EDITORIAL

Time for Precision Medicine in the Diagnosis of Acute Kidney Injury

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Acute kidney injury (AKI) is a frequent complication of critical illnesses and is associated with both short- and long-term adverse outcomes. Although we do not yet have therapeutic strategies to reverse or abort the renal injury, an early diagnosis does enable the timely institution of renoprotective measures that may prevent aggravated injury.

The diagnosis of AKI is currently based on the acute changes in two functional parameters—urine output and serum creatinine. These have the advantage of being universally available, enabling the diagnosis of AKI even in resource-restricted regions, and allow the staging and severity of AKI. However, these are functional markers and inherently appear a little later in the course of illness than the timing of the ultrastructural injury that precedes them. They are thus late markers, appearing 48–72 hours after the injury when the window period for possible protective interventions has already elapsed. Underestimation of AKI in critical illnesses based on low creatinine values secondary to muscle wasting or dilutional lowering due to fluid overload is an often-overlooked problem, leading to underdiagnosis of AKI and underestimation of its severity.

The study of biomarkers of structural injury instead of functional markers has brought a greater understanding of the pathogenesis of AKI and the possibility of early diagnosis of AKI at a time in the evolution of the disease when therapeutic interventions could mitigate further injury. Various biomarkers have been under the scanner such as plasma and urinary neutrophil gelatinase-associated lipocalin (pNGAL and uNGAL), interleukin-18 (IL-18), kidney injury molecule 1 (KIM-1), L-fatty acid–binding protein (L-FABP), insulin-like growth factor–binding protein-7 (IGFBP-7), and tissue inhibitor of metalloproteinase (TIMP-2), to name a few.[1]

NGAL is the biomarker that has been most extensively studied and has now entered the arena of bedside medicine. NGAL is a stress molecule and is one of the most rapidly upregulated genes in ischemic AKI in animals. Kidney tubular cells, mainly the loop of Henle and the collecting ducts, produce NGAL in response to various insults. Preclinical studies have shown that uNGAL appears as early as two hours after the onset of a renal injury. One of the early studies on AKI in children undergoing cardiac surgery showed that the appearance of NGAL in the urine 2 hours after cross-clamping had a high predictive value for the development of clinical AKI after 72 hours with a sensitivity of 100% and an area under the receiver operating curve (AUC) of 0.998.[2]

Subsequent studies in other clinical states, such as sepsis, have shown more variable results. In a recent meta-analysis, uNGAL predicted septic AKI with an AUC of 0.9.[3] This is in contrast to a large adult study that found uNGAL to have a poor predictive value for the diagnosis of AKI with an AUC of 0.69.[4] In the article by Kapalavai et al. published in this issue, the authors have evaluated the value of NGAL in predicting AKI in a heterogeneous group of critically ill children and showed that uNGAL had a sensitivity of 81.4% and specificity of 83.6% in diagnosing AKI and had a significant predictive value with an AUC of 0.842, when the cut-off value for diagnosing AKI was taken as NGAL >88.5 ng/mL, a cutoff that is lower than what has been used in many other studies.[5]

One reason for these variable results is that unlike the situation of cross-clamping in conditions, such as sepsis, the exact time of injury to the kidneys is not known and NGAL measurement occurs at a variable time after the injury. Another confounding factor is that NGAL is also produced by cells other than renal tubular cells, especially in response to infection and inflammation. Neutrophils release NGAL which is filtered by the kidney and when produced in large quantities may exceed the reabsorptive capacity of the proximal tubules and spill over into the urine leading to high urinary NGAL levels even when a renal injury has not occurred. Inflammation of the renal tubules by urinary tract infections can result in high urinary NGAL even in the absence of AKI. Although the molecular identity of NGAL from neutrophils is distinct from NGAL from the renal tubular cells, there is yet no rapid bedside method of differentiating the two.

One of the pitfalls in the study of biomarkers is the default methodology used in most studies that attempt to validate a structural injury marker against the so-called "gold standard" creatinine, which is a functional marker that is both insensitive and a late marker. NGAL-positive but creatinine normal situations are no longer considered false positives but are now recognized as subclinical AKI and have been shown to have the potential for both long- and short-term adverse outcomes.

One of the other interesting biomarkers that goes beyond diagnosis is the KIM-1 molecule which is released very early by the proximal tubular cells in response to injury and can be an early

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predictive marker for AKI. KIM-1 attracts macrophages to the site of injury. Persistent KIM-1 elevation has been shown to be associated with interstitial fibrosis and may have adverse implications for long-term outcomes.

Some of the other injury biomarkers that have found a space in bedside medicine are TIMP-2 and IGFBP-7 which are alarm molecules. When renal tubular cells experience injury, the cells reduce their oxygen and metabolic needs by undergoing cell cycle arrest as a measure to protect themselves from irreversible harm. TIMP-2 and IGFBP-7 are markers of cell cycle arrest and appear in urine due to a combination of mechanisms including increased filtration, leakage from tubules, and failure of tubular reabsorption. TIMP-2 is secreted by distal tubular cells and IGFBP-7 by proximal cells, thus giving an idea of the extent as well as the mechanism of injury. The product of the two has been shown to be a good predictor of AKI in several studies with an AUC of 0.8 and is now commercially available as a bedside test with results in 20 minutes.[1]

The understanding of the origin of the biomarkers, their role in the body in response to kidney injury, the quantum, as well as chronology of their appearance and disappearance actually unfolds the theater of AKI with insights into the mechanisms of injury, severity, repair, recovery, and chronicity.

A pathophysiology-driven panel of urinary biomarkers, rather than a single biomarker, may play a central role in the management of AKI in the coming years, as we move from general algorithmic care to precision and personalized medicine.

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