FEATURE ARTICLE

Net Fluid Balance Impacts Pediatric Continuous Renal Replacement Therapy Liberation

Sameer Thadani, MD[1,2]
Harsha V. Jujjavarapu, MD[3]
Christin Silos, MS[2]
Katja M. Gist, DO[4]
Poyyapakkam Srivaths, MD[2]
Katri Typpo, MD[1]
Christopher Horvat, MD[5]
Michael J. Bell, MD[6]
Dana Y. Fuhrman, DO[5,7,8]
Ayse Akcan Arikan[1,2]

OBJECTIVES: The optimal fluid management strategy on continuous renal replacement therapy (CRRT) is unknown for critically ill children. The pace of ultrafiltration has been highlighted as a risk predictor for adverse outcomes in adult cohorts. Whether CRRT can cause dialytrauma through excessive ultrafiltration rates (UFRs) in children is undetermined. Although fluid overload (FO) at CRRT start has been associated with adverse outcomes, net fluid balance (NFB) on CRRT has not been investigated as a predictor for renal recovery.

DESIGN: Retrospective cohort study.

SETTING: Two quaternary PICUs.

PATIENTS OR SUBJECTS: Children and young adults admitted between 2/2014 and 2/2020 at two quaternary pediatric hospitals who received CRRT.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Three hundred and seventy-one patients were included in this study with the median age of 85 months (interquartile range [IQR] 17–172), 180 (50%) were female. Three hundred and forty-five (96%) had acute kidney injury at CRRT start, 102 (28%) patients had FO > 15%. The median NFB on day 1 was 0.33 mL/kg/hr (–0.43 to 1.18), day 2 was –0.14 mL/kg/hr (–0.72 to 0.52), and day 3 was –0.24 mL/kg/hr (–0.85 to 0.42). Patients with a preserved urine output (UOP) greater than 0.3 mL/kg/hr over the study period had 5.6 more CRRT-free days and had decreased odds of major adverse kidney events at 30 days (MAKE-30). A NFB between –4.46 and –0.305 mL/kg/hr was independently associated with more CRRT-free days (β 2.90 [0.24–5.56]) and decreased odds of MAKE-30 (adjusted odds ratio 0.41 [0.22–0.79]).

CONCLUSIONS: Ultrafiltration practices in children receiving CRRT are substantially different compared to adult cohorts. Patients with a more positive NFB had fewer CRRT-free days. Preservation of UOP was associated with more CRRT-free days. Whether UFR causes direct dialytrauma in critically ill children through impairment of organ perfusion and hemodynamics require further study to allow personalization of CRRT prescriptions to improve outcomes.

KEYWORDS: continuous renal replacement therapy; fluid overload; pediatric intensive care; treatment outcome; ultrafiltration

Despite advances in technology, substantial experience, and knowledge gained over the last several decades, acute kidney injury necessitating dialysis (AKI-D) has an unacceptably high mortality rate ranging from 31% to 60% (1–5). Although the underlying disease process is frequently the driver of adverse outcomes, recent evidence in critically ill adults suggests that dialysis-induced morbidity (collectively called dialytrauma) might be responsible for some modifiable risk attributable to renal replacement therapy (RRT) (6).

Copyright © 2025 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

DOI: 10.1097/CCM.0000000000006636

Copyright © 2025 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

KEY POINTS

Question: What is the impact of net fluid balance (NFB) on the outcomes of children receiving continuous renal replacement therapy (CRRT)?

Findings: Those patients who achieved a NFB between –4.26 and –0.305 mL/kg/hr over the first 72 hours of CRRT had more CRRT-free days and a decreased odds of major adverse kidney events at 30 days (MAKE-30). Urine output had a significant association with NFB across the observation period.

Meaning: Ultrafiltration practices in children receiving CRRT are heterogeneous, but those patients with NFB over the first 72 between –4.26 and –0.305 mL/kg/hr had more CRRT-free days and decreased odds of MAKE-30.

Continuous RRT (CRRT) is the preferred modality for critically ill children (7–10). CRRT delivers controllable ultrafiltration, minimizing osmotic and hemodynamic changes, and allows for liberalization from fluid restrictions (11). RRT ultrafiltration uses hydrostatic pressure to push plasma H_2O and electrolytes, excluding cells, through a biosynthetic membrane. Dialytrauma occurs when the ultrafiltration rate (UFR) exceeds the intradialytic refill time (time for fluid to shift from the interstitial to intravascular space), leading to circulatory stress and end-organ ischemia (6, 12). A secondary analysis of a randomized controlled trial in critically ill adults with AKI-D found that negative daily fluid balance was associated with improved outcomes (13). The same association between negative cumulative fluid balance and decreased risk of mortality has also been identified in young children receiving CRRT (14). However, recent evidence in critically ill adults has indicated that a high net UF is associated with an increase in mortality.

In adults receiving CRRT, researchers have shown that a net UF > 1.45 mL/kg/hr (> 35 mL/kg/d) is associated with decreased odds of 30-day mortality. Yet, as the net UF exceeds 1.75 mL/kg/hr (42 mL/kg/d), mortality increases independently of hemodynamic derangements or fluid overload (FO) (15–17). These findings suggest that in adults receiving CRRT a J-shaped response to UF exists, where both high and low net UF are associated with an increased risk of morbidity and mortality. In children on maintenance chronic intermittent hemodialysis (iHD), myocardial strain on echocardiography was associated with change in blood volume independent of age, dialysis vintage, or blood pressure (18). As a result, UFR related dialytrauma has been proposed as a potentially modifiable factor to improve outcomes in patients with AKI-D (12).

Unlike adults, the varying stages of development, puberty, and sex impact maturing cardiovascular and renal functions, complicating the establishment of universally safe UFR thresholds for the pediatric population (19). Furthermore, net UF only considers fluid removal via dialysis, overlooking losses from chest tubes, abdominal drains, or gastrointestinal losses (20). Therefore, our aim was to investigate the impact of fluid balance (which captures the entirety of a patient's fluid inputs and outputs) measured by net fluid balance (NFB) on CRRT-free days and major adverse kidney events at 30 days (MAKE-30) in critically ill children. We hypothesized that children receiving more aggressive fluid removal will have fewer CRRT-free days and higher odds of MAKE-30.

METHODS

Two-center observational study, spanning from February 2014–2020 in critically ill children and young adults who received CRRT at Texas Children's Hospital or University of Pittsburgh Medical Center Children's Hospital of Pittsburgh. The research was approved by the institutional review boards of Baylor College of Medicine (protocol H-47321, "Thrombocytopenia and Major Adverse Kidney Outcomes in Pediatric Patients who Underwent CRRT for Acute Renal Failure," approved 4/2020) and the University of Pittsburgh (number 19070409, "Thrombocytopenia and MAKE Outcomes in Patients who Received CRRT," approved 10/2019). Both institutions waived informed consent. The protocols adhered to the 1975 Helsinki Declaration. Patients with chronic kidney disease, end-stage renal disease, ingestion, or non-AKI/FO indications for CRRT were excluded.

Patient variables, such as age, sex, weight, height, body surface area, primary ICU admission reason, main comorbid condition, organ transplantation history, vasoactive dose/type and use, urine output (UOP), and admission creatinine, were extracted from the electronic health record, along with CRRT

Copyright © 2025 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

variables (initial prescription, blood flow rate, filter used, concurrent therapeutic plasma exchange, or extracorporeal membranous oxygenation). AKI was classified based on the Kidney Disease Improving Global Outcomes serum creatinine and UOP criteria (21). Illness severity was evaluated using the Pediatric Logistic Organ Dysfunction-2 (PELOD-2) score at ICU admission and CRRT initiation (22, 23). Baseline creatinine, used to determine the estimated glomerular filtration rate (eGFR), was defined as the lowest creatinine level recorded in the 90 days before CRRT initiation. If a baseline eGFR was unavailable, a default value of 100 mL/min/1.73 m^2 was assigned.

We used NFB, defined as net intake – net output in mL, instead of net UFR to better reflect each patient's daily fluid balance, considering the significant obligatory fluid intake. NFB data were collected daily for the first 3 days of CRRT, indexed to weight, and expressed in mL/kg/hr for comparison with existing studies. The first day of CRRT was the day of initiation, which began at 7:00 AM, regardless of the time of CRRT start. Each day was defined as commencing at 7:00 AM and ending at 6:59 AM on the following day. Percent FO was calculated at the start of CRRT using ([Fluid in−Fluid out]/[ICU admission weight (kg)]) × 100 (24). A FO > 10% threshold was used to identify patients for whom FO was the CRRT indication. Data on UOP in mL/kg/hr were collected over the initial 3 days of CRRT (25).

The primary outcome was the number of CRRT-free days censored at 30 days. In the event of the patient's death prior to 30 days, they were assigned a value of zero CRRT-free days. The secondary outcome was the occurrence of MAKE-30, a composite of: 1) persistent renal dysfunction, defined as a decrease in eGFR of ≥ 25% from baseline, calculated using the bedside Schwartz formula (26), 2) persistent dialysis dependence, or 3) death (27). Renal recovery was defined as the absence of any component of MAKE-30 days after CRRT initiation. If a patient did not have a serum creatinine measurement 30 days postCRRT initiation, their status was documented as renal recovery.

Statistical Analysis

Continuous variables were summarized by medians and interquartile ranges (IQR), and categorical variables by counts and frequencies. Univariate analyses used linear regressions for CRRT-free days and logistic regressions for MAKE-30. Least absolute shrinkage and selection operator regression was conducted for variable selection. Selected variables were then entered into linear regressions for CRRT-free days and logistic regressions for MAKE-30. Backward selection optimized Akaike information criterion (AIC) to determine the final adjusted model. Final associations were expressed as beta coefficients (β) or adjusted odd ratios (aOR) with 95% CIs

Given the non-linear relationship between NFB and MAKE-30, we investigated several grouping strategies to best split the wide range of NFB into groups (**Fig. 1**). NFB was divided by median, spline, tertiles, and quartiles. Each group underwent unadjusted logistic regression with MAKE-30 as the outcome. Comparisons using AIC determined that the tertile grouping was optimal. The tertiles were classified by NFB values: negative (−4 to −0.305 mL/kg/hr), even (−0.304 to 0.571 mL/kg/hr) and positive (0.572–8.24 mL/kg/hr). We also compared group characteristics and outcomes across NFB tertiles, using analysis of variance or Kruskal-Wallis test to identify significant differences.

Lastly, we conducted a Pearson's correlation analysis to assess the strength and direction of the relationship between NFB and UOP. All statistical analyses were completed using R version 4.3.1 and packages tableone_0.13.2, epiDisplay_3.5.0.2, MASS_7.3 to 60, survival_3.5 to 5, glmnet_4.1 to 7, and skimr_2.1.5.

RESULTS

Between February 2014 and February 2020, 418 children and young adults received CRRT. After excluding 57 patients, 361 were analyzed (**Supplemental Fig. 1**, http://links.lww.com/CCM/H700), with a median age of 85 months (IQR 17–172); 180 (50%) were female. Continuous venovenous hemodiafiltration was administered to 353 (97%) patients. Baseline serum creatinine was unavailable for 166 (46%) patients before admission, and the median CRRT duration was 10 days (IQR 4–20). At CRRT initiation, 345 (96%) patients had AKI; 124 (34%) met AKI criteria based solely on serum creatinine, 22 (6%) based only on UOP, and 199 (58%) based on both serum creatinine and UOP. The most common reason for ICU admission was septic shock/sepsis for 87 (24%) patients. At CRRT initiation, the median FO was 9% (3–18%), with 102 (28%) patients having a FO > 15%. The median PELOD-2 at ICU admission and PELOD-2 at CRRT start scores were 6 (4–9) and 9 (7–11), respectively.

Copyright © 2025 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

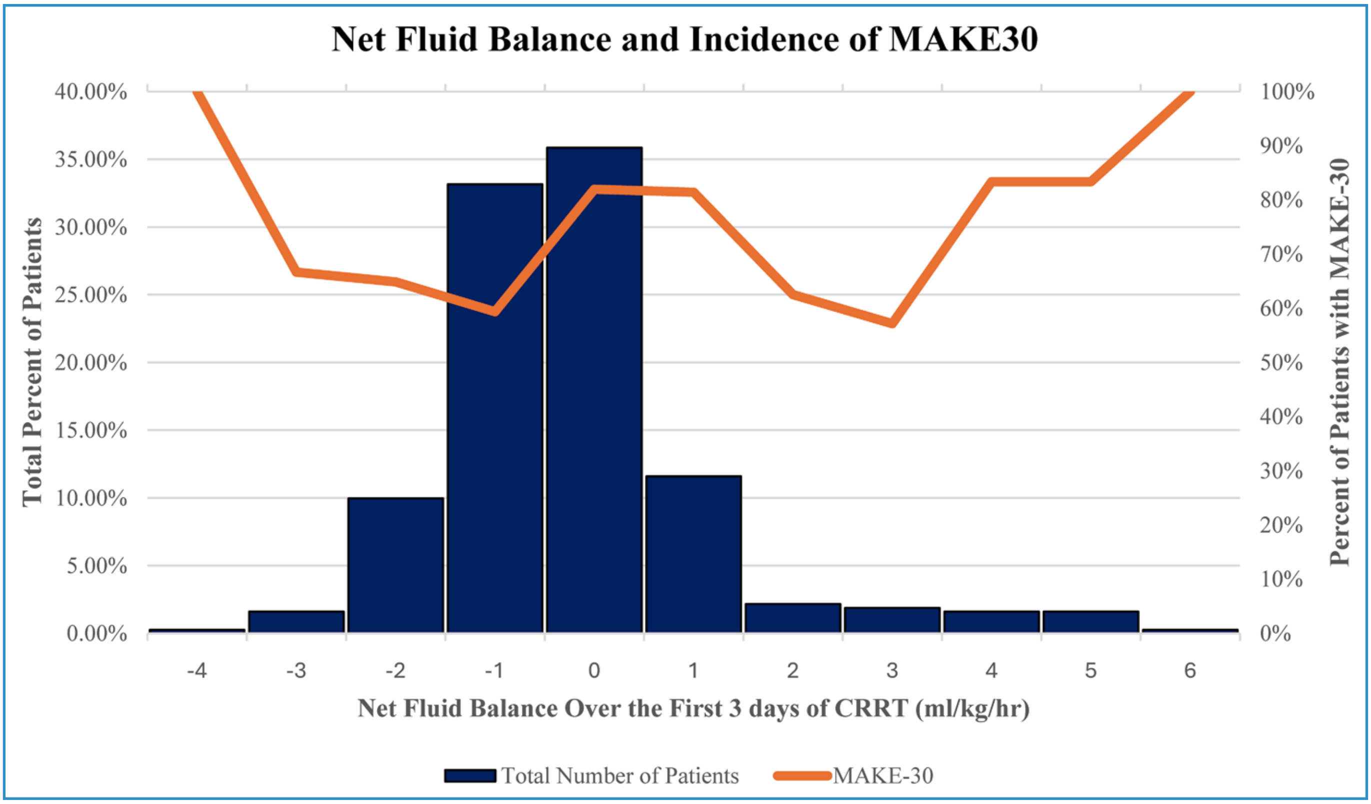

Figure 1. Net fluid balance and the incidence of major adverse kidney events at 30 days. The *graph* displays the distribution of net fluid balance (NFB) over a 3-day observation period, binned into 1 mL/kg/hr intervals (*blue bars*). Superimposed on these intervals is the incidence of major adverse kidney events at 30 days (MAKE-30) following continuous renal replacement therapy (CRRT) initiation (*orange line*), reflecting the incidence within each NFB bin.

The median number of CRRT-free days were 6 (0–24); 263 (73%) patients had MAKE-30. (**Table 1**).

Fluid Balance

NFB varied widely over the first 3 days of CRRT from −4.46 to 8.24 mL/kg/hr with a median of 0.1 mL/kg/hr (IQR −0.47 to 0.81). Daily median NFB became more negative over the first 3 days of CRRT, from 0.33 mL/kg/hr (−0.43 to 1.18) on day 1, −0.14 mL/kg/hr (−0.72 to 0.52) on day 2, and −0.24 mL/kg/hr (−0.85 to 0.42) on day 3. There was a difference in NFB between days 1 and 2 ($p < 0.01$) as well as day 1 and 3 ($p < 0.01$) (**Fig. 2**). One hundred and sixty-five (46%) patients achieved an overall negative NFB over the first 3 days of CRRT. The median UOP decreased daily from 0.34 (0.09–0.82) to 0.19 mL/kg/hr (0.02–0.45), and 0.10 mL/kg/hr (0.01–0.41), for days 1, 2, and 3, respectively. One hundred and sixty-one (45%) patients had preserved UOP with an average UOP > 0.3 mL/kg/hr over the first 3 days of CRRT (Table 1). There was a weak negative correlation ($\rho = -0.20$, 95% CI: −0.30 to −0.10) between NFB and UOP over the 3-day observation period.

Significant differences were found between the NFB groups in sex, age, ICU admission weight, transplantation history, primary ICU admission diagnosis, PELOD-2 Score at CRRT initiation, and daily and cumulative 3-day UOP during CRRT (**Table 2**).

CRRT-Free Days

The median number of CRRT-free days was 6 (IQR 0–24). In unadjusted analyses, older patients, a metabolic/endocrine comorbid condition, and a negative NFB were all associated with more CRRT-free days. Respiratory conditions or sepsis as primary reason for ICU admission, FO > 15%, and a more positive average NFB over the first 3 days were all associated with fewer CRRT-free days (**Supplemental Table 1**, http://links.lww.com/CCM/H700).

The final adjusted model included height (cm), history of organ transplantation, FO > 15%, PELOD-2 Score at CRRT start, UOP > 0.3 mL/kg/hr over the first

Copyright © 2025 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

TABLE 1.
Demographics

Patient Characteristics ($n = 361$)	Median (IQR) or n (%)
Gender (female)	180 (50%)
Age at ICU admission (mo)	85 (17–172)
Weight (kg)	22 (11–52)
AKI criteria at CRRT start	345 (96%)
Serum creatinine	124 (36%)
UOP	22 (6%)
Both serum creatinine and UOP	199 (58%)
Primary reason for ICU admission	
Respiratory	81 (22%)
Septic shock/sepsis	87 (24%)
Other shock	51 (14%)
Cardiac/cardiac postoperative	34 (9%)
Trauma	1 (1%)
Postoperative/pain	13 (4%)
CNS	29 (8%)
Other	65 (18%)
Primary comorbid condition	
None	79 (22%)
Cardiovascular	63 (17%)
Respiratory	10 (3%)
Neuromuscular	17 (5%)
Gastrointestinal/liver	59 (16%)
Renal/urological	11 (3%)
Hematological/oncological	80 (22%)
Metabolic/endocrine	30 (9%)
Other	12 (3%)
History of transplant (no)	271 (75%)
% Fluid overload at CRRT start	9% (3–18%)
Vasoactive use at CRRT start (yes)	265 (73%)
CRRT indication – AKI	345 (96%)
CRRT indication – fluid overload	155 (43%)
UOP day 1 (mL/kg/hr)	0.34 (0.09–0.82)
UOP day 2 (mL/kg/hr)	0.19 (0.02–0.45)
UOP day 3 (mL/kg/hr)	0.1 (0.01–0.41)
NFB day 1 (mL/kg/hr)	0.33 (–0.43 to 1.18)
NFB day 2 (mL/kg/hr)	–0.14 (–0.72 to 0.52)
NFB day 3 (mL/kg/hr)	–0.24 (–0.85 to 0.42)
NFB (mL/kg/hr)	0.1 (–0.47 to 0.81)
NFB (negative)	165 (46%)

AKI = acute kidney injury, CRRT = continuous renal replacement therapy, IQR = interquartile range, NFB = net fluid balance, UOP = urine output.

Copyright © 2025 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

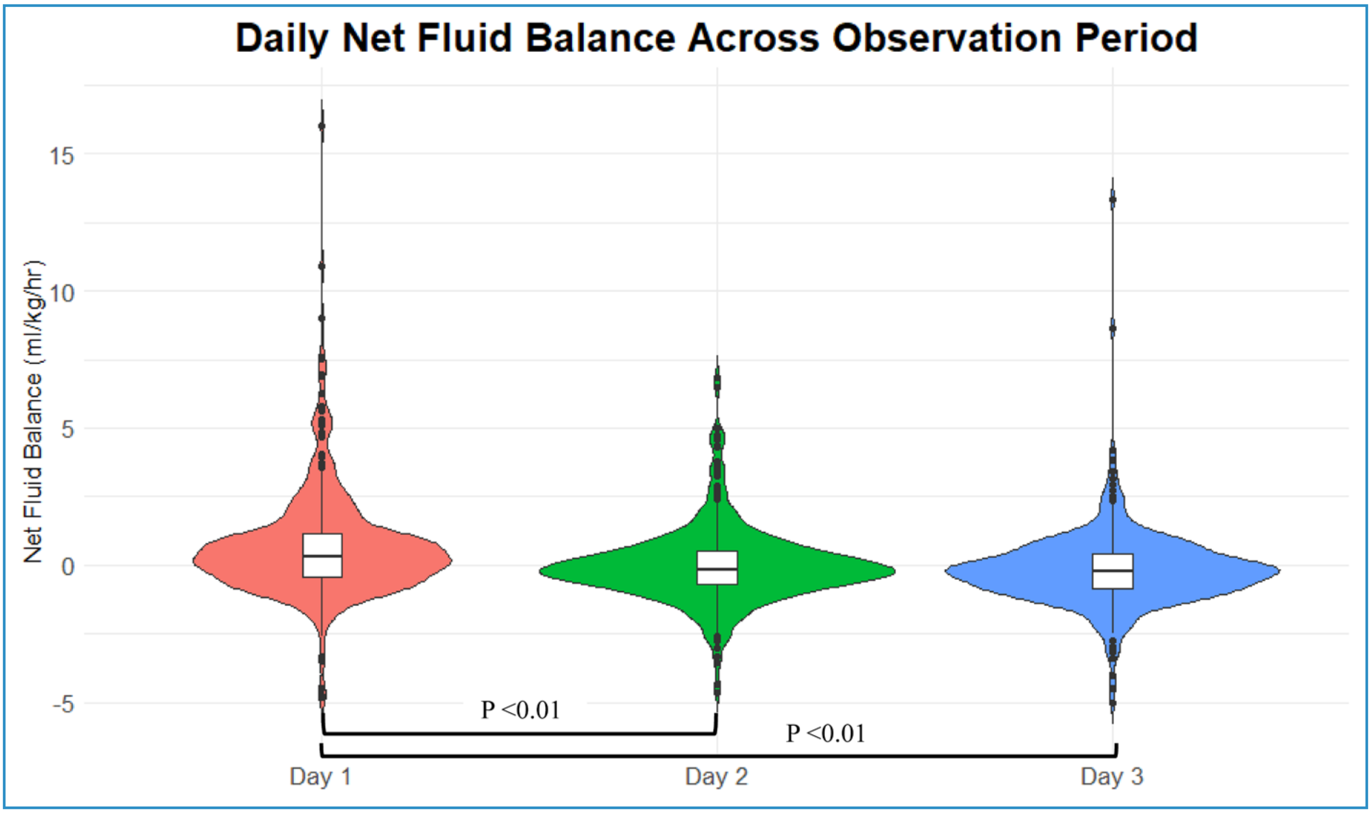

Figure 2. *Violin plots* of net fluid balance across the 3-day observation period. *Violin plots* illustrating the net fluid balance (NFB) across the 3-day observation period. Statistically significant differences were observed between NFB day 1 and 2, as well as between day 1 and 3.

72 hours of CRRT, primary reason for ICU admission and comorbid conditions, and NFB tertiles. History of organ transplantation, FO > 15%, higher PELOD-2 score at CRRT start, primary reason for ICU admission as respiratory failure or shock (other than septic or cardiogenic), hematologic/oncologic comorbid condition were independently associated with fewer CRRT-free days. UOP > 0.3 mL/kg/hr during CRRT, metabolic/endocrine comorbid conditions, and NFB −4.46 to −0.305 mL/kg/hr were independently associated with more CRRT-free days (**Table 3**).

Major Adverse Kidney Events at 30 Days

Two hundred and sixty-three (73%) patients met criteria for MAKE-30, of those, 113 (43%) died, 107 (41%) remained on dialysis, and 43 (16%) had persistent kidney dysfunction but liberated from dialysis. In univariate analyses, FO > 15%, AKI by UOP criteria at CRRT start, gastrointestinal/liver comorbid or hematological/oncological comorbid condition, history of transplant, and a more positive NFB of the first 3 days of therapy (mL/kg/hr) were all associated with increased odds of MAKE-30, whereas those patients with a NFB over the first 3 days between −4.46 to −0.305 mL/kg/hr and UOP > 0.3 mL/kg/hr over the first 72 hours of CRRT had decreased odds of MAKE-30 (**Supplemental Table 2**, http://links.lww.com/CCM/H700).

In adjusted analysis, history of transplantation (aOR 2.28 [CI 1.14–4.55]), FO > 15% (aOR 3.91 [CI 1.97–7.78]) were independently associated with increased odds of MAKE-30. UOP > 0.3 mL/kg/hr during CRRT (aOR 0.16 [CI 0.09–0.29]), and a NFB between −4.46 and −0.305 mL/kg/hr (aOR 0.41 [CI 0.22–0.79]) were associated with decreased odds of MAKE-30 (**Table 4**).

DISCUSSION

Our dual-center study in critically ill pediatric and young adult AKI-D patients undergoing CRRT revealed a broad range of NFB within the initial 3 days of therapy. An inverse correlation was observed between NFB and UOP. We observed significant differences in anthropometric measurements, indications for ICU admission, history of organ transplantation,

Copyright © 2025 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

TABLE 2.
Comparison of Group Characteristics and Outcomes Across the Tertiles of Net Fluid Balance

Characteristic	NFB −4.46 to −0.305 mL/kg/hr, ($n = 119$)	NFB −0.304 to 0.571 mL/kg/hr, ($n = 123$)	NFB 0.572–8.24 mL/kg/hr, ($n = 119$)	p
Sex (male)	70 (60%)	55 (45%)	54 (45%)	0.03
Age at ICU admission (mo)	64 (16,157)	120 (25,192)	58 (11,157)	0.02
Weight at ICU admission (kg)	20 (10, 54)	34 (13, 59)	20 (8, 46)	0.04
Primary diagnosis at ICU admission				0.03
Respiratory	30 (25%)	23 (19%)	28 (24%)	
Septic shock/sepsis	34 (29%)	28 (23%)	25 (21%)	
Other shock	12 (10%)	16 (13%)	23 (19%)	
Cardiac/cardiac postoperative	13 (11%)	16 (13%)	5 (4.2%)	
Trauma	0 (0%)	1 (0.8%)	0 (0%)	
Postoperative/pain	2 (1.7%)	4 (3.3%)	7 (5.9%)	
Neurologic	7 (5.9%)	7 (5.7%)	15 (13%)	
Other	21 (18%)	28 (23%)	16 (13%)	
Primary comorbid condition				0.20
None	31 (26%)	20 (16%)	28 (24%)	
Cardiovascular	18 (15%)	33 (27%)	12 (10%)	
Respiratory	4 (3.4%)	4 (3.3%)	2 (1.7%)	
Neuromuscular	7 (5.9%)	4 (3.3%)	6 (5.0%)	
Gastrointestinal/liver	16 (13%)	20 (16%)	23 (19%)	
Renal/urological	4 (3.4%)	4 (3.3%)	3 (2.5%)	
Hematological/oncological	24 (20%)	23 (19%)	33 (28%)	
Metabolic/endocrine	9 (7.6%)	11 (8.9%)	10 (8.4%)	
Other	6 (5.0%)	4 (3.3%)	2 (1.7%)	
History of transplant (yes)	22 (19%)	40 (33%)	25 (22%)	0.03
Fluid overload > 15%	37 (31%)	27 (22%)	38 (32%)	0.22
Vasoactive support (yes)	82 (69%)	92 (75%)	89 (75%)	0.40
PELOD-2 score at ICU admission	6.0 (4.0, 8.0)	7.0 (4.0, 10.0)	7.0 (4.0, 9.0)	0.40
PELOD-2 score at CRRT start	8.0 (7.0, 10.5)	10.0 (7.0, 12.0)	9.0 (7.0, 11.5)	0.03
NFB	−0.81 (−1.14, −0.49)	0.09 (−0.07, 0.30)	1.09 (0.82, 1.81)	< 0.01
Day 1 mL/kg/hr	−0.63 (−0.98, −0.14)	0.25 (0.01, 0.83)	1.24 (0.81, 2.95)	< 0.01
Day 2 mL/kg/hr	−0.84 (−1.30, −0.44)	−0.03 (−0.35, 0.27)	0.86 (0.22, 1.62)	< 0.01
Day 3 mL/kg/hr	−0.85 (−1.32, −0.47)	−0.05 (−0.36, 0.26)	0.66 (−0.02, 1.14)	< 0.01
UOP day 1 mL/kg/d	0.58 (0.24, 1.10)	0.19 (0.08, 0.67)	0.25 (0.06, 0.62)	< 0.01
UOP day 2 mL/kg/d	0.33 (0.13, 0.69)	0.14 (0.02, 0.29)	0.11 (0.00, 0.30)	< 0.01
UOP day 3 mL/kg/d	0.29 (0.05, 0.58)	0.12 (0.02, 0.32)	0.04 (0.00, 0.18)	< 0.01
Median UOP	0.46 (0.22, 0.83)	0.20 (0.05, 0.44)	0.22 (0.06, 0.46)	< 0.01
UOP > 0.3 mL/kg/hr over the first 3 d of CRRT	76 (64%)	46 (37%)	39 (33%)	< 0.01
CRRT-free days	20 (0, 26)	5 (0, 21)	0 (0, 20)	< 0.01
Major adverse kidney events at 30 d (yes)	64 (54%)	98 (80%)	101 (85%)	< 0.01

CRRT = continuous renal replacement therapy, NFB = net fluid balance, PELOD-2 = Pediatric Logistic Organ Dysfunction-2, UOP = urine output

Copyright © 2025 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

TABLE 3.
Adjusted Model for Continuous Renal Replacement Therapy-Free Days

Variable	Beta Coefficient	CI	*p*
Height (cm)	0.02	−0.005 to 0.05	0.11
History of transplant (yes)	−3.71	−6.40 to −1.02	< 0.01
Fluid overload > 15%	−4.33	−6.92 to −1.75	< 0.01
Pediatric Logistic Organ Dysfunction-2 score at CRRT start	−0.43	−0.75 to −0.11	< 0.01
Urine output > 0.3 mL/kg/hr during CRRT	5.57	3.34 to 7.79	< 0.01
Primary reason for ICU admission			
Respiratory	−5.14	−8.52 to −1.75	< 0.01
Septic shock/sepsis	−3.35	−6.64 to −0.06	0.05
Other shock	−5.28	−9.16 to −1.41	< 0.01
Cardiac/cardiac postoperative	−1.13	−6.06 to 3.76	0.65
Trauma	10.94	−9.76 to 31.63	0.30
Postoperative/pain	−5.68	−12.03 to 0.66	0.08
CNS	−2.70	−7.15 to 1.75	0.23
Other	Reference	Reference	
Primary comorbid condition			
None	Reference	Reference	
Cardiovascular	0.11	−3.78 to 4.01	0.95
Respiratory	−0.30	−7.17 to 6.57	0.93
Neuromuscular	−2.97	−8.23 to 2.30	0.27
Gastrointestinal/liver	−4.37	−8.12 to −0.61	0.02
Renal/urological	0.98	−5.69 to 7.65	0.77
Hematological/oncological	−5.58	−8.82 to −2.34	< 0.01
Metabolic/endocrine	4.32	0.05 to 8.57	0.05
Other	4.90	−1.27 to 11.08	0.12
Net fluid balance			
−4.46 to −0.305 mL/kg/hr	2.90	0.24 to 5.56	0.03
−0.304 to 0.571 mL/kg/hr	Reference	Reference	
0.572 to 8.24 mL/kg/hr	−0.08	−.72 to 2.56	0.95

CRRT = continuous renal replacement therapy.

illness severity, and UOP during CRRT among our NFB groups. Paradoxically, preserved UOP (> 0.3 mL/kg/hr) and a NFB between −4.26 and −0.305 mL/kg/hr over the first 3 days of CRRT were associated with more CRRT-free days and decreased odds of MAKE-30. Contrary to adult data, we were unable to identify a threshold at which a negative NFB became associated with adverse outcomes (14).

Dialytrauma is an overarching term that describes harmful adverse events related to dialysis. In adults receiving chronic iHD, a high UFR (> 13 mL/kg/hr) is a modifiable factor that, if exceeded, leads to an increase in all-cause mortality (28, 29). Despite fewer cardiovascular risk factors in children receiving iHD, pace of ultrafiltration has been associated with decreased cardiac output and myocardial strain (18, 30, 31). Hence, CRRT has become the modality of choice for critically ill children in resource-replete settings (32). Despite the theoretically improved hemodynamic tolerance of CRRT, higher UFRs are associated with worse outcomes in adults receiving CRRT. Researchers have noted that an "optimal" UFR range of 1.5–1.75 mL/

Copyright © 2025 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

TABLE 4.
Adjusted Model for Major Adverse Kidney Events at 30 Days

Variable	Adjusted OR	CI	*p*
History of transplant (yes)	2.28	1.14–4.55	0.02
Fluid overload > 15% (yes)	3.91	1.97–7.78	< 0.01
Urine output > 0.3 mL/kg/hr during continuous renal replacement therapy	0.16	0.09–0.29	< 0.01
Net fluid balance			
−4.46 to −0.305 mL/kg/hr	0.41	0.22–0.79	< 0.01
−0.304 to 0.571 mL/kg/hr	Reference	Reference	
0.572–8.24 mL/kg/hr	1.42	0.68–2.94	0.35

OR = odds ratio.

kg/hr in adults receiving CRRT is associated with improved outcomes, yet a safe threshold has not been identified in children (16, 33). We attempted to elucidate a NFB threshold associated with adverse outcomes. Surprisingly, we showed that patients who achieved a NFB (–4.46 to –0.305 mL/kg/hr) over the observation period achieved better outcomes. We theorize, the current conservative practice of CRRT at participating institutions, where clinical teams restrict NFB to less than 2 mL/kg/hr, explains why a danger threshold was not identified. Ninety-seven percent of patients with negative NFB were prescribed NFB between –2 and 0 mL/kg/hr (Fig. 1). This “net UF limitation” may not be implemented at other centers, limiting the generalizability of our study.

Previously published literature in children receiving CRRT has noted significant heterogeneity in both the patient and CRRT characteristics (34, 35). We identified significant differences among our NFB groups, which we believe provide insight into the practice of fluid removal in children receiving CRRT. Our findings indicate two main categories of variables (anthropometric and clinical characteristics). We hypothesized that the variations in NFB within our study cohort reflect the clinical features pediatric intensivist and nephrologist use to prescribe UF in critically ill patients (36, 37). Future studies should further investigate the impact of patient factors that influence the prescription of UF in children receiving CRRT.

FO is associated with poor outcomes in critically ill adults and children. In our cohort FO > 15% at CRRT initiation was associated with fewer CRRT-free days and MAKE-30. A multinational study identified more ventilator and ICU-free days in children who had an FO < 10% at CRRT initiation (25). We recently showed that children with FO > 15% vs. those with FO < 15% at CRRT initiation have higher systemic vascular resistance and lower cardiac index (38), indicating differential cardiovascular function when FO exceeds 15%. Advanced hemodynamic monitoring to better define FO thresholds linked to organ dysfunction and poor outcomes in children undergoing CRRT could shed light on different hemodynamic phenotypes.

The median NFB in our cohort became negative on day 2 at –0.14 mL/kg/hr, with a 3-day median of 0.1 mL/kg/hr, aligning with adult data (39). Yet, in contrast to the adult literature, we observed a decrease in UOP over our observation period (39). The reduction in UOP is concerning, as it has consistently been a reliable predictor of CRRT liberation. Given the weak but significant inverse correlation between NFB and UOP, we propose that fluid removal with higher UFR could decrease renal perfusion, diminish UOP, and potentially impair renal recovery. More studies are required to better understand the practice of safe and effective fluid management in children undergoing CRRT.

There is no consensus in critical care nephrology on the most patient-centered parameter for describing, measuring, and assessing fluid removal. Currently, two clinical trials in critically ill adults receiving CRRT are using different fluid balance metrics: NFB and net UF (40, 41). We used NFB to measure fluid removal because it comprehensively assesses net fluid input and output. However, net UF, the fluid directly removed from circulation, might better evaluate circulatory strain and identify dialytrauma. Despite NFB’s clinical

Copyright © 2025 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

utility, future studies should document both net UF and NFB for a holistic assessment of fluid status in CRRT patients.

This study has several limitations. The retrospective nature, reliant on accurate documentation, may not capture all clinical factors related to CRRT prescription. Our findings might be confounded by indication, as FO is an indication for CRRT and impacts outcomes in critically ill children. We only recorded NFB during the first 3 days of therapy. Future research should examine UFR changes throughout the entire therapy duration and their effect on renal outcomes. Our NFB data collection reflects the whole 24 hours, not just CRRT time, potentially making NFB on day 1 more positive depending on CRRT initiation time. Despite controlling for UOP in multivariable models, collinearity between UOP and NFB confounds establishing a directional association between NFB and outcomes. We propose that UFR, which is independent of UOP, might be a better measure of circulatory strain and should be used in future studies. Lastly, our findings require external validation (34). A recently published study from the Worldwide Explorations of Renal Replacement Outcomes Collaborative in Kidney Disease identified that an earlier negative NFB is associated with decreased odds of liberation from dialysis (42). These seemingly contradictory findings might indicate that not just the NFB, but the timing of when a negative NFB is achieved might impact patient outcomes.

CONCLUSIONS

A negative NFB during the initial 3 days of CRRT in children and young adults was associated with decreased odds of MAKE-30 and more CRRT-free days. Patients with preserved UOP > 0.3 mL/kg/hr during the first 3 days of CRRT had more CRRT-free days and decreased odds of MAKE-30. Personalized ultrafiltration targets for children undergoing CRRT require further investigation focusing on CRRT liberation and preservation of UOP while on dialysis to minimize morbidity and mortality in critically ill children.

1 Department of Pediatrics, Division of Critical Care Medicine, Baylor College of Medicine, Houston, TX.

2 Department of Pediatrics, Division of Nephrology, Baylor College of Medicine, Houston, TX.

3 Department of Pediatrics, Baylor College of Medicine, Houston, TX.

4 Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH.

5 Department of Critical Care Medicine, Division of Pediatric Critical Care Medicine, UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA.

6 Department of Critical Care Medicine, Children's National Hospital, Washington DC.

7 Department of Pediatrics, Division of Nephrology, UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA.

8 The Center for Critical Care Nephrology, Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Dr. Gist's institution received funding from the Gerber foundation; she received funding from Bioporto Diagnostics; she received support for article research from the Gerber foundation. Dr. Typpo's institution received funding from the National Institute of Child Health and Human Development. Dr. Arikan's institution received funding from Bioporto and Mozarc. The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: sameer.thadani@bcm.edu

REFERENCES

1. 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. *Am J Kidney Dis* 2010; 55:316–325
2. Chang J-W, Jeng M-J, Yang L-Y, et al: The epidemiology and prognostic factors of mortality in critically ill children with acute kidney injury in Taiwan. *Kidney Int* 2015; 87:632–639
3. Choi SJ, Ha EJ, Jhang WK, et al: Factors associated with mortality in continuous renal replacement therapy for pediatric patients with acute kidney injury. *Pediatr Crit Care Med* 2017; 18:e56–e61
4. Cortina G, McRae R, Hoq M, et al: Mortality of critically ill children requiring continuous renal replacement therapy: Effect of fluid overload, underlying disease, and timing of initiation. *Pediatr Crit Care Med* 2019; 20:314–322
5. Starr MC, Banks R, Reeder RW, et al; for the Life After Pediatric Sepsis Evaluation (LAPSE) Investigators: Severe acute kidney injury is associated with increased risk of death and new morbidity after pediatric septic shock. *Pediatr Crit Care Med* 2020; 21:e686–e695
6. Maynar Moliner J, Honore PM, Sánchez-Izquierdo Riera JA, et al: Handling continuous renal replacement therapy-related adverse effects in intensive care unit patients: The dialytrauma concept. *Blood Purif* 2012; 34:177–185

Copyright © 2025 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

7. Augustine JJ, Sandy D, Seifert TH, et al: A randomized controlled trial comparing intermittent with continuous dialysis in patients with ARF. *Am J Kidney Dis* 2004; 44:1000–1007
8. Uehlinger DE, Jakob SM, Ferrari P, et al: Comparison of continuous and intermittent renal replacement therapy for acute renal failure. *Nephrol Dial Transplant* 2005; 20:1630–1637
9. Vinsonneau C, Camus C, Combes A, et al; Hemodiafe Study Group: Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: A multicentre randomised trial. *Lancet (London, England)* 2006; 368:379–385
10. Mehta RL, Mcdonald B, Gabbai FB, et al; Collaborative Group for Treatment of ARF in the ICU: A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. *Kidney Int* 2001; 60:1154–1163
11. De Galasso L, Picca S, Guzzo I: Dialysis modalities for the management of pediatric acute kidney injury. *Pediatr Nephrol* 2020; 35:753–765
12. Murugan R, Bellomo R, Palevsky PM, et al: Ultrafiltration in critically ill patients treated with kidney replacement therapy. *Nat Rev Nephrol* 2021; 17:262–276
13. RENAL Replacement Therapy Study Investigators, Bellomo R, Cass A, Cole L, et al: An observational study fluid balance and patient outcomes in the randomized evaluation of normal vs. augmented level of replacement therapy trial. *Crit Care Med* 2012; 40:1753–1760
14. Andersson A, Norberg A, Broman LM, et al: Fluid balance after continuous renal replacement therapy initiation and outcome in paediatric multiple organ failure. *Acta Anaesthesiol Scand* 2019; 63:1028–1036
15. Naorungroj T, Neto AS, Zwakman-Hessels L, et al: Mediators of the impact of hourly net ultrafiltration rate on mortality in critically ill patients receiving continuous renal replacement therapy. *Crit Care Med* 2020; 48:e934–e942
16. Tehranian S, Shawwa K, Kashani KB: Net ultrafiltration rate and its impact on mortality in patients with acute kidney injury receiving continuous renal replacement therapy. *Clin Kidney J* 2021; 14:564–569
17. Naorungroj T, Neto AS, Zwakman-Hessels L, et al: Early net ultrafiltration rate and mortality in critically ill patients receiving continuous renal replacement therapy. *Nephrol Dial Transplant* 2021; 36:1112–1119
18. Idrovo A, Pignatelli R, Loar R, et al: Preserved cerebral oxygenation with worsening global myocardial strain during pediatric chronic hemodialysis. *J Am Soc Nephrol* 2021; 32:2912–2919
19. Dahiya A, Pannu N, Soranno DE: Sex as a biological variable in acute kidney injury. *Curr Opin Crit Care* 2023; 29:529–533
20. Murugan R, Hoste E, Mehta RL, et al; Acute Disease Quality Initiative (ADQI) Consensus Group: Precision fluid management in continuous renal replacement therapy. *Blood Purif* 2016; 42:266–278
21. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group: KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int Suppl* 2012; 2:1–138
22. Leteurtre S, Duhamel A, Salleron J, et al; Groupe Francophone de Réanimation et d'Urgences Pédiatriques (GFRUP): PELOD-2: An update of the PEdiatric logistic organ dysfunction score. *Crit Care Med* 2013; 41:1761–1773
23. Leteurtre S, Duhamel A, Deken V, et al; Groupe Francophone de Réanimation et Urgences Pédiatriques: Daily estimation of the severity of organ dysfunctions in critically ill children by using the PELOD-2 score. *Crit Care* 2015; 19:324
24. Goldstein SL, Currier H, Graf JM, et al: Outcome in children receiving continuous venovenous hemofiltration. *Pediatrics* 2001; 107:1309–1312
25. Gist KM, Menon S, Anton-Martin P, et al; WE-ROCK Investigators: Time to continuous renal replacement therapy initiation and 90-day major adverse kidney events in children and young adults. *JAMA Netw Open* 2024; 7:e2349871
26. Schwartz GJ, Haycock GB, Edelmann CM, et al: A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. *Pediatrics* 1976; 58:259–263
27. Billings IV FT, Shaw AD: Clinical trial endpoints in acute kidney injury. *Nephron Clin Pract* 2014; 127:89–93
28. Flythe JE, Kimmel SE, Brunelli SM: Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality. *Kidney Int* 2011; 79:250–257
29. McIntyre CW: Effects of hemodialysis on cardiac function. *Kidney Int* 2009; 76:371–375
30. Mitsnefes MM: Cardiovascular disease in children with chronic kidney disease. *J Am Soc Nephrol* 2012; 23:578–585
31. Groothoff JW, Lilien MR, Van De Kar NCAJ, et al: Cardiovascular disease as a late complication of end-stage renal disease in children. *Pediatr Nephrol* 2005; 20:374–379
32. Basu RK, Wheeler DS, Goldstein S, et al: Acute renal replacement therapy in pediatrics. *Int J Nephrol* 2011; 2011:1–8
33. Murugan R, Kerti SJ, Chang C-CH, et al: Association of net ultrafiltration rate with mortality among critically ill adults with acute kidney injury receiving continuous venovenous hemodiafiltration: A secondary analysis of the Randomized Evaluation of Normal vs Augmented Level (RENAL) of renal replacement therapy trial. *JAMA Netw Open* 2019; 2:e195418
34. Menon S, Krallman KA, Arikan AA, et al; WE-ROCK Investigators: Worldwide Exploration of Renal Replacement Outcomes Collaborative in Kidney Disease (WE-ROCK). *Kidney Int Rep* 2023; 8:1542–1552
35. Thadani S, Wu T-C, Wu DTY, et al; Worldwide Exploration of Renal Replacement Outcomes Collaborative in Kidney Diseases (WE-ROCK) Collaborators: Machine learning-based prediction model for ICU mortality after continuous renal replacement therapy initiation in children. *Crit Care Explor* 2024; 6:e1188
36. Lumlertgul N, Murugan R, Seylanova N, et al: Net ultrafiltration prescription survey in Europe. *BMC Nephrol* 2020; 21:522
37. Fuhrman DY, Gist KM, Akcan-Arikan A: Current practices in pediatric continuous kidney replacement therapy: A systematic review-guided multinational modified Delphi consensus study. *Pediatr Nephrol* 2023; 38:2817–2826
38. Thadani S, Lang A, Silos C, et al: Fluid overload modifies hemodynamic impact of CRRT: Evidence of a covert cardiorenal syndrome? *Shock* 2024; 63:233–239
39. White KC, Laupland KB, Ostermann M, et al: Current fluid management practice in critically ill adults on continuous renal replacement therapy: A binational, observational study. *Blood Purif* 2024; 53:624–633
40. Bitker L, Pradat P, Dupuis C, et al: Fluid balance neutralization secured by hemodynamic monitoring versus protocolized standard of care in critically ill patients requiring continuous

Copyright © 2025 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

renal replacement therapy: Study protocol of the GO NEUTRAL randomized controlled trial. *Trials* 2022; 23:798

41. Murugan R, Chang C-CH, Raza M, et al: Restrictive versus Liberal Rate of Extracorporeal Volume Removal Evaluation in Acute Kidney Injury (RELIEVE-AKI): A pilot clinical trial protocol. *BMJ Open* 2023; 13:e075960
42. Stenson EK, Alhamoud I, Alobaidi R, et al: Factors associated with successful liberation from continuous renal replacement therapy in children and young adults: Analysis of the worldwide exploration of renal replacement outcomes collaborative in Kidney Disease Registry. *Intensive Care Med* 2024; 50:861–872

Copyright © 2025 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.