Neonatal Acute Kidney Injury Association With Mortality—Culprit, Innocent Bystander, or Canary in the Coal Mine?

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In their study on acute kidney injury (AKI) in extremely preterm infants, Aziz et al1 provide supportive information about the prevalence of AKI and its association with mortality in extremely low-birth-weight (ELBW) neonates. Using a contemporary neonatal AKI definition, this retrospective, observational, single-center cohort study of 436 ELBW infants shows a prevalence of early AKI of 44%, and those with any AKI had a 2.77 (95% CI, 1.63-4.72) higher odds of death compared with those without AKI (odds ratio for severe AKI, 3.52; 95% CI, 2.15-5.76). Similar findings have been reported by other groups in retrospective and prospective multicenter neonatal studies,2,3 as well as large, prospective, multicenter epidemiology studies in pediatric4 and adult5 critical care patients.

This study then addresses another critical question.1 Does AKI directly cause death or is it an innocent bystander (ie, not contributory)? Using the Shapley Additive Explanations (SHAP) analysis, a machine learning approach that shows the relative association of each variable being measured with a given outcome, they found that, after controlling for vasoactive inotrope score (VIS) and the neonatal Sequential Organ Failure Assessment (nSOFA) measure, AKI was not associated with mortality. Like the adult and pediatric SOFA scores, the nSOFA measure incorporates hematologic (platelet counts) respiratory, and cardiovascular scores. However, as opposed to the adult and pediatric SOFA scores, the nSOFA score does not include markers of liver, kidney, and central nervous system dysfunction.

A few possible reasons could explain these results. First, it is possible that early AKI has nothing to do with the causative pathway between sickness and death. If true, this reason negates the work in the basic and translational science fields that suggest that AKI is not an innocent bystander in multiorgan disease failure but instead has a central role in the systemic inflammatory process, with direct effects on the heart, lungs, brain, gut, liver, and immune system. If indeed AKI is not contributory to clinical outcomes in ELBW infants, this population would be unique, given that the association between AKI and outcomes has been clearly shown in multiple pediatric4 and adult5 critically ill populations, even after adjustment for comorbidities and severity of illness scores (ie, SOFA).

A second possible reason to explain these findings is that, although the investigators use the most contemporary definition of neonatal AKI, it is suboptimal. This empirical definition, which was borrowed from the adult literature, has empowered the community with a standard way to define AKI allowing comparison of studies; however, it has important limitations, especially in the first postnatal week. At birth, neonatal and maternal serum creatinine (sCr) levels are identical. Over the next 36 to 48 hours, the neonate attains a sCr steady state level that will be determined by nephron mass and gestational age. If the maternal sCr value is low (ie, 0.6 mg/dL [to convert to micromoles per liter, multiply by 88.4]) and the neonate is extremely premature, an expected increase in the SCr level in 48 hours (ie, 1.1 mg/dL) is expected. This change can be confused with worsening kidney function. For these reasons, several groups have eliminated the first 2 postnatal days from the calculation of the baseline values.3,6 In addition, an absolute sCr level increased threshold is superior to percent sCr increase in the first postnatal week, and incorporating percent sCr decreases the predictability of mortality.7 Finally, recent studies require a minimum sCr level of 0.4 mg/dL to eliminate a diagnosis of AKI based on small changes that could be due to variability in laboratory error (ie, sCr increase from 0.2 to 0.3 mg/dL is a 50% increase).3,6 The AKI definition used by Aziz et al1 comprised any prior sCr value (including day 0 and 1) to define the baseline, did not use minimum sCr values, and in most cases, met the sCr percent change criterion, resulting in very low peak sCr values.
overall in infants with mild AKI (mean sCr, 0.68 mg/dL; IQR, 0.32-1.08 mg/dL). For these reasons there is a possibility for misclassification bias.

These interactions that make an sCr-based definition complex in neonates are compounded in this and other populations because sCr is not a marker of kidney injury—rather, it is a marker of kidney function. After an injury, it can take up to 48 hours to detect an increase in the sCr level. Also, all sCr level increases are not the same. For example, when there is low kidney perfusion (ie, dehydration), a decrease in glomerular filtration rate occurs to maintain fluid homeostasis by decreasing urine output without true injury. Urine biomarkers that increase shortly after injury and can differentiate tubular injury from changes in kidney function will hopefully be available soon. Further work to understand how different neonatal AKI endotypes (hypoperfusion, nephrotoxicity, sepsis, and ischemia) impact outcomes is greatly needed as outlined in recent consensus guidelines on pediatric AKI in JAMA Network Open in October 2022.

A third possible reason for the findings of Aziz et al suggesting that AKI has a negligible influence on death is the possibility of biases and collinearity in the statistical approach. Machine learning processes are not a panacea and are still subject to bias through incorrectly classified variables and models or incorrectly collected data points. Furthermore, one must cautiously interpret models that contain variables that are associated with each other, such as AKI with the nSOFA and VIS in the current analysis. Although the machine learning methods used by Aziz et al attempt to account for collinearity, it is difficult to determine the effects of including AKI, VIS, and nSOFA in the same model without seeing the effects on the respective associations as each variable is entered into the model. In addition, one must be cautious of studies that report small CIs for dichotomous exposures and smaller sample sizes—such as the associations reported for late sepsis and AKI in the present study—because they are suggestive of potential model specification issues that can snowball into later interpretability issues, particularly when using methods such as SHAP values that rely on the results of statistical models for interpretation. Of note, spontaneous intestinal perforation and early sepsis, like AKI, also become negligible in this model, but clinically we see these syndromes impact care and outcomes. It is likely that the effect of other categorical conditions (ie, meningitis, pneumothorax) may also become negligible using the same approach in a study of this sample size.

Nevertheless, this study corroborates that neonates with AKI clearly have a different risk for death than those without AKI. Whether AKI is directly causing death, an innocent bystander, or a “canary in the coal mine” has been the subject of debate for decades in critical care nephrology. For those not familiar with the etymology, a canary in the coal mine is an allusion to caged canaries (birds) that miners would carry down into the tunnels with them. If dangerous odorless gases (eg, carbon monoxide) collected in the mine, it would cause the birds to become sick, thus providing a warning that a change in the environment or prompt exit from the tunnel was needed. Using this analogy, even if AKI is just a signal, a focused attention to optimize organ perfusion with fluids, inotropes, or vasoactive mediations to avoid further injury from ischemic and/or nephrotoxic injury is needed. Simply watching the canary get sicker without acting is not the right option. Efforts to optimize the signal and develop evidence-based interventions to act when the signal is present are needed.
Conflict of Interest Disclosures: Dr Askenazi reported receiving grants and consultant fees from Baxter, grants and personal fees from Nuwellis, grants and personal fees from Medtronic, grants from Bioparto, grants from Seastar, grants from Portero, and personal fees from Zorro-Flow outside the submitted work; in addition, Dr Askenazi had a patent for a urine collection device pending and a patent for enhancements to continuous renal replacement therapy pending. No other disclosures were reported.

REFERENCES