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Assessment of the Independent and Synergistic Effects of Fluid Overload and Acute Kidney Injury on Outcomes of Critically Ill Children

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Abstract

Purpose—Evaluate the independent and synergistic associations of fluid overload (FO) and acute kidney injury (AKI) with outcome in critically ill pediatric patients.

Design—Secondary analysis of the AKI in Children Expected by Renal angina and Urinary Biomarkers (AKI-CHERUB,) prospective observational study

Setting—Single center quaternary level pediatric intensive care unit (PICU)

Patients—149 children aged 3 months to 25 years with predicted PICU length of stay >48 hours, and an indwelling urinary catheter enrolled (9/2012–3/2014). AKI (defined by creatinine or urine output on day 3) and FO (≥20% on day 3) were used as outcome variables and risk factors for ICU endpoints assessed at 28 days.

Results—AKI and FO occurred in 19.4% and 24.2% respectively. Both AKI and FO were associated with longer ICU length of stay (LOS) but neither maintained significance after multivariate regression. Delineation into unique FO/AKI classifications demonstrated that FO⁺ patients experienced a longer ICU and hospital LOS and higher rate of mortality compared to FO[−]

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patients, regardless of AKI status. FO⁺/AKI⁻ patients had increased odds of death ($p=0.013$). After correction for severity of illness, ICU LOS remained significantly longer in FO⁺/AKI⁺ patients compared to patients without both classifications (17.4 (11.0–23.7; 95%CI) vs. 8.8 (7.3–10.9; 95%CI), $p=0.05$). Correction of AKI classification for net fluid balance led to AKI class switching in 29 patients and strengthened the association with increased mechanical ventilation and ICU LOS on bivariate analysis, but reduced the increased risk conferred by FO for mortality.

Conclusion—The current study suggests the effects of significant fluid accumulation may be delineable from the effects of AKI. Concurrent fluid overload and AKI significantly worsens outcome. Correction of AKI assessment for net fluid balance may refine diagnosis and unmask AKI associated with deleterious downstream sequelae. The unique effects of fluid overload and AKI on outcome in critically ill patients warrant further study.

Keywords

Acute kidney injury; fluid overload; pediatric intensive care; corrected serum creatinine; KDIGO AKI

INTRODUCTION

Acute kidney injury (AKI) occurs commonly in critically ill patients and is associated with poor prognosis. Recent large, multi-national multi-center epidemiologic studies indicate AKI is associated with increased mechanical ventilation duration, prolonged hospital stay, and higher rates of death in neonates, children, and adults (1–3). Simultaneously, parallel data indicates significant positive net fluid balance or fluid accumulation, termed fluid overload (FO), is also associated with worse patient outcome, particularly in children (4). Higher degrees of FO are associated with adverse outcomes and complications including increased rates of infection, delayed wound healing, prolonged mechanical ventilation, utilization of renal replacement therapy, and mortality (5–17).

The timing of AKI and FO is important. Consensus statements now recognize Day 3 of hospitalization as the time point for which creatinine elevation is damage associated AKI (18). Creatinine elevation prior to this time may be functional damage and not be indicative of meaningful AKI (19). Evidence indicates Day₃-AKI is associated with an increased duration of mechanical ventilation, longer intensive care unit length of stay (ICU LOS) and higher mortality rates (20). Early fluid accumulation may be less deleterious on patient outcome than late fluid accumulation (21, 22). Though volume restoration is central to initial resuscitation and stabilization efforts in critically ill patients (23), distinct phases of fluid balance likely exist in ICU patients (24).

While AKI and FO each seem to be associated with adverse outcomes, it remains unclear if they carry independent effects. The interplay between the two phenomena is complicated as they are physiologically linked; AKI is a risk factor for fluid accumulation and fluid accumulation is a risk factor for AKI (25). However, despite the bidirectional risk, not all AKI patients suffer excessive fluid accumulation and not all patients with significant fluid accumulation suffer AKI. Recent evidence from both adult and pediatric populations suggest AKI diagnosed by creatinine elevation and oliguria is associated with worse outcome than

either criteria independently (26, 27). Unfortunately, even though AKI and FO are frequently assessed, very few studies have attempted to delineate the independent and synergistic impact of both factors. A paucity of data specifically discusses the deleterious associations of FO in the absence of AKI. The relationship of AKI and fluid balance is further complicated by the dilutional effect of fluid on serum creatinine concentration. Several recent reports detail how correction of serum creatinine concentration for net fluid balance refines AKI diagnosis, ultimately changing the epidemiology of both AKI incidence and outcome associations (28–31).

An understanding of the individual and potentially synergistic effects of fluid accumulation in the context of AKI is needed. We studied a population of critically ill pediatric patients to test the hypothesis that fluid overload is a distinct phenotype of critical illness, associated with poor downstream patient outcome both in isolation and in combination with AKI.

METHODS

Study Design

We conducted a secondary analysis of data from the Acute Kidney Injury in Children Expected by Renal angina and Urinary Biomarkers (AKI-CHERUB, [NCT01735162](#)) study, a prospective observational study conducted in a single-center, quaternary care pediatric intensive care unit (PICU) (32). AKI-CHERUB served as the pilot study for the AKI-Assessment of Worldwide AKI in Pediatrics, Renal Angina and Epidemiology (AWARE, [NCT01987921](#))(3). The study was approved by the Institutional Review Board with waiver of the need for informed consent. Study procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2000.

Population

Primary inclusion criteria for AKI-CHERUB study were all children admitted to the PICU aged 3 months to 25 years predicted to have a ICU length of stay (LOS) > 48 hours with an indwelling urinary catheter. Primary exclusion criteria included a history of end-stage renal disease and admission immediately following renal transplant. Only patients with full data on Day 3 (inclusive of serum creatinine, urine output, and net fluid balance) were included in this analysis.

Data

Demographic and initial available laboratory parameters, including Pediatric Risk of Mortality III score (PRISM-III) were collected on the day of PICU admission. Sepsis presence or absence was determined on the day of admission to ICU based on consensus pediatric sepsis criteria. Data were collected for seven consecutive days (Days 1–7 denoted as Day₁, Day₂, and so on). Daily collected variables were assessed at 8:00 am for each patient on Days_{1–7} and included vital signs, serum and urine laboratory values, mechanical ventilation support level, urine output, and total ICU fluid balance. Day-3 of ICU stay (Day₃) was used to assess the principal outcome variables of AKI and FO

Definitions

Fluid Overload—Daily fluid input and output (in liters) were recorded for each day of hospital admission. Daily FO was calculated as a percentage (%FO) relative to admission weight as previously described (9):

$$\%FO = \frac{(\text{Fluid in} - \text{Fluid out})}{\text{ICU Admission Weight (kg)}} \times 100$$

%FO on Day₃ was determined for each patient and for this analysis, %FO ≥ 20 was used as the cut-off for “FO”.

Acute Kidney Injury—AKI was classified on Day₃. Kidney Disease Improving Global Outcomes (KDIGO) serum creatinine (SCr) and urine output (UOP) based AKI criteria were utilized to stage AKI (33). The worse of either criterion were used to denote AKI stage and all stages of AKI (1–3) were denoted as “AKI” for this analysis. The baseline SCr was defined as the lowest value in the 3 months before ICU admission. If no baseline SCr was available, a baseline SCr was imputed to an estimated creatinine clearance of 120 mL/min/1.73m², as previously validated (3, 34).

Fluid Overload/AKI phenotypes—Four unique patient phenotypes were created based on the achievement of FO and AKI on Day 3. These phenotypes were classified: FO⁻/AKI⁻, FO⁺/AKI⁻, FO⁻/AKI⁺ and FO⁺/AKI⁺.

Fluid Corrected Creatinine—Fluid balance was used to correct creatinine as previously described by the following formula (28, 30):

$$\text{Corrected SCr} = \text{Measured creatinine} \times [1 + (\text{accumulated net fluid balance}/\text{total body water}^*)]$$

*Total body water by age classification:

$$3 \text{ months} - 1 \text{ year} = 0.8 \times \text{weight (kg)}$$

$$1 \text{ year} - 2 \text{ year} = 0.7 \times \text{weight (kg)}$$

$$2 \text{ years} = 0.6 \times \text{weight (kg)}$$

The correction was performed on Day₃ using the Day₃-SCr and Day₃ net fluid balance data. AKI classified using corrected SCr was denoted “AKI_{corr}”.

Outcomes

Short-term and long-term outcomes were studied. Both AKI and FO were used as outcome variables for initial comparison (and creation of phenotypes) and then also used as independent variables for the modeling of longer term outcomes. Additionally, they were included in bivariate analyses when analyzing patient outcome on Day₂₈: duration of mechanical ventilation, ICU and hospital LOS (both assessed on review of chart at one year following enrollment (data censored at this time if patient still hospitalized), time of

discharge from hospital, or time of death), use of continuous renal replacement therapy (CRRT), and 28-day mortality.

Statistical Analysis

Descriptive statistics for continuous variables were summarized as mean and standard deviation or median and inter quartile range when determined skewed by a Shapiro-Wilks test. Categorical variables were summarized as counts and percentages. Summary statistics are presented in tabular form. Differences in ordinal outcome such as length of stay and PRISM-III score were compared with Unpaired T-Tests or Wilcoxon Rank Sum tests, and dichotomous outcomes by Chi-Squared or Fisher's Exact tests. Logistic regression models assessed bivariate associations between dichotomous outcomes and fluid overload as a continuous variable, Spearman's correlation assessed bivariate associations between ordinal variables. Multiple general linear regression models were used to derive estimated associations between AKI, FO and the outcomes of duration of mechanical ventilation and length of stay (hospital and ICU). The regression models incorporated the model terms of age, fluid overload, AKI, and PRISM-III scores – to a priori limit the effects of collinearity but also to use practical, highest relevance of importance. Pairwise differences between the four FO/AKI phenotypes were analyzed yielding model estimated means. Statistical significance level was set at $\alpha < 0.05$ level. The data analysis was performed using SAS software 9.4, Cary, NC, USA, and JMP. Copyright © 2002–2012 SAS Institute Inc.

RESULTS

Demographics

From 184 enrolled patients in CHERUB, 149 had complete Day₃ and Day₂₈ data and were included in this analysis (Table 1). A slight majority of patients were male, most were school age, and came from an evenly balanced proportion of admission sources. Mortality remained lower than mortality risk (MR) predicted by severity of illness (6% vs. PRISM-III 8 (4–14), MR 10–15%).

Acute Kidney Injury & Fluid Overload

Twenty-nine (19.5%) patients had AKI on Day 3 and 36 (24.2%) had FO. Ten (6.7%) patients had both AKI and FO. (Table 2). The median age of patients with AKI was 12.9 [5.0,17.3], but 2.9 [1.4, 12.5] for patients with FO. Sepsis was more prevalent and the median PRISM-III score was higher in patients with AKI than those without AKI ($p=0.008$ and 0.0004 respectively). Conversely, the PRISM-III score was not significantly different in patients with or without FO. AKI was significantly associated with longer LOS (ICU and hospital) while FO was significantly associated with ICU LOS. All associations lost significance on multivariate regression (Supplemental Table 1). Both AKI and FO were associated with mortality on bivariate analysis ($p=0.002$ and 0.05 , respectively) (Supplemental Table 2), but lost significance on adjustment for severity of illness (data not shown).

Separation of AKI and Fluid Overload

Separation into four FO/AKI phenotypes demonstrated nearly equal distribution of both conditions in isolation with 6.7% patients suffering both (Table 3). Paired analyses to control for AKI was used to determine bivariate associations of FO with outcome. In patients without AKI, severity of illness scores (PRISM-III) were not significantly different in patients with FO compared to those without FO. In patients without AKI, mortality was higher in FO patients ($p=0.001$). Although the median duration of mechanical ventilation and ICU LOS were longer in patients with FO, these differences were not significant (Supplemental Table 1). In patients with AKI, there were no significant differences in severity of illness or ICU outcomes, including mortality, in patients with or without FO. In regression modeling, the median of ICU LOS was significantly longer in the FO⁺/AKI⁺ phenotype than any of the other three phenotypes (17.4, 95% CI: 11.0, 23.7; $p = 0.05$) (Figure 1, top panel). Additionally, mortality incidence increased through the phenotype groups as did the odds of death. The odds of death were 23.3 times greater in FO⁺/AKI⁺ compared to patients FO⁻/AKI⁻ (95% CI: 1.9 – 285.2; $p = 0.014$) (Figure 1, bottom panel). The relative risk to mortality conferred by the exposure of FO (in AKI negative patients) was 14.5 (95% CI: 1.69–123.9, $p=0.015$). The relative risk to mortality conferred by the exposure of AKI (in FO negative patients) was (9.9; 95% CI: 0.94–103.7, $p=0.056$).

Correction of Creatinine Strengthens Outcome Associations with AKI

After correction of serum creatinine on Day 3 for net fluid balance, corrected AKI classifications were determined. “Class switching” between AKI stages occurred in 21 patients (Figure 2). AKI_{corr} demonstrated stronger bivariate associations with both MV duration and ICU LOS ($p=0.003$ and 0.0005 , respectively) compared to the AKI without correction ($p=0.079$ and 0.028) (Table 4). When AKI_{corr} was used to identify FO/AKI phenotypes, the conferred increased risk of mortality with FO (in AKI⁺ patients) seen in the uncorrected phenotype separation was reduced and there was no longer a significant increase in odds of mortality (Supplemental Table 3).

DISCUSSION

This study attempts to delineate the independent and synergistic effects of AKI and significant fluid accumulation in a heterogeneous population of critically ill children. Our findings suggest multiple associations of fluid overload with patient outcome: 1) FO may increase ICU resource utilization (longer MV duration and ICU LOS), 2) independent of AKI status, FO may increase mortality, and 3) correction of creatinine for net fluid balance may improve the precision of both AKI diagnosis and associated sequelae, including the associations with FO.

The adjudication and precision of the diagnosis of AKI continues to evolve. The importance of accounting for UOP in AKI diagnosis has been highlighted (3). In this study, we operationalize the directives from the 16th Acute Dialysis and Quality Initiative (determination of AKI by persistent SCr change on Day 3) (18). Our study defined % FO as the assessment made at Day 3. This time window represents an epoch of ICU care almost assuredly outside the resuscitation phase of critical illness and likely beyond the stabilization

phase. Theoretically, this time frame is a period for titration of therapy and was intentionally chosen to match the day of AKI assessment. Additionally, in addition to incorporating the correction of serum creatinine for fluid balance to adjust AKI diagnosis, this study separates patients into phenotypes, stratifying patients by AKI and FO status. Importantly, we incorporated an adjustment in the correction factor by age for total body water composition (the correction factor increases by up to 33% in young children and infants).

While many recent publications indicate excessive fluid accumulation is associated with poor patient outcome in multiple patient populations (4, 6, 35–37), very few attempt to extricate the independent effects of fluid balance from AKI. Physiologically, the two diagnoses of AKI and FO are linked as AKI patients with oliguria are at high risk of fluid accumulation. Data from adults and children suggest oliguria alone is an independent risk factor for poor outcome and if oliguria is assumed to be a significant factor (in addition to iatrogenic fluid accumulation and fluid creep) for FO, our data mirror these reports. Separation of patients into FO and AKI “phenotypes” facilitated the identification of potential contribution of FO in the context of controlling for AKI status. Our findings are not conclusive but suggest independent risks with FO and a significant deleterious effect of FO and AKI in concert. This finding also parallels the aforementioned data about oliguric-AKI; patients with AKI by both creatinine elevation and oliguria suffered a significantly worse outcome than either classification alone (26, 27). This finding may be impactful. While a singular (or multi-modal) therapy for AKI has yet to be discovered, fluid balance is addressed regularly in the ICU and offers a range of management options. Importantly, net fluid balance is modifiable. Decisions regarding fluid management are made on critically ill patients multiple times daily – pertaining to fluids delivered and fluids removed either independently, using medicine such as diuretics, or even mechanical fluid removal. Notably, on reclassification of the four phenotypes using corrected serum creatinine concentration, the increased conferred risk of mortality by FO seen in the uncorrected phenotype was reduced – suggesting that routine correction of serum creatinine for fluid balance (when diagnosis of AKI is made) may be a first step to identifying the true associations with fluid overload. Together, management of fluid balance by taking into consideration the relationship of FO with AKI diagnosis and downstream outcomes may represent practical opportunities to improve patient care.

Refining the precision of creatinine concentration may be the most feasible novel biomarker for many providers. Even though biomarkers of AKI are gaining more attention in the medical literature, access at the bedside to these diagnostics is not commonplace (particularly in the United States and even more particularly in pediatrics). Analyzing the change in creatinine over time, translated into the kinetic estimate of glomerular filtration rate (KeGFR) is a practical method (38). Correction of creatinine for fluid balance is simple and may “unmask” AKI (28–30). Liu et al reported that the correction of serum creatinine for FO uncovered an additional 15% of cases of AKI and further solidified the association of AKI with adverse outcomes (28). Two studies analyzing children following cardiopulmonary bypass reported parallel findings in 2 different populations surgery (30, 31). This is particularly concerning given the recent data suggesting FO may predate AKI. Hassinger et al recently reported in a cohort of 98 patients following cardiopulmonary

bypass that the development of FO (5%) preceded the development of AKI prior to meeting SCr based definitions (11).

This report has several weaknesses. Although we prospectively studied a heterogeneous population of critically ill patients, the sample size was relatively small. The requirement of an indwelling urinary catheter and expected stay > 48 hours (inclusion / exclusion criteria) skewed enrollment to a subset of PICU patients. The urinary catheter on enrollment criteria also missed patients who did not actually have a catheter on Day 0 of ICU course and subsequently had one placed. Many of the associations uncovered by bivariate analysis failed to hold significance on multivariate regression, potentially due to the smaller sample size. There were patterns of AKI and FO classifications based on age and size in addition to the severity of illness that we did not incorporate into our regression models. Additionally, we did not perform dichotomization of continuous variables for the purposes of linear or logistic regression as we felt the additive analyses would miss the exploratory findings of this preliminary report. Finally, our data are limited to a single-center and subject to the practice consistencies inherently associated with providers of a single institution. The findings of this report were derived from a pilot study (AKI-CHERUB) which was halted as the larger, multi-center AWARE study was initiated (3).

CONCLUSION

Both FO and AKI are associated with poor outcomes. Our findings suggest excessively positive net fluid balance, now termed fluid overload, may confer increased risk for poor outcome for critically ill patients, irrespective of severity of illness or AKI status. Correcting creatinine for net fluid balance provides a simple way of improving AKI diagnostic precision and also of identifying additional patients at risk for poor outcomes. Mitigation of fluid accumulation before Day 3 of ICU course may, if possible, be associated with improved patient outcomes. These findings warrant analysis in larger populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Jetton JG, Boohaker LJ, Sethi SK, et al. Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study. *The Lancet Child & Adolescent Health* 2017;1(3):184–194.

2. Hoste EA, Bagshaw SM, Bellomo R, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. *Intensive Care Med* 2015;41(8):1411–1423. [PubMed: 26162677]
3. Kaddourah A, Basu RK, Bagshaw SM, et al. Epidemiology of Acute Kidney Injury in Critically Ill Children and Young Adults. *N Engl J Med* 2017;376(1):11–20. [PubMed: 27959707]
4. Alobaidi R, Morgan C, Basu RK, et al. Association Between Fluid Balance and Outcomes in Critically Ill Children: A Systematic Review and Meta-analysis. *JAMA Pediatr* 2018;172(3):257–268. [PubMed: 29356810]
5. Alkandari O, Eddington KA, Hyder A, et al. Acute kidney injury is an independent risk factor for pediatric intensive care unit mortality, longer length of stay and prolonged mechanical ventilation in critically ill children: a two-center retrospective cohort study. *Crit Care* 2011;15(3):R146. [PubMed: 21663616]
6. Arikan AA, Zappitelli M, Goldstein SL, et al. Fluid overload is associated with impaired oxygenation and morbidity in critically ill children. *Pediatr Crit Care Med* 2012;13(3):253–258. [PubMed: 21760565]
7. Flori HR, Church G, Liu KD, et al. Positive fluid balance is associated with higher mortality and prolonged mechanical ventilation in pediatric patients with acute lung injury. *Critical care research and practice* 2011;2011:854142. [PubMed: 21687578]
8. Foland JA, Fortenberry JD, Warshaw BL, et al. Fluid overload before continuous hemofiltration and survival in critically ill children: a retrospective analysis. *Critical care medicine* 2004;32(8):1771–1776. [PubMed: 15286557]
9. Goldstein SL, Currier H, Graf C, et al. Outcome in children receiving continuous venovenous hemofiltration. *Pediatrics* 2001;107(6):1309–1312. [PubMed: 11389248]
10. Goldstein SL, Somers MJ, Baum MA, et al. Pediatric patients with multi-organ dysfunction syndrome receiving continuous renal replacement therapy. *Kidney Int* 2005;67(2):653–658. [PubMed: 15673313]
11. Hassinger AB, Wald EL, Goodman DM. Early postoperative fluid overload precedes acute kidney injury and is associated with higher morbidity in pediatric cardiac surgery patients. *Pediatr Crit Care Med* 2014;15(2):131–138. [PubMed: 24366508]
12. Hazle MA, Gajarski RJ, Yu S, et al. Fluid overload in infants following congenital heart surgery. *Pediatr Crit Care Med* 2013;14(1):44–49. [PubMed: 23249789]
13. Li Y, Wang J, Bai Z, et al. Early fluid overload is associated with acute kidney injury and PICU mortality in critically ill children. *Eur J Pediatr* 2016;175(1):39–48. [PubMed: 26206387]
14. Selewski DT, Cornell TT, Blatt NB, et al. Fluid overload and fluid removal in pediatric patients on extracorporeal membrane oxygenation requiring continuous renal replacement therapy. *Critical care medicine* 2012;40(9):2694–2699. [PubMed: 22743776]
15. Sinitsky L, Walls D, Nadel S, et al. Fluid overload at 48 hours is associated with respiratory morbidity but not mortality in a general PICU: retrospective cohort study. *Pediatr Crit Care Med* 2015;16(3):205–209. [PubMed: 25581632]
16. Sutherland SM, Zappitelli M, Alexander SR, et al. Fluid overload and mortality in children receiving continuous renal replacement therapy: the prospective pediatric continuous renal replacement therapy registry. *American journal of kidney diseases: the official journal of the National Kidney Foundation* 2010;55(2):316–325. [PubMed: 20042260]
17. Selewski DT, Askenazi DJ, Bridges BC, et al. The Impact of Fluid Overload on Outcomes in Children Treated With Extracorporeal Membrane Oxygenation: A Multicenter Retrospective Cohort Study. *Pediatr Crit Care Med* 2017;18(12):1126–1135. [PubMed: 28937504]
18. Chawla LS, Bellomo R, Bihorac A, et al. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. *Nature reviews Nephrology* 2017;13(4):241–257. [PubMed: 28239173]
19. McCullough PA, Shaw AD, Haase M, et al. Diagnosis of acute kidney injury using functional and injury biomarkers: workgroup statements from the tenth Acute Dialysis Quality Initiative Consensus Conference. *Contrib Nephrol* 2013;182:13–29. [PubMed: 23689653]

20. Blinder JJ, Asaro LA, Wypij D, et al. Acute Kidney Injury After Pediatric Cardiac Surgery: A Secondary Analysis of the Safe Pediatric Euglycemia After Cardiac Surgery Trial. *Pediatr Crit Care Med* 2017;18(7):638–646. [PubMed: 28492399]
21. Murphy CV, Schramm GE, Doherty JA, et al. The importance of fluid management in acute lung injury secondary to septic shock. *Chest* 2009;136(1):102–109. [PubMed: 19318675]
22. Silversides JA, Fitzgerald E, Manickavasagam US, et al. Deresuscitation of Patients With Iatrogenic Fluid Overload Is Associated With Reduced Mortality in Critical Illness. *Crit Care Med* 2018;46(10):1600–1607. [PubMed: 29985214]
23. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med* 2017;43(3):304–377. [PubMed: 28101605]
24. Hoste EA, Maitland K, Brudney CS, et al. Four phases of intravenous fluid therapy: a conceptual model. *Br J Anaesth* 2014;113(5):740–747. [PubMed: 25204700]
25. Ostermann M, Straaten HM, Forni LG. Fluid overload and acute kidney injury: cause or consequence? *Crit Care* 2015;19:443. [PubMed: 26707872]
26. Kaddourah A, Basu RK, Goldstein SL, et al. Oliguria and Acute Kidney Injury in Critically Ill Children: Implications for Diagnosis and Outcomes. *Pediatr Crit Care Med* 2019.
27. Kellum JA, Sileanu FE, Murugan R, et al. Classifying AKI by Urine Output versus Serum Creatinine Level. *J Am Soc Nephrol* 2015;26(9):2231–2238. [PubMed: 25568178]
28. Liu KD, Thompson BT, Ancukiewicz M, et al. Acute kidney injury in patients with acute lung injury: impact of fluid accumulation on classification of acute kidney injury and associated outcomes. *Crit Care Med* 2011;39(12):2665–2671. [PubMed: 21785346]
29. Macedo E, Bouchard J, Soroko SH, et al. Fluid accumulation, recognition and staging of acute kidney injury in critically-ill patients. *Crit Care* 2010;14(3):R82. [PubMed: 20459609]
30. Basu RK, Andrews A, Krawczeski C, et al. Acute kidney injury based on corrected serum creatinine is associated with increased morbidity in children following the arterial switch operation. *Pediatr Crit Care Med* 2013;14(5):e218–224. [PubMed: 23439467]
31. SooHoo MM, Patel SS, Jagers J, et al. Acute Kidney Injury Defined by Fluid Corrected Creatinine in Neonates After the Norwood Procedure. *World J Pediatr Congenit Heart Surg* 2018;9(5):513–521. [PubMed: 30157730]
32. Menon S, Goldstein SL, Mottes T, et al. Urinary biomarker incorporation into the renal angina index early in intensive care unit admission optimizes acute kidney injury prediction in critically ill children: a prospective cohort study. *Nephrol Dial Transplant* 2016;31(4):586–594. [PubMed: 26908772]
33. Kellum JA, Lameire N, Group KAGW. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Crit Care* 2013;17(1):204. [PubMed: 23394211]
34. Zappitelli M, Parikh CR, Akcan-Arikan A, et al. Ascertainment and epidemiology of acute kidney injury varies with definition interpretation. *Clin J Am Soc Nephrol* 2008;3(4):948–954. [PubMed: 18417742]
35. Valentine SL, Sapru A, Higgerson RA, et al. Fluid balance in critically ill children with acute lung injury. *Crit Care Med* 2012;40(10):2883–2889. [PubMed: 22824936]
36. Mah KE, Hao S, Sutherland SM, et al. Fluid overload independent of acute kidney injury predicts poor outcomes in neonates following congenital heart surgery. *Pediatr Nephrol* 2018;33(3):511–520. [PubMed: 29128923]
37. Flores-Gonzalez JC, Valladares CM, Yun Castilla C, et al. Association of Fluid Overload With Clinical Outcomes in Critically Ill Children With Bronchiolitis: Bronquirolitis en la Unidad de Cuidados Intensivos Pediatricos (BRUCIP) Study. *Pediatr Crit Care Med* 2019;20(3):e130–e136. [PubMed: 30664037]
38. Chen S Retooling the creatinine clearance equation to estimate kinetic GFR when the plasma creatinine is changing acutely. *J Am Soc Nephrol* 2013;24(6):877–888. [PubMed: 23704286]

Figure 1. Associations of Fluid Overload and Acute Kidney Injury Phenotypes with Outcome. **(Top)** The model estimated mean length of stay for each phenotype are shown in the figure after regression modeling with interaction terms of fluid overload (FO) and acute kidney injury (AKI) and severity of illness scores. The estimated differences between FO⁺/AKI⁺ were compared to the other groups. **(Bottom)** Odds ratios for mortality were calculated and compared between each phenotype and the absence of both FO and AKI (FO⁻/AKI⁻).

Figure 2. AKI Class Switching After Correction of Creatinine for Net Fluid Balance.

Net fluid balance was used to correct serum creatinine concentration and a subsequent revised classification of AKI status was made (AKI_{corr}). Panels depict patients switching classes after the correction from an uncorrected state of No AKI (a), Stage 1 (b), Stage 2 (c), and Stage 3 (d).

Table 1.

Demographics, Clinical Characteristics and Outcomes of the included patients

Characteristic	Data (n = 149)
Male, n (%)	77 (51.7)
Age (years)	7.6 [2.7, 15.2]
Weight, kg	25.3 [13.3, 54.7]
Height, cm	122.5 [87.5, 157.5]
Baseline creatinine	0.4 [0.3, 0.6]
Admit from	
Emergency Department	45 (30.2)
Hospital Floor	35 (23.5)
Surgical Services	56 (37.6)
Transfer from another ICU	13 (8.7)
History of transplant [*] , n (%)	20 (13.4)
Sepsis, n (%)	40 (26.9)
PRISM-III	8 [4, 14]
AKI [#] , n (%)	29 (19.5)
FO [@] , n (%)	36 (24.2)
MV duration (days)	3 [0, 7]
CRRT use, n (%)	7 (4.7)
ICU LOS (days)	6 [4, 12]
Hospital LOS (days)	17 [9,36]
Mortality, n (%)	9 (6.04)

All continuous variables are presented as median with interquartile range. Categorical variables are presented as number with percent.

* Includes solid organ or stem cell transplantation

[#] All-stage AKI on Day 3

[@] FO% 20 on Day 3.

Pediatric Risk of Mortality-III (PRISM-III), Mechanical ventilation (MV), Continuous Renal Replacement Therapy (CRRT), Intensive Care Unit (ICU), Length of Stay (LOS)

Demographics, Clinical Characteristics and Outcomes Associated with acute kidney injury and fluid overload

Table 2.

Characteristic	No AKI (n = 120)	AKI (n = 29)	P-value	No FO (n = 113)	FO (n = 36)	P-value
Male	57 (47.5)	20 (68.9)	0.062	52 (46.0)	25 (69.4)	0.024
Age, (years)	6.3 [2.7, 14.3]	12.9 [5.0, 17.3]	0.129	10.5 [3.5, 16.1]	2.9 [1.4, 12.5]	0.002
Weight (kg)	23.4 [13.3, 46.5]	41.1 [18.7, 66.9]	0.101	31.3 [14.7, 56.0]	14.8 [11.2, 31.9]	0.005
History of transplant *	11 (9.2)	9 (31.0)	0.005	11 (9.7)	9 (25)	0.039
Sepsis	26 (21.7)	14 (48.3)	0.008	31 (27.4)	9 (25)	0.943
PRISM-III	7 [3, 13]	12 [8, 19]	0.0004	8 [3, 14]	8 [5, 14]	0.629
AKI [#]	n/a	n/a		19 (16.8)	10 (27.8)	0.148
FO [@]	26 (21.7)	10 (34.5)	0.148	n/a	n/a	
MV duration (days)	2 [0, 6]	6 [1, 8]	0.079	2 [0, 6]	4 [1, 7]	0.356
CRR ^T use, n (%)	0 (0.00)	7 (24.14)	<0.0001	4 (3.5)	3 (8.3)	0.465
ICU LOS (days)	6 [4, 11]	8 [6, 18]	0.028	6 [3, 12]	10 [6, 15]	0.042
Hospital LOS (days)	16 [8, 30]	30 [16, 49]	0.021	16 [9, 34]	18 [10, 41]	0.619
Mortality	5 (4.2)	4 (13.8)	0.129	3 (2.7)	6 (16.7)	0.008

All continuous variables are presented as median with interquartile range. Categorical variables are presented as number with percent.

* Includes solid organ or stem cell

[#] All-stage AKI on Day 3

[@] FO% 20 on Day 3

Acute kidney injury (AKI), fluid overload (FO), Pediatric Risk of Mortality-III (PRISM-III), Mechanical ventilation (MV), Continuous Renal Replacement Therapy (CRR^T), Intensive Care Unit (ICU), Length of Stay (LOS)

Table 3.

Demographics, Clinical Characteristics and Outcomes by Fluid Overload/Acute Kidney Injury Phenotypes

Characteristic	All (n = 149)	FO-/AKI- (n = 94)	FO-/AKI+ (n = 19)	FO+/AKI- (n = 26)	FO+/AKI+ (n = 10)
Male	77 (51.7)	41 (43.6)	11 (57.9)	16 (61.5)	9 (90)
Age (years)	7.6 [2.7, 15.2]	8.0 [3.1, 15.5]	15.4 [8.8, 18.2]	2.9 [1.4, 12.1]	3.9 [1.7, 11.0]
Weight (kg)	25.3 [13.3, 54.7]	29.8 [14.1, 49.8]	54.7 [26.1, 73.6]	14.8 [11.3, 30.7]	15.6 [10.5, 47.3]
History of transplant *	20 (13.42)	6 (6.4)	5 (26.3)	5 (19.2)	4 (40)
Sepsis	40 (26.85)	22 (23.4)	9 (47.4)	4 (15.3)	5 (50)
PRISM-III	8 [4, 14]	7 [2, 14]	12 [8, 18]	7 [4, 12]	12 [8, 23]
MV duration (days)	3 [0, 7]	2 [0, 6]	4 [2, 12]	4 [1, 6]	7 [0, 8]
CRRT use	7 (4.7)	0 (0)	4 (21.1)	0 (0)	3 (30)
ICU LOS (days)	6 [4, 12]	5 [3, 11]	8 [5, 17]	9 [5, 12]	14 [7, 18]
Hospital LOS (days)	17 [9, 36]	40 [7, 49]	15 [8, 30]	26 [16, 61]	17 [10, 29]
Mortality	9 (6.0)	1 (1.1)	2 (10.5)	4 (15.4)	2 (20)

All continuous variables are presented as median with interquartile range. Categorical variables are presented as number with percent.

* Includes solid organ or stem cell

All-stage AKI on Day 3

@ FO% 20 on Day 3

Acute kidney injury (AKI), fluid overload (FO), Number (N), Pediatric Risk of Mortality-III (PRISM-III), Mechanical ventilation (MV), Continuous Renal Replacement Therapy (CRRT), Intensive Care Unit (ICU), Length of Stay (LOS). Data expressed as medians [interquartile ranges]

Table 4.

Demographics, Clinical Characteristics and Outcomes by Day 3 Acute Kidney Injury Diagnosed by Corrected Creatinine

	No AKI _{corr} (n = 109)	AKI _{corr} (n = 40)	P-value
Male	51 (46.8)	26 (65)	0.074
Age (years)	7.7 [2.8, 15.2]	6.0 [1.7, 14.5]	0.401
Weight (kg)	25.3 [13.9, 47.5]	26.1 [11.8, 56.7]	0.721
History of transplant *	9 (8.3)	11 (27.5)	0.005
Sepsis	25 (22.9)	15 (37.5)	0.117
PRISM-III	7 [2, 12]	12 [7, 19]	0.0003
MV duration (days)	2 [0, 5]	6 [2, 8]	0.003
CRRT use	0 (0)	7 (17.5)	0.0001
ICU LOS (days)	5 [3, 11]	10 [7, 16]	0.0005
Hospital LOS (days)	16 [8, 30]	23 [11, 48]	0.058
Mortality	4 (3.7)	5 (12.5)	0.106

All continuous variables are presented as median with interquartile range. Categorical variables are presented as number with percent.

* Includes solid organ or stem cell transplantation

AKI on Day 3 By Corrected Creatinine (AKI_{corr}), Pediatric Risk of Mortality-III (PRISM-III), Mechanical ventilation (MV), Continuous Renal Replacement Therapy (CRRT), Intensive Care Unit (ICU), Length of Stay (LOS). Data expressed as medians [interquartile ranges]