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Editorial Comment

Acute kidney injury: where's the consensus about its definition?

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Over the last 5 years, an important foundation has been laid for addressing the morbidity and mortality associated with acute changes in kidney function [currently described as acute kidney injury (AKI)], especially in the hospital setting. Previous intervention and treatment trials have not had any significant impact on overall outcomes of patients with AKI [1], while, in parallel, there is growing recognition of the strong association between the severity of AKI and subsequent morbidity and mortality, as well as costs during hospitalization [2,3] and in the longer term following hospital discharge [4]. The epidemiology and pathogenesis of AKI, assessment of baseline and changes in renal function, risk assessment and stratification and preventive strategies are areas of active research interest. The mortality associated with AKI can be extraordinarily high, especially in the intensive care setting when it is accompanied by multiple organ failure, underlining the importance of making significant progress in this area. A recent meta-analysis data of 48 reports described the mortality rate as 89 deaths per 1000 person-years in survivors of AKI and 43 deaths per 1000 patient-years in survivors without AKI (rate ratio, 2.59; 95% confidence interval, 1.97 to 3.42). The incidence rate of chronic kidney disease (CKD) after an episode of AKI was 78 events per 1000 patient-years and the rate of end-stage renal disease was 49 events per 1000 patient-years [5].

A common need for prospective studies is a workable definition of what constitutes AKI, with the realization that the more severe the injury, the more likely the overall outcome will be unfavorable. On the other hand, if the threshold is set too low, there is a legitimate concern that minor, clinically insignificant changes in kidney function will be included so that any imposed intervention will not affect the overall outcome [6].

Four important initiatives have brought some order to the diagnostic and classification uncertainties that have surrounded AKI:

- An important start was made by the Contrast Media Safety Committee of the European Society of Urogenital Radiology, which published a report in 1999 defining contrast-induced nephropathy (CIN) as an increase in serum creatinine of 25% or 44 μmol/L (0.5mg/dl). Although often cited as a ‘consensus report’, the actual publication described disagreements about the definition of CIN, the threshold dose of contrast media above which renal complications may develop, the safe period between repeated exposures to contrast agents and whether contrast media have long-term adverse effects on renal function [7].
- Following consensus efforts started by the NIH [8] and the Acute Renal Failure Working Group of the American Society of Nephrology [9], the terminology ‘acute kidney injury (AKI)’ was put forth as the preferred nomenclature for the familiar clinical disorder, with the understanding that its spectrum is broader than the subset of patients found in intensive care units with an acute need for dialysis support. The issues of nomenclature, classification and assessment of severity were among the major themes of the National Institutes of Health consensus conference on acute renal failure held in 1997 [8]; progress on these issues has been modest in the interval [6].
- Representatives from nephrology and critical care medicine formed a working group called the Acute Dialysis Quality Initiative [10,11] and proposed a classification for AKI based on physiologic measurements including serum creatinine and urine output [12,13]. Systematic efforts were then launched to develop a rational approach to grading the severity of AKI by the Adequacy of Dialysis Quality Initiative Group, which established a systematic approach to grading the severity of AKI, which was referred to as the Risk, Injury, Failure, Loss-of-function, End-stage renal failure (RIFLE) criteria [13].
- A subsequent effort by the Acute Kidney Injury Network (AKIN) refined this approach and emphasized that relatively ‘minor’ changes in serum creatinine occurring within a 48-h window are associated with significant risk of adverse outcome and included urine output criteria similar to the RIFLE criteria [14].

In the current issue of the journal, Zoltan and Pickering [15] have provided a scholarly and exhaustive review of the published trials that have used the RIFLE criteria, the AKIN consensus definition or the CIN definition of AKI as outcome variables for prospective studies of AKI. They conducted a PubMed search from January 2005 through the end of 2008 and also accessed nine trial registries for randomized control trials for prevention or intervention treatment trials for AKI or CIN. RIFLE or AKIN criteria were used in outcome variables in eight of the 22 published trials (36%) and four of the 22 ongoing trials (18%), for a total of 12 out of 44 trials (27.3%). The urine output definition of RIFLE and AKIN was an outcome in only two trials. The CIN definition (serum creatinine increase ≥25% and/or ≥44 μmol/L) was used as the primary outcome in 21 out of 45 (46.7%) of CIN trials, while three published CIN trials used RIFLE or AKIN as an outcome measure. The major conclusion is, despite the aforementioned efforts at developing consensus and more recent but unpublished efforts by the International Consensus Conferences organized by the European Society for Critical Care Medicine, the American Thoracic Society, the European Respiratory Society, the Society of Critical Care Medicine and the Société de Réanimation de Langue Française, consensus has not emerged about the definition and management of AKI. The lack of common outcome variables, especially in current ongoing trials, means that these trials will remain difficult to compare and their interpretation will continue to be plagued by inadequate prospective risk stratification for any planned interventions. Unfortunately, there remains a need for a durable and workable consensus on the use of surrogate outcome variables in AKI, with definitions that can be readily applied to inpatient and intensive care unit settings. This need is further heightened by the current interest in using biomarkers as surrogate end-point measures, especially when there is simply no consensus about the 'gold standard' for assessing renal function or damage against which such biomarkers can be compared [16].

Another effort is in the offing, organized under the aegis of the 'Kidney Disease: Improving Global Outcomes (KDIGO)' initiative [17], with a mission statement to 'Improve the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration and integration of initiatives to develop and implement clinical practice guidelines'. The preliminary steps have been taken to organize the workgroups and conferences that will culminate in the development of clinical practice guidelines for AKI. A special area of emphasis will be the burden of AKI in developing countries with limited resources because, once AKI progresses to kidney failure, the facilities for chronic dialysis or transplantation are simply not available.

KDIGO convened a work group, with its first meeting to taking place in June 2008. The work group will be charged with developing clinical practice guidelines for the diagnosis, evaluation, classification, prevention and management of AKI. The evidence review process and the expertise of the work group will be utilized to identify gaps in knowledge regarding the diagnosis, evaluation, classification, prevention and management of AKI and make research recommendations for implementation subsequent to the release of the guidelines. The publication of the Clinical Practice Guideline for Acute Kidney Injury, under the leadership of Norbert Lameire and John Kellum, is anticipated in 2010 [18]. Whether or not this consensus effort will prove to be more successful than its predecessors remains to be seen, but Zoltan and Pickering [15] have provided the metrics and set a high standard by which the success of any such effort can be measured and compared to the previous attempts to classify and define the relevant outcome measures for AKI.

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