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The use of renal replacement therapy in critically ill pediatric small bowel transplantation candidates and recipients: Experience from one center

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Abstract: Outcomes for pediatric SBT patients requiring perioperative RRT in the PICU remain unknown. The objectives were to document our center's experience with PICU SBT patients receiving perioperative RRT and to identify variables predictive of survival to discharge. A retrospective chart review of patients (ages, 0–18 yr) between January 1, 2000 and December 31, 2011 that received RRT within a SBT perioperative period and were transplanted at our university-affiliated, tertiary care children's hospital was performed. Six SBT patients received perioperative RRT (ages, 5–12 yr). Three patients (50%) survived to hospital discharge. Among survivors, RRT was required for a total of 1–112 days (mean, 49.7 days). All three survivors survived to hospital discharge without renal transplantation and free of RRT. There was a trend toward increased survival among older patients receiving RRT ($p = 0.05$). Survivors had a higher I-125 GFR prior to PICU admission ($p = 0.045$). A higher I-125 GFR prior to PICU admission among survivors may support this test's utility during SBT evaluation. In our experience, a high survival rate and freedom from RRT at the time of discharge support RRT use in the SBT population.

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As survival in pediatric SBT and OLT recipients improves, acute and chronic renal failure is becoming more frequent (1, 2). Therefore, the use of RRT in this population will likely increase. The SBT population is particularly at risk for renal dysfunction before and after transplantation due to chronic total parenteral nutrition usage, higher doses of immunosuppression, volume depletion, secondary infections, nephrotoxic antibiotics and diuretic use (3). In adult patients, the incidence of chronic renal failure was highest in SBT patients when compared to other non-renal solid organ transplants (2).

To our knowledge, there has been no previous report on the prognosis of SBT patients requiring RRT, specifically. Farmer et al. (4) reported improved patient and graft survival in SBT patients with a cGFR >90 mL/min/1.73 m^2. The limited literature on the prognosis of OLT patients may be relevant to SBT patients given their common reliance on immunosuppression and intra-abdominal procedures. Several adult studies have reported poor outcomes among OLT patients requiring RRT (5). The only known survival rate among pediatric liver transplant patients receiving RRT was reported to be 30% in a multicenter study (6).

Abbreviations: cGFR, calculated glomerular filtration rate; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration; HD, hemodialysis; I-125 GFR, iothalamate-125 glomerular filtration rate; OLT, orthotopic liver transplantation; PICU, pediatric intensive care unit; RRT, renal replacement therapy; SBT, small bowel transplantation.

The objectives of this study were to quantify survival in SBT patients in the PICU receiving perioperative RRT and to identify variables associated with survival to discharge. We hypothesized (i) that children receiving an SBT have worse survival when RRT is required in the perioperative period and (ii) that older age is associated with survival.

Methods

After obtaining institutional review board approval, medical records from patients (ages 0–18 yr) receiving care at our university-affiliated, tertiary care children's hospital were reviewed. Those receiving RRT in a PICU within a SBT perioperative period during the same hospitalization between January 1, 2000 and December 31, 2011 were eligible for inclusion. Those receiving RRT immediately before the current SBT admission or with chronic renal failure were excluded to prevent bias from prior renal dysfunction. Multiple variables were analyzed and categorized into three groups: (i) demographic data, (ii) renal data, and (iii) outcome data.

Renal function was assessed by (i) cGFR using the Schwartz formula (GFR = $K \times$ length/serum creatinine; $K = 0.45$ for full-term infants, 0.55 for children and adolescent females, and 0.7 for adolescent males) at PICU admission and (ii) pre-PICU I-125 GFR.

Other RRT data included modalities of dialysis (intermittent HD, CVVHDF, and CVVHD), time of initiation and termination of dialysis, reason for starting dialysis, incidence of renal transplantation, anticoagulation type, days between SBT and RRT, and total days of RRT. Each run of dialysis at our center was considered an independent event if dialysis was stopped for longer than 12 h, thereby excluding runs that ended due to technical reasons, such as circuit thrombosis. If a patient had started dialysis at a referring hospital, that patient's first dialysis after the transport at our institution would be considered the beginning of a new run.

Statistical analysis

Differences between survivors and non-survivors were compared using Fisher's exact test for categorical variables and the Student's *t*-test for continuous variables. Statistical analysis was conducted using SAS (version 9.2; SAS Institute, Cary, NC, USA) and IBM SPSS (version 22; Armonk, NY, USA). Statistical significance was considered $p < 0.05$.

Results

Demographic data

Six pediatric patients (two males, four females; ages, 5–12 yr) received RRT within a perioperative SBT period from January 1, 2000 to December 31, 2011. One patient was initiated on RRT and transferred from an outside PICU to our center. The mean body weight at PICU admission was 18.3 kg (range, 9–29.8 kg), and body surface area was 0.70 m^2 (range, 0.43–1.04 m^2). Graft types for the first SBT included combined liver–intestinal transplantation (50%), multivisceral transplantation (33%), and isolated intestinal transplantation (17%). Four recipients (67%) were retransplanted subsequently due to rejection. Most of these patients received a combined liver–intestinal transplantation (75%). Gastroschisis and necrotizing enterocolitis were the most common causes of intestinal failure in our population. One patient required a kidney transplantation but did not survive to hospital discharge (Table 1).

Renal data

Numbers of patients receiving specific renal replacement therapies at our center were as follows: CVVHDF (n = 2), CVVHD and HD (n = 1), CVVHD (n = 1), HD (n = 1), and a combination of CVVHD, HD and CVVHDF (n = 1). For the seven runs of continuous RRT performed at our center, five runs were anticoagulated with citrate, one run was anticoagulated with heparin, and one run received no anticoagulation. Fluid overload was at least one indication for the first run of RRT in each patient at our center (Table 2). Three patients required RRT either

Table 1. Demographic data

Patient number	Age at RRT initiation (yr)	Gender	Survival to discharge	Etiology of intestinal transplantation	Renal transplantation	Runs of dialysis at our center	1st SBT	2nd SBT	RRT pre- and post-SBT vs. post-SBT only
1	5	Female	No	Necrotizing enterocolitis		3	LIT		Pre-SBT only
2	8	Male	No	Gastroschisis, necrotizing enterocolitis, Intestinal failure associated liver disease	Yes	1	LIT	LIT	Post-SBT only
3	12	Female	Yes	Intestinal pseudo-obstruction		4	MVT	MVT	Pre-SBT and post-SBT
4	5	Female	No	Ileal atresia		1	LIT		Post-SBT only
5	8	Female	Yes	Gastroschisis		4	MVT	LIT	Pre-SBT and post-SBT
6	11	Male	Yes	Necrotizing enterocolitis		1	IIT	LIT	Post-SBT only

IIT, isolated intestinal transplantation; LIT, combined liver–intestinal transplantation; MVT, multivisceral transplantation. Runs included continuous and intermittent.

Table 2. Reason for first RRT run at our center

Category	Number of patients
Acidosis	1
Electrolyte abnormality	1
Fluid overload	6
Uremia	2

Some patients had more than one reason for their first or only RRT run.

pre-SBT or both pre- and post-SBT, while the other half required RRT post-SBT only (Table 1).

The mean cGFR at PICU admission was 100 mL/min/1.73 m^2 (range, 47–144 mL/min/1.73 m^2). cGFR at PICU admission was not associated with survival (mean, 101 mL/min/1.73 m^2 for survivors vs. 99 mL/min/1.73 m^2 for non-survivors, $p = 0.95$). Survivors had a higher pre-PICU I-125 GFR (153.6 mL/min/1.73 m^2 vs. 64.8 mL/min/1.73 m^2, $p = 0.045$). The time between pre-PICU I-125 GFR and initiation of RRT was not different between survivors and non-survivors (mean, 461 days vs. 159 days, $p = 0.14$).

Outcome data

Three patients (mean, 10 yr; median, 11 yr; range, 8–12 yr) survived to hospital discharge (50%). We observed three mortalities. Causes of death included sepsis-related multiorgan failure, cerebral edema complicated by uncal herniation, and cardiac arrest with progression to multiorgan failure. Among survivors, RRT was required for a total of 1–112 days (mean, 49.7 days). There was a trend toward increased survival among older patients who received RRT (mean, six yr vs. 10 yr, $p = 0.05$). None of the survivors required a renal transplant prior to hospital discharge. In addition, all three patients were discharged off RRT. Overall patient survival from RRT initiation was 67% at one month, 50% at six months, and 50% at one yr. One patient was known to be alive at 22 months, and a second patient was known to be alive at 45 months.

Discussion

We present a case series of PICU patients receiving RRT within an SBT perioperative period that reveals a survival to hospital discharge rate of 50% as well as a one-yr survival rate of 50%. We identified a trend toward increased survival to hospital discharge among older patients. In addition, survivors had a higher pre-PICU I-125 GFR. To our knowledge, this is the first case series documenting the prognosis of and variables associated with survival among PICU patients receiving RRT within an SBT perioperative period.

Although pediatric intestinal transplantation rates continue to decrease, 40% of all SBT recipients are pediatric patients (7). There is growing evidence that renal disease is significantly higher after SBT compared to other non-renal solid organ transplantations and is associated with a fourfold increase in the relative risk of death (2, 3). In a study that evaluated the impact of tacrolimus on renal function in pediatric intestinal transplantations, Ueno et al. (8) report a 19% drop of cGFR at 18 and 24 months post-intestinal transplantation. A prior study at our institution examining adult and pediatric intestinal transplantation recipients found that patients with a cGFR <75% of normal at seven, 28 and 365 days were six times more likely to die than those with a higher cGFR (3). Of note, five of our patients received RRT following transplantation. Although we did not examine our cohort's renal function or any potential nephrotoxic medication exposure longitudinally, despite our cohort's 50% survival rate at one yr, practitioners should monitor renal function and likely employ robust renal protection among similar patients following transplantation. Additional studies are required to determine whether similar patients have further worsened renal function longitudinally following SBT.

The timing of RRT and the effect on outcome in SBT patients remain unknown. Uncertainty remains whether patients that require this intervention pre- or post-SBT have a higher mortality (9). Furthermore, variables predictive of successful termination of RRT are unknown in this population. Although this series provides some information for clinicians treating renal insufficiency and failure in the pediatric SBT population, further multicenter analyses are required before any recommendations can be made regarding RRT initiation and management.

The best way to identify such patients at risk for renal dysfunction is unknown. Measured GFR by renal clearance of inulin continues to be the gold standard for the evaluation of renal function in children. However, this evaluation is technically difficult, time-consuming, and invasive (10). Although cGFR is a convenient method, the applicability of cGFR in liver disease, short gut syndrome, and any severely malnourished state has been questioned. Several studies report the limited accuracy of cGFR in this population due to decreased muscle mass and subsequent low serum creatinine leading to an overestimated cGFR (10–13). Other filtration

markers used include I-125, iohexol, EDTA, diethylenetriaminopenta-acetic acid and cystatin C.

Our institution measured GFR in this cohort using I-125, a radioisotope that is used as a single injection. Plasma disappearance curves are then monitored to measure GFR in children (14). In our study, when comparing cGFR between survivors and non-survivors at PICU admission, cGFR was not associated with survival. Survivors, however, had a higher pre-PICU I-125 GFR ($p = 0.045$). These findings perhaps suggest that I-125 may be superior in assessing renal function and predicting survival among pediatric patients requiring RRT in a SBT perioperative period. Further study is necessary, however, to answer this question while comparing this test to other testing and evaluation methods available.

We did not analyze whether I-125 was a predictor of RRT need due to possible selection bias among providers declining to offer RRT. We also did not analyze whether I-125 was associated with survival among all SBT recipients. Controlling for RRT within such a heterogeneous group would likely prove difficult. Further analyses should also include the use of potentially nephrotoxic medications as well as the effect of renal transplantation. A large multicenter registry would likely be needed to control for these and additional variables effectively. Creation and analysis of such a registry would be valuable to identify variables contributing to survival among all SBT patients.

Symons et al. (6) report a survival rate of 31% in pediatric liver disease/transplantation patients requiring RRT. In view of our observed freedom rate from RRT at the time of discharge (100%) and 50% survival rate to discharge compared to the 80% survival rate reported nationally among all pediatric SBT recipients, we advocate that renal dysfunction and RRT should not be absolute contraindications to SBT (7). We also speculate that with additional evaluation of renal function among SBT candidates and recipients, further improvement in outcome will likely be achieved. Additional study, however, is needed to confirm this.

We report a trend toward increased survival among older patients receiving RRT ($p = 0.05$). Our findings may be related to better overall survival among older patients receiving SBT (12). Furthermore, Venick et al. (15) report a trend toward improved survival among older patients receiving OLT.

This present series has several limitations. Our study is a retrospective, non-randomized study of SBT patients. Our cohort was small and lacked adjustment for illness severity. An illness severity score was not calculated because such a score would likely vary significantly throughout an SBT patient's hospital course. The KDIGO criteria for acute kidney injury had not been finalized when we initiated this study. We also did not control for RRT modality, changes in critical care during the study period and individual physician practices.

Conclusion

In our experience, pediatric patients requiring RRT around the time of SBT achieved a 50% survival to hospital discharge rate, and all survivors were RRT-free at the time of hospital discharge. Older age may be associated with improved survival, and a higher I-125 GFR prior to PICU admission among survivors may support this test's utility among SBT candidates and recipients. Future studies with a larger patient cohort are needed to investigate these and other potential predictors of appropriate RRT utilization in the pediatric SBT population.

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Authors' contributions

Carol Pineda: Contributed to concept, design, data collection, data analysis, drafting of the article, and critical revision and approval of the article; Tristan Grogan: Participated in data analysis, statistics, drafting of the article, and critical revision and approval of the article; James A. Lin and Robert B. Kelly: Contributed to concept, design, data analysis, and critical revision and approval of the article; Joshua Zaritsky and Robert Venick: Participated in concept, design, and approval of the article; Douglas G. Farmer: Contributed to data collection, and critical revision and approval of the article.

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