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An Update on Neonatal and Pediatric Acute Kidney Injury

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Abstract

Purpose of Review The purpose of this review is to highlight the major advances of pediatric and neonatal acute kidney injury (AKI) research over the last 5 years with particular interest in describing renal physiology, the definition of AKI, risk factors, epidemiology, interventions, and outcomes.

Recent Findings The utilization of standardized definitions of AKI has revolutionized our understanding of the incidence and impact of AKI. This has culminated in the seminal Assessment of Worldwide Acute Kidney Injury, Renal Angina and Epidemiology in critically ill children (AWARE), and Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) publications in pediatric and neonatal AKI, respectively. These studies have clearly shown an independent association of AKI with mortality in critically ill children and neonates. Recent work aimed at the prevention of AKI has demonstrated that nephrotoxic medication-induced AKI occurs commonly and can be prevented with protocolized renal function monitoring. This review also highlights advances in the early identification of patients at risk for the development of AKI via scoring systems (renal angina index), functional tests (furosemide stress test), or novel biomarkers. Furthermore, fluid overload has clearly been shown to impact outcomes in those with the most severe forms of AKI requiring renal replacement therapy. Recent single-center studies have highlighted that children with AKI are at increased risk of chronic kidney disease.

Conclusions The incidence and adverse impact of AKI on outcomes across critically ill pediatric and neonatal populations have been clearly established The importance of fluid overload in children with severe AKI requiring renal replacement therapy is clear. Children with AKI are at increased risk of chronic kidney disease and require long-term outpatient follow-up. As the impact of AKI has become clear, efforts have shifted to prevention of nephrotoxic-induced AKI, early identification, risk stratification (renal angina), and the development of novel biomarkers.

Keywords Acute kidney injury · Fluid overload · Pediatric neonate · Continuous renal replacement therapy

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Introduction

Acute kidney injury (AKI) is a sudden decrease in kidney function resulting in decreased glomerular filtration rate (GFR), build-up of nitrogenous waste products, abnormalities in electrolyte homeostasis, and dysregulation of fluid balance. Over the last 5 years, our understanding of the epidemiology and impact of AKI in a variety of pediatric populations have grown exponentially. It is now clear that even small disturbances in renal function can have a significant deleterious impact on outcomes. The purpose of this review is to highlight the major advances of pediatric and neonatal AKI research over the last 5 years with particular interest in describing renal physiology, the definition of AKI, risk factors, epidemiology, interventions, and outcomes.

Renal Physiology

To appreciate the risk factors and pathophysiology of neonatal and pediatric AKI, a basic discussion of normal pediatric and neonatal renal physiology as well as the pathophysiology of AKI is necessary. The complex physiology of the kidney is controlled through multiple feedback loops affecting renal blood flow (RBF), which in turn drives glomerular filtration, processing of solute and free water, and oxygen delivery to the individual filtering units of the kidney known as the glomeruli. The gatekeepers of the kidney are the afferent and efferent arterioles, controlling the blood flow to and from the glomeruli. Through the response to afferent dilatory factors (prostaglandins, nitric oxide, and bradykinin), and efferent constrictive factors (sympathetic activation, endothelin, and angiotensin II), the kidney attempts to maintain stable blood flow and steady glomerular filtration rate (GFR). Various disease processes and medications can alter this tight control and lead to injury through distorted renal perfusion or direct injury [1, 2].

An appreciation of the nuances of renal development and physiology is critical to understanding the mechanism and management of AKI in the neonatal period [3•]. Following birth, neonates undergo significant changes in RBF, GFR, and tubular function. As RBF increases, there are corresponding increases in the GFR, from a GFR of 10–20 ml/min/1.73 m^2 in neonates to 30–40 ml/min/1.73 m^2 by 2 weeks of life to an adult GFR by 2 years of age [4, 5]. The significantly reduced GFR in neonates may make this population particularly susceptibility to the development of AKI, especially when exposed to nephrotoxic medications.

With decreased RBF, the kidney compensates by attempting to expand extracellular volume by increasing water resorption. The resorption of water is driven by the increases absorption of sodium and urea. Sodium retention is driven by renin angiotensin system and increased sympathetic nerve activity. Antidiuretic hormone drives the reabsorption of urea.

These reflex mechanisms explain the utility of the fractional excretion of sodium and urea to help differentiate the etiologies of AKI (pre-renal vs. intrinsic, Table 1). The immaturity of these compensatory mechanisms in neonates explains why neonates have unique urinary findings (ex: fractional excretion of sodium) in AKI.

Akin to the selective vulnerability zones in ischemic brain injury, the kidney has particularly vulnerable areas of damage. The most highly susceptible area of damage in the kidney are the third segment of the proximal tubule and the medullary thick ascending limb of the Loop of Henle, while the glomeruli are relatively preserved. These areas are particularly impacted because of their high metabolic demand and decreased ability to convert to anaerobic metabolism. The most conspicuous morphologic features of AKI involve the proximal tubule. These changes include the loss of the proximal tubule brush border, patchy loss of tubule cells, focal areas of proximal tubule dilation with distal tubular casts, and areas of cellular regeneration [6].

Definition

Acute Kidney Injury

The most critical advance in AKI research over the last 30 years has been development and utilization of standardized definitions for AKI to better describe the spectrum of organ injury that can occur. During this time, the definition of AKI has evolved from more than 35 divergent definitions to the currently utilized modern Kidney Disease: Improving Global Outcomes (KDIGO) AKI definition (Table 2). Since 2004, there have been a series of definitions followed by refinements to systematically define AKI including: the Risk, Injury, Failure, Loss of Kidney Function, and End-stage kidney disease (RIFLE, 2004), *pediatric* RIFLE (2007), and the Acute Kidney Injury Network (AKIN, 2010) definitions [7–9]. Most recently, the KDIGO AKI definition has been put forth as a harmonized consensus definition, incorporating important aspects of each of the previous definitions [10••]. All of these systems define AKI according to stage of severity based on graded changes in serum creatinine (SCr) or estimated creatinine clearance from a defined baseline and/or urine output. The KDIGO definition has been validated in single-center studies and the international multicenter Assessment of Worldwide Acute Kidney Injury, Renal Angina and Epidemiology in critically ill children (AWARE) study [11, 12••]. Consensus expert opinion has endorsed the KDIGO AKI definition as the definition that should be utilized for research and clinical care in pediatric patients going forward [13, 14].

Just as the definition of pediatric AKI has evolved, the neonatal AKI definition has similarly progressed, particularly

Table 1 Calculating and Interpreting the fractional excretion of sodium and urea

$$\text{Fractional Excretion of Sodium, } \% = \frac{(\text{Urine Sodium} * \text{Plasma Creatinine})}{(\text{Plasma Sodium} * \text{Urine Creatinine})} * 100$$

$$\text{Fractional Excretion of Urea, } \% = \frac{(\text{Urine Urea} * \text{Plasma Creatinine})}{(\text{Plasma Urea} * \text{Urine Creatinine})} * 100$$

Interpretation

Test	Pre-renal AKI	Intrinsic AKI
Fractional excretion of sodium (FeNa)	< 1% (neonates < 2%)	> 2% (neonates > 2.5%)
Fractional excretion of urea (FeUrea)	< 35%	> 50%

over the last 5–10 years. As interest in neonatal AKI has increased, investigators have abandoned the previously utilized, arbitrary definition of neonatal AKI (defined by a single SCr > 1.5 mg/dl) and adopted the staged definition put forth by Jetton et al., the neonatal modified KDIGO AKI definition (Table 2) [3•, 15]. This system is based upon a rise SCr above a previous trough. The neonatal modified KDIGO AKI criteria is currently the most widely accepted definition for neonatal AKI after a 2013 National Institute of Diabetes and Digestive and Kidney Diseases-sponsored neonatal AKI workshop endorsed this definition [16]. It has subsequently been validated in the multicenter Assessment of Worldwide Acute Kidney injury Epidemiology in Neonates (AWAKEN) study [17••]. While the neonatal modified KDIGO definition remains the current definition to utilize in clinical care and for research purposes, this definition will likely be refined with further study.

Importantly, the AWARE and AWAKEN studies have highlighted the contribution of urine output to the diagnosis of AKI. While oliguria has consistently been a poor prognostic indicator in critically ill children, urine output was often not reported or collected in single-center studies evaluating the epidemiology of AKI [18–23]. These AWARE and AWAKEN studies clearly demonstrate that urine output measures are critical to the identification of clinically relevant AKI that would be missed if SCr alone was assessed [12••, 17••].

Fluid Overload

Pediatricians have led the way in identifying fluid overload (FO) as an independent risk factor for adverse outcomes in critically ill patients. This effort began by demonstrating a clear association between the degree of FO at continuous renal replacement therapy (CRRT) initiation and increased mortality and now has extended across all of critical care. The two commonly utilized methods to calculate FO include cumulative fluid balance since ICU admission and a weight-based methodology [24, 25]. The earliest and most commonly

utilized method defines FO based on cumulative fluid balance since ICU admission [24]:

%Fluid Overload

$$= \frac{\text{Sum of daily (Fluid in−Fluid out)(liters)}}{\text{ICU Admission Patient Weight (kilograms)}} * 100$$

A second method to define FO utilizes change in weight from a baseline weight (ICU admission weight, hospital admission weight, or birthweight) [25–28]:

%Fluid Overload

$$= \frac{\text{Daily Weight−ICU Admission Weight}}{\text{ICU Admission Weight}} * 100$$

In order to accurately calculate FO based on changes in weight, it is critical to have standardized methods for the measurement of daily weights [29]. While either fluid balance methodology or weight-based methodology may be utilized in pediatric patients, in the neonatal population, weight-based method is favored [30, 31].

Risk Factors, Epidemiology, and Outcomes

Over the last two decades, there has been an increasing divergence in the etiologies and outcomes of AKI in hospitalized children in developed countries when compared to developing countries. Dehydration and primary renal diseases remain the most common etiologies for AKI in developing countries, but major epidemiologic studies are lacking. A global effort with a particular focus on low- to middle-income countries termed "0by25 initiative" has been undertaken and will increase our understanding of the epidemiology and outcomes of AKI in developing countries. This effort aims to eliminate preventable deaths from AKI by 2025 by employing strategies that allow for the timely diagnosis and treatment of potentially reversible AKI [32]. In developed countries, the etiology of AKI is more clear and most often multifactorial in nature

Table 2 Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury (AKI) Classification including neonatal modifications

Stage	Pediatric		Neonatal	
	Serum creatinine	Urine output	Serum creatinine	Urine output[a]
1	1.5–1.9 times baseline OR ≥ 0.3 mg/dl increase*	< 0.5 ml/kg/h for 6–12 h	≥ 0.3 rise within 48 h or ≥ 1.5–1.9 × rise from baseline (previous lowest value) within 7 days	≤ 1 ml/kg/h for 24 h
2	2.0–2.9 times baseline	< 0.5 ml/kg/h for ≥ 12 h	2.0–2.9 times baseline	≤ 0.5 ml/kg/h for 24 h
3	3.0 times baseline OR Increase in serum creatinine to ≥ 4.0 mg/dl OR Initiation of renal replacement therapy OR In patients < 18 years, decrease in eGFR to < 35 ml/min per 1.73 m²	< 0.3 ml/kg/h for ≥ 24 h OR Anuria for ≥ 12 h	≥ 3 × rise from baseline or serum creatinine ≥ 2.5 mg/dl or renal replacement therapy initiation	≤ 0.3 ml/kg/h for 24 h

[a] Urine output criteria utilized in the AWAKEN study. May also consider utilizing the pediatric urine output data for neonates if the granularity of data allows

* Increase in SCr by X0.3 mg/dl within 48 hours; or K Increase in SCr toX1.5 times baseline, which is known or presumed to have occurred within the prior 7 days

mg/dl milligrams per deciliter, *eGFR* estimated golumerular filtration rate, *ml/min* milliliters per min, *ml/k/h* milliliters per kilogram

reflecting the increasing medical complexity in neonatal and pediatric patients. Our understanding of risk factors, epidemiology, and outcomes associated with AKI across a variety of neonatal and pediatric populations has expanded exponentially over recent years. Here, we will highlight some of these advances in particular groups.

General Pediatric Critical Care

Among critically ill pediatric populations, the incidence of AKI is variable depending on the sub-population studied, with an incidence as high as 82% in the sickest patients (those requiring mechanical ventilation) [9]. Three large single-center, retrospective studies have shown the incidence of AKI in more general pediatric critical care populations to range from 10 to 19.1% [11, 21, 23]. Each of these studies document an association between AKI and adverse outcomes, including increased length of mechanical ventilation, intensive care unit (ICU) length of stay, and mortality. In a study of 3009 critically ill children, Selewski et al. reported an association between AKI and increased mortality (OR 3.4), confirming the findings previously reported by Alkanderi et al. in 2106 children [11, 21]. Varying incidence with similar associations has been reported in a variety of other critically ill pediatric sub-populations including, but not limited to, those with sepsis, cardiac arrest, and respiratory failure [19, 33–37]. These studies were often limited in their size or single center in nature, which makes generalizability challenging.

In 2017, the AWARE study was published; this international prospective, multicenter study of children and young adults (3 months to 25 years) evaluated the incidence and impact of AKI over a 3-month period in 32 centers across 4 continents [12••]. The overall incidence of AKI in this population was 26.9%, with 11.6% having severe AKI (stage 2 or 3). Severe AKI conferred an increased risk of death by day 28 after

adjustment for 16 covariates (aOR, 1.77) and was also associated with increased length of mechanical ventilation. Furthermore, this is the largest study to date to evaluate the contribution of urine output to the diagnosis of AKI. In this study, 67% of patients that developed AKI by urine output criteria did not meet SCr-based AKI criteria; the diagnosis of AKI would have been missed had SCr alone been used to diagnose AKI in these children. More importantly, these patients had worse outcomes than those without AKI. This study suggests that it is essential to incorporate accurate urine output measurement into AKI diagnosis in critically ill patients. The AWARE study has cemented the findings of multiple single-center studies demonstrating definitively that AKI is associated with increased length stay, duration of mechanical ventilation, and mortality.

Congenital Cardiac Surgery

AKI associated with congenital cardiac surgery (CS-AKI) has been well studied over the last 15 years, and it is clear that CS-AKI has defined risk factors (cardiopulmonary bypass (CPB), surgical complexity, and perioperative morbidities) and is associated with adverse outcomes [18, 22, 38–43]. Interestingly, the frequency of CS-AKI varies dramatically by study, ranging from 15 to over 50% despite seemingly similar surgical complexity [18, 22, 38–42]. Recently, a secondary analysis of the Safe Pediatric Euglycemia after Cardiac Surgery (SPECS) trial evaluating the incidence and impact of CS-AKI in 799 patients provided insight into potential explanations for this phenomenon [18]. The SPECS trial was a randomized controlled trial comparing the impact of tight glycemic control on outcomes following cardiac surgery at two centers. The incidence of CS-AKI was 36% in the study, with significant differences between institutions (66% at University of Michigan vs 15% Boston Children's Hospital, *p* < 0.001). Perioperative characteristics were similar between the centers with the

exception of the utilization of intraoperative modified ultrafiltration (91% at University of Michigan vs 8% Boston Children's Hospital, $p < 0.001$). CS-AKI at the University of Michigan resolved quicker and did not confer the same negative consequence as it did at Boston Children's. The authors theorized that modified ultrafiltration may prevent the development of FO while resulting in a short-lived rise in SCr on postoperative day 1 potentially driven by fluid shifts [18]. While this study suggests that all CS-AKI is not created equal, it will be important to further delineate the impact of intraoperative practices on the development of CS-AKI and to investigate incorporation of biomarkers into its definition, to help identify sub-phenotypes that could drive post-CS-AKI care.

Extracorporeal Membrane Oxygenation

Children receiving extracorporeal membrane oxygenation (ECMO) represent some of the most critically ill patients and are at high risk of developing AKI for reasons inherent to their underlying disease process (hypotension, sepsis, cardiac failure, nephrotoxic medication exposure) as well as for factors related to provision of ECMO (blood flow characteristics, systemic inflammation, hypercoagulable state, hemolysis) [44]. Early single-center reports confirmed this by documenting that infants requiring ECMO following congenital heart surgery and neonates with congenital diaphragmatic hernia (CDH) receiving ECMO have an incidence of AKI of up to 72% [45, 46]. In a large 14-year study of 242 ECMO-treated neonates, 64% experienced AKI [47]. Each of these single-center studies demonstrated an association between severe AKI and worsened outcomes. The Kidney Interventions During Extracorporeal Membrane Oxygenation (KIDMO) study group performed a retrospective, observational, multicenter cohort study of 834 neonatal and pediatric patients receiving ECMO at 6 centers over 5 years [48••]. In this cohort, the incidence of AKI was 74%, with 93% of episodes occurring within 48 h of cannulation. There was also a significant association between AKI and outcomes including mortality (aOR 2.5) and length of ECMO [48••].

Subsequently, the KDIMO study group evaluated the epidemiology and impact of FO on outcomes [49•]. This study showed that FO is common in children on ECMO with median peak FO of 30.9% (IQR 15.4–54.8); additionally, peak FO predicted in-hospital mortality and increased length of ECMO after multivariable analysis [49•]. This data, coupled with previous work demonstrating that earlier CRRT initiation improves fluid management and prevents FO in neonates on ECMO, raises questions about the role for early initiation of CRRT in children on ECMO [50, 51]. A multicenter trial evaluating this question is greatly needed.

Neonates

Over the past 10 years, neonatal AKI has seen a rapid expansion of our knowledge on the subject with dozens of studies examining risk factors, epidemiology, and outcomes associated with AKI in a variety of at-risk populations (Table 3). Specific neonatal populations that have been studied include sick term/near term infants, neonates with perinatal asphyxia, very low birthweight infants (VLBW), extremely low birthweight infants, and neonates with concurrent disease processes including necrotizing enterocolitis (NEC), CDH, and intraventricular hemorrhage (IVH). In each of these studies, AKI occurred commonly and was associated with adverse outcomes (length of stay, mechanical ventilation, mortality). Furthermore, in those with perinatal asphyxia undergoing therapeutic hypothermia, AKI has been shown to be independently associated with adverse neurologic outcomes including hypoxic-ischemic MRI findings at postnatal days 7–10 [70]. While these studies provide important epidemiologic information, they are limited in their single-center nature, again making generalizations difficult.

In 2017, the AWAKEN study was published by the Neonatal Kidney Collaborative [17••]. This study was performed at 24 centers worldwide and included all neonates admitted to a level II or III neonatal intensive care units (NICU) who received intravenous fluids for ≥ 48 h between January 1 and March 31, 2014. The incidence of AKI was 30% in the 2022 neonates and differed by gestational age (48% in those < 29 weeks, 18% in those 29 weeks to < 36 weeks, 37% in those ≥ 36 weeks). Multivariable analysis documented a clear association between AKI and outcomes including mortality (aOR 4.6, $p < 0.0001$) and increased length of stay (adjusted parameter estimate 8.8 days, $p < 0.0001$). This was the first study to systematically evaluate the inclusion of urine output criteria in the definition of neonatal AKI and showed that urine output contributes significantly to the definition of AKI in neonates. Another critical finding in this study is the broad center-level variability in serum creatinine testing, varying from a median of 1 SCr measurement per neonate (IQR 1.1) to 11 [3•, 26] during the entirety of NICU admission. Furthermore, 10 centers had a median number of SCr checked of ≤ 3. The AWAKEN study provides critical epidemiologic data and will serve to continue to expand our knowledge about multiple topics including a refinement of the definition of neonatal AKI, the impact of fluid balance, and the impact of AKI on a variety of outcomes (bronchopulmonary dysplasia, IVH) [17••].

General Pediatric and Specific Populations

With the recognition of the incidence and impact of AKI on outcomes in critically ill populations, there has been

increasing interest in studying the impact of AKI outside of the critical care setting. In a study of 13,914 non-critically ill pediatric admissions between 2011 and 2012 at a tertiary care hospital, the incidence of AKI was found to be at least 5%. More importantly, this study showed that 17% of admissions had ≥ 2 serum creatinine values checked. Of those that had two or more SCr checked, the incidence of AKI was 30%. The authors argue that there needs to be improved surveillance and recognition of AKI on general pediatric floors [75]. In a single-center study of pediatric emergency department visits over 1 year at a large academic center, the incidence of community-acquired AKI was 1.5%. This study also showed that only 19% of these episodes were recognized by the treating physician [76]. Each of these studies argues for improved recognition and surveillance in general pediatric populations.

Nephrotoxic Medication Exposure

Children exposed to nephrotoxic medications represent a patient population at particular risk for AKI irrespective of their location in the hospital. It is critical that providers understand this risk and identify those at risk, as nephrotoxic medication exposure may be the single most modifiable risk factor for the development of AKI in hospitalized patients. Epidemiologic studies clearly identify subpopulations at risk including, but not limited to, those exposed to aminoglycosides, non-steroidal anti-inflammatory drugs, vancomycin with piperacillin/tazobactam, or multiple nephrotoxins concurrently [77–79]. Recent work has suggested that AKI induced by nephrotoxic medications has long-standing consequences with evidence of residual kidney damage at 6-month follow-up in 70% of a cohort of 100 children with nephrotoxic medication-induced AKI [80].

The magnitude of this problem led to the development and implementation of electronic medical record (EMR) surveillance initiatives aimed at identifying and ultimately decreasing the rates of nephrotoxic medication-induced AKI. In 2013, Goldstein et al. first reported on a surveillance system called Nephrotoxic Injury Negated by Just-in-time Action (NINJA). This study utilized the EMR to identify patients at risk of AKI (intravenous aminoglycosides ≥ 3 days or ≥ 3 nephrotoxic medications) and subsequently trigger renal function monitoring with daily SCr. In the initial and follow-up studies, the authors showed that such a system could be deployed through a multidisciplinary effort on an institutional level and the quality improvement initiative could be sustained over time [81, 82••]. The sustained effort resulted in a 64% decrease in AKI rate over the 43-month study period [82••].

Early Recognition, Therapeutics, and Interventions and Advancements

Early Recognition

Despite significant advances in our understanding of the risk factors, epidemiology, and outcomes associated with AKI, there has been little progress in the development of new therapeutic options for neonates and children with AKI. Our current therapeutic repertoire is largely limited to patient optimization (nutrition, renal perfusion), prevention (decreased nephrotoxic medication exposure, improved surveillance), and management of sequelae (FO, etc.) The failure to develop and execute successful interventional trials stems at least in part from the utilization of SCr as a biomarker. SCr has a number of limitations including a delay in rise after insult, and, more importantly, it is solely a marker of kidney function instead of injury. Based on these characteristics, it is not surprising that studies utilizing rise in SCr as entry criteria, or even as endpoints, have been unsuccessful. As a result, there has been a significant amount of research to identify novel biomarkers to allow for the earlier recognition and diagnosis of AKI [83].

The identification and study of the "novel" AKI biomarkers largely began in patients undergoing CPB where insult timing is largely known. These biomarkers detect damage, rather than describe function, and include urine neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1, interleukin 18, liver fatty acid binding protein, and others [84]. Each of these biomarkers has been shown to rise 2–12 h following an insult, and each was predictive of AKI at 48 h in several studies [84]. As with any biomarker in medicine, when these are used indiscriminately, they perform very poorly. However, when used in conjunction with risk factor assessments, these biomarkers provide significant promise to improve care and clinical trials in AKI [84].

A critical step to improve the care of children with AKI is to shift the focus to earlier identification of AKI. While biomarkers undoubtedly play a role in this, it is critical to risk-stratify patients in order to optimally deploy biomarkers. The first effort to systematically risk-stratify critically ill pediatric patients has come in the form of the Renal Angina Index (RAI). The RAI is a scoring system derived from existing literature based on clinical risk factors for AKI (pediatric ICU admission, stem cell transplant, mechanical ventilation, ionotrope utilization) and signs of injury (FO, rise in SCR; Fig. 1) [85–87]. In 2014, Basu et al. described the derivation and validation of the RAI in four cohorts of critically ill children. In this study, the RAI performed very well with a negative predictive value of > 92% for severe day 3 AKI [86]. A follow-up single-center, prospective trial in 184 critically ill children further validated the RAI and, more importantly, showed that the addition of urinary NGAL significantly

Table 3 Neonatal acute kidney injury publications over the past 5 years

Study	Population (n)	% patients with AKI	Findings
Chowdhary, 2018 (n = 483) [52]	ELBW infants	56%-pRIFLE 59%-AKIN 60%-KDIGO	AKI is associated with increased mortality, prolonged NICU stay, and poor growth in ELBW infants regardless of definition used to diagnose AKI.
Velazquez, 2018 (n = 151) [53]	Preterm infants admitted to NICU who received PDA screening	27%	Preterm infants with hemodynamically significant PDA had similar rates of AKI and HTN as infants with no or non-hemodynamically significant PDAs.
Bakhoum, 2018 (n = 77) [54]	Premature infants with NEC	42.9%	AKI is common among premature infants with NEC and when present increases mortality significantly. Severe NEC puts patients at higher risk for AKI.
Harer, 2018 AWAKEN database (n = 675) [55]	Multicenter study of premature infants	18%	Caffeine use within 7 days of birth in preterm infants is associated with reduced incidence and severity of AKI.
SooHoo, 2018 (n = 95) [56]	Infants status post Norwood procedure	44%	Correction of serum creatinine for fluid overload increased the precision of AKI diagnosis and improved the identification of adverse outcomes associated with AKI. AKI is independently associated with development of perioperative infection.
Garcia, 2018 (n = 48) [57]	Infants status post Norwood or Hybrid procedure	29%	AKI occurs commonly after Norwood or Hybrid procedure and is associated with longer ICU stays and time to extubation.
Srinivasan, 2018 (n = 457) [58]	VLBW infants	19.5%	AKI is associated with impaired postnatal renal adaptation, BPD, longer NICU stay, and increased mortality
Chock, 2018 (n = 38) [59]	Infants with moderate to severe HIE	39%	During therapeutic hypothermia, infants with AKI had higher renal saturations measured by NIRS than those without AKI.
Criss, 2018 (n = 181) [20]	Infants with NEC	54%	AKI is common in infants with NEC and is associated with increased mortality.
Jetton, 2017 AWAKEN database (n = 2022) [17••]	Multicenter study of all critically ill neonates admitted to NICU over a 3 month period	29.9%	Incidence of AKI is ~ 30% with rates of AKI varying by GA. AKI is associated with increased mortality and longer hospital stay.
Carlo, 2017 (n = 56) [60]	Infants status post CTA and cardiac surgery with CPB	75%	Exposure to CTA and CPB surgery does not increase risk of AKI after neonatal cardiac surgery.
Maqsood, 2017 (n = 222) [61]	ELBW infants	50%	Infants with stage 2 or 3 AKI have higher diastolic BP at discharge than infants with stage 1 AKI or no AKI. ELBW infants are at risk for CKD at ≥2 years of life.
Constance, 2017 (n = 594) [62]	Infants with PDA and received gentamicin (n = 594)	12%	In infants with PDA who receive gentamicin, NSAID therapy increase risk of AKI.
Stoops, 2016 (n = 125) [63]	Premature infants	30.5%	Infants with AKI were more likely to develop grade 2 or higher IVH than those without AKI.
Carmody, 2016 (n = 140) [64]	VLBW infants	25%	VLBW infants who are exposed to caffeine are less likely to experience AKI than unexposed infants.
Weintraub, 2016 (n = 357) [65]	Infants admitted to NICU	30.3%	GA, initial Cr, maternal magnesium, and volume resuscitation were associated with early AKI. Volume resuscitation, umbilical arterial line and receipt of NSAIDs for PDA were associated with intermediate AKI. GA, steroid use for hypotension, NEC, and sepsis were associated with late AKI.
Wong, 2016 (n = 136) [66]	Infants with single ventricle physiology status post Norwood evaluated at each of 3 staged surgery	75% - stage 1 surgery 68% - stage 2 surgery 58% - stage 3 surgery	Severe AKI after Stage 1 palliation increases risk for developing severe AKI at Stage 2. Severe AKI after Stage 1 is associated with prolonged duration of mechanical ventilation after Stage 3.
Kumar, 2016 (n = 102) [67]	Infants status post cardiac surgery with CPB	10.7%	AKI following cardiac surgery and CPB is low at a single institution with novel perioperative strategies
Askenazi, 2015 (n = 122) [68]	Premature infants	30%	AKI is associated with BPD and mortality in premature infants

Table 3 (continued)

Study	Population (n)	% patients with AKI	Findings
Piggott, 2015 (n = 95) [69]	Infants status post cardiac surgery	45%	CPB time, selective cerebral perfusion, perioperative aminoglycoside use, and small kidneys were risk factors for AKI in infants with CHD who underwent surgery. Fluid overload and AKI was associated with increased length of hospitalization and post-operative ventilator days.
Sarkar, 2014 (n = 88) [70]	Infants with HIE (n = 88)	39%	AKI is independently associated with hypoxic ischemic lesions on brain MRI at 7–10 days of life in infants with HIE treated with therapeutic hypothermia.
Carmody, 2014 (n = 455) [71]	VLBW infants (n = 455)	39.8%	AKI is associated with increased mortality and length of stay adjusted for severity of illness.
Rhone, 2014 (n = 107) [72]	VLBW infants	26.2%	AKI is associated with nephrotoxic medication exposure.
Askenazi, 2013 (n = 58) [26]	Sick near-term infants	15.6%	AKI associated with increased mortality and positive fluid balance.
Selewski, 2013 (n = 96) [73]	Infants with HIE	38%	AKI predicted prolonged mechanical ventilation and length of stay.
Alabbas, 2013 (n = 122) [74]	Infants status post cardiac surgery	62%	Cardiac surgery-associated AKI is common among infants and associated with increased length of ICU stay and mortality. CPB duration of ≥ 120 min was associated with AKI.
Zwiers, 2013 (n = 242) [47]	ECMO-treated infants	64%	Infants who receive ECMO are at risk to develop AKI. Those with severe AKI/renal failure have increased risk of mortality.

increased the ability of the RAI to predict severe day 3 AKI (AUC/ROC 0.80 to 0.97) [88]. The RAI has subsequently been studied and validated in a single-center study and in the multicenter AWARE study [89, 90••].

Another important component in the improved care of children with AKI is the development of a functional kidney test to identify the patients at highest risk for severe AKI. The "furosemide stress test" (FST) represents such a test and utilizes a single dose of furosemide followed by a 6-h period of monitored urine response to identify patients at risk for severe AKI. In a study of adults, urine output < 200 ml in the first 2 h had a sensitivity of 87.1% and specificity 84.1% to predict the development of stage 3 AKI [91]. A recent single-center study of 99 children undergoing cardiac surgery supports this concept. In this study, the furosemide response in the first 24 h following cardiac surgery predicted subsequent AKI and FO [92]. This is consistent with another recent study in children following cardiac surgery [93]. While the RAI, novel biomarkers, and FST all represent interesting tools, the answer for early AKI identification undoubtedly lies in a multifaceted approach incorporating many, if not all, of these tools.

Therapeutics

While there remains a paucity of medical interventions for established AKI, in recent years, there have been several important studies that have evaluated the ability of medications to prevent the development and/or progression of AKI in high-risk populations. Here, we will review recent studies evaluating aminophylline/theophylline, caffeine, dexmedetomidine, and rasburicase.

Theophylline, caffeine, and aminophylline are adenosine receptor antagonists that have recently shown promise as agents that may prevent or ameliorate AKI in high-risk populations (congenital cardiac surgery, perinatal asphyxia, and premature neonates) [55, 64, 94–99]. These medications impact renal perfusion by inhibiting adenosine-induced vasoconstriction. There have now been four randomized controlled trials evaluating the impact of a single dose of theophylline given in the first hour of life on renal function in neonates suffering from perinatal asphyxia. The most recent of these trials was published in 2016 and included 159 neonates with perinatal asphyxia. This study showed that those that received theophylline had less AKI (15% vs 48%, $p < 0.01$), less oliguria, and better fluid balance at postnatal day 3 [99]. While these positive studies have clearly shown promise for the utilization of theophylline in this population, theophylline has to be studied in a population undergoing therapeutic hypothermia.

In premature neonates, caffeine is commonly utilized to prevent and/or treat apnea of prematurity and its impact on AKI has recently drawn interest. In a single-center retrospective study of 140 VLBW neonates, caffeine exposure was associated with less AKI (aOR 0.21) [64]. These findings were confirmed in a secondary analysis of 675 premature neonates in the AWAKEN study, where after multivariable adjustment, administration of caffeine reduced the odds of developing AKI (aOR, 0.20), indicating that for every 4.3

Fig. 1 Renal Angina Index (RAI)

Risk Score				Injury Score		
Risk	Score		Decrease in eCCl	%FO	Score	
Moderate	1		No Change	<5	1	
High	3	X	0-25%	≥5	2	= RAI (1-40)
Very High	5		25-50%	≥10	4	
			≥50%	≥15	8	

*Risk: Moderate (ICU admission), High (History of solid organ or bone marrow transplant),Very High (Intubated plus at least one vasopressor or inotrope use)
**Calculated as Risk Score x Injury Score

neonates exposed to caffeine, a case of AKI was prevented [55].

Children undergoing cardiac surgery represent a population where there have been a number of recent studies evaluating a variety of agents to prevent or ameliorate AKI. Aminophylline initially has shown promise in a single-center retrospective study of children with AKI following cardiac surgery, which demonstrated improved renal function and urine output in those treated with aminophylline. A well done follow-up single-center double-blinded, placebo-controlled, randomized clinical trial showed no impact on AKI or fluid balance in those treated for 72 h with aminophylline following CPB [98]. Dexmedetomidine is an α2-adrenergic receptor agonist that has been reported to be renal protective in adults after heart surgery [100]. A single-center study of 29 children undergoing atrial or ventricular septal defect repair suggested that dexmedetomidine may decrease the incidence of postoperative AKI. Each of these agents warrants further study.

Rasburicase is a recombinant urate oxidase that catalyzes the conversion of uric acid to allantoin and has been used extensively to treat hyperuricemia associated with tumor lysis syndrome. A number of case reports have shown successful use of rasburicase in the treatment of severe hyperuricemia associated with AKI in a variety of populations including neonates, rhabdomyolysis, and pediatric patients with hemolytic uremic syndrome [101–104]. Currently, firm recommendations about its use cannot be made, and additional studies investigating the role of hyperuricemia and its status as a modifiable risk factor in AKI and the use of rasburicase are needed.

Interventions and Advancements

The indications for renal replacement therapy (RRT) in children with AKI include uremia (typically blood urea nitrogen (BUN) > 100–120 mg/dl), electrolyte abnormalities, inability to provide adequate nutrition, and FO. CRRT has become one of the more commonly prescribed modalities for delivering RRT in critically ill children. This has been done utilizing devices designed for adults, creating significant challenges

in providing CRRT to our smallest patients. The development of CRRT devices that are specifically designed for neonates and small infants (smaller extracorporeal volumes, improved precision, lower blood flows, smaller catheters) will revolutionize our ability to provide this therapy to our smallest patients. Two such machines include the CARPEDIEM® (Cardio-Renal Pediatric Dialysis Emergency Machine), which is currently in use outside of North America, and NIDUS® (Newcastle Infant Dialysis and Ultrafiltration System) [105, 106]. The timely mobilization of these devices is critical to improving outcomes for our smallest patients.

Over the last decade, pediatricians have been at the forefront of identifying the association of FO at CRRT initiation with increased mortality [24, 49•, 107–109]. These studies clearly suggest that FO of 10–20% represents a critical point when providers must consider intervention with RRT in critically ill infants and children. In those receiving ECMO, FO of 20–30% likely represents an important benchmark based on the current literature [49•]. The timing for the initiation of RRT remains a critical area for further study in children.

Long-Term Outcomes

In recent years, it has become clear that the implications of AKI extend beyond short-term morbidity and mortality to include an increased risk of subsequent chronic kidney disease (CKD). This association has been clearly shown in the adult literature, and an association is being shown in small pediatric studies with increasing frequency [80, 110–113]. The seminal pediatric publication on this topic was published in 2012 and evaluated renal outcomes at 1–3 years following an AKI episode during critical care in 126 patients. Ten percent of patients had evidence of chronic kidney disease (GFR < 60 ml/min/1.73 m^2), and an additional 47% were at risk for CKD (GFR of 60–90 ml/min/1.73 m^2, persistent hypertension, and/or hyperfiltration (≥ 150 ml/min/1.73 m^2)) [111]. Subsequent small single-center studies have shown abnormal long-term renal function in those with AKI following nephrotoxic medication exposure, VLBW neonates, and CPB-associated AKI

[80, 113, 114]. While there appears to be a signal present, confirmation with long-term follow-up studies of cohorts such as AWARE and AWAKEN are critical. Based upon expert opinion, the KDIGO guidelines currently recommend follow-up evaluation after an episode of AKI within 3 months of hospital discharge [10••].

Conclusion

In recent years, there have been many exciting advances in neonatal and pediatric AKI. Through the utilization of standardized definitions, there has been a revolution in understanding the epidemiology and impact of AKI across all populations in pediatrics. This has culminated in the recent publication of the AWARE and AWAKEN studies, which definitively describe the incidence and negative impact of AKI in pediatric and neonatal populations, respectively. Efforts now must turn to the prevention, early recognition, and therapies for AKI. The NINJA study clearly demonstrates the importance of standardized protocols to improve surveillance in patients receiving nephrotoxic medications. Translating these protocols to the ICUs, including increased monitoring of neonatal renal function, is a critical next step to improving short- and long-term outcomes. In addition, the further deployment and development of risk stratification strategies (RAI, FST), coupled with the utilization of novel biomarkers, have the opportunity to change the paradigm of AKI from one of the reactions to one of the early interventions.

Compliance with Ethical Standards

Conflict of Interest   The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent   This article does not contain any studies with human or animal subjects performed by any of the authors.

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