Progression From Acute Kidney Injury to Chronic Kidney Disease: A Pediatric Perspective

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Although 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 multidimensional 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, liver-type fatty acid–binding protein, and kidney injury molecule-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.

Index Words: Acute kidney injury; Acute renal failure; Chronic kidney disease; Biomarkers; Neutrophil gelatinase-associated lipocalin; Kidney injury molecule-1; Liver-type fatty acid–binding protein

The epidemiology of pediatric acute kidney injury (pAKI) has mainly been studied in acutely ill hospitalized patients because nonoliguric forms of pAKI may be self-limited and go undetected in the outpatient setting. Although multicenter data do not exist, single-center studies from the 1980s and 1990s 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] pAKI epidemiologic study has 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 1980s through 2004,[4] likely because of 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 serum creatinine (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 SCr, 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 SCr) 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 toward an underestimation of AKI because 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

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SCr, much less than would be considered indicative of the need for RRT, are now recognized to contribute to poor outcomes. Chertow et al[14] showed that increases in SCr 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 SCr rise showed 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 SCr or estimated creatinine clearance and urine output (Table 1). The first study that 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 1 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.

Table 1. pRIFLE Criteria

	Estimated CCl (eCCl) by Schwartz Formula	Urine Output
Risk	eCCl decrease by 25%	<0.5 mL/kg/h for 8 hours
Injury	eCCl decrease by 50%	<0.5 mL/kg/h for 16 hours
Failure	eCCl decrease by 75% or eCCl <35 mL/min/1.73 m^2	<0.3 mL/kg/h for 24 hours or anuric for 12 hours
Loss	Persistent failure > 4 weeks	
End stage	ESRD (persistent failure > 3 months)	

Abbreviations: CCl, creatinine clearance; pRIFLE, pediatric risk, injury, failure, loss, end-stage renal disease; ESRD, end-stage renal disease.

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. Although, it is clear 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 with 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 a particularly high risk of developing substantial fluid overload.[21]

Children undergoing cardiopulmonary bypass are at a high risk of postoperative AKI, with recent studies showing 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 using 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 Chronic Kidney Disease

Pediatric chronic kidney disease (CKD) epidemiologic data can be derived from large national or multinational database registries