Acute Kidney Injury in Children

An Update on Diagnosis and Treatment

James D. Fortenberry, MD, MCCM[a,*], Matthew L. Paden, MD[a], Stuart L. Goldstein, MD[b]

KEYWORDS

• Acute kidney injury • Pediatrics • Continuous renal replacement therapy
• Fluid overload • Septic shock • Extracorporeal therapies

KEY POINTS

- The definitions and characterization of acute kidney injury (AKI) in children have advanced significantly over the past 2 decades.
- AKI is common in critically ill children and is associated with increased morbidity and mortality.
- AKI in association with sepsis, multiple organ involvement, and fluid overload carries heightened risk.
- Gene probes and urinary biomarkers represent intriguing tools for predicting and monitoring pediatric AKI, as well as potentially guiding treatment intervention.
- Treatment of AKI is problematic, but extracorporeal approaches in AKI and multiple organ system failure continue to grow in use and potential benefit.

"In the kidneys are seated reasonings, and there dwells in them the faculty of discernment; they distinguish truth from falsehood, and judge what is base and what is noble."

—Saint Ephraem (ca 306–373 CE)[1]

Ancient authors viewed the kidneys to be both the seats of reason and of discernment.[1] The kidneys, later termed "reins" in the English vernacular, were also seen as a source of divine punishment. Job described, among his many maladies, "my reins consume me."[1] Although our scientific understanding of the kidney has markedly evolved, we still find that the kidney does provide both a marker of outcome in critically ill adults and children, and a potential target for improving morbidity and mortality. This review focuses on updates in definition, epidemiology and outcomes, associated

[a] Critical Care Division, Department of Pediatrics, Emory University School of Medicine, Children's Healthcare of Atlanta at Egleston, 1405 Clifton Road North East, Atlanta, GA 30322, USA; [b] Center for Acute Care Nephrology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
* Corresponding author.
E-mail address: james.fortenberry@choa.org

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organ injury and sepsis, and treatment options for the critically ill child with acute kidney injury (AKI).

The profound clinical and translational research transformation observed in the AKI field over the past decade has been generated in large part by 3 major advancements: understanding that AKI is an independent risk factor for mortality, development and refinement of standardized multidimensional AKI definitions, and discovery and validation of novel urinary AKI biomarkers that reflect kidney damage before loss of kidney function. The concept that patients were dying "from" and not just "with" renal failure provided the impetus to change the terminology from acute renal failure (ARF) to AKI.[2] The acceptance of this terminology change in the research literature was quite rapid, and reflected a controversial paradigm shift in how to define the AKI syndrome clinically. A seminal publication by Chertow and colleagues[3] demonstrated increases in serum creatinine of as little as 0.3 mg/dL were independently associated with patient morbidity and mortality. These findings underscored the inadequacy of creatinine change as an early marker of disease. Price and colleagues[4] observed a similar association between a rise of 0.3 mg/dL in serum creatinine and poor outcomes in children with acute decompensated heart failure, where this rise conferred an adjusted odds ratio (OR) of 10.2 (95% confidence interval [CI] 1.2–61.1) for the combined end point of mortality or need to go on to mechanical circulatory support. Reliance on serum creatinine emanated from its use to estimate glomerular filtration rate to define stages of chronic kidney disease, guide medical intervention, and direct the initiation of maintenance renal replacement therapy. Because serum creatinine change occurs only with more than 50% loss of functional nephron mass, it is not surprising that small changes in this functional marker can portend poor prognoses, leading to the need to standardize the AKI definition reflecting these associations.

In 2004, the Acute Dialysis Quality Initiative, a work group of nephrologists and critical care physicians, developed the first consensus multidimensional AKI definition, termed the RIFLE criteria.[5] RIFLE has 3 AKI staging strata, Risk, Injury, Failure, and 2 outcome criteria, Loss and End-Stage Kidney Disease. AKI development by RIFLE (RIFLE-R) is defined as a 50% rise in serum creatinine (or 25% decrease in estimated creatinine clearance) over baseline or by urine output of less than 0.5 mL/kg per hour for 6 hours. RIFLE-I and RIFLE-F are each defined by greater changes in creatinine or urine output (UOP). Studies in adult patients in many different settings, including the intensive care unit (ICU), emergency center, and post cardiac surgery, have validated the RIFLE criteria. A recent literature review of these studies in more than 500,000 patients demonstrated increased independent mortality for each increasing RIFLE strata.[6] In 2007, we developed and validated a pediatric modified version of the RIFLE criteria (pRIFLE) in 150 critically ill children receiving invasive mechanical ventilation.[7] In this study, children who developed pRIFLE-I or pRIFLE-F had higher mortality or more prolonged AKI than patients with pRIFLE-R or no AKI. A recent systematic review of 11 pediatric studies comprising nearly 10,000 patients (ICU, emergency center, post cardiac surgery, and nephrotoxic medication–associated AKI) revealed similar associations, although the application of pRIFLE was inconsistently applied in these studies.[8]

The RIFLE was modified by the Acute Kidney Injury Network (AKIN) in 2007 to include a 0.3 mg/dL serum creatinine rise in less than 48 hours for the AKI definition (**Table 1**).[9] The pRIFLE and AKIN definitions have been used in pediatric studies, and yield similar results; RIFLE-I (AKIN Stage II) or worse is associated with increased patient morbidity.[10–12] In 2012, an international guideline developed by the Kidney Disease Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group harmonized RIFLE, AKIN, and pRIFLE into a single standardized definition (see **Table 1**).[13]