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Pediatric patients with multi-organ dysfunction syndrome receiving continuous renal replacement therapy

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Background. Critical illness leading to multi-organ dysfunction syndrome (MODS) and associated acute renal failure (ARF) is less common in children compared to adult patients. As a result, many issues plague the pediatric ARF outcome literature, including a relative lack of prospective study, a lack of modality stratification in subject populations and inconsistent controls for patient illness severity in outcome analysis.

Methods. We now report data from the first multicenter study to assess the outcome of pediatric patients with MODS receiving continuous renal replacement therapy (CRRT). One hundred twenty of 157 Registry patients (63 male/57 female) experienced MODS during their course.

Results. One hundred sixteen patients had complete data available for analysis. The most common causes leading to CRRT were sepsis ($N = 47$; 39.2%) and cardiogenic shock ($N = 24$; 20%). Overall survival was 51.7%. Pediatric Risk of Mortality (PRISM 2) score, central venous pressure (CVP), and % fluid overload (%FO) at CRRT initiation were significantly lower for survivors versus nonsurvivors. Multivariate analysis controlling for severity of illness using PRISM 2 at CRRT initiation revealed that %FO was still significantly lower for survivors versus nonsurvivors ($P < 0.05$) even for patients receiving both mechanical ventilation and vasoactive pressors. We speculate that increased fluid administration from PICU admission to CRRT initiation is an independent risk factor for mortality in pediatric patients with MODS receiving CRRT.

Conclusion. We suggest that after initial resuscitative efforts, an increased emphasis should be placed on early initiation of CRRT and inotropic agent use over fluid administration to maintain acceptable blood pressure.

Key words: pediatric, acute renal failure, continuous renal replacement therapy.

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Advancements and improvements in care for critically ill neonates, infants with congenital cardiac disease, and children with sepsis, bone marrow and solid organ transplantation have lead to a dramatic broadening of pediatric acute renal failure (ARF) epidemiology [1–3]. Transition from the use of adaptive continuous renal replacement therapy (CRRT) equipment to dedicated hemofiltration machines with more precise volumetric control [4] engendered a change in pediatric renal replacement therapy modality prevalence patterns for critically ill children, as surveys of U.S. pediatric nephrologists demonstrate increased CRRT use over the past five years as the preferred modality for treating critically ill pediatric patients with ARF [5, 6].

Critical illness leading to multi-organ dysfunction syndrome (MODS) and associated ARF is less common in children compared to adult patients. As a result, many issues plague the pediatric ARF outcome literature, including a relative lack of prospective study, a lack of modality stratification in subject populations, and the inconsistent controls for patient illness severity in outcome analysis [7–9]. A previous single-center pediatric study suggested increased volume overload status at CRRT initiation was associated with mortality, irrespective of severity of illness as measured by Pediatric Risk of Mortality (PRISM 2) score [10]. Other pediatric studies that do not assess severity of illness with a scoring system suggest that

increased inotropic agent requirement is associated with mortality [1, 11].

We now report data from the first multicenter study to assess the outcome of pediatric patients with MODS receiving CRRT. The present study aims to assess for potential associations between multiple clinical variables and survival in this critically ill pediatric population.

METHODS

The Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT) Registry Group is a multicenter collaborative effort to evaluate various clinical and therapeutic aspects of pediatric CRRT. The ppCRRT Registry Group is currently designed in a prospective observational format; all centers practice according to local standard of care, and have agreed to collect the same data. The decisions to initiate, alter and terminate CRRT are made by the Principal Investigator and/or colleagues at the local institution; the ppCRRT Registry does not direct any aspect of patient care. The current analysis comprises data collected between 1/1/2001 and 8/31/2003 from seven United States pediatric centers with at least 10 patients enrolled: Texas Children's Hospital/Baylor College of Medicine (Houston, TX), The Children's Hospital (Boston, MA), Children's Hospital & Regional Medical Center (Seattle, WA), C.S. Mott Children's Hospital (Ann Arbor, MI), University of Alabama Children's Hospital (Birmingham, AL), Children's Mercy Hospital and Clinics (Kansas City, MO), and Children's Healthcare of Atlanta at Egleston (Atlanta, GA). The Institutional Review Board for each center approved the study before patient enrollment.

Subject population and data collected

The ppCRRT Registry data are divided into three components: pre-CRRT initiation data, pediatric intensive care unit (PICU) data, and filter data. All subject records are encoded with a unique identifier that corresponds to the center and respective patient number. Data are transmitted using each center's password-protected database and incorporated into the main database at Baylor College of Medicine/Texas Children's Hospital, Houston, Texas.

For the present study, only data from subjects with MODS were analyzed. A subject was defined as having MODS if the underlying primary disease process leading to ARF affected at least one organ system other than the kidneys. Patient data were only collected once the local center's investigator obtained informed consent from the subject's parent or legal guardian.

Pre-CRRT initiation data collected were comprised of the following: gender, age (years), primary disease leading to CRRT initiation, relevant comorbid illnesses, reason for CRRT initiation (development of or prevention of fluid overload, electrolyte imbalance, or both), days in PICU until CRRT initiation, height (cm), PICU admission weight (kg), urine output in 24 hours before CRRT initiation (mL/kg/hr), fluid input from PICU admission to CRRT initiation (Fluid In; L), fluid out (urine, stool, chest tube, etc.) from PICU admission to CRRT initiation (Fluid Out; L), serum creatinine at PICU admission and CRRT initiation (mg/dL), and blood urea nitrogen at CRRT initiation (BUN; mg/dL). From these data, the degree of fluid overload at CRRT initiation (%FO) was calculated using the following formula [10]:

$$\%\text{FO} = (\text{Fluid In} - \text{Fluid Out})/(\text{PICU admission weight}) \times 100\%.$$

Patient GFR at CRRT initiation was calculated using the Schwartz formula [12].

PICU data collected were comprised of the following: PRISM 2 score [13] at PICU admission and CRRT initiation, central venous pressure at CRRT initiation (CVP, mm Hg), inotropic agent number at CRRT initiation, inotropic medications used and their initial and maximum doses, inotropic medications weaned off (yes/no), diuretic use (yes/no), and mechanical ventilation mean airway pressure (Paw) at CRRT initiation and termination. The PRISM 2 score assesses 14 clinical variables from five different organ domains: cardiovascular (SBP, DBP, pulse), respiratory (Resp rate, pO_2, pCO_2), neurologic (Glasgow Coma score, pupillary reaction), hepatic (bilirubin), and metabolic (potassium, calcium, total CO_2, glucose).

Filter data collected comprised the following: CRRT machine brand, anticoagulation method, priming solution, blood pump flow rate, dialysis/replacement solution composition and flow rates, hemofiltration/hemodialysis/hemodiafiltration rates, caloric (kcal/kg/day) and protein (g/kg/day) administration rates, circuit functional life (hours), and reasons to terminate a circuit [scheduled change, access malfunction, machine malfunction, unrelated patient reason (e.g., to take a patient to CT scan), clotting, or modality change]. In addition, at the end of each filter lifespan, each patient was assessed for attainment of dry weight by physical exam. Reasons to terminate CRRT were: patient death/withdrawal of support, tolerates intermittent hemodialysis, inability to perform CRRT, or regained renal function.

The predominant CRRT modality prescribed [continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF)] was recorded by each center for their patients. While all patients received some convective component of clearance as a result the ultrafiltration of excessive fluid, and we report total clearance in terms of the sum of the convective and diffusive clearance for all patients, we opted to

conform to the accepted convention of defining modality in terms of the use of replacement fluid alone (CVVH), countercurrent dialysis fluid for diffusional clearance without replacement fluid (CVVHD), or both dialysis fluid and replacement fluid (CVVDHF). Analysis of the convective contribution of ultrafiltration to clearance to patients receiving CVVHD revealed a mean relative contribution of 17.6 ± 9.0% (median 17.8%); thus, for primarily diffusion-based CVVHD, less than one fifth of clearance resulted from ultrafiltration-associated convection.

Each center's investigator initially characterized the primary illness leading to CRRT use for each of its own subjects. At the time of data analysis, the ppCRRT principal investigator (S.L.G.) reviewed all subjects' primary illness designation and, from these, created a standard definition set of primary illnesses. Each patient was assigned to one primary illness category based on the standard definition set. The standard definition set and each patient's assignment was reviewed by each center PI and either approved, or an amendment was made based on the recommendation of the center PI. A center PI reassigned only one patient after review.

The primary outcome measure was survival to PICU discharge. The secondary outcome measure was attainment of subject dry weight during the CRRT course (i.e., was the patient euvolemic at some point during the CRRT course), irrespective of ultimate patient survival.

Statistical analysis

Potential association between various clinical variables and patient survival was assessed by independent *t* test. Multiple regression analysis using PRISM 2 score to control for severity of illness on subject survival was performed for those variables demonstrating an association with survival by *t* test. In addition, in order to further control for illness severity in the most ill patients, a subgroup multiple regression analysis was performed for those patients receiving both mechanical ventilation (as a surrogate of respiratory failure) and vasoactive pressors (as a surrogate for cardiovascular compromise); thus, in this manner, patients with three-organ involvement were analyzed. Nonparametric analysis was performed to assess for potential effects of <20% FO versus >20% FO, and attainment of dry weight upon survival rates. One-way analysis of variance was used to assess for potential associations between survival rates and inotropic agent number. Since a well-designed adult study demonstrated increased survival with CVVH clearances >35 mL/kg/hr (approximately 2000 mL/hour/1.73 m^2) [14], we assessed for an association between CRRT clearance <2000 mL/hour/1.73 m^2 versus >2000 mL/hour/1.73 m^2 and survival. A P value < 0.05 was considered significant.

Table 1. Demographic and clinical data at PICU admission and CRRT initiation

	Mean ± SD	Median (range)
Age *years*	8.5 ± 6.8	7.2 (1 day to 25.1 years)
PICU admit weight *kg*	11.1 ± 25.5	25 (1.8 to 107.8)
PICU admit PRISM 2	15.4 ± 9.0	14 (0 to 45)
Days in PICU to CRRT Init	7.3 ± 14.1	3 (0 to 103)
CRRT Init GFR *mL/min/1.73 m^2*	38.8 ± 32.2	28.4 (1.4 to 150)
CRRT Init PRISM 2	16.4 ± 7.7	15 (0 to 38)
CRRT Init %FO %	17.4 ± 17.9	13.4 (−6.4 to 72.3)
CRRT Init inotrope number	1.5 ± 1.1	2 (0 to 5)

Abbreviations are: CRRT Init, CRRT initiation; PRISM 2, Pediatric Risk of Mortality Score; %FO, percent fluid overload.

RESULTS

Demographic data

At the time of study analysis, 157 patients were entered into the ppCRRT Registry and received a total of 20,062 hours of CRRT. One hundred twenty of 157 patients (63 male/57 female) experienced MODS during their course and comprised the cohort for the present study.

Demographic data for patients with MODS are listed in Table 1. The geographic distribution for the cohort is: 36 patients from Texas Children's Hospital/Baylor College of Medicine (26.7%), 23 from C.S. Mott Children's Hospital (19.2%), 20 from The Children's Hospital, Boston (16.7%), 20 from University of Alabama Children's Hospital (16.7%), 12 from Children's Hospital & Regional Medical Center (10%), 10 from Children's Healthcare of Atlanta at Egleston (8.3%) and three from Children's Mercy Hospital and Clinics (2.5%). The primary reasons for CRRT initiation were treatment of fluid overload and electrolyte imbalance ($N = 65$; 54.1%), treatment of fluid overload only ($N = 35$; 29.2%), treatment of electrolyte imbalance ($N = 10$; 8.3%), prevention of fluid overload or electrolyte imbalance ($N = 6$; 5.0%), and other reasons ($N = 4$; 3.3%).

The most common causes leading to CRRT were sepsis ($N = 47$; 39.2%) and cardiogenic shock ($N = 24$; 20%). The most common comorbid underlying illnesses included bone marrow transplant (BMT) in 18 patients and solid organ transplants in eight patients (6 liver, 2 heart). Eight patients had no cause other than MODS identified as leading to need for CRRT.

One hundred of 120 patients (83.3%) were receiving mechanical ventilation, and 53/120 patients (44.1%) were receiving diuretics at the time of CRRT initiation.

Outcome data

Complete outcome data were available for 116/120 patients with MODS. Sixty patients survived (51.7%), and 56 patients did not survive to discharge from the

Table 2. Clinical variables and outcome

Variable[a]	Survivors	Nonsurvivors	*P* value
Patient age *years*	8.49 ± 6.74	8.51 ± 7.19	NS
Patient weight *kg*	34.2 ± 25.4	31.7 ± 25.8	NS
PICU days to CRRTInit	6.5 ± 14.2	8.1 ± 14.0	NS
PRISM 2 at PICU admit	14.3 ± 8.2	16.2 ± 9.7	NS
PRISM 2 at CRRTInit	13.9 ± 8.2	18.6 ± 7.2	<0.003
CVP at CRRT Init mmH_2O	16.5 ± 6.1	21.2 ± 6.6	<0.003
Intropes at CRRT Init	1.4 ± 1.1	1.7 ± 1.1	NS
P_{aw} at CRRT Init mmH_2O	16.9 ± 7.5	19.5 ± 10.0	NS
GFR at CRRT Init *mL/min/1.73 m²*	36.3 ± 32.2	41.4 ± 32.2	NS
BUN at CRRT Init *mg/dL*	61.1 ± 41.8	67.8 ± 45.7	NS
%FO at CRRT Init	14.2 ± 15.9	25.4 ± 32.9	<0.03
CRRT clearance *mL/hr/1.73 m²*	1680 ± 994	1774 ± 1340	NS
Urine output *mL/kg/hour*	0.93 ± 1.3	0.92 ± 1.1	NS

[a]Values expressed as mean ± SD.

PICU. Survival rates were not statistically different between units with more than 10 complete outcome data sets (range 40% to 50%). For the most common primary causes leading to CRRT, survival rates were as follows: sepsis (61%) and cardiogenic shock (53%); patients with BMT or with hepatic dysfunction had a 33% survival rate.

Table 2 lists data comparing clinical variables for survivors versus nonsurvivors. Days from PICU admission to CRRT initiation, patient age, weight, PRISM 2 score at PICU admission, and inotrope number, GFR, urine output, and BUN level at CRRT initiation were no different for survivors compared to nonsurvivors. In contrast, PRISM 2 score, central venous pressure (CVP), and %FO at CRRT initiation were significantly lower for survivors versus nonsurvivors. P_{aw} at CRRT initiation was somewhat higher, and improvement in P_{aw} (i.e., decrease in P_{aw}) over the course of CRRT was significantly better for survivors (-6.6 ± 8.7 mmH_2O) compared to nonsurvivors (-0.5 ± 12.3 mmH_2O; $P < 0.05$). Multivariate analysis controlling for severity of illness using PRISM 2 at CRRT initiation for the entire cohort revealed that CVP and %FO were still significantly lower for survivors versus nonsurvivors ($P < 0.05$).

Seventy-six patients received both mechanical ventilation and inotropic agents at CRRT initiation, and 35 of these patients (46%) survived. Multivariate analysis of this cohort using PRISM 2 demonstrated that %FO was still significantly lower for survivors versus nonsurvivors in this subgroup analysis.

Survival rates were no different for patients receiving 1 (40% survival), 2 (55%), or ≥3 (45%) inotropic agents at CRRT initiation. Survival rates were significantly better for patients with <20% FO (58% survival) versus >20% FO (40%) at CRRT initiation ($P < 0.002$), even though PRISM 2 scores for patients with <20% FO versus >20% FO were no different at PICU admission (14.3 ± 7.6 vs. 17.3 ± 10.3) or CRRT initiation (16.1 ± 8.1 vs. 17.0 ± 7.5). Survival rates were also significantly better for patients who were able to attain dry weight during their CRRT course (76% survival) versus patients who did not return to their dry weight during the CRRT course (36%; $P < 0.001$).

Eighty-eight patients received CRRT with an AN-69 membrane, and 28 patients received CRRT with a polysulfone membrane. Sixty-nine patients were treated with a diffusion only–based CRRT modality (CVVHD), 35 patients were treated with only a convective modality (CVVH), and 12 patients were treated with a combination of diffusion and convection (CVVHDF). Patients receiving CVVHDF had lower PRISM 2 scores at PICU admission (9.9 ± 4.6) versus patients receiving CVVH (14.1 ± 8.9) or CVVHD (17.2 ± 9.1) ($P < 0.05$). However, PRISM 2 scores, %FO, and CVP at CRRT initiation were no different between the three CRRT modalities. Patient survival did not differ significantly between CRRT modalities [CVVH (58%), CVVHD (44%), CVVHDF (58%)]. No association was observed between CRRT clearance <2000 mL/hr/1.73 m^2 versus >2000 mL/hr/1.73m^2 and survival rates.

DISCUSSION

Data from the current study comprise the largest cohort reported to date detailing the PICU course and outcome of critically ill children with MODS and ARF receiving CRRT. We chose to study patients with MODS in the current analysis because they represent the most critically ill patients, and most pediatric centers use CRRT as the initial RRT modality for children with ARF [15].

Our data suggest that greater patient fluid overload at the time of CRRT initiation is associated with decreased survival in critically ill pediatric CRRT patients. Although the present study was not designed to randomize patients to differing degrees of %FO, which would be unethical, examination of other clinical variables during the PICU course lends insight into the potential effect of fluid overload on outcome. Interestingly, severity of illness as measured by PRISM 2 score was no different between survivors and nonsurvivors at PICU admission, yet was significantly lower for survivors compared to nonsurvivors at CRRT initiation. In addition, CVP values were significantly lower for survivors compared to nonsurvivors. We speculate that CRRT patients who receive more fluid from PICU admission to CRRT initiation develop higher CVPs with greater extravasation into the pulmonary interstitium and other extravascular spaces. Because CRRT survivors and nonsurvivors had similar PRISM 2 scores at PICU admission, yet nonsurvivors had higher PRISM 2 scores at CRRT initiation, we hypothesize that increased fluid administration was associated with an increased risk of mortality in this cohort.

The present study findings strengthen preliminary conclusions reported in a previous small pediatric study [10]. The additional data examined herein led to observations that nonsurvivors had higher %FO, demonstrated less improvement in P_{aw} during CRRT, and were less likely to reattain their target dry weight. While physical examination is a crude assessment of dry weight and volume status, patients with critical illness are often too unstable to receive accurate weight measurements. Thus, resolution of peripheral and sacral edema, coupled with a decrease in P_{aw}, may be reasonable indicators of decreased fluid overload. These additional findings provide indications that prevention of excessive fluid overload may be a hallmark of optimal care for the pediatric patient with MODS and ARF.

Cautious interpretation of these ppCRRT Registry data is warranted, and determining optimal fluid management for critically ill children may be controversial. It is certainly possible that increased %FO merely delineated more critically ill patients who had exaggerated capillary leak and required more fluid resuscitation to maintain cardiac output and end-organ perfusion. However, controlling for severity of illness using PRISM 2 scores for the entire cohort, and for patients with both respiratory and cardiovascular compromise, demonstrated that lower %FO status remained an independent predictor of survival.

We realize a potential criticism of our study is that PRISM 2 score investigators did not intend for PRISM 2 to be used as a marker of severity of illness for any time except PICU admission [13]. For this reason, we did not attempt to predict patient survival using PRISM 2. Rather, we employed PRISM 2 scores at PICU admission and CRRT initiation as a surrogate for severity of illness. A previous report shows PRISM 2 to be a poor predictor of outcome in children with ARF [16], likely because the PRISM 2 score does not directly account for renal function. Since no pediatric severity of illness scoring system has been validated for children with ARF receiving renal replacement therapy, and yet, controlling for patient severity of illness is critical for outcome analysis, we attempted to overcome PRISM 2 limitations by assessing renal function with creatinine clearance and normalized urine output at CRRT initiation—both of which were no different between survivors and nonsurvivors.

We do not interpret our findings to advocate the withholding of fluid administration for critically ill children in shock. Rather, we suggest that our data support a practice of goal-directed fluid therapy in this cohort, a concept that has gained attention in adult patients. Fluid resuscitation in critically ill children is essential with appropriate use in acute hypovolemic and septic shock states [17, 18]. The subacute effects of fluid overload, however, are more uncertain. Several studies have suggested an association between excessive fluid retention and negative patient outcome. Adult surgical ICU patients who develop fluid retention have increased morbidity, increased requirements for blood products, prolonged dependency on pressors, and a two-fold increase in death [19]. Fluid overload has also been associated with decreased survival in adult patients with ARDS [20–22]. Use of strict fluid restriction protocols was associated with fewer ventilator and ICU days in one adult study [22].

CONCLUSION

A recent adult study [18] demonstrated that adult patients who received early goal-directed fluid therapy in the emergency center received more fluid in the emergency center, but received less fluid and had better survival in the ICU compared to patients who received standard therapy. This adult study used a number of physiologic end points to guide fluid resuscitation, including mean arterial blood pressure and CVP, which can easily be measured in pediatric patients. Our current observations that greater fluid overload and CVP were associated with patient mortality, coupled with adult study experience that goal-directed fluid resuscitation support led to less post-resuscitation fluid administration and better patient outcomes, supports development of a pediatric practice that accounts for fluid administration in critically ill patients. We suggest that after initial resuscitative efforts in critically ill children, an increased emphasis should be placed on early initiation of CRRT and inotropic agent use over fluid administration to maintain acceptable blood pressure. Ongoing assessment of %FO using the simple formula presented in this study may serve as an important parameter to evaluate patient fluid overload status and guide the fluid management in critically ill pediatric patients with ARF.

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