Towards a Definition and Classification of Acute Kidney Injury

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Chertow and colleagues (1) have an interesting and provocative paper in this issue of JASN that brings a pragmatic approach to bear on the issue of defining acute renal failure. This area is rapidly gaining prominence and was the theme of one of the American Society of Nephrology’s research focus groups last spring. In that meeting, the terminology “acute kidney injury” (AKI) was put forth as the preferred nomenclature for the clinical disorder that we are all familiar with, with the understanding that its spectrum is broader than the subset of patients who find themselves in an intensive care unit with an acute need for dialysis support.

The issues of nomenclature, classification, and assessment of severity have long been recognized as problematic, and they were one of the foci of a National Institutes of Health consensus conference on acute renal failure nearly 10 yr ago (2); progress on these issues has been rather modest in the interval. The critical care community has been active, and representatives from nephrology and critical care medicine have developed a working group called the Acute Dialysis Quality Initiative (3,4). The efforts of this group have been focused on the issues involved with intensive and critical care, and a classification proposal has been developed that is based on physiologic measurements including serum creatinine and urine output (5,6).

The fact that the mortality with AKI injury in the intensive care setting can be extraordinarily high and that AKI is often accompanied by multiple organ failure underlies the importance of making significant progress in this area. In the most recent survey, the prevalence of severe AKI in the intensive care setting that required some form of renal replacement therapy approached 6%, with an in-patient mortality rate of 60.3% (7). A number of clinical trials have been carried out in AKI, but on these issues has been rather modest in the interval. The critical care community has been active, and representatives from nephrology and critical care medicine have developed a working group called the Acute Dialysis Quality Initiative (3,4). The efforts of this group have been focused on the issues involved with intensive and critical care, and a classification proposal has been developed that is based on physiologic measurements including serum creatinine and urine output (5,6).

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This is the context in which the paper by Chertow et al. (1) makes its contribution. Based on a survey of >19,000 hospital admissions, a subset of patients were selected for whom the clinical caregivers had obtained more than one serum creatinine determination. The analysis considered both the absolute and fractional increase in serum creatinine, and evaluated mortality, length of stay, and other outcome measures associated with the changes in serum creatinine. This approach can be criticized because there may have been an ascertainment bias (e.g., Why was more than one creatinine ordered?), measurements of urine output (e.g., oliguric versus nonoliguric or even anuric AKI) were not available, and the baseline kidney function for these admitted patients was not known.

Despite these shortcomings, which are inherent in the design of a large-scale surveillance study, the results presented by Chertow et al. are well worth considering. When outcome was simply defined as death, there was a graded impact on outcome that clearly reflected the severity of AKI (see Table 2 in the authors’ article [11]). Even with only a modest 0.3 mg/dl increase in the serum creatinine level, there was a 4.1-fold risk of mortality. The increased relative risk was still present when the association was adjusted for age, and disease severity. Some would be inclined to reject a modest 0.3 mg/dl increase in serum creatinine as “clinically insignificant” or explainable by prerenal issues, but the fact that the relative risk of a poor outcome increased as the severity of injury increased, judged by the magnitude of the creatinine increases, argues that the predictive power of even a modest change in serum creatinine should not be ignored.

Chronic kidney disease (CKD) has been defined by the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines with stages based on estimates of the GFR (8). This process has been rigorous, and clinical action plans have been developed for each stage. The impact of this approach has been impressive, and the stages of CKD are now codified in the next iteration of the International Classification of Disease, Ninth Revision (ICD-9) codes that will be published in October 2005. Of note, the risk for overall outcomes, including death, cardiovascular events, and even number of hospital days are related to the severity of CKD, with the first increase apparent in stage 3 CKD (9). The similarity of this finding, also published by Cher-
tow and colleagues (9), to the graded degree of risk reported in the current paper for AKI (1) lends strong support for developing a coherent definition and terminology for AKI, and for discerning some measure of the severity of the injury, insofar as that can be related to outcomes in an analogous manner to what has been so successful for CKD. The skeptic is still bothered that such a “trivial” increase of serum creatinine can have anything to do with actual kidney injury. If one remembers the basic physiology of creatinine clearance, there are both filtration and secretory components (10). Modest changes in serum creatinine may not reflect changes in filtration, but could reflect subtle derangements in the plasma-flow–dependent component of active creatinine secretion by the organic ion transport systems in the proximal tubule (11,12). From this perspective, serum creatinine becomes more than a marker for glomerular filtration—it can then be viewed as a biomarker for acute tubular injury. Other biomarkers, such as cystatin C (13), KIM-1 (14), and neutrophil gelatinase–associated lipocalin (15) are also being actively investigated as biomarkers of AKI. The role of reactive oxygen molecules is surely important, and an improved understanding of the role of inflammation has suggested, targeting strategies for this aspect of AKI (16). If subtle changes in biomarkers for acute cellular injury can be validated as predicting overall outcome in patients with AKI, then the field will have taken a major step forward (14). This approach may well provide new avenues for designing intervention studies that could actually affect the outcomes for patients with AKI.

References