Acute Kidney Injury: A Not So Silent Disease

Edward D. Siew, MD, MSCI and
Division of Nephrology and Hypertension, Vanderbilt University Medical Center, 1611 21st Avenue South, MCN S3223, Nashville, TN 37232-2372, USA, 615-322-3146, 615-343-7156

Susan L. Furth, MD, PhD
Professor of Pediatrics and Epidemiology, Perelman School of Medicine at the University of Pennsylvania, Chief, Division of Nephrology, Children’s Hospital of Philadelphia, 3400 Civic Center Blvd, Philadelphia, PA 19104, USA

Edward D. Siew: edward.siew@vanderbilt.edu; Susan L. Furth: furths@email.chop.edu

Abstract

Hospitalized children are experiencing acute kidney injury (AKI) with increasing frequency and are especially vulnerable to its long-term complications. Attempts to leverage novel biomarkers to improve phenotyping of this disease are limited by untargeted testing within broadly selected populations. Here, we review efforts by Basu et al. to use readily available clinical information to identify critically ill children at higher risk for developing severe AKI and who may benefit from novel diagnostic and prognostic information.

Acute systemic illness has recently surpassed primary renal disease as the leading cause of AKI in children.1 As evidence which strengthens the link between AKI and future CKD accumulates,2 children may stand to benefit the most from therapies that can prevent the long-term impact of AKI. However, the hope of using novel injury markers to translate potential therapies has recently been challenged, in part, by an inability to identify populations where testing may be most beneficial in discriminating high from low risk individuals.

In this issue of *Kidney International*, Basu and colleagues leverage readily available information from the medical record to develop and test a scoring system that identifies critically ill children at risk for developing severe AKI.3 The system, known as the renal angina index (RAI), couples suggestive physiologic derangements, including early decline in kidney function or signs of fluid overload, with the clinical setting to derive a total point score. Within both the inception and 3 validation cohorts, the authors found that patients accumulating enough points to meet criteria for ‘renal angina’ were more likely to double their baseline serum creatinine within 72 hours than patients who did not. In contrast, children without renal angina, who represented between 32–85% of each cohort, were highly unlikely to develop severe AKI. The RAI scale displayed moderate ability to

Disclosures:
EDS reports consulting agreements with Abbvie and Alere, Inc.
discriminate between patients developing or not developing severe injury (AUCs 0.74–0.81) that outperformed a validated severity of illness scoring system. The presence or absence of renal angina also seemed to have higher predictive value than mild injury criteria alone. The authors conclude that the RAI can be used to risk stratify patients and serve as screening tool to enhance care and facilitate more directed biomarker measurement.

Basu and colleagues should be commended for taking a “back to basics” approach to clinical risk stratification. Integrating intuitive clinical information allows for widespread application of this tool. Its simplicity contrasts with bulkier prediction systems that are often difficult to generalize and wieldy to implement at the point of care. The extensive collaboration yielding multiple validation cohorts also increases the generalizability of these findings within a population where powerful studies of AKI are sorely needed. Importantly, their results also suggest potential utility for milder injury definitions now entrenched within current consensus definitions. While epidemiologic evidence has consistently linked smaller changes in creatinine to poor outcome, usefulness within clinical practice is not firmly established. These data confirm that detecting such changes already falls well within current practice standards and should alert providers to the potential development of more severe injury. However, the superior performance of RAI compared to mild injury criteria alone also reminds us that the clinical context in which these changes occur are equally important and should not be lost among continued efforts to stress the relevance of less severe injury.

The results from this study also illustrate how current tools may augment how we determine biomarker utility. The evaluation of novel AKI biomarkers has recently been challenged by larger validation studies suggesting less robust performance than observed in initial studies. Many of these studies have relied heavily on determining whether biomarkers can discriminate AKI status using incremental changes in serum creatinine as the reference standard. However, as lesser stages of injury did not reliably predict evolution to severe AKI in this study, these data also remind us that moderate changes in creatinine alone may not always reflect significant parenchymal damage. Determining the ability of novel biomarkers to predict less ambiguous outcomes is therefore essential. However, a critical first step towards this goal will be defining the optimal population in which to test their prognostic value.

Studies to date have often measured biomarkers broadly within a given study setting, usually including all patients admitted from an emergency room, within an ICU, or undergoing cardiac surgery. While such settings undoubtedly carry higher risk, the relatively low prevalence of severe AKI can increase the likelihood of false positive results and reduce positive predictive value. Despite comparable AUCs to many biomarkers examined, the positive predictive value of RAI was only modest during validation, with values partially reflecting the lower prevalence of severe AKI in these critically ill children (10–19%). Even among patients with the highest RAI scores, only 41–67% developed severe AKI, suggesting caution is still warranted before basing treatment decisions on the presence of renal angina alone. While further refinements to RAI may improve performance incrementally, these results reinforce the limitations of current tools and provide insight into how novel biomarkers may best complement these data. For example, the ability of RAI to effectively filter out patients with a low likelihood of severe AKI may alternatively identify
patients with higher disease prevalence in which the prognostic value of biomarkers may be enhanced. In a given population where 10% of patients develop severe AKI, a hypothetical test with a sensitivity of 70% and specificity of 93% will yield a positive predictive value of only 54%. (Figure) However, if applied to a population with a higher prevalence of underlying disease (e.g., 40%), the predictive value of a positive test may increase significantly. The importance of the latter would be instrumental, for example, when using such tests to guide enrollment into a future trial where the intervention carries substantial risk.

Another potential benefit of RAI may be that it enhances the timing of biomarker measurement. Unlike troponin, whose elevation may last for days during cardiac ischemia, available biomarker kinetic data from cardiac surgery and ICU settings suggest that peak elevation of several candidate markers may occur early and only last a few hours. As the onset of injury is often difficult to anticipate, these findings may partially explain the heterogeneity in results observed between biomarker studies. Since the majority of AKI results from acute illness rather than a planned procedure, the presence of renal angina may better define a ‘window of detection’ where improved timing of biomarker measurement can maximize yield.

In summary, the absence of overt ‘kidney pain’ should not dismiss the value of using readily available information to identify patients that warrant further phenotyping and risk assessment. Early context-specific changes in kidney function are a common sense and cost-effective approach to avoid the status quo of awaiting AKI to ‘declare itself’ before warranting further examination. Additional work needs to be done to develop and apply similar systems in different demographic population and settings. Nevertheless, this important work helps set the stage to combine current and future tools rather than testing them against each other in an unselected fashion. Doing so may offer the best opportunity for a timely, accurate, and complete picture of ongoing kidney injury that can guide the translation of long-overdue treatment strategies.

Acknowledgments

EDS is supported by NIH K23 DK088964-02

References

1. Hui-Stickle S, Brewer ED, Goldstein SL. Pediatric ARF epidemiology at a tertiary care center from 1999 to 2001. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2005; 45:96–101. [PubMed: 15696448]

2. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney international. 2011

3. Basu R, Zappitelli M, Brunner L, Wang Y, Charla LS, Wheeler D, Goldstein S. Derivation and Validation of the Renal Angina Index, Improving the Prediction of Acute Kidney Injury in Critically Ill Children. Kidney Int. 2013

4. Mishra J, Dent C, Tarabishi R, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet. 2005; 365:1231–1238. [PubMed: 15811456]
5. Parikh CR, Devarajan P, Zappitelli M, et al. Postoperative biomarkers predict acute kidney injury and poor outcomes after pediatric cardiac surgery. Journal of the American Society of Nephrology: JASN. 2011; 22:1737–1747. [PubMed: 21836147]

6. Siew ED, Ware LB, Gebretsadik T, et al. Urine neutrophil gelatinase-associated lipocalin moderately predicts acute kidney injury in critically ill adults. J Am Soc Nephrol. 2009; 20:1823–1832. [PubMed: 19628673]

7. Waikar SS, Betensky RA, Emerson SC, et al. Imperfect gold standards for kidney injury biomarker evaluation. Journal of the American Society of Nephrology: JASN. 2012; 23:13–21. [PubMed: 22021710]

8. Hsu RK, Hsu CY. We can diagnose AKI “early”. Clinical journal of the American Society of Nephrology: CJASN. 2012; 7:1741–1742. [PubMed: 23065498]

9. Endre ZH, Walker RJ, Pickering JW, et al. Early intervention with erythropoietin does not affect the outcome of acute kidney injury (the EARLYARF trial). Kidney international. 2010; 77:1020–1030. [PubMed: 20164823]
Figure. Improvements in Positive Predictive Value of a Hypothetical Biomarker Test with Increasing Disease Prevalence

A hypothetical example illustrating how a biomarker test with a sensitivity of 70% and specificity of 93% will have a positive predictive value of 54% if the prevalence of severe AKI is 10%. However, if the disease prevalence increases to 40% in patients with renal angina, the same test characteristics may improve positive predictive value to 88%.

| Biomarker outcome | Severe AKI |  |  |  |  |
|-------------------|------------|---|---|---|---|
|                  | +          | 7 | 6 |   |   |
|                  | -          | 3 | 84|   |   |

Sensitivity = 70%  Specificity = 93%

Positive predictive value = TP/TP + FP = 54%

Negative predictive value = TN/TN + FN = 97%

| Biomarker outcome | Severe AKI |  |  |  |  |
|-------------------|------------|---|---|---|---|
|                  | +          | 28| 4 |   |   |
|                  | -          | 12| 56|   |   |

Sensitivity = 70%  Specificity = 93%

Positive predictive value = TP/TP + FP = 88%

Negative predictive value = TN/TN + FN = 82%