A New Pediatric AKI Definition: Implications of Trying to Build the Perfect Mousetrap

Stuart L. Goldstein
Division of Nephrology and Hypertension, Center for Acute Care Nephrology, Heart Institute Research Core, The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

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"If you look for perfection, you'll never be content." Leo Tolstoy

Researchers have made the epidemiology of AKI and its outcomes in hospitalized patients an area of intense focus over the past two decades. Standardization and subsequent calibration of AKI diagnostic and severity criteria have been critical to advancing our understanding of how this condition contributes to patient morbidity and mortality. Without such standardization, it would be impossible to compare outcomes across patient populations and studies.

The initial AKI diagnostic construct RIFLE provided both serum creatinine and urine output as diagnostic and staging criteria for AKI.[1] Critically ill adult patients who develop RIFLE-defined AKI show increased morbidity and mortality, an association that is stronger with increasing AKI severity regardless of the condition's underlying cause.[2] Because a 0.3-mg/dl increase in serum creatinine over baseline is also associated with poor adult patient outcomes,[3] the AKI Network (AKIN) subsequently adjusted AKI diagnostic criteria to include this threshold.[4]

In 2007, in our attempt to build a more pediatric-specific AKI mousetrap, my colleagues and I developed pediatric RIFLE (pRIFLE), a pediatric modification of the adult RIFLE criteria. Instead of changes in serum creatinine concentrations, pRIFLE uses changes in estimated creatinine clearance (eCCl), which uses patient size in the calculation.[5] Our rationale for this approach was concern that a standard serum creatinine change threshold would not account for the childhood growth and development that leads to increased muscle mass and resultant physiologic increases in normal serum creatinine concentrations. Children who developed AKI defined by the pRIFLE criteria also had increased morbidity and mortality rates, although the association was only shown in patients who developed pRIFLE-Injury (eCCl decreased by 50% and urine output of $<$0.5 ml/kg per hour for 16 hours) or pRIFLE-Failure (eCCl decreased by 75% or eCCl$<$35 ml/min per 1.73 m^2 and urine output $<$0.3 ml/kg per hour for 24 hours or anuria for 12 hours). A subsequent systematic review of 12 pediatric studies confirmed the nature of this association.[6]

Five years later, in 2012, the Kidney Disease Improving Global Outcomes (KDIGO) AKI Work Group developed AKI diagnostic and staging criteria that harmonized the RIFLE, AKIN, and pRIFLE systems.[7] In a recent comparison of AKI epidemiology and associated outcomes in hospitalized children using pRIFLE, AKIN, and KDIGO,[8] we found that, although use of the these definitions resulted in differences in incidence and staging, all three showed similar associations with patient morbidity and mortality. We concluded that "KDIGO offers applicability to both pediatric and adult populations" and viewed that as an advantage, citing the "necessity of a unified AKI definition." To that end, two large, prospective, multinational studies of AKI epidemiology and outcomes in critically ill adults (the AKI–Epidemiologic Prospective Investigation [AKI-EPI] study)[9] and children (the Assessment of Worldwide AKI, Renal Angina and Epidemiology [AWARE] study)[10] used the KDIGO criteria as the outcome measure. Both showed that AKI defined by the KDIGO criteria confers an incremental risk for patient morbidity and mortality.

In this issue of the *Journal of the American Society of Nephrology*, Hou *et al.*[11] describe their development of a novel pediatric-specific creatinine-based AKI diagnostic tool called pediatric reference change value optimized criterion for AKI in children (pROCK). The investigators' rationale for building their better AKI mousetrap was similar to the rationale for developing pRIFLE: concern that pRIFLE and KDIGO are problematic in individuals with low and highly variable serum creatinine levels, which are characteristics of young children. This concern is validated in the study mentioned above that compared the pRIFLE, AKIN, and KDIGO criteria,[8] in which approximately one half of the children had stage 1 (pRIFLE-Risk) AKI.

The pROCK study investigators undertook an extremely thorough statistical process to assess the serum creatinine reference change values for three separate age-based groups and then used these results to develop the 95% confidence threshold that could be considered the upper limit of normal for each group. As a result of this analysis, the pROCK AKI diagnostic criteria were bidimensional, defining pediatric AKI as a serum creatinine increase of 20 μmol/L (0.23 mg/dl) and a 30% increase over baseline. In terms of staging, pROCK classified AKI stage 2 as a serum creatinine increase of $\geq$40 μmol/L (0.45 mg/dl) and a $\geq$60% increase over baseline and AKI stage 3 as a serum creatinine increase of $\geq$80 μmol/L (0.91 mg/dl) and a $\geq$120% increase over baseline.

The investigators then compared AKI epidemiology and associated outcomes defined by the pRIFLE, KDIGO, and pROCK criteria using data from a database of $>$102,000 hospitalized children who had at least two serum creatinine tests $\leq$7 days apart. The primary outcome was mortality during the hospitalization, with secondary outcomes of mortality at 15, 30, 60, and 90 days, in patients with or without AKI. They observed that using the pROCK definition resulted in an AKI

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Correspondence: Dr. Stuart L. Goldstein, Division of Nephrology and Hypertension, Center for Acute Care Nephrology, Heart Institute Research Core, The Heart Institute, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45206. Email: stuart.goldstein@cchmc.org

incidence rate (5.3%) that was much lower than rates generated using KDIGO or pRIFLE criteria (10.2% and 15.2%, respectively). They also found AKI incidence as defined by KDIGO and pRIFLE was much higher in children with lower baseline serum creatinine values, highlighting the advantage of pROCK's bidimensional nature.

In addition, the investigators found that pROCK-defined AKI was more strongly associated with mortality than AKI defined by the other two systems, but it should be noted that pRIFLE- and KDIGO-defined AKI was associated with mortality as well. Furthermore, the differences in the *c* statistic for predicting time to death, while statistically significant, are small and do not seem to necessarily be clinically disparate. They conclude that a large proportion of children with KDIGO- and pRIFLE-defined stage 1 AKI were within normal serum creatinine variability and that pROCK may avoid overdiagnosis of AKI. They imply that pROCK should be used as the AKI diagnostic criteria for children.

Evaluating diagnostic criteria usually involves an emphasis on optimizing either sensitivity or specificity. As the investigators note, using overly sensitive criteria to diagnose AKI may lead to patients receiving potentially unnecessary and possibly costly or invasive tests or therapeutic interventions. However, is it really the case, for example, that clinicians would initiate dialysis or other aggressive measures for a patient with stage 1 AKI? I sincerely doubt it.

I would argue that clinicians should err on the side of sensitivity rather than the specificity that pROCK leverages, because the risk of AKI progression means that children require more attention, not less. Moreover, given that serum creatinine does not rise until renal reserve has been removed, using a more specific definition would place the clinician farther behind with respect to initiating any potential intervention. AKI is a syndrome, not a disease, and ruling out the various injurious diseases that cause it is the key to evaluating stage 1 AKI, which often progresses to more severe stages. Thus, there is a danger that use of more specific criteria, such as pROCK, could lead to clinicians not ordering follow-up creatinine tests for patients who had AKI "ruled out" by pROCK. Indeed, the original RIFLE article envisioned the acronym's "R" as denoting a patient "at risk" for renal dysfunction rather than having AKI *per se*.[1]

Therefore, the consequence of using sensitive criteria, such as KDIGO, might be ordering another inexpensive blood test; the consequence of using specific criteria, such as pROCK, might be missing the brief window to stop nephrotoxic antibiotics or to diagnose sepsis and give life-saving antibiotics. It is possible that pROCK may be useful for research and studying AKI-related outcomes, but for clinical use and risk stratification studies, this method cannot be considered fully evaluated and is, in fact, deficient.

The investigators acknowledged that not controlling for other factors that can be associated with mortality and not using urine output criteria were limitations of their study. Fluid overload (which represents an indirect measure of urine output relative to fluid intake) has been repeatedly shown to confer poor outcomes in critically ill children.[12] Importantly, pROCK was assessed for AKI and associated outcomes in the absence of fluid overload. The concept of identifying patients at risk for AKI has been the driving force to develop risk stratification systems that incorporate fluid overload (*e.g.*, the Renal Angina Index[13] and the Fluid Overload Kidney Injury Score[14]) to predict stage 2 and 3 AKI in children. Given that the current study also found strong associations between pRIFLE- and KDIGO-defined AKI and poor outcomes, it is not clear that there is a major advantage of using the more precise mousetrap that pROCK represents until fluid overload is assessed.

A continued quest for the perfect specificity criteria to identify, in the investigators' words, "true" AKI might have additional negative consequences. Serum creatinine is well documented as a late and functional marker of AKI, and the fact that an AKI diagnosis by any of the criteria studied is associated with mortality speaks to this syndrome's systemic nature and the need for better biomarkers. We as nephrologists tend to get hung up on pursuing the perfect (and unachievable) proof or process, thereby rejecting previous work that has moved the field ahead. My concerns in no way detract from the investigators' excellent work, which was detailed and valid (and in fact, I am sure that we will test pROCK in the AWARE dataset). However, the community has worked hard to develop and calibrate a creatinine/urine output–based definition that is acceptable for all, feasible, and strongly associated with poor outcomes. Although it may seem strange for a pediatrician to not advocate for a pediatric-specific system, harmonizing pRIFLE with AKIN and RIFLE was an important consensus decision and has, in fact, allowed for assessment of AKI across the adolescent and young adult age range,[15] something that would not be possible with different definitions. Expending efforts to further refine the definition for pediatric AKI on the basis of creatinine data alone (instead of something novel, like biomarkers) will, I fear, distract us from moving the field forward.

DISCLOSURES

None.

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See related article, "A New Criterion for Pediatric AKI Based on the Reference Change Value of Serum Creatinine," on pages 2432–2442.