Kidney Medicine

From Surviving Sepsis to Surviving Sepsis-Associated Acute Kidney Injury: Focusing on Risk Stratification of Acute Kidney Injury / Acute Kidney Disease After Sepsis

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Acute kidney injury (AKI) and chronic kidney disease (CKD), including end-stage kidney disease, enjoy primacy in the lexicon of nephrologists. Murkier is acute kidney disease (AKD) and the related concept of kidney recovery.[1] The causal loop of AKI and CKD—that AKI increases risk for CKD, and CKD increases risk for AKI—is well appreciated in nephrology. AKD captures the "in-between" limb of this loop connecting AKI to CKD. For this reason, we are well served to understand how AKI patients may be risk stratified with respect to their risk of progression to new CKD (or progression of existing CKD).

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One particularly high-risk population for development of AKI and exposure to its attendant complications are patients with sepsis and septic shock.[2,3] Given the continued under-recognition of CKD by both patients and clinicians,[4,5] the identification and risk stratification of patients with sepsis-associated AKI/AKD who are likely to develop complications is essential, particularly as the long-term effects of sepsis-associated AKI/AKD remain understudied. Appropriate referral to nephrology for people who develop sepsis-associated AKI/AKD remains difficult for many clinicians—specifically, does a person with mostly recovered AKI still merit outpatient nephrology evaluation? The role of reduced kidney function in assessing sepsis severity is clear, but we do not yet fully understand how to incorporate sepsis into AKI/AKD staging and prognostication.

Flannery et al[6] have skillfully explored the complex paradigm of AKI-AKD-CKD in a population of patients with sepsis-associated AKI. As described in this issue of *Kidney Medicine*, a multidisciplinary team including pharmacists, data scientists, and physicians performed a retrospective analysis of 2,307 critically ill patients admitted with severe sepsis/septic shock. The goal of the study was to assess the merit of risk-stratifying patients at risk for long-term kidney outcomes (such as CKD, requirement for kidney replacement therapy, or death) based on the severity of residual kidney injury—specifically AKD—at or around hospital discharge. Adult patients with severe sepsis or septic shock, who survived the admission and were not dialysis-dependent at 90 days postdischarge, were stratified according to AKD staging based on recommendations from the Acute Disease Quality Initiative Workgroup[7] (Table 1) and followed after discharge. The primary composite outcome was CKD incidence, progression of premorbid CKD, kidney failure with need for kidney replacement therapy, or death.

Patients were followed for a median of 14 months, with most having at least 2 serum creatinine values for CKD staging during the follow-up period after initial hospital discharge. Compared with stage 0A AKD over the follow-up period, rates of CKD incidence/progression, kidney failure with need for kidney replacement therapy, or death were significantly higher among those with AKD stages 0C and ≥1. No significant difference in the primary composite outcome was demonstrated between stages 0A and 0C AKD in patients without CKD at baseline. In general, higher AKD stages were associated with progressively worse kidney outcomes. Similarly robust associations persisted in separate analyses of incident/progressive CKD and kidney replacement therapy / death. The authors concluded that AKD stage may be an important risk stratification tool for post-AKI care in patients surviving sepsis-associated AKI.

The concept of adapting readily available data for rapid prognostication is exciting but should be taken with caution in the setting of a single-center, retrospective study. These results from patients with and without CKD are particularly intriguing when considering the results of ASSESS-AKI, a study of hospitalized patients for whom AKI was associated with substantially higher rates of incident CKD.[8] Unlike the Flannery study in this issue of *Kidney Medicine*, AKI (not AKD) was the independent variable studied, and patients without sepsis and without intensive care unit admission were included. Nevertheless, a clear association between AKI and adverse kidney outcomes (such as incident/progressive CKD) as well as heart failure events and death was demonstrated. Notably, accounting for kidney recovery and proteinuria at 3 months postdischarge attenuated the associations between AKI and heart failure / death to nonsignificance. These data again suggest the relevance of postdischarge assessment of kidney function (perhaps AKD) for risk stratification, though generalizability regardless of sepsis status may be limited until additional data are available.

Table 1. Staging of Kidney Disease per Acute Disease Quality Initiative Workgroup Recommendations[7]

0-7 Days	7-90 Days	>90 Days
Acute Kidney Injury (AKI)	Acute Kidney Disease (AKD)	Chronic Kidney Disease (CKD)
Subacute (stage 0)	Subacute (stage 0A): no evidence of injury	
	Stage 0B: biomarker or loss of renal reserve indicates injury	
	Stage 0C: Cr not returned to baseline	
Stage 1: Cr 1.5× baseline	Stage 1: Cr 1.5× baseline	
Stage 2: Cr 2× baseline	Stage 2: Cr 2× baseline	
Stage 3: Cr 3× baseline or dependent on KRT	Stage 3: Cr 3× baseline or dependent on KRT	

Abbreviations: Cr, serum creatinine; KRT, kidney replacement therapy.

While strong risk-stratification tools for sepsis-associated AKI/AKD are presently in demand, risk-stratification tools for sepsis are well entrenched in clinical practice. These tools (eg, SIRS, APACHE II, SOFA) are based on sound data, are easily implementable by caregivers of all types, and are quickly recognized as parts of standard medical practice across specialties and practice locations. Unfortunately, despite efforts in this direction, tools for guiding appropriate referrals to nephrology for sepsis-associated AKI/AKD remain inadequate, with substantial consequences of morbidity and mortality for the unreferred population.

Additional consideration of the baseline characteristics of the patients studied may be helpful for understanding the potential value of this study. Forty percent of patients without AKI were documented to have oliguria. While the challenges of obtaining accurate measures of urine output for hospitalized patients are well known to any physician, the exclusion of oliguria from the study definition of AKI may have led to some cases of incident AKI being missed, which is particularly important given worsened outcomes in patients with oliguric AKI.[9,10] Significantly higher rates of albuminuria were also observed in those with higher AKD stages.

The correlation between inpatient AKI and subsequent adverse kidney outcomes is well documented. Nevertheless, significant challenges exist with regard to translating results obtained during hospitalization to effective outpatient follow-up. Frequently, outpatient clinicians are not provided with complete records of inpatient stays: is a diagnosis of AKI equally relevant if it resolved during the hospitalization? This may be particularly important for patients with milder AKI/AKD. While it may seem obvious that substantially worsened kidney function persisting after hospital discharge portends future adverse outcomes, objective guidelines for appropriately timed referrals to nephrology in this setting are necessary. As we move toward advanced decision support tools (such as using machine learning), there may be a role for automated referrals, perhaps using an AKD-based scoring system to determine the appropriate timing. Given the relative ease of assessing AKD in the outpatient setting, as well as the benefit of not requiring complete inpatient records to make the assessment, this would likely be an easily implementable intervention. Careful outpatient observation and monitoring of all patients with sepsis who develop AKI is necessary. While further study would be necessary to correlate AKD stages to appropriate nephrology referrals, an objective, easy-to-use assessment of AKD would allow improved coordination across phases of care, facilitating more prompt nephrology evaluation and potentially limiting the incidence of adverse kidney outcomes for this population in the future.

ARTICLE INFORMATION

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