

Review

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Acute Kidney Injury in Iranian Children -What Do We Know About It? - Part 2

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Nakysa Hooman

Pediatric Nephrology
Department, Ali-Asghar
Children Hospital, Pediatric
Transplantation and Dialysis
Research Center (PTDRC), Iran
University of Medical Sciences.
Tehran, Iran.

*Corresponding Author

Nakysa Hooman- N193, Ali-
Asghar Children Hospital,
Vahid Dasgerdi St., Tehran-
Iran, 1919816766.
Email:
nakisa45@yahoo.com
hooman.n@iums.ac.ir
Tel:+98(21)23046387
Fax:+98(21)22220063

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Introduction

Acute kidney injury (AKI) is reversible deterioration of renal function in which waste products accumulate and fluid imbalance occurs. The incidence is 5-50% in pediatric intensive care units [1].

The wide range of incidence depends on the definition and setting. There are a lot of definitions on AKI and the insight to early diagnosis is improving by detecting new biomarkers. AKI is associated with a longer stay in ICU, more need for mechanical ventilation, and a higher rate of mortality [2]. The risk of developing chronic kidney disease stages 1-3 is 10% in

Acute kidney injury (AKI) is reversible deterioration of renal function in which waste products accumulate and fluid imbalance occurs. The epidemiology of AKI has been changing over years. The aim of this study was to evaluate the epidemiology of AKI in hospitalized children in Iran. A literature search from March 2000 to March 2014 was conducted through MEDLINE, EMBASE, Scholar.google, IranMedex, MagIran, SID, and manual reference search of identified articles. Retrospective and prospective cross-sectional studies with a clear definition of acute kidney injury or failure were included.

Seven out of twenty three articles which were found met the criteria. The incidence of AKI declined from 36% (2006-2008) to 15.4% (2010-2011) in the PICU setting of three referral teaching hospitals in Tehran. According to the classification, 10% had pre-renal failure, 86% had intrinsic renal failure, and 4% had post-obstructive uropathy. Follow-up was limited to the days of hospitalization. The overall reported mortality rate was 18% in pediatric departments. Acute glomerulonephritis including hemolytic uremic syndrome was the most common underlying disease (46.5%). Acute tubular necrosis was reported in 33% of the cases. One third of the cases of acute renal failure occurred in children less than two years. The real incidence of acute kidney injury might be higher considering a unified standard definition. Acute glomerulonephritis and acute tubular necrosis comprised the majority of the etiologies.

Keywords: Acute Kidney Injury; Middle East; Iran; Etiology; Child; Incidence; Review Systematic.

Running Title: Acute Kidney Injury in Iranian Children

patients with a history of AKI in ICU [3]. In a 3-5 year follow-up of children with a history of AKI, renal damage including hyperfiltration, decreased glomerular filtration rate, hypertension, or microalbuminuria was detected in 58.6% of the cases [4].

Younger age, longer duration of renal replacement therapy, and specific etiology are associated with a worse long term renal outcome in AKI survivors [5]. There are some studies on AKI in children in different cities of Iran. A recent study in the emergency room of a tertiary center in Tehran revealed 83% of children who presented with acute gastroenteritis had some degrees of acute

kidney injury according to pRIFLE and 38% of them were in the failure category [6].

The aim of this study was to find the epidemiology of AKI in hospitalized children in Iran by collecting the published data.

Material and Methods

A literature search from March 2000 to March 2013 was conducted through MEDLINE, EMBASE, Scholar.google, IranMedex, MagIran, SID, Thesis, and the abstract books of congresses, using English and Persian equivalent keywords for kidney injury, renal failure, pre-renal azotemia. The age limit was neonates up to less than 18 years. The definition of acute kidney injury was sudden rise in creatinine (> 1.5 mg /dl, > 2SD, or twice the normal level). Pre-renal failure was defined as response to fluid therapy in less than 12 hours as increased urine output (>0.5 ml/kg/h and decrease serum creatinine), or utilizing RIFLE criteria. Case reports and articles related to renal transplantation or the lab tests for diagnosis of acute kidney injury were excluded. The databases were searched for the following terms and their equivalents in Persian: (((“Acute Kidney Injury”[Mesh]) AND “Iran”[Mesh]) AND “Child”[Mesh]) OR “Infant, Newborn”[Mesh], which yielded 487286 results in PubMed, 13500 in scholar.google, and 135 in Persian search engines. Then, the search was modified through using the subheading of Iran and age range for children.

Results

Seven out of twenty two articles that were found were included in the study while six case reports, one review article, and three diagnostic lab test studies were excluded.

According to [Table 1](#), the incidence of acute kidney injury declined in PICU of training referral hospitals of Tehran from 35% to 15% in a period of five years. This incidence was calculated according to the RIFLE classification. The results of studies are summarized in [Table 2](#). According to the classification of acute kidney injury, 10% had pre-renal failure, 86% had intrinsic renal failure, and 4% had post-obstructive uropathy.

[Table 3](#) shows the overall reported etiologies of acute kidney injury. The overall reported mortality rate was 18% in pediatric departments. Acute glomerulonephritis including hemolytic uremic syndrome was the most common underlying disease (46.5%). Acute tubular necrosis was reported in 33% of the cases.

Table 1. The incidence of acute kidney injury in PICU using pRIFLE criteria [↑](#)

Author	Population	Setting	Outcome
Mohkam M (7) 2006-2007	N=121 (AKI=44) INCIDENCE= 36.4% 1M-16 Y	Cross-sectional PICU	Risk UA Injury UA Failure UA Death=UA ESRD=3(8.3%)
Hooman N (8) 2006-2007	N= 217 (AKI=76) INCIDENCE= 35% 0.08-19 yr	Prospective cohort PICU	Risk 35.5% Injury 20.7% Failure 10.3% Death: 23(20.2%)
Ataei N (9) 2011-2012	N= 107(AKI=17) INCIDENCE= 15.8% 0.25-3 yr	Prospective cross-sectional PICU	Risk UA Injury UA Failure UA Death=UA

One third of the cases of acute renal failure occurred in children less than two years of age. Mortality during hospitalization was high. The long term outcome of children who recovered was unknown.

Discussion

According to the pRIFEL criteria, the incidence of AKI declined from 35% to 15% in the PICU setting of tertiary centers. The incidence of AKI was high in developing countries [Table 4](#) [14-15].

In 80s - 90s, hemolytic uremic syndrome, primary renal disease, sepsis, and burn were the leading causes of AKI. Then, the etiology shifted to renal ischemia, nephrotoxins, and sepsis [16].

Acute glomerulonephritis was the most common etiology and comprised more than one third of underlying diseases in Iranian children. However, in Turkey, the most common causes were hypoxic/ischemic injury and sepsis (20%). In this review, we found the incidence of AKI secondary to sepsis (5%) was lower than the incidence reported from India (55.4%), Turkey (20%), and Nigeria (25.7%) [17-20].

Post streptococcal glomerulonephritis was the most common cause (92%) of acute glomerulonephritis in Iranian children [21]. The follow-up study showed some degrees of renal impairment and elevation of blood pressure [22-23]. Through scoring the clinical and laboratory parameters at presentation, we found a correlation between the follow-up score and the admission score. Patients with a lower GFR at presentation showed more renal damage on follow-up [23]. One retrospective study suggested antibiotic prescription reduced the severity at

presentation and duration of the acute phase of PSGN [24].

In all developing countries, sepsis and its related morbidities were the first or second cause of acute kidney injury. However, it only comprised 5% of the etiologies in Iran. Hemolytic uremic syndrome (HUS) constituted 18% of the underlying diseases. In our previous study, we found that neurologic involvement was associated with a poor short-term outcome in HUS patients. In addition, the long term outcomes were hypertension, chronic kidney disease, and need for dialysis [25].

Moreover, surgical gastrointestinal complications were associated with higher mortality [26].

The renal pathology in these atypical HUS children revealed thickening of arterial medial and intimal layers and thrombosis that were associated with higher mortality while a vascular score higher than 0.14 and a final score of higher than 0.2 were linked to CKD progression [27].

Drug induced nephrotoxicity was only reports in 6% as the etiology of AKI in Iranian children. It might be due to less attention to the subclinical nephrotoxicity in outpatient or inpatient settings. In a prospective cross-sectional study, we observed that cancer children with a history of chemotherapy who received different nephrotoxic antibiotics and agents had episodes of acute renal failure, or those who underwent nephrectomy had some degrees of renal impairment in at least one year follow-up [28].

The mortality rate and need for dialysis was much lower in Iranian children when compared to other developing countries (Table 4) [29-30]. In a prospective study in a PICU setting, we found that need for mechanical ventilation and vasopressor were correlated with a poor outcome. Therefore, acute kidney injury and severity per se were not the cause of mortality while co-morbidities such as severe sepsis, fluid resistance shock, decreased sensorium, and a higher PRISM score were significantly correlated with mortality in those patients [31]. However, a high serum uric acid level at the time of admission was not associated with higher mortality, and prescription of rasburicase was effective in rapid recovery of renal injury secondary to hyperuricemia [32].

Cerda et al compared the characteristics of AKI in developed and developing countries in a review article and briefly discussed that community - acquired AKI was more frequent than hospital acquired AKI that in developing countries, and the location of AKI in developed country was predominantly in the ICU in contrast to the rural and urban regions of developing countries where

AKI was mostly due to envenomation and specific infections. The third difference was the patients' age; AKI occurred in older patients in developed countries while younger patients (age less than 40 years) and children were affected more in developing countries. The age difference partially affected survival. Discrimination was an important influential factor in developing countries. The etiology of AKI in developed country was predominantly shock and sepsis while gastroenteritis and glomerulonephritis were the most common etiologies in developing countries. The resources of dialysis equipment, its costs, and the distance of dialysis centers were other main limitations in developing countries [33].

The limitations of studies were utilizing different criteria for classification, limiting follow-up to the days of hospitalization, lack of reports on the long term outcomes, lack of a unified definition of renal failure, ignoring some important causative factors such as drug toxicity or sepsis, limitation of information on the risk factors, and inadequate reports on the need for renal replacement therapy including dialysis. There was no report of renal injury post cardiac surgery, surgery units and transplantation from searching literature about AKI in Iran. Because Iran has different tribes and different geographical climates, a multicenter study might help to collect more precise information.

Conclusions

The real incidence of acute kidney injury might be higher considering a unified standard definition. The high rate of intrinsic renal diseases including drug induced nephropathy was detected the reason of acute renal failure in neonates.

Conflict of Interest

None declared

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Table 2. The Etiology and Outcome of Iranian Children with Acute Kidney Injury [↑](#)

Authors	Population	Type study	Criteria of diagnosis	Etiology	Outcome
Gheissari A ⁽¹⁰⁾ 2001-2011 Isfahan	N=180 (110 M,70 F) Mean age: 5.28 (6.3)yrs	Retrospective	RIFLE	Pre-renal: 25(15%) Renal: 150(76.2%) ATN-Tubular=87 (48%) Sepsis: 65(36%) Nephrotoxic: 5(2.8%) GN: 44(24.4%) HUS: 24(13.3%) Post-renal: 10 (5.5%) Unknown: 6(3.3%)	Died: 40(22.2%) Dialysis; 62(34.4%) HD :36 PD:26
AhmadzadehA ⁽¹¹⁾) 2003-2005 Ahwaz	N= 113 (77 M, 36 F) Median: 6.8 yr 10 d-15 yr	Retrospective	Rise cr (x2) & Oliguria	Pre-renal: 21(18.6%) Renal: 84(74.3%) ATN:10 Scorpion sting: 7(6.2%) GN: 66 HUS:3 (2.8%) Post-renal; 8(7%)	Died: 1 Dialysis: 8(7%) HD: 3 PD: 5 ESRD: 1 Lost to follow up; the majority
Otukesh H ⁽¹²⁾ 1989-2003 Tehran	N=267 (M190, F110) 1m-16 yr	Retrospective cohort	Rise cr 0.1mg/d/day In one wk & UO<0.5 ml/kg/hr(infant) <400ml/d(older children)	Pre-renal: 3 (1%) Renal: 259 (97%) ATN: 91(22.8%) Nephrotoxic: 19(17%) GN: 161(60%) HUS: 72 (27%) Post-renal: 4(1.5%)	Died: 74 (24.6%) Dialysis: HD: 37(39%) PD:57(61%)
DerakhshanA ⁽¹³⁾ 1999-2000 shiraz	N=50 (M37;F13) 1-15y	Prospective Cross-sectional	Cr>1 mg/dl BUN>30 mg/dl	Pre-renal=14(28%) Renal: 35(70%) ATN:18(36%) Nephrotoxic: 7(14%) GN=17(26%) HUS=4(8%) Post-renal=1(2%)	Died: UA Dialysis: UA ESRD;1

Table 3 Demographic data extracted from the literatures related to ARF in Iranian children [↑](#)

Frequency of age(n=734)	
< 2 yr	286(38%)
2-5 yr	116 (16%)
5-10 yr	203 (28%)
10-19 yr	129(18%)
Gender (n=947)	
Male	585(62%)
Female	362(38%)
ARF classification- (n=653)	
Pre-renal	73 (11%)
Renal	549(84%)
Post-renal	31(5%)
Cities (n=7)	
Ahwaz	1(14%)
Isfahan	1(14%)
Shiraz	1(14%)
Tehran	4(57%)
Total study population	1095
Number of acute renal failure	757
Setting-(n=7)	
PICU	3(43%)
Pediatric departments	4(57%)
Etiology AKI-(n=562)	
Acute tubular necrosis	99 (18%)
Tumor lyses syndrome	34 (6%)
Drug induced nephrotoxicity	31(6%)
Scorpion poisoning	13(2%)
Hemolytic uremic syndrome	102(18%)
Acute glomerulonephritis	185(33%)
Sepsis	29(5%)
Dehydration	53(9%)
Nephrolithiasis	12(2%)
others	4(1%)
Short outcome- (n=757)	
Death during hospitalization	138 (18%)
Temporary dialysis	169(22%)
Discharged	450(59%)

Table 4. Acute Kidney Injury in Children living in Developing Countries [↑](#)

	Iran N=757	Turkey ⁽¹⁷⁾ N=318	India ⁽¹⁴⁾ N=2376	Nigeria ⁽¹⁸⁾ N=70	Brazil ⁽¹⁵⁾ N=110	Kuwait ⁽²⁹⁾ N=32	Thailand ⁽³⁰⁾ N=318
Period	2000-2013	2006-2007	2010-2011	2010-2012	2002-2004	2003-2006	1982-2004
Setting	PICU	Multicenter	PICU, ward	ward	PICU	PICU	ward
incidence	35 to15%	UA	25% , 5.2%	17.4/1000	8%	UA	0.5-9.9/1000
Etiology	AGN-33% ATN-18% HUS-18%	HIE-20.4% Sepsis-15.5% AGN-15.4%	Infection-55.4% AGN-16.9% Cardiac disease-4.8%	PKD-38.6% Sepsi-38.6% Malaria-11.4%	Septic shock-36.3% Sepsis-18.2% Hypovolemic shock-16.4%	Sepsis-46.9% TLS-12.5%	Sepsis-21.4% Hypovolemia- 12.3% PSAGN-12%
Dialysis	22%	33.6%	14.5%	31.4%	49.1%	71.9%	17.3%
Mortality	18%	27.9%	46.2%	28.4%	33.6%	43.8%	41.5%

AGN= Acute glomerulonephritis, ATN= Acute tubular necrosis, HUS= Hemolytic uremic syndrome, PKD= Primary Kidney Disease, TLS= Tumor lysis syndrome