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Pediatric Acute Kidney Injury: Different From Acute Renal Failure But How And Why

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Abstract

Acute kidney injury [AKI] refers to a clinical syndrome encompassing various etiologies and occurring in a variety of clinical settings, with manifestations ranging from subtle biochemical and structural changes, to minimal elevation in serum creatinine, to anuric renal failure. Understanding the spectrum of AKI and the importance of the early pre-clinical damage stage has resulted in an improved ability to define and stage pediatric AKI, to understand the AKI-to-CKD transition, and harness novel damage biomarkers to predict AKI and its adverse outcomes. These concepts are expanded upon in this review, with an emphasis on publications from the past three years.

Keywords

acute kidney injury; acute renal failure; biomarkers; neutrophil gelatinase-associated liopcalin

Introduction

For several decades, clinicians have used the term acute renal failure [ARF] to designate the discrete event of a failed kidney, characterized by a rapid accumulation of blood urea nitrogen and creatinine. However, "ARF" over-emphasizes the failure of kidney function, and does not account for the diverse molecular, biochemical, and structural processes that transpire in an acutely injured kidney, well before the decline in function. Thought leaders have therefore proposed the term "acute kidney injury" (AKI). This refers to a broad clinical syndrome encompassing various etiologies and occurring in a variety of clinical settings, with manifestations ranging from subtle biochemical and structural changes, to minimal elevation in serum creatinine, to anuric renal failure [1]. The conceptual model for AKI starts with subjects who are at increased risk (due to genetic or clinical risk factors), and proceeds through an intermediate and previously unrecognized damage stage (now identified by novel biomarkers) to the stage of functional ARF [1, 2]. Embracing the spectrum of AKI and the importance of the early pre-clinical damage stage has resulted in several paradigm-shifting outcomes. First, there has been an improvement in our ability to define, classify, and stage pediatric AKI [1, 3]. Second, we now know that even very small early increases in serum creatinine predict the subsequent development of overt clinical AKI in children [4]. Third, we have witnessed a revolution in the early prediction of AKI and its outcomes using novel damage biomarkers pioneered largely in pediatric studies [5]. Fourth, we have come to realize that pediatric AKI is plagued with common and serious adverse

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outcomes [6–8]. These concepts are expanded upon in the subsequent sections of this review, with an emphasis on publications from the past three years.

Pediatric AKI should be defined in a standardized manner

Historically, progress in pediatric AKI was hindered by the myriad definitions. During the past decade, two major classification systems have emerged (RIFLE and AKIN), based on serum creatinine and urine output criteria. A modification of the RIFLE criteria was suggested for pediatric use (pRIFLE), substituting serum creatinine values with estimated creatinine clearance [using the Schwartz formula]. Recent pediatric AKI studies have employed the pRIFLE criteria to report on AKI incidence, severity of illness, length of hospital stay, and mortality [4, 9–11]. However, a systematic review of 12 pediatric studies using RIFLE or pRIFLE classification reported wide variations in the application of the criteria, and inconsistencies in the relationships between the RIFLE class and measures of morbidity and mortality [12]. Consequently, the precise incidence, prevalence, and outcomes of pediatric AKI still remain unclear.

Recognizing the need for a single consensus definition and staging system that could be applied to both children and adults, the Kidney Disease: Improving Global Outcomes (KDIGO) group has proposed the following definition for AKI [1]:

- Increase in serum creatinine by ≥0.3 mg/dl [≥26.5 μmol/l] within 48 hours; OR
- Increase in serum creatinine to ≥1.5 times baseline within the prior 7 days; OR
- Urine volume <0.5 ml/kg/h for 6 hours

The KDIGO staging of AKI is illustrated in Table 1, and incorporates RIFLE, pRIFLE, and AKIN classifications. Both the definition and staging feature a 0.3 mg/dl increase in serum creatinine to specifically be applicable to pediatric AKI. The KDIGO staging also allows for a child with eGFR <35 ml/min per 1.73 m^2 to be classified as Stage 3, in contrast with the adult criterion of ≥4 mg/dl serum creatinine (which would be unrealistic in infants and young children). The uniform adoption of the KDIGO definition and staging of AKI holds significant promise for improving our understanding of pediatric AKI epidemiology, and therefore deserves our undivided attention.

Pediatric AKI is common but lacks awareness

There is now growing evidence to indicate that pediatric AKI is not only common, but also rising in incidence. Potential explanations for the mounting incidence rate include the increased availability of treatment options for many critical illnesses (sepsis, congenital heart disease, bone marrow transplants), and advances in neonatal and pediatric intensive care. While pediatric centers have previously reported an AKI incidence of only 1% of all general hospital admissions, the incidence is substantially higher in specialized populations with critical illnesses that are now routinely managed. Recent retrospective and prospective studies from around the globe indicate an AKI incidence of 10–35% (by RIFLE or AKIN criteria) among children admitted to pediatric intensive care units [13–15]. This incidence jumps up to nearly 90% if only mechanically ventilated children with trauma or vasopressor requirement are included [16]. In children undergoing cardiac surgery, reports from several countries indicate an AKI incidence (by RIFLE or AKIN criteria) of 30–50% [17–22]. Even among non critically ill children, the incidence of AKI by pRIFLE criteria was high at 34% when those receiving potentially nephrotoxic medications were analyzed [23]. Thus, pediatric AKI is reaching epidemic proportions, especially among critically ill children, in whom kidney failure is just as common as other major organ failures. Indeed, among adults, AKI has a general incidence of 2.1/1000 population, similar to that of acute myocardial

infarction, the latter condition clearly much more widely appreciated by clinicians, researchers, and the general public [24]. Future studies employing consensus definitions in a rigorous manner will be necessary to raise awareness of this increasingly common condition.

Pediatric AKI epidemiology has changed

The epidemiology and etiology of pediatric AKI is greatly influenced by the clinical setting and geographic location. In developed countries, the epidemiology of pediatric AKI has shifted during the past two decades from primary glomerular diseases to a hospital-acquired complication of other systemic illnesses. The most prevalent causes now include sepsis, congenital heart disease, ischemic injury in critically ill neonates and children, nephrotoxins, and malignancy [9, 10]. Even in underdeveloped countries, the pattern of pediatric AKI in urban areas closely resembles that seen in the more developed countries [10]. Ironically, even tragically, pediatric AKI has become the consequence of improved critical care.

Pediatric AKI has important consequences

The short-term outcomes of AKI have been well documented in children undergoing cardiac surgery. In a prospective multinational study of 311 children undergoing cardiac surgery, AKI was independently associated with prolonged mechanical ventilation and increased length of hospital stay [19]. This independent association has now been confirmed in other large studies from several countries [20–22]. Importantly, a retrospective analysis of infants who developed AKI after cardiac surgery revealed a mortality rate of 7%; multivariable logistic regression analysis showed that more severe AKI was associated with greater in-hospital mortality [20]. For AKIN stage II, the odds ratio of death was 5.1 and for AKIN stage III, it was 9.46.

The short-term outcomes of children with AKI as a complication of critical illness are also well known. In a multicenter retrospective analysis of 2,106 pediatric ICU admissions, AKI was independently associated with longer ICU stay and mechanical ventilation [14]. A recent large retrospective study of 3,396 admissions to a single pediatric ICU illustrated that those who presented with AKI on admission had a 32% mortality rate and those who developed AKI at any time during the ICU stay had a 30% mortality rate [13]. Remarkably, this persistently high mortality rate of 30–40% in critically ill children with AKI has been consistently demonstrated in several very recent studies [9, 10, 14–16, 25].

Thus, notwithstanding advances in pediatric renal and critical care, severe AKI requiring renal replacement therapy in children is still associated with a mortality rate of 30–50%, and this has not changed appreciably over the past two decades. This may reflect, in part, the fact that those with severe AKI also have increasing severity of their primary illness, so that an improvement in survival rates is not readily apparent despite renal replacement therapy. This notion is supported by a multicenter retrospective analysis of 344 children requiring continuous renal replacement therapy, in whom the overall mortality rate was 42% [26]. However, there was significantly better survival in patients with less severity of their primary illness, including drug intoxication (100%), primary renal disease (84%), and tumor lysis syndrome (83%). Despite dialysis, survival was lowest in the sickest children with liver disease (43%), pulmonary disease (45%), and bone marrow transplant (45%).

The previous assumption that patients who survived an episode of AKI would recover kidney function has been challenged. A recent meta-analysis of 13 published cohort studies showed that adults with AKI are at a 9-fold higher risk of developing CKD, and a 3-fold increased risk of developing ESRD, when compared to patients without AKI [27]. Similar evidence is accumulating in the pediatric population [6–8, 28]. In a prospective study of children who developed AKI and were followed up for 3–5 years, 60% developed evidence

for CKD (proteinuria, decreased GFR, hypertension), 9% developed ESRD, and 20% died [29]. A shorter 1–3 year follow up of 126 critically ill children who suffered an episode of AKI [30] showed that 10% developed CKD (eGFR < 60 ml/min per 1.73 m^2 or albuminuria), but 47% showed evidence of CKD risk (eGFR 60–90 ml/min per 1.73 m^2 or hypertension). However, several unknowns remain. Can clinical risk factors (e.g. etiology and severity of AKI, pre-existing CKD, other co-morbid factors) determine the risk of CKD after AKI? Can novel biomarkers predict this risk? Can early interventions prevent progression of CKD? Ongoing long-term follow up studies in both children and adults [31] are expected to clarify some of these questions, but clearly a lot more work is needed to strengthen the emerging recommendation that children with AKI require long-term evaluation for CKD. Future studies should also incorporate lessons learned from contemporary basic science studies that have unveiled the mechanisms leading to vascular rarefaction and progressive interstitial fibrosis after AKI [32], and the role of novel regulatory proteins such as neutrophil gelatinase-associated lipocalin and kidney injury molecule-1 as pathogenic factors as well as early biomarkers for the AKI-to-CKD transition [33].

The causes of death in pediatric AKI have changed

Modern renal replacement therapies have largely eliminated the traditional life-threatening complications of AKI, including hyperkalemia, arrhythmias, and uremic coma. Why, then, do children with AKI still die? Both clinical and experimental evidence points to four major factors. First, the detrimental cross-talk between the acutely injured kidney and other organs implicates AKI as an instigator and multiplier of pulmonary, cardiac, hepatic, and neurologic dysfunction, which likely accounts for the vicious cycle of AKI and multi-organ failure leading to mortality [34]. Second, AKI impairs the immune function and markedly escalates susceptibility to infection [35]. This sets up another vicious cycle whereby infections lead to sepsis and AKI, and sepsis-induced immune dysfunction is further exacerbated by the AKI-induced immune dysregulation. Third, AKI contributes to medication failure from many reasons. On the one hand, critically ill children with AKI are at substantial risk for adverse outcomes of drug therapy, due to reduced renal clearance, decrease in protein binding, and decrease in drug metabolism [36–38]. On the other hand, under-dosing of critical medications such as antibiotics often occurs, due to unstable elimination rates and volumes of distribution, and significant clearance by renal replacement therapies [36–38].

Fourth, and perhaps most importantly, AKI often results in fluid overload, and fluid overload is a common accompaniment to several clinical situations (e.g. sepsis, hypotension, cardiac surgery) that lead to AKI. Pediatric studies have pioneered the concept now well established in all ages that fluid overload is an independent risk factor for mortality in AKI. A recent analysis of 340 children used a tripartite classification for percent fluid overload at initiation of renal replacement therapy [39]: < 10%, 10–20%, and ≥20% fluid overload. Those with ≥20% fluid overload had a 66% mortality rate, whereas those with 10–20% fluid overload displayed a lower mortality rate of 43%, and those with < 10% fluid overload had the lowest mortality rate of 29%. The association between degree of fluid overload and mortality remained after adjusting for intergroup differences and severity of illness [39]. Patients with ≥20% fluid overload had an 8.5-fold greater adjusted odds ratio of death than those with <20% fluid overload. Preventing fluid overload and rapid correction of fluid overload with early initiation of renal replacement therapy may represent “low-hanging” fruits in pediatric AKI therapeutics that deserve investigation.

Can pediatric AKI risk be predicted using clinical measures?

AKI lacks physical symptoms and signs in the early stages when interventions are likely to be most effective. Investigators have recently sought to integrate contextual risk factors with evidence of renal injury to stratify AKI risk [40, 41]. Termed “renal angina”, a three-tiered schema empirically places children into moderate (any ICU admission plus doubling of serum creatinine or fluid overload >15%), high (heart failure or stem cell transplant plus serum creatinine increase ≥0.3 mg/dl or fluid overload >10%), and very high risk for AKI (mechanical ventilation and vasoactive medication plus any increase in serum creatinine or fluid overload >5%). Thus, as the AKI risk increases (e.g. mechanical ventilation), less evidence of AKI is needed (e.g. small changes in serum creatinine) to meet the threshold for renal angina. In analogy with cardiac angina, the major goal of renal angina determination is to identify children who will maximally benefit from biomarker measurement for prediction and early treatment of AKI. Studies to validate the utility of renal angina are currently in progress.

Can pediatric AKI and its outcomes be predicted using biomarkers?

The genomic and proteomic tools of modern science have identified novel markers for the early stress response of the kidney to AKI, which are induced in the kidney tubules during the early damage phase, and serendipitously appear in the urine or plasma well before a change in serum creatinine is detected [2, 5]. Many are being developed and validated as early non-invasive biomarkers for the prediction of AKI and its clinical outcomes in humans. This is a rapidly evolving field, and the current status of the most promising examples is shown in Table 2.

The most widely studied and validated early biomarker of AKI in children is neutrophil gelatinaseassociated lipocalin (NGAL). In prospective studies of children undergoing cardiopulmonary bypass, levels of NGAL in the urine and plasma were significantly elevated within 2–6 hours of bypass in those who subsequently developed AKI [42–47]. Strong associations between early NGAL measurements and hard clinical outcomes, including length of hospital stay and the duration and severity of pediatric AKI, have now been documented [43–47]. Furthermore, the additional of NGAL significantly improves the risk prediction for AKI after cardiac surgery over clinical models alone [47]. Studies in the more heterogeneous pediatric intensive care [48, 49] and pediatric emergency department settings [50] also demonstrated that NGAL predicted AKI about 1–2 days prior to the rise in serum creatinine, with high sensitivity. Two large multicenter pooled analyses of existing NGAL studies in children and adults have recently been published, confirming the utility of this marker for the early diagnosis of AKI and its clinical outcomes [51, 52].

A recent study examined a combination of biomarkers in 220 children undergoing cardiac surgery [46]. Urinary NGAL was increased in AKI patients within 2 hours of bypass initiation, urine IL-18 and L-FABP were increased within 6 hours, and urine KIM-1 increased at the 12 hour time point. All markers correlated with AKI severity and clinical outcomes, and improved the risk prediction for AKI over clinical models. Thus, they represent temporally sequential markers, and a panel of such biomarkers may therefore help establish the timing of injury and plan appropriate therapies [46]. Standardized clinical laboratory platforms for the measurement of urine [44] and plasma [43] NGAL are now available in most countries.

It is anticipated that biomarkers of early structural AKI such as NGAL will provide critical diagnostic and prognostic stratification, independent of functional markers such as serum creatinine. While biomarker combinations may be necessary to provide the best information in a context-specific manner, the technical and financial challenges of developing biomarker

panels are substantial. It is therefore vital that large enough future studies demonstrate (a) the association between early structural biomarkers and hard outcomes such as dialysis, cardiovascular events, and death, both with and independent of functional markers, and (b) that randomization to a treatment for AKI based on high structural biomarker levels results in an improvement in kidney function and amelioration of adverse clinical outcomes.

Conclusion

The Kidney Disease: Improving Global Outcomes (KDIGO) group has provided a consensus definition and classification for pediatric AKI, the uniform adoption of which will improve our understanding of pediatric AKI epidemiology and raise awareness of this increasingly common condition. Pediatric AKI leads to CKD and ESRD, but we need to identify clinical risk factors and novel biomarkers that predict these outcomes. A concerted effort is needed to strengthen the emerging recommendation that children with AKI require long-term evaluation for CKD. Preventing fluid overload and rapid correction of fluid overload with early initiation of renal replacement therapy represent pediatric AKI therapeutics that deserves urgent investigation. Excellent point-of-care early biomarkers of AKI have now become available. Biomarker-guided therapies, based on “renal angina” scoring, should be the next major challenge to overcome, in order to dramatically improve the outcome of pediatric AKI.

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Table 1

KDIGO Staging of AKI

Stage	Serum Creatinine	Urine Output
1	1.5–1.9 times baseline, OR ≥0.3 mg/dl (≥26.5 mol/l) increase	<0.5 ml/kg/h for 6–12 hours
2	1.0–2.9 times baseline	<0.5 ml/kg/h for ≥12 hours
3	3.0 times baseline, OR SCr ≥4.0 mg/dl (≥353.6 μmol/l), OR Initiation of renal replacement therapy, OR eGFR <35 ml/min per 1.73 m^2 (< 18 years)	<0.3 ml/kg/h for ≥24 hours, OR Anuria for ≥12 hours

Adapted from Reference 1.

Table 2

Novel urinary biomarkers for the prediction of AKI and its outcomes

Biomarker	Source	Function	Cardiac Surgery	Kidney Transplant	ICU/ED
NGAL	Distal tubule and collecting duct	Regulates iron trafficking, promotes tubule cell survival	2 hours post CPB 2 days pre AKI Predicts AKI severity, dialysis, and death	6 hours post transplant 2–3 days pre DGF Predicts long-term graft loss	On admission 1–2 days pre AKI Predicts AKI severity, dialysis, and death
IL-18	Proximal tubule	Promotes tubule cell apoptosis and necrosis	6 hours post CPB 2 days pre AKI Predicts AKI severity, dialysis, and death	6 hours post transplant 2–3 days pre DGF Predicts long-term graft loss	On admission 1–2 days pre AKI Predicts AKI severity, dialysis, and death
L-FABP	Proximal tubule	Antioxidant, suppresses tubule-interstitial damage	6 hours post CPB 2 days pre AKI Not tested for outcomes	Not tested	On admission 1–2 days pre AKI Predicts AKI severity, dialysis, and death
KIM-1	Proximal tubule	Promotes epithelial regeneration, regulates apoptosis	12 hours post CPB 1 day pre AKI Not tested for outcomes	Not tested	On admission 1–2 days pre AKI Predicts AKI severity, dialysis, and death

Abbreviations for Table 2: AKI, acute kidney injury, defined as AKIN Stage I or greater; CPB, cardiopulmonary bypass; DGF, delayed graft function; ICU, intensive care unit; ED, emergency department; IL-18, interleukin-18; KIM-1, kidney injury molecule 1; L-FABP, liver-type fatty acid binding protein; NGAL, neutrophil gelatinase-associated lipocalin. Times shown (in hours or days) are the earliest time points when the biomarker becomes significantly increased from baseline.

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