Acute Kidney Injury in Children

Scott M. Sutherland and David M. Kwiatkowski

Acute kidney injury (AKI) has become one of the more common complications seen among hospitalized children. The development of a consensus definition has helped refine the epidemiology of pediatric AKI, and we now have a far better understanding of its incidence, risk factors, and outcomes. Strategies for diagnosing AKI have extended beyond serum creatinine, and the most current data underscore the diagnostic importance of oliguria as well as introduce the concept of urinary biomarkers of kidney injury. As AKI has become more widespread, we have seen that it is associated with a number of adverse consequences including longer lengths of stay and greater mortality. Though effective treatments do not currently exist for AKI once it develops, we hope that the diagnostic and definitional strides seen recently translate to the testing and development of more effective interventions.

Key Words: Acute kidney injury, Child, Pediatrics

INTRODUCTION

Historically, the term acute kidney failure was used to describe an abrupt decline in kidney function hallmarked by reduced excretion of waste products, disordered electrolytes, and disrupted fluid homeostasis. Regrettably, this term poorly described the phenomenon of kidney injury and disease, and furthermore, it proved too vague a definition. Clinically, there was a lack of consensus, and academically, diagnostic criteria were inconsistently applied. In 2004, however, the Acute Dialysis Quality Initiative group replaced acute kidney failure with the term acute kidney injury (AKI).[1] This more effectively described the disease state, and the Acute Dialysis Quality Initiative used the opportunity to create the first consensus definition for AKI which they termed the Risk, Injury, Failure, Loss, End Stage (RIFLE) criteria.[1] Though RIFLE pertained only to adults, pediatricians have since helped optimize the definition of AKI across the age spectrum. The development of broadly relevant AKI diagnostic strategies has proved to be a tremendous boon to the nephrology and critical care communities. Nowhere has this benefit been more pronounced than in the realm of pediatric AKI. Once plagued by a lack of data and inconsistent methods, the last decade has seen tremendous growth in our knowledge regarding AKI in hospitalized children. The goal of this manuscript is to describe the current state of pediatric AKI knowledge and to highlight differences between the disease in adults and children.

DEFINING ACUTE KIDNEY INJURY IN CHILDREN

Following the publication of the RIFLE criteria, a group of pediatric nephrologists and intensivists developed a modified AKI definition for children which they termed the pediatric RIFLE (pRIFLE) criteria.[2] The pRIFLE staging criteria are shown in Table 1. From this point forward, the pediatric and adult communities worked together toward a harmonized definition. This process culminated in the development of the Kidney Disease Improving Global Outcomes (KDIGO) classification system.[3] KDIGO unified the existing definitions, creating a single diagnostic standard that was applicable to both adults and children (Table 1). Great strides have been made to standardize the definition of AKI, and it is now imperative that all studies utilize a consensus classification system.

The importance of using a single definition is exemplified by a pediatric study that compared the incidence of AKI in hospitalized children using the pRIFLE, AKIN, and KDIGO definitions.[4] The incidence of AKI ranged from 37% to 51% depending on the definition employed, and interdefinitional agreement was as low as 77%. Each definition has theoretical advantages and disadvantages; however, the need to move toward the use of a single definition is unambiguous. It is our opinion that the best currently available data support the use of the KDIGO criteria to diagnose AKI in children. This was the definition used by the Assessment of Worldwide AKI, Renal angina, and Epidemiology (AWARE) study, the largest and most comprehensive epidemiologic analysis of AKI in children performed to date.[5] Use of KIDGO allows the entire AKI community to apply the same definitional rigor to their populations and will allow more effective comparative studies.

DIAGNOSING ACUTE KIDNEY INJURY IN CHILDREN

Creatinine

In practice, the diagnosis of AKI is typically made based upon an increase in serum creatinine levels. At this point, a number of studies have demonstrated that creatinine is a functional biomarker that is insensitive to kidney tubular injury. Commonly, significant elevations are not apparent until 24-48 hours after the inciting insult.[6-8] In pediatrics, this is further complicated by the fact that children have low serum creatinine values at baseline which can be exaggerated by malnutrition and fluid overload.[9-11] As a result, despite substantial relative increases, elevated values do not register as abnormally high; creatinine can

From the Division of Nephrology, Department of Pediatrics, Stanford University, Palo Alto, CA; and Division of Cardiology, Department of Pediatrics, Stanford University, Palo Alto, CA.

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Address correspondence to Scott M. Sutherland, MD, Division of Nephrology, Department of Pediatrics, Stanford University Medical Center, 300 Pasteur Drive, Room G-306, Palo Alto, CA 94304. E-mail: suthersm@stanford.edu

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double or triple and remain within the laboratory defined normal range. Despite these limitations in children, a relative change in serum creatinine remains the principal method of diagnosing AKI.

Urine Output and Oliguria

In addition to the creatinine-based AKI criteria, both pRIFLE and KDIGO include urine output (UOP) parameters. Until recently, the vast majority of pediatric AKI studies did not utilize these urinary criteria.[4,12] This is likely related to a number of pediatric-specific issues. The first is that many pediatric intensive care unit (ICU) patients and nearly all acute care patients do not have Foley catheters in place. There has been a push to avoid bladder catheter use in hospitalized children in order to prevent urinary tract infections; additionally, many practitioners are reluctant to place them in kids given the invasive nature of the procedure. Second, especially in small children outside of the ICUs, UOP may be documented as a void count rather than volumetrically. However, the more recently published AWARE study clearly demonstrated that disregarding the UOP criteria leads to an underdiagnosis of AKI. In this study, isolated use of the creatinine criteria would have missed over a third of AKI cases.[5] Thus, despite the challenges, oliguria remains an integral part of AKI diagnosis in children and decreases in UOP should prompt evaluation of kidney function and a search for injurious events.

CLINICAL SUMMARY

- Acute kidney injury (AKI) is increasingly common in hospitalized children, and recent standardization of the definition has improved our epidemiologic understanding of the disease.
- AKI has traditionally been diagnosed based upon an increase in serum creatinine levels; however, recent data demonstrate the significance of oliguria in recognizing AKI and the potential benefit of using novel urinary biomarkers of kidney injury.
- In hospitalized children, AKI has been associated with prolonged duration of mechanical ventilation, longer lengths of stay, and greater mortality; sequelae may include CKD.
- Children with AKI who require renal replacement therapy are a unique population that tends to have a poorer prognosis.

Biomarkers

As previously stated, creatinine is a marker of kidney function, not injury, and there has been a push to identify biomarkers of structural injury to facilitate earlier identification of kidney tubular damage. While the majority of data available are from adult populations, it is helpful to understand the pediatric-specific aspects. Neutrophil gelatinase-associated lipocalin (NGAL) is one of the most extensively studied biomarkers in children, especially in the cardiac surgery population. NGAL may be elevated as early as 2 hours after cardiopulmonary bypass and has been shown to be associated with AKI severity, duration of mechanical ventilation, and length of ICU stay.[13,14] In children with septic shock and contrast-induced nephropathy, as well as those undergoing solid organ transplantation, NGAL has been shown to be superior to creatinine for early detection of AKI.[15-18] NephroCheck (Astute Medical, San Diego, California) is a urine assay that assigns a risk score derived from the product of the concentration of insulin-like growth factor-binding protein-7 and tissue inhibitor of metalloproteinases-2, two inducers of cell cycle arrest. While the test is only FDA approved for use in adults, the few small pediatric studies available demonstrate that the risk score effectively predicts AKI in children.[19-21] Interestingly, several studies suggested that the threshold score in children is higher (0.7-0.8 $[ng/mL]^2/1000$) than it is in adults (0.3 $[ng/mL]^2/1000$).[20,22] While few urinary biomarkers are commercially available and none are approved for use in children, it is apparent that these assays will be a significant part of AKI diagnostic strategies and risk profiling in the near future.

PATHOPHYSIOLOGY OF PEDIATRIC ACUTE KIDNEY INJURY

The pathophysiology of AKI is multifactorial and incompletely understood. The most frequent and best-studied insults, however, are hemodynamic perturbations that result in kidney ischemia. The kidney modulates blood flow via neurohormonal feedback pathways capable of regulating kidney arteriolar constriction and dilation, thus maintaining relatively consistent perfusion pressure. This process, however, is less effective at extremes of blood pressure and may be hampered by medications such as vasoactive agents, steroids, nonsteroidal anti-inflammatory drugs, and renin-angiotensin-aldosterone system inhibitors. This reduced effectiveness is also seen in the setting of proinflammatory states such as following cardiopulmonary bypass or in patients with sepsis.[23] In hospitalized children, use of the aforementioned medications is ubiquitous and inflammatory conditions are common. Thus, in pediatric inpatients, the homeostatic feedback mechanisms aimed to preserve adequate blood pressure may operate under maladaptive conditions. While this mechanism is similar in both adults and children, there are age-related physiologic differences that bear mention. The first is nephrogenesis, the process by which nephrons are developed, which it is not complete until the 34th-36th week of gestation. Children born earlier than this have an incomplete nephron mass and are particularly susceptible to hemodynamic changes. This susceptibility is enduring since the extrauterine environment is less conducive to nephrogenesis, and these patients will never have a full complement of nephrons.[24] The second aspect that affects pediatric AKI risk is the fact that glomerular filtration rate (GFR) and tubular function change over time.[24,25] GFR at birth is 10-20 $mL/min/1.73m^2$, and while it gradually increases, it does not reach the full adult level of function (100-120 $mL/min/1.73m^2$) until 2 years of age.