# Advances in Neonatal Acute Kidney Injury

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In this state-of-the-art review, we highlight the major advances over the last 5 years in neonatal acute kidney injury (AKI). Large multicenter studies reveal that neonatal AKI is common and independently associated with increased morbidity and mortality. The natural course of neonatal AKI, along with the risk factors, mitigation strategies, and the role of AKI on short- and long-term outcomes, is becoming clearer. Specific progress has been made in identifying potential preventive strategies for AKI, such as the use of caffeine in premature neonates, theophylline in neonates with hypoxic-ischemic encephalopathy, and nephrotoxic medication monitoring programs. New evidence highlights the importance of the kidney in "crosstalk" between other organs and how AKI likely plays a critical role in other organ development and injury, such as intraventricular hemorrhage and lung disease. New technology has resulted in advancement in prevention and improvements in the current management in neonates with severe AKI. With specific continuous renal replacement therapy machines designed for neonates, this therapy is now available and is being used with increasing frequency in NICUs. Moving forward, biomarkers, such as urinary neutrophil gelatinase–associated lipocalin, and other new technologies, such as monitoring of renal tissue oxygenation and nephron counting, will likely play an increased role in identification of AKI and those most vulnerable for chronic kidney disease. Future research needs to be focused on determining the optimal follow-up strategy for neonates with a history of AKI to detect chronic kidney disease.

Since the publication of the "Neonatal Acute Kidney Injury" review in 2015, our understanding of the epidemiology and impact of neonatal acute kidney injury (AKI) has exponentially increased.[1] Single-center and multicenter work has clearly revealed that AKI occurs commonly in critically ill neonates and adversely impacts outcomes.[2–4] In parallel to these advancements, our ability to identify AKI early, mitigate AKI, and provide renal replacement therapy (RRT) with devices designed for neonates has improved.[5,6] In this state-of-the-art review, we will review neonatal kidney physiology, provide an update of neonatal AKI knowledge (definitions, prevalence, outcomes, and complications), discuss the current state of research, and appraise cutting edge data on therapeutics and devices that will improve care in the coming decade.

## NEONATAL KIDNEY PHYSIOLOGY AND IMPLICATIONS FOR AKI

A basic understanding of kidney structure and function during

abstract

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development is essential to understand neonatal AKI and its consequences.[1] Nephrogenesis begins at 5 weeks' gestation and continues until 34 to 36 weeks' gestation.[7] The nephron number is highly variable at birth, ranging from 200 000 to 2.7 million, and is impacted by a multitude of factors, including prematurity.[8,9]

There are several core principles of neonatal physiology that uniquely impact the diagnosis and management of neonatal AKI. First, both renal blood flow and perfusion pressure increase over the first weeks of life in neonates. The proportion of cardiac output delivered to the kidneys increases from 5% during fetal life to 20% by 2 years.[10] Much of this increased blood flow occurs after birth, with renal blood flow doubling in the first 2 postnatal weeks. After birth, the distribution of blood flow transitions from deeper, more mature glomeruli to superficial, cortical glomeruli.[11] This change in blood flow can be altered by medications (such as indomethacin), perinatal asphyxia, and maternal hemorrhage, which all predispose neonates to AKI. Second, congruent with the increased blood flow, the glomerular filtration rate (GFR) increases dramatically after birth and reaches adult levels by 2 years of age.[12] The GFR is low in infants, both in absolute value and when corrected for body surface area (milliliters per minute per 1.73 meters$^2$). For example, premature infants born at 26 weeks have a GFR as low as 0.7 mL/minute per kg on day 1 of age, which improves only slightly during the first several weeks of life.[12] In neonates with a physiologically low GFR, additional stressors, such as sepsis, hypoxia, hypotension, or other clinical conditions common in prematurity, may increase the risk AKI. Third, urinary concentrating ability is low at birth and reaches adult levels by 1 year of age.[13] Poor urinary concentrating ability, particularly in neonates with high insensible losses or critical illness, predisposes neonates to volume depletion and subsequent prerenal azotemia. Finally, neonatal kidneys appear to be particularly susceptible to ischemic injury to the renal tubules, even after a mild and short-term insult. This is further complicated when nephrotoxic medications, such as gentamicin and other aminoglycosides, are commonly prescribed to critically ill neonates and result in tubular injury.

## DEFINITIONS OF AKI

The neonatal modified Kidney Disease: Improving Global Outcomes (KDIGO) definition is the most commonly used definition used in clinical practice and most epidemiological studies (Table 1). This empirical definition stages AKI severity on the basis of a rise in serum creatinine (SCr) levels from a previous trough and/or a decrease in urine output (UOP).[14,15] The National Institutes of Health–sponsored Neonatal AKI Workshop in 2013 recommended that researchers and clinicians use the neonatal modified KDIGO definition to define AKI but emphasized that this definition should be a starting point for an iterative process, which is based on clinically meaningful and long-term outcomes.[16]

Since the publication of this definition, there have been several observational studies highlighting potential areas for future refinement to account for chronological and gestational age (GA). For example, whereas some researchers advocate for excluding the SCr level from the first postnatal 48 hours when calculating the baseline SCr level, others believe that this value is a surrogate of the nephron number and is clinically meaningful.[2,3,17–19] Researchers have also pointed out that deviations in the GA-appropriate SCr trajectory (which steadily drops from birth in healthy term neonates) could signify AKI, but this is not captured in the current KDIGO definition.[20]

The current neonatal modified KDIGO AKI definition incorporates UOP. Despite studies in older populations revealing that UOP is critically important to properly identify AKI, few studies in neonatal AKI have included UOP. One study using diaper weights every 3 hours found that UOP <1.5 mL/kg per hour was associated with increased mortality.[21] Furthermore, they found that lower thresholds of UOP (<1 mL/kg per hour) were associated with an even higher mortality rate.[21] Few studies, including the Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) study, included UOP measurement in the assessment of

**TABLE 1** Neonatal AKI KDIGO Classification

| Stage | SCr | UOP |
|---|---|---|
| 0 | No change in SCr level or rise <0.3 mg/dL | ≥0.5 mL/kg per h |
| 1 | Increase in SCr level of ≥0.3 mg/dL within 48 h or rise in SCr level ≥1.5–1.9 times the reference SCr level[a] within 7 d | <0.5 mL/kg per h for 6–12 h |
| 2 | Rise in SCr level ≥2–2.9 times the reference SCr level[a] within 7 d | <0.5 mL/kg per h for ≥12 h |
| 3 | SCr level ≥3 times the reference SCr level[a] or SCr level >2.5 mg/dL[b] or receipt of RRT | <0.3 mL/kg per h for ≥24 h or anuria for ≥12 h |

[a] Differences between the neonatal AKI definition and KDIGO definition: reference SCr level defined as the lowest previous SCr value.

[b] Differences between the neonatal AKI definition and KDIGO definition: SCr value of 2.5 mg/dL represents <10 mL/min per 1.73m$^2$.

AKI, thus limiting the available data on which to base thresholds for diagnosis and determination of severity of AKI. In future studies, researchers should carefully measure UOP to determine the impact of UOP on AKI diagnosis in neonates.

Given the interest and focus on AKI diagnostic thresholds, it is likely that a refined definition of neonatal AKI will emerge. Two recent publications, including an analysis of the AWAKEN study, suggest an alternative definition for neonatal AKI.[22,23] In this study, the authors proposed different cutoffs for the first postnatal week by GA, compared with the subsequent weeks, and provided cutoffs by GA group.[23] For example, in infants ≤29 weeks' GA, a rise in the SCr level of 0.6 mg/dL confers the highest prediction of mortality, whereas in infants >29 weeks' GA, a rise of 0.3 mg/dL is of highest mortality prediction.[23] Furthermore, we anticipate that novel approaches of using urine biomarkers, SCr thresholds, UOP thresholds, and fluid balance metrics will be used to enhance the current neonatal KDIGO definition. In the interim, we recommend that the neonatal modified KDIGO definition be used as the standard until newer definitions are widely validated in large multisite trials and correlated with long-term outcomes.

## EPIDEMIOLOGY, RISK FACTORS, AND ASSOCIATED FINDINGS WITH AKI

AKI is common in critically ill neonates. We present a summary of the risk factors associated with neonatal AKI (Table 2) and the most notable studies evaluating the epidemiology and impact of neonatal AKI in the last 5 years (Table 3). Much of this increased knowledge stems from the AWAKEN study, which enrolled neonates at risk for AKI (determined by >48 hours of intravenous fluids). In this cohort, the risk of AKI occurred in a bimodal pattern, with extremely low gestational age neonates (ELGANs) (<28 weeks) and term infants at the greatest risk.[4] The AWAKEN study identified a clear variation in SCr monitoring practices across centers, with less than half of centers checking ≥5 SCr levels during hospital admission. Not surprisingly, the rates of AKI by center were directly correlated with the average number of SCr samples ascertained per subject.[4] This practice variation is particularly notable in the context of the recent Baby Nephrotoxic Injury Negated by Just-in-Time Action (NINJA) publication, which revealed that by monitoring SCr more frequently in neonates with high nephrotoxic medication exposure, there was an increased awareness of the risk for AKI that, in turn, resulted in a lower rate and duration of AKI.[17] These data suggest that critically ill neonates may benefit from protocolized SCr monitoring during high-risk events.

### Preterm Neonates

The risk of AKI increases markedly with decreasing GA.[2,3] In cohorts of very low birth weight (VLBW) neonates, the incidence of AKI is reported between 18% and 40%.[3,24] In ELGANs enrolled in the Preterm Erythropoietin Neuroprotection Trial, 38% had at least 1 episode of AKI.[2] In the AWAKEN study, AKI occurred in 45% of neonates <29 weeks' GA and in 14% of neonates 29 to 36 weeks' GA. In the AWAKEN study, the potentially modifiable risk factors for early AKI in ELGANs were mainly medication exposures.[25] Given immature tubular function and resulting poor urinary concentration ability, along with the increased insensible losses common in preterm neonates, volume depletion leading to prerenal azotemia is a common factor predisposing this population to AKI.

Patent ductus arteriosus (PDA) is an important clinical issue for preterm infants and is associated with a higher risk of AKI.[26,27] PDA represents a clinical challenge because AKI may result if it is left untreated; however, classic PDA therapies may also be associated with AKI. Although nonsteroidal antiinflammatory drug (NSAID) treatment of PDA added an additional risk for mild AKI, severe AKI was less likely when NSAID treatment was effective.[26]

### Term or Near-Term Critically Ill Neonates

In the AWAKEN study, the incidence of AKI in neonates born at ≥36 weeks and admitted to a NICU was 37%.[4] The etiology of AKI in term neonates is often multifactorial and includes risk factors related to their illness and management (Table 2).[25,28] Multiorgan dysfunction is common and occurs in up to 70% of neonates with AKI.[29–31] Some of the major risk factors for AKI include hypoxic-ischemic encephalopathy (HIE), cardiac disease, surgery, and nephrotoxic medications.

**TABLE 2** Epidemiology, Risk Factors and Associated Findings with Neonatal AKI

| Prenatal | Perinatal | Postnatal |
|---|---|---|
| Factors that increase risk of a preterm or LBW neonate, placental insufficiency | Exposure to nephrotoxic medications (ACE inhibitors, NSAIDs), delivery complications resulting in hypoxia and/or asphyxia, HIE | Prematurity, LBW, CHD, inborn errors of metabolism, sepsis, nephrotoxin exposure, PDA, extracorporeal therapies |

ACE, angiotensin-converting enzyme; LBW, low birth weight.

**TABLE 3** Summary of Neonatal AKI Studies Published Between 2015 and 2020

| Author (Year), *N* | Study Design and Population Details | Main Findings |
|---|---|---|
| Jetton et al[4] (2017), *N* = 2162 | Neonates requiring >48 h of intravenous fluids in the NICU | AKI occurred in 45% of the infants at ≤28 wk GA and in 14% of infants at 29–36 wk GA. |
| Charlton et al[25,28] (2019), *N* = 2162 | Secondary analysis of infants from the AWAKEN study | Antimicrobial agents, methylxanthines, diuretics, NSAIDs, hypertensive disorders of pregnancy, and hypoglycemia were associated with lower odds of early AKI. In infants at 29–25 wk GA, outborn status, saline bolus during resuscitation, and more frequent SCr monitoring were associated with higher odds of early AKI. |
| Askenazi et al[2] (2000), *N* = 923 | Prospective study of ELGANs in the PENUT trial | Thirty-eight percent had at least 1 episode of stage 1 or higher AKI, and 18.2% had 1 episode of stage 2 or higher AKI. |
| Selewski et al[51] (2019), *N* = 645 | Retrospective analysis of infants at ≥36 wk GA from the AWAKEN study | Median peak fluid balance was 1.0% (IQR: −0.5 to 4.6) over the first postnatal week and occurred on postnatal d 3 (IQR: 1 to 5). Mechanical ventilation on postnatal d 7 was associated independently with the following measures of fluid balance over the first postnatal week: peak fluid balance (aOR: 1.12; 95% CI: 1.08 to 1.17), lowest fluid balance in first postnatal week (aOR: 1.14; 95% CI: 1.07 to 1.22), fluid balance on postnatal d 7 (aOR: 1.12; 95% CI: 1.07 to 1.17), and negative fluid balance at postnatal d 7 (aOR: 0.3; 95% CI: 0.16 to 0.67). |
| Selewski et al[53] (2020), *N* = 1007 | Retrospective analysis of infants at <36 wk GA from the AWAKEN study | Median peak fluid balance was 0% (IQR: −2.9 to 2) and occurred on postnatal d 2 (IQR: 1 to 5). Mechanical ventilation on postnatal d 7 was associated independently with the following measures of fluid balance over the first postnatal week: peak fluid balance (aOR: 1.14; 95% CI: 1.10 to 1.19), lowest fluid balance (aOR: 1.12; 95% CI: 1.07 to 1.16), fluid balance on postnatal d 7 (aOR: 1.10; 95% CI: 1.06 to 1.13), and negative fluid balance at postnatal d 7 protected against the need for mechanical ventilation at postnatal d 7 (aOR: 0.21; 95% CI: 0.12 to 0.35). |
| Nour et al[120] (2020), *N* = 30 | Retrospective analysis in neonates with HIE who underwent cooling via selective head cooling | No difference in AKI between the those receiving selective head cooling and those not. SCr levels and UOP were significantly improved on d 4 and d 10 samples compared with baseline samples in both groups regardless of cooling. There was a difference in NGAL levels, but not CysC levels, on d 4 and 10. |
| Bellos et al[90] (2019), *N* = 458 | Meta-analysis of effectiveness of theophylline administration in neonates with perinatal asphyxia | Incidence of AKI significantly lower in neonates receiving theophylline (OR: 0.24; 95% CI: 0.16 to 0.36), whereas mortality rates were similar between the 2 groups (OR: 0.86; 95% CI: 0.46 to 1.62). Theophylline administration was associated with significantly decreased SCr levels (MD: −0.57 mg/dL; 95% CI: −0.68 to −0.46) in the third day of life. |
| Harer et al[89] (2018), *N* = 675 | Retrospective analysis of premature infants at <33 wk GA from the AWAKEN study | AKI occurred less frequently in neonates who received caffeine in the first week of life than in those who were not treated with caffeine (11.2% vs 31.6%; $P < .01$). Neonates who received caffeine had more AKI risk factors, including lower average GA, lower birth wt, and high severity of illness scores, and were still less likely to develop stage 2 or 3 AKI. The No. needed to treat with caffeine to prevent 1 episode of AKI was 4.3. |
| Stoops et al[17] (2019) | Prospective quality improvement effort to reduce nephrotoxic medication–associated AKI in the NICU | Reduced high nephrotoxic medication exposures from 16.4 to 9.6 per 1000 patient-days ($P = .03$), reduced nephrotoxic medication–associated AKI from 30.9% to 11.0% ($P < .001$), and reduced AKI severity from 9.1 to 2.9 per 100 susceptible patient-days ($P < .001$) prevented 100 AKI episodes during the 18-mo sustainability era. |
| Starr et al[103] (2019), *N* = 546 | Retrospective analysis of premature infants at <32 wk GA from the AWAKEN study | Infants born between 29 and 32 wk GA with AKI had fourfold higher odds of moderate or severe BPD or death after controlling for multiple factors (aOR: 4.21; 95% CI: 2.07 to 8.61). |

aOR, adjusted odds ratio; BPD, bronchopulmonary dysplasia; IQR, interquartile range; MD, mean difference; PENUT, Preterm Erythropoietin Neuroprotection Trial.

### *HIE*

There is a general agreement that the presence of AKI in the setting of HIE is associated with poor outcomes (increased mortality, poor neurodevelopmental outcomes, longer hospital stay, and longer duration of mechanical ventilation).[30,32,33] In addition, there is a correlation between severity of HIE and AKI, with 70% of those with stage III HIE having AKI, compared with 7.4% of those with stage II HIE.[32]

### *Cardiac Disease and Extracorporeal Membrane Oxygenation*

Infants who require cardiac surgery and those who need extracorporeal membrane oxygenation (ECMO) are at high risk for AKI. AKI occurs in 30% to 50% of patients undergoing surgery for congenital heart disease (CHD).[34–36] One single-center retrospective study of neonates with single ventricle physiology undergoing stage 1 Norwood palliation found that 21% developed AKI.[36] A large Danish registry study revealed that 33% of neonates had AKI within 5 days of surgery.[35] In a multicenter retrospective cohort study of 832 pediatric patients on

ECMO, 74% had AKI.[34] AKI was present at initiation of ECMO in the majority of cases and was associated with a longer ECMO duration and increased mortality.[34] The risk of AKI in those on ECMO varies by underlying diagnosis; those with congenital diaphragmatic hernia were more likely to require RRT.[37]

### *Surgery*

The incidence of AKI is high in noncardiac surgery; 34% of neonates undergoing abdominal and thoracic surgery have an episode of AKI.[38] Infants with AKI after surgery were more likely to have VLBW. They were also more likely to have sepsis, a longer duration of mechanical ventilation, an operative time >120 minutes, necrotizing enterocolitis (NEC), and a higher risk of mortality.[38] Among infants with surgically managed NEC, almost 60% had severe AKI (stage 2 or 3).[39]

### *Nephrotoxic Medications*

Many neonates are exposed to nephrotoxic medications in the NICU, which can contribute to AKI. Although there are many nephrotoxic medications, these primarily include antimicrobial agents (eg, acyclovir, amphotericin B, aminoglycosides, vancomycin).[25,28] It was recently reported in Baby NINJA, a single-center quality improvement program focused on reducing nephrotoxic medication–associated AKI, that attention to high-risk neonates, including daily SCr monitoring, reduces nephrotoxic medication exposures ($P = .03$), nephrotoxic medication–associated AKI ($P < .001$), and AKI duration ($P < .001$).[17] This suggests that identification and monitoring of high-risk neonates, with a thoughtful consideration of nephrotoxic medications, may minimize AKI and its consequences in critically ill neonates.

## FLUID BALANCE

The development of fluid overload is an independent predictor of adverse outcomes across pediatric critical care populations.[40–49] The development of fluid overload is often multifactorial, resulting from AKI, iatrogenic fluid administration, capillary leak from systemic inflammation, and aberrant homeostatic mechanisms.[41] Additionally, fluid overload can make the diagnosis of AKI more challenging because SCr is diluted in the setting of a positive fluid balance, resulting in a potential underdiagnosis of AKI.[41] Precise definitions are essential to understanding the epidemiology and impact of excessive fluid accumulation on outcomes in neonates (Table 4).[50] The 2 most common methods used to calculate fluid balance are the cumulative fluid balance and weight-based methods. The weight-based method to describe fluid balance is used to calculate the degree of fluid overload on the basis of a change in weight from a baseline weight (birth weight or determined dry weight)[51]: daily fluid balance = change in daily weight day to day; cumulative fluid balance = daily weight − baseline weight; percentage fluid overload[44] = ([daily weight − baseline weight]/baseline weight) × 100.

Although each method has been used in older children, the weight-based methods represent the standard in neonates because fluid balances have been shown to be inaccurate.[51–53] It is critical to use standardized weight measurement protocols to properly perform the weight-based technique.[52,54]

Fluid balance in the early postnatal period can be challenging to interpret in the setting of normal postnatal diuresis and expected negative fluid balance. Although an average weight loss of 7% from birth weight is described in term neonates, the normal fluid balance for neonates of other GAs is less clearly defined, particularly in extremely preterm neonates with excessive skin permeability.[55] Early positive postnatal fluid balance is associated with adverse short- (death, mechanical ventilation on day 7) and long-term outcomes (bronchopulmonary dysplasia) in neonates.[51,53,56–59] There remains a paucity of data defining the pathologic state of fluid overload in critically ill neonates, which in older children, is commonly defined as a cumulative positive fluid balance of ≥10% to 20%.[48,60] Multiple critical gaps exist in our understanding of the causes and impact of abnormal fluid balance in neonates. These gaps include interpreting fluid balance in neonates, especially those who have spent a considerable time in the NICU. Research is greatly needed to understand the optimal threshold to define appropriate fluid balance and to understand the detrimental effects of neonatal fluid overload on extrarenal organ systems (eg, oxygenation index and cardiac dysfunction due to excessive fluid and reduced contractility). Understanding the role of fluid

**TABLE 4** Definitions of Excessive Fluid Accumulation in Neonates

| Term | Definition |
|---|---|
| Daily fluid balance | Daily difference between input and output or change in wt over a 24-h period |
| Cumulative fluid balance | Change in fluid balance over a given duration |
| Fluid overload | Cumulative fluid balance expressed as a percentage of body wt; used to refer to the pathologic state of excessive fluid accumulation associated with the development of sequelae attributable to fluid accumulation and adverse outcomes |

balance in various neonatal populations (premature versus term neonates) at critical time points (perinatal versus postnatal versus postsurgical) in the context of underlying disease process (NEC, lung disease, and sepsis) is a critical knowledge gap. Answers to these questions will drive therapeutic interventions designed to prevent and mitigate harm from fluids.

## NEW ADVANCES IN AKI RESEARCH

### Biomarkers of AKI

Proteins and metabolites are 2 examples of biomarkers that can be measured consistently and correlate with the disease occurrence or progression.[61] Given the diversity of GA and etiologies of AKI in neonates, 1 biomarker does not appear to reliably predict AKI. However, more reference ranges are becoming available for novel urinary biomarkers by GA and postnatal age.[62] SCr represents the current standard for diagnosing neonatal AKI. However, it is critical to understand the shortcomings of SCr and develop novel biomarkers that fill these gaps. A rise in the SCr level indicates a loss of kidney function, reflecting injury that occurred up to 48 to 72 hours before.[63] As a result, biomarker studies, such as the ones below, have been focused on identifying injury and functional changes before permanent damage (Table 5).

Cystatin C (CysC) is a cysteine protease inhibitor that is freely filtered by glomeruli and reabsorbed in the proximal tubule. Although both serum and urinary CysC have been assessed as early markers of AKI, a rise in the serum CysC level reflects a change in kidney function, whereas an elevated urinary CysC level is considered reflective of tubular injury.[12,64–68] A recent systematic review of neonates across all GA groups suggested that serum CysC may be superior to SCr for assessing the GFR.[65] Furthermore, an elevated urinary CysC level has been shown to have an area under the curve of 0.85 (95% confidence interval [CI]: 0.81 to 0.88) in predicting a rise in the SCr level 24 to 96 hours later in neonates post surgery or after perinatal asphyxia.[67]

There are several other biomarkers that may help identify injury and functional changes before permanent damage in neonates with AKI. Neutrophil gelatinase–associated lipocalin (NGAL) is a protein bound to neutrophil granules, filtered by the glomerulus, and reabsorbed by the proximal tubules.[69] NGAL is highly sensitive (87%–93%) and specific (87%–93%) for AKI in neonates with perinatal asphyxia.[70] The combination of G1 cell cycle arrest biomarkers urinary tissue inhibitor of metalloproteinase 2 (TIMP-2) and insulinlike growth factor binding protein 7 (IGFBP-7) is promising for detecting early AKI. It has been shown to have a sensitivity of 89% and a specificity of 51% for predicting AKI in critically ill neonates.[71] This combination has been evaluated in pediatric and adult populations and has been shown to perform well in predicting subsequent severe AKI.[63] Both NGAL and TIMP-2 and IGFBP-7 are currently used off label in multiple pediatric and adult ICUs to evaluate for AKI, and there are several ongoing studies assessing their utility in pediatric AKI.[72] Kidney injury molecule 1 is a transmembrane protein that is upregulated in kidney injury, and elevated levels have been shown to predict AKI.[73] By using SCr as the gold standard, the areas under the curve of several of these biomarkers (in particular, NGAL and TIMP-2 and IGFBP-7) are highly predictive for AKI.[73] It is imperative that we begin to incorporate novel biomarkers into future definitions of neonatal AKI and into clinical care.

### Nephron Number

In humans, there is wide variability in the nephron number present, even in the neonatal period because the completion of nephrogenesis occurs at 26 to 34 weeks.[8,9,74] The mechanisms (in utero and ex utero) that influence nephrogenesis, and ultimately nephron endowment, and the processes regulating nephron loss are poorly understood.[7] Preclinical advancements have been made in measuring the whole-kidney functional nephron number in vivo with a novel contrast agent. Cationic ferritin-enhanced MRI has

**TABLE 5** Biomarkers in Use or Under Study to Assist With AKI Prediction and Diagnosis

| Biomarker | Location of Injury | Notes |
|---|---|---|
| SCr | Reflects kidney function, not injury; metabolic product of skeletal muscle creatine | Delayed marker (48–72 h) of kidney function |
| CysC | Reflects kidney function, not injury (serum); proximal tubule injury (urine) | Increase in the serum CysC level is thought to reflect a change in GFR or kidney function, whereas an elevated urinary CysC level is considered reflective of tubular injury |
| NGAL | Distal tubule and collecting duct | Highly sensitive for ischemia and nephrotoxins |
| Kidney injury molecule 1 | Proximal tubule injury | Regulates apoptosis, promotes epithelial regeneration |
| TIMP-2 and IGFBP-7 | Tubule cells | Limits proliferation of damaged tubule cells; marker of early AKI |

been used to measure the glomerular number and size in health and disease.[75,76] The radial glomerular count, a surrogate marker of glomerulogenesis, suggests that the nephron number is decreased in both premature neonates and in those with AKI.[77] Further work is necessary to translate this technique to humans, including neonates, to further understand those at risk for future chronic kidney disease (CKD).[78]

### Tissue Oxygenation

Noninvasive continuous monitoring of renal oxygen saturation with near-infrared spectroscopy (NIRS) is a new diagnostic tool that may lead to earlier diagnosis of AKI.[79] Renal tissue oxygenation ($RrSO_2$) monitoring is a surrogate for local tissue oxygen use. In neonates with CHD, NIRS monitoring of the kidney postoperatively can predict AKI.[80] In premature neonates, those who subsequently develop AKI have lower $RrSO_2$ in the first postnatal day or week.[81,82] In postoperative cardiac patients, NIRS detected a decline in $RrSO_2$ before AKI was defined by SCr or UOP.[83] In those undergoing therapeutic hypothermia for HIE, neonates with AKI had higher $RrSO_2$ values, likely pointing to a different cause or type of injury, than preterm infants or infants with CHD.[84] Further work is needed to establish normative $RrSO_2$ values in neonatal populations and treatment guidelines incorporating $RrSO_2$ values.

## EVALUATION OF NEONATAL AKI

Evaluating a neonate who develops AKI requires a systematic approach, which includes consideration of common factors contributing to AKI. A detailed history should be obtained to assess for risk factors for AKI, including birth weight and GA, antenatal events (including prenatal ultrasounds), pregnancy complications, birth history (interventions required at delivery), nephrotoxic medications exposure, and postnatal events. Physical examination should include an assessment of volume status, which should also include weight, daily fluid balance, and cumulative fluid balance. Fluid balance assessment is essential because volume depletion is a common cause of AKI and volume overload is a common complication of AKI. Positive fluid balance still may mean poor renal perfusion if neonates have ongoing third spacing due to capillary leak. Maintaining euvolemia is a challenging but essential management strategy in infants both to prevent AKI and to mitigate severe volume overload and complications. Focused laboratory evaluation should be performed, including measurement of serum electrolytes and serum urea nitrogen, as well as of SCr and/or CysC for GFR assessment.[65] At this time, there is not a definitive role for urine biomarker assessment in all neonates, but growing data suggest that it may be useful in certain clinical settings to predict AKI.[71] Fractional excretion of sodium may be helpful in some infants in differentiating volume depletion from intrinsic causes of AKI but can be challenging to interpret in premature infants because of tubular immaturity.[12] We recommend that an ultrasound be obtained to evaluate for evidence of obstruction as well as congenital abnormalities of the kidney. An ultrasound can also determine kidney size. However, more studies are needed to know if kidney size is helpful in understanding clinically kidney-related meaningful outcomes.[85]

## MANAGEMENT OF NEONATAL AKI

Although the search for treatments or interventions for established neonatal AKI has remained elusive, medications have been evaluated in high-risk neonatal cohorts to prevent AKI. There have been multiple therapeutics evaluated for AKI prevention in neonates (without positive results), including erythropoietin, therapeutic hypothermia, remote ischemic preconditioning, and corticosteroids.[86–88] Methylxanthines have been evaluated in multiple neonatal populations and have had promise as a preventive treatment of AKI in high-risk populations.[89,90]

After diagnosis of AKI, careful management of fluid balance and medications is essential to preventing the development of complications. Strict documentation of all fluid input and output, along with daily weights, is essential to optimizing fluid balance. Nephrotoxic medications should be assessed daily and reduced or eliminated whenever possible.[17] Cumulative fluid balance should be carefully monitored to assess overall volume status. Infants with volume depletion may require additional fluid in the form of either enteral feeding, intravenous boluses, or drips. In infants with volume overload, diuretics can be trialed to maintain UOP.[91] Response to furosemide (furosemide stress test) has been used as a functional biomarker for predicting severe AKI.[92] Although furosemide has not been evaluated in all neonatal populations, term infants with CHD with a lower response to furosemide (median UOP at 2 hours after furosemide treatment 1.2 vs 3.4 mL/kg per hour; $P = .01$) have an increased risk for persistent AKI. Although furosemide responsiveness is a potential functional marker of kidney status, more studies in neonates are needed to standardize the dose and definitions used.

Theophylline and its related salt, aminophylline, have had success in increasing UOP and may prevent

AKI in infants with HIE. Theophylline is an adenosine receptor antagonist that prevents AKI by inhibiting adenosine-induced renal vasoconstriction. A recent meta-analysis of 7 randomized controlled trials (458 neonates with asphyxia not receiving therapeutic hypothermia) found that theophylline administration was associated with a significantly lower incidence of AKI (odds ratio [OR]: 0.24; 95% CI: 0.16 to 0.36).[90] On the basis of this evidence, a single dose of theophylline within the first 6 postnatal hours in newborns with HIE is endorsed in the 2012 KDIGO guidelines to prevent AKI.[15] Aminophylline has also had promise as a rescue therapy in neonates with AKI treated with therapeutic hypothermia.[93]

Caffeine is also an adenosine receptor antagonist that has been evaluated for renoprotective effects in preterm cohorts. Two studies revealed that AKI occurred less frequently in VLBW infants and preterm infants <33 weeks' GA who received caffeine within the first postnatal week. In a retrospective study of 140 VLBW neonates,[94] AKI occurred less frequently in those who received caffeine (17.8% vs 43.6%; $P = .002$). In a secondary analysis of the AWAKEN study, AKI occurred less frequently in neonates <33 weeks GA who received caffeine in the first postnatal week (11.2% vs 31.6%, $P < .01$).[89] On the basis of these data, the number that needed to be exposed to caffeine to prevent 1 episode of AKI was 4.3.[89]

### RRT

RRT remains the primary therapy for the complications of severe AKI. The indications for RRT in neonates include acidosis, fluid overload, electrolyte abnormalities, and uremia refractory to medical management. The 2 most common modalities for RRT in neonates are peritoneal dialysis (PD) and continuous renal replacement therapy (CRRT). CRRT can be added to the extracorporeal circuit in infants receiving ECMO therapy. Between PD and CRRT, the choice often depends on the available resources, center experience, and patient characteristics.[95] These therapies are complementary in that some neonates or situations will have a higher chance of success with PD, whereas others will benefit from CRRT. PD remains a common first choice for RRT in most institutions because it does not require vascular access, is more available, and is often technically easier in the smallest patients.[95] PD can be performed by using a temporary catheter if the RRT requirement is thought to be short-term. Depending on the catheter used, PD can be successful in neonates as small as 830 g.[96]

CRRT may be preferred in hemodynamically unstable infants, those with a history of abdominal surgery or NEC (which makes PD technically challenging), or those in whom tight control of volume status is necessary. In the past, the sole availability of CRRT equipment designed for adults and larger children presented a challenge to perform CRRT in neonates. This necessitated the use for larger catheters, tubing, and filters, resulting in high extracorporeal volumes and greater hemodynamic instability, often requiring either blood transfusions or blood priming with each circuit change. Recent advances have made CRRT increasingly accessible and successful for neonates. Introduction of smaller filters, such as the HF-20 (total extracorporeal vol of 60 mL), which was recently approved by the US Food and Drug Administration for use in the United States, has improved both the availability and acceptance of therapies by decreasing the extracorporeal volume and improving fluid removal precision.[97]

In recent years, industry has made significant innovations in neonatal RRT by developing neonatal-specific CRRT machines and repurposing machines for neonatal use.[98] The Cardio-Renal Pediatric Dialysis Emergency Machine (Medtronic, Minneapolis, MN) was approved for use in children between 2.5 and 8 kg the United States in 2020 and has been used in multiple countries outside the United States. This machine was developed specifically for neonates and small children.[5] In contrast, Aquadex (Aquadex FlexFlow; CHF Solutions, Eden Prairie, MN) is an ultrafiltration device designed for adults but with an extracorporeal vol of 33 mL, making it ideal to adapt to safely provide CRRT to infants.[5] Successful CRRT using Aquadex has been reported in infants as small as 1.4 kg.[5] These machines and others, such as the Newcastle Infant Dialysis and Ultrafiltration System (Newcastle National Health Service Foundation Trust, Newcastle, United Kingdom), have begun to revolutionize the field of CRRT for neonates by lowering the associated risks and will change the conversation about when and in whom to initiate CRRT.[6,99]

## COMPLICATIONS OF AKI

### Cross Talk Between AKI and Other Organs

AKI has been shown to adversely impact other organs.[100] Initially thought to be only an association, studies suggest a causal relationship in which AKI appears to drive other organ dysfunction and vice-versa, referred to as "crosstalk."[101] Experimental models describe a lung-focused inflammatory process, driven in part by cytokines such as

interleukins after AKI, which are deleterious to the lungs.[102] Both preterm and term infants with AKI have worse lung outcomes than their peers without AKI, including longer durations of mechanical ventilation and higher rates of bronchopulmonary dysplasia.[103,104] Neonatal AKI has been shown to be an independent risk factor for neurologic complications, such as intraventricular hemorrhage, poor long-term neurocognitive outcomes, and cardiovascular disease (hypertension).[105,106]

### Risk of CKD After AKI

The risk of developing CKD or end-stage kidney disease after AKI is well detailed in adults.[107] The evidence of progression from AKI to CKD is less established in children with AKI. In a systematic review of 346 children (mean follow-up 6.5 years), the incidence of an abnormal GFR <90 mL/minute per 1.73 $m^2$ was 6.3% (95% CI: 5.1 to 7.5).[108] The mechanisms for progression to CKD are incompletely understood but likely are secondary to maladaptive repair, ongoing inflammation, and disordered regeneration.[109,110] Histologic findings of preterm neonates reveal abnormal glomeruli likely to develop sclerosis later, which could be the explanation for later CKD in those with AKI.[111] These changes may be superimposed on a decreased nephron number and reduction in future development of nephrons due to prematurity.[74]

The evidence for progression from AKI to CKD in neonates is less clear. Several studies have identified evidence of kidney abnormalities in preterm infants with a history of AKI.[112,113] In contrast, other studies have failed to identify differences in CKD or GFR in follow-up of preterm infants who had AKI as neonates.[86,114,115] The lack of appropriately powered studies, consensus definitions for AKI and CKD, and a consistent follow-up period are barriers to clearly defining the relationship between neonatal AKI and subsequent CKD. Although the Chronic Kidney Disease in Children study manages children with CKD and includes information on birth weight, it does not include detailed data on neonatal course and AKI. Large multicenter long-term follow-up studies of neonates after AKI are needed to completely understand the future risk of CKD.

## CONCLUSIONS

Dramatic advances in the diagnosis and epidemiology of neonatal AKI and our ability to care for neonates with kidney disease have occurred in the last decade.[116] New technologies and therapies designed to prevent and treat neonatal AKI augment these findings. Future work, including interventional trials of therapeutics to treat AKI (methylxanthines, RRT with novel devices), prospective long-term follow-up studies to understand risk factors for CKD development, and improved definitions of fluid overload, is needed. Additionally, continued integration of biomarkers into routine clinical use, more widespread availability and use of neonatal-specific extracorporeal devices for kidney support therapy, and standardization of monitoring and follow-up of neonates with AKI will continue to advance the field of neonatal AKI.[117,118] Ongoing collaboration between neonatologists, pediatricians, and nephrologists (including the Neonatal Kidney Collaborative; www.babykidney.org) will help drive these research initiatives, mentor young faculty, educate clinicians, inform families, and advocate for neonates at risk for short- and long-term kidney-related disease.[98,119]

### ABBREVIATIONS

Abbreviations

AKI: acute kidney injury
AWAKEN: Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates
CHD: congenital heart disease
CI: confidence interval
CKD: chronic kidney disease
CRRT: continuous renal replacement therapy
CysC: cystatin C
ECMO: extracorporeal membrane oxygenation
ELGAN: extremely low gestational age neonate
GA: gestational age
GFR: glomerular filtration rate
HIE: hypoxic-ischemic encephalopathy
IGFBP-7: insulinlike growth factor binding protein 7
KDIGO: Kidney Disease Improving Global Outcomes
NEC: necrotizing enterocolitis
NGAL: neutrophil gelatinase–associated lipocalin
NINJA: Nephrotoxic Injury Negated by Just-in-Time Action
NIRS: near-infrared spectroscopy
NSAID: nonsteroidal antiinflammatory drug
OR: odds ratio
PD: peritoneal dialysis
PDA: patent ductus arteriosus
$RrSO_2$: Renal tissue oxygenation
RRT: renal replacement therapy
SCr: serum creatinine
TIMP-2: tissue inhibitor of metalloproteinase 2
UOP: urine output
VLBW: very low birth weight

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## REFERENCES

1. Selewski DT, Charlton JR, Jetton JG, et al. Neonatal acute kidney injury. *Pediatrics*. 2015;136(2). Available at: www.pediatrics.org/cgi/content/full/136/2/e463
2. Askenazi DJ, Heagerty PJ, Schmicker RH, et al; PENUT Trial Consortium. Prevalence of acute kidney injury (AKI) in extremely low gestational age neonates (ELGAN). *Pediatr Nephrol*. 2020;35(9):1737–1748
3. Carmody JB, Swanson JR, Rhone ET, Charlton JR. Recognition and reporting of AKI in very low birth weight infants. *Clin J Am Soc Nephrol*. 2014;9(12):2036–2043
4. Jetton JG, Boohaker LJ, Sethi SK, et al; Neonatal Kidney Collaborative (NKC). Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study. *Lancet Child Adolesc Health*. 2017;1(3):184–194
5. Menon S, Broderick J, Munshi R, et al. Kidney support in children using an ultrafiltration device: a multicenter, retrospective study. *Clin J Am Soc Nephrol*. 2019;14(10):1432–1440
6. Vidal E, Garzotto F, Parolin M, et al. Therapeutic plasma exchange in neonates and infants: successful use of a miniaturized machine. *Blood Purif*. 2017;44(2):100–105
7. Chambers JM, Wingert RA. Advances in understanding vertebrate nephrogenesis. *Tissue Barriers*. 2020;8(4):1832844
8. Chevalier RL. Evolutionary nephrology. *Kidney Int Rep*. 2017;2(3):302–317
9. Straub RH, Schradin C. Chronic inflammatory systemic diseases: an evolutionary trade-off between acutely beneficial but chronically harmful programs. *Evol Med Public Health*. 2016;2016(1):37–51
10. Iacobelli S, Guignard JP. Maturation of glomerular filtration rate in neonates and infants: an overview. *Pediatr Nephrol*. 2021;36(6):1439–1446
11. Hyink DP, Abrahamson DR. Origin of the glomerular vasculature in the developing kidney. *Semin Nephrol*. 1995;15(4):300–314
12. Abitbol CL, Seeherunvong W, Galarza MG, et al. Neonatal kidney size and function in preterm infants: what is a true estimate of glomerular filtration rate? *J Pediatr*. 2014;164(5):1026–1031.e2
13. Su SW, Stonestreet BS. Core concepts: neonatal glomerular filtration rate. *Neoreviews*. 2010;11(12):e714–e721
14. Jetton JG, Guillet R, Askenazi DJ, et al; Neonatal Kidney Collaborative. Assessment of worldwide acute kidney injury epidemiology in neonates: design of a retrospective cohort study. *Front Pediatr*. 2016;4:68
15. Kellum JA, Lameire N; KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (part 1). *Crit Care*. 2013;17(1):204
16. Zappitelli M, Ambalavanan N, Askenazi DJ, et al. Developing a neonatal acute kidney injury research definition: a report from the NIDDK neonatal AKI workshop. *Pediatr Res*. 2017;82(4):569–573
17. Stoops C, Stone S, Evans E, et al. Baby NINJA (Nephrotoxic Injury Negated by Just-in-Time Action): reduction of nephrotoxic medication-associated acute kidney injury in the neonatal intensive care unit. *J Pediatr*. 2019;215:223–228.e6
18. Thayyil S, Sheik S, Kempley ST, Sinha A. A gestation- and postnatal age-based reference chart for assessing renal function in extremely premature infants. *J Perinatol*. 2008;28(3):226–229
19. Askenazi DJ, Ambalavanan N, Goldstein SL. Acute kidney injury in critically ill newborns: what do we know? What do we need to learn? *Pediatr Nephrol*. 2009;24(2):265–274
20. Gupta C, Massaro AN, Ray PE. A new approach to define acute kidney injury in term newborns with hypoxic ischemic encephalopathy. *Pediatr Nephrol*. 2016;31(7):1167–1178
21. Bezerra CT, Vaz Cunha LC, Libório AB. Defining reduced urine output in neonatal ICU: importance for mortality and acute kidney injury classification. *Nephrol Dial Transplant*. 2013;28(4):901–909
22. Bruel A, Rozé JC, Flamant C, Simeoni U, Roussey-Kesler G, Allain-Launay E. Critical serum creatinine values in very preterm newborns. *PLoS One*. 2013;8(12):e84892
23. Askenazi D, Abitbol C, Boohaker L, et al; Neonatal Kidney Collaborative. Optimizing the AKI definition during first postnatal week using assessment of worldwide acute kidney injury epidemiology in neonates (AWAKEN) cohort. *Pediatr Res*. 2019;85(3):329–338
24. Koralkar R, Ambalavanan N, Levitan EB, McGwin G, Goldstein S, Askenazi D. Acute kidney injury reduces survival in very low birth weight infants. *Pediatr Res*. 2011;69(4):354–358
25. Charlton JR, Boohaker L, Askenazi D, et al; Neonatal Kidney Collaborative.

Incidence and risk factors of early onset neonatal AKI. *Clin J Am Soc Nephrol.* 2019;14(2):184–195

26. Majed B, Bateman DA, Uy N, Lin F. Patent ductus arteriosus is associated with acute kidney injury in the preterm infant. *Pediatr Nephrol.* 2019;34(6): 1129–1139
27. Guillet R, Selewski DT, Griffin R, Rastogi S, Askenazi DJ, D'Angio CT; Neonatal Kidney Collaborative. Relationship of patent ductus arteriosus management with neonatal AKI. *J Perinatol.* 2021;41(6): 1441–1447
28. Charlton JR, Boohaker L, Askenazi D, et al; Neonatal Kidney Collaborative (NKC). Late onset neonatal acute kidney injury: results from the AWAKEN Study. *Pediatr Res.* 2019;85(3):339–348
29. Polglase GR, Ong T, Hillman NH. Cardiovascular alterations and multiorgan dysfunction after birth asphyxia. *Clin Perinatol.* 2016;43(3):469–483
30. Bozkurt O, Yucesoy E. Acute kidney injury in neonates with perinatal asphyxia receiving therapeutic hypothermia. *Am J Perinatol.* 2021;38(9):922–929
31. Kirkley MJ, Boohaker L, Griffin R, et al; Neonatal Kidney Collaborative (NKC). Acute kidney injury in neonatal encephalopathy: an evaluation of the AWAKEN database. *Pediatr Nephrol.* 2019;34(1): 169–176
32. Michniewicz B, Al Saad SR, Karbowski LM, Gadzinowski J, Szymankiewicz M, Szpecht D. Organ complications of infants with hypoxic ischemic encephalopathy before therapeutic hypothermia. *Ther Hypothermia Temp Manag.* 2021;11(1):58–63
33. Selewski DT, Jordan BK, Askenazi DJ, Dechert RE, Sarkar S. Acute kidney injury in asphyxiated newborns treated with therapeutic hypothermia. *J Pediatr.* 2013;162(4):725–729.e1
34. Fleming GM, Sahay R, Zappitelli M, et al. The incidence of acute kidney injury and its effect on neonatal and pediatric extracorporeal membrane oxygenation outcomes: a multicenter report from the kidney intervention during extracorporeal membrane oxygenation study group. *Pediatr Crit Care Med.* 2016; 17(12):1157–1169
35. Madsen NL, Goldstein SL, Frøslev T, Christiansen CF, Olsen M. Cardiac surgery in patients with congenital heart disease is associated with acute kidney injury and the risk of chronic kidney disease. *Kidney Int.* 2017;92(3):751–756
36. Wong JH, Selewski DT, Yu S, et al. Severe acute kidney injury following stage 1 Norwood palliation: effect on outcomes and risk of severe acute kidney injury at subsequent surgical stages. *Pediatr Crit Care Med.* 2016;17(7):615–623
37. Murphy HJ, Gien J, Sahay R, et al. Acute kidney injury, fluid overload, and renal replacement therapy differ by underlying diagnosis in neonatal extracorporeal support and impact mortality disparately [published online ahead of print January 18, 2021]. *Blood Purif.* doi: 10.1159/000512538
38. Wu Y, Hua X, Yang G, Xiang B, Jiang X. Incidence, risk factors, and outcomes of acute kidney injury in neonates after surgical procedures. *Pediatr Nephrol.* 2020;35(7):1341–1346
39. Garg PM, Britt AB, Ansari MAY, et al. Severe acute kidney injury in neonates with necrotizing enterocolitis: risk factors and outcomes [published online ahead of print January 14, 2021]. *Pediatr Res.* doi: 10.1038/s41390-020-01320-6
40. Flori HR, Church G, Liu KD, Gildengorin G, Matthay MA. Positive fluid balance is associated with higher mortality and prolonged mechanical ventilation in pediatric patients with acute lung injury. *Crit Care Res Pract.* 2011;2011:854142
41. Gist KM, Selewski DT, Brinton J, Menon S, Goldstein SL, Basu RK. Assessment of the independent and synergistic effects of fluid overload and acute kidney injury on outcomes of critically ill children. *Pediatr Crit Care Med.* 2020;21(2): 170–177
42. Goldstein SL, Currier H, Graf JM, Cosio CC, Brewer ED, Sachdeva R. Outcome in children receiving continuous venovenous hemofiltration. *Pediatrics.* 2001; 107(6):1309–1312
43. Gorga SM, Sahay RD, Askenazi DJ, et al. Fluid overload and fluid removal in pediatric patients on extracorporeal membrane oxygenation requiring continuous renal replacement therapy: a multicenter retrospective cohort study. *Pediatr Nephrol.* 2020;35(5):871–882
44. Hassinger AB, Wald EL, Goodman DM. Early postoperative fluid overload precedes acute kidney injury and is associated with higher morbidity in pediatric cardiac surgery patients. *Pediatr Crit Care Med.* 2014;15(2): 131–138
45. Li Y, Wang J, Bai Z, et al. Early fluid overload is associated with acute kidney injury and PICU mortality in critically ill children. *Eur J Pediatr.* 2016;175(1): 39–48
46. Mah KE, Hao S, Sutherland SM, et al. Fluid overload independent of acute kidney injury predicts poor outcomes in neonates following congenital heart surgery. *Pediatr Nephrol.* 2018;33(3):511–520
47. Selewski DT, Cornell TT, Lombel RM, et al. Weight-based determination of fluid overload status and mortality in pediatric intensive care unit patients requiring continuous renal replacement therapy. *Intensive Care Med.* 2011; 37(7):1166–1173
48. Sutherland SM, Zappitelli M, Alexander SR, et al. Fluid overload and mortality in children receiving continuous renal replacement therapy: the prospective pediatric continuous renal replacement therapy registry. *Am J Kidney Dis.* 2010;55(2):316–325
49. Valentine SL, Sapru A, Higgerson RA, et al; Pediatric Acute Lung Injury and Sepsis Investigator's (PALISI) Network; Acute Respiratory Distress Syndrome Clinical Research Network (ARDSNet). Fluid balance in critically ill children with acute lung injury. *Crit Care Med.* 2012;40(10):2883–2889
50. Hoste EA, Maitland K, Brudney CS, et al; ADQI XII Investigators Group. Four phases of intravenous fluid therapy: a conceptual model. *Br J Anaesth.* 2014;113(5):740–747
51. Selewski DT, Akcan-Arikan A, Bonachea EM, et al; Neonatal Kidney Collaborative. The impact of fluid balance on outcomes in critically ill near-term/term neonates: a report from the AWAKEN study group. *Pediatr Res.* 2019;85(1):79–85
52. van Asperen Y, Brand PL, Bekhof J. Reliability of the fluid balance in neonates. *Acta Paediatr.* 2012;101(5):479–483
53. Selewski DT, Gist KM, Nathan AT, et al; Neonatal Kidney Collaborative. The impact of fluid balance on outcomes in

premature neonates: a report from the AWAKEN study group. *Pediatr Res.* 2020;87(3):550–557

54. Bontant T, Matrot B, Abdoul H, et al. Assessing fluid balance in critically ill pediatric patients. *Eur J Pediatr.* 2015; 174(1):133–137
55. Paul IM, Schaefer EW, Miller JR, et al. Weight change nomograms for the first month after birth. *Pediatrics.* 2016; 138(6):e20162625
56. Wadhawan R, Oh W, Perritt R, et al. Association between early postnatal weight loss and death or BPD in small and appropriate for gestational age extremely low-birth-weight infants. *J Perinatol.* 2007;27(6):359–364
57. Schmidt B, Roberts RS, Fanaroff A, et al; TIPP Investigators. Indomethacin prophylaxis, patent ductus arteriosus, and the risk of bronchopulmonary dysplasia: further analyses from the Trial of Indomethacin Prophylaxis in Preterms (TIPP). *J Pediatr.* 2006;148(6):730–734
58. Oh W, Poindexter BB, Perritt R, et al; Neonatal Research Network. Association between fluid intake and weight loss during the first ten days of life and risk of bronchopulmonary dysplasia in extremely low birth weight infants. *J Pediatr.* 2005;147(6):786–790
59. Askenazi DJ, Koralkar R, Hundley HE, Montesanti A, Patil N, Ambalavanan N. Fluid overload and mortality are associated with acute kidney injury in sick near-term/term neonate. *Pediatr Nephrol.* 2013;28(4):661–666
60. Selewski DT, Goldstein SL. The role of fluid overload in the prediction of outcome in acute kidney injury. *Pediatr Nephrol.* 2018;33(1):13–24
61. Askenazi DJ, Koralkar R, Patil N, Halloran B, Ambalavanan N, Griffin R. Acute kidney injury urine biomarkers in very low-birth-weight infants. *Clin J Am Soc Nephrol.* 2016;11(9):1527–1535
62. DeFreitas MJ, Seeherunvong W, Katsoufis CP, et al. Longitudinal patterns of urine biomarkers in infants across gestational ages. *Pediatr Nephrol.* 2016;31(7):1179–1188
63. Wasung ME, Chawla LS, Madero M. Biomarkers of renal function, which and when? *Clin Chim Acta.* 2015;438:350–357
64. Chowdhary V, Vajpeyajula R, Jain M, et al. Comparison of different definitions of acute kidney injury in extremely low birth weight infants. *Clin Exp Nephrol.* 2018;22(1):117–125
65. Renganathan A, Warner BB, Tarr PI, Dharnidharka VR. The progression of serum cystatin C concentrations within the first month of life after preterm birth-a worldwide systematic review. *Pediatr Nephrol.* 2021;36(7):1709–1718
66. Yang Y, Li SJ, Pan JJ, et al. Reference values for serum cystatin C in very low-birthweight infants: from two centres of China. *J Paediatr Child Health.* 2018; 54(3):284–288
67. Nakashima T, Inoue H, Fujiyoshi J, Matsumoto N. Longitudinal analysis of serum cystatin C for estimating the glomerular filtration rate in preterm infants. *Pediatr Nephrol.* 2016;31(6):983–989
68. Treiber M, Pečovnik Balon B, Gorenjak M. A new serum cystatin C formula for estimating glomerular filtration rate in newborns. *Pediatr Nephrol.* 2015; 30(8):1297–1305
69. Devarajan P. Neutrophil gelatinase-associated lipocalin: a promising biomarker for human acute kidney injury. *Biomarkers Med.* 2010;4(2):265–280
70. Tanigasalam V, Bhat V, Adhisivam B, Sridhar MG. Does therapeutic hypothermia reduce acute kidney injury among term neonates with perinatal asphyxia?–a randomized controlled trial. *J Matern Fetal Neonatal Med.* 2016;29(15): 2545–2548
71. Chen J, Sun Y, Wang S, et al. The effectiveness of urinary TIMP-2 and IGFBP-7 in predicting acute kidney injury in critically ill neonates. *Pediatr Res.* 2020; 87(6):1052–1059
72. Fan W, Ankawi G, Zhang J, et al. Current understanding and future directions in the application of TIMP-2 and IGFBP7 in AKI clinical practice. *Clin Chem Lab Med.* 2019;57(5):567–576
73. Stojanović VD, Barišić NA, Vučković NM, Doronjski AD, Peco Antić AE. Urinary kidney injury molecule-1 rapid test predicts acute kidney injury in extremely low-birth-weight neonates. *Pediatr Res.* 2015;78(4):430–435
74. Charlton JR, Baldelomar EJ, Hyatt DM, Bennett KM. Nephron number and its determinants: a 2020 update. *Pediatr Nephrol.* 2021;36(4):797–807
75. Baldelomar EJ, Charlton JR, deRonde KA, Bennett KM. In vivo measurements of kidney glomerular number and size in healthy and $Os^{/+}$ mice using MRI. *Am J Physiol Renal Physiol.* 2019;317(4): F865–F873
76. Baldelomar EJ, Charlton JR, Beeman SC, Bennett KM. Measuring rat kidney glomerular number and size in vivo with MRI. *Am J Physiol Renal Physiol.* 2018;314(3):F399–F406
77. Rodríguez MM, Gómez AH, Abitbol CL, Chandar JJ, Duara S, Zilleruelo GE. Histomorphometric analysis of postnatal glomerulogenesis in extremely preterm infants. *Pediatr Dev Pathol.* 2004;7(1): 17–25
78. Charlton JR, Baldelomar EJ, deRonde KA, et al. Nephron loss detected by MRI following neonatal acute kidney injury in rabbits. *Pediatr Res.* 2020;87(7): 1185–1192
79. Harer MW, Chock VY. Renal tissue oxygenation monitoring-an opportunity to improve kidney outcomes in the vulnerable neonatal population. *Front Pediatr.* 2020;8:241
80. Hazle MA, Gajarski RJ, Aiyagari R, et al. Urinary biomarkers and renal near-infrared spectroscopy predict intensive care unit outcomes after cardiac surgery in infants younger than 6 months of age. *J Thorac Cardiovasc Surg.* 2013;146(4):861–867.e1
81. Bonsante F, Ramful D, Binquet C, et al. Low renal oxygen saturation at near-infrared spectroscopy on the first day of life is associated with developing acute kidney injury in very preterm infants. *Neonatology.* 2019;115(3):198–204
82. Dorum BA, Ozkan H, Cetinkaya M, Koksal N. Regional oxygen saturation and acute kidney injury in premature infants. *Pediatr Int.* 2021;63(3):290–294
83. Harer MW, Adegboro CO, Richard LJ, McAdams RM. Non-invasive continuous renal tissue oxygenation monitoring to identify preterm neonates at risk for acute kidney injury. *Pediatr Nephrol.* 2021;36(6):1617–1625
84. Chock VY, Frymoyer A, Yeh CG, Van Meurs KP. Renal saturation and acute kidney injury in neonates with hypoxic ischemic encephalopathy undergoing therapeutic hypothermia. *J Pediatr.* 2018;200:232–239.e1

85. Sanderson KR, Chang E, Bjornstad E, et al. Albuminuria, hypertension, and reduced kidney volumes in adolescents born extremely premature. *Front Pediatr.* 2020;8:230

86. Askenazi DJ, Heagerty PJ, Schmicker RH, et al. The impact of erythropoietin on short- and long-term kidney-related outcomes in neonates of extremely low gestational age. Results of a multicenter, double-blind, placebo-controlled randomized clinical trial. *J Pediatr.* 2021; 232:65–72.e7

87. Pedersen KR, Ravn HB, Povlsen JV, Schmidt MR, Erlandsen EJ, Hjortdal VE. Failure of remote ischemic preconditioning to reduce the risk of postoperative acute kidney injury in children undergoing operation for complex congenital heart disease: a randomized single-center study. *J Thorac Cardiovasc Surg.* 2012;143(3):576–583

88. Lomivorotov V, Kornilov I, Boboshko V, et al. Effect of intraoperative dexamethasone on major complications and mortality among infants undergoing cardiac surgery: the DECISION randomized clinical trial. *JAMA.* 2020;323(24):2485–2492

89. Harer MW, Askenazi DJ, Boohaker LJ, et al; Neonatal Kidney Collaborative (NKC). Association between early caffeine citrate administration and risk of acute kidney injury in preterm neonates: results from the AWAKEN study. *JAMA Pediatr.* 2018;172(6):e180322

90. Bellos I, Pandita A, Yachha M. Effectiveness of theophylline administration in neonates with perinatal asphyxia: a meta-analysis. *J Matern Fetal Neonatal Med.* 2019;34(18):3080–3088

91. Mohamed TH, Klamer B, Mahan JD, Spencer JD, Slaughter JL. Diuretic therapy and acute kidney injury in preterm neonates and infants [published online ahead of print May 21, 2021]. *Pediatr Nephrol.* doi: 10.1007/s00467-021-05132-6

92. Kakajiwala A, Kim JY, Hughes JZ, et al. Lack of furosemide responsiveness predicts acute kidney injury in infants after cardiac surgery. *Ann Thorac Surg.* 2017;104(4):1388–1394

93. Chock VY, Cho SH, Frymoyer A. Aminophylline for renal protection in neonatal hypoxic-ischemic encephalopathy in the era of therapeutic hypothermia. *Pediatr Res.* 2021;89(4):974–980

94. Carmody JB, Harer MW, Denotti AR, Swanson JR, Charlton JR. Caffeine exposure and risk of acute kidney injury in a retrospective cohort of very low birth weight neonates. *J Pediatr.* 2016;172: 63–68.e1

95. Kaddourah A, Goldstein SL. Renal replacement therapy in neonates. *Clin Perinatol.* 2014;41(3):517–527

96. Harshman LA, Muff-Luett M, Neuberger ML, et al. Peritoneal dialysis in an extremely low-birth-weight infant with acute kidney injury. *Clin Kidney J.* 2014;7(6):582–585

97. Munshi R, Lee-Son K, Hackbarth RM, et al. Clinical evaluation of the Prismaflex™ HF 20 set and Prismaflex™ system 7.10 for acute continuous kidney replacement therapy (CKRT) in children. *Pediatr Nephrol.* 2020;35(12):2345–2352

98. Askenazi DJ. AWAKEN-ing a new frontier in neonatal nephrology. *Front Pediatr.* 2020;8:21

99. Garzotto F, Vidal E, Ricci Z, et al. Continuous kidney replacement therapy in critically ill neonates and infants: a retrospective analysis of clinical results with a dedicated device. *Pediatr Nephrol.* 2020;35(9):1699–1705

100. Faubel S, Shah PB. Immediate consequences of acute kidney injury: the impact of traditional and nontraditional complications on mortality in acute kidney injury. *Adv Chronic Kidney Dis.* 2016;23(3):179–185

101. Basu RK, Wheeler DS. Kidney-lung crosstalk and acute kidney injury. *Pediatr Nephrol.* 2013;28(12):2239–2248

102. Grigoryev DN, Liu M, Hassoun HT, Cheadle C, Barnes KC, Rabb H. The local and systemic inflammatory transcriptome after acute kidney injury. *J Am Soc Nephrol.* 2008;19(3):547–558

103. Starr MC, Boohaker L, Eldredge LC, et al; Neonatal Kidney Collaborative. Acute kidney injury and bronchopulmonary dysplasia in premature neonates born less than 32 weeks' gestation. *Am J Perinatol.* 2020;37(3):341–348

104. Starr MC, Boohaker L, Eldredge LC, et al; Neonatal Kidney Collaborative. Acute kidney injury is associated with poor lung outcomes in infants born ≥32 weeks of gestational age. *Am J Perinatol.* 2020;37(2):231–240

105. Stoops C, Sims B, Griffin R, Askenazi DJ. Neonatal acute kidney injury and the risk of intraventricular hemorrhage in the very low birth weight infant. *Neonatology.* 2016;110(4):307–312

106. Kraut EJ, Boohaker LJ, Askenazi DJ, Fletcher J, Kent AL; Neonatal Kidney Collaborative (NKC). Incidence of neonatal hypertension from a large multicenter study [Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates-AWAKEN]. *Pediatr Res.* 2018;84(2):279–289

107. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney Int.* 2012;81(5): 442–448

108. Greenberg JH, Coca S, Parikh CR. Long-term risk of chronic kidney disease and mortality in children after acute kidney injury: a systematic review. *BMC Nephrol.* 2014;15:184

109. Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. *N Engl J Med.* 2014;371(1): 58–66

110. Basile DP, Bonventre JV, Mehta R, et al; ADQI XIII Work Group. Progression after AKI: understanding maladaptive repair processes to predict and identify therapeutic treatments. *J Am Soc Nephrol.* 2016;27(3):687–697

111. Sutherland MR, Gubhaju L, Moore L, et al. Accelerated maturation and abnormal morphology in the preterm neonatal kidney. *J Am Soc Nephrol.* 2011;22(7):1365–1374

112. Abitbol CL, Bauer CR, Montané B, Chandar J, Duara S, Zilleruelo G. Long-term follow-up of extremely low birth weight infants with neonatal renal failure. *Pediatr Nephrol.* 2003;18(9):887–893

113. Harer MW, Pope CF, Conaway MR, Charlton JR. Follow-up of Acute Kidney Injury in Neonates During Childhood Years (FANCY): a prospective cohort study. *Pediatr Nephrol.* 2017;32(6): 1067–1076

114. Bruel A, Rozé JC, Quere MP, et al. Renal outcome in children born preterm with neonatal acute renal failure: IRENEO-a prospective controlled study. *Pediatr Nephrol.* 2016;31(12):2365–2373

115. Maqsood S, Fung N, Chowdhary V, Raina R, Mhanna MJ. Outcome of extremely

low birth weight infants with a history of neonatal acute kidney injury. *Pediatr Nephrol*. 2017;32(6):1035–1043

116. Askenazi DJ, Morgan C, Goldstein SL, et al. Strategies to improve the understanding of long-term renal consequences after neonatal acute kidney injury. *Pediatr Res*. 2016;79(3):502–508

117. Starr MC, Kula A, Lieberman J, et al. The impact of increased awareness of acute kidney injury in the neonatal intensive care unit on acute kidney injury incidence and reporting: results of a retrospective cohort study. *J Perinatol*. 2020;40(9):1301–1307

118. Vincent K, Murphy HJ, Ross JR, Twombley KE. Acute kidney injury guidelines are associated with improved recognition and follow-up for neonatal patients. *Adv Neonatal Care*. 2020; 20(4):269–275

119. Kent AL, Charlton JR, Guillet R, et al. Neonatal acute kidney injury: a survey of neonatologists' and nephrologists' perceptions and practice management. *Am J Perinatol*. 2018;35(1):1–9

120. Nour I, Elmaghraby R, Shehata R, et al. Selective head cooling and acute kidney injury in neonates with hypoxic ischemic encephalopathy. *J Neonatal Perinatal Med*. 2020;13(1): 21–30

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