EDITORIAL

Acute Kidney Injury in the Intensive Care Unit: The Most Reliable Way to Predict the Future is to Create It

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While Occam's razor approach to managing patient problems (the simplest solution is usually the best) is intuitive and adequate in most situations, it is not in acute kidney injury (AKI) in the intensive care unit (ICU). Often, hidden complexities in patient physiology and interactions with the disease process make Hickam's dictum (in a complex system, problems usually have more than one cause) more appropriate for critically ill patients. A third of patients develop in-hospital AKI; suboptimal care is noted in half, considered avoidable by early risk detection.[1] AKI, a common complication in surgical and medical ICUs, is recognized as a major public health problem, impacting mortality, morbidity, and health costs.[2,3] Despite advances in treatment, mortality of ICU patients with AKI remains between 50 and 80%.[4]

Guidelines for renal care focus on avoiding injury from intravenous contrast, nephrotoxic drugs, and maintaining an optimal fluid status.[5] The definitions of "injury" have evolved since 2004 [risk, injury, failure, loss, and end-stage (RIFLE) criteria][3] through 2012 [kidney disease improving global outcomes (KDIGO) classification].[6] AKI is indicated clinically either by a decrease in the urine output or a rise in serum creatinine. Both are situations that present *after* the onset of organ dysfunction, possibly irreversible damage.

How idyllic would it be then to have the perfect predictive tool that alerted us to possible AKI even before urine output or serum creatinine changed! As Abraham Lincoln said: "The most reliable way to predict the future is to create it." The holy grail for managing AKI in the ICU has been a quest to develop the perfect algorithm for accurate prediction[7] to enable timely risk stratification and preventive treatment.[8] Over the last decades, seekers of this perfect predictive instrument have worked on different areas, such as new tools, models, and biomarkers. Many have been tested in varied clinical settings.[7]

Biomarkers in the urine and serum are the accessible indicators of AKI. The hope has been that one or more of these, in combination, will facilitate prediction and early detection of AKI to guide interventions targeted at renal protection and repair. Neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, kidney injury molecule-1, interleukin-18, and liver-type fatty acid-binding protein are among the more promising ones, with a diagnostic accuracy (receiver-operating characteristic curve) varying between 0.53 and 0.96.[7] Unfortunately, despite promising early results, incomplete understanding of reasons of rising levels and lack of accuracy have not justified their clinical use in the face of the prohibitive costs involved.[9,10] Serum and urine NGAL (sNGAL and uNGAL) levels are influenced by the severity of illness and inflammation, which are found to be independent of the presence of AKI. There is a strong correlation between sNGAL and uNGAL levels in patients with sepsis, indicating that increased levels of uNGAL can also be due to overspill from the systemic circulation, blurring the discriminative value of NGAL as a biomarker for AKI in patients with sepsis.[11]

Other ways to predict the susceptibility and risk of developing AKI and long-term patient prognosis are the furosemide stress test[12] and the renal function reserve (RFR) tests.[13] A urine output of <200 mL (100 mL/hour) after 1 to 1.5 mg/kg of furosemide "stress" predicts severe AKI with a sensitivity of 87.1% and a specificity of 84.1%—outperforming most of the biomarkers in predicting progression to renal replacement therapy and mortality.[14] The ability of the kidney to increase renal plasma flow and glomerular filtration rate (GFR) after a stimulus such as a protein load indicates the presence of intact nephron mass and is the basis for the RFR test.[13] A protein load coupled with ultrasound measurements of resistivity and pulsatility indices can help calculate the RFR clinically.[15] Unfortunately, there is no validated protocol or cutoff values for clinical use.

Various groups have put forth AKI prediction models to acquire an accurate, validated prediction model for AKI after surgery or other high-risk therapeutic procedures. The goal is to enhance clinical decision-making, patient optimization, counseling, and resource utilization. Most of these models are from small-size trials in patients undergoing cardiothoracic surgery, based on "good clinical observation," and can predict postoperative AKI fairly well (area under the curve between 0.76 and 0.84).[16]

Fractional excretions of sodium (FENa) and urea (FEUr) are indices frequently used to assess AKI. Once considered useful in distinguishing functional (prerenal) and structural AKI (acute tubular necrosis), these parameters have now been questioned for poor discrimination in transient vs persistent AKI, septic vs non-

septic AKI, and elevation in the absence of renal hypoperfusion. Urine sodium (UNa), FENa, and FEUr are unreliable predictors of biomarker release, AKI, or mortality.[17] More recently, while attempting to study these parameters as predictors of AKI, Maciel et al. observed that an increase in urinary potassium may indicate a decrease in the GFR even before a rise in serum creatinine.[18] The same group demonstrated, in a retrospective analysis of postoperative patients, that while serum creatinine increases two days after ICU admission, higher fractional excretion of potassium values may appear as early as the day of admission, indicating patients at a higher risk of AKI.[19] Smyth et al. estimated 24 hours urinary sodium and potassium excretion in 28,879 participants at high cardiovascular risk to conclude that urinary potassium excretion predicted clinically significant renal outcomes better than UNa.[20]

In this edition of IJCCM, Nikhilesh et al.,[21] have tested a similar hypothesis as Burns et al.[22] before them to answer a simple bedside question: can urinary potassium level at admission to ICU predict AKI in the subsequent week? An elegant idea tested in 100 patients in a mixed medical–surgical ICU found a moderate uphill correlation of creatinine clearance with urine potassium. The area under the curve for prediction of AKI was similar between the two studies, especially in furosemide-naïve patients, and not worse than most serum markers mentioned previously. While both the studies come from a small subset of patients and the clinical utility of the cutoffs from the results are difficult to interpret and apply clinically, the idea of exploring this test further as a readily available, inexpensive standalone test or a part of an algorithm is alluring.

As technology advances, clinical prediction tools based on big data and artificial intelligence-based predictive models for patient-specific, "omic" risk estimation may be more reliable, affordable, and time-sensitive than single-test-based predictions.[23,24] Machine-learning-based prediction models have their limitations of lack of external validation, being based on retrospective data and variability of reliable electronic medical record data across centers.[25]

Irrespective of the prediction tool being used, what is perhaps more important is combining these risk prediction models with early care bundles rationally to improve patient outcomes—because, in the end, predictions are only as good as the actions they generate.

"The consequences of our actions are always so complicated, so diverse, that predicting the future is a very difficult business indeed."—**J. K. Rowling**

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