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Is Acute Kidney Injury a Harbinger for Chronic Kidney Disease?

David T. Selewski¹, Dylan M. Hyatt², Kevin M. Bennett³, and Jennifer R. Charlton⁴

¹Department of Pediatrics & Communicable Diseases, University of Michigan Medical School, Ann Arbor, Michigan

²University of Virginia, School of Medicine, Charlottesville, VA

³University of Hawaii at Manoa, Department of Biology, Honolulu HI

⁴Department of Pediatrics, Division of Nephrology University of Virginia, Charlottesville Virginia

Abstract

Purpose of review—Despite abundant evidence in adults, the relationship between acute kidney injury (AKI) and chronic kidney disease (CKD) remains unanswered in pediatrics. Obstacles to overcome include the challenges defining these entities and the lack of long-term follow up studies. This review focuses on pediatric populations at high-risk for AKI, the evidence of the long-term effect of AKI on renal health, and biomarkers to detect renal disease.

Recent findings—AKI in critically ill children and neonates is common and independently associated with adverse outcomes. Patients with diabetes and sickle cell disease along with neonates with necrotizing enterocolitis have been identified as high-risk for AKI. Preterm birth and neonates with AKI have signs of renal dysfunction early in childhood. Urinary biomarkers may identify AKI and CKD earlier than traditional biomarkers, but more work is necessary to determine their clinical utility. Promising technological advances including the ability to determine nephron number noninvasively will expand our ability to characterize the AKI to CKD transition.

Summary—AKI is common and associated with poor outcomes. It is probable that AKI is a harbinger to CKD in pediatric populations. However, we currently lack the tools to definitely answer this question and more research is needed.

Keywords

Acute kidney injury; chronic kidney disease; biomarkers

Corresponding author: Jennifer Charlton, MD, MSc, University of Virginia, Box 800386, Charlottesville, VA 22908, jrc6n@virginia.edu, 434-924-2096.

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INTRODUCTION

Acute kidney injury (AKI) has become increasingly recognized as an independent risk factor for adverse outcomes. However, whether AKI is a harbinger for the development of chronic kidney disease (CKD) is still under investigation in neonates, infants and children. The answer to this question remains elusive for many reasons: inconsistency in the definition of AKI, insensitivity of serum creatinine as a biomarker, time between AKI and the detection of CKD, and inability to noninvasively determine nephron endowment. Moreover, there is a general lack of tools to interrogate kidney health. This review focuses on the advancements made in the last year to describe the epidemiology, risk factors, and outcomes associated AKI expanding our understanding of AKI across the broad spectrum of illness severity in pediatrics. Finally, we will highlight studies in biomarkers and expanding research efforts to detect noninvasive tools to aid in the earlier detection of AKI and CKD.

Pediatric Intensive Care Unit

Until recently, the epidemiology of AKI in critically ill children has been limited to single-center retrospective studies. These studies have shown that AKI impacts between 10 to 40% of critically ill children and is associated with adverse outcomes¹⁻⁴. Published in 2017, the Assessment of Worldwide Acute Kidney Injury, Renal Angina, and Epidemiology (AWARE) study is a seminal study evaluating the incidence and outcomes associated with AKI in 32 pediatric intensive care units across the world. The incidence of AKI was 26.9%, with an incidence of severe AKI of 11.6%, in the 4683 patients evaluated. This study definitively showed that AKI in critically ill children and young adults is associated with adverse outcomes⁵. To date there is no long term follow-up of this particular multi-center cohort.

Data from single center studies continues to add to the growing evidence for permanent renal damage after AKI in children hospitalized in the pediatric intensive care unit (PICU)^{6,7}. Al-Otaibi et al assessed the 2-year outcome of a cohort of patients admitted to the PICU with a diagnosis of AKI (pRIFLE criteria)⁸. In this study with a high mortality rate (35%) and large dropout rate (44%), survivors at a 2 year follow up demonstrated many signs of renal dysfunction (73% with hypertension, 33% with proteinuria and 33% with some degree of renal impairment)⁸.

Congenital heart disease

Cardiac surgery associated-acute kidney injury (CS-AKI) commonly occurs following cardiac surgery and adversely impacts short-term and long-term outcomes. Several studies have evaluated perioperative risk factors and treatments associated with the development of AKI. Blinder et al performed a secondary analysis of the Safe Pediatric Euglycemia after Cardiac Surgery (SPECS) trial evaluating the incidence and impact of CS-AKI in the 799 enrolled patients⁹. This randomized controlled trial was performed at 2 centers and compared tight glycemic control versus those with standard of care¹⁰. The secondary analysis showed that CS-AKI occurred in 36% of patients, tight glycemic control did not protect against the development of AKI, and CS-AKI was associated with adverse outcomes. Interestingly, the incidence of CS-AKI was significantly different between the two participating centers (66% at the University of Michigan vs 15% at Boston Children's

Hospital, $p<0.001$) despite similar surgical complexity. Furthermore, University of Michigan patients with CS-AKI had shorter duration of ventilation, shorter ICU and hospital stays. This study suggests that there are likely significant practice pattern variations that may contribute to the development of CS-AKI and that all CS-AKI may not be created equal.

While the epidemiology of CS-AKI has been well published recent work has begun to focus on the long-term implications of CS-AKI for those who underwent congenital heart surgery. Hollander et al evaluated the impact of AKI on long term renal outcomes in 88 children who underwent an orthotopic heart transplant¹¹. In this study AKI occurred in 72% of patients and renal recovery was less likely for those with Stage 2 or 3 AKI. This study showed that non-recovery from AKI occurs more commonly in those with severe AKI and is associated with the development of CKD during the first year¹¹. Madsen et al recently published a longitudinal analysis of Danish registry data evaluating the impact of CS-AKI on the subsequent development of CKD in 382 patients¹². CS-AKI occurred in 33% and those with CS-AKI had a significantly increase risk of chronic kidney disease with an adjusted hazard ratio of 3.8 (95% CI 1.4,10.4). In adjusted analysis the CS-AKI group was significantly more likely to develop stage 2 CKD or higher, even when analysis was adjusted for age and severity of CHD¹². The concept that the duration of AKI may impact on the development of CKD has been further explored in adult cardiac studies where AKI lasting longer than 3 days was strongly associated with both development of CKD and increased mortality¹³. Duration of AKI was a stronger predictor of CKD development than traditional markers such as diabetes and hypertension¹³.

A confounder in the congenital heart disease population is that heart lesions are heterogenous, and some may directly impact renal development. Each study must recognize the risk of CKD even prior to CPB or AKI exposure and account for this in the relationship between AKI and CKD¹⁴.

Neonatal Intensive Care Unit

Neonatal AKI represents a very active area of research over the last several years with over 20 epidemiologic studies published in a variety of neonatal populations. More than the pediatric studies, the neonatal AKI studies have managed unique issues such as the most appropriate definition for AKI after birth, ongoing renal development, and medications and diagnoses almost exclusive to the neonatal intensive care unit. In single center studies¹⁵, very low birth weight infants, sick near-term neonates, neonates with perinatal asphyxia, infants with congenital heart disease and necrotizing enterocolitis (NEC)^{16–21} have been recognized as populations vulnerable to AKI. Published in September 2017, investigators at the University of Michigan demonstrated that over half of the neonates diagnosed with NEC developed AKI and those with AKI were more likely to die despite similar clinical care (HR: 2.4 CI 1.2-4.98, $p=0.009$)²¹.

In 2013 the Neonatal Kidney Collaborative (NKC) was created to address the differences and unique aspects of neonatal AKI. This group of neonatologists and nephrologists confirmed the impact of AKI on outcomes in critically ill neonates by the findings of the Assessment of Worldwide Acute Kidney injury Epidemiology in Neonates (AWAKEN) study published in 2017²². This international multi-center study described the epidemiology

and outcomes of AKI in critically ill neonates over a 3-month period from 24 centers. This study showed that AKI occurred in 30% of infants and varied with gestational age, occurring in 48% born at 22-28 weeks, 18% 29-35 weeks, and 37% born at 36 weeks. This study clearly demonstrated that neonatal AKI was independently associated with increased mortality and length of stay.

Although there are no long-term data from the neonates included in the AWAKEN study, three studies were published in the last year that focus on the long term renal health of those born preterm. Magsgood et al measured renal outcomes in extremely low birth weight (ELBW, <1000g) infants with and without a history of neonatal AKI, using changes in diastolic blood pressure and estimated glomerular filtration rate (eGFR) as the primary outcomes²³. In a retrospective analysis of participants had significantly higher diastolic blood pressures than those without AKI at NICU discharge, but there was no difference in the blood pressure of the children studied three years after discharge from the NICU and the presence of CKD was observed in 4% of patients, but did not correlate with AKI status²³. The lack of observed differences may have been attributable to the retrospective design of the study which only included participants with a follow up visit.

Bruel et al took a different approach to assessing the role of AKI in the long term renal health of a very low birth weight cohort²⁴. In this study the investigators assessed children who were enrolled in IRENEO, a prospective study conducted in 2013 where AKI was assessed. Their group defined AKI based on creatinine cut offs that varied with gestational age. Propensity-matching strategy to compare preterm children 3-10 years who did (n=25) and did not have AKI (n=49)²⁴. The investigators demonstrated smaller kidneys in the AKI group. However there was no difference between the AKI and no AKI groups in eGFR as assessed by serum creatinine even though 23% of the entire cohort had an eGFR of <90 ml/min/1.73m².

Although a smaller study, the Follow-up of Acute kidney injury in Neonates during Childhood Years (FANCY) study concluded that neonatal AKI was associated with the development of CKD²⁵. A cohort of 34 very low birth weight (VLBW, <1500g) infants, 20 of which experience AKI in the NICU and 14 that did not were assessed for renal dysfunction: proteinuria, hypertension, and low GFR. At an average age of 5 years, 26% had a GFR of <90 ml/min/1.73m² estimated by cystatin C. Exposure to AKI was associated with 4.5 times higher risk of renal dysfunction. Similar to previously reported adult studies, longer AKI (days with serum creatinine >1.0 mg/dl), the number of AKI episodes and the peak serum creatinine were all associated with long term renal dysfunction.

General Pediatric Populations

To understand the burden of AKI it is critical to describe the incidence and impact of AKI outside of the intensive care unit in general pediatric patient populations and those with chronic medical conditions. McGregor performed a study of 13,914 general pediatric admissions at a tertiary care hospital. In this study they showed that AKI occurred in at least 5% of admissions²⁶. AKI research has extended into other pediatric groups such as children with diabetes²⁷ and sickle cell disease^{28,29}.

Published in May 2017, 64% of the 164 children with type 1 diabetes who presented with diabetic ketoacidosis met AKI criteria²⁷. If AKI is a harbinger of CKD, these data are particularly frightening as they indicate an increased number of risk factors for CKD in a particularly vulnerable population. In the sickle cell population, another group at risk for CKD, AKI occurred in 8% of admissions for acute chest pain and 17% of admissions for vaso-occlusive pain crisis^{28,29}. The long term renal outcomes of pediatric patients with diabetes or sickle cell disease who have an AKI event have yet to be studied.

Noninvasive tools to Detect Renal Disease

Early detection is one of the greatest challenges surrounding the treatment of AKI and CKD. Serum creatinine, despite its well-known flaws, remains the most common biomarker for acute and chronic renal injuries. Presently, only urinary TIMP-2xIGFBP7 (tissue inhibitor of metalloproteinase 2 and insulin-like growth factor binding protein 7)³⁰ has been approved by the United States Food and Drug Administration for the specific detection of AKI. However, based on its performance in children, TIMP-2xIGFBP7 is only approved in patients over the age of 21 years. Therefore, the pediatric AKI research community continues to search for serum and urine biomarkers which can improve phenotyping of AKI and early detection of CKD. In the last year 2 studies have examined urinary biomarkers in neonates and children with the goal of early detection of AKI or CKD^{31,32}.

Despite the high prevalence of AKI in neonates who suffer perinatal asphyxia, investigators from Ireland hypothesized that many of these neonates may have AKI not detected by serum creatinine-based definitions³¹. Neonates with and without perinatal asphyxia (with n=82, without, n=10) were enrolled and several urinary biomarkers were assessed on days 0-3 and day 7. In the perinatal asphyxia group without AKI, neutrophil gelatinase-associated lipocalin (NGAL), on day 1 was higher than the control group. Additionally in the perinatal asphyxia group without AKI several urinary biomarkers such as epidermal growth factor (EGF), osteopontin (OPN), and uromodulin (UMOD) were lower than the control group and followed the trend of the perinatal asphyxia group with AKI. This study showed that cystatin C on day 2 strongly predicted AKI with an AUC of 0.89, $p < 0.001$. The neonates with the higher grades of encephalopathy had significantly high levels of cystatin C, NGAL and lower EGF in their urine than the lower grades of encephalopathy. This, like most biomarker studies, lacks long-term follow up.

The Follow-up Renal Assessment of Injury Long-term after Acute Kidney Injury (FRAIL-AKI) study evaluated the long-term renal function and urinary biomarker status in 51 children at mean of 7 years following cardiac surgery³². While there was no evidence in abnormalities of estimated glomerular filtration rates or proteinuria, this was the first long term follow up study to demonstrate persistent abnormalities in urinary biomarkers long after the cardiac surgery⁹. At follow up the AKI group demonstrated higher concentrations of IL-18, kidney injury molecule-1 (KIM-1), and liver-type fatty acid-binding protein (L-FABP) than the AKI-negative or healthy controls. Pre-operatively there was no difference in these urinary markers but NGAL, IL-18, KIM-1 and L-FABP were all significantly higher the AKI-positive group at 24 hours after surgery. The persistently elevated urinary markers

at 7 years after surgery suggests a role not only for the earlier detection of AKI with these markers but also the potential to use these markers to predict CKD outcomes³².

Medical imaging techniques are emerging as important tools to develop direct, noninvasive markers of kidney damage with development of either AKI or CKD. Some imaging techniques attempt to develop imaging surrogates of established histologic markers, such as glomerular or interstitial fibrosis, which can overcome the recognized limitations of biopsy- and post-mortem diagnosis^{33–37}. Other techniques have identified entirely new parameters for diagnosis in living subjects, including blood flow, glomerular filtration, and nephron number. Further work is needed to clinically assess renal reserve in children and renal growth as measured by sonography of the kidney may help but it still an imperfect surrogate of nephron number³⁸. However preclinical work has support the concept that nephron number may be measurable *in vivo*. The first direct *in vivo* measurement of glomerular number and volume in rodents using magnetic resonance imaging was published in 2017³⁹. As these new imaging technologies are developed, preclinical investigations are beginning to reveal new relationships between renal structure and function that are likely to impact patient diagnosis and care. Imaging thus has the potential to complement and improve upon existing blood and urinary markers of AKI and CKD. However larger studies of these biomarkers must be still be done to account for the heterogeneity of renal disease, kidney development, differences in sex, along with the appropriate validation.

CONCLUSIONS

Over the last year, evidence continues to demonstrate that AKI is common in neonates and children and is associated with poor outcomes. It is logical to believe that AKI is a harbinger to CKD in pediatric populations. However, we currently lack the long-term studies and tools to assess renal function to definitely answer this question.

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KEY POINTS

- AKI during childhood is common and associated with poor outcomes.
- There are findings of renal dysfunction during childhood in many groups who had AKI including those with congenital heart disease, born preterm or critically ill children.
- Further work is necessary to develop biomarkers of early AKI and CKD detection.