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Do Children With Acute Kidney Injury Require Long-term Evaluation for CKD?

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Acute kidney injury (AKI) affects a growing number of children and is associated with high morbidity and mortality. The incidence of AKI in children differs according to the population described. Approximately 10% of all children admitted to a pediatric intensive care unit develop AKI,[1] which doubles if only those admitted for longer than 12 hours are considered.[2] Critically ill children on mechanical ventilation and receiving vasopressive/inotropic medications have an 82% incidence of AKI.[3] Neonates with perinatal asphyxia, those with birth weight <1,500 g,[4] and those who receive extracorporeal membrane oxygenation[5] also have high rates of AKI. Mortality in neonates and children with AKI is higher than for those without AKI even after controlling for potential confounders.[2,3,5] It previously was assumed that those who survive an episode of AKI would recover kidney function without long-term sequelae. However, during the last decade, epidemiologic data from critically ill children[6] and adults[7–19] with AKI suggest that survivors are at risk of developing chronic kidney disease (CKD).

A recent meta-analysis showed that adults with AKI are at a 9-fold increased risk of developing CKD, a 3-fold increased risk of developing end-stage kidney disease, and a 2-fold increased long-term mortality risk compared with patients without AKI.20 Despite these strong associations, several limitations in these studies limit our ability to decisively conclude that AKI causes CKD. First, although control for known confounders has been attempted, sample size limits the ability to test for multiple confounders, interactions among variables have not been explored, and unmeasured variables cannot be accounted for. Second, these studies are limited by selection bias because individuals with AKI often have comorbid conditions that predispose to CKD, and those with CKD are more likely to develop AKI.21 Long-term follow-up studies of children with AKI help mitigate these limitations because children are less likely to have CKD before AKI occurs and usually do not have the typical comorbid conditions (e.g., diabetes mellitus and hypertension) associated with CKD.

In this month's issue of the *American Journal of Kidney Diseases*, Mammen et al[22] report results of the largest long-term follow-up study of AKI in children conducted to date, which included 126 critically ill children with AKI and no pre-existing CKD. For the mentioned reasons, this cohort provides a unique opportunity to examine the association between AKI and the subsequent development of CKD. At 1–3 years of follow-up, 13 of 126 (10%) children developed CKD (defined as estimated glomerular filtration rate [eGFR] <60

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mL/min/1.73 m^2 or persistent albuminuria). In addition, 59 of 126 (47%) patients were considered at risk of CKD (defined as eGFR of 60–90 mL/min/1.73m^2, hyper-filtration [eGFR>150 mL/min/1.73 m2], or hypertension). The authors were diligent in their evaluation of kidney-related parameters whereby they repeated abnormal urinalyses (on first morning voids) and performed ambulatory blood pressure monitoring to confirm the presence of hypertension.

The major limitation of the study is inherent to the loss of follow-up whereby only a subset of hospital survivors (126 of 299 [42%] children) had subsequent evaluations. There were minimal differences between the 2 groups, including a lower proportion of stage 1 AKI (35% vs 50%), lower nadir hemoglobin level (9.2 vs 9.9 g/dL), and higher peak mean airway pressure (16.2 vs 13 cm H2O) in children who were included in the cohort compared with those lost to follow-up. Although not described in the report, many children who have AKI die within a few years after hospital discharge.[6] A previous follow-up study of children with AKI found that at least 18% of hospital survivors died several years after the index hospitalization. Whether these patients had CKD and whether CKD had a direct impact on long-term mortality are unknown.

This epidemiologic study is supported by animal models showing thatAKI has long-term kidney consequences. After ischemia-reperfusion injury, there is substantial damage to tubular and endothelial cells,[23] leading to vascular injury and dropout as well as tubulointerstitial fibrosis.[24] The vascular dropout after AKI results in endothelial cell damage, endothelial cell differentiation, and impaired regenerative capacity, which might contribute to progressive CKD.[25]

What is unclear is an understanding of which patients are at the highest risk of developing CKD. Certain causes of AKI or disease severity might pose different risks. Novel biomarkers of kidney injury measured at different times in the course of AKI might help risk-stratify those who will progress to CKD. In 2009, Ko et al[26] analyzed the transcriptome in the repair stage of the mouse ischemia-reperfusion AKI model. Their findings suggest that kidney injury molecule 1 and neutrophil gelatinase-associated lipocalin, 2 of the most promising biomarkers for the early detection of AKI, also might be useful markers for identifying sustained kidney injury and progression to CKD after episodes of AKI. In addition, these authors found changes in expression levels of hypertension related regulatory genes, which could reveal the underlying mechanisms responsible for persistent kidney and vascular injury after AKI.

Although animal AKI models do not mirror human studies, these types of data along with human epidemiologic studies provide evidence that children with AKI are at risk of CKD. Therefore, after AKI, it is the opinion of the author that children should be monitored and treated for CKD-related problems. Our current practice is to follow up children with AKI within 1 month of hospital discharge, quarterly for 2 visits, and then annually for 2 years. If CKD or hypertension develops, treatment and additional monitoring are required. After several years of follow-up, if CKD or hypertension does not develop, patients and their primary care providers are advised to periodically monitor blood pressure and urinalysis for markers of kidney damage as potential early indicators of CKD.

Despite the growing evidence showing a strong association between AKI and CKD, further work is required to better understand the relationship between AKI and CKD in children. Several questions remain unanswered and should be pursued. First, there is a need to identify clinical factors (e.g., comorbid conditions and causes and severity of AKI) and potential biomarker profiles during the various stages of AKI that can help stratify patients at risk of developing CKD. Second, well-designed clinical trials are needed to show that a therapy aimed at preventing AKI or attenuating its severity might decrease the future development of CKD. Such studies could not only provide evidence that AKI leads to CKD, but also offer life-altering interventions to halt the progression of CKD and reduce medical expenditures after AKI.

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