RENAL REPLACEMENT THERAPY IN THE TREATMENT OF CONFIRMED OR SUSPECTED INBORN ERRORS OF METABOLISM

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Objective Analysis of mortality and risk factors for mortality in the use of renal replacement therapy to correct metabolic disturbances associated with confirmed or suspected inborn errors of metabolism.

Study design A retrospective review of an institutional review board–approved pediatric acute renal failure data base at the University of Michigan. Eighteen patients underwent 21 renal replacement therapy treatments for metabolic disturbances caused by urea cycle defects (n = 14), organic acidemias (n = 5), idiopathic hyperammonemia (n = 1), and Reye syndrome (n = 1).

Results There were 14 boys (74%) and 4 girls (26%), with a mean age and weight of 56.2 ± 71.0 months and 18.5 ± 19.2 kg, respectively, at the initiation of renal replacement therapy. Overall treatment mortality rate was 57.2% (12 of 21 treatments), with 11 of the 18 patients (61.1%) dying before hospital discharge. Two-year follow-up on those patients demonstrated that 5 patients (71.4%) remained alive. Initial therapy with hemodialysis was associated with improved survival. Ten treatments (47.6%) required transition to another form of renal replacement therapy to maintain ongoing metabolic control, with a mean duration of 6.1 ± 9.8 days. Time to renal replacement therapy >24 hours was associated with an increased risk of mortality, whereas a blood pressure >5th percentile for age at the initiation of therapy and the use of anticoagulation were associated with a decreased risk of mortality.

Conclusions Renal replacement therapy can correct the metabolic disturbances that accompany suspected or confirmed inborn errors of metabolism. Our experience demonstrates an approximately 60% mortality rate associated with renal replacement treatment, with more than 70% of survivors living longer than 2 years.
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The diagnosis of an inborn error of metabolism in a child may be delayed as the result of the nonspecific symptoms. The initial presentation often includes hypotonia, irritability, somnolence, and metabolic acidosis.[1-6] Further evaluation may demonstrate hyperammonemia or ketoacidosis, thereby suggesting an inborn error of metabolism. Definitive diagnosis is based on the detection of abnormal levels of amino acids or organic acids, or their metabolites, in urine and/or serum specimens. This may require an additional 24 to 72 hours, further delaying the initiation of specific medical therapy until the exact metabolic defect is identified. Multiple previous studies have demonstrated that the neurologic and developmental morbidities of children with acute metabolic disturbances caused by inborn errors of metabolism increase with prolonged duration of the metabolic derangement.[2-4] Thus, children with a suspected or confirmed inborn error of metabolism often require an extracorporeal therapy to achieve a rapid correction of their metabolic disturbance. Such extracorporeal therapies have included exchange transfusions, peritoneal dialysis (PD), hemodialysis (HD), and continuous renal replacement therapy (CRRT).[7,8] Renal replacement therapy (RRT), such as PD, HD, and CRRT, allows for the efficient removal of toxic metabolites to safer levels while diagnostic studies are being performed and minimizes the duration of the metabolic derangements shown to adversely affect long-term outcome.[9-20]

CRRT	Continuous renal replacement therapy	OA	Organic acidemias
CVVH	Continuous venovenous hemofiltration	PD	Peritoneal dialysis
CVVHD	Continuous venovenous hemodialysis	RRT	Renal replacement therapy
HD	Hemodialysis	UCD	Urea cycle disorders

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The application of RRT to metabolic disturbances has changed dramatically over the past 20 years. Initial studies by Donn et al[7] compared exchange transfusion, PD, and HD and concluded that HD is the preferred modality for treating hyperammonemia caused by urea cycle defects. Now, with the increasing application of HD in neonates and the development of CRRT, the choice currently is between HD, CRRT, or both modalities.[21,22]

We present our single-center retrospective experience with RRT for the treatment of acute disturbances in suspected or confirmed inborn errors of metabolism over a 10-year period.

METHODS

An institutional review board–approved acute renal failure database maintained at C.S. Mott Children's Hospital of the University of Michigan allowed for the monitoring of pediatric patients (defined as ages 0 to 21 years) who required RRT from 1991 to 2000. During this decade, 18 patients underwent 21 RRT treatments (defined as beginning of RRT to either clinical recovery or death) for control of metabolic disturbances associated with either suspected or confirmed inborn errors of metabolism. The two patients who underwent multiple RRT treatments were during separate hospitalizations and at different ages and therefore were treated as independent events. The nephrologist on service at the time of RRT initiation determined the specific modality of RRT.

The prescription for HD for children with metabolic derangements differed from that prescribed for children with acute renal failure in three ways. First, the blood flow rate was increased to between 5 to 10 mL/kg per minute (based on access pressures) to allow for maximal clearance of toxins and toxic metabolites. Second, the dialysis bath varied from a standard renal failure bath by the addition of physiologic levels of phosphorus (1.5 mmol/L [4.6 mg/dL]) and potassium (4 mmol/L). Finally, the dialysate flow rate was set to a standard 500 mL/min. The standard dialysate used for HD at the University of Michigan was prepared on-line during the treatment using Renasol® (Minntech Corp, Minneapolis, MN) acid and bicarbonate concentrates in a 36.83X dilution system. The final dialysate had 137 mmol/L of sodium, 103.25 mmol/L of chloride, 33 mmol/L of bicarbonate, 4.0 mmol/L of acetate, 0.75 mmol/L of magnesium, 2.5 mmol/L of calcium, and 11.1 mmol/L (200 mg/dL) of dextrose. Potassium chloride was added to the acid concentrate to raise the dialysate potassium concentration to 4 mmol/L, and sodium phosphate was added (45 mL or 90 mL of intravenous sodium phosphate preparation) to raise the dialysate phosphorus concentration to 0.75 or 1.5 mmol/L, respectively. The dialysis filter was selected by its filter surface area, being approximately equal to the child's estimated or calculated body surface area.

Previous experience with CRRT demonstrated equal ammonia clearance between continuous venovenous hemofiltration (CVVH) and continuous venovenous hemodialysis (CVVHD) (unpublished personal observation). Therefore, all children underwent CVVHD for consistency. The CVVHD prescription included a blood flow rate of 5 to 8 mL/kg per minute and a dialysate flow rate of 2000 mL/1.73m^2 per hour. The dialysate fluid for CVVHD also contained physiologic levels of phosphorus (1.5 mmol/L [4.6 mg/dL]) and potassium (4 mmol/L). The CRRT membrane was either an HF-400 (Minntech Renal Systems, Minneapolis, MN) or a Multiflow-60 (COBE Renal Intensive Care, Lakewood, CO), depending on the size of the child. The standard dialysate or filter replacement fluid solution for CRRT used at the University of Michigan was compounded by the pharmacy. The solution consisted of 3 liters of sterile water, 100 mmol/L of sodium chloride (NaCl), 40 mmol/L of sodium bicarbonate ($NaHCO_3$), 0 to 2 mmol/L of potassium chloride, 0 to 0.45 mmol/L (0 to 1.5 mg/dL) of potassium phosphate, 0 to 0.75 mmol/L (0 to 1.5 mEq/L) of magnesium sulfate, and 5.5 mmol/L (100 mg/dL) of dextrose.

The goal of HD was to achieve a plasma ammonia concentration of <200 μmol/L, irrespective of the duration of HD. Plasma ammonia concentrations were measured every hour during the acute HD treatment, and the HD treatment was ended on receipt of a level <200 μmol/L. Similarly, the duration of CRRT was determined by the maintenance of the plasma ammonia concentration <200 μmol/L while receiving medical therapies. Patient survival was assessed at 2 years after hospital discharge to evaluate patient outcome not complicated by the families' decisions to withdraw medical support or as a consequence of the RRT modality, as no patient required ongoing RRT after discharge.

Data analysis is presented as a mean ± SEM. Continuous variables are analyzed by using a Mann-Whitney *U* test for nonparametic data, and dichotomous variables are analyzed using the Fisher exact test. All *P* values are 2-sided. Risk ratio and 95% confidence intervals are calculated by using a 2 × 2 table.

RESULTS

The subsequent diagnoses in these children included urea cycle disorders [ornithine transcarbamylase deficiency (n = 5), argininosuccinic lyase deficiency (arginosuccinic aciduria; n = 3), arginosuccinic acid synthetase deficiency (citrullinemia; n = 2), and carbamoyl phosphate synthetase deficiency (n = 1)], organic acidurias [methylmalonic acidemia (n = 3), propionic acidemia (n = 1), and isovaleric acidemia (n = 1)], idiopathic hyperammonemia (n = 1), and Reyes syndrome (n = 1).

Overall

There were 14 boys (77.8%) and 4 girls (22.2%) identified from the database for inclusion in this study. Their ages and weights are shown in Table I, and differences between survivors and nonsurvivors are shown in Table II.

Ten of 20 (50.0%) RRT treatments were complicated by acute renal failure, as manifested by elevated serum creatinine measurements. The primary indication for RRT listed by the registry was for the correction of an acute metabolic