Neonatal Acute Kidney Injury: Diagnosis, Exposures, and Long-term Outcomes

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Education Gaps

1. Neonatologists need to recognize the appropriate surveillance strategies for acute kidney injury (AKI) and the impact of fluid balance on neonatal outcomes of AKI.
2. Nephrologists should recognize normal preterm physiology and the impact of neonate-specific diseases and conditions on renal function.
3. There is a lack of consensus regarding a definition for neonatal AKI.
4. There is a gap in knowledge on long-term outcomes of neonates with AKI.

Abstract

Neonatal acute kidney injury is an underappreciated condition among patients cared for in the NICU. It may have both short- and long-term implications in this population. Improved surveillance during the initial hospitalization and during the first 2 decades of life has the potential to improve outcomes.

Objectives

After completing this article, readers should be able to:

1. Identify risk factors for neonatal acute kidney injury (nAKI) and know when and how to screen high-risk neonates.
2. Explain how the presence of nAKI affects overall morbidity and mortality in the NICU.
3. Have increased awareness of the potential long-term implications of nAKI and know how to conduct surveillance for high-risk NICU graduates.

INTRODUCTION

Little is known about neonatal kidney function and injury, especially in preterm infants. This includes the paucity of data on how in utero and postpartum exposures affect renal function later in life. This review focuses on the current state of knowledge of neonatal acute kidney injury (nAKI), including how renal

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ABBREVIATIONS

AKI acute kidney injury
AWAKEN Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates
BP blood pressure
CKD chronic kidney disease
CPAP continuous positive airway pressure
ECMO extracorporeal membrane oxygenation
eGFR estimated glomerular filtration rate
GFR glomerular filtration rate
HIE hypoxic-ischemic encephalopathy
HTN hypertension
KDIGO Kidney Disease: Improving Global Outcomes
nAKI neonatal acute kidney injury
NIH National Institutes of Health
PDA patent ductus arteriosus
SGA small for gestational age
VLBW very low birthweight
The future in the association of the issues, knowledge gaps, and opportunities for the goal of this article is for readers to gain a better appreciation of the issues, knowledge gaps, and opportunities for the future in the field of nAKI.

There are few other places in the era of modern medicine that have gone through such an evolution as has occurred in the NICU. Therapies such as continuous positive airway pressure (CPAP), surfactant, maternal corticosteroids, extracorporeal membrane oxygenation (ECMO), and cooling protocols have existed for only 30 to 40 years; some therapies have been standard of care for an even shorter period. It is clear that today, neonates admitted to the NICU who in another era would not have been resuscitated or who would have died within a matter of hours are now surviving to adulthood. Of nearly 4,000,000 live births in 2015 in the United States, 9.6% were born at less than 37 weeks’ gestation: 0.7% were 27 weeks’ gestation or less and 2.1% were 28 to 33 weeks’ gestation. (3) Thus, the population graduating from the NICU is not small. Amazingly, most infants born weighing between 500 and 1,500 g survive to discharge (90%), and 60% leave with no major neonatal morbidity. (4) However, the long-term consequences of a critically ill beginning are far less clear. (5) There is emerging evidence from the basic science and clinical arenas to suggest that both prematurity and the required lifesaving therapies may have serious long-term consequences for kidney health.

Although much work has been dedicated to advancing the field of AKI in adults and children, there are still many areas in the field of nAKI that remain unclear or unanswered. This may be due in part to the silos of neonatology and pediatric nephrology. Neonatologists care for the “whole” infant, balancing all organ systems; few neonatologists have expertise in the area of neonatal kidneys. Most neonatologists focus on the infant population only, many of whom have little follow-up with patients after discharge from the NICU or after the newborn period. Pediatric nephrologists focus only on renal physiology and are more familiar with issues in older pediatric patients.

We identified similarities and differences in these knowledge gaps in a survey taken by neonatologists and nephrologists that was published in 2017. (3) Herein we present cases that are similar to the published ones highlighting the unique features of nAKI and summarizing the current state of knowledge in this field. Rectifying these information gaps will take dedicated collaborations between neonatologists and pediatric nephrologists.

CLINICAL SCENARIO: BABY A

Baby A was born to a 28-year-old woman with preterm rupture of membranes who received betamethasone for fetal pulmonary maturation and 3 doses of indomethacin for tocolysis. The female infant was delivered at 25 2/7 weeks’ gestation, weighing 650 g. She was intubated at birth, received surfactant, and was extubated on day 2 of age. She received 2 days of ampicillin and gentamicin during a sepsis evaluation. Gentamicin levels were not obtained and serum creatinine level was not included in the routine electrolyte panels. Later in the first week after birth, a clinically significant patent ductus arteriosus (PDA) was diagnosed and treated with indomethacin. The serum creatinine level was 0.8 mg/dL (70.7 μmol/L) before starting indomethacin therapy and peaked at 1.2 mg/dL (106.1 μmol/L) after the third dose. Concomitantly, the urine output decreased during treatment but remained greater than 1.0 mL/kg per hour. Following the course of indomethacin, the serum creatinine level decreased to 0.4 mg/dL (35.4 μmol/L).

The scenario described in Baby A is very common, one that all neonatologists encounter, and unlikely to involve a nephrologist. This is an extremely low birth-weight infant exposed both in utero and after birth to at least 2 drugs that may be nephrotoxic. A PDA can result in decreased renal blood flow (as well as decreased splanchnic blood flow) and can sometimes be treated if there are signs that it is “clinically significant.”

There are at least 2 potentially significant risk factors for impaired renal function highlighted in this scenario: extreme prematurity and the presence of a PDA treated with a nephrotoxic drug. In addition, we need to distinguish between impaired renal function and acute injury in this population.

Whether a consequence of treatment (ie, indomethacin) or due to the indication for the therapy (ie, PDA), the question remains, “Did this baby have AKI?” In this case, is the rise in creatinine level a sign of AKI or is it just an indication that the indomethacin is acting as predicted, causing vasoconstriction that is not restricted to just the ductus? If solely vasoconstriction related, does that impact the developing kidney, causing damage, or is it just a change in the renal hemodynamics? Given incomplete nephrogenesis, is the change in creatinine level a surrogate for low nephron numbers?

Definition of AKI

AKI is defined as an abrupt decline in renal function that results in a derangement of fluid balance, electrolytes, and...
waste products. Both adult and pediatric nephrologists are attuned to the impact of AKI because it is clearly associated with poor outcomes. In adults, AKI is independently associated with increased risk of death, length of hospitalization, and cost. (6) In children, the situation is similar: AKI is independently associated with increased risk of death, ventilator days, and length of stay. (7) However, there are limited data in neonates. There is currently no standard of care for renal function surveillance in neonates. Renal function, measured by serum creatinine level, often is a part of an electrolyte panel for neonates and is not likely to be assessed independently of an electrolyte panel.

There have been many definitions for AKI in the adult, pediatric, and neonatal literature. Arbitrary cutoff levels of serum creatinine greater than 1.5 mg/dL (>132.6 μmol/L) or greater than 2.0 mg/dL (>176.8 μmol/L) (8) have been used in neonates, in addition to gestational age cutoff points (9) and rate of decline in term neonates. (10) However, the most often used categorical definition for nAKI that has been independently associated with mortality and length of stay is the modified neonatal Kidney Disease: Improving Global Outcomes (KDIGO) definition. (11) This definition accounts for a change in serum creatinine level from a previous base, includes urine output criteria, and has 3 stages accounting for AKI severity (Table 1).

Serum creatinine level is imperfect as a surrogate for renal function. It is a late functional marker that takes 24 to 48 hours to change after injury. Serum creatinine level is particularly problematic for very small neonates with low muscle mass and provides no specificity for the type of injury. Depending on the type of assay used, there can be interfering substances. Specifically in neonates, the creatinine level detected at the time of birth reflects maternal renal function and can be elevated in the neonate in the setting of maternal renal disease or placental dysfunction. The modified neonatal KDIGO definition does not address the situation in which the serum creatinine level does not decrease and neonates may be misclassified. Often in immature neonates, urine output can be maintained despite significant injury. There are clearly many limitations to the neonatal AKI definition; however, at a 2013 National Institutes of Health (NIH) workshop, experts in the field agreed that despite its limitations, the KDIGO definition for nAKI was the most appropriate definition. (12)

Using the categorical definitions, the rates of nAKI range from 16% to 71%. (13) The incidence of AKI in preterm infants ranges from 18% to 40% and is independently associated with mortality and length of stay. (14)(15)(16) An understudied but large population of neonates includes those born late preterm. (17) The only study to examine this population using the KDIGO definition for nAKI showed that 16% developed AKI. (15) Congenital anomalies, including heart defects and diaphragmatic hernias, and perinatal asphyxia are admission diagnoses of term neonates that confer a high risk for developing AKI, with a prevalence rate ranging from 3.8% to 71%. (18)(19)(20)(21)(22)(23)

Renal Development

The neonate in scenario A was born extremely preterm, a factor that may exacerbate potentially nephrotoxic episodes because kidney development was incomplete. The development of nephrons in humans begins at approximately 9 weeks’ gestation (24)(25) and is complete at approximately 36 weeks’ gestation. (26) A full-term neonate has the final nephron endowment at birth. The kidney continues a maturational process for nearly 2 years, at which time adult glomerular filtration rate (GFR) is established. Important in the setting of prematurity, the third trimester is a very active

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**TABLE 1. Neonatal Acute Kidney Injury Based on KDIGO Classification (11)**

<table>
<thead>
<tr>
<th>STAGE</th>
<th>SERUM CREATININE</th>
<th>URINE OUTPUT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No change in sCr or rise &lt;0.3 mg/dL (&lt;26.5 μmol/L)</td>
<td>≥0.5 mL/kg per hour</td>
</tr>
<tr>
<td>1</td>
<td>sCr rise ≥0.3 mg/dL (≥26.5 μmol/L) within 48 h or sCr rise ≥1.5–1.9 times the reference sCr* within 7 d</td>
<td>&lt;0.5 mL/kg per hour for 6 to 12 h</td>
</tr>
<tr>
<td>2</td>
<td>sCr rise ≥2–2.9 times the reference sCr†</td>
<td>&lt;0.5 mL/kg per hour for ≥12 h</td>
</tr>
<tr>
<td>3</td>
<td>sCr rise ≥3 times the reference sCr‡ or sCr ≥2.5 mg/dL (≥221 μmol/L) or receipt of dialysis</td>
<td>&lt;0.3 mL/kg per hour for ≥24 h or anuria for ≥12 h</td>
</tr>
</tbody>
</table>

 KDIGO=Kidney Disease: Improving Global Outcomes, sCr=serum creatinine.

Differences between the proposed neonatal AKI definition and KDIGO include:

*Reference sCr is defined as the lowest previous sCr value.

†An sCr value of 2.5 mg/dL (221 μmol/L) represents less than 10 mL/min/1.73 m².
time for nephrogenesis, with up to 60% of nephron development occurring during this window. (27) Nephrons do not regenerate, (28) and once the self-renewing population of metanephric mesenchyme has been depleted, new glomeruli cannot be created. Please refer to the article by Yanik et al in a 2015 issue of NeoReviews for a more complete review of renal development. (29)

It is commonly taught that a human has approximately 1,000,000 nephrons per kidney. Although this is a fundamentally true statement, it is based on relatively few published studies, with averages that range from 617,000 to 1.4 million. (30)(31)(32) It is also important to understand that nephron number is highly variable among humans (210,000 to 2,700,000). (31) Many factors can affect an individual’s nephron number, including sex, race, comorbid conditions, and even birthweight (Table 2). In 2006, Australian investigators examined the association of birthweight and nephron number and found that a 1-kg increase in birthweight conferred nearly 200,000 additional nephrons. (56) However, nephron number can currently be assessed postmortem only because stereologic techniques are used to estimate glomerular number. (57) A kidney biopsy alone is insufficient to determine nephron number.

### Postnatal Nephrogenesis

Little is known about postnatal nephrogenesis after preterm birth. Two descriptive histologic autopsy studies have shown that glomerulogenesis does seem to continue after preterm birth, but the window of nephrogenesis may be shortened and abnormal. An autopsy study of a cohort of gestational age–matched preterm neonates from Australia showed acceleration of the maturation of the kidney and a smaller nephrogenic zone. (58) The investigators described structurally abnormal-appearing glomeruli in their cohort. A second study by investigators at the University of Miami demonstrated ongoing glomerulogenesis for 40 days after birth in infants born weighing less than 1,000 g, but their kidneys had fewer layers of glomeruli than their full-term counterparts. (8) This study also took into account the role of AKI, and infants who had a sustained serum creatinine level greater than 2.0 mg/dL (>176.8 μmol/L) had fewer layers of glomeruli than those without AKI. If nAKI independently leads to fewer glomeruli, then it is not surprising that the preterm population is at risk for CKD.

### Commonly Used Nephrotoxic Medications

As described in scenario A, nonsteroidal anti-inflammatory drugs are another lifesaving and commonly used class of medications. In addition to their anti-inflammatory effects, nonsteroidal anti-inflammatory drugs also have the potential to affect renal function by interfering with the production of prostaglandins, which are essential for maintaining glomerular filtration rate. Other medications that have been shown to have a nephrotoxic effect include aminoglycosides, which can cause irreversible damage to the renal tubules, and corticosteroids, which can suppress the immune system and lead to decreased renal blood flow. Additionally, tobacco and ethanol have been linked to decreased nephron number, likely due to their effects on renal blood flow and oxygen supply. Hyperglycemia has also been shown to impair nephrogenesis, likely due to its negative effects on renal growth and development.

### Table 2: Factors Affecting Nephron Number During In Utero and Early Neonatal Development

<table>
<thead>
<tr>
<th>FACTORS AFFECTING NEPHRON NUMBER</th>
<th>MECHANISM OF ACTION</th>
<th>REF. NO.(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caloric restriction</td>
<td>Reduced nephron number</td>
<td>33, 34</td>
</tr>
<tr>
<td>Protein restriction</td>
<td>Reduced nephron number with increased apoptosis and reduced progenitor cells</td>
<td>35–37</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>Reduction in hepatic mobilization of vitamin A</td>
<td>38</td>
</tr>
<tr>
<td>Vitamin A deficiency</td>
<td>Reduced ureteric bud branching Reduced nephron number</td>
<td>39</td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
<td>Increased nephron number Potential mechanisms: active (1,25-OH) vitamin D stimulates cell differentiation and inhibits proliferation or active vitamin D negatively regulates renin expression, increased levels of angiotensin II could stimulate nephrogenesis</td>
<td>40–44</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Reduced nephron number</td>
<td>45, 46</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>Reduced nephron number</td>
<td>47</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Exposing metanephros culture media to dexamethasone for 2 d decreased the number of ureteric buds, resulting in fewer nephrons even when dexamethasone was removed</td>
<td>48–50</td>
</tr>
<tr>
<td>Tobacco</td>
<td>Reduced nephron number</td>
<td>51</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Reduced nephron number</td>
<td>52, 53</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>Metanephros development is impaired by hyperglycemia</td>
<td>54, 55</td>
</tr>
</tbody>
</table>
medications to treat or prevent PDA. These drugs are nephrotoxic largely due to their vasoconstrictive properties. In a single-center study, Rhone et al (59) reported that approximately 50% of very low-birthweight (VLBW) infants received indomethacin, with nearly 5 days of use and an average cumulative dose of 1.0 mg/kg. In rodents, the administration of indomethacin during the window of nephrogenesis resulted in the formation of fewer nephrons, and in a premature baboon model, ibuprofen reduced the nephrogenic zone. (58)(59) Possibly more alarming was a publication by Kent et al in 2012 (60) demonstrating an increased number of podocytes in the urine of infants receiving indomethacin. The podocyte is a terminally differentiated cell in the glomerulus that supports the glomerular filtration barrier, and permanent glomerular damage (focal segmental glomerulosclerosis) occurs when there is a reduction of podocytes.

CLINICAL SCENARIO: BABY B

Baby B was born at 30 weeks’ gestation after a pregnancy complicated by maternal pregnancy-induced hypertension (HTN) and severe intrauterine growth restriction. The pregnant woman was treated with betamethasone and magnesium sulfate in anticipation of an early delivery. The male infant weighed 890 g at birth and was assigned Apgar scores of 7 and 8 at 1 and 5 minutes, respectively. He was started on nasal CPAP but required transient intubation for surfactant at 6 hours of age. On day 7, his serum creatinine level was 0.3 mg/dL (26.5 μmol/L). Although the baby did well initially, at 14 days of age he began to have significant apnea and bradycardia requiring intubation. At the time of intubation, he had a mixed respiratory and metabolic acidosis. His creatinine level was 0.6 mg/dL (53.0 μmol/L), and his urine output had decreased to less than 0.5 mL/kg per hour. A sepsis evaluation was performed, and gentamicin and ampicillin were administered. Because the baby was hypotensive, he received a normal saline bolus and was started on dopamine therapy. The next day his creatinine level was 0.75 mg/dL (66.3 μmol/L). Within 24 hours, the blood culture was reported positive for Staphylococcus epidermidis resistant to ampicillin, so this was stopped and vancomycin alone was administered for 10 days. The baby’s creatinine level decreased to 0.6 mg/dL (53.0 μmol/L) at the completion of the course of vancomycin and 0.3 mg/dL (26.5 μmol/L) at discharge.

Sepsis is a common concern in the NICU population. Although most patients receive brief courses of nephrotoxic drugs, predominantly aminoglycosides and vancomycin, during sepsis evaluations, true sepsis occurs and warrants a prolonged course of treatment. In scenarios A and B, it is not clear whether the condition (PDA or sepsis) or its treatment (prostaglandin inhibitor or antibiotics) is the more important risk factor for renal injury or whether the two are additive or synergistic. Intrauterine growth restriction affects a significant proportion of patients in the NICU. The etiologies of impaired growth are numerous, including maternal and fetal factors. How these factors affect kidney development and ultimate function remains to be fully elucidated.

NICU Exposures that Influence Renal Development

Patient susceptibility factors and kidney stressors influence the risk of AKI. Patient susceptibility factors have been identified in adult studies, but many apply to neonates, including diabetes in the form of maternal exposure, congenital anomalies of the kidney, malnutrition, and birthweight. Nevertheless, even the least susceptible patients can have kidney injury if the stress is significant. Common kidney stressors in the NICU include volume depletion, sepsis, shock, hypoxemia, nephrotoxic medications (61) (including vancomycin, aminoglycosides, non-steroidal anti-inflammatory drugs, iodinated contrast), and invasive mechanical ventilation. Animal and human data demonstrate how many exposures in the NICU may affect renal development. It is critical to identify these factors to improve short- and long-term outcomes, to preserve as much as possible of the very short window of nephrogenesis.

As described in scenario B, aminoglycosides are commonly used in the NICU because they are excellent antimicrobial agents to treat neonatal sepsis despite their nephrotoxic potential. In a single-center study, nearly 86% of the VLBW neonates received an aminoglycoside, with an average of 10 days of use and an average cumulative dose of 32 mg/kg. (59) These drugs accumulate in the cortex and can be toxic because of this accumulation despite therapeutic systemic levels. It is proposed that some of the infants with the lowest gestational age might be “protected” from aminoglycosides owing to their immature endocytic transport system in the proximal tubule, but further work needs to be done to confirm this hypothesis. Animal data would suggest that the aminoglycoside effect on the kidney may be present despite an immature transport system. In a rodent study in which gentamicin was given daily to pregnant rats beginning midway through the gestation, the offspring had few glomeruli at birth and developed glomerulosclerosis during adulthood; it is unclear whether the glomerulosclerosis is a direct impact of the low nephron number at birth or a long-term consequence of the drug. (45)(62)

However, not all unique exposures in the NICU may increase the risk of nAKI. Recently published data suggest that early treatment with caffeine may be protective and
prevent or ameliorate nAKI in the preterm population. (63) In this single-center retrospective observational study, infants born before 32 weeks’ gestation who received caffeine had a significantly lower rate of early AKI compared with those not receiving caffeine (11.5% vs 31.4%; *P* < .01). (63) In addition, the caffeine-exposed group experienced significantly less severe nAKI (*P* < .01). Of note, in comparing the percentage of stage 3 AKI, the no caffeine group had 6 times the rate of stage 3 AKI compared with the caffeine group.

Neonatologists are well aware of the benefits of vitamin A regarding lung development. However, the benefit of vitamin A also extends to the developing kidney. Vitamin A may modulate nephron number via interaction with the RET receptor. Vitamin A deficiency may downregulate this receptor, resulting in decreased branching of ureteric bud tips. The relationship of plasma retinol levels and nephron number is demonstrated in a French study that showed that plasma retinol levels were highly correlated to lower nephron numbers in rats in a dose-dependent manner. (64) Vitamin A deficiency rarely occurs in developed countries but is common in many underdeveloped countries, affecting nearly 20 million pregnant women globally. Intriguing data have been published demonstrating smaller kidney volumes in offspring of pregnant women with vitamin A deficiency, suggesting that vitamin A status may also affect renal development in humans. (65)(66)

**CLINICAL SCENARIO: BABY C**

Baby C was born at 41 3/7 weeks’ gestation weighing 4,850 g to a 38-year-old woman with uncontrolled gestational diabetes. Shoulder dystocia occurred, and the male infant required extensive resuscitation. He was assigned Apgar scores of 1 at 1 minute and 3 at 5 minutes. The arterial cord gas had a pH of 6.9 and a base deficit of 18. He was resuscitated and underwent therapeutic hypothermia. He required vasopressors to maintain an appropriate blood pressure (BP). Macroscopic hematuria was noted, followed by anuria at 30 hours of age. He remained anuric at 5 minutes. The rate of stage 3 AKI compared with the caffeine group.

Neonatologists are well aware of the benefits of vitamin A regarding lung development. However, the benefit of vitamin A also extends to the developing kidney. Vitamin A may modulate nephron number via interaction with the RET receptor. Vitamin A deficiency may downregulate this receptor, resulting in decreased branching of ureteric bud tips. The relationship of plasma retinol levels and nephron number is demonstrated in a French study that showed that plasma retinol levels were highly correlated to lower nephron numbers in rats in a dose-dependent manner. (64) Vitamin A deficiency rarely occurs in developed countries but is common in many underdeveloped countries, affecting nearly 20 million pregnant women globally. Intriguing data have been published demonstrating smaller kidney volumes in offspring of pregnant women with vitamin A deficiency, suggesting that vitamin A status may also affect renal development in humans. (65)(66)

**AKI and HIE**

Multiple organ failure is commonly associated with HIE. Both in the era before therapeutic hypothermia and after adoption of cooling strategies to ameliorate neurodevelopmental impairment after acute perinatal asphyxial events, AKI remains prevalent. This association may be due to a common etiology or AKI may exacerbate organ system injury via inflammatory mechanisms, as suggested by Sarkar et al. (67) Because these investigators were able to predict the presence of magnetic resonance imaging abnormalities from their participants’ AKI status, the recognition of nAKI may suggest the need for heightened long-term neurodevelopmental follow-up.

As discussed previously herein, the diagnosis of AKI in neonates presents unique challenges. Gupta et al (10) suggest that in the asphyxiated newborn, the rate of decline in serum creatinine level during the first 5 to 7 days after birth is a feasible means of identifying clinically significant AKI. Neonates whose creatinine levels did not fall required more respiratory support and vasopressor treatment, had an increased average fluid balance, and had a longer length of stay compared with those whose creatinine levels declined within the first week.

**Defining CKD**

A critically important clinical question is: Will Baby C develop CKD? Most nephrologists would say that this child is at significant risk for the development of CKD. However, in a recent survey, neonatologists were less convinced. (68) Nephrologists agree that there is a relationship between AKI and CKD, but where AKI is on the causal pathway is still debated (Table 3). Many nephrologists believe that AKI results in a reduction of nephrons due to the AKI event and that this reduction of nephrons leads to CKD. Others believe that AKI reflects a “lack of reserve” or a lower endowment of nephrons, which eventually would have manifested as CKD later in life. Regardless of the pathway, there is an association between AKI and CKD, and this relationship may be even more important than in adults because neonates have a far longer life to live with the burden of CKD. In the most simple of definitions, CKD is too few nephrons to do the work of the kidney. CKD is independently associated with death and cardiovascular disease. When stratified by stage of CKD, there is a stepwise increased risk of death, cardiovascular event, or hospitalization. (77) CKD is expensive (78) and a burden to the health-care system, patients, and families.

The 5 stages of CKD are defined by GFR, most commonly estimated by serum creatinine concentrations. Stage 1 is...
normal kidney function with a GFR greater than 90 mL/min per 1.73 m² but with some “kidney damage.” For example, a child with a single kidney and an estimated GFR (eGFR) of 110 mL/min/1.73 m² has stage 1 CKD. There is radiologic evidence of renal agenesis, but this child’s renal function is normal. There are a few notable limitations with this construct for CKD for neonates. First, there is a developmental increase in GFR where adult GFR is reached at age 2 years, making the assessment for CKD difficult in neonates, infants, and young children. Second, GFR is a functional metric of the whole kidney and is defined by the GFR of each nephron multiplied by the number of nephrons in the kidney. When nephron number is low, the remaining glomeruli hypertrophy to increase the single-nephron GFR; therefore, surface area to complete filtration is maintained despite an absolute fewer number of nephrons. Third, most estimates of GFR are calculated using serum creatinine. This is particularly problematic in the neonate, infant, and young child because muscle mass is small. Last, creatinine is secreted into the urine, overestimating the true GFR.

In 2009, White and colleagues (79) published a meta-analysis of 31 studies showing that low birthweight conferred a 73% increased risk of developing adulthood CKD. Even more concerning was that this risk was present not only in adults but could also be detected in childhood. In 2014, Hsu and colleagues (80) showed that the odds of developing CKD were nearly 3 times higher in individuals born weighing less than 2,500 g. Neither of the aforementioned studies accounted for AKI.

During the past year, 2 publications have examined the effect of AKI on long-term renal health in the VLBW population. Bruel et al (84) used a gestational age cutoff criteria for AKI and prospectively matched kids with AKI with those who did not have AKI. They found that the children with AKI had smaller kidneys but no difference in eGFR using creatinine levels. However, 23% of their cohort had an eGFR less than 90 mL/min/1.73 m². In a smaller study published by Harer et al in 2017, (85) the modified KDIGO criteria were used to define AKI. In this study, the VLBW infants exposed to AKI had a 4.5 times higher risk of a composition outcome of elevated BP, proteinuria, or eGFR less than 90 mL/min/1.73 m² estimated using cystatin C levels.

There are several groups of full-term neonates in which AKI has been accounted for as a risk factor for the development of CKD. In 2014, a group from the Netherlands described the long-term renal follow-up of children who were exposed to ECMO. (20) Of the 423 participants who were exposed to ECMO from 1992 through 2002, the researchers assessed 169 at the average age of approximately 8 years. Nearly one-third of these children had some evidence of renal dysfunction, including an eGFR less than 90 mL/min/1.73 m², HTN, or proteinuria. Moderate or severe

<table>
<thead>
<tr>
<th>FACTORS AFFECTING THE DEVELOPMENT OF CKD</th>
<th>POTENTIAL MECHANISMS OF ACTION</th>
<th>REF. NO.(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low birthweight</td>
<td>Unclear, but may be secondary to lower nephron number</td>
<td>27, 69, 70</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>Nephron maldevelopment, reduced nephron number, AKI, nephrotoxic exposure</td>
<td>58, 71–74</td>
</tr>
<tr>
<td>Perinatal asphyxia</td>
<td>Hypoxia</td>
<td>20</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>Hypoxia, abnormal renal hemodynamics</td>
<td>75, 76</td>
</tr>
</tbody>
</table>

AKI=acute kidney injury, CKD=chronic kidney disease.

Small single-center cohort studies with various renal dysfunction outcome metrics continue to be published and provide insight into the best ways to assess the renal health of the NICU population. A Japanese study showed that 38% of 5-year-olds born VLBW had an eGFR less than 90 mL/min/1.73 m² and higher urinary angiotensinogen levels. (82) Similarly, a Polish study looking at approximately 7-year-olds born extremely low birthweight had smaller kidney sizes, higher BPs, and higher serum cystatin C levels. (83) These studies suggest that serum cystatin C may be a better marker to detect early renal dysfunction than serum creatinine to assess renal health in follow-up.

Table 3. Risk Factors for Development of CKD in NICU Graduates
AKI was the only predictive factor in neonates who later developed CKD or HTN, with a risk that was 4 times as high. Nearly 50% of adults with congenital heart disease develop CKD. Investigators at Cincinnati Children’s Hospital examined a cohort of neonates who required cardiopulmonary bypass for long-term kidney injury. The researchers used traditional CKD measurements such as eGFR, albuminuria, and HTN but also examined their urine to determine whether there were structural differences in those exposed to AKI. The mean follow-up was 7 years, and there was no difference in the traditional markers of renal disease between the AKI and no AKI groups. However, there were striking and sustained differences in structural urinary biomarkers, with an increased amount of interleukin-18 and L-fatty acid binding protein in the urine of the AKI group.

Kidney disease is a public health epidemic. Because of very high individual and societal costs of treatment, prevention is the most effective approach to sustainably address the mounting global burden of kidney disease. Therefore, it is the aim of all nephrologists to reduce the risk of progression of renal disease, but there are currently no guidelines that describe which neonates require follow-up, when to institute this screening and educational visit, or the best approach to screen for CKD.

Screening for CKD

The KDIGO is a global organization that is developing and implementing evidence-based clinical practice guidelines in kidney disease. The generalized guidelines designed for follow-up in adults advocate for follow-up 3 months after the AKI. Most would agree that follow-up for neonatal AKI should occur, but it is unlikely that the 3-month timeframe is an optimal follow-up period, particularly because GFR is not established until 2 years and it is very difficult to interpret GFR criteria in this young cohort. Primary care physicians may be able to obtain a child’s gestational age and birthweight, but a “history of AKI in the neonatal period” is not often included in discharge summaries. AKI must first be recognized and then must be communicated.

To date, the American Academy of Pediatrics does not have any guidelines for screening for CKD aside from a recommendation that children with a history of prematurity, VLBW, or “other” neonatal conditions have their BP measured before 3 years of age. The American Academy of Pediatrics does highlight prematurity as a potential high-risk group for HTN in the 5th Report of the Clinical Practice Guidelines for high BP. Children at higher risk for CKD are those with early HTN because this may be a clinical indicator of low nephron number. There is evidence that preterm infants, irrespective of the presence or absence of nAKI, have abnormal BP parameters early in childhood. In a Swedish national population-based cohort, 44% of children who were born with extremely low birthweight had office systolic BP readings greater than the 90th percentile at age 2.5 years compared with age, sex, and height standards. Ambulatory BP monitoring also reveals that preterm infants may be at risk for abnormal circadian BP patterns. The diagnosis and appropriate management of HTN may be an important target to protect the kidney and slow or halt the potential progression of CKD.

Abnormal growth parameters may also be associated with CKD. Children with CKD can have impaired linear growth even when their GFR is only mildly to moderately impaired. Given the potential for poor linear growth and reduced muscle mass in preterm infants, estimating GFR by serum creatinine level may represent a further challenge for screening for CKD in this population. In addition to earlier screening of growth parameters, adolescents are in another period of rapid growth that may unmask renal dysfunction. If at any of these screening visits the child has a BP at the 95% level or higher, microalbuminemia or proteinuria, an elevated creatinine or cystatin C level, or abnormal renal ultrasonography findings, he or she should be referred to a pediatric nephrologist. In addition, as the child transitions to adult care, it will be important to alert the new primary care provider of important early life events that may put them at risk for more rapidly deteriorating renal function as they age. In 2013, an algorithm was proposed to address who should be screened for CKD and when (Fig).

![Figure. Suggested algorithm for the assessment of NICU graduates at risk for chronic kidney disease (CKD).](http://neoreviews.aappublications.org/)
Although there is no specific medication or therapy to preserve renal health, there are educational opportunities to reduce the risk of renal dysfunction progression. The avoidance of unhealthy lifestyles may be beneficial along with education on the ill effects of obesity, HTN, smoking, nephrotoxic drugs, urinary tract infections, and a high sodium diet.

CURRENT EFFORTS TO BETTER UNDERSTAND nAKI, INCLUDING DIAGNOSIS, TREATMENT, AND LONG-TERM PROGNOSIS

The NIH organized a workshop in 2013, bringing together nephrologists and neonatologists with leadership from the National Institute of Diabetes and Digestive and Kidney Diseases. In particular, much attention was given to the role of AKI as an antecedent for CKD. Several key elements were outlined that are needed to conduct a long-term follow-up study (Table 4).

One of the outcomes of this workshop was the formation of the Neonatal Kidney Collaborative with the specific goal of neonatologists and pediatric nephrologists working together to better understand AKI in neonates. The goal of the collaboration is to improve the understanding and ultimately the lives, health, and well-being of newborns at risk for kidney disease by assembling an international multidisciplinary team that can perform clinically relevant hypothesis-driven studies. Multicenter data could then be used to answer critical gaps in knowledge with the long-term goal of improving outcomes for neonates at risk for kidney disease.

The first endeavor for the Neonatal Kidney Collaborative was the Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWaken) study. This was a retrospective cohort study involving 24 sites. Each participating site was asked to review all NICU admissions from January 1 through March 31, 2014. Patients in the NICU were eligible if they received at least 48 hours of intravenous fluids as their source of fluids and nutrition. Infants were excluded if they were admitted to the NICU more than 2 weeks after birth, required congenital heart disease repair before 7 days of age, died within 48 hours of admission, or had a known lethal chromosomal anomaly. Data collection included basic demographics (maternal and neonatal), delivery interventions, daily physiologic parameters during week 1 (weight, BP, intake and output, respiratory support, clinically obtained laboratory results), weekly “snapshots” (as during week 1, but limited to only 1 day per week), discharge information (growth parameters, final diagnoses, relevant discharge medications, need for renal replacement therapy [dialysis]), and all serum creatinine values.

Initial analyses focused on the epidemiology of nAKI, identification of risk factors that may predispose newborns

<table>
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<tr>
<th>TABLE 4. Issues Raised and Addressed at the National Institutes of Health Workshop on Neonatal AKI</th>
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<tbody>
<tr>
<td><strong>What population should be studied?</strong></td>
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<tr>
<td>An entire cohort of hospital survivors with and without AKI?</td>
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<tr>
<td>Neonates with known AKI, regardless of underlying conditions or cause of AKI?</td>
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<tr>
<td>Inclusion of controls is important so that true incidence, risk factors, and relative risk can be assessed</td>
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<tr>
<td><strong>Sample size</strong></td>
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<tr>
<td>Estimates of 1,000–1,500 survivors may be needed to provide sufficient power</td>
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<tr>
<td>It would take 12–18 centers, each enrolling 40 patients per year for 2 y to achieve this number</td>
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<tr>
<td><strong>Exposure variables</strong></td>
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<tr>
<td>Frequent determination of serum creatinine level</td>
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<td>Careful measurement of urine output</td>
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<tr>
<td>Urine biomarkers</td>
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<tr>
<td><strong>Outcome measures</strong></td>
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<tr>
<td>Primary: glomerular filtration rate and blood pressure</td>
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<tr>
<td>Secondary: microalbuminuria, renal ultrasonography, evaluation of tubular function, growth and growth velocity, neurodevelopmental assessments</td>
</tr>
<tr>
<td>Exploratory: new imaging techniques, biomarkers, renal functional reserve assessment</td>
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<tr>
<td><strong>Study duration</strong></td>
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<td>Serial evaluations until transition to adult care clinicians (17–18 years of age)</td>
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<td><strong>Challenges</strong></td>
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<td>Recruitment and retention</td>
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<td>Close contact with families; buy-in from families</td>
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<tr>
<td>Inclusion of specific populations that may be underrepresented in clinical studies (low socioeconomic status in particular)</td>
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<tr>
<td>Collection of meaningful, accurate data</td>
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<tr>
<td>Proper measurement of blood pressure</td>
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<tr>
<td>Standardized collection of blood and urine samples</td>
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<tr>
<td>Standardized measurement of glomerular filtration rate</td>
</tr>
<tr>
<td><strong>Ethical issues</strong></td>
</tr>
<tr>
<td>In pediatric studies, if a procedure does not provide any direct benefit, it must be low risk or an IRB will not approve it</td>
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Continued
to AKI, and the contribution of fluid balance to overall morbidity, mortality, and likelihood of AKI. Not surprisingly, the incidence of AKI varied as a function of gestational age. Neonates of 22 to 29 weeks’ gestation comprised only 14% of the neonates (n = 273), but nearly half had AKI. Of the 916 neonates of 30 to 35 weeks’ gestation, approximately 18% had AKI, and of the 833 neonates of 36 weeks’ gestation and older, approximately 37% had AKI. These incidences are approximate because this was a retrospective study and data collection, especially creatinine levels and complete intake and output data needed to diagnose AKI was not complete for all neonates. However, the data do highlight the significant proportion of infants at risk for AKI. More importantly, the data support the hypothesis that the presence of AKI has a significant effect on morbidity and mortality. After adjustment for a variety of confounders, infants with AKI were 4 times more likely to die, and their length of stay in the NICU was almost 9 days longer. Moreover, the more severe the injury, the higher the mortality rate and the longer the length of stay among the survivors.

We hypothesized that identifiable maternal, perinatal, and neonatal characteristics could predict neonatal AKI. Indeed, neonates born at outside facilities, with lower Apgar scores at 5 minutes, and exposed to meconium, sepsis, or surgery all had an increased likelihood of AKI. Conversely, multiple gestation, vasopressor exposure, antimicrobial exposure, and treatment with methylxanthines were all associated with a decreased risk of AKI. Although it seems counterintuitive that antimicrobial exposure was found to be associated with reduced risk for AKI, it can likely be explained because most neonates received short courses of treatment and were not septic. It is likely that this finding is confounded by indication, or in this case, the lack of indication. Treatment with methylxanthine is a fascinating observation and needs further exploration. Of 689 neonates of 32 weeks’ gestation and less, 460 received a methylxanthine and 229 did not. The incidence of AKI in these 2 cohorts was 11.5% and 31.4%, respectively. That caffeine may be protective can be justified physiologically, but currently this remains only an association.

The determination of fluid balance in neonates presents several challenges. Although in adult and pediatric populations there is evidence that fluid overload is associated with increased mortality and morbidity, this is very difficult to study in newborns because complete and accurate ascertainment of intake and output is nearly impossible. Therefore, a change in weight compared with birthweight was used as a surrogate for fluid balance. Because both the admission diagnoses and the underlying physiology of term and preterm neonates are quite different, the AWAKEN population was divided into 2 cohorts for these analyses: infants at least 35 weeks’ gestation at birth and infants less than 35 weeks’ gestation. In the older cohort, there was a clear association between fluid balance and outcome, with infants whose weights increased by more than 10% during the first postnatal week having an increased need for mechanical ventilation at 7 days of age and those with the most negative fluid balance more likely to survive to discharge from the NICU.

One of the major limitations of AWAKEN was that it was a retrospective record review, and the collection of data was according to the local standard of care. Herein lies another of the important issues related to nAKI. The AWAKEN study has begun to identify the highest-risk populations, but the current laboratory studies may not be sensitive enough to detect early kidney injury. Creatinine increases only after considerable injury has already occurred. We need other biomarkers that can identify injury of a lesser degree so that efforts can be made to modify our care and minimize further injury. There are some candidate urinary biomarkers, but more work needs to be done to determine the most sensitive and cost-effective means of detection.

As neonatologists become more aware of the potential implications of AKI in the NICU population, practice guidelines for both early identification and amelioration of injury are needed. Appropriate surveillance paradigms, treatment regimens, and follow-up recommendations should be the goal of collaborations between neonatologists and pediatric nephrologists to improve the long-term outcomes and renal health of vulnerable neonates.

**American Board of Pediatrics Neonatal-Perinatal Content Specifications**

- Know how to interpret various renal function tests (eg, urinalysis, creatinine clearance).
- Know the clinical manifestations, imaging, and laboratory features of renal failure in the neonate.
References


35. Welham SJ, Wade A, Woolf AS. Protein restriction in pregnancy is associated with increased apoptosis of mesenchymal cells at the start of rat metanephrogenesis. Kidney Int. 2002;61(4):1231–1242


1. A male infant born at 28 weeks’ gestational age is now 2 weeks old and weighs 1,150 g. He has abdominal distention and increasing cardiovascular instability and is diagnosed as having necrotizing enterocolitis. He is given nothing by mouth and placed on intravenous nutrition at 120 mL/kg per day. You are called to his bedside the next day to evaluate decreased urine output to 5 mL over the past 12 hours. His laboratory findings are significant for a blood urea nitrogen level of 26 mg/dL (9.3 mmol/L) and a serum creatinine level of 1.2 mg/dL (106.1 μmol/L) (compared with 12 mg/dL [4.3 mmol/L] and 0.7 mg/dL [61.9 μmol/L], respectively, the previous day). You suspect neonatal acute kidney injury (nAKI). Using the Kidney Disease: Improving Global Outcomes (KDIGO) classification system, what stage of nAKI does this infant have?
   A. Stage 0.
   B. Stage 1.
   C. Stage 2.
   D. Stage 3.
   E. The stage of AKI cannot be determined with the information presented.

2. An infant born at 28 weeks’ gestation with necrotizing enterocolitis is suspected of having nAKI. Preterm infants’ susceptibility to nAKI is related to the typical course of renal development and nephrogenesis. Which of the following statements regarding renal development is CORRECT?
   A. Nephron development begins at approximately 7 weeks’ gestation and is complete at approximately 39 weeks’ gestation.
   B. Preterm birth halts glomerulogenesis.
   C. Growth restriction is a key element of renal development, with nearly 200,000 additional nephrons for each increase of 500 g in birthweight.
   D. The kidney continues a maturational process for nearly 5 years, at which time adult glomerular filtration rate is established.
   E. Up to 60% of nephron development occurs during the third trimester.

3. In utero and NICU exposures have the potential to adversely impact renal development. Which of the following exposures predisposes to decreased ureteric bud branching?
   A. Tobacco exposure.
   B. Aminoglycoside exposure.
   C. Corticosteroid exposure.
   D. Vitamin D deficiency.
   E. Protein restriction.

4. According to the Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) retrospective cohort study, the presence of AKI has a significant effect on morbidity and mortality in neonates. Which of the following statements regarding infants with AKI is CORRECT?
   A. They are 4 times more likely to die.
   B. Their length of stay in the NICU increases by an average of 3 days.
   C. They have a 30% increased risk of hospital readmission in the first month after discharge.
   D. They have an increased need for packed red blood cell transfusions in the NICU, approximately a 10-fold likelihood.
   E. They are at increased risk for threshold retinopathy of prematurity requiring laser surgery.
5. Infants with a history of nAKI are at increased risk for chronic kidney disease (CKD) later in life. CKD stages are defined by glomerular filtration rate, most commonly estimated by serum creatinine concentrations. What other metric can be used to evaluate renal dysfunction in these patients?

A. Large kidney size secondary to glomerular hypertrophy.
B. Decreased serum cystatin C levels.
C. Impaired linear growth crossing at least 2 percentile lines.
D. Sustained blood pressure of at least the 95th percentile.
E. Decreased urinary angiotensinogen levels.
# Neonatal Acute Kidney Injury: Diagnosis, Exposures, and Long-term Outcomes

Jennifer R. Charlton and Ronnie Guillet

*NeoReviews* 2018;19;e322

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