

## Clinical Study

# Acute Renal Replacement Therapy in Children with Diarrhea-Associated Hemolytic Uremic Syndrome: A Single Center 16 Years of Experience

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Acute kidney injury (AKI) is becoming more prevalent among hospitalized children, its etiologies are shifting, and new treatment modalities are evolving; however, diarrhea-associated hemolytic uremic syndrome (D+HUS) remains the most common primary disease causing AKI in young children. Little has been published about acute renal replacement therapy (ARRT) and its challenges in this population. We describe our single center's experience managing 134 pediatric patients with D+HUS out of whom 58 (43%) required ARRT over the past 16 years. In our cohort, all but one patient were started on peritoneal dialysis (PD). Most patients, 47 (81%), received acute PD on a pediatric inpatient ward. The most common recorded complications in our cohort were peritoneal fluid leaks 13 (22%), peritonitis 11 (20%), and catheter malfunction 5 (9%). Nine patients (16%) needed surgical revision of their PD catheters. There were no bleeding events related to PD despite a mean platelets count of  $40.9 (\pm 23.5) \times 10^3/\text{mm}^3$  and rare use of platelets infusions. Despite its methodological limitations, this paper adds to the limited body of evidence supporting the use of acute PD as the primary ARRT modality in children with D+HUS.

## 1. Introduction

The incidence of acute kidney injury (AKI, previously called acute renal failure) in children is not well defined, however, a number of recent studies suggest that it is increasing. This observation may be related to the changing etiology of AKI in children particularly in the tertiary care pediatric care hospital setting. Primary renal disease used to account for the majority of hospitalized children with AKI, whereas now the leading cause for AKI in this population is multifactorial including ischemic/hypoxic and nephrotoxic injury secondary to primary conditions such as prematurity, postcardiac surgery, or bone marrow transplantation. The lack of a well-accepted universal definition of AKI has been one of the major hurdles for researchers trying to establish incidence and etiology of AKI in children, however, the recent validation of the pediatric RIFLE criteria promises to

offer a solution to this problem. RIFLE criteria (*R* risk for renal dysfunction, *I* injury to the kidney, *F* failure of kidney function, *L* loss of kidney function, and *E* end-stage renal disease) is a standardized classification method for AKI in adults which has been adapted for and validated in pediatric patients as pRIFLE [1–3].

Despite the shift in the most common etiologies for AKI in hospitalized children from primary kidney disease to injury secondary to nonrenal diseases, diarrhea-associated hemolytic uremic syndrome is still considered the most common primary disease causing acute kidney injury in young children [4]. Currently, there is no effective preventive or specific treatment for this disease leaving symptomatic and supportive treatments as the main management options for children with D+HUS [5, 6]. Acute renal replacement therapy (ARRT) is frequently required in the acute phase of D+HUS. Older published series have reported that ARRT

is needed in up to 100% of patients; however, more recent studies report that it is required in about 40%–60% of children with D+HUS [5, 7]. All available ARRT modalities are considered equally effective in the management of children with D+HUS although peritoneal dialysis (PD) has been mentioned to potentially enhance clearance of plasminogen activator inhibitor 1, therefore facilitating renal recovery [8]. Available literature supporting any one specific AART modality and even sharing practice experience performing ARRT in children with D+HUS is very limited.

We recently reviewed patients treated for D+HUS in our center to calculate the incidence of childhood D+HUS in Southern Alberta, a region previously shown to be endemic for D+HUS (in press). The objective in this current paper is to summarize and share our single center's experience with ARRT in children with D+HUS over the past 16 years.

## 2. Methods

**2.1. Patient Recruitment and Inclusion Criteria.** Institutional ethics approval was obtained for this study from the University of Calgary. Alberta Children's Hospital (ACH) is a sole tertiary care pediatric referral center providing care for 1.6 million inhabitants of Southern Alberta, Canada.

An electronic database search for all cases of D+HUS documented at ACH from March 1st, 1994 to March 31st, 2010 was conducted. Charts of identified patients were reviewed to confirm the diagnosis of D+HUS based on the following criteria: history of diarrhea-associated with intravascular hemolytic anemia (hemoglobin <105 gm/L with schistocytes), thrombocytopenia (platelets <150 × 10<sup>9</sup>/L), and evidence of renal injury (serum creatinine concentration above the 95th percentile for age or >10 erythrocytes per high-power field on light microscopy of a urine sample). Chart documentation of all 3 criteria was required to confirm a case of D+HUS. Patients younger than 18 years at diagnosis were included. Patients with atypical hemolytic uremic syndrome (HUS) such as inherited forms of HUS and HUS secondary to organisms other than Shiga-like toxin producing *E.coli* (STEC) were excluded.

**2.2. Acute Renal Replacement Therapy.** The need for ARRT was assessed by the attending nephrologist in a case-by-case manner for each one of the patients included in this cohort. Nonspecific indication for ARRT in the context of AKI were applied, the most common being progressive oligoanuria and rapid metabolic deterioration secondary to AKI (rapidly raising urea, creatinine, potassium, or progressive metabolic acidosis). While these indications are nonspecific and strict parameters have not been adopted, the general consensus in our center is that ARRT should be offered early. In cases where patients were not offered ARRT during their acute illness, the attending nephrologist felt that there was no need for it based on the general criteria mentioned above.

Acute renal replacement modalities available in our center include PD, intermittent hemodialysis (IHD), or continuous venovenous hemofiltration with or without dialysis (CVVH ± D). The preferred choice for D+HUS patients in

our center is PD however the choice is made by the attending pediatric nephrologist in a case by case manner. Cook spiral double cuffed Tenckhoff peritoneal dialysis catheters are usually used in our center; however, straight and other types of catheters are available. An omentectomy is not routinely performed at the initial insertion of a Tenckhoff catheter but is always done during catheter revisions performed due to technical failure of PD. The preferred access for CVVH in our institution is a temporary internal jugular line usually placed by the ICU attending physician or occasionally by the interventional radiologist. Urgently needed permanent hemodialysis lines for IHD are usually placed by the attending general surgeon or the interventional radiologist in the operating room.

PD is routinely performed on the general pediatric inpatient ward by appropriately trained nurses, whereas CVVH requires admission to the ICU. IHD can be performed in the hemodialysis unit; however, during the acute phase, patients with D+HUS are frequently hemodynamically or neurologically unstable enough to require ICU care.

**2.3. Data Collection.** Data was obtained from medical charts of identified patients and included age at presentation, gender, highest creatinine level, lowest platelet count, ARRT modality, duration of anuria, duration of ARRT, technical challenges, and complications related to ARRT. Outcome data collected included documentation of residual chronic renal failure, proteinuria, and hypertension at last follow-up visit. Patients were followed for a minimum 1 year and up to 14 years after presentation.

## 3. Results

After completion of the chart review, 134 children were confirmed to have been treated for D+HUS at the Alberta Children's Hospital from April 1994 to March 2010; fifty eight of them (43%), required ARRT in the acute phase of their management. Characteristics of these patients as well as the rest of the patients and ARRT details are presented in Table 1. Outcome parameters for patients who required ARRT and those who did not are shown in Table 2.

Fifty four patients (93%) of the total 58 who required ARRT were managed exclusively by PD. The remaining 4 patients were managed with PD and an additional modality: one patient who was septic and hemodynamically unstable on admission was started on CVVH in the ICU and then transitioned to PD after 5 days. The other 3 were initiated on PD but were temporarily switched to CVVHD or IHD due to severe peritoneal fluid leak, bowel necrosis, and development of a pleura-peritoneal communication with a pleural effusion.

One patient was diagnosed with bowel perforation while on PD due to feculent PD effluent. An urgent left hemicolectomy and resection at the hepatic flexure was performed after which CVVH was attempted but failed because of an inability to establish adequate vascular access. The patient successfully resumed PD and received intraperitoneal antibiotics for treatment of peritonitis caused by the bowel perforation.

TABLE 1: Patient characteristics and ARRT details.

Number of patients ( <i>n</i> )	58
Male/Female	25/34
Highest creatinine, mean ( $\pm$ SD), $\mu$ mol/L	261.3 ( $\pm$ 240.1)
Lowest platelet count, mean ( $\pm$ SD), $\times 10^3/\text{mm}^3$	40.9 ( $\pm$ 23.5)
Patients that received platelets transfusion	3 (5%) Mean
duration of anuria ( $\pm$ SD), days	8.47 ( $\pm$ 8.9)
Duration of RRT ( $\pm$ SD), days	20 ( $\pm$ 32.4)
Duration of admission ( $\pm$ SD) days	23.8 ( $\pm$ 11.6)
Peritoneal fluid leak	13 (22%)
PD catheter malfunction	5 (9%)
Pleuro-peritoneal communication and leak	2 (3%)
PD catheter surgical revisions	9 (16%)
Bleeding events	0
Patients treated for suspected peritonitis	11 (20%)
Patients that required ICU admission	11 (20%)
Mortality	1 (2%)

TABLE 2: Outcomes after ARRT for D+HUS.

Number of patients ( <i>n</i> )	58
Patients with GFR $< 80$ mL/min/1.73 m <sup>2</sup>	7 (12%)
Patients with GFR $< 40$ mL/min/1.73 m <sup>2</sup>	1 (2%)
Hypertensive at followup	3 (5%)
Proteinuria	18 (31%)

Among the 4 patients who were managed by CVVH or IHD in our cohort, 3 vascular access catheters clotted or did not function after insertion. The only death among the patients who required ARRT, and in fact among all 134 patients with D+HUS, was caused by an episode of massive gastrointestinal bleeding due to bowel necrosis.

#### 4. Discussion

Diarrhea-associated hemolytic uremic syndrome is the most common primary disease causing acute kidney injury in children and among hospitalized children; it is second only to ischemic/nephrotoxic injury as a cause for acute kidney injury [4].

The prognosis of D+HUS has improved dramatically since the disease was first reported mostly due to the now widespread availability of acute renal replacement therapy in children [7]. Indications for initiation of ARRT in children with D+HUS are nonspecific, for the management of oligoanuria, metabolic acidosis, and electrolyte abnormalities. Effective management of these complications can be achieved by all available methods of ARRT, including hemodialysis and hemofiltration; however, PD is in many centers the preferred ARRT modality for children with D+HUS [6, 8]. Our experience reported here supports this practice by demonstrating that the vast majority of children with D+HUS requiring ARRT can be safely and successfully managed with acute PD performed on a pediatric ward after surgical insertion of a PD catheter. The most common

technical difficulty associated with this modality in our cohort was peritoneal fluid leaking around the catheter followed by catheter malfunction which did not always require surgical revision of the catheter. In the majority of cases, these complications did not result in discontinuation or change of modality. Peritoneal fluid leaks, for example, were in most cases successfully managed by temporarily reducing the dwell volumes.

Despite the profound thrombocytopenia experienced by the majority of the patients, platelets transfusion were almost never used, and bleeding events associated with the surgical insertion of the PD catheter did not occur. This was also shown by a recent retrospective study, which found no bleeding after insertion of PD catheters in children with D+HUS, with or without platelets transfusions [9].

Sepsis and severe gastrointestinal injury such as bowel perforation in patients with D+HUS have been mentioned as possible indications for selecting a different modality of ARRT [10]. One patient from our cohort was successfully managed with PD even after bowel perforation requiring emergency hemicolectomy. In fact, PD allowed for a very rapid diagnosis of the perforation, prompt surgical management, resumption of PD, and antibiotic treatment of the intra-abdominal infection. Two additional patients in our cohort that were on PD when they developed bowel obstruction secondary to intestinal strictures were managed conservatively without changing their ARRT.

Patients who are slow to recover their kidney function or require chronic dialysis can choose to continue with home PD using the original PD catheter that was inserted during the acute phase of their D+HUS. In our cohort, there were two such patients that continued on chronic home PD for 93 and 240 days, respectively, before regaining enough function to be able to come off dialysis.

Most of our patients did not require admission to the ICU and were managed on a regular pediatric ward by nursing staff that had previous training in PD. In our center, selection of other ARRT modalities would have led to many more days spent in the ICU. The availability of IHD and CVVH  $\pm$  D in children has been facilitated by significant technological advances leading to increasing popularity of these methods among pediatric nephrologists and intensivists, while the use of acute PD for children needing ARRT is declining [4, 11]. However, there is currently no evidence to support superiority of any specific ARRT modality in children with D+HUS.

The outcome data shown in Table 2 illustrates the excellent renal recovery which ultimately occurs in most patients as previously shown by many investigators [7]. The data also demonstrates that residual proteinuria is a frequent complication, suggesting that these patients have suffered significant renal injury with potentially long-term consequences and, therefore, need careful followup.

This study is limited by its retrospective descriptive methodology as well as the biased preference for PD in our center. However, despite these limitations, we believe that the experience reported here represents a worthy addition to the currently modest body of evidence supporting the use of PD in children with D+HUS needing ARRT.

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