	76.9	0.03
Race			
Caucasian	80%	85%	0.26
African American	8%	7%	0.62
Hispanic	6%	4%	0.35
Asian/Pacific Islands	4%	4%	0.95
Other/Mixed Race	2%	1%	0.65
Comorbidities:			
History of CKD	31%	21%	0.06
Surgery prior to or/on ICU admission day	35%	53%	0.0004
History of hypertension	53%	44%	0.09
History of diabetes mellitus	31%	21%	0.04
History of COPD	16%	16%	0.97
History of liver disease	20%	19%	0.91
History of heart failure	30%	22%	0.09
History of coronary artery disease	39%	34%	0.31
Clinical measures at AKI diagnosis			
Systolic BP (mm Hg)	116	111	0.07
Diastolic BP (mm Hg)	58	58	0.87
Mean arterial pressure (mm Hg)	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 ($\leqslant$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

AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; BP, blood pressure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; FiO2, inspired oxygen fraction; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.
[a]Fluid overload defined as fluid accumulation $>$10% of baseline body weight.

Fluid status and mortality

Mortality at 30 days (37 vs 25%, $P=0.02$), 60 days (46 vs 32%, $P=0.006$), and at hospital discharge (48 vs 35%, $P=0.01$) was significantly higher in patients with fluid overload (that is, percentage fluid accumulation $>$10%). Fluid-overloaded patients had a higher risk of death early in the course and the difference in survival was maintained over 60 days (Figures 1a and b).

We assessed the association of fluid accumulation with mortality at different time points. In all patients, the percentage fluid accumulation at AKI diagnosis was lower in survivors than in non-survivors (4.9 ± 8.4 vs 7.1 ± 9.1%, $P=0.01$); however, this difference was not significant after adjustment for APACHE III score ($P=0.12$). In patients requiring renal replacement therapy (RRT), survivors had a significantly lower mean percentage fluid accumulation at dialysis initiation and cessation compared with non-survivors (8.8 vs 14.2%; $p<0.001$ and $P=0.01$ after adjustment and 13.0 vs 22.1%; $P=0.002$ and $P=0.004$ after adjustment, respectively). The OR for death associated with fluid overload at dialysis initiation and adjusted for severity of illness and dialysis modality was 2.07 (95% CI 1.27–3.37). In non-dialyzed patients, the percentage fluid accumulation at AKI diagnosis was lower in survivors than non-survivors (3.9 ± 7.0 vs 8.5 ± 9.1%; $P=0.01$ and $P=0.05$ after adjustment for APACHE III) and the adjusted OR for death

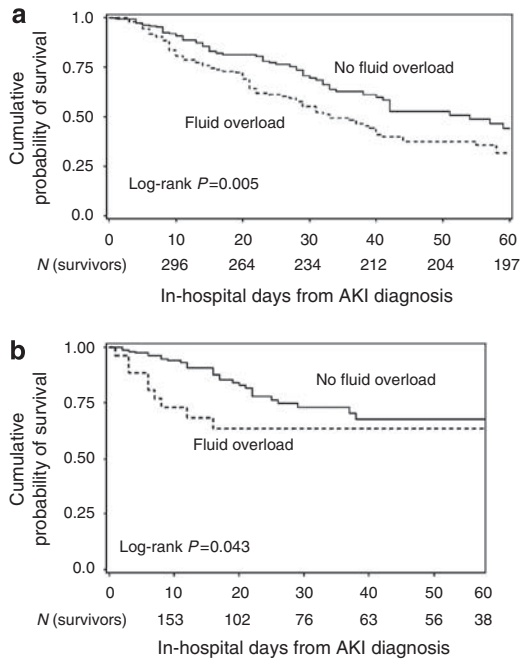

Figure 1 | Cumulative probability of survival by fluid overload status. (**a**) Kaplan–Meier survival estimates by fluid overload status at dialysis initiation. There was a significant difference in survival among patients with or without fluid overload at dialysis initiation ($P = 0.005$). (**b**) Kaplan–Meier survival estimates by fluid overload status at AKI diagnosis in non-dialyzed patients. There was a significant difference in survival among patients with or without fluid overload ($P = 0.04$).

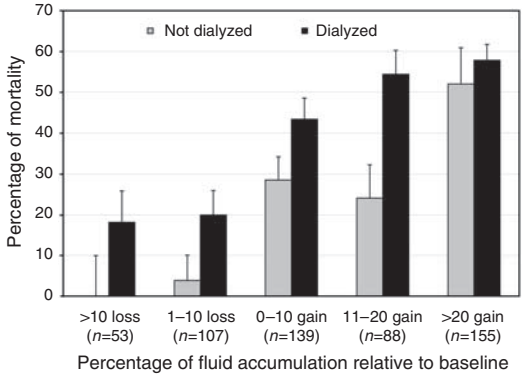

Figure 2 | Mortality rate by final fluid accumulation relative to baseline weight and stratified by dialysis status.

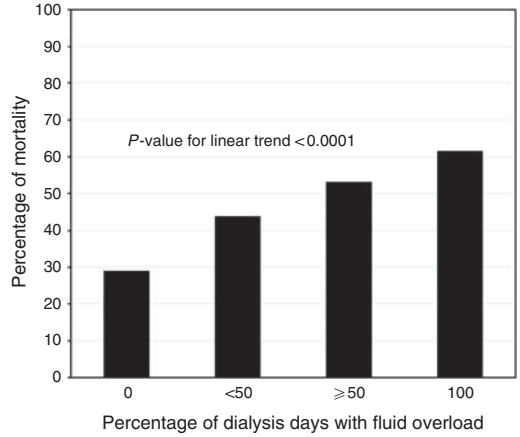

Figure 3 | Mortality rate by categorical percentage of dialysis days with fluid overload. The first column represents patients without fluid overload, and the others, patients with <50, $\geqslant 50\%$, and 100%, respectively, of their dialysis days with fluid overload. The *P*-value for the linear trend is <0.001.

associated with fluid overload at AKI diagnosis was 3.14 (95% CI 1.18–8.33). The percentage fluid accumulation at the first peak in serum creatinine was significantly lower in survivors compared with non-survivors (4.5 ± 9.4 vs $10.1 \pm 13.4\%$; $P = 0.003$, $P = 0.03$ after adjustment for APACHE III). The adjusted OR for death associated with fluid overload on the first day of peak creatinine attainment was 1.36 (95% CI 0.58–3.19). These results were consistent when using either the percentage fluid accumulation adjusted for body weight or the absolute fluid accumulation in liters (data not shown).

Progression and duration of fluid accumulation

Next, we assessed the association between the progression and duration of fluid accumulation and mortality. Patients who remained with fluid accumulation during their hospitalization had a higher mortality rate that was proportional to the degree of fluid accumulation (Figure 2). There was an incremental increase in mortality in patients with a higher proportion of days with fluid overload after AKI diagnosis ($P < 0.0001$). In addition, in dialyzed patients, mortality increased in relation to the proportion of dialysis days with fluid overload ($P < 0.0001$) (Figure 3). In patients with fluid overload at dialysis initiation, those who ended dialysis without fluid overload (that is, percentage fluid accumulation $\leqslant 10\%$) were less likely to die than those who still had fluid overload at dialysis cessation (35 vs 56%; $P = 0.0002$). Patients on continuous renal replacement therapy were more likely to reduce the percentage of fluid accumulation compared with patients treated with intermittent hemodialysis (Figure 4). The adjusted OR for death associated with fluid overload at dialysis cessation was 2.52 (95% CI 1.55–4.08).

Recovery of kidney function

Fluid overload at AKI diagnosis was not associated with recovery of kidney function (47% in non vs 40% in fluid overloaded; $P = 0.24$) and neither did fluid overload at dialysis initiation influence dialysis independence at hospital discharge (41 vs 32%; $P = 0.21$). However, patients with fluid overload at peak serum creatinine (median days after AKI diagnosis 4, interquartile range 1–11) were less likely to recover kidney function (35 vs 52%; $P < 0.001$ and $P = 0.007$ after adjustment for APACHE III score).

DISCUSSION

In critically ill patients and in patients with AKI, fluid accumulation has been shown to worsen prognosis.[4–9] In

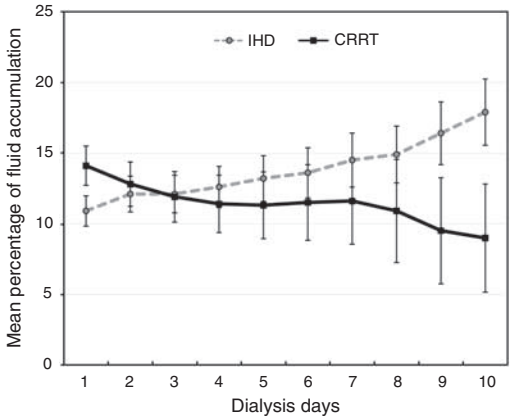

Figure 4 | Fluid accumulation over time in patients on continuous renal replacement therapy and on intermittent hemodialysis.

adult patients, Van Biesen *et al.*[12] found that septic patients with AKI had higher central venous pressure and an increasing need for oxygen compared with those without AKI. No data on mortality were reported. In another recent study, Payen *et al.*[13] found an inverse relation between fluid accumulation and survival among 1120 patients with sepsis-related AKI, defined as a creatinine $>309\,\mu mol/l$ or urine output <500 ml/day. Mean daily fluid balance was 0.15 ± 1.06 l/24 h in survivors compared with 0.98 ± 1.5 l/24 h in non-survivors. This association was evident only in patients with AKI occurring within 2 days of intensive care unit admission (0.14 ± 1.05 l/24 h vs 1.19 l/24 h; $P<0.001$).

Additional data supporting these findings are provided from small retrospective pediatric studies in dialyzed patients.[6,7,9] Goldstein *et al.*[7] reviewed charts from 21 pediatric patients undergoing CRRT. The degree of percentage fluid accumulation at RRT initiation among survivors was $16.4 \pm 13.8\%$ compared with $34.0 \pm 21.0\%$ in non-survivors ($P=0.03$). This association remained significant after controlling for severity of illness. The mean percentage of accumulated fluid removed by RRT did not differ among survivors and non-survivors. In another study, Foland *et al.* found that median percentage fluid accumulation before hemofiltration was significantly lower in survivors (7.8% vs non-survivors 15.1%; $P=0.02$).[6] Gillespie *et al.* found that children treated with CRRT who had fluid overload at dialysis initiation (using the same definition we applied) experienced a threefold increase in the risk of death compared with those with lower or no fluid overload (OR 3.02, 95% CI 1.50–6.10, $P=0.002$).[9] Only one multicenter prospective study has assessed the relation between percentage fluid accumulation and survival.[8] The results were comparable to those from previous studies, with the percentage fluid accumulation at CRRT initiation being significantly lower in survivors vs non-survivors (14.2 ± 15.9 vs $25.4 \pm 32.9\%$; $P<0.03$) even after adjustment for severity of illness. One retrospective study, in pediatric patients who received stem cell transplantation and developed AKI, suggested that survival may be improved by an aggressive use of diuretics and early initiation of dialysis.[14] All survivors ($n=11$) maintained or remained with percentage fluid accumulation $<10\%$ with diuretics and RRT. Among the 15 non-survivors, only six (40%) had percentage fluid accumulation $<10\%$ at the time of death.

In our study, we found that fluid overload was independently associated with mortality, with or without the requirement of dialysis. The association between fluid overload and mortality was highly significant even after adjustment for severity of illness and the need for dialysis. Patients with fluid overload had lower urine outputs, lower serum creatinine, and BUN at AKI diagnosis, as well as a higher incidence of ventilator-requiring respiratory failure. One of the key features of our study is the recognition that fluid accumulation resulting in a positive fluid balance is a frequent event in critically ill patients with AKI. Although it is difficult to ascertain the events leading to fluid accumulation, the higher incidence of sepsis, surgery, and multiorgan failure constitutes settings in which more fluid is typically administered for resuscitation. In our study, we have made a distinction between fluid accumulation and fluid overload. We have chosen the term fluid accumulation to specify conditions when there is a positive fluid balance and stratified the data to delineate a fluid accumulation of $>10\%$ as 'fluid overload' because prior studies had shown that a 10% fluid accumulation was associated with adverse outcomes in other clinical settings. In the Payen *et al.*[13] study, the association between fluid accumulation and mortality was significant in patients with 'early' AKI (within 2 days), suggesting that resuscitative strategies could be contributory. Our data provide additional insight into the possible effect of fluid accumulation on outcomes. The progression, duration, and correction of fluid overload emerge as important attributes associated with mortality. Patients who continued to have fluid accumulation through their hospital stay were more likely to die. The duration of fluid overload while remaining on dialysis was similarly associated with increased mortality, suggesting a cumulative effect of fluid overload on mortality. Mortality was lower when fluid overload was corrected by dialysis. Whether this reflects a therapeutic effect of ultrafiltration or better outcomes in patients who were able to be ultrafiltered is unknown. Finally, patients who required dialysis and were treated with CRRT were more likely to correct fluid accumulation than those treated with intermittent dialysis. Cumulative fluid overload may also be associated with a decreased likelihood of renal recovery. This finding is in opposition to the common belief that fluid accumulation somehow 'protects' the kidneys.

This study has several strengths. We included patients from five different centers across the United States with different demographics and clinical conditions, increasing the generalizability of our results. Our population included patients with and without sepsis, requiring and not requiring dialysis, and all patients had detailed data on the progression of fluid accumulation during hospitalization, which expands on findings from previous studies. There are also important limitations. First, patients or their proxies were required to

sign informed consent and only patients for whom a nephrology consultation was obtained were included. Therefore, our sample was limited to those patients who were recognized as having AKI and for whom a nephrologist was consulted.[11] Second, although we recorded fluid balance 3 days before nephrology consultation, a longer observation period could have provided more detailed data on the time course and sequence contributing to fluid overload. We could not correlate the calculated fluid balance with invasive measures, such as central venous pressures or pulmonary capillary wedge pressures, because these were only infrequently obtained and for minimal duration. Although we showed that the associations among fluid overload, mortality, and recovery of kidney function were significant after adjustment for severity of illness (using APACHE III or SOFA), as with all observational studies, there was likely residual confounding for which we could not adjust. Finally, the positive cumulative fluid balance could have resulted in delayed recognition of AKI, owing to dilution of serum markers of kidney function (BUN and creatinine), which might have also influenced overall prognosis.[15]

Although our study is observational and has important limitations, it is important to highlight the association of fluid overload with mortality in AKI. Other studies in critically ill patients have provided similar information suggesting that fluid overload may have a causal association that might in some manner mediate the adverse outcomes. To determine causality between a risk factor and an adverse event, several conditions are needed, such as a temporal association, a strong dose–response relationship, biological plausibility, and replication of the findings.[16] Several of these conditions appear to be met with respect to the association of fluid overload with outcomes; however, additional prospective studies are required to further establish a causal mechanism.

In summary, we have shown an association between fluid overload and mortality among critically ill patients with AKI. Moreover, the magnitude, progression, duration, and reversibility of fluid accumulation also play a role. Our study expands on prior knowledge by providing insight on the importance of cumulative fluid accumulation in terms of degree and duration. Fluid overload may also be associated with a decreased likelihood of renal recovery. To assess whether fluid overload is an important causal contributor to mortality or non-recovery of kidney function, prospective randomized clinical trials comparing the results of different fluid administration strategies in patients with AKI are required.

METHODS

Study participants

From February 1999 to August 2001, all patients who underwent a consultation for AKI in the intensive care unit of five academic medical centers were evaluated by PICARD study personnel for potential study participation. A complete description of PICARD data elements, data collection, and management strategies has been published earlier.[11] In PICARD, AKI was defined as an increase in serum creatinine $\geqslant 44\,\mu mol/l$ when baseline serum creatinine was $<133\,\mu mol/l$ or an increase in serum creatinine $\geqslant 88\,\mu mol/l$ when baseline creatinine was $\geqslant 133\,\mu mol/l$ and lower than $442\,\mu mol/l$.[11] Baseline creatinine was defined as the closest value within 6 months of hospital admission. Exclusion criteria included age <18 years, prisoners, pregnant women, serum creatinine $>442\,\mu mol/l$, previous dialysis, kidney transplantation, AKI from urinary tract obstruction, and hypovolemia responsive to fluid. Fluid management, dialysis parameters, and all other interventions were determined by the attending physicians and not influenced by the study personnel. The institutional review board at each site approved the study protocol. Informed consent was required from all study participants or their proxy.

We included 610 patients (99%) who had complete data and, among these, the 396 (65%) who required RRT during their initial nephrology consultation. Detailed fluid intake and output data were available in 353 of 396 (89%) patients who required dialysis. In non-dialyzed patients, data were available in 189 of 214 (88%) patients.

Definition of percentage of fluid accumulation

All available intake and output data from 3 days before nephrology consultation until hospital discharge were included in the analyses. We computed fluid balance for each day using the sum of daily fluid intake (L) from which we subtracted total output (L). To quantify cumulative fluid balance in relation to body weight, we used the following formula: (Σ daily (fluid intake (L) – total output (L))/body weight (in kilograms)) $\times$ 100. We used the term 'percentage of fluid accumulation' to define the percentage of cumulative fluid balance adjusted for body weight. Baseline body weight was based on initial hospital admission weight. We arbitrarily defined fluid overload (a discrete exposure variable) as a percentage of fluid accumulation $>10\%$ over baseline weight at hospital admission. We chose this cutoff point because this value was used in a similar study of pediatric AKI.[9] In companion analyses, we explored outcomes among persons with fluid accumulation >15 and $>20\%$ above baseline.

Duration of fluid overload

For each patient, the earliest date on which he or she met the criteria for AKI was identified and designated the AKI diagnosis date. For 94% of patients, this was prior to or on the day of consultation. Patients were categorized as fluid overloaded or not based on their fluid balance at AKI diagnosis and at first peak serum creatinine in non-dialyzed patients. In patients requiring dialysis, we assessed the fluid status at AKI diagnosis, dialysis initiation, and dialysis cessation. For patients requiring multiple episodes of RRT, only the first course of dialysis was analyzed. The duration of fluid overload (total number of days with $>10\%$ of body weight) was computed for all patients through their hospital stay.

Recovery of kidney function

Complete recovery of kidney function was defined as a serum creatinine level $\leqslant 44\,\mu mol/l$ or $\leqslant 20\%$ above the baseline value. In patients who required dialysis, partial recovery of kidney function corresponded to dialysis independence at hospital discharge.

Statistical analyses

Continuous variables were expressed as mean $\pm$ s.d. or median and interquartile range and compared using the Student's *t*-test or Wilcoxon's rank sum test where appropriate. Categorical variables

were expressed as proportions and compared with the χ^2 or Fisher's exact test where appropriate. We examined the time to death within 60 days of intensive care unit admission using the Kaplan–Meier product limit estimates and compared survival curves using the log-rank test. For patients who received dialysis, we performed multivariable analysis with survival as the dependent variable and Acute Physiology and Chronic Health Evaluation III (APACHE III) score and initial dialysis modality as independent variables. For non-dialyzed patients, we adjusted only for APACHE III score. Results obtained by adjusting for APACHE III score were similar to those published earlier.[17] We conducted parallel analyses adjusting for the Sequential Organ Failure Assessment (SOFA) score, without the renal component, and the results were not appreciably different. All statistical tests were two-sided and $P<0.05$ was considered significant. Statistical analyses were conducted using SAS 8.2 (SAS Institute, Cary, NC, USA).

DISCLOSURE

All the authors declared no competing interests.

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REFERENCES

1. Waikar SS, Curhan GC, Wald R *et al.* Declining mortality in patients with acute renal failure, 1988 to 2002. *J Am Soc Nephrol* 2006; **17**: 1143–1150.
2. Druml W, Lax F, Grimm G *et al.* Acute renal failure in the elderly 1975–1990. *Clin Nephrol* 1994; **41**: 342–349.
3. Druml W. Acute renal failure is not a 'cute' renal failure!. *Intensive Care Med* 2004; **30**: 1886–1890.
4. Wiedemann HP, Wheeler AP, Bernard GR *et al.* Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; **354**: 2564–2575.
5. Brandstrup B, Tonnesen H, Beier-Holgersen R *et al.* Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Ann surg* 2003; **238**: 641–648.
6. 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**: 1771–1776.
7. Goldstein SL, Currier H, Graf C *et al.* Outcome in children receiving continuous venovenous hemofiltration. *Pediatrics* 2001; **107**: 1309–1312.
8. Goldstein SL, Somers MJ, Baum MA *et al.* Pediatric patients with multi-organ dysfunction syndrome receiving continuous renal replacement therapy. *Kidney Int* 2005; **67**: 653–658.
9. Gillespie RS, Seidel K, Symons JM. Effect of fluid overload and dose of replacement fluid on survival in hemofiltration. *Pediatr Nephrol* 2004; **19**: 1394–1399.
10. Lane PH, Mauer SM, Blazar BR *et al.* Outcome of dialysis for acute renal failure in pediatric bone marrow transplant patients. *Bone marrow transplant* 1994; **13**: 613–617.
11. Mehta RL, Pascual MT, Soroko S *et al.* Spectrum of acute renal failure in the intensive care unit: the PICARD experience. *Kidney Int* 2004; **66**: 1613–1621.
12. Van Biesen W, Yegenaga I, Vanholder R *et al.* Relationship between fluid status and its management on acute renal failure (ARF) in intensive care unit (ICU) patients with sepsis: a prospective analysis. *J Nephrol* 2005; **18**: 54–60.
13. Payen D, de Pont AC, Sakr Y *et al.* A positive fluid balance is associated with a worse outcome in patients with acute renal failure. *Crit Care* 2008; **12**: R74.
14. Michael M, Kuehnle I, Goldstein SL. Fluid overload and acute renal failure in pediatric stem cell transplant patients. *Pediatr Nephrol* 2004; **19**: 91–95.
15. Mehta RL, McDonald B, Gabbai F *et al.* Nephrology consultation in acute renal failure: does timing matter? *Am J Med* 2002; **113**: 456–461.
16. Gordis L. *Epidemiology*. 3rd ed Elsevier Saunders: Philadelphia, 2004 pp 212–215.
17. Chertow GM, Soroko SH, Paganini EP *et al.* Mortality after acute renal failure: models for prognostic stratification and risk adjustment. *Kidney Int* 2006; **70**: 1120–1126.