Increasing Awareness of Early Risk of AKI in Neonates

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AKI is common in neonates in the intensive care unit (ICU), with an incidence of 16%–70% in different clinical settings (1,2). The neonatal population is heterogenous and has unique risk factors for AKI related to gestational age, birth weight, and maternal, congenital, and perinatal conditions (1–4). In addition, critically ill neonates are often exposed to nephrotoxic medications, must undergo surgeries, and face nutritional challenges, which may further increase AKI risk (3,5). Neonatal AKI is associated with preterm birth and lower nephron number; however, it is unclear whether nephron numbers are lower as a result of AKI or if they are a predisposing factor (6). Modified Kidney Disease Improving Global Outcomes (KDIGO) criteria have recently been introduced to standardize the definition of neonatal AKI (4); however, serum creatinine in neonates is influenced by gestational age and maternal creatinine, making the diagnosis challenging (7).

The Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) study on neonatal AKI is the largest to date (8). Retrospective analysis of over 2000 neonates admitted to neonatal ICUs from 24 sites in four countries revealed an overall incidence of AKI of 30%. AKI was inversely related to gestational age, and it was independently associated with short-term mortality and longer length of stay. In this issue of the *Clinical Journal of the American Society of Nephrology*, Charlton *et al.* (9) report clinical associations in a subgroup of the AWAKEN study cohort who developed AKI in the first week of life ("early AKI"), hypothesizing that risk factors in this early period may differ from those seen in later weeks. In total, 2110 neonates admitted to the neonatal ICU in the first week of life who required intravenous fluids for >48 hours were deemed to be at high risk for AKI, and they were included in the analysis. Neonates who died within 48 hours of birth, had lethal chromosomal or severe congenital kidney abnormalities, or required cardiac surgery within 7 days of birth were excluded. AKI was defined using the neonatal modified KDIGO criteria on the basis of clinically collected serum creatinine and/or urine output. Follow-up continued until discharge from the neonatal ICU, death, or 120 days after birth.

Overall, early AKI was diagnosed more frequently using urine than creatinine criteria (62% versus 50%) or both (13%); however, these proportions varied by gestational age. Neonates who developed early AKI tended to have more frequent creatinine measurements. Whether this occurred in response to the diagnosis of AKI or was in response to a clinical preconception of higher risk is unknown.

Early AKI occurred in 21% of all enrolled neonates, but it varied with gestational age (28% at 22–28 weeks, 14% at 29–35 weeks, and 27% ≥36 weeks). Almost one half of the AKI was stage 1; however, the mortality with stage 1 was similar to that with stage 3. AKI was diagnosed at a mean of 2.8±1.8 days, and 18% experienced a second AKI episode within the 7-day study period. Mortality and length of stay were significantly higher among neonates with early AKI compared with those without early AKI.

Maternal factors associated with a lower risk of early AKI included multiple gestation and planned cesarean section birth. A trend toward lower risk of early AKI was observed among infants of mothers who had hypertensive pregnancies and/or received exogenous steroids. Neonatal factors associated with a lower risk of early AKI included the use of antimicrobials, methylxanthines, diuretics, and vasopressors. The use of nonsteroidal anti-inflammatory drugs was not associated with AKI. Neonatal factors associated with a higher risk of early AKI included being out born, requiring transfer to a higher-care unit, resuscitation with epinephrine, need for surgery, hyperbilirubinemia, having an inborn error of metabolism, and being admitted to a children's hospital without perinatal services.

The maternal and neonatal factors associated with a lower risk of early AKI in this study are interesting, but they raise many questions. That multiple gestation and planned cesarean section are independently associated with lower early AKI risk is not intuitive, and it could rather reflect an effect of more vigilant prenatal care. Caution must be exercised in highlighting a lower AKI risk after planned cesarean section to avoid encouraging unnecessary cesarean sections. The observed trend toward a lower risk of early AKI among infants of mothers who had hypertensive pregnancies and/or received exogenous corticosteroids may be plausible as the authors suggest, but it requires further prospective study to determine whether steroids themselves or other concomitant clinical factors may lower early AKI risk.

The possible "protective" or neutral effects of potentially nephrotoxic medications must also be

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interpreted with much caution. The use of nephrotoxic antibiotics and nonsteroidal anti-inflammatory drugs is common in the neonatal ICU, and it has been associated with lower GFR in infants at short-term follow-up and lower nephron numbers in animals (1,4,10). The authors themselves suggest that the counterintuitive findings of a lower or unaffected risk for AKI in association with these medications may reflect classification bias, potential confounding by indication, too short a time window to detect nephrotoxicity, or masking of the effect by other more significant AKI risk factors given that all infants were high risk.

Among the neonatal risk factors associated with a higher risk of early AKI, several are known and likely relate to overall severity of illness. This study, however, begins to bridge a knowledge gap by documenting some novel risk factors for early AKI in the perinatal period that are easily identifiable, are important to raise awareness, and may be generalizable despite the study being predominantly United States based. In resource-limited settings, out-born deliveries, need for transport, resuscitation with epinephrine, and need for surgery must be recognized as risk factors for early AKI, because most deliveries occur in smaller hospitals and neonates may be transferred to pediatric surgical units that are not sensitized to AKI risk. Identification of risk suggests that implementation of preventive strategies may be possible, but this requires prospective study.

In terms of AKI diagnosis, the use of urine output may be a feasible tool for screening, but given that AKI in neonates is often nonoliguric, reliance on urine output alone requires further validation, especially in resource-limited settings. The observed variability in frequency of creatinine measurement between centers highlights the need for more uniform guidance for AKI surveillance in neonates. Reliance on serum creatinine for diagnosis and AKI staging in the first week of life remains challenging, and serum creatinine is a relatively late marker of kidney injury rather than kidney risk (11). Future prospective studies are required to explore the value of other biomarkers for earlier diagnosis and investigate whether early diagnosis may modify outcomes.

Importantly, the long-term implications of neonatal AKI and especially, repeated episodes of AKI (which occurred in almost one in five neonates with early AKI in this study) are not yet known. The ability of the neonatal kidney to withstand and/or recover from kidney insults is likely dependent on the severity and repetitiveness of kidney injury, and it may be modulated by intrinsic nephron number. In contrast to prior studies (1), being small for gestational age was not associated with a higher risk of early AKI in this study. Being preterm or small for gestational age is, however, associated with higher long-term risk of CKD; therefore, follow-up of the long-term effect of AKI in neonates individually and as a group is necessary (1).

This study has several strengths and some limitations. Use of the modified KDIGO diagnostic criteria is important for standardization and validation given the background of studies with variable definitions of neonatal AKI. The concept of classifying AKI occurring in the first week of life as "early AKI" is novel and clinically relevant. To better validate this time point as a useful cutoff, however, comparison with risk factors for AKI in neonates who only experienced AKI beyond this time point would have been useful. The use of 48 hours of intravenous fluids as an inclusion criterion to define high-risk neonates is objective. However, the indication for fluids was unknown; therefore, this might have included a population with variable AKI risk. In this retrospective analysis, relevant data, such as indications for creatinine measurement, medication, and surgery, as well as details of clinical management were not captured. Potential confounding of the relationship between early AKI and some of the identified risk factors and outcomes, therefore, cannot be excluded. Given lack of standardization of creatinine monitoring frequency, it is possible that some early AKI may have been missed or diagnosed late, which may have biased associations. In addition, the analysis of outcomes of early AKI relative to the entire AWAKEN cohort, which included those who developed AKI after 7 days and those who may have had multiple episodes of AKI over time, may have led to underestimation of the effect of early AKI on mortality and hospital stay.

Overall, this large, multicenter, retrospective cohort study highlights important easily identifiable factors in the perinatal period that may predispose a neonate to develop early AKI, which is highly clinically relevant. These factors should serve as red flags for treating physicians, signaling AKI risk and calling for enhanced surveillance and proactive management in this high-risk group.

Disclosures

None.

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