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Determinants of modality of management of acute kidney injury in children seen at a tertiary hospital in Nigeria

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Abstract *Background:* The cost of taking care of children with acute kidney injury (AKI) is enormous and beyond the reach of many caregivers in sub-Saharan Africa which are largely resource poor. It is therefore imperative to determine those who may benefit from conservative management which is comparatively cheaper to the renal replacement therapy (RRT).
Objectives: To determine the clinical characteristics of children who were offered conservative and renal replacement therapy and evolve the most statistically significant eligibility criteria.
Methods: A descriptive cross-sectional study of children presenting with AKI admitted into the Emergency Paediatric Unit (EPU) of the University of Ilorin Teaching Hospital (UITH) between January 2008 to December 2012 was carried out. Demographic, clinical, and laboratory data were collected. A serial blood chemistry and urine analysis were also obtained. A total of 22 cases of acute kidney injury were seen within the period. Fourteen were conservatively managed while eight underwent sessions of dialysis.
Results: The age range for those who had conservative management was 4-17 years with a mean ±SD of 8.11±3.91 years while the corresponding value in those with renal replacement therapy was 1.5-16 years with a mean ±SD of 9.68±5.54years. There was no statistical significant difference in the highest serum potassium, urea and creatinine. However, the lowest urine output was significantly different among the two groups ($p< 0.05$).
Conclusion: Urine output could be used as an eligibility criterion to determine children with AKI who will require renal replacement therapy or benefit from a trial of conservative management.

Keyword: Acute kidney injury; conservative management; dialysis

Introduction

Definitions for AKI vary widely between studies, ranging from absolute or relative increases in creatinine from baseline to the requirement for RRT.[1-2] The lack of a uniform definition may explain the large differences in reported incidence and outcomes of AKI in the literature [1], and as a consequence in 2004, a consensus on the definition of acute renal failure known as the Risk-Injury-Failure-Loss-End stage renal disease (RIFLE) classification was reached by a group of international experts.[1] The RIFLE classification was based on two important parameters, changes in serum creatinine or GFR from baseline and urine output at specific time points. The severity of acute renal failure was determined by the more severe of the two parameters, which were categorized into three stages. The three stages described in RIFLE include Risk, Injury and Loss, all of which have increasing prognostic significance.

In 2007, the Acute Kidney Injury Network (AKIN) replaced the term acute renal failure with acute kidney injury (AKI) in an attempt to include the entire spectrum of acute renal dysfunction.[3] AKI encompasses a complex clinical entity characterized by an abrupt decline in kidney function which clinically manifests as azotemia, rising serum creatinine, and in most cases oliguria. [4-5] Furthermore, AKI continues to be associated with significant mortality, hospital length of stay and economic costs, particularly in the context of critically ill patients in the intensive care setting.[6-7]
Although the incidence of AKI continues to rise, the optimum management of AKI remains uncertain with no uniform standard of care, as reflected by wide disparity

in clinical practice.[8-10] This is aside from the fact that the management of AKI can be most challenging in resource poor countries of Africa where management can be anything but ideal.[11] This is because resources are inadequate and the people living below the poverty line are too many. Furthermore, people have to pay out of pocket to procure urgent services.[11] In this circumstance, it would be unwise to offer expensive management first. Rather it is instructive to identify those predictive factors that will help anticipate those who will respond to less invasive and costly treatment such as conservative management. Hence this study aims to determine eligibility criteria to determine children with AKI who could benefit from conservative management and dialysis.

Methods

A descriptive cross sectional study of children presenting with features suggestive of AKI admitted into the Emergency Paediatric Unit (EPU) of the University of Ilorin Teaching hospital, Ilorin, Nigeria was carried out between January 2008-December 2012. Informations obtained on them included; age, sex, cause of AKI, lowest urine output over 24 hours in ml/kg /hr during admission, the highest serum potassium, urea and creatinine and the lowest sodium. These parameters were then compared in those that received conservative management and those that had to be placed on dialysis. The inclusion criteria included reduced GFR, oliguria, anuria, oedema, raised serum creatinine and urea. Reduced GFR is GFR less than standard value for age.[12] Hypertension is elevated blood pressure above the 90th percentile for age and sex.[13] oliguria is urine output below 300mls/m^2 or 1ml/kg/hr, while anuria is urine output less than 1ml/kg/day.[14] Serum creatinine and urea are raised when the values are above standard values for age groups e.g. >62µmol/l for non-adolescent children and > 88µmol/l for adolescents. Serum urea is raised when it is >6.4 mmol/l.[15]

The conservative management group comprised of those managed with fluid challenge, fluid restriction, control of hyperkalemia, acidosis, hypocalcaemia, anemia and hypertension. Hypertension was controlled with captopril (0.5mg/kg/dose 8hourly (maximum dose 6mg/kg/24hours) and nifedipine (0.5mg/kg/dose 12hourly (maximum dose 3mg/kg/24hrs). Hyperkalemia was managed with restriction of potassium containing food, fluid and medication. The type of dialysis offered in our center was only haemodialysis and no peritoneal dialysis as there was no peritoneal fluid available. There was no exact randomization to any specific treatment rather they were need or fund driven. In other words, some of those who were offered dialysis based on our clinical judgment continued on conservative management, while awaiting availability of fund. In a few cases, there was remarkable improvement which obviated the further need for dialysis. Similarly, some of those who were considered eligible for conservative management but who deteriorated were commenced on dialysis.

The sensitivity, specificity, positive and negative predictive value of parameters found to be significant was calculated. To aid the calculation, the patients were categorized into true positives and negatives and false positives and negatives respectively. True positives (TP) are those who rightly received corresponding appropriate management using the significant parameter. True negatives (TN) are those who did not rightly receive the corresponding appropriate management using the significant parameter. False negatives (FN) are those who did not receive inappropriate corresponding management using the significant parameter and false positives (FP) are those who received inappropriate management using the significant parameter.

Hence sensitivity is (TP/TP+FN) X 100%. Specificity is (TN/TN+FP) X 100%. Positive predictive value is (TP/TP+FP) X 100%. Negative predictive value is (TN/TN+FN) X 100%.

Results

A total of 22 patients were recruited for the study. Their age range was 1.5-17 years. There were 11 males and 11 females giving a male female ratio of 1:1. Fourteen (63.6%) received conservative management while 8 (36.4%) of them received dialysis. Three of those who received dialysis were referred to sister institutions and word reaching us indicated that they all died. One of those that benefited from conservative management was also referred to a sister institution for dialysis but recovered fully there, without it. Five of the eight patients that received dialysis did so in our center. They all received haemodialysis. The age range for those who had conservative management was 4-17 years with a mean±SD of 8.11±3.91 years, while the corresponding value in those who received dialysis was 1.5- 16 years with a mean ±SD of 9.68±5.54 years.

The leading cause of AKI in the conservative management group was severe malaria with haemoglobinuria which resulted in acute tubular necrosis (ATN) in 6 (42.9%) followed by sepsis in 4(28.5%). The leading causes in the dialysis group was Acute glomerulonephritis (AGN) with uraemic encephalopathy in 4(50%) followed by sepsis in 2(25%) (Table 1).

Table 1: Causes and outcome of AKI in the study population

Cause of AKI	Conservative group n-14	Dialysis group n-8
Malaria+hbnuria	6	0
Sepsis	4	2
AGN	2	4
Burkitt lymphoma	1	0
Neuroblastoma	1	0
Diarrhoeal disease	0	1
Nephrotic syndrome	0	1
No. of deaths (%)	1(7.1%)	4(50%)
Causes of death	Burkitt Lyphoma TLS(1)	AGN+ uraemic encepahalopath (3) Diarrhoeal Disease(1)

AGN-acute glomerulonephritis, TLS-tumor lysis syndrome, hbnuria-haemoglobinuria

The mean±SD of lowest urine output in the conservative management group was 0.63±0.40ml/kg/hr and the dialysis group was 0.12±0.09 ml/kg/hr respectively. The mean highest potassium in the conservative management group was 5.01±1.09mmol/l while it was 5.41±0.95mmol/l in the dialysis group. The mean highest serum urea in the conservative management group was 38.05±13.60mmol/l, while that in the dialysis group was 43.86±14.88mmol/l. The mean serum creatinine in the conservative management group was 692.5±507.15µmol/l, while that in the dialysis group was 1095.5±531.03µmol/l. The lowest serum sodium in the conservative management group was 126.21±6.91 mmol/l, while it was 124.62±4.97mmol/l in the dialysis group (Table 4). The individual biochemical parameters of children who received conservative management and dialysis respectively are shown in Tables 2 and 3 respectively.

Table 2: Biochemical parameters in the conservative group

Patient	Age	Sex	Cause	Lowest U/o	highest Umol/l	Cr highest urea mmol/l	highest K mmol/l	lowest Na mmol/l	outcome
C1.	4	M	SM	0.5	542	27	6.7	113	Alive
C2.	5	M	SM	1	421	22.3	4.7	118	Alive
C3.	9	M	NB	0.48	248	26.4	4.1	132	Alive
C4.	17	F	AGN	0.7	220	19.9	4.4	132	Alive
C5.	10	F	SM	1.2	1824	59	4.8	129	Alive
C6.	5	F	SEP	1.4	315	46.1	7.0	128	Alive
C7.	7	M	SEP	0.48	296	28.6	3.5	136	Alive
C8.	13	F	BUR	0.2	222	39.2	3.7	122	Died
C9.	5	M	SM	0.3	789	53.9	3.8	130	Alive
C10.	6.5	M	SM	0.8	1079	44.2	5.9	121	Alive
C11.	5	M	SEP	0.7	210	18.8	4.5	127	Alive
C12.	6	M	SM	0.01	929	42.3	6.3	132	Alive
C13.	13	F	SEP	0.82	1520	46.7	5.3	129	Alive
C14.	6	M	AGN	0.2	1080	58.3	5.5	115	Alive

SM-severe malaria, NB- neuroblastoma, BUR,-Burkitt lymphoma, SEP-Sepsis, AGN-acute glomerulonephritis

Table 3: Biochemical parameters in the dialyzed group

Patient	Age	Sex	Cause	lowest U/O	highest Umol/l	Cr highest urea mmol/l	highest K mmol/l	lowest Na mmol/l	outcome
D1.	9	F	AGN	0.16	1450	73.7	5.0	121	Died
D2.	1.5	M	AGN	0.06	342	27.5	5.4	118	Died
D3.	11	F	AGN	0.1	1998	45	5.3	127	Died
D4.	16	F	NS	0.3	1013	29.4	6.0	127	Alive
D5.	14	F	AGN	0.02	1655	46.5	6.7	130	Alive
D6.	15	F	SEP	0.01	981	58	4.9	131	Alive
D7.	2	M	DIA	0.08	521	30.2	3.5	126	Died
D8.	9	F	SEP	0.2	804	40.6	6.5	117	Alive

AGN-acute glomerulonephritis, NS-nephrotic syndrome, SEP-sepsis, DIA-diarrhea

When all the parameters were compared in both groups, only the lowest urine output was found to significantly predict whether dialysis or conservative management would be required ($p<0.05$). While the highest serum creatinine, urea and potassium were found to be higher in the dialysis group, it was found not to be statistically significant. Similarly the lowest serum sodium was found to be lower in the dialysis group but it was not statistically significant (Table 4).

Table 4: Clinical and biochemical determinants of modality of treatment

Parameter	Conservative Mean±SD n=14	Dialyzed Mean±SD n=8	t	p
Lowest urine	0.63±0.40	0.12±0.09	-3.094	0.006
Highest Cr	692.5±507.15	1095.5±531.03	1.709	0.103
Highest Urea	38.05±13.60	43.86±14.88	0.945	0.354
Highest K	5.01±1.09	5.41±0.95	0.823	0.420
Lowest Na	126.21±6.91	124.62±4.97	-0.381	0.707

The mean lowest urine output (when approximated to one decimal place) in the dialysis group was 0.1±0.1 ml/kg/hr compared to 0.6ml±0.4/kg/hr in the conservative group. When the urine output benchmark of ≥0.6ml/kg/hr for conservative group and ≤0.1ml/kg/hr for dialysis group was used amongst all the 22 patient to determine eligibility for either conservative or renal replacement therapy, true positives (i.e. those who rightly received the corresponding appropriate management i.e. conservative management for children with urine output ≥0.6mls/kg/hr and dialysis for children with urine output ≤0.1ml/kg/hr) were 12 patients, true negative (those who did not rightly receive the corresponding appropriate management using the urine output eligibility criteria) 10 patients, false positive (those who received corresponding inappropriate management using the urine output eligibility criteria) 10 patients, false negative (those who did not receive corresponding inappropriate management using the urine output eligibility criteria) 12 patients. Hence the sensitivity, specificity , positive predictive value and negative predictive value using the urine as eligibility criteria for choice of modality of management was 50%, 50%,37.5% and 31.2% respectively.

The outcome was better in the conservative group which recorded one death out of a total of 14 patients (7.14%) compared to 4 deaths amongst 8 patients managed with dialysis (50%). Most of the deaths 3(75%) recorded among the dialysis group were due to AGN with uraemic encephalopathy with the rest being due to AKI from diarrhoeal diseases. The only death recorded in the conservative group was in a child with Burkitt lymphoma who developed AKI from Tumor lysis syndrome. Even then, the death was not as a result of AKI as all the parameters had improved before his death. The overall mortality in both groups was 5 (22.72%) out of 22 patients.

Discussion

AKI is one of the causes of childhood morbidity and mortality.[16-17] This follows some of the major childhood conditions in the tropics such as malaria and sepsis.[11-12] The kidney is not spared in the fatal progression of these two illnesses as seen in the causes of the AKI in this series. It is however gratifying to note that most of them responded to conservative management. Indeed, most of the AKI resulting from malaria subsided after conserva-

tive management with none requiring dialysis. It is likely that the appropriate treatment of the underlying malaria contributed to this good outcome. Similarly, the use of appropriate antibiotics to treat sepsis would have also contributed to the good outcome. The bottom line therefore is that the fatal progression of these two illnesses can be interrupted with the use of appropriate potent pharmacologic agents. Once this is done, the consequent AKI is reversed in most cases if acute cortical necrosis has not developed.

In contrast, renal replacement therapy was required in the glomerulopathies whose course sometimes carry poor prognosis once AKI sets in.[18] The causes of AKI in the glomerulopathies may include the disease process itself which are irreversible in some cases and the effect of drug used in the management of the condition such as frusemide which could cause interstitial nephritis.

A close look at the serum creatinine of the conservative group shows that it was lower when compared with the dialysis group even though it was not statistically significant. Hence as serum creatinine rises, the corresponding most appropriate intervention must be offered immediately. However in resource poor countries of Africa, conservative management are more readily offered because of limited facilities and uneven distribution and availability of renal replacement therapy.[19] In Nigeria, the spread and availability of dialysis facilities is gradually improving. However there are still challenges of ability of caregivers to pay for the services and when they can pay, certain logistics may be unavailable.[19-20] Our study indicated that offering conservative management may not be a bad option at serum creatinine ≤676.79µmol/l. However at serum creatinine >676.7µmol/l, dialysis remains the best option, even though there may still be a few patients that may benefit from conservative management as evidenced by six patients in Table 2 with elevated serum creatinine due mainly to severe malaria. As earlier indicated, AKI reverses in most cases of severe malaria once appropriate antimalaria is administered. Similarly at serum urea ≤37.34mmol/l, conservative management may be considered, while at serum urea above that, dialysis remains the best option. Mean serum potassium were on the higher level of normal in both the conservative and dialysis group but the difference in both groups was not statistically significant even though there were individual cases of hyperkalemia as shown in Tables 2&3. The serum sodium was comparably low in both groups because of the consequent fluid retention common to both groups. Of all the biochemical determinants of modality of management, only serum creatinine may be considered in isolation. The others must be considered relative to the serum creatinine. In other words, if the serum urea is elevated and the serum creatinine is not proportionately elevated, it may be of no effect as other conditions such as dehydration may have contributed to that.

The most significant determinant of modality of treatment in this study was the urine output. It had an appreciable sensitivity and specificity, however, the positive and negative predictive value was marginal. This is in tandem with the RIFLE and AKIN recommendation which uses both (urine output and GFR) and (urine output and serum creatinine) respectively as criteria for determining severity and hence mode of management of AKI.[1, 3] Therefore, if the mean lowest urine output in both groups (shown in Table 4) is approximated to one decimal place, it would give (0.6±0.4ml/kg/hr for the conservative group) and (0.1±0.1 ml/kg/hr for the dialysis group). The implication therefore is that children with urine output of ≥0.6ml/kg/hr would benefit from conservative management, while children with urine output of ≤0.1ml/kg/hr would require dialysis.

There is the group in between >0.1ml/kg/hr (benchmark for dialysis group) and <0.6ml/kg/hr (benchmark for the conservative group) i.e. 0.11-0.59ml/kg/hr which is left hanging. It is our opinion that any urine output between 0.11-0.59ml /kg/hr may be offered a "trial of conservative management" when all other biochemical parameters are considered. However to minimize risk to the patients, the best form of intervention available should be promptly offered.

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