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Acute Kidney Injury in Children and Its Potential Consequences in Adulthood

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Key Words
Acute kidney injury · Chronic kidney disease · Pediatrics

Abstract
While emerging evidence indicates that the incidence of both acute kidney injury (AKI) and chronic kidney disease (CKD) in children is rising, and the etiologies are dramatically changing, relatively little is currently known regarding the potential for transition from AKI to CKD. In both situations, early intervention can significantly improve the dismal prognosis. Fortunately, recent data have validated a multidimensional AKI classification system for children, and led to the investigation of the chronic kidney sequelae in many pediatric populations with AKI, or at risk for AKI (children with hemolytic uremic syndrome, neonates or those exposed to repeated nephrotoxic medications). The purpose of this article is to review the changing epidemiology of pediatric AKI and its potential effect on the development of CKD in children.

Introduction

Advancement in the care of children with kidney disease has led to dramatic improvements in patient survival. However, most pediatric kidney epidemiological studies have focused on long-term outcomes in children with end-stage renal disease (ESRD) [1, 2]. Care for the critically ill child with acute kidney injury (AKI) has improved greatly, with survival rates reaching 60–70%, even for children who require renal replacement therapy (RRT) [3, 4]. Recently, researchers have recognized that episodes of AKI can lead to more rapid progression to chronic kidney disease (CKD) in adult patients; the 2009 United States Renal Data System report revealed that adults with an AKI episode during hospitalization have an approximately tenfold greater risk of progressing to ESRD within 6–12 months than patients who have not experienced AKI [5]. No similar data exist in children; however, with the potential for survival for many decades after an AKI episode, identification of children at risk for CKD progression after AKI is especially important. The purpose of this article is to review the changing epidemiology of pediatric AKI and its potential effect on the development of CKD in children.

Epidemiology of Pediatric AKI

The epidemiology of pediatric acute kidney injury (pAKI) has mainly been studied in acutely ill hospitalized patients, since nonoliguric forms of pAKI may be self-limited and go undetected in the outpatient setting. While

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Table 1. Shift in pAKI epidemiology

Author	Time span	Cohort	AKI cause
Williams et al. [8], 2002	1978–1998	all hospital	1978–88: HUS 38%, oncology 8% 1988–98: HUS 22%, oncology 17%
Hui-Stickle et al. [4], 2005	1999–2001	all hospital	ischemic 21% nephrotoxins 16% primary renal 7%
Akcan-Arikan et al. [20], 2007	2005–2006	pediatric intensive care unit	pneumonia 33% SIRS/sepsis 27% cardiogenic 10%
Ball and Kara [10], 2008	2001–2006	pediatric intensive care unit receiving RRT	cardiogenic 58% HUS 17% sepsis 13%

multicenter data do not exist, single center studies from the 1980s and 1990s report hemolytic uremic syndrome (HUS), other primary renal causes, sepsis, and burns as the most prevalent causes leading to pAKI [6, 7]. More recent pediatric data [4, 8–10] reveal a dramatic shift in the epidemiology of pAKI (table 1), with the most common causes being renal ischemia (often after cardiopulmonary bypass surgery [10]), nephrotoxin use, and sepsis; thus, pAKI more often develops in hospitalized children as a result of another systemic illness or its treatment and not from primary kidney disease. pAKI epidemiological study has intensified over recent years, likely as a result of more widespread provision of acute RRT modalities to critically ill children [11]. Hospital and pediatric intensive care unit-acquired pAKI rates appear to have increased more than ninefold from the 1980s through 2004, likely due to increased use of more invasive management and higher illness severity of critically ill children [9].

Until recently, pAKI studies suffered from a lack of a standardized definition, with differing definitions from varying increases in serum creatinine or decreases in urine output, to RRT provision. The incidence of the most severe forms of pAKI, defined by dialysis requirement, ranges from 1 to 2% of all critically ill children [9, 12]. In children undergoing cardiopulmonary bypass, the incidence of AKI is in the range of 10–50%, depending on the definition used [13–15]. In addition, a long-held concept that critically ill patients died 'with' and not 'from' AKI has recently been challenged [16]. Even small increases in serum creatinine, much less than would be considered indicative of the need for RRT, are now recognized to contribute to poor outcomes. Chertow et al. [17] demonstrated that increases in serum creatinine of 0.3 mg/dl were associated with increased adult patient mortality, even when outcome was controlled for significant patient comorbidity. Similar results were noted in pediatric patients with acute decompensated heart failure; patients with a 0.3-mg/dl or greater serum creatinine rise demonstrated a sevenfold increased mortality risk [18]. These studies highlight the need for more refined AKI definitions and to focus on earlier detection of AKI.

In 2004, a standardized AKI consensus definition was proposed by the Acute Dialysis Quality Initiative: the RIFLE criteria (risk, injury, failure, loss, ESRD), which based AKI diagnosis and severity on changes in serum creatinine from baseline and/or degree and duration of oliguria [19]. The adult-derived RIFLE definition was modified, and then applied and validated in pediatric patients and renamed the pediatric RIFLE (pRIFLE) criteria. pRIFLE stratifies AKI from mild (RIFLE-R, 'risk') to severe (RIFLE-F, 'failure') based on *changes* in serum creatinine or estimated creatinine clearance and urine output (table 2). The rationale for using estimated creatinine clearance instead of absolute changes in serum creatinine emanated from the widely varying body mass seen in the pediatric population of neonates to young adults, leading to different levels of normal baseline serum creatinine.

The first study which defined AKI using the pRIFLE criteria found that AKI occurred in 82% of critically ill children admitted to a pediatric intensive care unit who received invasive mechanical ventilation and at least one vasoactive medication [20]. Similar to adult studies [21, 22], worsening pAKI defined by pRIFLE criteria was an independent risk factor for mortality and increased hos-

Table 2. Pediatric modified RIFLE criteria [20]

	Pediatric modified RIFLE criteria	
	eCCl by Schwartz formula	urine output
Risk	eCCl decrease by 25%	<0.5 ml/kg/h for 8 h
Injury	eCCl decrease by 50%	<0.5 ml/kg/h for 16 h
Failure	eCCl decrease by 75% or eCCl <35 ml/min/1.73 m^2	<0.3 ml/kg/h for 24 h or anuric for 12 h
Loss	persistent failure >4 weeks	
End stage	ESRD (persistent failure >3 months)	

eCCl = Estimated creatinine clearance.

pital length of stay. Subsequent reports confirm the utility of the pRIFLE criteria to stratify pAKI severity, highlighting the potential association between pAKI severity and patient outcome [23–25]. Additionally, pRIFLE strata have served as useful outcome measures in terms of the validation of novel urinary pAKI biomarkers to predict pAKI severity in critically ill children [26, 27]. The adult RIFLE criteria have been modified by the Acute Kidney Injury Network (AKIN) to specify a >0.3-mg/dl serum creatinine rise in 48 h denotes mild AKI (AKIN stage 1 or RIFLE-R) [28]. The AKIN criteria were developed with input from pediatric nephrologists; preliminary comparisons show that pRIFLE and AKIN lead to similar diagnostic AKI rates, with a potential difference in AKI severity distribution [25, 29].

Few prospective studies exist to accurately assess risk factors for pAKI development. Most pAKI studies assess patients who have already developed AKI, examining the variables common among the pAKI population of interest. However, such studies do not examine a control population with similar exposure risks to determine the true risk associated with each clinical variable. It is clear, though, that worsening illness severity in itself is a risk factor for developing AKI. The critically ill patient who is intubated and receiving vasoactive medications should prompt early vigilance for AKI occurrence. pAKI incidence is extremely high (82%) in more severely ill patients [20] compared to all patients admitted to the pediatric intensive care unit (4.5%) [12].

The recent research into pAKI epidemiology has begun to yield new and important data. Nonetheless, further prospective epidemiologic research utilizing a common definition, with a detailed description of the particular population studied, will be crucial to understanding the true incidence of mild-to-severe AKI in patient populations with different underlying diagnoses. In fact, a recent publication proposed the concept of a 'renal angina equivalent' to prompt investigation into the presence and causes of AKI, much as chest pain and associated signs and symptoms prompt evaluation for acute coronary syndrome and myocardial infarction [30]. The pediatric metrics for renal angina include invasive mechanical ventilation, vasoactive substance use, history of recent stem cell transplantation, and/or the development of relative fluid overload. In fact, given that data from over 700 children in six studies demonstrated a consistent association between intensive care unit fluid overload of >10–20% at continuous RRT initiation and mortality in children, fluid overload may be a strong indicator of pAKI. In the very near future, we will be able to clinically stratify patients at risk for pAKI using the renal angina concept to direct and optimize the use of novel pAKI biomarkers to detect pAKI early (i.e. prior to a rise in serum creatinine or decrease in urine output), and hopefully test interventions to prevent or mitigate the effects of AKI. Based on the clinical situation, pAKI biomarkers could be incorporated into a further refined pRIFLE AKI definition.

Epidemiology of Pediatric CKD

Pediatric CKD epidemiological data can be derived from large national or multinational database registries including from the European Dialysis and Transplantation Association-European Renal Association, United States Renal Data Renal Data System, Canadian Organ Replacement Register, Registry of the Japanese Society for Dialysis Therapy, Australia and New Zealand Dialysis and Transplant Registry, and North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) [31]. Each registry differs with respect to the detail of the data obtained regarding patient age stratification, specific dis-

ease categories leading to CKD available for selection, and whether the data come from government mandated versus voluntary enrollment.

While a detailed description of each registry is beyond the scope of this paper, the focus of most of the registries is placed upon patients with ESRD. The NAPRTCS database, which is a voluntary registry from North American pediatric centers, established a separate chronic renal insufficiency arm in 1994 [32]. The 2008 NAPRTCS Annual Report (www.naprtcs.org) contains data from 7,037 children <20 years of age with chronic renal insufficiency, defined as an estimated creatinine clearance of <75 ml/min/1.73 m^2. The leading primary diagnoses responsible for chronic renal insufficiency mirror those reported for ESRD and include both anatomical/hereditary lesions such as dysplasia, reflux nephropathy, and obstructive uropathy, as well as chronic glomerulopathies. Of note, no specific categories for AKI or cortical necrosis are listed, which may result from a lack of recognition of AKI as a primary diagnosis leading to CKD. Long-term longitudinal study of pAKI survivors is warranted to determine if pAKI will become a more prevalent cause of CKD.

Future insights into the epidemiology of pediatric CKD will be gained from the ongoing North American Chronic Kidney Disease in Children trial [33]. This represents a prospective cohort study of 540 children aged 1–16 years with an estimated GFR between 30 and 75 ml/min/1.73 m^2, established to identify novel risk factors for CKD progression. More importantly, the Chronic Kidney Disease in Children cohort study has recently reassessed old GFR estimation equations [34] and validated a new GFR estimation equation used to classify children with different stages of CKD [35]. This new formula, i.e. estimated GFR = 0.413 · (height (in cm)/serum creatinine), has been validated prospectively with iohexol renal scans and will likely identify many more children with CKD as the older formula overestimated GFR due to its study in mostly children with normal GFR or ESRD. Those studies yielded a higher coefficient (0.45–0.75, based on patient age and gender) than the newer validated formula. As with AKI, future research may lead us to define CKD by means other than serum creatinine, such as cystatin C [36, 37] or other urinary biomarkers [13, 38–41].

Does Pediatric AKI Lead to CKD?

The long-term sequelae of pAKI have only been the subject of recent investigation, since, as noted above, no systematic assessment of pAKI survivors has been undertaken. Ball and Kara [10] found that 40% of surviving pAKI patients who received acute RRT had signs of a kidney abnormality (decreased GFR, hypertension, hematuria, or proteinuria) at the time of hospital discharge, and patients with primary renal disease-associated pAKI had a higher rate of renal dysfunction at hospital discharge. Hui-Stickle et al. [4] demonstrated that 34% of 176 children had either reduced kidney function or were dialysis dependent upon discharge from a tertiary center after a pAKI episode. Askenazi et al. [42] followed this cohort for 3–5 years and found patient survival to be 56.8%, with the majority of mortality occurring within 2 years of the pAKI episode. Sixteen children progressed to ESRD, with the majority (91%) having an underlying renal or urological disease. In addition, 17 of 29 patients studied in a follow-up clinic visit demonstrated evidence of CKD, manifesting as hyperfiltration, reduced kidney function, hypertension, or microalbuminuria. More concerning was that the majority of the children with CKD had more than one sign or symptom of CKD, yet only six of the children were actively being followed by a pediatric nephrologist. This early small-scale study should prompt the pediatric nephrology community to perform systematic longitudinal evaluations for pediatric CKD in children who survive a pAKI episode. Currently, the Translational Research Investigating Biomarker Endpoints for Acute Kidney Injury study consortium has formed an ancillary study group, the Assessment, Serial Evaluation, and Subsequent Sequelae in Acute Kidney Injury consortium, which will look at long-term kidney outcomes in patients with bypass-associated AKI, including children from two pediatric centers.

Other large cohort studies lend additional insight into the potential for pediatric AKI to lead to CKD. Recent meta-analyses and single-center data have been reported to assess the risk for CKD development in children suffering from HUS, pediatric cancer survivors, and premature birth. Garg et al. [43] performed an extensive meta-analysis of the long-term consequences of HUS. While this study did not directly address whether or not AKI led to CKD, the investigators did assess for an association between initial serum creatinine levels, RRT provision (presumably for AKI), and long-term renal outcomes. After screening nearly 3,400 articles, the authors included 49 studies comprising 3,476 patients for review.

The analyses primary aims were determining the incidence of, and risk factors for, the development of death, ESRD, or CKD (defined as an estimated GFR <80 ml/

min/1.73 m^2). Secondary renal endpoints included proteinuria and hypertension. The death and ESRD rates from the individual studies ranged from 0–23 and 0–17%, respectively, with a combined death-ESRD rate of 12% (95% CI: 10–15). The pooled estimates for CKD development were 8% (95% CI: 5–11) for 60–80 ml/min/1.73 m^2, 6% (95% CI: 3–8) for GFR 30–59 ml/min/1.73 m^2, and 1.8% (95% CI: 0.8–3) for GFR 5–29 ml/min/1.73 m^2. In addition, the pooled rates for proteinuria and hypertension were 15% (95% CI: 10–20) and 10% (95% CI: 8–12), respectively. The combined renal sequelae estimated was 25% (95% CI: 20–30), indicating that fully one quarter of HUS survivors are at risk for long-term kidney damage. Severity of clinical illness, defined as central nervous system symptoms, need for RRT, higher white blood cell counts, or initial serum creatinine concentrations were all associated with increased likelihood of death or long-term kidney sequelae. An important finding of this study was the observation of the development of long-term kidney sequelae in 8–61% of patients who had return of normal GFR and/or loss of proteinuria after the acute HUS episode. Thus, as with the previous study of Askenazi et al. [42], long-term follow-up for at risk patients is warranted, even for those patients who seem to have 'renal recovery' after an acute HUS episode.

Premature neonates provide an informative pediatric population for study since they can be exposed to numerous nephrotoxic insults (e.g. sepsis, nephrotoxic medications) before nephrogenesis is complete. White et al. [44] recently performed a meta-analysis of studies examining low birth weight infants and CKD development later in life. After reviewing 1,600 studies, they were able to include 32 papers comprising 17 case-control or cohort studies (46,249 patients) and 1 genetic record linkage study. Low birth weight, defined as birth weight between 1,500 and 2,500 g, imparted a 70% risk of developing CKD later in life (HR: 1.73, 95% CI: 1.44–2.08) and an 80% greater risk of developing albuminuria later in life (HR: 1.81, 95% CI: 1.19–2.77) compared to normal birth weight infants.

Pediatric cancer survivors also serve as an informative cohort for long-term CKD development given the dramatic improvement in cancer treatment outcomes and their potential exposure to multiple nephrotoxic medications and insults (e.g. sepsis-induced AKI). Pediatric stem cell transplant (SCT) recipients seem to be at a particularly high risk of developing AKI, with reposted rates of 11–21% using a pRIFLE-I equivalent (serum creatinine doubling) for an AKI definition [45–48]. As a result, the SCT cohort has been followed for the development of CKD [47, 49, 50]. Gronroos et al. [49] reported the 7-year renal follow-up of 187 children with normal GFR before receiving SCT and found renal impairment in 41% of patients at 1 year, in 31% at 3 years, and in 11% at 7 years after SCT. Hingorani et al. [47] reported long-term kidney outcomes in 1,635 SCT recipients (279 children) with normal GFR prior to SCT and demonstrated a 23% CKD rate with a median time to CKD of 191 days (CKD was defined as a GFR <60 ml/min/1.73 m^2). The CKD rate in children was 4%. Of note, AKI for the whole cohort was independently associated with an increased risk of CKD development (HR: 1.7, 95% CI: 1.3–2.1), although pediatric patients were not analyzed separately for CKD risk factors. Finally, Frisk et al. [50] demonstrated a 27% CKD rate in children 10 years after SCT who received total body irradiation.

Multiple studies have assessed for an association between nephrotoxic chemotherapeutic medication administration and chronic kidney injury in pediatric cancer patients. One study summarized the late renal effects of childhood cancer of the Children's Oncology Group, a multicenter clinical consortium, to develop guidelines for kidney-related health screening of pediatric cancer survivors [51]. This review identified that the following exposures should necessitate initial screening for hypertension, proteinuria, abnormal GFR, and electrolyte abnormalities: radiation therapy, ifosfamide, nephrectomy, methotrexate, and cisplatin/carboplatin. The recommendations did not specify the timing of initial evaluation. After the baseline evaluation, the authors recommended annual blood pressure measurement and urinalysis, with an annual assessment for hydroceles in males who have undergone nephrectomy.

More recently, two studies have specifically evaluated long-term renal function in large cohorts of pediatric long-term cancer survivors [52, 53]. Arjmandi-Rafsanjani et al. [52] evaluated 108 children in a single Iranian center and observed a 25.2% rate of renal toxicity, including tubular disorders and hypertension. Of note, 7.5% of patients had an estimated GFR <90 ml/min/1.73 m^2. We performed a similar study in 150 children to assess for CKD and chronic kidney injury, manifested by abnormal estimated GFR, proteinuria, microalbuminuria, hypertension, and/or tubulopathy [53]. We observed a high CKD/chronic kidney injury rate: 71% had at least 1 sign, 22% had 2 signs, 2 patients had 3 signs of CKD/injury, respectively. Nearly half of the patients had signs of CKD with an elevated or decreased estimated GFR.

Conclusions and Future Directions

The incidence of both AKI and CKD is rising and reaching epidemic proportions. In both situations, early intervention can significantly improve the dismal prognosis. Pediatric primary care practitioners have not been as accustomed to screening for CKD as their internal medicine counterparts since CKD is a relatively rare disorder in children. However, as children with complex systemic disease, prematurity, or other severe acute primary kidney disease now survive AKI episodes, their risk for CKD development is becoming evident. While most of the late-effects pediatric chronic disease literature focuses on pediatric cancer survivors, we expect that children surviving sickle cell disease, cystic fibrosis, cardiac disease, and rheumatologic disease are also at risk for repeated acute renal insults that could lead to CKD. The clinical situations reviewed in this article support a practice of long-term follow-up of any child who has a severe AKI episode.

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