Editorial

Is It Time to Evolve Past the Prerenal Azotemia *versus* Acute Tubular Necrosis Classification?

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For more than 70 years, the cornerstone for the diagnosis and management of acute kidney injury (AKI) has been the paradigm wherein its etiologies have been broken down into categories of prerenal, intrinsic, and postrenal disease (1). With postrenal obstruction usually readily apparent, the critical diagnostic distinction has typically been between prerenal and intrinsic causes, specifically acute tubular necrosis (ATN). Since the advent of nephrology as a discipline, the dichotomization of prerenal azotemia (PRA) and ATN has been a shibboleth of the renal community.

Although AKI is the most common indication for an inpatient nephrology consultation and eliciting an accurate diagnosis is critical, the traditional biomarkers used to distinguish PRA from ATN, time honored and familiar to every medical student, are, in practice, inadequate. The most commonly used parameters are the fractional excretion of sodium (FE_{Na}) and urine microscopy. Originally described in a cohort of 17 patients with oliguria (2), FE_{Na} should theoretically be low (<1%) in the sodium avid state of PRA and elevated (>1% or 2%) in a setting of compromised tubular integrity such as ATN. However, in numerous circumstances including the administration of diuretics or iodinated contrast or alterations in effective circulating blood volume as seen in congestive heart failure or cirrhosis, this pattern would not be expected to hold. Several clinical settings in which patients had ATN and FE_{Na} <1% have been described in the literature (3). Although another commonly used test, urine microscopy, can be useful in AKI for both diagnosis (4) and prognosis (5), it is operator dependent and requires expertise. Other tests, such as serum blood urea nitrogen to creatinine ratio and urine specific gravity, are even less reliable.

This diagnostic conundrum has been compounded by an evolving conceptualization of what constitutes AKI. As our diagnostic criteria for AKI have become more sensitive, with the modern Acute Kidney Injury Network (AKIN) definition requiring only a rise in serum creatinine of 0.3 mg/dl, our tools for evaluating it have lost specificity. A large percentage of AKI now occurs in the setting of existing chronic kidney disease (CKD), forcing us to reassess what the results of our tests "should" be with this changing epidemiology. No studies exist on what constitutes "normal" sediment in CKD, thus complicating the interpreta-

tion of microscopy performed for AKI in this setting. Similarly, as noted in the original description of FE_{Na}, a ratio of 1% should not be considered "normal" in patients with CKD and the test must be interpreted with caution with these patients (2).

More fundamental, attempting to cram all patients into a single diagnostic box is both futile and counterproductive. PRA and ATN can and often do coexist in the same patient. Because of the patchy nature of ATN, it is possible that some regions of the kidneys can have severe morphologic and functional ATN, whereas other parts may be structurally intact, awaiting only reperfusion to resume normal filtration. The primary problem, then, is that PRA and ATN, with their arbitrary cutoffs and distinctions, are diagnoses rather than diseases, constructed concepts without operational definitions, and thus their usage in both clinical practice and research necessarily renders each as not evidence based. The subjective nature of these diagnoses is demonstrated when clinical adjudication is attempted within a study. Even with the full clarity of hindsight, adjudicating the etiology of AKI at the time of discharge produces only modest agreement (6).

With our current classifications so flawed, is it even worthwhile to try to distinguish where patients are on the continuum of hypoperfusion and tubular injury? Or, in the era of AKIN and RIFLE, where too often even nephrology notes will include the diagnosis of "AKI stage 2" as the cause of a patient's acute rise in creatinine, are there compelling reasons to abandon the current simplistic yet readily accessible designations? In fact, such a change is not only desirable but necessary. Clinically, the historic retrospective approach to diagnosis—fluid loading virtually everyone and then labeling those who respond as having PRA—has increasingly been found to be not only unscientific but dangerous (7). From a research perspective, with our rapidly advancing understanding of AKI on a molecular level, spurred by novel proteomic techniques, it seems inevitable that we will soon have new drugs to try as targeted treatments for kidney injury (8,9). To prevent stacking the deck in trials and to improve precision, we need to avoid misclassification wherein we treat for ATN patients who lack true structural injury and who would have improved regardless of treatment.

How can we do better? The primary focus in the

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setting of rising creatinine should not be assigning the diagnosis of PRA or ATN but determining where the dysfunction lies on the spectrum between purely functional and completely structural (two extremes that likely do not exist). Does the patient have an actual acute kidney injury, or does he or she simply meet clinical criteria for "AKI"? Recently, a raft of novel biomarkers specific to kidney tubule injury have been investigated to assist with the early detection, differential diagnosis, and prognostication of AKI. An ideal renal biomarker for differential diagnosis would be inexpensive, noninvasive, sensitive and specific, and easy to measure at the point of care. Among the myriad markers studied to date, IL-18, neutrophil gelatinase associated lipocalin (NGAL), and kidney injury molecule 1 (KIM-1) have shown the most promise in the differential diagnosis of AKI (10). The utility of IL-18 for the diagnosis of different kidney diseases was assessed in 50 patients with a mixture of established ATN, PRA, urinary tract infection (UTI), and CKD and healthy control subjects. IL-18 levels were significantly increased in patients with ATN compared with all other groups with an accuracy of 95%. KIM-1 also has shown the ability to discriminate ATN from other causes of AKI, including acute interstitial nephritis, obstructive nephropathy, and PRA, whereas emergency department measurement of NGAL can distinguish AKI from PRA and CKD (11,12).

The study by Heller *et al.* (13) in this issue of *CJASN* examines a new candidate as a biomarker for structural damage to discriminate PRA and intrinsic AKI. Calprotectin, a mediator of the innate immune system, is released in response to mucosal or epithelial inflammation. Measured in stool, calprotectin is a well established parameter for differentiating between irritable bowel syndrome and inflammatory bowel disease. The authors cleverly postulated that, with PRA analogous to inflammatory bowel disease as a functional condition, urinary calprotectin might also serve to distinguish PRA from intrinsic AKI. The median urinary calprotectin in the group with intrinsic AKI, 1692 ng/ml, was significantly higher than that in the patients with PRA, 28 ng/ml, and those in the control group, 45 ng/ml. The area under the curve for the detection of intrinsic AKI of calprotectin was 0.97, whereas proteinuria (undefined) was 0.82 and FE_{Na} was 0.52. The association of calprotectin with hard end points such as worsening of AKI stage, dialysis, and death was not evaluated.

Although the discriminatory ability of calprotectin seems remarkable, several caveats need to be considered. Because of its role in the activation of Toll-like receptor 4, calprotectin would be expected to be elevated in nonischemic conditions such as glomerulonephritis, vasculitis, and interstitial nephritis as well as in ATN through ischemia-reperfusion injury. Indeed, of the 52 patients with intrinsic AKI, only six are explicitly noted to have ATN. Many of the alternative diagnoses are typically easily diagnosable, and utility of calprotectin in distinguishing functional from structural AKI will need to be verified in cohorts with much higher numbers of ATN. UTIs are expected to raise urinary calprotectin levels, and it seems likely that the presence of a UTI will complicate interpretation of calprotectin results.

It is apparent that a new approach—and nomenclature—

incorporating biomarkers is required to re-imagine the way in which nephrologists perceive AKI. A biomarker panel would not replace serum creatinine and the AKIN/RIFLE system but augment them to provide greater diagnostic granularity with regard to presence of injury. A staging system for AKI quantifying the acute decline in renal function could be retained, but each stage would be subdivided by the presence or absence of tubular injury as evidenced by biomarker levels. Given the continuum between PRA and ATN, such a biomarker designation need not be "positive/negative" but instead will be able to quantify the burden of injury as AKIN does the extent of dysfunction, together giving a complete picture of the state of the kidney and informing treatment decisions and prognosis. Recently, tremendous attention has been focused on both short- and long-term consequences of minimal changes in serum creatinine, even down to 0.1 mg/dl (14). It stands to reason that a predominantly hypoperfusion-mediated dysfunction will not impart the lasting effects associated with actual injury. That our current AKI classification system makes no distinction between PRA and ATN, providing no guidance as to who with AKI is most likely to progress to CKD, is revealing of its inadequacies. This shift would be analogous to the recent modification to CKD classification to include proteinuria, a structural biomarker, for further stratifying the GFR stages, which are based on serum creatinine (15).

From the early days of nephrology, its practitioners have been ensorcelled by the primacy in AKI of categorizing disease, embracing the paradigm of prerenal, intrinsic, and postrenal etiologies. The most attractive feature of this system, simplicity, is also emblematic of its shortcomings. Medicine at its most fundamental involves knowing whom to treat, when, and with which agents. In the setting of AKI, that means prospectively determining who will require volume alone to reverse the majority of the fall in GFR and who will require specific targeted treatments. To do so, we must focus not on trying to figure out what the patient "has," intellectually satisfying although that may be, but instead on objectively characterizing the nature of the kidney injury and function to guide evidence-based therapies. By incorporating tubular injury biomarkers such as NGAL, IL-18, KIM-1, or calprotectin into our approach to AKI, we might finally achieve the necessary clarity to bring about this long overdue paradigm shift.

Disclosures

None.

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