Published in final edited form as:
Intensive Care Med. 2011 July ; 37(7): 1166–1173. doi:10.1007/s00134-011-2231-3.

Weight-based determination of fluid overload status and mortality in pediatric intensive care unit patients requiring continuous renal replacement therapy

David T. Selewski,
Division of Nephrology, Department of Pediatrics and Communicable Diseases, C.S. Mott Children's Hospital, University of Michigan, Ann Arbor, MI, USA

Timothy T. Cornell,
Division of Critical Care, Department of Pediatrics and Communicable Diseases, C.S. Mott Children's Hospital, University of Michigan, Ann Arbor, MI, USA

Rebecca M. Lombel,
Division of Nephrology, Department of Pediatrics and Communicable Diseases, C.S. Mott Children's Hospital, University of Michigan, Ann Arbor, MI, USA

Neal B. Blatt,
Division of Nephrology, Department of Pediatrics and Communicable Diseases, C.S. Mott Children's Hospital, University of Michigan, Ann Arbor, MI, USA

Yong Y. Han,
Division of Critical Care, Department of Pediatrics and Communicable Diseases, C.S. Mott Children's Hospital, University of Michigan, Ann Arbor, MI, USA

Theresa Mottes,
Division of Nephrology, Department of Pediatrics and Communicable Diseases, C.S. Mott Children's Hospital, University of Michigan, Ann Arbor, MI, USA

Mallika Kommareddi,
Division of Nephrology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA

David B. Kershaw,
Division of Nephrology, Department of Pediatrics and Communicable Diseases, C.S. Mott Children's Hospital, University of Michigan, Ann Arbor, MI, USA

Thomas P. Shanley, and
Division of Critical Care, Department of Pediatrics and Communicable Diseases, C.S. Mott Children's Hospital, University of Michigan, Ann Arbor, MI, USA

Michael Heung
Division of Nephrology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA

Abstract

Purpose—In pediatric intensive care unit (PICU) patients, fluid overload (FO) at initiation of continuous renal replacement therapy (CRRT) has been reported to be an independent risk factor

dselewsk@med.umich.edu, Tel.: +1-734-9364210, Fax: +1-734-7636997.

for mortality. Previous studies have calculated FO based on daily fluid balance during ICU admission, which is labor intensive and error prone. We hypothesized that a weight-based definition of FO at CRRT initiation would correlate with the fluid balance method and prove predictive of outcome.

Methods—This is a retrospective single-center review of PICU patients requiring CRRT from July 2006 through February 2010 (n = 113). We compared the degree of FO at CRRT initiation using the standard fluid balance method versus methods based on patient weight changes assessed by both univariate and multivariate analyses.

Results—The degree of fluid overload at CRRT initiation was significantly greater in nonsurvivors, irrespective of which method was used. The univariate odds ratio for PICU mortality per 1% increase in FO was 1.056 [95% confidence interval (CI) 1.025, 1.087] by the fluid balance method, 1.044 (95% CI 1.019, 1.069) by the weight-based method using PICU admission weight, and 1.045 (95% CI 1.022, 1.07) by the weight-based method using hospital admission weight. On multivariate analyses, all three methods approached significance in predicting PICU survival.

Conclusions—Our findings suggest that weight-based definitions of FO are useful in defining FO at CRRT initiation and are associated with increased mortality in a broad PICU patient population. This study provides evidence for a more practical weight-based definition of FO that can be used at the bedside.

Keywords

Acute kidney injury; Pediatric intensive care; Fluid overload; Continuous renal replacement therapy

Introduction

Acute kidney injury (AKI) occurs commonly in pediatric intensive care unit (PICU) patients and is associated with increased mortality of up to 50% [1–5]. Over the past two decades, continuous renal replacement therapy (CRRT) has emerged as a standard therapy for patients in the PICU with AKI [6–8]. Despite such technological advances there remains significant room for improvement in the outcomes of pediatric patients with AKI.

A growing body of literature suggests that the degree of fluid overload at initiation of renal replacement therapy is associated with increased mortality and may represent an important target for intervention. While first reported in pediatric bone marrow transplant patients [9–11], the importance of the concept of fluid overload has been extended to broader PICU patient populations requiring CRRT [12–17]. The American College of Critical Care Medicine practice guidelines for pediatric and neonatal septic shock have recognized a threshold of 10% volume overload as a key time to act, although they do not specify interventions [18]. The clinical significance of fluid overload has also been demonstrated in adult patients with sepsis [19], respiratory distress syndrome [20, 21], and acute kidney injury [22–25].

Several important questions remain regarding fluid overload as a clinical marker, including the optimal method for calculating fluid overload. To date, most pediatric studies have relied on the definition put forth by Goldstein et al. in 2001, which is based on measuring fluid input and output from PICU admission [16]. The accuracy of this formula relies on precise accounting of fluid balance on a daily basis and can be cumbersome for the clinician to calculate and error prone. In clinical practice, weight is frequently used as a surrogate to define fluid overload, yet there are no studies comparing weight-based definitions of fluid

overload and their association with mortality in pediatric patients requiring CRRT. There remains no consensus as to what the optimal clinical definition of fluid overload should be.

The aims of this study are to confirm the association between fluid overload and outcome in a large and diverse PICU population undergoing CRRT and to assess the predictive value and correlation of weight-based methods versus the fluid balance method for calculating fluid overload. We hypothesized that a practical weight-based definition of fluid overload at CRRT initiation would correlate with the fluid balance method and prove predictive of outcome in pediatric patients requiring CRRT.

Methods

Study population

We conducted a retrospective review of all pediatric patients undergoing CRRT between July 2006 and February 2010 in C.S. Mott Children's Hospital at the University of Michigan. Patients were admitted to the neonatal intensive care unit, cardiothoracic unit or the PICU. Patients were excluded if they were in the PICU for >2 months prior to initiation of CRRT. Patients who had multiple courses of CRRT separated by >24 h were included for the first course of CRRT only. This study was approved by the institutional investigational review board.

The primary modality of CRRT performed was continuous venovenous hemodiafiltration (CVVHDF) for patients not requiring extracorporeal life support (ECLS). In patients receiving CVVHDF, CRRT was performed using the Gambro Prismaflex system (Gambro, Lund, Sweden). Until December 2008, patients requiring ECLS received continuous venovenous hemodialysis by having a dialysis filter placed in line with the ECLS circuit. After December 2008, we began to perform CVVHDF using the Prismaflex system for patients on ECLS. For patients weighing <25 kg, CRRT was performed using an AN-69 M60 filter (Hospal, France). A polysulfone HF 1000 (Hospal, France) was used for the remainder of patients, who were not on ECLS. Polysulfone HF 400 (Renalflo II, MN) or Optiflux (Fresenius, Germany) filters were used in line for patients requiring ECLS based on body surface area. Anticoagulation was performed using a standardized regional citrate protocol [26]. Prior to 2008, heparin was used for anticoagulation in patients requiring CRRT in line with ECLS.

Data collection

Data collection included demographic data, comorbidity data, laboratory data, indication for CRRT defined by the pediatric nephrology note, and characteristics of each subject's hospital and ICU course (e.g., length of stay, requirement for vasoactive agents, requirement for mechanical ventilation, etc.). Pediatric Risk of Mortality (PRISM) III scores were calculated at ICU admission [27].

AKI was classified by the RIFLE and pRIFLE criteria based on serum creatinine, estimated creatinine clearance (eCCl), and urine output in the 24 h prior to initiation of CRRT [28] [29]. The pRIFLE was modified slightly to exclude the "failure" component of eCCl < 35 ml/min/1.73 m^2 for children ≤14 days. Estimated glomerular filtration rate (GFR) was calculated using the Schwartz equation in patients <18 years old [30] and the Modification of Diet in Renal Disease (MDRD) formula in patients >18 years old [31].

For fluid status determination we recorded weight upon hospital admission, weight at ICU admission, weight upon CRRT initiation, fluid intake from ICU admission until CRRT initiation, and fluid output from ICU admission until CRRT initiation. It is standard of care at our institution to weigh patients on ECLS daily. Fluid intake included blood products,

intravenous fluids and flushes, medications, and all forms of nutritional support. Fluid output included urine output, drain output, blood loss, nasogastric tube output, stool volume, and wound drainage. For each patient, the daily flow charts were reviewed and 24 h totals of fluid intake and output were recorded for each patient for every day on the intensive care unit prior to CRRT initiation. These daily totals were then used to calculate the degree of fluid overload as described by Goldstein et al. [16]:

$$\text{Method 1:\%FO} = \frac{\text{Sum of daily(fluid in} - \text{fluid out)}}{\text{ICU admission weight}} \times 100.$$

This method was then compared with two weight-based formulas. These formulas calculated fluid overload based upon ICU admission weight and hospital admission weight:

$$\text{Method 2:\%FO} = \frac{\text{CRRT initiation weight} - \text{ICU admission weight}}{\text{ICU admission weight}} \times 100,$$

$$\text{Method 3:\%FO} = \frac{\text{CRRT initiation weight} - \text{Hospital admission weight}}{\text{Hospital admission weight}} \times 100.$$

The primary outcome was all-cause ICU mortality.

Statistical methods

Due to skewness of several variables, continuous variables are represented as median (25th percentile, 75th percentile). A small amount of missing data in explanatory variables was handled via multiple imputation. Univariate comparisons were made using the nonparametric Mann–Whitney *U* and Kruskal–Wallis tests, as well as chi-square and Fisher's exact tests, as appropriate.

Methods of calculating fluid overload were compared directly via Pearson correlation coefficients. The distribution of each method was also examined and compared, and differences between each patient's fluid-based and weight-based methods were assessed.

Due to high correlations between the methods for fluid overload determination, separate multivariate logistic regression models predicting ICU mortality were conducted for all three fluid overload calculation methods. Each set of models adjusted for the same covariates, including PRISM III score and variables with $p < 0.10$ after backward selection on models containing method 1. Regression models were then compared using receiver–operator characteristic (ROC) curves, and the area under the curve (AUC) was calculated.

Subanalyses were conducted to assess the impact of fluid overload on survival within ECLS and non-ECLS patients. Models were refitted without extreme outliers, with no substantial difference in results. Significance for all statistical tests was set at two-sided $\alpha = 0.05$. Analyses were conducted using SAS 9.1 (SAS Institute, Cary, NC).

Results

Patient characteristics

During the study period a total of 116 patients underwent CRRT in our institution. Three patients were excluded from our data analysis because of prolonged intensive care unit stays

(>2 months) prior to CRRT initiation, resulting in a final study population of 113 patients. Median patient age was 19 months [interquartile range (IQR) 0.2, 181 months]. This included 37 patients 1 month of age or younger (30 patients on ECLS). Median number of hospital days prior to CRRT initiation was 6 (2, 16), and median number of PICU days prior to CRRT initiation was 3 (2, 6). Ninety-eight (87%) patients were on mechanical ventilation at time of CRRT initiation, and 85 (75%) patients were receiving vasoactive agents at CRRT initiation. Fifty (44%) patients were receiving ECLS at CRRT initiation. Nineteen (17%) patients received therapeutic plasma exchange (TPE) while on CRRT. Baseline characteristics of the study population, both overall and by ECLS status, are summarized in Table 1.

Median PRISM score at ICU admission was 13 (7,18). Fluid overload was the primary indication for initiation of CRRT in 73 patients (65%, Table 2). The most common underlying diagnosis was heart disease, in 41 patients (36%, Table 3).

Outcome variables

Overall survival to ICU discharge was 44% and was significantly lower for patients treated with ECLS compared with those patients who did not receive ECLS (32% versus 54%, $p = 0.0195$). On univariate analysis, several variables were significantly different between survivors and nonsurvivors (Table 4). These included age, number of hospital days prior to CRRT initiation, number of ICU days prior to CRRT initiation, presence of vasoactive medications, number of vasoactive medications, and mechanical ventilation at CRRT initiation. The degree of fluid overload at initiation of CRRT was significantly greater among nonsurvivors when compared with survivors, regardless of the method used to calculate fluid overload (Table 5, $p < 0.05$). This remained true for patients on ECLS (Table 5, $p < 0.05$). Univariate analysis yielded a significant association between fluid overload at CRRT initiation and mortality (Table 6, $p < 0.05$).

Multivariate logistic regression analysis found patient age, number of hospital days prior to CRRT initiation, presence of ECLS, pRIFLE score of failure, and number of vasoactive agents present at initiation to predict survival. While trending toward predicting mortality, fluid overload did not reach statistical significance on multivariate analysis (Table 6). Using method 1, the odds ratio for a 1% increase in fluid overload was 1.04 (95% CI 1.00–1.07, $p = 0.0529$). Method 2 gave an odds ratio of 1.03 (95% CI 0.99–1.07, $p = 0.0829$), and method 3 also gave an odds ratio of 1.03 (95% CI 0.99–1.06, $p = 0.10$). Additional analysis using fluid overload as a categorical variable (cutoff of either 10% or 20% fluid overload) did not demonstrate statistically significant associations either (data not shown).

Comparison of methods

There was a high degree of correlation between methods 1 and 2 (Pearson's coefficient 0.77), methods 1 and 3 (Pearson's coefficient 0.75), and methods 2 and 3 (Pearson's coefficient 0.92). All three methods shared similar predictive ability as assessed by the construction of ROC curves. The AUC for the multiple logistic regression models for method 1 was 0.881 compared with 0.858 for method 2 and 0.855 for method 3.

Discussion

This study is the first to systematically evaluate weight-based methods as a means to calculate fluid overload in pediatric patients at initiation of CRRT and its association with mortality. Our study is consistent with previous reports showing an association between fluid overload at CRRT initiation and mortality [9, 12–14] while providing a more practical weight-based approach to determining degree of fluid overload. Our study extends this

finding to a broader pediatric patient population that includes a significant number of neonatal and ECLS patients.

In their recent analysis of the multicenter Prospective Pediatric CRRT (ppCRRT) registry of 297 patients, Sutherland and colleagues reported an adjusted mortality odds ratio of 1.03 (95% CI 1.01–1.05) [12] associated with increasing fluid overload at time of CRRT initiation. Using both fluid balance and weight-based methods to define fluid overload, we found nearly identical results. We observed high correlation and comparable predictive values (AUC) between the methods, suggesting that they may be used interchangeably. We chose to assess the weight-based method because this is a more practical and less labor-intensive approach compared with calculating cumulative fluid balance. In addition, studies have reported that methods utilizing fluid balance to determine fluid overload are often inaccurate and unreliable when compared with daily weights in ICU [32, 33] or general floor settings [34]. Fluid balance calculations are generally unable to account for insensible fluid losses, and so weight-based calculations could provide for improved control of this variable. It is worth noting that daily weights also have the potential for inaccuracy related to the use of differing scales and techniques for weighing patients. There are potential safety issues around weighing ECLS patients daily; if done improperly, weighing patients on ECLS can pose dangers to the patient, including decannulation.

Nearly all previous studies examining fluid overload have defined baseline weight at the time point of ICU admission. However, fluid overload can begin to develop during the hospital stay prior to ICU admission, and thus ICU admission weights may underestimate the degree of fluid overload. We compared fluid overload definitions based on hospital admission (method 3) and ICU admission (method 2) weights. As expected, fluid overload was consistently higher using method 3. Interestingly, both methods demonstrated significant differences in percentage fluid overload between survivors and nonsurvivors, and both had similar predictive value for mortality. This was in part due to the fact that the values were identical (i.e., hospital admission was directly to the ICU) in 72% of cases. In addition, both methods correlated with the fluid balance method. Based on our limited data, we cannot conclude whether one approach is superior in providing prognostic information, and future studies are needed to explore the optimal definition of baseline weight.

In previous studies, neonates and patients requiring ECLS were underrepresented or excluded when investigating the association of fluid overload at CRRT initiation and mortality. At our institution, patients less than 1 month of age accounted for a large proportion of our CRRT population. Symons and colleagues previously reported a high mortality in patients less than 10 kg requiring CRRT [35], but the contribution of fluid overload at CRRT initiation was not investigated. We strengthen the findings of the ppCRRT group about the association of fluid overload at CRRT initiation and increased mortality in patients 1 month of age or younger [12, 36]. By the inclusion of these patients we extend the clinical importance of fluid overload to a previously understudied patient population.

This study is the first to include a significant ECLS patient population (50 patients) in the evaluation of the association between fluid overload at CRRT initiation and mortality. The importance of fluid overload in ECLS patients was reported by Swaniker and colleagues, who noted a significant difference in fluid overload at ECLS initiation between survivors and nonsurvivors in a single-center review of 128 patients [37]; only 14% of the patients required renal replacement therapy. Paden and colleagues recently reported a large single-center review of 154 pediatric patient on ECLS requiring CRRT with 44% survival, but did not report on fluid overload at CRRT initiation [38]. The importance of fluid overload at CRRT initiation in patients on ECLS has not been investigated. The majority of patients in

our study were placed on ECLS for underlying heart disease, and there was an overall high incidence of heart disease as the primary disease. The importance of fluid overload and early initiation of CRRT in patients with cardiorenal syndrome has become increasingly recognized [39]. Our results further emphasize this, as subgroup analysis of the ECLS population showed fluid overload at CRRT initiation to be significantly greater in nonsurvivors compared with survivors by weight-based or fluid balance methods. Future studies examining fluid overload status in patients on CRRT should consider inclusion of patients requiring ECLS.

Some limitations of this study should be noted. The pRIFLE criteria have not been validated in patients <28 days of age, and we modified the criteria slightly to allow for classification of younger patients. This was done to allow for a measure of renal failure in the analysis. Interestingly, the RIFLE and pRIFLE criteria provided very similar rates of "failure" at CRRT initiation in this study. In addition, we were not able to completely stratify for severity of illness or multiple organ dysfunction. The inclusion of a large ECLS population makes severity of illness scores at CRRT initiation unreliable, as Pediatric Logistic Organ Dysfunction (PELOD) scores have not been validated in patients on ECLS and PRISM scores have only been validated at time of ICU admission. We attempted to account for this with a robust multivariate model that included PRISM III score at ICU admission. Lastly, due to heterogeneity of the patient population, our study was underpowered to detect a difference by the multivariate model. With our current sample size, we had 60% power to detect the anticipated odds ratio of 1.03 in a multivariate model, and 250 patients would have been needed to achieve 90% power.

This study confirms the association between fluid overload and mortality in a broad PICU patient population. We show that weight-based definitions of fluid overload can be useful alternatives in predicting increased mortality at CRRT initiation in a broad PICU patient population. We extend the literature on fluid overload by including a significant patient population on ECLS and patients less than 1 month of age. The results of this study support a more practical weight-based definition of fluid overload for use at the bedside to guide medical decision-making.

Acknowledgments

David T. Selewski is supported by the Cellular and Molecular Biology in Pediatrics Training Program grant (T-32 HD007513-13). Timothy T. Cornell is supported by the Pediatric Critical Care Scientist Development Program (K12HD047349) and an individual Career Development Award (K08HD062142). Neal B. Blatt is supported by a Child Health Research Career Development Award (National Institutes of Health, K12 HD 028820 (T32 DK 065517).

References

1. Bunchman TE, McBryde KD, Mottes TE, Gardner JJ, Maxvold NJ, Brophy PD. Pediatric acute renal failure: outcome by modality and disease. Pediatr Nephrol. 2001; 16:1067–1071. [PubMed: 11793102]
2. Bresolin N, Silva C, Halllal A, Toporovski J, Fernandes V, Goes J, Carvalho FL. Prognosis for children with acute kidney injury in the intensive care unit. Pediatr Nephrol. 2009; 24:537–544. [PubMed: 19050934]
3. Fernandez C, Lopez-Herce J, Flores JC, Galaviz D, Ruperez M, Brandstrup KB, Bustinza A. Prognosis in critically ill children requiring continuous renal replacement therapy. Pediatr Nephrol. 2005; 20:1473–1477. [PubMed: 16047225]
4. Schneider J, Khemani R, Grushkin C, Bart R. Serum creatinine as stratified in the RIFLE score for acute kidney injury is associated with mortality and length of stay for children in the pediatric intensive care unit. Crit Care Med. 2010; 38:933–939. [PubMed: 20124891]

5. Plotz FB, Bouma AB, van Wijk JA, Kneyber MC, Bokenkamp A. Pediatric acute kidney injury in the ICU: an independent evaluation of pRIFLE criteria. Intensive Care Med. 2008; 34:1713–1717. [PubMed: 18521567]
6. Warady BA, Bunchman T. Dialysis therapy for children with acute renal failure: survey results. Pediatr Nephrol. 2000; 15:11–13. [PubMed: 11095002]
7. Brophy PD. Renal supportive therapy for pediatric acute kidney injury in the setting of multiorgan dysfunction syndrome/sepsis. Semin Nephrol. 2008; 28:457–469. [PubMed: 18790365]
8. Goldstein SL. Overview of pediatric renal replacement therapy in acute kidney injury. Semin Dial. 2009; 22:180–184. [PubMed: 19426425]
9. Flores FX, Brophy PD, Symons JM, Fortenberry JD, Chua AN, Alexander SR, Mahan JD, Bunchman TE, Blowey D, Somers MJ, Baum M, Hackbarth R, Chand D, McBryde K, Benfield M, Goldstein SL. Continuous renal replacement therapy (CRRT) after stem cell transplantation. A report from the prospective pediatric CRRT Registry Group. Pediatr Nephrol. 2008; 23:625–630. [PubMed: 18228045]
10. Michael M, Kuehnle I, Goldstein SL. Fluid overload and acute renal failure in pediatric stem cell transplant patients. Pediatr Nephrol. 2004; 19:91–95. [PubMed: 14634863]
11. Lane PH, Mauer SM, Blazar BR, Ramsay NK, Kashtan CE. Outcome of dialysis for acute renal failure in pediatric bone marrow transplant patients. Bone Marrow Transplant. 1994; 13:613–617. [PubMed: 8054914]
12. Sutherland SM, Zappitelli M, Alexander SR, Chua AN, Brophy PD, Bunchman TE, Hackbarth R, Somers MJ, Baum M, Symons JM, Flores FX, Benfield M, Askenazi D, Chand D, Fortenberry JD, Mahan JD, McBryde K, Blowey D, Goldstein SL. Fluid overload and mortality in children receiving continuous renal replacement therapy: the prospective pediatric continuous renal replacement therapy registry. Am J Kidney Dis. 2010; 55:316–325. [PubMed: 20042260]
13. Hayes LW, Oster RA, Tofil NM, Tolwani AJ. Outcomes of critically ill children requiring continuous renal replacement therapy. J Crit Care. 2009; 24:394–400. [PubMed: 19327959]
14. 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. [PubMed: 15517417]
15. Foland JA, Fortenberry JD, Warshaw BL, Pettignano R, Merritt RK, Heard ML, Rogers K, Reid C, Tanner AJ, Easley KA. Fluid overload before continuous hemofiltration and survival in critically ill children: a retrospective analysis. Crit Care Med. 2004; 32:1771–1776. [PubMed: 15286557]
16. Goldstein SL, Currier H, Graf C, Cosio CC, Brewer ED, Sachdeva R. Outcome in children receiving continuous venovenous hemofiltration. Pediatrics. 2001; 107:1309–1312. [PubMed: 11389248]
17. Goldstein SL, Somers MJ, Baum MA, Symons JM, Brophy PD, Blowey D, Bunchman TE, Baker C, Mottes T, McAfee N, Barnett J, Morrison G, Rogers K, Fortenberry JD. Pediatric patients with multi-organ dysfunction syndrome receiving continuous renal replacement therapy. Kidney Int. 2005; 67:653–658. [PubMed: 15673313]
18. Brierley J, Carcillo JA, Choong K, Cornell T, Decaen A, Deymann A, Doctor A, Davis A, Duff J, Dugas MA, Duncan A, Evans B, Feldman J, Felmet K, Fisher G, Frankel L, Jeffries H, Greenwald B, Gutierrez J, Hall M, Han YY, Hanson J, Hazelzet J, Hernan L, Kiff J, Kissoon N, Kon A, Irazuzta J, Lin J, Lorts A, Mariscalco M, Mehta R, Nadel S, Nguyen T, Nicholson C, Peters M, Okhuysen-Cawley R, Poulton T, Relves M, Rodriguez A, Rozenfeld R, Schnitzler E, Shanley T, Kache S, Skippen P, Torres A, von Dessauer B, Weingarten J, Yeh T, Zaritsky A, Stojadinovic B, Zimmerman J, Zuckerberg A. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. Crit Care Med. 2009; 37:666–688. [PubMed: 19325359]
19. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001; 345:1368–1377. [PubMed: 11794169]
20. Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, de Boisblanc B, Connors AF Jr, Hite RD, Harabin AL. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006; 354:2564–2575. [PubMed: 16714767]

21. Upadya A, Tilluckdharry L, Muralidharan V, Amoateng-Adjepong Y, Manthous CA. Fluid balance and weaning outcomes. Intensive Care Med. 2005; 31:1643–1647. [PubMed: 16193330]
22. Payen D, de Pont AC, Sakr Y, Spies C, Reinhart K, Vincent JL. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. Crit Care. 2008; 12:R74. [PubMed: 18533029]
23. Prowle JR, Echeverri JE, Ligabo EV, Ronco C, Bellomo R. Fluid balance and acute kidney injury. Nat Rev Nephrol. 2010; 6:107–115. [PubMed: 20027192]
24. Cerda J, Sheinfeld G, Ronco C. Fluid overload in critically ill patients with acute kidney injury. Blood Purif. 2010; 29:331–338. [PubMed: 20173320]
25. Antonelli M, Azoulay E, Bonten M, Chastre J, Citerio G, Conti G, De Backer D, Lemaire F, Gerlach H, Groeneveld J, Hedenstierna G, Macrae D, Mancebo J, Maggiore SM, Mebazaa A, Metnitz P, Pugin J, Wernerman J, Zhang H. Year in review in Intensive Care Medicine, 2008: I. Brain injury and neurology, renal failure and endocrinology, metabolism and nutrition, sepsis, infections and pneumonia. Intensive Care Med. 2009; 35:30–44. [PubMed: 19066847]
26. Bunchman TE, Maxvold NJ, Barnett J, Hutchings A, Benfield MR. Pediatric hemofiltration: Normocarb dialysate solution with citrate anticoagulation. Pediatr Nephrol. 2002; 17:150–154. [PubMed: 11956849]
27. Pollack MM, Patel KM, Ruttimann UE. PRISM III: an updated pediatric risk of mortality score. Crit Care Med. 1996; 24:743–752. [PubMed: 8706448]
28. Bellomo R, Ronco C, Kellum J, Mehta R, Palevsky P. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004; 8:R204–R212. [PubMed: 15312219]
29. Akcan-Arikan A, Zappitelli M, Loftis L, Washburn K, Jefferson L, Goldstein S. Modified RIFLE criteria in critically ill children with acute kidney injury. Kidney Int. 2007; 71:1028–1035. [PubMed: 17396113]
30. Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. Pediatr Clin North Am. 1987; 34:571–590. [PubMed: 3588043]
31. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006; 145:247–254. [PubMed: 16908915]
32. Eastwood GM. Evaluating the reliability of recorded fluid balance to approximate body weight change in patients undergoing cardiac surgery. Heart Lung. 2006; 35:27–33. [PubMed: 16426933]
33. Pflaum SS. Investigation of intake-output as a means of assessing body fluid balance. Heart Lung. 1979; 8:495–498. [PubMed: 254670]
34. Mank A, Semin-Goossens A, Lelie J, Bakker P, Vos R. Monitoring hyperhydration during high-dose chemotherapy: body weight or fluid balance? Acta Haematol. 2003; 109:163–168. [PubMed: 12853687]
35. Symons JM, Brophy PD, Gregory MJ, McAfee N, Somers MJ, Bunchman TE, Goldstein SL. Continuous renal replacement therapy in children up to 10 kg. Am J Kidney Dis. 2003; 41:984–989. [PubMed: 12722032]
36. Symons JM, Chua AN, Somers MJ, Baum MA, Bunchman TE, Benfield MR, Brophy PD, Blowey D, Fortenberry JD, Chand D, Flores FX, Hackbarth R, Alexander SR, Mahan J, McBryde KD, Goldstein SL. Demographic characteristics of pediatric continuous renal replacement therapy: a report of the prospective pediatric continuous renal replacement therapy registry. Clin J Am Soc Nephrol. 2007; 2:732–738. [PubMed: 17699489]
37. Swaniker F, Kolla S, Moler F, Custer J, Grams R, Barlett R, Hirschl R. Extracorporeal life support outcome for 128 pediatric patients with respiratory failure. J Pediatr Surg. 2000; 35:197–202. [PubMed: 10693665]
38. Paden ML, Warshaw BL, Heard ML, Fortenberry JD. Recovery of renal function and survival after continuous renal replacement therapy during extracorporeal membrane oxygenation. Pediatr Crit Care Med. 2010 [Epub ahead of print].

39. Ronco C, Giomarelli P. Current and future role of ultrafiltration in CRS. Heart Fail Rev. 2010 [Epub ahead of print].

Table 1

Patient characteristics, overall and by ECLS status

Variable	Overall	ECLS		*p*-Value*
	***N* = 113**	**Yes (*N* = 50)**	**No (*N* = 63)**	
Survival to ICU discharge, *N* (%)	50 (44)	16 (32)	34 (54)	0.0195
Age (months), median (IQR)	19 (0.2, 181)	0.8 (0, 10)	151 (19, 213)	<0.0001
Sex: female, *N* (%)	46 (40.7)	20 (40)	26 (41.3)	0.8915
Hospital days prior to CRRT, median (IQR)	6 (2, 16)	6 (3, 13)	4 (2, 17)	0.3491
ICU days prior to CRRT, median (IQR)	3 (2, 6)	4 (3, 11)	2 (1, 6)	0.0015
Vasoactive medications at initiation, *N* (%)	85 (75)	47 (94)	38 (60.3)	<0.0001
>2 vasoactive medications at initiation, *N* (%)	46 (40.7)	31 (62)	15 (23.8)	<0.0001
Number of vasoactive agents at initiation, median (IQR)	2 (1, 3)	3 (2, 4)	1 (0, 2)	<0.0001
Diuretic exposure, *N* (%)	81 (71.7)	45 (90)	36 (57.1)	<0.0001
Diuretic infusion, *N* (%)	51 (45.1)	33 (66)	18 (28.6)	<0.0001
Mechanical ventilation at initiation, *N* (%)	98 (86.7)	50 (100)	48 (76.2)	0.0002
Therapeutic plasma exchange, *N* (%)	19 (16.8)	8 (16)	11 (17.5)	0.8367
Patients qualifying as failure by RIFLE, *N* (%)	67 (59.3)	28 (56)	39 (61.9)	0.5257
Patients qualifying as failure by pRIFLE, *N* (%)	59 (52.2)	25 (50)	34 (54)	0.6749
PRISM III score at ICU admission, median (IQR)	13.0 (7, 18)	16 (9, 21)	11 (7, 15)	0.0085

ECLS extracorporeal life support, *CRRT* continuous renal replacement therapy

* Comparisons are between ECLS and non-ECLS groups

Table 2

Indication for continuous renal replacement therapy

Indication	Total 113 patients	
	Number	% of total patients
Fluid overload	73	64.6
Uremia	7	6.2
Electrolyte abnormalities	10	8.9
Acute on chronic renal failure	2	1.8
Hyperammonemia/intoxication	8	7.1
Multiple indications	13	11.5

Table 3

Primary disease

Primary disease	Total 113 patients	
	Number	% of total patients
Heart disease	41	36.3
Primary renal disease	6	5.3
Bone marrow transplant	12	10.6
Oncologic disease	10	8.9
Metabolic	8	7.1
Poisoning	2	1.8
Liver disease	15	13.3
Sepsis without underlying disease	8	7.1
Congenital diaphragmatic hernia	5	4.4
Other	6	5.3

Table 4

Patient characteristics by survival status

Variable	Survival		*p*-Value
	Yes (*N* = 50)	No (*N* = 63)	
Age (months), median (IQR)	131.5 (19,203)	1 (0, 85)	<0.0001
Sex: female, *N* (%)	21 (42.0)	25 (39.6)	0.8033
Hospital days prior to CRRT, median (IQR)	3 (2, 10)	8 (4, 19)	0.0104
ICU days prior to CRRT, median (IQR)	2 (1, 4)	4 (2, 11)	0.0009
Vasoactive medications at initiation, *N* (%)	29 (58.0)	56 (88.8)	0.0002
>2 vasoactive medications at initiation, *N* (%)	10 (20.0)	36 (57.1)	0.0001
Number of vasoactive agents at initiation, median (IQR)	1 (0, 2)	3 (1, 4)	<0.0001
Diuretic exposure, *N* (%)	29 (58.0)	52 (82.5)	0.0040
Diuretic infusion, *N* (%)	20 (40.0)	31 (49.2)	0.3287
Mechanical ventilation at initiation, *N* (%)	36 (72.0)	62 (98.4)	<0.0001
Presence of ECLS, *N* (%)	16 (32.0)	34 (53.9)	0.0195
Therapeutic plasma exchange, *N* (%)	10 (20.0)	9 (14.2)	0.4198
Patients qualifying as failure by RIFLE, *N* (%)	32 (64.0)	35 (55.5)	0.3641
Patients qualifying as failure by pRIFLE, *N* (%)	30 (60.0)	29 (46.0)	0.1398
PRISM III score at ICU admission, median (IQR)	11.5 (5, 16)	13 (10, 19)	0.0838

CRRT continuous renal replacement therapy, *ECLS* extracorporeal life support

Table 5

Degree of fluid overload at CRRT initiation, overall and among ECLS patients, stratified by survival status

Variable	Overall	Survival		*p*-Value
All patients	***N* = 113**	**Yes (*N* = 50)**	**No (*N* = 63)**	
Method 1 fluid overload %, median (IQR)	14 (6, 32)	8 (2, 14)	25 (13, 38)	<0.0001
Method 2 fluid overload %, median (IQR)	8 (0, 27)	3 (0, 15)	18 (2, 41)	0.0006
Method 3 fluid overload %, median (IQR)	16 (2, 30)	5 (0, 24)	23 (9, 47)	<0.0001
Patients on ECLS	*N* = 50	Yes (*N* = 16)	No (*N* = 34)	
Method 1 fluid overload %, median (IQR)	26.5 (14, 42)	13 (8.5, 27.5)	35 (22, 46)	0.0012
Method 2 fluid overload %, median (IQR)	29.5 (16, 49)	24 (5.5, 26.5)	38 (21, 51)	0.0093
Method 3 fluid overload %, median (IQR)	34 (22, 50)	24 (5.5, 26.5)	41 (30, 51)	0.0009

CRRT continuous renal replacement therapy, *ECLS* extracorporeal life support

Methods 1–3 are defined in text

Table 6

Results of logistic regression analysis assessing odds of death based on degree of fluid overload at CRRT initiation

Variable[a]	Odds ratio	95% CI	*p*-Value
Univariate analysis			
Method 1 fluid overload	1.056	1.025, 1.087	0.0002
Method 2 fluid overload	1.044	1.019, 1.069	0.0005
Method 3 fluid overload	1.045	1.022, 1.07	0.0002
Multivariate analysis[b]			
Method 1 fluid overload	1.04	1.00, 1.07	0.0529
Method 2 fluid overload	1.03	0.99, 1.07	0.0829
Method 3 fluid overload	1.03	0.99, 1.06	0.1

CRRT continuous renal replacement therapy

[a] Methods 1–3 are defined in text

[b] Model adjusting for age, hospital days pre CRRT, extracorporeal life support status, pRIFLE score of failure, and number of vasoactive agents