Clinical Outcomes of Acute Renal Failure in Children

Çocuklarda Akut Böbrek Yetmezliğinin Klinik Sonuçları

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SUMMARY

Aim: The aim of this study was to investigate the etiological factors, clinical progression and management of acute renal failure (ARF) in hospitalized children.

Materials and Method: Medical records of 63 patients aged between 1 month and 18 years who were hospitalized at Uludag University, Department of Pediatrics or at various intensive care departments of the faculty and diagnosed with ARF between January 2005 and August 2006 were retrospectively analyzed.

Results: Forty two of study patients were male and 21 were female. Mean age was 5.4±5.3 years. ARF was found in 4.9% of all hospitalized patients. Sepsis was the most frequent etiological factor with a ratio of 23.8%; which was followed by gastroenteritis (19.1%), tumor lysis syndrome (17.4%) and cardiac surgery (15.9%). Oliguria, sepsis, hyperkalemia, acidosis and dialysis were found to be associated with increased mortality ($p<0.05$). The mortality rate in the study population was 49.2%.

Conclusion: Dialysis and mechanical ventilation was found to be associated with a poor outcome in our patients. *(Journal of Current Pediatrics 2009; 7: 57-61)*

Key words: Acute renal failure, children, dialysis, prognosis

ÖZET

Amaç: Bu çalışmanın amacı, hastaneye yatırılan çocuklarda akut böbrek yetmezliğinin (ABY) klinik progresyonu, tedavisini ve etyolojik faktörlerinin araştırılmasıdır.

Gereç ve Yöntem: Uludağ Üniversitesi Tıp Fakültesi çocuk yoğun bakım ve hastanenin diğer yoğun bakım ünitelerinde Ocak 2005 ile Ağustos 2006 tarihleri arasında ABY tanısı konmuş 1 ay ile 18 yaş arasında 63 hastanın dosyaları retrospektif olarak incelendi.

Bulgular: Çalışmaya alınan hastaların 42'si erkek, 21'i kız olup, ortalama yaş 5,4±5,3 yıl idi. Yoğun bakım ünitesine yatırılan hastaların %4,9'unda ABY saptanmıştır. ABY'nin etyolojisinde sepsis %23,8 oranı ile en sık etyolojik faktör olarak saptandı. Bunu sırasıyla, gastroenteritler (%19,1), tümör lisis sendromu (%17,4) ve kalp cerrahisi (%15,9) sonrası gelişen ABY izlemiştir. Oligüri, sepsis, hiperpotasemi, asidoz ve diyaliz yapılması artmış mortalite oranı ile ilişkili bulundu ($p<0,05$) ve mortalite oranı %49,2 olarak saptandı.

Sonuç: Diyaliz uygulanması ve mekanik ventilasyon ihtiyacının hastalardaki kötü sonuçlarla ilişkili olduğu saptandı. *(Güncel Pediatri 2009; 7: 57-61)*

Anahtar kelimeler: Akut böbrek yetmezliği, çocuk, diyaliz, prognoz

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Introduction

Acute Renal Failure (ARF) is defined as a rapid decline in glomerular filtration rate (GFR), resulting in the disturbance of renal physiological functions including impairment of nitrogenous waste product excretion, loss of water and electrolyte regulation and loss of acid-base regulation (1). ARF is an important contributing factor to the morbidity and mortality of critically ill infants and children (1-3). ARF may be divided into 3 categories: prerenal, intrinsic and postrenal. Renal failure usually follows sepsis, metabolic diseases, chemotherapy, acute gastroenteritis, hemolytic uremic syndrome (HUS), major cardiac interventions and the use of nephrotoxic agents (4-8). Prerenal form is most frequent during childhood (2,3). Although the incidence of

ARF varies with geographical localization and countries, it has been reported in 2-5% of hospitalized children and in 4.5-30% of children in intensive care units. Mortality rates of 35 to 80% have been reported in patients developing ARF (2,8-11). The present study aimed at retrospectively investigating the outcomes, etiological causes, treatment methods and mortality rates of ARF in children aged 1 month to 18 years who were hospitalized in pediatric wards and intensive care units.

Materials and Method

This retrospective study included children, hospitalized at Uludag University Medical Faculty Department of Pediatrics or at various intensive care units of the faculty and who developed ARF between January 2005 and August 2006. Among 1282 hospitalized patients, 63 developed ARF. Medical records were screened for estimated GFR, and patients with a GFR of 75 ml/min/1.73 m^2 or less were selected for additional analysis. GFR was determined by using Schwartz formula (12). ARF was defined as a rapid and progressive decline in renal function, manifested as rising plasma urea and creatinine levels, which are usually accompanied by oliguria (<1 ml/kg/hour) or occasionally by polyuria.

Patient records were retrospectively analyzed for age, sex, body weight, underlying etiological factors, blood pressure, urine amount, duration of renal failure, treatments, blood chemistry (urea, creatinine, electrolytes) and whole blood count, urinary analysis and findings of renal ultrasonography.

Normal proteinuria in children was defined as urinary excretion of proteins to be less than 4 mg/m^2/h in the 24-hour urine collection or random urine sample protein/creatinine (mg/dl)/(mg/dl) ratio by definition less than 0.2 (2). Oliguria was defined as a urinary output of <1ml/kg/hour for infants and young children, and <400 ml/day for adolescents (1,2). In urinary analysis, the presence of >5/hpf (high power field) erythrocytes or leukocytes or the presence of proteinuria was considered abnormal (13). A diagnosis of sepsis was made when bacteria was isolated from blood culture. In children with ARF hyperkalemia was defined as a serum potassium >6.5 mEq/L for infants and >5.5 mEq/L for young children and adolescents (in the absence of alkalosis or polycythemia) (14). Systolic and/or diastolic blood pressure levels equal or greater than 95 percentile were considered as hypertension, whereas following formula was used for the definition of hypotension: a systolic blood pressure <70 mmHg+2xAge(yr) (14). Metabolic acidosis was defined as a pH<7.2 and bicarbonate <8 meq/l in arterial blood gas analysis (2,14). Hemodialysis (HD) or peritoneal dialysis (PD) was performed in patients with severe metabolic acidosis, hyperkalemia not responding to treatment, volume overload, and pulmonary edema and in patients unresponsive to medical treatment. Patients with a history of chronic renal failure were excluded.

Statistical Analysis

Multiple logistic regression analysis was used for the correlation of parameters to mortality and survival. For the analysis of the association between etiological factors and mortality of dialysis treatment, Pearson Chi-Square test and Kolmogorov-Smirnov test were used. A p value <0.05 was considered significant.

Results

ARF was diagnosed in 63 patients [42 (66.7%) were male and 21 (33.3%) were female]. The mean age was 5.4±5.3 years (range: 1 month to 18 years). ARF was found in 4.9% (63/1282) of all patients hospitalized in our center. This rate was 3.1% (27/847) for pediatrics clinic and 8.2% (36/435) for intensive care unit patients. The most frequent etiological factor for ARF was sepsis (23.8%) and this was followed by gastroenteritis (19.1%), tumor lysis syndrome (TLS) (17.4%) and cardiac surgery (15.9%). Etiological factors resulting in ARF are shown in Table 1.

Mean serum urea, creatinine and potassium concentrations were 108.6±44.3 mg/dl (range: 56-292 mg/dl), 2.3±1.0 mg/dl (range: 0.8-5.7 mg/dl) and 4.9±1.4 mEq/L (range: 3.0-9.8 mEq/L), respectively. Hematuria was found in 41.3% (n:26) and proteinuria was found in 12.6%

Table 1. Etiological factors for renal failure

Etiology	Number	Percentage (%)
Sepsis	15	23.8
Gastroenteritis	12	19.1
Tumor lysis syndrome	11	17.4
Cardiovascular surgery	10	15.9
Congenital heart disease	5	7.9
Hemolytic uremic syndrome	4	6.3
Convulsion	2	3.2
Poisoning	1	1.6
Others	3	4.8

(n:8) of cases. Mean GFR was 31.3±12.9 ml/min/1.73m^2 (range: 12-66 ml/min/1.73m^2). Oliguria was the most frequent clinical finding with a ratio of 73% (n:46). Initial finding was dehydration in 34.9% (n:22), hypertension in 11.1% (n:7), hypotension in 33.3% (n:21) and edema in 39.6% (n:25) of patients. Clinical characteristics of the patients are shown in Table 2.

Patients were evaluated for the presence of dehydration, hypovolemia and hypervolemia, and accordingly appropriate intravenous (i.v.) fluid treatment was administered. In hypovolemic patients with no urinary output, fluid was administered with a rate of 20 ml/kg/h and this was repeated when necessary. In addition to the intravenous fluid treatment, replacement of electrolytes was also done. Inhaled salbutamol (0.25 μgr/kg/dose), i.v. calcium gluconate (1 ml/kg/15 min), 8.4% sodium bicarbonate (1 ml/kg/30 min) and glucose treatment with tamponized insulin were given to patients with hyperkalemia. Dialysis was performed in patients developing severe metabolic acidosis, hyperkalemia not responding to treatment, volume overload or pulmonary edema and in patients unresponsive to medical treatments.

Conservative treatment was given to 15 ARF patients with sepsis and 1 received peritoneal dialysis. Seven of these patients died during follow-up (mortality rate was 46.6%). In 6 of 10 patients that developed ARF following major cardiac surgery, peritoneal dialysis was performed for a mean duration of 2±0.9 days (range: 1-3 days) and all of these patients died. The mortality rate in patients developing ARF following major cardiac surgery was 60%. ARF developed due to chemotherapy related TLS in 11 patients with acute lymphoblastic leukemia (ALL) or lymphoma. Of these patients, 6 received hemodialysis and 3 of them died due to the primary disease. The relation between mortality and etiological factors resulting in ARF is shown in Table 3.

Table 2. Clinical features of acute renal failure in the study population

Clinical feature	Number	Percentage (%)
Oliguria	46	73.0
Hematuria	26	41.3
Edema	25	39.7
Dehydration	22	34.9
Hypertension	7	11.1
Convulsion	3	4.8

In 9 patients who developed ARF after cardiac surgery (n:6) or due to sepsis (n:1), hemolytic uremic syndrome (n:1) or intracranial hemorrhage (n:1), peritoneal dialysis was performed for a mean duration of 8.4±3.7 days. Mean age of these patients was 9±1.2 months (1 month to 3 years). Seven (77.7%) of these patients died due to primary disease.

Hemodialysis with a mean duration of 6.4±5.1 day (range: 1 to 27 days) was performed in 8 patients developing ARF following chemotherapy (n:6), poisoning (n:1) and sepsis (n:1); 4 (50%) of these patients died during follow-up. The mean age of patients receiving hemodialysis was 9.4±5 years (range: 3 to 15 years).

Overall, 31 (49.2%) of patients died, despite all supportive and renal replacement treatments. Mortality rate was significantly higher among patients that developed ARF following sepsis and cardiac surgery ($p<0.05$). The overall mortality rates of children treated with HD and peritoneal dialysis (PD) were 50% (4/8) and 77.7% (7/9), respectively ($p>0.05$, HD vs PD). Prognostic factors for ARF are shown in Table 4.

Table 3. Etiology and outcome of acute renal failure in the study population

Etiology	Survivors (n)	Non-Survivors (n)	Mortality (%)
Sepsis	8	7	46.6
Gastroenteritis	11	1	8.3
Tumor lysis syndrome	8	3	27.2
Cardiovascular surgery	4	6	60
Congenital heart disease	3	2	40
Hemolytic uremic syndrome	4	0	0
Convulsion	2	0	0
Poisoning	1	0	0
Others	2	1	33.3

Table 4. Markers of poor prognosis in ARF

Marker	Survivors	Non-Survivors	P value
Oliguria	29 (67.4%)	17 (85%)	<0.05
Age (y)	6.0±5.3	5.3±4.9	>0.05
Male/female	30/13	12/8	>0.05
Sepsis	8 (9%)	7 (35%)	<0.05
Hypertension	5 (11.6%)	2 (10%)	>0.05
Hypotension	13 (30%)	8 (40%)	>0.05
Hyperkalemia	6 (13.2%)	10 (50%)	<0.05
Acidosis	11 (25.5%)	14 (70%)	<0.05
Mechanical ventilation	4 (9.2%)	9 (45%)	<0.05
Dialysis	6 (13.9%)	11 (55%)	<0.05

Multiple logistic regression models revealed that among the factors that showed a significant difference between survivors and nonsurvivors, only the necessity of dialysis ($p<0.05$), use of mechanical ventilation ($p<0.05$) and sepsis ($p<0.05$) could be regarded as independent determinants of the prognosis of ARF in children (Table 5).

Oliguria, sepsis, hyperkalemia, acidosis, mechanical ventilation and requirement for dialysis were found to be associated with increased mortality ($p<0.05$).

Discussion

Although the incidence of ARF in children varies with geographical region and countries, incidences between 2-5% have been reported among hospitalized children (9-11). We found ARF in 4.9% of all hospitalized pediatric cases. Hui-Stickle et al. reported an incidence of 5%, which is quite similar to our finding. Incidences between 4.5 and 30% have been reported for intensive care unit patients (9,11,16). This variation may be attributed to the presence of different underlying etiological factors. In our study, 8.2% incidence was found among intensive care unit patients, which is also in line with previous findings.

ARF is usually characterized with a sudden reduction in renal functions accompanied with oliguria. However, occasionally patients may be nonoliguric or polyuric (2,11). Anochie et al. found oliguric ARF (OARF) in 87.2% of their patients (7). Similarly, oliguria was the major presenting finding in 73% of patients in our study.

ARF presents as prerenal, intrinsic or postrenal at childhood, prerenal being the most frequent form (4,10,17). In our study, prerenal ARF secondary to dehydration was most frequent, although many other etiologies were also found. Dehydration was due to gastroenteritis or insufficient fluid treatment of patients with congestive heart failure. Anochie et al. reported prerenal causes as the most frequent etiological factor among children (7). Similarly, prerenal ARF patients constituted the majority of our patients. Several studies from developed countries have reported that intrinsic renal failure mostly develops due to nephrotoxic agents (18-21) and several studies have found HUS as the major cause of ARF (11,22). Anochie et al and Vachvanichsanong et al reported HUS related ARF incidences of 3.3% and 2%, respectively; and they attributed this low incidence to the difficulties in diagnosing HUS or underreporting (7,21). We found HUS related ARF in 6.3% of our cases, representing a higher frequency compared to the results of Anochie et al. Among our patients, sepsis was the second major cause of ARF (23.8%). Several studies have reported sepsis as the most frequent cause (7-11,21).

Malignant conditions like leukemia or lymphoma involving kidneys are less frequent than sepsis. However, children with malignancy have a tendency to develop sepsis or TLS during chemotherapy (6,21). Eleven of our ALL or lymphoma cases developed TLS and 6 received hemodialysis. Three of these patients died due to the underlying primary disease.

ARF following cardiac surgery was the 4th most frequent cause in the present study. In such patients, major causes of death have been reported to be hypoxia resulting in multiorgan failure (MOF) and poor perfusion (19). Sixty percent of our patients that received cardiac surgery died and this high mortality rate is in line with previous studies.

Renal replacement treatment is globally a common modality in children developing ARF and unresponsive to supportive treatment (18,22). We performed peritoneal dialysis (n:9) or hemodialysis (n:8) in patients not responding to conservative treatment. Sixty-five (11/17) percent of patients receiving dialysis died during follow-up. Mortality was significantly higher in patient receiving dialysis compared to others ($p<0.05$). Previous studies have reported mortality rates between 35% and 73% among patients requiring dialysis (19,20,22). Our overall high mortality rate among dialysis patients is similar to previous studies; however, 77.7% of our patients receiving peritoneal dialysis died, which was slightly higher than the rate reported by Flynn et al (22). This may be explained by the younger age of our patients and a relatively higher proportion of ARF cases developed following cardiac surgery. Our mortality rate among hemodialysis patients is similar to previous results.

Table 5. Multiple regression models[a] of predictive factors of ARF in children

Predictive factors	β	Standard error	Significance	EXB(β)
Need of dialysis	-3.45	1,34	<0.05	0.032
Sepsis	-2.96	1.39	<0.05	0.056
Mechanical ventilation	-3.82	1.28	<0.05	0.024
Constant	-1.112	0.36	<0.05	0.368

[a]Model significance: 0.000, method, backward stepwise ward, R-square: 80%

The reported mortality rate from ARF is still as high as 60% in critically ill children (20), ranging between 35 and 80% (7-11,19,21). Our 49.2% overall mortality rate is similar to both the rates reported from developing and developed countries.

Various underlying etiological factors may result in different mortality rates. Mortality rates among patients who developed ARF following major cardiac surgery may be as high as 45-75% (5,16,19,21). Corresponding figure was 60% in our study. Mortality rates for ARF developing after sepsis range between 15 and 60% (7,16,20). For such patients, we found a similar rate in our study (46%) (19,21). When mortality rates specific for etiological factors were compared, rates following sepsis and cardiac surgery were significantly higher ($p<0.05$) in our patients.

Oliguria and anuria are poor prognostic signs for children with ARF and previous studies have reported oliguria rates between 30% and 85% among children developing ARF (5,7,11). In our study, oliguria was the initial finding in 73% of patients. Various studies suggested oliguria and/or requirement for dialysis as an important predictive factor for mortality (15,18,19). Similarly, we found a worse prognosis among ARF patient with oliguria. Other than oliguria, presence of acidosis, the need for mechanical ventilation and the need for dialysis have been associated with increased mortality in ARF (18,19,21,22).

The multiple logistic regression models in our study revealed that significant determinants of prognosis in children with ARF include the need for dialysis ($p<0.005$), presence of oliguria ($p<0.05$), acidosis ($p<0.05$) and mechanical ventilation ($p<0.05$).

Our study found that presence of acidosis and the need for dialysis or mechanical ventilation increase the mortality rate and they are predictive of a worse prognosis. In conclusion, ARF usually develops due to preventable causes such as asphyxia, dehydration and sepsis, and it frequently resolves with supportive treatment. Early diagnosis and treatment is important in terms of prognosis.

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