Acute Kidney Failure

A Pediatric Experience Over 20 Years

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Background: Acute kidney failure in children is a catastrophic, life-threatening event.

Objective: To compare and contrast 2 decades of data, analyzing the underlying causes, associated multiple organ system failures, outcome of dialysis procedures, and other variables of interest.

Design: Retrospective examination of clinical data collected between January 1, 1979, and December 31, 1998.

Setting: Regional health care center in the mid-Atlantic area.

Participants: Two hundred twenty-eight patients, aged from 1 day to 18 years, had acute kidney failure and were referred to a pediatric nephrology service.

Main Outcome Measures: Characteristics, percentage of mortality, intensive care unit admission, procedures, and other variables and causes of acute renal failure.

Results: The total number of cases analyzed represented 7% of all patients presented to the pediatric nephrology service. Sex distribution, ethnicity, and survival statistics were unchanged between both decades. The overall survival rate was 73%. One hundred fifty-four patients (68%) were admitted to the pediatric intensive care unit. The following 106 acute extracorporeal procedures were performed on 93 patients (41%): 12 patients received extracorporeal membrane oxygenation, 52 patients underwent peritoneal dialysis, 32 patients underwent hemodialysis, 3 patients received continuous venovenous hemofiltration, and 7 patients received continuous arteriovenous hemofiltration. Sepsis and burns, other leading causes of acute renal failure in the first decade, are replaced in the second decade by hematologic-oncologic complications and pulmonary failure.

Conclusions: Acute kidney failure following repair of cardiac lesions remains unchanged as a leading risk factor of mortality in both decades. Three organ system failures were associated with more than a 50% mortality rate. Predialysis low serum albumin concentrations emerged as a significant copredictor of mortality.

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Between January 1979 and December 1998, 228 consecutive pediatric cases of acute renal failure were diagnosed and treated at the Medical College of Virginia Hospital, Richmond, a regional health care center in the mid-Atlantic area. All medical data were entered prospectively each day on standard forms ("the yellow sheets" advocated by Frederic C. Bartter, MD*) under direction of the same pediatric nephrologist (J.C.M.C.).

These forms remained unchanged in the 2 decades of the study and were intended for future review as well as for clinical use as a flow sheet. We obtained institutional review board approval for this study.

The diagnosis of acute kidney failure was made by the same attending nephrologist (J.C.M.C.) using the following criteria: a sudden cessation of kidney function characterized by oliguria, less than 0.5 mL/kg per hour, confirmed by rising levels of serum urea nitrogen and creatinine to double that of normal for age.1,6 Patients with preexisting chronic kidney diseases* were excluded. The criteria for admission to the ICU was determined by the same 2 attendings (S.S.S. and J.J.M.), and were as follows: (1) the requirement of monitoring of critically ill patients, such as those who were recovering from postcardiac surgery; (2) patients requiring invasive monitoring, that is, arterial lines, ventriculostomies, and others; (3) those in congestive heart failure or respiratory failure requiring intubation; and (4) patients with MOSFs* requiring invasive monitoring. The established criteria for MOSF were used. All values were expressed as mean ± SD. P < .05 denotes statistical significance.

The 228 patients with acute kidney failure represented 7% of all inpatient and outpatient referrals made to the pediatric nephrology service over these 2 decades.* The clinical characteristics were as follows: slightly more male than female patients (60% vs 40% and 57% vs 43%, respectively). Comparing the first (1979-1988) and second (1989-1998) decades, the ethnic distribution was, respectively, 53% and 54% white; 38% and 33% black; and 9% and 13% others. No statistically significant differences were noted between the first and the second decade in these patient characteristics as given in Table 1.

Between the 2 decades, patient survival was 71% and 74%, respectively, for an overall survival rate of 73%. The mortality rates between the 2 decades were not significantly different as well, at 29% and 26%, respectively (Table 1). Table 2 lists the age of patients in relationship to mortality.

Among the survivors, the order of underlying causes for acute kidney failure hardly change between the 2 decades. (Table 3) Hemolytic uremic syndrome (HUS)* in the survivors was the leading cause of acute kidney failure in both decades, 38% and 22%, respectively. There was 1 death from HUS in the 2 decades, of a total of 49 patients, making the mortality rate 2% for this condition. Twenty-one percent and 57% of these patients required dialysis in their respective decades.

Postcardiac surgery remained the leading cause of acute kidney failure among the nonsurvivors in both decades. However, sepsis as a cause of acute kidney failure dropped significantly from 23% (1979-1988) to 3% (1989-1998) (P < .001). Figure 1 shows the organisms responsible for sepsis in each decade. Also, extensive burns precipitating acute kidney failure accounted for 13% of acute kidney failure in the first decade, but dropped significantly to 0% in the second decade. Pulmonary causes of acute kidney failure among the nonsurvivors increased between the 2 decades, 7% to 12%, but this did not reach statistical significance. Hematologic-oncologic causes of acute kidney failure among the nonsurvivors also increased from 10% in the first decade to 22% in the second decade, in association with bone marrow transplant rejections, leukemia, tumor lysis, hyperuricemia, and other complications (Figure 2). While tumor lysis was an important cause of death in the first decade (Figure 2), it was not so in the second, where the mortality rate from this cause was 0%. “Anticipatory” intervention is prevalent and the improved results may be attributed to this. The use of peritoneal dialysis (PD) dropped from 60% of all acute renal replacement therapy in the first decade to 44% in the second decade (Table 4). The use of hemodialysis, continuous venovenous hemofiltration (CVVH), and continuous arteriovenous hemofiltration (CAVH) increased to 43% of acute renal replacement therapy in the second decade. Also, the interval between renal consultation for acute kidney failure to the initiation of acute renal replacement therapy was 2.0 ± 1.8 days vs 1.9 ± 1.4 days, respectively, between the 2 decades.

Figure 3 shows the data on mortality in acute kidney failure in association with other organ failures. In the

*Frederic C. Bartter, possibly the longest serving branch chief of the National Heart, Lung, and Blood Institute at the National Institutes of Health, always advocated the use of the National Institutes of Health’s data forms, referred by generations of clinical associates as “the yellow sheets,” to keep patient data and to plan research studies.
first decade, 27% of the patients died with 2 MOSFs; 3 MOSFs, 57%; and 4 MOSFs, 100%. However, in the second decade of this study, 2 MOSFs had a mortality rate of 13%; 3 MOSFs, 68%; and 4 MOSFs, 88%.

Examination of all serum variables on the comprehensive metabolic profile, for example, sodium, potassium, chloride, carbon dioxide, cholesterol, calcium, glucose, and others, obtained immediately before acute kidney replacement therapy did not show significant differences between survivors and nonsurvivors, with the exception of the serum albumin concentrations (Figure 4). The serum albumin concentrations were 2.6 ± 0.7 g/dL in nonsurvivors vs 3.3 ± 0.9 g/dL in survivors (P < .05). Figure 5 shows a survival distribution plot for serum albumin concentration. Hypoalbuminemia was significantly associated with the nonsurvivors.

We reviewed all English-language published reports since 1977 of acute kidney failure with 50 children or more (Table 5). It was surprising to find a persisting scarcity of published data specifically addressing acute kidney failure and its risk factors and morbidity and mortality in the pediatric population. In regard to our patient data on morbidity and mortality and critical illness, our criteria for ICU admission were (1) the requirement of close monitoring of critically ill patients, such as those who were recovering from cardiac surgery; (2) patients requiring invasive monitoring, that is, arterial lines, ventriculostomies, and others; (3) those in congestive heart failure or respiratory failure requiring intubation; and (4) patients with MOSFs, as established previously, requiring invasive monitoring. Similar criteria for ICU admission were used by Moghal et al7 resulting in 48% of their 227 patients with acute kidney failure admitted to their ICU compared with the 68% ICU admission rate in our present series. If criteria for admission to the ICU are to be taken as life-threateningly ill, our patients can be considered at least as critical as those in the other series (Table 5). Also, the overall mortality rate of 27% in our study compares favorably with the other published series, despite the persistent requirement of ICU admissions for this disease.

Smoyer et al17 and Zobel et al18 indicated that pediatric patients with acute kidney failure with MOSF, even when treated with continuous kidney replacement therapy, sustained a 60% to 100% mortality rate. In further review of the pediatric literature (Table 5), we noted that few studies examined the number of organ failures in relationship to mortality rate in acute kidney failure.19-24 Our data (Figure 3) show that the mortality rate between the 2 decades dropped, even with 4 organs failing. The mortality rate fell from 100% to 88% in the second decade (1989-1998), possibly related to advances in antibiotics, earlier diagnosis, and better volume control in the recent decade. Smoyer et al17 and Zobel et al18 also noted that pediatric patients with acute kidney failure with MOSF, even when treated with continuous kidney replacement therapy, sustained a 60% to 100% mortality rate. In further review of the pediatric literature (Table 5), we noted that few studies examined the number of organ failures in relationship to mortality rate in acute kidney failure.19-24 Our data (Figure 3) show that the mortality rate between the 2 decades dropped, even with 4 organs failing. The mortality rate fell from 100% to 88% in the second decade (1989-1998), possibly related to advances in antibiotics, earlier diagnosis, and better volume control in the recent decade. The examination by Shaw et al25 and Meeks and Sims26 established series, despite the persistent requirement of ICU admissions for this disease.
amination of 831 children with MOSFs did not provide specific data on the 5% of their patients who developed kidney failure. However, our data of 57% to 68% mortality with 3 MOSFs are lower than the 89% mortality reported by Shaw et al and Meeks and Sims, again verifying that advances in technology appear to have allowed us to improve our management of this particular risk factor.

Despite the tremendous advances in the last decade of both critical care management and kidney replacement therapy, however, the significant finding in our study was the persistently high mortality rate of critically ill patients after cardiac surgery. Patients frequently developed acute kidney failure as a result of poor perfusion and hypoxia secondary to prolonged pump time during surgery for congenital heart disease, 27% in the first decade, 44% in the second decade among the nonsurvivors. The younger the patient, the poorer the prognosis, especially in patients younger than 1 year (Table 2). It is also possible that the difference is due to changes in the attending surgeons, increased complexity of patients with heart disease in the second decade, and differences in techniques.

Although mortality from acute kidney failure secondary to an underlying cardiac diagnosis did not appear to have changed significantly when data between the 2 decades were compared, there was a shift in other underlying diagnoses. In the first decade, acute kidney failure associated with cardiac surgery was the major cause of mortality, followed by sepsis (Table 3), burns, pulmonary, and hematologic-oncologic complications. Among nonsurvivors, sepsis-associated acute kidney failure dropped from 23% in the first decade to 3% in the second decade (P < .001) presumably, again, because of advances in antibiotic therapy and better management of fluid volume control. Although the organisms causing sepsis did not change in the 2 decades (Figure 1), there was an increased emergence of methicillin-resistant Staphylococcus aureus in the first decade and of penicillin-resistant Streptococcus pneumoniae in the second decade. Despite these changes in sensitivity, we managed to have better outcomes in the second decade.

Figure 1. Organisms responsible for sepsis in acute renal failure.

Figure 2. Hematologic-oncologic complications associated with acute renal failure.

Table 4. Need for ECMO, PD, HD, and CVVH

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>ECMO</td>
<td>3 (9)</td>
<td>9 (13)</td>
</tr>
<tr>
<td>PD</td>
<td>21 (60)</td>
<td>31 (44)</td>
</tr>
<tr>
<td>HD</td>
<td>11 (31)</td>
<td>21 (29)</td>
</tr>
<tr>
<td>CVVH</td>
<td>0</td>
<td>3 (4)</td>
</tr>
<tr>
<td>CAVH</td>
<td>0</td>
<td>7 (10)</td>
</tr>
<tr>
<td>Total</td>
<td>35 (100)</td>
<td>71 (100)</td>
</tr>
</tbody>
</table>

*Data are given as the number (total percentage) of the procedure. ECMO indicates extracorporeal membrane oxygenation; PD, peritoneal dialysis; HD, hemodialysis; CVVH, continuous venovenous hemofiltration; and CAVH, continuous arteriovenous hemofiltration.
Also, in the second decade, the noncardiac causes of death shifted to hematologic- oncologic complications, for example, leukemic-tumor lysis, hyperuricemia, bone marrow transplantation (Figure 2), and respiratory failure. The incidence of hematologic-oncologic complications associated with death in acute kidney failure increased in the second decade possibly because of the increase in aggressive chemotherapy, management, and bone marrow transplantation availability. The latter procedure was unavailable in the first decade of this study (Figure 2).

The significant drop in burns as a cause of acute kidney failure in the second decade may be partly due to a change in burn care management, as the care of pediatric burn patients was taken over by a newly developed burn unit independent of the pediatric ICU in the second decade. It would also appear that burn prevention and management have improved to a degree that the hypovolemia of burns is successfully eliminated as a significant cause of acute kidney failure in the second decade.

Another important and significant risk factor for mortality was age. The youngest patients showed a higher mortality rate. Most published studies of acute kidney failure in early life are small series19-26 of fewer than 25 patients, yet the mortality rate is high.19-26 In our study, neonates and infants, aged 1 day to 1 year, represented 57% of the total nonsurvivor group (Table 2), and they composed a very large part of the postcardiac acute kidney failure group. In addition, the 12 patients requiring extracorporeal membrane oxygenation were all in the neonatal age group. Extracorporeal membrane oxygenation, in turn, led to the choice of CVVH or CAVH over PD in all of these infants because of the availability of dialysis access. These observations in morbidity and mortality are in accord with the observations of Gong et al10 that coma, hypovolemia, respiratory failure, and acute tubular necrosis in infants younger than 1 year remain significant mortality risk factors. Acute kidney failure in neonates and infants19-27 also represents a special clinical and technical challenge, because of the tiny body size of the patients. Finally, the higher mortality rate in this age group could possibly be due to other associated congenital anomalies.19-27

Our data indicated that in the more recent decade (1989-1998), the use of acute PD had decreased significantly (Table 4). Acute hemodialysis, CVVH, CAVH, and renal replacement procedures were used more frequently than before, with a corresponding decrease in the use of PD. This trend of moving away from acute PD in favor of acute hemodialysis, CVVH, or CAVH in renal replacement therapy in acute kidney failure was first suggested by a questionnaire survey of pediatric nephrologists by Warady and Bunchman.28 Our data over the span of 20 years substantiated this trend. Acute PD, of course, will still be done via Tenckhoff cannula, especially for our younger patients. However, CVVH and CAVH will probably be preferred, especially whenever extracorporeal membrane oxygenation is used with its need to limit the risk of infection from PD in this particular group, as well as dialysis access availability.

In addition, acute kidney replacement therapy was initiated within 1.9 ± 1.4 days in the more recent
Table 5. Critically Ill Pediatric Patients With Acute Renal Failure*

<table>
<thead>
<tr>
<th>Study Period</th>
<th>Year of Publication</th>
<th>Source</th>
<th>Country</th>
<th>Total Sample Size</th>
<th>Overall Mortality Rate, %</th>
<th>Survival Rate, %</th>
<th>% of Patients Needing Dialysis</th>
<th>Age</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1971-1975</td>
<td>1977</td>
<td>Counahan et al^29</td>
<td>UK</td>
<td>70</td>
<td>20</td>
<td>80</td>
<td>63</td>
<td>1.8-11.2 y</td>
<td>Close association with adult renal unit an advantage</td>
</tr>
<tr>
<td>1968-1977</td>
<td>1978</td>
<td>Hodson et al^31</td>
<td>USA</td>
<td>53</td>
<td>45</td>
<td>55</td>
<td>100</td>
<td>1 d-15 y</td>
<td>Underlying and/or concomitant disorders have major influence; early dialysis improves survival</td>
</tr>
<tr>
<td>1980-1982</td>
<td>1983</td>
<td>Elzouki et al^32</td>
<td>Libya</td>
<td>93</td>
<td>8</td>
<td>92</td>
<td>10</td>
<td>1 d-14 y</td>
<td>Dehydration ATN major cause of ARF; excellent recovery after fluid replacement techniques</td>
</tr>
<tr>
<td>1969-1982</td>
<td>1985</td>
<td>Niaudet et al^23</td>
<td>France</td>
<td>125</td>
<td>11</td>
<td>89</td>
<td>98</td>
<td>1 d-16 y</td>
<td>Outcome depended primarily on underlying disease</td>
</tr>
<tr>
<td>1987-1990</td>
<td>1991</td>
<td>Reznik et al^34</td>
<td>USA</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>100</td>
<td>1 d-15.5 y</td>
<td>Acute PD safer than extracorporeal techniques</td>
</tr>
<tr>
<td>1978-1990</td>
<td>1993</td>
<td>Gallego et al^35</td>
<td>Spain</td>
<td>138</td>
<td>39</td>
<td>61</td>
<td>38</td>
<td>2 d-15 y</td>
<td>Assisted ventilation and dialysis are comortality factors</td>
</tr>
<tr>
<td>1989-1994</td>
<td>1996</td>
<td>Arora et al^1</td>
<td>India</td>
<td>80</td>
<td>43</td>
<td>58</td>
<td>69</td>
<td>&lt;15 y</td>
<td>Neurological, respiratory, or cardiac complications poor prognostic factors; HUS still significant mortality</td>
</tr>
<tr>
<td>1986-1994</td>
<td>2000</td>
<td>Lowrie^4</td>
<td>USA</td>
<td>62</td>
<td>89</td>
<td>11</td>
<td>100</td>
<td>1 d-15 y</td>
<td>An important goal of renal support in MOSF is prevention of fluid overload; CHDF appears more effective than PD in maintaining fluid balance</td>
</tr>
<tr>
<td>1980-1998</td>
<td>2000</td>
<td>Gong et al^34</td>
<td>Singapore</td>
<td>66</td>
<td>68</td>
<td>32</td>
<td>91</td>
<td>1 d-19 y</td>
<td>Despite increasing use of CHDF over last 3 years, no significant improvement; probably related to patients being more critically ill</td>
</tr>
<tr>
<td>1979-1998</td>
<td>2002</td>
<td>Williams</td>
<td>USA</td>
<td>228</td>
<td>27</td>
<td>73</td>
<td>38</td>
<td>1 d-18 y</td>
<td>CHF with ARF; a significant mortality risk especially in young patient after cardiac surgery</td>
</tr>
</tbody>
</table>

*Only includes studies with 50 children or more. UK indicates United Kingdom; USA, United States of America; ATN, acute tubular necrosis; ARF, acute renal failure; PD, peritoneal dialysis; HUS, hemolytic uremic syndrome; MOSF, multiple organ system failure; CHDF, continuous hemodiafiltration; ECMO, extracorporeal membrane oxygenation; and CHF, congestive heart failure.

decade (1989-1998) compared with 2.0 ± 1.8 days in the previous decade (1979-1988) between the renal consultation and the start of acute kidney dialysis. Our data begin with our initial consultation, which naturally affects our initiation of dialysis. Thus, together, our data suggest more favorable outcomes with earlier, rather than later, time lags of 4.2 to 4.8 days between the onset of kidney failure and the start of dialysis as reported by Arora et al.¹

An interesting finding in our analysis was that HUS²⁹ represented the largest group of survivors, without differences between the 2 decades. There was only 1 death in our group of 49 patients with HUS, a 2½-year-old, resulting in a 2% mortality rate. This conforms to the decrease in HUS mortality from 40% in the past to 5% in recent years.³⁰ Although we used the same criteria for initiation of dialysis in acute kidney failure throughout the 2 decades, we were more aggressive in using dialysis in the recent decade. For example, we used dialysis in 57% of the patients with HUS in the second decade compared with 21% in the first decade. The improved survival in HUS in our study may be related to our more aggressive dialysis therapy. These findings contrast with the current 68% mortality rate in India. In this series of 25 patients with HUS reported by Arora et al,¹ late referral resulting in more critically ill patients was the reason given for the higher mortality rate. This is understandable with the persistence of significant differences in availability of medical care and gross national income between the United States and India. This continuing difference also has a greater significant effect on both chronic and acute kidney diseases and the long-term survival of children in India. In long-term dialysis for end-stage kidney disease,⁴⁴¹³³⁴ hypoalbuminemia is shown to be an index of malnutrition and a predictor of mortality. Although Obialo et al³⁵ showed that hypoalbuminemia (<3.5 g/dL) can be a useful predictor of mortality in adults with acute kidney failure, this had not been examined in children. Our data (Figure 4) showed that there is a significantly lower serum albumin predialysis level between nonsurvivors (2.6 ± 0.7 g/dL) and survivors (3.3 ± 0.9 g/dL) (P<.05). In addition, the cumulative survival data (Figure 5) clearly established that hypoalbuminemia could discriminate between the survivors and the nonsurvivors, with 40% dying by day 30. Thus, our data ascertain the efficacy of using serum albumin concentration as a copredictor of mortality in pediatric acute kidney failure. Obialo et
al also suggested that low albumin concentrations in adult patients may be correlated with the activation of inflammatory mediators. Studies on a molecular basis of these observations may illuminate new avenues to improve survival in these patients.

CONCLUSIONS

We have seen that postcardiac surgery associated with acute kidney failure remains the leading mortality risk factor. Hematologic-oncologic complications have become a more frequent cause of acute kidney failure in the recent decade because of advances in care management. Sepsis as an associated cause of acute kidney failure dropped from 23% to 3% in the last 2 decades although the organisms responsible for the sepsis did not change. Our data on acute dialysis indicated less PD being done in the recent decade, a trend previously suggested in a questionnaire survey. Also, although mortality risks increase significantly with MOSFs in association with acute kidney failure in adults, our data in this study suggest a slightly better prognosis in children. Another significant comorbidity factor is young age (ie, <1 year), combined with the need for extracorporeal membrane oxygenation due to respiratory failure secondary to problems in fluid management. Finally, our data suggest that hypoalbuminemia is a copredictor of mortality in pediatric acute kidney failure.

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