New Biomarkers Offer Hope for Identifying Acute Kidney Injury Risk

By Eric Seaborg

A relatively new pair of biomarkers may give a valuable early signal of acute kidney injury (AKI), according to two papers, including a study that selected the pair from a competition with more than 300 potential candidates. Only further research will determine their actual clinical utility, but the findings reflect an intense effort to bring some AKI biomarkers to market—with some experts expecting a test to be available in the U.S. sometime this year. At least two assays are available in Europe, and researchers eagerly await data on their effectiveness.

AKI is very common among hospitalized patients and leads to increased mortality, with mortality rates ranging from 30 percent to 70 percent, and even higher among those requiring dialysis. But the condition continues to vex clinicians because a lack of overt symptoms makes diagnosis difficult before the loss of organ function. Serum creatinine and urine output remain the leading AKI indicators, but they signal that damage may already be occurring. Even the terminology illustrates the intensified interest in improving care and understanding of this condition. The term AKI replaced acute renal failure in recent years to recognize that the kidney undergoes a spectrum of impairment—and biomarkers could help identify the earliest stages.

“arly is an effort to stratify patients to identify those who are at the highest risk, separating them from the patients that have a more baseline risk, so treatment resources can be deployed most effectively,” said John Kellum, MD, professor of critical care medicine at the University of Pittsburgh and corresponding author for both studies. “There is quite a lot of information on what you should do to try to mitigate the risk of acute kidney injury in patients, but it all begins with identifying patients at high risk.”

Kellum and colleagues published a paper last year in Critical Care describing a two-pronged discovery and validation study. The researchers started with more than 1000 potential markers that they narrowed down to about 340 candidates for closer study. They then conducted a procurement biopsies are not predictive of posttransplant outcomes and may only serve to dissuade the use of kidneys that are otherwise suitable for transplant. The findings suggest that other methods are needed when weighing whether to transplant a deceased-donor kidney.

Biopsy-reported acute kidney injury and allograft outcomes

Given ever-increasing numbers of patients with end stage renal disease, the medical community has pushed to expand the deceased-donor organ supply. Unfortunately, a clear and consistent balance between organ acceptance and discard after procurement has been difficult to achieve given a lack of precise tools to assess donor kidney quality and prognosis.

“Kidney researchers are investigating newer, non-invasive tools to assess kidney tissue injury, but we need to fully

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Studies Indicate that Biopsies Do Not Determine Suitability of Organs for Transplantation

Deceased-donor kidneys retrieved for transplantation are increasingly being discarded, and the most common reason given for discarding the kidneys is biopsy results. Two new studies published in the Clinical Journal of the American Society of Nephrology suggest that procurement biopsies are not predictive of posttransplant outcomes and may only serve to dissuade the use of kidneys that are otherwise suitable for transplant. The findings suggest that other methods are needed when weighing whether to transplant a deceased-donor kidney.

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multicenter study of these 340 markers in more than 500 adults, including patients with sepsis, shock, major surgery, and trauma. This study found that the most effective test was for a combination of two markers, insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP-2).

Kellum told *Kidney News* that these two markers were somewhat of a surprise, but on further examination they made sense. Although they are involved in a variety of different pathways, they share one characteristic—they both induce G1 cell cycle arrest, which is considered a key and very early mechanism in AKI. “[Cell cycle arrest] is one of the ways that epithelial cells attempt to protect themselves when they are under stress, and the two biomarkers together cover virtually every conceivable stress that an epithelial cell in the kidney might be exposed to,” Kellum said. In a second phase of this Critical Care study, the researchers enrolled 750 adults with critical illness and compared TIMP-2 and IGFBP7 with other known markers, including neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, kidney injury marker-1 (KIM-1), interleukin-18 (IL-18), and liver fatty acid-binding protein (L-FABP).

The primary end point was the development within 12 hours of sample collection of stage 2 or 3 AKI using Kidney Disease: Improving Global Outcomes (KDIGO) criteria. The TIMP-2/IGFBP-7 combination achieved an area under the receiver-operating characteristics curve (AUC) score of 0.80, whereas none of the other markers achieved an AUC value greater than 0.72.

A follow-up prospective, multicenter validation study of an immunoassay for the two markers, just published online in the *American Journal of Respiratory and Critical Care Medicine*, involved 420 critically ill patients. The study tested the ability of urinary TIMP-2/IGFBP7 at a predetermined cutoff to predict the development of moderate to severe AKI within 12 hours of sample collection. Three independent nephrologists judged whether the patients developed AKI. Patients whose levels exceeded the cutoff had seven times the risk of progressing to AKI compared with patients whose levels were below the cutoff. But in terms of specificity and absolute risk, only about 25 percent of those with levels above the cutoff progressed to AKI within 12 hours, compared with 4 percent of the patients with levels below the cutoff.

The study was funded by Astute Medical (San Diego, CA) to gain performance data to submit to the U.S. Food and Drug Administration (FDA) on the company’s NephroCheck immunoassay. Whether the FDA will approve the test, and how long any decision might take, are, of course, open questions. The FDA accepted data in 2011 from BioPorto on a test for what is probably the most-studied AKI marker—NGAL—with apparently no word yet on any decision. Both the NGAL and the TIMP-2/IGFBP-7 tests are available as easily run immunoassays in Europe, and data on both are just beginning to trickle in.

Whatever the outcome of these applications, most specialists anticipate that ultimately a panel of biomarkers is likely to be more helpful than a single marker or test, according to Sarah Faubel, MD, associate professor of medicine at the University of Colorado, Denver, and chair of the American Society of Nephrology’s AKI Advisory Group.

Faubel said that although the studies by Kellum and colleagues were well-thought-out and examined an important and heterogeneous population, she was not ready to declare the new markers better than or likely to displace the other contenders. But they are likely to provide another potential tool.

She noted that the study was based on measuring the markers at a single point, within 15 hours of ICU admission, so “the question is, how does this integrate with other time points during the course of AKI, and how does it integrate with other biomarkers . . . [which could] perhaps identify different phases of AKI.”

Ravindra Mehta, MD, professor of clinical medicine in the division of nephrology at the University of California, San Diego, said that AKI markers fall into two categories, markers of normal function and markers of damage. The TIMP-2/IGFBP7 combination falls into the damage category, and they do seem to stand out in comparison to other markers with their ability to predict the progression to AKI. But he noted that a lot more experience is required before they are likely to be useful in a clinical sense, and whether they will perform outside the study, in clinical practice, is a question only time will answer.

Researchers and clinicians continue to advance the field of AKI, reaching consensus on defining the condition and establishing best practices for patient care. The best practices recognize the importance of early diagnosis and intervention, which in turn make biomarkers potentially so valuable. As these studies indicate, this quest continues to move forward. “The general anticipation in the community is that sometime in 2014 we will have access to some biomarker,” Mehta said. 

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