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PROGRESSION FROM ACUTE KIDNEY INJURY TO CHRONIC KIDNEY DISEASE: A PEDIATRIC PERSPECTIVE:

An invited review for Advances in Chronic Kidney Disease

Stuart L. Goldstein[§] and **Prasad Devarajan**[¥,¥]

§ *Department of Pediatrics, Renal Section, Baylor College of Medicine, Houston, TX*

¥*Nephrology and Hypertension, Cincinnati Children's Hospital Medical Center, University of Cincinnati School of Medicine, Cincinnati, OH*

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. However, the lack of a uniform AKI definition and the paucity of early, predictive biomarkers have impaired our ability diagnose AKI early to institute potentially effective therapies in a timely manner. Fortunately, recent data has validated a multi-dimensional AKI classification system for children. In addition, the application of innovative technologies has identified candidates that are emerging as early biomarkers of both AKI and CKD. These include neutrophil gelatinase-associated lipocalin (NGAL), liver-type fatty acid binding protein (L-FABP) and kidney injury molecule-1 (KIM-1). Studies to validate the sensitivity and specificity of these biomarkers in clinical samples from large cohorts and from multiple clinical situations are currently in progress, facilitated by the development of commercial tools for the reproducible measurement of these biomarkers across different laboratories.

Keywords

Acute kidney injury; acute renal failure; chronic kidney disease; biomarkers; neutrophil gelatinase-associated lipocalin; kidney injury molecule-1; liver-type fatty acid binding protein

EPIDEMIOLOGY OF PEDIATRIC AKI

The epidemiology of pediatric acute kidney injury (pAKI) has mainly been studied in acutely ill hospitalized patients, since non-oliguric forms of pAKI may be self-limited and go undetected in the outpatient setting. While multi-center data do not exist, single center studies from the 1980's and 1990's report hemolytic uremic syndrome, other primary renal causes, sepsis and burns as the most prevalent causes leading to pAKI [1]. A more recent retrospective study has revealed a dramatic shift in the epidemiology of pAKI, with the most common causes being renal ischemia, nephrotoxin use and sepsis [2]. Pediatric AKI epidemiological study has

¥Corresponding Author: Prasad Devarajan, MLC 7022, 3333 Burnet Avenue, Cincinnati, OH 45229-3039, USA. Phone: (513) 636-4531. FAX: (513) 636-7407. E-mail: prasad.devarajan@cchmc.org.

intensified over recent years, likely as a result of more widespread provision of acute renal replacement therapy (RRT) modalities to critically ill children [3]. Hospital and pediatric intensive care unit (PICU)-acquired pAKI rates appear to be increasing over 9-fold from the 1980's through 2004 [4], likely due to increasing use of more invasive management and higher illness severity of critically ill children.

Until recently, pAKI studies suffered from a lack of standardized definition, with differing definitions from varying increases in SCr 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 [4,5]. When less strict definitions are used, such as doubling of serum creatinine, the incidence rises to 21% [4–6]. In children undergoing cardiopulmonary bypass, the incidence of AKI is in the range of 10 to 50%, depending on the definition used [7–11]. Children receiving stem cell transplants are also at higher risk, with an incidence of AKI (defined by doubling of serum creatinine) of 20% [12]. Estimating the true incidence of AKI in the general pediatric population or even in hospitalized patients may suffer from a significant ascertainment bias towards an underestimation of AKI, since previous diagnostic criteria were based on large increases in serum creatinine.

In addition, a long held concept that patients died "with" and not "from" AKI has recently been challenged [13]. 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 and colleagues 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 co-morbidity [14]. 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 7-fold increased mortality risk [15]. These studies highlight the need for more refined AKI definitions, and to a focus on earlier detection of AKI before a patient requires RRT.

In 2004, a standardized AKI consensus definition was proposed by the Acute Dialysis Quality Initiative: the RIFLE criteria (Risk, Injury, Failure, Loss, End-Stage Renal Disease) [16]. The adult-derived RFILE 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 (SCR) or estimated creatinine clearance (eCCl) and urine output (Table 1). The first study which defined AKI using the pRIFLE criteria, found that AKI occurred in 82% of critically ill children admitted to a PICU who received invasive mechanical ventilation and at least one vasoactive medication [6]. Similar to adult studies [17–20], worsening pAKI defined by pRIFLE criteria was an independent risk factor for mortality and increased hospital length of stay.

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. Pediatric AKI incidence is extremely high (82%) in more severely ill patients [6] compared to all patients admitted to the pediatric intensive care unit (4.5%) [5].

Patients receiving stem cell transplants are at substantial risk of developing AKI for several reasons, including the extensive use of nephrotoxic medications, veno-occlusive disease in association with hepatorenal syndrome, the high incidence of sepsis and tumor lysis syndrome

[12,21]. Because of the large amounts of fluid received during their treatment, these patients are also at particularly high risk of developing substantial fluid overload [21].

Children undergoing cardiopulmonary bypass are at high risk of post-operative AKI, with recent studies demonstrating a 30 to 50% incidence as defined by a 50% or greater increase in serum creatinine, corresponding to the "R" category of the RIFLE criteria [10,11]. The pathophysiology of AKI in this setting is multifactorial, including diminished renal blood flow, loss of pulsatile flow, hypothermia, atheroembolism, and a generalized inflammatory response [9].

The recent research into pAKI epidemiology has begun to yield new and important data. Nonetheless, further prospective epidemiologic research utilizing a common definition, with detailed description of the particular population studied, will be crucial to understanding the true incidence of mild to severe AKI in a wide range of geographic and diagnostic patient populations.

EPIDEMIOLOGY OF PEDIATRIC CKD

Pediatric chronic kidney disease (CKD) epidemiological data can be derived from large national or multi-national database registries including European Dialysis and Transplantation Association-European Renal Association (EDTA-ERA), the United States Renal Data Renal Data System (USRDS), the Canadian Organ Replacement Register (CORR), Registry of the Japanese Society for Dialysis Therapy, and the Australia and New Zealand Dialysis and Transplant Registry (ANZ DATA) and the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) [22]. Each registry differs with respect to the detail of the data obtained regarding patient age stratification, specific disease categories leading to CKD available for selection and if the data come from government mandated *versus* voluntary enrollment. While 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 (CRI) arm in 1994 [23]. The 2007 NAPRTCS Annual Report (www.naprtcs.org) contains data from 6,794 children less than 20 years of age with CRI, defined as an estimated creatinine clearance of less than 75 ml/min/1.73m2. The leading primary diagnoses responsible for CRI 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 (CKid) trial [24]. This is a prospective cohort study of 540 children aged 1 to 16 yr with an estimated GFR between 30 and 75 ml/min per 1.73 m^2, established to identify novel risk factors for CKD progression.

DOES PEDIATRIC AKI LEAD TO CKD?

The long-term sequelae of pAKI have been subject of only recent investigation, since, as noted above, no systematic assessment of pAKI survivors has been undertaken. Hui-Stickle and colleagues 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 [25]. Askenazi [26] followed this cohort for 3 to 5 years and found patient survival to be 56.8%, with the majority of mortality occurring within 2 years of the pAKI episode. In addition, 17/29 patients studied in a follow up clinic visit patients demonstrated evidence of CKD, manifesting as hyperfiltration, reduced kidney function, hypertension or microalbuminuria. 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.

BIOMARKERS FOR MONITORING PROGRESSION FROM AKI TO CKD

Chronic kidney disease (CKD) is a devastating illness that has reached epidemic proportions worldwide [27]. CKD is characterized by a progressive decline in kidney function that is associated with excess morbidity and mortality. If CKD is recognized and treated in a timely manner, the deterioration of kidney function can be delayed and patient outcomes markedly improved [28]. Monitoring CKD activity requires biomarkers that provide clinicians with quick, noninvasive and specific measurements that correlate with pathophysiologic processes occurring within the kidney. Current biomarkers of CKD and its progression in widespread clinical use, the serum creatinine and urine protein, have limitations in serving these goals [29]. Remarkably, much of the confusion surrounding the early diagnosis of AKI and CKD is being solved by the adaptive response of the stressed kidney itself [30]. The application of innovative technologies such as functional genomics and proteomics has begun to identify novel biomarkers that reflect tissue pathology and predict disease progression prior to the development of abnormalities in traditional biomarkers [31]. Some of these biomarkers hold tremendous promise as methods for monitoring the progression from AKI to CKD, since they are emerging as diagnostic tools in both these clinical situations [28]. These include neutrophil gelatinase-associated lipocalin (NGAL), liver-type fatty acid binding protein (L-FABP), and kidney injury molecule-1 (KIM-1). The present status of this subset of biomarkers is briefly mentioned below. Biomarkers that pertain primarily to AKI and not to CKD, are discussed elsewhere in this issue [32].

Neutrophil Gelatinase-Associated Lipocalin (NGAL)

In animal models, NGAL was identified by microarray analysis as one of the earliest induced genes and proteins in the kidney after ischemic or nephrotoxic injury, and NGAL protein was easily detected in the blood and urine soon after AKI [33–35]. NGAL has now been validated as an early predictive biomarker of AKI in cardiopulmonary bypass [9–11], kidney transplantation [36,37], diarrhea-associated hemolytic uremic syndrome [38], contrast nephropathy [39], and in the critical care setting with unknown timing of kidney injury [40].

In CKD, there is now a growing literature suggesting that NGAL is also a marker of kidney disease and severity. In children with CKD secondary to renal dysplasia, obstructive uropathy and glomerular and cystic diseases, plasma NGAL levels were inversely associated with measured GFR [41]. As kidney function declined to less than 30 mL/minute, NGAL outperformed cystatin C as a biomarker of kidney failure [41]. Other recent studies in adults have also shown an elevated serum or urine NGAL in subjects with CKD, which correlated with serum creatinine, GFR and proteinuria [42–45]. Prospective longitudinal studies are required to determine the pathophysiologic role NGAL is playing in models of chronic kidney disease, and to better discern the association of urinary and plasma NGAL with CKD progression.

Liver-type fatty acid-binding protein (L-FABP)

In an animal model of cisplatin-induced AKI, there was increased shedding of urinary L-FABP within the first 24 hours, whereas a rise in serum creatinine was not detectable until after 72 hours of cisplatin treatment [46]. In a study involving living-related kidney transplant patients immediately after reperfusion of their transplanted organs, a significant direct correlation was found between urinary L-FABP level and both peritubular capillary blood flow and the ischemic time of the transplanted kidney [47]. In a recent prospective study of children

undergoing cardiac surgery, urine L-FABP measured within 4 hours of the procedure was shown to be a powerful early predictor of AKI [48].

L-FABP expression and urinary excretion are also increased in the setting of CKD. In subjects with nondiabetic CKD, urine L-FABP levels correlated with urine protein and serum creatinine levels. Notably, L-FABP levels were significantly higher in the group of patients who progressed to more severe disease [49]. Additional studies are needed to demonstrate L-FABP's ability to predict CKD and its progression in cohorts with CKD of multiple etiologies.

Kidney injury molecule-1 (KIM-1)

KIM-1 is upregulated in dedifferentiated proximal tubule cells after ischemic or nephrotoxic AKI in animal models, and a proteolytically processed domain is easily detected in the urine [50]. In a human cross-sectional study, urinary KIM-1 distinguished ischemic AKI from prerenal azotemia and chronic renal disease [51]. In a case-control study of children undergoing cardiac surgery, urinary KIM-1 obtained 12 hours post-surgery was a very good early predictive biomarker of AKI [52].

Emerging evidence indicates that KIM-1 in the kidney and urine is also induced in a variety of chronic proteinuric, inflammatory, and fibrotic disease states in humans [53,54]. Additional studies are required to better define the temporal pattern and predictive potential of urinary KIM-1 measurements with CKD progression.

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. However, the paucity of early, predictive, non-invasive biomarkers has impaired our ability to institute potentially effective therapies in a timely manner. Fortunately, the application of innovative technologies has identified candidates that are emerging as early biomarkers of both AKI and CKD. The most promising of these are chronicled in this review. These include NGAL, L-FABP and KIM-1. It is likely that they will be useful for timing the initial insult and assessing the duration and severity of disease (analogous to the cardiac panel for evaluating chest pain). Biomarkers may also serve to discern disease subtypes, identify etiologies, predict clinical outcomes, allow for risk stratification and prognostication, and monitor the response to interventions. Studies to validate the sensitivity and specificity of these biomarkers in clinical samples from large cohorts and from multiple clinical situations are currently in progress, facilitated by the development of commercial tools for the reproducible measurement of these biomarkers across different laboratories. The widespread availability of such information promises to revolutionize renal care in both children and adults, and allow for the practice of personalized and predictive medicine at an unprecedented level.

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Table 1

Pediatric modified RIFLE (pRIFLE) criteria

	Pediatric Modified RIFLE Criteria	
	Estimated CCl (eCCl) by Schwartz formula	**Urine Output**
Risk	eCCl decrease by 25%	<0.5 ml/kg/hour for 8 hours
Injury	eCCl decrease by 50%	<0.5 ml/kg/hour for 16 hours
Failure	eCCl decrease by 75% or eCCl <35ml/min./1.73 m^2	<0.3 ml/kg/hour for 24 hours or anuric for 12 hours
Loss	Persistent Failure >4 weeks	
End Stage	End Stage Renal Disease (persistent Failure >3 months)	