We Can Diagnose AKI "Early"

Raymond K. Hsu and Chi-yuan Hsu

Clin J Am Soc Nephrol 7: 1741–1742, 2012. doi: 10.2215/CJN.09740912

Proteinuria and AKI

Proteinuria was first identified as a strong risk factor for AKI in 2008 (1). These observations were subsequently confirmed and extended in several other clinical scenarios and patient groups (2). Huang *et al.* showed that *preoperative* proteinuria was an independent risk factor for AKI after coronary artery bypass grafting (3). In this issue of the *Clinical Journal of the American Society of Nephrology*, two observational studies—both developed as part of the National Institutes of Health–sponsored Translational Research Investigating Biomarker Endpoints in AKI (TRIBE-AKI) consortium—extend the association in the setting of cardiac surgery to *postoperative* proteinuria (4,5).

Molnar and colleagues studied 1198 adult patients undergoing coronary artery bypass graft and/or valve surgery who were at high risk of AKI (including those with baseline creatinine level ≥ 2 mg/dl and age >70 years). They found that higher levels of urine albumin at approximately 6 hours after surgery measured by urine albumin concentrations or by urine dipstick levels (but not by urine albumin-to-creatine ratios) were associated with increased risk for postoperative AKI, defined as requiring dialysis or doubling of serum creatinine (4). Zappitelli and colleagues report that in a group of 294 children aged 1 month to 18 years undergoing cardiac surgery, postoperative urine albumin-to-creatine ratio at about 6 hours after surgery predicts AKI on the basis of Acute Kidney Injury Network (AKIN) serum creatinine criteria, with greater prediction of lower stage AKI in children ≥2 years (5).

Both studies are strengthened by their multicenter design, which enhances the generalizability of the findings, and by the careful and standardized prospective collection of clinical data and biospecimens in their participants. The investigators also took into account detailed patient and perioperative characteristics as part of their multivariate-adjusted models. The researchers for the adult study should be further commended because of the large sample and supplementary sensitivity analyses modifying the outcome to AKIN stage I and stage III AKI. These analyses allow us to see that the association between albuminuria and AKI remains fairly robust across gradations of AKI severity.

Although the exact mechanisms underlying these associations are not known definitively, one can hypothesize that perhaps preoperative proteinuria identifies patients with underlying CKD and reduced renal reserve who are more susceptible to AKI, whereas postoperative proteinuria is an early reflection of renal parenchymal damage, the cause of the subsequent observed increase in serum creatinine.

New and Old Biomarkers

These are important findings for the following reason. One oft-repeated mantra in the AKI field is that our failure thus far to devise effective therapies for most cases of AKI (specifically acute tubular necrosis) is due to an inability to detect AKI "early." The accompanying discussion sometimes makes it sound as if this were the predominant explanation for the lack of progress, crowding out other possibilities, such as reliance on excessively simplistic animal models or incomplete understanding of complex and heterogeneous pathophysiologic pathways in human AKI. This emphasis on "early" detection of AKI has resulted in a plethora of studies of promising biomarkers. Some of those garnering a lot of interest include neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1, IL-18, and liver-type fatty acid–binding protein.

Results from TRIBE-AKI, the largest AKI biomarker study performed to date, have considerably advanced the field by quantifying how much traditional and novel biomarkers contribute to improvement in risk prediction. Both papers in this issue (4,5) tested the risk prediction performance of postoperative albuminuria by using area under the receiver-operating characteristic curve (AUC) to determine ability to discriminate between AKI and non-AKI and continuous net reclassification improvement analyses to quantify the added value of albuminuria on AKI risk prediction beyond routinely considered clinical information. Notably, Molnar and colleagues found that albuminuria (as urine albumin concentration at 6 hours after surgery) performed better than both urine IL-18 and NGAL in AKI risk prediction when combined with clinical risk factors (6). Similarly, Zappitelli and colleagues found that in children, first postoperative urine albumin-to-creatinine ratio had an AKI risk prediction performance that was on par with models that include clinical factors and other biomarkers (urine IL-18, NGAL) (5).

As Molnar *et al.* put it: "Of note, a measure as accessible and simple as albuminuria performed better than IL-18 and NGAL (AUC, 0.76, $P=0.03$, for IL-18 plus clinical model; AUC, 0.73, $P=0.12$, for urine NGAL plus clinical model; AUC, 0.75, $P=0.01$, for plasma NGAL plus clinical model).... In our study,

Division of Nephrology, Department of Medicine, University of California, San Francisco, San Francisco, California

Correspondence: Dr. Chi-yuan Hsu, Division of Nephrology, University of California, San Francisco, 521 Parnassus Avenue, C443, Box 0532, San Francisco, CA 94143-0532. Email: hsuchi@medicine.ucsf.edu

postoperative albuminuria gave an AUC of 0.81 and [a net reclassification improvement] of 0.55."

There is reason to think that the AUC of 0.81 may in fact be an underestimation of the predictive ability now available to clinicians because not all clinically available measures were fully exploited. For example, urine output immediately after surgery was not considered, although adults undergoing cardiac surgery routinely have urine output measured hourly. (Both the Molnar and the Zappitelli studies used modified versions of the AKIN criteria as the outcomes of interest without including urine output.) Serum creatinine was measured approximately 6 hours after surgery in TRIBE-AKI but was not incorporated into the analysis (most of the AKI cases qualified by serum creatinine values were measured after 6 hours). A recent cohort study of adults undergoing cardiac surgery demonstrated that serum creatinine measurements obtained within 6 hours of operation predicted subsequent postoperative AKI (7). In that study, a ≥10% level increase in serum creatinine predicted significantly higher AKI risk (odds ratio, 6.38; 95% confidence interval, 2.73–17.2) compared with reference participants with ≤10% change in serum creatinine; AKI risk prediction also improved considerably after immediate postoperative creatinine was added to the base clinical model (0.09 increase in AUC). Finally, urine sediment was not examined. In the only head-to-head study of "novel" biomarkers (NGAL, kidney injury molecule-1, IL-18) versus "old-fashioned" urine microscopy (granular casts and renal tubular epithelial cells) that we are aware of, Hall *et al.* showed that the test characteristics of urine microscopy was not much worse than those of the biomarkers (8).

The Future

It appears that on the basis of information currently available to clinicians and researchers, including preoperative risk factors for AKI (such as estimated baseline GFR), intraoperative characteristics (such as bypass time), and immediate postoperative data (such as proteinuria quantification approximately 6 hours after surgery), we can identify quite well cardiac surgery patients who will go on to develop AKI, as defined by the latest consensus definition. An AUC of 0.81 is better than the Framingham risk score plus novel risk factors for predicting major cardiovascular events (9). Thus, it is no longer tenable to argue that inability to diagnose AKI "early" is a reason for lack of effective therapies in this setting. The onus is now on the renal community to overcome other barriers and devise interventions that work.

References

1. Hsu CY, Ordoñez JD, Chertow GM, Fan D, McCulloch CE, Go AS: The risk of acute renal failure in patients with chronic kidney disease. *Kidney Int* 74: 101–107, 2008
2. Hsu RK, Hsu CY: Proteinuria and reduced glomerular filtration rate as risk factors for acute kidney injury. *Curr Opin Nephrol Hypertens* 20: 211–217, 2011
3. Huang TM, Wu VC, Young GH, Lin YF, Shiao CC, Wu PC, Li WY, Yu HY, Hu FC, Lin JW, Chen YS, Lin YH, Wang SS, Hsu RB, Chang FC, Chou NK, Chu TS, Yeh YC, Tsai PR, Huang JW, Lin SL, Chen YM, Ko WJ, Wu KD: Preoperative proteinuria predicts adverse renal outcomes after coronary artery bypass grafting. *J Am Soc Nephrol* 22: 156–163, 2011
4. Molnar AO, Parikh CR, Sint K, Coca SG, Koyner J, Patel UD, Butrymowicz I, Shlipak M, Garg AX: Association of postoperative proteinuria with AKI after cardiac surgery among patients at high risk. *Clin J Am Soc Nephrol* 7:1749–1760, 2012
5. Zappitelli M, Coca SG, Garg AX, Krawczeski CD, Thiessen HP, Sint K, Li S, Parikh CR, Devarajan P; for the TRIBE-AKI Consortium: The association of albumin/creatinine ratio with postoperative AKI in children undergoing cardiac surgery. *Clin J Am Soc Nephrol* 7: 1761–1769, 2012
6. Parikh CR, Coca SG, Thiessen-Philbrook H, Shlipak MG, Koyner JL, Wang Z, Edelstein CL, Devarajan P, Patel UD, Zappitelli M, Krawczeski CD, Passik CS, Swaminathan M, Garg AX; TRIBE-AKI Consortium: Postoperative biomarkers predict acute kidney injury and poor outcomes after adult cardiac surgery. *J Am Soc Nephrol* 22: 1748–1757, 2011
7. Ho J, Reslerova M, Gali B, Nickerson PW, Rush DN, Sood MM, Bueti J, Komenda P, Pascoe E, Arora RC, Rigatto C: Serum creatinine measurement immediately after cardiac surgery and prediction of acute kidney injury. *Am J Kidney Dis* 59: 196–201, 2012
8. Hall IE, Coca SG, Perazella MA, Eko UU, Luciano RL, Peter PR, Han WK, Parikh CR: Risk of poor outcomes with novel and traditional biomarkers at clinical AKI diagnosis. *Clin J Am Soc Nephrol* 6: 2740–2749, 2011
9. Wang TJ, Gona P, Larson MG, Tofler GH, Levy D, Newton-Cheh C, Jacques PF, Rifai N, Selhub J, Robins SJ, Benjamin EJ, D'Agostino RB, Vasan RS: Multiple biomarkers for the prediction of first major cardiovascular events and death. *N Engl J Med* 355: 2631–2639, 2006

Published online ahead of print. Publication date available at www.cjasn.org.

See related articles, "Association of Postoperative Proteinuria with AKI after Cardiac Surgery among Patients at High Risk," on pages 1749–1760 and "The Association of Albumin/Creatinine Ratio with Postoperative AKI in Children Undergoing Cardiac Surgery," on pages 1761–1769.