Pediatric ARF Epidemiology at a Tertiary Care Center From 1999 to 2001

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• ***Background:*** **Previous epidemiological data for pediatric patients with acute renal failure (ARF) predate current intensive care unit (ICU) technology and practice, and do not reflect newer disease therapies for bone marrow, hepatic, and cardiac transplantation and congenital heart disease surgery.** ***Methods:*** **We conducted a retrospective review of 254 ARF episodes in 248 children discharged from a tertiary referral center, Texas Children's Hospital (Houston, TX), between January 1998 and June 2001 to update current pediatric ARF epidemiological characteristics.** ***Results:*** **The most common causes of ARF were renal ischemia (21%), nephrotoxic medications (16%), and sepsis (11%). Primary renal diseases accounted for only 17 cases (7%), and hemolytic uremic syndrome accounted for only 3 cases. Overall ARF survival for the entire cohort was 176 of 254 patients (70%), whereas 110 of 185 patients (60%) requiring ICU admission and 43 of 77 patients (56%) receiving renal replacement therapy survived.** ***Conclusion:*** **These current pediatric ARF data show that pediatric ARF epidemiological characteristics have changed from primary renal disease to renal involvement secondary to other systemic illness. Longitudinal data from this cohort are underway to determine the long-term sequelae of pediatric ARF.** ***Am J Kidney Dis*** **45:96–101.**
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INDEX WORDS: Acute renal failure (ARF); children; epidemiology.

PREVIOUS ORIGINAL epidemiological data for pediatric patients with acute renal failure (ARF) predate current intensive care unit (ICU) technology and practice, and do not reflect newer disease therapies for bone marrow, hepatic, and cardiac transplantation and congenital heart disease surgery[1-4] or span the periods when these treatments were first applied to children.[5] Most pediatric ARF reports in the 1990s consist of review articles[6-9] and focus on a specific disease entity[10-15] or only patients requiring renal replacement therapy (RRT).[16-24] Many of these articles cite burns and hemolytic uremic syndrome as the most common causes leading to ARF in children.

Because children with acute and chronic illnesses recently receive more complex treatments that can be associated with ARF, it is critical to reevaluate the cause, incidence, and prognostic factors for children with ARF to advance prevention strategies and implement appropriate supportive care. The aims of the current study are to detail current pediatric ARF epidemiological characteristics, assess the incidence and modality of RRT use, describe the incidence of referral to pediatric nephrologists, and determine the outcome of pediatric ARF with respect to mortality and persistence of chronic renal failure at our center.

METHODS

We conducted a search of medical records for patients 21 years or younger with ARF listed as a diagnosis on either the discharge or death summary after admission to Texas Children's Hospital, Houston, TX, from January 1998 to June 2001. Charts were screened for estimated corrected glomerular filtration rate (GFR), and only patients with a GFR of 75 mL/min/1.73 m^2 or less were selected for additional analysis. The Baylor College of Medicine Institutional Review Board approved the study. The retrospective chart review collected the following data: patient age and weight, primary disease/condition leading to ARF, whether a renal biopsy was performed, whether a pediatric renal service consult was obtained, corrected estimated GFR (in milliliters per minute per 1.73 m^2) by means of the Schwartz formula,[25] lowest GFR during the ARF course, GFR at the time of pediatric renal service consult, RRT required, ICU care required, inotropic medications required, ICU length of stay (days), and renal function at time of hospital discharge. Survival is defined as discharge from Texas Children's Hospital.

Primary Disease Definitions

Causes of ARF are numerous and may be multifactorial for a particular patient. For purposes of the current study, the primary ARF cause listed was that considered to be the most important factor leading to renal dysfunction. For instance,

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Table 1. Clinical Variables for Pediatric Patients With ARF Stratified by Age

Age (no. of patients)	GFR	Survival	ICU Stay/LOS	RRT*	Most Common ARF Cause
0-30 d (62)	11.5 ± 9.8	34 (56)	59 (97), 46	34 (58)	Ischemic 16 (26)
1-12 mo (37)	18.4 ± 14.3	22 (59)	32 (86), 26	10 (32)	Ischemic 13 (35)
1-5 y (43)	32.9 ± 20.1	36 (84)	30 (70), 21	8 (27)	Ischemic 10 (23)
6-15 y (83)	29.3 ± 20.4	61 (73)	49 (59), 18	28 (57)	Nephrotoxins 22 (26)
16-21 y (29)	35.5 ± 17	23 (79)	15 (52), 23	8 (53)	Nephrotoxins 6 (21)
Total (254)	35.2 ± 39.2	176 (70)	185 (73), 26	80 (43)	Ischemic 45 (22)

NOTE. Values expressed as mean ± SD or number (percent).
Abbreviation: LOS, average length of ICU stay in days.
*Percentages reflect fraction of patients admitted to the ICU that required RRT.

patients with septic shock can experience ARF from hypotension leading to renal ischemia (acute tubular necrosis from decreased renal perfusion) and nephrotoxic medications. In these instances, sepsis was assigned as the primary ARF cause. Patients with congenital heart disease can be more susceptible to nephrotoxin-induced ARF; however, we decided to list renal ischemia from congenital heart disease surgery as the primary ARF cause in the current study.

Age Categories

Data were stratified by patient age at admission into the following categories: neonates (1 through 30 days), infants (31 days through 12 months), toddlers (1 year through 5 years), school age (6 years through 15 years), and adolescents (16 years through 20 years). The school age range of 6 through 15 years was chosen because children in Harris County are legally required to attend school through 15 years of age. Patients younger than 21 years were chosen to study because the American Academy of Pediatrics defines pediatric patients as younger than 21 years of chronological age.

Statistical Analysis

All statistical analyses were performed using the Statistica Software package, version 6.0 (StatSoft Inc, Tulsa, OK). Some patients experienced more than 1 ARF episode during the time course of study. Because we wanted to assess ARF epidemiological characteristics, all descriptive statistics are calculated using number of ARF episodes as the denominator, unless otherwise stated. Potential associations between GFR and survival were evaluated by means of paired *t*-test. Survival rates were compared between various groups by using chi-square analysis. P less than 0.05 is considered significant.

RESULTS

Epidemiological Characteristics

Hospital record review showed that 248 pediatric patients aged 21 years or younger (138 males, 110 females; mean age, 6.47 ± 6.5 years) experienced 254 separate ARF episodes (range, 1 to 4 episodes) from January 1998 through June 2001.

Table 1 lists the age distribution of the studied cohort. Of note, although the neonatal age range is the shortest of all categories, neonates comprised the second largest age group (n = 62; 22%). Sex distribution was similar among the different age categories. The ethnic distribution of patients with ARF was similar to that of all patients admitted to Texas Children's Hospital during the study period.

One hundred eighty-seven ARF episodes occurred in patients with an underlying comorbid condition; cardiac (43 patients), hematologic/oncological (33 patients), urological (20 patients), renal (20 patients), genetic (19 patients), prematurity (15 patients), and gastrointestinal/liver transplantations (11 patients) were the most common comorbid disease categories.

Primary Causes of Acute Renal Failure

The most common causes of ARF were ischemic (21%), nephrotoxic drugs (antibiotics, chemotherapy, nonsteroidal anti-inflammatory medications; 16%), sepsis (11%), and unknown (11%). Primary renal diseases accounted for only 17 cases (7%; acute glomerulonephritis [9 patients], pyelonephritis [5 patients], and hemolytic uremic syndrome [3 patients]). The most common ARF causes for the entire study population and for specific age ranges are listed in Table 1. Table 2 lists the most common ARF causes for patients with different underlying systemic diseases, for which ischemia and nephrotoxic medications were the most common.

Ischemia associated with congenital heart disease was the most common ARF cause in neonates (17 of 62 cases), 9 of which were attributed to hypoplastic left heart syndrome. Ischemia was the most common ARF cause for infants and

Table 2. ARF Causes for Patients With Underlying Systemic Disease

Underlying Systemic Disease	Most Common Primary ARF Causes
Cardiac (n = 43)	Ischemic (69%) Nephrotoxins (7%) Sepsis (7%)
Hematology/oncology (n = 33)	Nephrotoxins (33%) Malignancy (24%) Sepsis (9%)
Gastrointestinal (n = 11)	Ischemic (45%) Nephrotoxins (27%)
Any systemic disease (n = 187)	Ischemic (27%) Nephrotoxins (18%) Sepsis (9%)

toddlers, whereas nephrotoxic medications were the most common ARF cause for older children and adolescents. ICU admission rates decreased steadily with age from 97% in infants to 52% in adolescents, whereas RRT provision rates for patients in the ICU varied widely (17% to 58%) by patient age.

The rate of no primary ARF cause identified in the chart was greater for patients without (9 of 46 patients) versus with renal service involvement (18 of 203 patients; $P < 0.05$); however, there was no difference in GFRs between patients with an unknown cause of ARF with or without renal service involvement.

Survival

Overall ARF survival for the entire cohort and for patients with underlying comorbid conditions was 70%. Whereas the majority of patients in each age group survived, patients older than 1 year showed significantly better survival than neonates and infants (121 of 155 versus 56 of 99 patients; $P < 0.0001$).

One hundred sixty-seven of 254 patients had nonoliguric renal failure (>1 mL/kg/h of urine output). Patients with nonoliguric renal failure had better survival (74%) versus patients with oliguric renal failure (60%; $P < 0.05$). One hundred ten of 185 patients (60%) requiring ICU admission and 43 of 77 patients (56%) receiving RRT survived. One hundred seventeen ICU patients were administered inotropic medications for multiorgan system dysfunction, and only 40% of these patients survived. Table 3 lists survival rates stratified by primary ARF cause. Eleven of 17 patients with congenital heart disease survived (65%). Four of 9 patients with hypoplastic left heart syndrome survived.

Renal Service Involvement, Intensive Care Unit Stay, and Renal Replacement Therapy

The Texas Children's Hospital Renal Service was primary in 29 cases (12%), consulted in 179 cases (71%), and not involved in 46 cases (18%). Eighteen patients (7%) underwent renal biopsy for a rapidly increasing serum creatinine level, and all were determined to have a primary renal cause of ARF. GFR for patients with renal biopsy was 23.3 ± 13.8 mL/min/1.73 m^2. The GFR nadir was lower for patients with (30 ± 29 mL/min/1.73 m^2) versus without a renal consult (58 ± 62 mL/min/1.73 m^2; $P < 0.00005$). Mean patient age, weight, length of hospital stay, and survival rates did not differ for patients with and without renal consult.

One hundred eighty-five patients were treated in the ICU setting; 146 of 185 ICU episodes (79%) had renal service involvement. ICU stay prevalence was greater for patients younger than 1 year versus older than 1 year (Table 1). Median ICU stay was 21 days for survivors versus 17 days for nonsurvivors. ICU lengths of stay did not differ significantly among age classifications, although patients younger than 30 days averaged 2 to 3 weeks' longer ICU stays than the rest of the cohort (Table 1).

Seventy-seven of 185 ICU patients with ARF episodes (42%) received RRT: 38 patients, peritoneal dialysis (PD); 17 patients, hemodialysis; and 22 patients, continuous RRT (CRRT). Forty-two percent of ICU patients with comorbid conditions received RRT. Almost half the patients receiving PD were immediately status post congenital heart surgery because it is our practice to

Table 3. Primary ARF Causes and Survival Rates

Causes of ARF	Survival Rate (%)
Acute glomerulonephritis	100
Known renal disease	95
Neoplasm/bone marrow transplant	85
Ischemia	81
Nephrotoxic drugs	77
Congenital heart disease	65
Unknown causes	62
Sepsis	41

initiate PD therapy for patients who have decreasing urine output after corrective heart surgery. RRT provision rates were no different for the various patient age groups when patients undergoing congenital heart surgery were excluded from analysis. Mean patient age for patients receiving RRT was 5.5 ± 6.7 years (range, 0 to 20 years; 28 patients, 0 through 30 days; 10 patients, 31 days through 12 months; 8 patients, 1 year through 5 years; 26 patients, 6 through 15 years; and 7 patients, 16 through 20 years of age). Fifty-six percent of patients receiving RRT survived. Survival for patients without congenital heart disease receiving RRT was 43%. The percentage of patients requiring ICU stay or RRT was no different between the younger and older groups.

Renal Function at Time of Hospital Discharge

One hundred sixteen of 176 survivors (66%) recovered renal function completely, 26 survivors (15%) had improved renal function, 24 survivors (14%) developed chronic renal failure, and 11 survivors (5%) were discharged requiring RRT. Forty-three patients who required renal RRT survived; at the time of discharge, 28 patients regained normal renal function, 4 patients had chronic renal failure, and 11 patients required RRT. Six of 11 patients sent home requiring RRT had primary renal disease: obstructive uropathy, membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis, posterior urethral valves, dysplastic kidneys, and renal neoplasm.

DISCUSSION

Previous pediatric ARF series reported data collected before the advent of recent technological advancements in pediatric intensive care, congenital heart surgery, and pediatric oncology and bone marrow transplantation. Because recent pediatric ARF epidemiological reports were lacking, we performed a large retrospective review detailing primary causes, treatment modalities and services, and outcomes for pediatric patients diagnosed with ARF at our urban tertiary-care children's hospital during a 3.5-year period.

Our data show that, as opposed to previous reports from the 1980s, pediatric ARF in the present day most often occurs as morbidity associated with other systemic illness, rather than primary renal disease. Systemic diseases led to ARF in children from either nephrotoxic medication use in their treatment or multiorgan dysfunction syndrome, in which patients with sepsis, liver failure, or respiratory failure developed hypotension-induced renal ischemia. In our current series, primary renal disease comprised only 7% of ARF cases. Interestingly, survival and RRT provision rates were the same for this ARF cohort regardless of the presence or absence of an underlying comorbid condition.

We recognize that the retrospective method used in the current study has some limitations. Because there are no established criteria for pediatric renal service consultation, ICU admission, or RRT, incidences of these variables in patients with ARF may pertain to only our institution. The decision to include only patients with an estimated GFR of 75 mL/min/1.73 m^2 or less by Schwartz formula might have led to the exclusion of some patients with ARF; the Schwartz formula can overestimate GFR because it reflects tubular secretion of creatinine in addition to creatinine filtration. Although we realize that no GFR estimation formula has been validated for pediatric or adult patients with ARF, we opted to use the most widely used pediatric formula instead of serum creatinine level change as an ARF indicator because normal serum creatinine concentrations vary with age, sex, and patient size. Recent multidimensional ARF criteria, termed the Risk, Injury, Failure, Loss, and End-Stage Renal Disease (RIFLE) criteria, using serum creatinine level, GFR estimation, and urine output recently have been devised, but not yet validated, by a consensus conference for adult patients with ARF.[26] We plan to examine a pediatric-modified version of the RIFLE criteria in a prospective cohort of patients soon. Our decision to cite a primary ARF cause for each episode can be criticized because some patients, especially those who are critically ill, often are exposed to a number of conditions that can lead to ARF. However, through careful review of a patient's record, one usually can identify the initial insult leading to ARF. It is concerning to find that a primary ARF cause was not cited in the medical record for 11% of patients with ARF. That the rate of unknown ARF causes was significantly greater for patients without renal service involvement, whereas GFRs were similar for cases with

unknown ARF cause with or without renal service involvement, suggests that some children with significant ARF are being managed without the input of a pediatric nephrologist. Additional study is required to determine whether such patients are at increased morbidity risk, including extended hospital stay or unnecessary or inadequate evaluation.

Not surprisingly, patients with sepsis and multiorgan system dysfunction (inferred by provision of inotropic support in the ICU) had lower survival rates than those with uncomplicated ischemia. Survival rates for septic patients and those administered inotropes in our series (40%) are similar to those reported in previous recent pediatric series[22,24] assessing survival in critically ill children who receive CRRT. In addition, patients younger than 1 year had lower survival than older children across all primary cause categories, which supports data from a recent study[27] of pediatric patients weighing less than 10 kg receiving CRRT that showed worse survival rates for patients weighing less than compared with greater than 3 kg.

The relatively high percentage of patients receiving PD compared with hemodialysis or CRRT in our series results from our center's practice of using PD early in the postoperative course after congenital heart surgery to assist with fluid management[28,29]; PD rarely was used for RRT for other patients because it is our center's preference to use CRRT for critically ill patients with ARF to more precisely control their ultrafiltration volumes.

The vast majority (95%) of surviving patients, including those requiring an ICU stay, completely or partially recovered renal function at the time of hospital discharge, a renal function recovery rate similar to that in an adult ARF outcome study.[30] Interestingly, the majority of children in the current study requiring long-term RRT at the time of hospital discharge had a primary renal cause for their ARF episode.

Although our data show a good immediate renal prognosis for most patients, no data exist to describe potential long-term sequelae, including hypertension and the development of proteinuria or chronic renal failure for pediatric patients who survive an ARF episode to hospital discharge. We plan to follow up the current patient cohort for hypertension, urine microalbumin and protein excretion, and renal function to determine whether children who experience an ARF episode are at risk for long-term renal complications.

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