Review

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Update on Acute Kidney Injury in Pediatrics- Part 1

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Acute kidney injury is known as an acute reversible insult to the kidney but its definition and classification is not uniform. Earlier classification of acute renal failure was according to pre-renal, renal, and post renal by using history, the time of response to fluid therapy, and some blood and urinary parameters and markers. Recently, efforts have been made to present a uniform definition of acute kidney injury for earlier disease detection in order to decrease the rate of morbidity, mortality, length of hospital stay, and even death. However, it is clear that serum creatinine is a late marker of renal injury and many new investigations have tried to find more sensitive biomarkers to recognize earlier stages of AKI, its exact underlying mechanism, and outcome. Here we provide the first section of a series about new concepts on AKI with focus on pediatrics.

Keywords: Acute Kidney Injury; Pediatrics; Biological Markers; Classification.

Running Title: Update on Acute Kidney Injury

Introduction

Acute renal failure is an abrupt and sustained decrease in renal function. It can be reversible if diagnosed early but diagnosis depends on the underlying etiology and the damage might be permanent. The incidence of AKI in children is not known exactly. It seems the incidence is increasing in hospitalized children. In adults, the incidence is estimated to be 209 per million populations. Unfortunately, there is no epidemiological study on children but the incidence has been assumed as 0.8 per one – hundred total populations [1]. One retrospective study demonstrated that drug induced AKI in one third of non-critically ill children[2]. The incidence in neonates is 8 to 24%. This figure is much higher in neonates from developing country. The incidence is 3.9 per 1000 live births and 34.5% are admitted to the neonatal units. The incidence is between 5- 50% in PICU or transplanted children[3,4].

Even non-critically ill-children who are exposed to medications are prone to AKI. The development of AKI is accompanied by higher length of hospitalization, need for replacement therapy, and death. In survivors, the risk of chronic kidney disease in adulthood increases. In this review, we focused on updates on definition and classification of AKI, new proteomics and biomarkers in AKI, and their advantages and limitations for children and neonates.

Definition,Classification,and Diagnosis(table-1):

More than 30 definitions exist for AKI in the literature based on a considerable rise in serum creatinine and decrease in urine volume. In 2004, the ADKI group proposed the RIFLE classification of AKI. Then, in 2007, it was modified for pediatric patients (pRIFLE). Subsequently, it was updated in 2007 by the Acute Kidney Injury Network. Recently, the Kidney Disease Improving Global Outcomes (KDIGO) produced an integrated definition and staging system. It is important to endorse that these SCr-based classification definitions of AKI have limitations despite providing great comprehension. Table-1 depicts a brief of each classification. pRIFLE (pediatric RIFLE) is based on changes in serum creatinine within the prior seven days, reduction of eGFR, and urine output. It is classified as risk, injury, failure, and two outcomes of loss and ESRD [5]. AKIN (Acute Kidney Injury Network) is based on changes in serum creatinine or eGFR in 48 hours. Classification is according to stage 1, 2, or 3. The outcomes of loss and ESRD are eliminated from AKIN [6]. ADQI (Acute Dialysis Quality Initiative) – uses a combination of AKIN and RIFLE for defining AKI; moreover, it added acute kidney disease with or without AKI. The baseline serum creatinine is sometimes unknown; therefore, it recommends back-estimation of the baseline serum creatinine value using the MDRD formula, assuming an eGFR of 75 ml/min/1.73 m2 [7].This formula is not applicable in children; therefore, Zapitteli evaluated eGFR based Schwartz formula and assumed eGFR of 100 or120ml/min/1.73m^2 in such conditions [8].

Using this definition and criteria might delay the diagnosis at early stages while acute kidney injury has still no clinical presentation. Incipient acute kidney injury is the presence of newly initiated proteinuria, increased biomarkers of AKI, or active urine microscopy for cells in the absence of clinical criteria of current AKI definition [12].

ADQOI the 10th consensus conference suggested a combination of functional changes (RIFLE or AKIN) and damage markers (biomarkers) and presented the categorization of no marker changes, no functional changes, only marker changes, only function changes, and both functional and damage marker changes [9].

The recommendation is to avoid the terms of pre-renal, renal and post-renal failure and to use the new terminology of functional changes and kidney damage. Dehydration and response to fluid resuscitation does not mean that no insult or injury has occurred and full recovery is expected. Even in animal models, microcirculation does not resume its function[10,11]. Nejat et al evaluated urine biomarkers in 529 children admitted to PICU in the first 24 hours and stratified the children to no AKI, AKI, and recovery by 24 to 48 hours. The group with pre-renal definition of AKI had significantly higher levels of KIM-1, IL-18, and Cystatin-C compared to no AKI [46].

RAI (Renal Angina Index) – It was developed and validated by Basu et al. The scoring of RAI is by multiplying the risk of injury by signs of injury and is scored between 1 and 40. A RAI score of 8 or more at day 0 predicts the progression to severe AKI on the 3rd day by 15-68%. It has been shown that it has a good performance with PRISM- II, KIDOGI stages of AKI [13,14].

Diagnosis:

Urine sediment score- Scoring is based on granular cast per low power field (a score of 0 for 0 cells, 1 for 1 cell, 2 for 2-4 cells, and point 3 for >=5 cells) and renal tubular epithelial cells (RTE) per high power field scored similar to granular cast . Subsequently, the total score is calculated by adding the scores of granular and of RET cells. The range of the total score is between 0 and 6. The urinary scoring system has more predictive value than the AKI network and is associated with worsening of AKI stages. [16] Interestingly, it increases in septic-AKI and its higher scores are correlated with uNGAL. [17]

Novel biomarkers: (Table-2)

Serum Cystatin-C is useful for discriminating between physiological changes in kidney hemodynamics (known as pre-renal) and AKI but it is insensitive to the difference between AKI and CKD. [15]

New urinary biomarkers are higher in premature infants (table-2). [18] Normalization of these urine biomarkers to urine cr could predicted death, need to dialysis, and development AKI; although they have no superiority to older ones in established AKI. [19] There are not enough studies to confirm their clinical utility, to improve clinical outcome, or to be cost effective [20] The biomarkers are targeted for the diagnosis of early AKI, its etiology, and prediction of the outcome. (table-2) The most frequently studied biomarkers are Neutrophil Gelatinase Associated Lipocalin (NGAL), Kidney Injury Molecule-1(KIM-1), Beta-2-

Microglobulin (B2-MG), IL-18, and osteopontin. Table- 2depicts a summary of studies in pediatric patients [21]. None of the urinary biomarkers have a predictive value for the progression of AKI to need for renal replacement therapy or death. The given cut-off values for the early diagnosis of kidney injury has some limitations as the bias of performing in very sick children, and the low specificity as compared to high sensitivity [22,23].

NGAL - It is secreted by neutrophils and expressed on many cells. In the kidney, it is mainly expressed in the loop of Henle and distal tubule segments. In addition, it is filtered by the glomerulus and reabsorbed by the proximal tubules and overexpression on proximal tubules are seen in highly filtered NGAL. Some studies in children who went on cardiac surgeries showed that elevation of NGAL in two-hours of surgery was strongly associated with progression to AKI [24,25]. The normal value of NGAL in the urine and serum is 20 ng/ml and a meta-analysis has revealed that NGAL >150 ng/ml or urine NGAL> 50 ng/ml is highly sensitive for AKI [47].

A systematic review on all studies showed that NGAL had diagnostic and prognostic values for AKI with a better predictive value in children than adults [26].

KIM-1 - It is a trans-membrane glycoprotein that is expressed in the normal kidney at low levels but after an ischemic or toxic AKI but its expression is highly up-regulated in S2/S3 segments of proximal tubules and subsequently appears in urine. The promising point is that the urinary dipstick of KIM-1 is available for early and rapid detection of kidney injuries for preclinical studies. [27] A recent meta-analysis about the value of KIM-1 in early diagnosis of AKI revealed a sensitivity of 74% and specificity of 86%. However, the populations were heterogeneous and comparison was made with serum creatinine similar to all other studies [48].

L-FABP (Liver-type fatty acid binding protein) - It is expressed in proximal tubular cells and helps to transport and metabolize free fatty acids. It has an anti-oxidant effect and a reno-protective role. In ischemic or toxic injury to the experimental kidneys, the urinary level of L-FABP increases n minutes to hours after renal insult [28,29].

Endre et al. evaluated the performance of urinary biomarkers in 562-ICU patients. They stratified the results according to the eGFR and the time of study. They concluded the duration of AKI and the baseline renal function should be considered to evaluate a novel biomarker performance for the diagnosis of AKI [30-33].

Definition of renal recovery- Recovery is complete or incomplete. When the convalescent serum creatinine does not show more than 50% increase from baseline, complete recovery occurs; otherwise, if the patient does not require dialysis but the serum creatinine shows >50% increase from baseline, it is considered partial recovery.

Limitations: Serum creatinine is a late marker and increases with a delay after insult to the kidney and even a very small increase in serum creatinine is associated with a higher rate of mortality and morbidity. The baseline or previous recent creatinine levels are not sometimes known.

Urine output is unreliable when the patient receives diuretics, when dehydration or previous underlying tubulopathy exists, and correct collection requires catheterization.

AKIN and pRIFLE need at least 6 hours to several days for the diagnosis AKI according to the criteria of definition and classification.

Novel biomarkers have proved to be useful in early detection of AKI, but they are expensive. One single biomarker will not perform well in all different types of AKI, and they rise in different time-points of the pathophysiology process. Therefore, we are still far from unifying the classification of acute kidney injury, especially in children and neonates. In addition, the value, cut-off point, and the therapeutic, prognostic and preventive role of the novel biomarkers are to be understood and validated [28].

Conflict of Interest

None declared

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Table 1. Criteria for diagnosis of Acute Kidney Injury and Estimation the Severity

	eCCL	UO	Stages	Outcome	
pRIFLE	↓≥ 25% ↓≥ 50% ↓≥75% or <35ml/min/1.73m ^{2}	<0.5 ml/kg/h for 8 h <0.5 ml/kg/h for 16 h <0.5 ml/kg/h for 24 h or anuria for 12 h	R- Risk I-Injury F- Failure		
			Persistent failure >4 wks	L- Loss	
			Persistent failure >8 mo.	E-End stage	
AKIN	**Cr** ↑≥0.3mg/kg/h or ↑150-200% baseline ↑200-300% baseline ↑to ≥ 300% baseline Or ≥ 4 mg/dl with an acute ↑ of 0.5 mg/dl or need to RRT	**UO** <0.5 ml/kg/h for 6 h <0.5 ml/kg/h for 12 h <0.3 ml/kg/h for 24 h or anuria for 12 h or need to RRT	**Stages** 1 2 3		
ADQI 10th	**Functional criteria** No Change No change Change	**(and /or) Injury criteria** No change Damage markers No change	 No AKI Subclinical AKI Dynamic change in Physiological condition	**outcome** Complete recovery Partial recovery CKD progression	
	RIFLE-R or AKIN-1 RIFLE-I Or AKIN-2 RIFLE-F or AKIN-3	Biomarker positivity (+) Biomarker positivity (++) Biomarker positivity (+++)	AKI	death	
RAI Basu 2013	**RISK of AKI** **PICU admission** **Stem cell transplantation** **Ventilation and inotropy**	**Score** Moderate (1) High (3) Very high (5)	**Sign of Injury** **↓eCCl** No change ↓0-25% ↓25-50% ↓≥50%	**Score** **FO%** <5% ≥ 5% ≥10% ≥15%	 1 2 4 8

RAI= renal angina index, eCCL= estimated creatinin clearance, FO= fluid overload

Table 2. Novel Biomarkers in AKI in Pediatric Populations.

Authors	Population / setting	AKI criteria	Biomarkers	Result
Sarafidis (34) 2014	N=35 Case-control GA=25-31 wks	Neonatal AKI (modified RIFLE)	Urine NGAL	Urine NGAL fails to predict AKI earlier
Sarafidis (37) 2012	N=13 Asphyxiated neonates GA≥ 36 wks	SCr≥1.5 mg/dl for >24-H Or ↑ >0.3 mg/dl form days of life	Serum Cystatin-C and NGAL urine Cystatin-C, NGAL, KIM-1	sNGAL, uCysC, and uNGAL are sensitive, early AKI biomarkers. Their measurement on the first day of life is predictive of post-asphyxia-AKI
Askenazi (18) 2011	N=123 Wt: 500-1500gr GA: <= 26 -36 wks	SCr>0.3 mg/dl in 48hr or >50% previous value Within first 7 postnatal day	Urine NCAL, KIM-1, Cys-C, B2mG (absolute or corrected to cr), OPN/Cr urine IL-18 (absolute or corrected to Cr)	inversely correlated with GA had no correlation with GA
DU (21) 2011	N=252 Mean age: 11.4(4.8) yrs Emergency Center	pRIFLE	Urine NGAL, KIM-1, B2MG, IL-18 , Osteopontin	NGAL, KIM-1, B2MG have good to very good accuracy to predict pRIFLE-injury
Wheeler (36) 2008	N=143 critically ill Case-control Age= 0.8-7 yrs PICU- Septic shock, SIRS	BUN>100 mg/dl or Cr>2mg/dl or Need to dialysis	Serum NGAL	Serum NGAL is sensitive but non-specific predictor of AKI.
Zapittelli (25) 2007	N= 140 Cohort Age=1m -21 yr Critically ill children	↑ ≥ 50% serum Cr	Urine NGAL	Urine NGAL is useful to predict severe AKI
Hirseh (37) 2007	N= 91 Age= 0-18 yrs Congenital Heart dis Went on angiography	↑ ≥ 50% serum Cr Contrast induced nephropathy	Serum and Urine NGAL	Urine and serum NGAL elevated 2 hours after catheterization.
Dent (38) 2007	N=120 Uncontrolled-cohort cardiopulmonary bypass	↑ ≥ 50% serum Cr	Plasma NGAL by point-of – care Triage(R)	Plasma NGAL is an early predictive marker of AKI, morbidity and mortality.
Mirsha (24) 2005	N= 71 Cardiopulmonary bypass	↑ ≥ 50% serum Cr	Plasma and Urine NGAL	Urine and serum NGAL elevated 2 hours after CPB.
Washburn (39) 2008	N=137 Age=6.5(6.4)yrs Critically ill children	pRIFLE	Urine IL-18	IL-18 rises is an early predictor of severe AKI and mortality in critically ill children.
Parikh (31) 2006	N=55 CPB	↑ ≥ 50% serum Cr	Urine IL-18 and NGAL	Il-18 elevate earlier in AKI. Combination of IL-18 and NGAL predict diagnosis and prognosis of AKI anytime after CPB.
Nguyen (40) 2008	N=106 Age <18 yrs CPB	↑ ≥ 50% serum Cr	Urine aprotinin	Urinary aprotinin 2 hour after CPB was predictor of AKI and adverse outcome.
Herrero-Morin (41) 2007	N= 27 Age= 0.1-13.9 yrs PICU	eCCl <80 ml/min/1.73m2 by Schwartz and 24-H urine sample	Serum Cystatin-C and beta-2 microglobulin	Inverse of B2M an Cystatin-C were better correlated with CCL than inverse serum Cr.
Beger (42) 2008	N=40 CPB	↑ ≥ 50% serum Cr	HAV-SO4 (metablonomic by mass spectrometry)	Predict AKI after 12 h of cardiac surgery.
Liu (43) 2009	N=18 (control=21) Case-control CPB	↑ ≥ 50% serum Cr	serum interleukin (IL)-1β, IL-5, IL-6, IL-8, IL-10, IL-17,IL-18, interferon (IFN)-γ, tumor necrosis factor-α (TNF-α), granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF)	Only IL-6 and IL-8 had predictive value of AKI.
Portilla (44) 2007	N= 40 CPB	↑ ≥ 50% serum Cr	Urinary L-FABP	Urinary L-FABP increase 4 to 12 hour after CPB and earlier biomarker of AKI than SCr
Han(45) 2008	N=40 CPB	↑ ≥ 50% serum Cr	Urine KIM-1	Urine KIM-1 increase 12 hour after CPB.

CPB=cardiopulmonary bypass, GA= gestational age, u= urine, s=serum, SCR= serum creatinin,