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Clinical Pearl: Understanding the Impact of Neonatal Acute Kidney Injury

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In recent years, we have significantly advanced our understanding of acute kidney injury (AKI) within the neonatal population. At birth, only about 4% of cardiac output reaches the kidneys; this is reflected in infants' low glomerular filtration rate, especially those born prematurely. Any additional stressors such as hypoxia, hemodynamic instability, or infection, all of which we frequently encounter in preemies, have the potential to impact renal perfusion further and induce AKI (1). The incidence of AKI in infants born before 29 weeks gestation has been reported to be as high as 43% (2). Thus, significant efforts have been made to define neonatal AKI better and identify the risk factors and the related short and long-term outcomes.

Over the past ten years, the neonatal modified Kidney Disease: Improving Global Outcomes (KDIGO) criteria have become the gold standard definition for neonatal AKI. It determines the severity of AKI based on the magnitude of the rise in serum creatinine from prior values and the decrease in urine output and may be used in patients <120 days of age (1,3). This definition, as many other ones used in pediatrics, was adapted mainly from an adult patient-driven one. For instance, it fails to account for the physiologic changes in neonatal creatinine, which initially reflects maternal creatinine. If maternal serum creatinine is low, it would be expected that in an extremely premature infant, their creatinine would increase over the first several days of life, which would not necessarily be representative of AKI.

Additionally, serum creatinine (SCr) is a marker of renal function, not injury. The initial insult must cause a significant decline in renal function in order to result in an increase in SCr, which can sometimes take several days (1). This issue leads to a delay in SCr increase in relation to the timing of the injury. Furthermore, the KDIGO criteria fail to account for the neonate's chronological and post-menstrual age (1). Despite its flaws, this definition has provided a certain degree of standardization and has allowed us to describe neonatal AKI's epidemiology and outcomes better.

The Assessment of Worldwide Acute Kidney Epidemiology in Neonates (AWAKEN) study (2) included 24 centers and collected data from almost one thousand neonates admitted to neonatal intensive care units. It has demonstrated that the risk of AKI increases significantly with decreasing gestational age and that neonates with AKI have higher odds of death and prolonged hospitalization. It has also expanded upon the neonatal-modified KDIGO definition to address neonatal physiology and redefine absolute serum creatinine thresholds based on gestational age. Using mortality as a meaningful clinical outcome, they tested the hypothesis that ideal cutoffs for serum creatinine levels within the first week of life will differ by gestational age. Their data shows that absolute and percent serum creatinine cutoffs are higher in those neonates born at less than 29 weeks gestation, suggesting that the neonatal modified KDIGO definition does not adequately account for physiologic differences seen within the first week of life and also between neonates of different gestational ages. This project marks an important milestone in AKI research in that previously, we relied on retrospective, single-center studies and lacked meaningful data on AKI incidence and risk factors in patients categorized by gestational age and time point in their hospital course.

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Last year, Aziz et al.'s smaller, single-center study provided supportive evidence for AKI being inversely proportional to both gestational age and birth weight and for an association between AKI and increased mortality in extremely low-birth-weight neonates. Interestingly, they suggested that while mortality is strongly associated with neonatal AKI, it does not directly result from it, and its amelioration does not reduce the risk of death in this population (4). In response to these findings, Askenazi et al. discussed in a commentary piece why this is less likely to be true (5). The authors note that there is a possibility of bias within the statistical approach of the initial study with the use of Shapley Additive Explanations Analysis (a structural model that shows the relative association of each measured variable with a given outcome) to determine the association between each variable and their relationship to mortality. Another reason this paper cites is the limitations of using the neonatal-modified KDIGO criteria in this pa-

tient population, especially in the first several days of life, some of which we have already discussed. Because of the potential for this miscalculation bias, many studies do not include serum creatinine from the first 48 hours of life, unlike Aziz et al. Since serum creatinine often does not increase for up to 48 hours following a renal insult, it becomes challenging to assess AKI›s relationship with mortality in this population when elevation in serum creatinine has been proven to lag behind the injury. As there seems to be a widespread consensus that serum creatinine is a suboptimal marker for monitoring neonatal renal function, identifying novel biomarkers that would allow for earlier identification and better classification of AKI continues to generate interest. Some of the ones that have been suggested thus far include urine neutrophil gelatinase-associated lipocalin, cystatin-c, and kidney injury molecule-1, although further work is needed before we will be able to use them in our clinical practice (1).

"Despite all the recent advances in neonatal AKI research, many questions remain unanswered. For instance, there seems to be insufficient data on its impact on long-term renal function. Mammen et al. studied a cohort of children hospitalized in the pediatric intensive care unit with AKI, demonstrating that 10% of these patients developed chronic kidney disease (CKD) (6). "

Despite all the recent advances in neonatal AKI research, many questions remain unanswered. For instance, there seems to be insufficient data on its impact on long-term renal function. Mammen et al. studied a cohort of children hospitalized in the pediatric intensive care unit with AKI, demonstrating that 10% of these patients developed chronic kidney disease (CKD) (6). Although some small, single-center studies suggest an increased risk of CKD following neonatal AKI, the shortage of meaningful data challenges neonatal providers when deciding which infants will require subspecialty follow-up and to what extent. Nevertheless, there is strong evidence that points towards a link between AKI and mortality, as well as its association with other unfavorable clinical outcomes. Ancillary studies based on the AWAKEN cohort have shown associations between AKI and hypertension, AKI and intra-ventricular hemorrhage, and AKI and chronic lung disease (2). These findings have important implications for clinicians and researchers, as they stress the need for more data on short- and long-term prevention and management strategies.

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