Section: Paediatrics

A study of clinical profile of Acute Kidney Injury in critically ill children admitted in Paediatric Intensive Care Unit aged between 2 months to 13 years

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ABSTRACT

Background: Acute renal failure (ARF) has an increasing prevalence in children, sometimes with devastating consequences and requiring long term renal replacement therapy (RRT). It is a common complication of critically ill children admitted in Pediatric Intensive Care Unit (PICU). ARF is an abrupt decline in renal functions due to renal, extra- renal or systemic diseases with sometimes more than one etiology affecting the same patient. However ARF reflects only an end of the clinical spectrum. Acute Kidney Injury (AKI) has replaced the term ARF constituting from mild changes in renal function to significant deterioration requiring RRT. Mild, reversible AKI can go unrecognized and have significant consequences including mortality. Early identification of decline in renal function is essential to improve outcome of children. The aim is to study the incidence, etiology and outcome of AKI in critically ill children admitted in PICU. **Methods:** This prospective observational study was conducted among critically ill children admitted in PICU of a medical college in Kerala from January 2014 to June 2015. Screening and grading was based on the AKI Network classification and children were followed till discharge or death. **Results:** The incidence of AKI was 20%. Infections were the commonest cause of AKI. Complete improvement in renal function was seen in 56% only. Mortality was high (35%). **Conclusion:** The incidence of AKI is high in critically ill children with high mortality, only 56% show complete improvement of renal functions and those with partial recovery either succumb or need RRT. Hence early recognition of AKI is crucial for better outcome.

Keywords: AKI, pRIFLE, critically ill, renal recovery, mortality.

INTRODUCTION

Acute renal failure (ARF) is a broad clinical syndrome with various etiologies which include specific renal diseases (acute glomerular and vasculitic disorders), non specific renal damage (ischemia, toxin induced) as well as extra renal pathology (prerenal azotemia and post renal obstructive nephropathy). ARF usually implies an end stage renal disease .Mild renal dysfunction can go unnoticed. Acute Kidney Injury (AKI) is an abrupt decline of renal function that comprises of ARF but is not just limited to it. Epidemiological evidence suggests that even mild, reversible AKI has devastating consequences including progression to chronic renal failure and increased risk of death.[1-3] Regardless of the etiology of renal dysfunction, the manifestations and consequences of AKI are clinically indistinguishable.[4,5] AKI is independently associated with poor outcome.[5] Hence guidelines for AKI suggest diagnostic approaches for early detection. These largely depend on early recognition of the etiological factors which cause renal impairment, even if the derangement is mild it benefits majority due to the early interventions. Focusing exclusively on patients with established renal failure or on those needing dialysis means failing to pick those less severe conditions which could end with devastating consequences. To prognosticate the AKI in critically ill children pRIFLE criteria is being used to stage as Risk, Injury, Failure, Loss, End-stage renal disease.[6] Only 14% of those patients reaching "F" of RIFLE criteria received RRT but there was at least 5 times more mortality in these children with AKI than in the population without AKI.[7] Sustained AKI leads to massive alterations in fluid, electrolyte, acid –base and hormonal regulation. It can also cause significant alteration in CNS and immune functions. Many studies have been done in developed countries primarily in adults to identify and study the epidemiology of AKI. In children few studies exist but these are primarily from developed countries and mostly retrospective in nature.[8,9] Reports from our country especially in pediatric population are scanty.[10,11] Mortality following AKI in these studies has been reported to be high from 37% to 43% with poor short term and long term outcomes with high requirement of RRT. This prospective study was conducted in our tertiary care centre with PICU facilities with an aim to identify the incidence, etiology and outcome of AKI in children critically ill and admitted to the PICU.

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MATERIALS AND METHODS

This is a prospective, observational study conducted in the PICU of Amala Institute of Medical Sciences, Trichur, Kerala over a period of 18 months from January 2014 to June 2015 in children admitted as critically ill aged 2 months to 14 years. The study was approved by the Institutional Ethics Committee. Informed parental consent was obtained prior to inclusion of the subjects in this study.

Objectives
To determine the incidence, etiology and short term outcome of AKI in PICU.

Inclusion criteria
Children aged 2 months to 14 years admitted in PICU and defined as critically ill based on the hospital policy.

Exclusion criteria
Those children already diagnosed as chronic renal disease stage 5 (estimated GFR <15ml/ml/1.73m2) and already on RRT, known AKI at admission with serum creatinine >1.5mg/dl, serum Bilirubin >5 mg/dl and those staying less than 24 hours in PICU.[12]

Sample size
The minimum sample size required for the study was calculated using the formula:
N=4pq/d2
P = prevalence of AKI in children from 2 months to 14 years
= 25.1%.[11]
Q = 100-p = 74.9%
D = 20% error of prevalence = 5.02%
The sample size was hence calculated as 298 (approximately as 300)

Sampling method:
300 consecutive children admitted in PICU, classified as critically ill and staying beyond 24 hours in PICU. As per the hospital policy, these were children hospitalized in the pediatric ward and transferred to PICU if any criteria for being critically ill were fulfilled. These also included children directly admitted to PICU from the emergency department with criteria of critically ill being fulfilled. The criteria were impaired level of consciousness (Glasgow Coma Scale<7), signs of raised intracranial tension (hypertension, bradycardia, papilledema), uncontrollable seizures, hypotension and needing vasopressor support, hypoventilation or respiratory failure and needing mechanical ventilation (oxygen saturation <90% or arterial oxygen PaO2 <60mm Hg with supplemental oxygen or arterial PaCO2 >60mmHg), reduced urine output.
At admission, the clinical data regarding the demographic characteristics (age, gender), baseline

diagnosis, and co-morbidities was noted. Basic blood investigations for the primary diagnosis were done as per standard protocol, urine microscopy was performed and urine protein creatinine ratio calculated. All children had a serum creatinine estimation as 'baseline' and thereafter every 24(+/-6) hours for 3 consecutive days. Subsequently the estimation was done at daily intervals till discharge or death from PICU. Serum creatinine estimation was done by auto analyzer using modified Jaffe method.[13] The diagnosis of AKI was based on Acute Kidney Injury Network (AKIN) definition and the children were graded.[4] Urine output was measured 6 hourly and was quantified as ml/kg/hour. Either serum creatinine or urine output was used to diagnose and stage the AKI and the criterion leading to higher grade was used to grade the patient. If there was a progressive rise in serum creatinine values or progressive reduction in urine output re-classification was done and progression to maximum stage of AKI during the PICU stay was recorded.

Based on the AKIN criteria, AKI was defined as abrupt reduction (within 48hours) in renal function with an increase in creatinine level.[4] The illness was categorized as stage 1(increase in serum creatinine by > or = 0.3 mg/dl or to 1.5 to 1.99 times the baseline value or urine output <0.5 ml/kg/hour >6 hours), stage 2 (increase to 2-2.99 times the baseline value or urine output as <0.5 ml/kg/hour for >12 hours) or stage 3 (increase to > or = 3 times the baseline value or >4 mg/dl with an acute rise >0.5mg/dl or urine output <0.3 ml/kg/hour or anuria for 12 hours).

The provisional and final diagnosis was noted. The patients were evaluated to ascertain the etiology of AKI. The outcome was examined in relation to the maximal stage of AKI. The recovery of renal function was assessed based on presence of hypertension, abnormal urine analysis and return of serum creatinine to normal values, Complete renal recovery was defined as normal serum creatinine for age (0.2mg/dl for infants, 0.3-0.7 mg/dl for 1-12 years and 0.5-1.0 mg/dl for above 12 years).[14] Partial renal recovery was defined as presence of hypertension, abnormal urinalysis (>1+ proteinuria, urine protein to creatinine ratio >0.2mg/mg, >5 leucocytes or red blood cells per high power field) or elevated serum creatinine at discharge.

Statistical Analysis: was performed by chi square test.

RESULTS

300 critically ill children admitted in PICU were screened for AKI .60 children had AKI giving an incidence of 20%. 240 were critically ill but had no features of AKI (non –AKI children). Of the 60 children with AKI, 40 (66.6%) were males and 20(33.4%)were females and age wise distribution of these cases was as follows- 23(38.3%) children were under 12 months,25(41.7%) children were between

13 months to 5 years and 12 (20%) children were from 6 years to 14 years.

Of the 240 non -AKI children ,146(61%) were males and 94 (39%) were females and age wise distribution was as follows-81(33.7%) were under 12 months, 102(42.5%) between 13 months to 5 years and 57(23.8%) were from 6years to 14 years

Table 1: The demographic parameters are depicted.

Parameters		AKI	Non AKI	p value
Gender	Male	40(66.6%)	146(61%)	0.405
	Female	20(33.4%)	94(39%)	
Age wise distribution	2 months-1 year	23(38.3%)	81(33.7%)	0.744
	13 months - 5 years	25(41.7%)	102(42.5%)	
	6 years - 14 years	12(20%)	57(23.8%)	

There was no statistical difference in the age and gender distribution when comparing the 2 groups of the AKI critically ill and non –AKI critically ill children.

Stage 1 AKI was detected in 37 children (61.6%) , stage 2 in 3(5%) and stage 3 in 20(33.3%) respectively. 15 patient(15%) showed progression from stage 1 to maximum stage of progression to stage 2 or stage 3 within 72 hours.

Table 2: shows the age wise distribution of the 3 stages of AKI.

Age distribution	Stage 1	Stage 2	Stage 3
2 months -1 year	13	2	8
13 months-5years	16	1	8
6 years - 14 years	8	0	4

p Value=0.831

There was no statistical difference observed among the different age groups and the various stages of AKI.

The etiology of AKI observed is summarized in [Table 3]. Common diagnosis at admission in AKI was infections followed by renal causes.

Table 3: Etiology of AKI

Diagnosis at admission	Number (%)
1.Infections	34(56%)
Acute watery diarrhoea	15(44.11%)
Pneumonia	5(14.7%)
CNS(Meningitis/encephalitis)	5(14.7%)
Dengue hemorrhagic fever	4(11.7%)
Urinary tract infections(UTI)	2(5.8%)
Acute bacillary dysentery	2(5.8%)
Leptospirosis	1(2.9%)
2. Renal	6(10%)
Infection related glomerulonephritis(IRGN)	5(8%)
Congenital nephrotic syndrome	1(2%)
3.Status epilepticus	5(8.3%)
4.Cardiac causes	5(8.3%)
Congestive cardiac failure	4(7%)

Congenital heart disease	1(2%)
5 .Malignancy	4(6.6%)
6. Trauma	3(5%)
7. Immunodeficiency	3(5%)

Among the infections, acute watery diarrhoea was a leading cause (44.11%) in these children followed by pneumonia (14.7%) and meningitis/encephalitis (14.7%).Other infective causes noted were UTI, dysentery and a single case of Leptospirosis was seen. Other causes observed were secondary to infection related glomerulonephritis (8%) and status epilepticus (8.3%).

Table 4: Etiology and diagnosis at admission in the non-AKI group.

Diagnosis on admission	Number (%)
1.Infections	122(50.8%)
Pneumonia	47
Bronchiolitis	36
Meningoencephalitis	15
Dengue fever	8
Viral hepatitis	6
Urinary tract infection	5
Acute diarrhea	5
2.Central nervous system diseases	77(32%)
Status epilepticus	75
Acute hemiplegia	2
3.Trauma	16(6.6%)
4.Cardiac	15(6.25%)
5.Metabolic	6 (2.5%)
6.Malignancy	2(0.8%)
7.Immunodeficiency	2(0.8%)

Table 5: differences between the etiology of AKI and non –AKI children

Diagnosis at admission	AKI	NON AKI
Infections	34	122
Central nervous system (CNS)diseases	5	75
Trauma	3	16
Malignancy	4	2
Cardiac	5	15
Immunodeficiency	3	2

p Value<0.0001

Infections are the primary etiology of critically ill children with AKI. Critically ill children with CNS disease and trauma but no infections have less incidence of AKI .This difference is statistically significant (p value <0.0001). Hence infections is the primary cause of AKI.

Table 6: difference between the infective etiology of the AKI and non-AKI groups.

Infections	AKI	NON AKI
Acute watery diarrhoea	15	4
Pneumonia	5	47
Meningoencephalitis	5	15
Dengue fever	4	8
Urinary tract infection	2	6

p Value<0.0001

There is a significant difference with acute diarrheal disease being the chief etiology for children critically ill needing PICU admission and presenting with features of AKI. Pneumonia and CNS infections

were the leading infective causes for critically ill children with non AKI.

Table 7: Duration of PICU stay for children with AKI.

Stage of AKI	<1 week	1 -2 weeks	>2 weeks
Stage 1	28	4	5
Stage 2	2	0	1
Stage 3	15	2	3

p value= 0.897

There is no statistical co relation seen between stages of AKI and duration of stay in PICU.

Table 8: Duration of PICU stay for non-AKI children.

Duration of stay	Number of patients
<1 week	211(88%)
1-2 weeks	22 (9%)
>2 weeks	7 (3%)

Table 9: Duration of stay in PICU in AKI and non-AKI

Duration of AKI	AKI	Non AKI
<1 week	45(75%)	211(88%)
1 to 2 weeks	6(10%)	22(9%)
>2 weeks	9(15%)	7(3%)

There is a statistical difference between the AKI and non-AKI groups and duration of PICU stay (p value<0.0001) with those with AKI having a significantly longer stay in PICU.

Outcome was analyzed in terms of renal recovery (complete or partial) and survivors or death.

Of the 300 patients critically ill, those with AKI were 60 and non- AKI were 240. In those with AKI, a Complete Recovery (CR) was seen in 34 of the 60 patients, Partial Recovery (PR) was seen in 26 of the 60 patients. All 34 patients with CR were from stage1 only ,none of the patients from stage 2 and stage 3 had CR. 3 patients from stage 1 had PR ,3 from stage 2 had PR(of which 2 died ,1 survived) and 20 from stage 3 had PR(of which 19 died,1 survived). There were no deaths noted in those with stage 1 AKI. 5 of the PR children (3+1+1) were referred for RRT.

Table 10: Recovery status of AKI

Stage of AKI	Number	CR	PR
1	37	34	3
2	3	0	3
3	20	0	20

Mortality was seen in 21 children with AKI as compared to 3 children of the 240 critically ill non AKI children.

Table 11: Difference in mortality between AKI and non-AKI

Total children (300)	Survivors (%)	Non survivors (%)
Without AKI(240)	237(98.7%)	3(1.3%)
With AKI (60)	39(65%)	21(35%)

p value<0.0001

There is a statistical difference (p value <0.0001) in mortality seen in critically ill children with AKI and

non-AKI children with definitely higher mortality in children with AKI.

The overall mortality in children with AKI is 35%. All children with stage 1 AKI survived, and mortality was 0%, 2 children with stage 2 AKI and 19 children with stage 3 AKI died.

Table 12: Difference in mortality between the 3 stages of AKI.

Staging of AKI	Survivors	Death
Stage 1	37/37 (100%)	0(0%)
Stage 2	1/3 (33.3%)	2(66.7%)
Stage 3	1/20 (5%)	19(95%)

p value<0.0001

Children with stage 1 had better survival rate and higher mortality was seen in stage 2 and stage 3 which is statistically significant (p value<0.0001).

Mortality was highest in infective etiology followed by CNS diseases and trauma in children with AKI but there was no statistically significant correlation observed between etiology and mortality as shown in [Table 13].

Table 13: showing etiology and mortality in patients with AKI

Primary diagnostic condition	Total number	Mortality
Infections	34	14(41%)
Status epilepticus	5	3(60%)
Trauma	3	2(66.6%)
Cardiac	5	1(20%)
Malignancy	4	1(25%)
Renal	6	0(0%)
Immunodeficiency	3	0(0%)

p value=0.13

There is no statistical co relation between age of children with AKI and mortality as seen in [Table 14].

Table 14: showing age distribution and correlation with mortality in AKI

Age wise distribution	Total number	Mortality
2 months to 1 year	23	9(39%)
13 months to 5 years	25	9(36%)
6 to 14 years	12	3(25%)

p Value=0.701

DISCUSSION

In this prospective observational study of 300 critically ill children in PICU the incidence of AKI was 20%. Previous data on AKI in children using pRIFLE criteria or AKIN criteria have reported incidence from 10% to 82%. This varying incidence is due to studies involving diverse populations, regional differences, different sample sizes and different level of ICU monitoring and care.[5,9-11,15,16] In a retrospective study in 2010 in USA which included a large number of children (3396) 5.7% had AKI on admission but 10% developed AKI during hospital stay in PICU and 75% reached maximal progression by 7th day of ICU stay.[8] In a similar

study the author has reported 50% incidence of AKI on admission and 40.4% patients developing AKI within 72 hours of admission.[16] Our study showed an incidence of AKI as 20% with progression noted in 15% children from stage 1 to stage 2 or 3 as maximal staging within 72 hours.

The etiology of AKI varies based on the study population. In developed countries the etiology primarily was noted to be post-operative cause of AKI, followed by malignancy, following use of nephrotoxic drugs and secondary to pulmonary failure.[17-19] In developing countries AKI follows hemolytic uremic syndrome, severe sepsis, acute diarrheal dehydration and post infectious glomerulonephritis. In tropical countries, a significant proportion of AKI follows febrile illnesses like dengue, scrub typhus, malaria and leptospirosis. In a study reported from South India, 9.3% of AKI was secondary to tropical infections.[11] Pneumonia accounted for a high incidence of AKI in some centers but a previous study has shown it remains under reported due to lack of awareness and failure to monitor renal parameters.[20] Our study has demonstrated infections as a common etiology for AKI (56%), with acute diarrheal disease as a leading cause (44%) followed by pneumonia (14.7%).The second common etiology is infection related glomerulonephritis (8%) and status epilepticus (8.3%). In critically ill children with no AKI but admitted to PICU the leading cause of admission was non infective CNS disease (status epilepticus, acute hemiplegia) This difference is statistically significant suggesting infections have a high incidence of AKI in our community and these children need careful monitoring of renal functions. However, critically ill children admitted in PICU and diagnosed to have infections as pneumonia (38.5%), bronchiolitis (29.5%) and meningoencephalitis (12.2%) had non AKI features as compared to those suffering from acute diarrheal disease. Hence children with acute diarrheal disease have a high risk of developing AKI indicating a need for better fluid replacement and close monitoring of renal parameters.

Regarding the duration of stay in PICU studied in our groups, there was no statistical difference in number of days in PICU among the various stages of AKI, but significant difference was demonstrated between the AKI and non AKI group. This indicates increase in health care expenditure. A similar observation showed prolonged hospital stay with AKI and especially in stages 2 and stages 3.[10]

The occurrence of AKI has significant short term and long term morbidity with mortality. Almost 6-45% of children with AKI need renal replacement therapy.[10,21,22] 3 of our stage 1 children and 2 of our children who progressed from stage 1 to stage 2 and stage 3 survived but had worsening renal functions and needed referral to a renal unit for RRT indicating long term morbidity in these 5 children.

The mortality observed in our study showed a high incidence of 21 deaths out of 60 children with AKI (35%)as compared to 3 out of 240 (1.3%) with no AKI, this difference is statistically significant (p value <0.0001). Various studies have demonstrated mortality rates varying from 9 to 67%.[21,22] All children with stage 1 survived with 34 showing a complete recovery .None of the children with stage 2 and stage 3 had complete recovery. Hence only 56% of AKI children in our study demonstrated a complete recovery.

Mortality was highest in infective group but there was no statistical co relation between the etiological agent and mortality. There was also no significant difference seen in incidence of mortality in the various age group of children. However previous studies have shown infections a primary cause of mortality in children with AKI and higher mortality in these younger than 2 years.[11,23]

Our present study has some limitations. The risk factors leading to AKI and factors preventing complete renal recovery in those with PR were not studied. Previous studies have shown that young age below 2 years, shock, fluid overload, and need for mechanical ventilation, multi organ dysfunction and late referrals were associated with poor outcome. Though this was not our objective, we did not compare risk factors leading to AKI and causing mortality and risk factors leading to mortality in non AKI children, and hence larger studies will be needed to assess the relevance of AKI as an individual factor leading to mortality and other predictors of mortality in those with AKI.

CONCLUSION

This present prospective observational study demonstrated a high incidence of AKI in critically ill hospitalized children (20%) with 15% progressing from stage 1 to stage 2 and stage 3 .The mortality in these children is high(35%) . In those with AKI, complete recovery was seen only in 56% and they were predominantly children with early stages of AKI mainly stage 1. Hence we can conclude that AKI is often preventable, treatable and reversible however have definite long term consequences, if not recognised early .Infective etiology was the primary factor leading to AKI and our study demonstrated a high incidence of AKI in acute diarrheal disease emphasizing need for early recognition of dehydration and better fluid management. AKI is associated with adverse outcomes with prolonged hospital stay and PICU stay thus increasing health care costs.

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