Moving Points in Nephrology

A Framework and Key Research Questions in AKI Diagnosis and Staging in Different Environments

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Background and objectives: Acute Kidney Injury (AKI) is common worldwide, and associated with significant morbidity, mortality, and resource utilization. The RIFLE system of staging AKI correlates with survival in AKI in several settings. A similar AKI definition and staging system that also incorporates lesser degrees of serum creatinine elevation was proposed at the inaugural Acute Kidney Injury Network (AKIN) meeting in 2005. At the Second AKIN meeting in Vancouver, Canada in September 2006, our group developed a research agenda that would test the utility of these diagnostic and staging criteria to predict patient outcomes in a variety of clinical settings and patient groups.

Design, setting, participants & measurements: Three-day, international, consensus conference. A multidisciplinary stakeholder committee was divided into work groups. Recommendations for clinical practice and for future research were developed by the committee as an iterative process. This procedure consisted of a literature review phase and focus group interactions with presentations to the entire committee.

Results: We first proposed a conceptual framework of disease that describes a series of AKI stages, antecedents and outcomes, and allows a description of research recommendations based on transition between AKI stages. We further proposed methods for testing of the definition and development of research questions to establish the utility of new biomarkers for the diagnosis and staging of AKI and associated illnesses.

Conclusions: Retrospective studies should be conducted to initiate the process of validating the AKIN definition of AKI, followed by comprehensive prospective studies that incorporate sampling for emerging AKI biomarkers.

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Acute kidney injury (AKI) is common worldwide and is associated with significant morbidity, mortality, and resource use (1,2). Efforts to provide effective prophylaxis or therapy for AKI have been hampered by the lack of a standard definition of this syndrome. In 2002, the Acute Dialysis Quality Initiative (ADQI) consensus group proposed a graded classification system (the "RIFLE" criteria [risk, injury, failure, loss, ESRD]) to "stage" the severity of acute kidney dysfunction incorporating levels of oliguria in addition to fractional serum creatinine elevation (1). Emerging evidence suggests that severity of acute renal dysfunction measured by this system correlates with survival in general populations of hospitalized or critically ill patients (3,4) and other settings; however, this system does not include lesser elevations of serum creatinine (<50% above baseline), and there is emerging evidence that lesser changes in serum creatinine are common and have important prognostic value in many of the same settings (5,6). Specifically, for example, in cardiac surgery patients, postoperative serum creatinine increments of 20–25% are associated with mortality increases from 0–1% to 12–14%, and even increments of 0.1–0.3 mg/dl are associated with significant increased mortality (5).

The Acute Kidney Injury Network (AKIN) was formed in 2004 with the overall objective of optimizing outcomes in AKI by leveraging the resources and perspectives of organizations that are interested in AKI around the globe. The AKIN definition of AKI was proposed after the group's inaugural consensus meeting in Amsterdam in 2005 (2). Compared with the

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RIFLE classification, the new definition includes lesser degrees of serum creatinine elevation (≥0.3 mg/dl or ≥50% above baseline within a 48-h period) to diagnose AKI, identical grades of oliguria, and a similar severity staging system. There are robust data supporting the use of small increments of serum creatinine or renal replacement therapy (RRT) to define clinical AKI, in hospitalized patients or those undergoing procedures. The modified definition of AKI has not been tested in prospective studies, in different populations, or in different settings. For example, validation studies will be required to determine whether AKI classified by the AKIN definition in patients with preexisting chronic kidney disease (CKD) is associated with similar risks as AKI in patients without preexisting CKD (2). Accordingly, the AKIN group met in Vancouver in September 2006 to develop a research agenda that would test the utility of these diagnostic and staging criteria to predict patient outcomes in a variety of clinical settings and patient groups.

Materials and Methods

Methods are described in the accompanying article by Kellum *et al.* (7) and included the creation of a multidisciplinary stakeholder group, a literature review phase and focused group interactions with presentations to entire committee, and subsequent selection and refinement of questions and methods (8).

Literature Review and Synthesis

A systematic review of the literature was conducted using the following databases: Medline (1966 through August 2006), EMBASE (1980 through 2006, week 36), CINAHL (1982 through August 2006), and PubMed. Articles in any language were considered. The purpose of the review was to identify key unanswered questions. A secure Internet Web site was setup with FTP capability; group members were able to upload and download full-text articles, and through a number of iterative steps, a series of clinical questions were developed.

Results

Agreement on Definition and Framework

AKI is defined on the basis of a reduction in kidney function as determined using serum creatinine or the presence of persistent oliguria. It is recognized that there are limitations to this definition, because it relies on a change in a serum marker that is known to occur late in the course of injury (serum creatinine) and a measurement of urine output (which is not as uniformly recorded in all patients). Nonetheless, the definition does reflect the current state of knowledge about the condition. Limitations of the definition are recognized, but in the absence of validated and clinically obtainable biomarkers, this definition will need to be studied in more detail.

Conceptual Framework

Of greater importance is the development of a conceptual framework of the condition of interest (AKI) that describes a series of stages, antecedents, and outcomes. The conceptual framework allows a description of research recommendations on the basis of transition between AKI stages (Figure 1). The utility of a definition is that it informs clinical practice, clinical and translational research, and clinical care. This conceptual framework allows the testing of the definition and development of research questions.

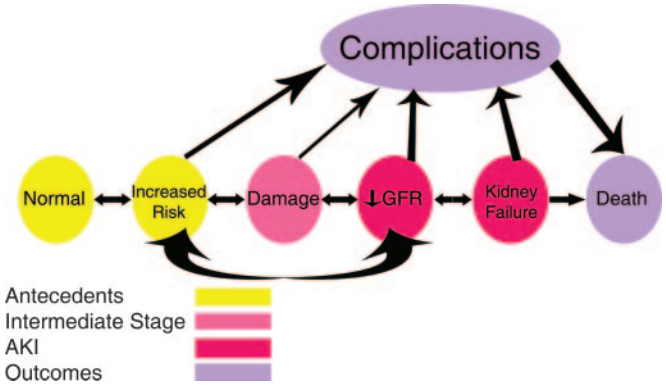

Figure 1. Conceptual model of acute kidney injury (AKI).

In Figure 1, ellipses on the horizontal axis depict stages in the development (left to right) ± recovery (right to left) of AKI. AKI (in magenta) is defined as reduction in GFR, including kidney failure. Specific diagnostic criteria have been defined for AKI (in magenta) on the basis of the change in serum creatinine concentration within 48 h or reduction in urine output. The stage of severity of AKI has also been classified on the basis of changes in serum creatinine. Kidney failure is a stage of AKI highlighted here because of its clinical importance. Kidney failure is defined as a GFR <15 ml/min per 1.73 m^2 body surface area or requirement for RRT, although it is recognized that RRT may be required earlier in the evolution of AKI. Kidney damage (in pink) is an intermediate stage preceding AKI in some but not all patients. This stage is emphasized because of the importance of ongoing research to identify earlier manifestations of AKI, including traditional markers of kidney damage (*e.g.*, urine chemistries, microscopy) (9), and emerging markers (10–14).

Antecedents (in yellow) of AKI include increased risk in certain patient groups, in some cases representing a continuum of normal, for example, those with older age. Patients with failure of organs other than the kidneys would represent another high-risk group for AKI.

Outcomes (in purple) of AKI include fatal or nonfatal complications in organ systems other than kidney or death from kidney failure. Nonkidney outcome factors affect the development, severity, and resolution of complications in other organ systems (including multisystem organ failure). It has long been recognized that AKI is associated with increased mortality; there is increasing evidence that AKI also leads to distant organ injury (*e.g.*, lung, heart, gut), and *vice versa*. Death specifically limits the utility of using solely kidney disease end points to study the effects of AKI, because nonsurviving patients are censored from further study.

Horizontal arrows between stages represent risk factors for development or recovery of AKI. Development and progression of AKI are indicated by left-to-right arrows. Patients are at increased risk as a result of exposure to a variety of known and unknown *initiation factors* that are capable of directly initiating

kidney damage or decreasing GFR or *susceptibility factors* that affect the outcome after exposure to an initiation factor. *Progression factors* affect the risk for progression from damage to AKI and development of higher stages of AKI, including kidney failure. Conversely, recovery of AKI is signified by reverse arrows, right to left. The nomenclature for *recovery factors* is still undefined. Recovery of AKI may be complete, partial, or absent. Kidney failure for >3 mo is chronic kidney failure and in the United States satisfies conditions for the designation of ESRD. GFR <60 ml/min per 1.73 m^2 or kidney damage for >3 mo is defined as CKD. AKI that leads to CKD (including ESRD) is an increasingly recognized phenomenon, particularly in patients with preexisting CKD (15).

The proposed model also encompasses the concept of prerenal azotemia: GFR decrease without kidney damage (left-to-right curved arrow), with reversibility (right-to-left curved arrow). These pathways could also be used to define AKI caused by acute urinary tract obstruction with prompt relief. These concepts will be reevaluated as AKI biomarkers are developed and validated.

Key Studies to Improve the Understanding of AKI

To improve the understanding of AKI, it will be important to develop a series of cross-sectional and longitudinal observational studies as well as interventional trials to characterize fully the different stages and transition points of the conceptual model of AKI described in Figure 1.

Key Questions for Consideration

The working group broadly addressed two questions, determined current knowledge in these areas, developed a research agenda for unanswered questions, and sought to develop some limited clinical practice recommendations. The first question focused on the necessity to validate the proposed AKIN consensus diagnostic criteria and staging. We then asked whether and how one could include emerging biomarkers of AKI in the AKI criteria.

At this time, using existing literature, both questions are not answerable. Thus, the groups focused on posing more fundamental questions to guide research design. Within the conceptual framework, we developed several research questions that are critical to understanding the utility of emerging structural biomarkers of kidney damage for the early diagnosis of subclinical AKI and potentially for prognostic stratification of patients with AKI (clinical or subclinical):

1. Does kidney damage without AKI lead to bad clinical outcomes?

2. Does AKI without evidence of kidney damage lead to bad outcomes?

3. Does the degree of kidney damage predict progression/bad outcomes?

Question 1: How should the AKIN consensus diagnostic criteria and staging be validated?

Question 1a: Do the development and severity of AKI predict renal and nonrenal clinical outcomes, in a variety of clinical settings? Does oliguria add to creatinine elevation to predict clinical outcomes (renal and nonrenal)?

Developing the Answer. A proven AKI definition and staging system will standardize the description and comparison of patient populations and cohorts in clinical and epidemiologic studies, and the development and staged severity of AKI may function as an outcome in therapeutic trials. The utility of the AKI definition and staging should be tested in developing and developed countries, as well as in both community-acquired and hospital-acquired AKI.

Initial studies should be retrospective, using large existing databases of groups at high risk for AKI. Community-acquired AKI databases may include populations with acute malaria or post-monsoon AKI or elderly patients from retirement homes with such community-acquired acute illnesses as pneumonia or urinary tract infections. Important patient populations for studies of hospital-acquired AKI include cardiac surgery, radiocontrast imaging, acutely decompensated heart failure, hepatorenal syndrome, renal transplantation, sepsis, and the broader population of hospitalized patients.

Of note, the use of databases that contain serial serum creatinine concentrations to evaluate the AKIN definition in radiocontrast-induced AKI should be limited to patients who did not receive N-acetylcysteine because of the nonrenal impact of this compound on serum creatinine levels. Although many such databases have already been used to study the impact of small changes in serum creatinine on outcomes in a variety of clinical settings, these sources will be of limited value in the retrospective testing of the utility of the AKIN definition and staging system. Most important, many programs do not have sufficient data to study graded levels of oliguria and their impact on outcomes, and this question will therefore require prospective study.

The ability to capture data that define a variety of important clinical outcomes (Figure 2) will be similarly difficult to obtain from retrospective database studies. It is important to expand the range of clinical outcomes examined in studies to validate the AKIN definition, because the current list of outcomes accepted to support new drug approval for the prevention or

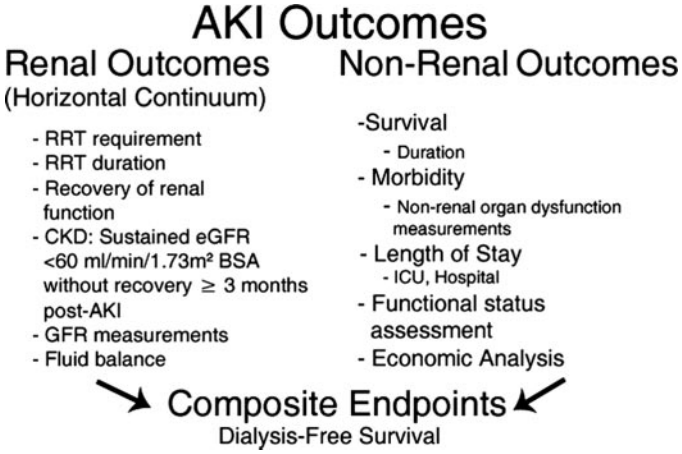

Figure 2. AKI outcomes. BSA, body surface area; CKD, chronic kidney disease; eGFR, estimated GFR; ICU, intensive care unit; RRT, renal replacement therapy.

therapy of AKI is extraordinarily limited: Survival and dialysis-free survival (16).

Emerging data regarding the role of AKI in accelerating the development of ESRD in patients with CKD (9) and the lack of acceptance of small increments of serum creatinine or oliguria as criteria for new drug approval underscore the need to expand the array of clinical outcomes included in AKI studies to include longer term outcomes, in particular the incidence of sustained GFR loss with new-onset or accelerated CKD. Thus, we propose that all studies to assess the utility of the AKI definition include broad ranges of renal end points (requirement and duration of RRT, RRT-free days, recovery of renal function, development and progression of CKD, and development of ESRD), nonrenal end points (nonrenal organ failure; length of stay in hospital and intensive care unit; hospital, 30-d, and long-term mortality; quality of life and discharge status as described by necessity of rehabilitation and short- and long-term care; and economic analysis), and composite end points (*e.g.*, RRT-free survival; Figure 2) (16). For these purposes, the use of retrospective methods may overestimate the severity and impact of AKI as a result of selection and ascertainment biases, particularly at later time points (when data collection will favor patients with greater morbidity and closer follow-up).

Combined with the limited availability of timed urine output data, it is apparent from careful consideration of the requirements to test fully the utility of the AKIN definition that prospective studies will be required in a variety of clinical settings. Optimally, prospective use of the AKIN definition along with routine capture of a full array of short-, medium-, and long-term clinical outcomes (renal and nonrenal) in future AKI studies will not only validate the definition but also uncover other useful surrogate outcome measures.

*Question 1b: What is the relationship of other GFR markers (*e.g.*, cystatin C, eGFR) to changes in serum creatinine and kidney and nonkidney outcomes in a variety of clinical settings?*

Developing the Answer. There is growing acceptance of another GFR marker (serum cystatin C) and estimated GFR (eGFR; calculated by the Modification of Diet in Renal Disease [MDRD] equation) as potential alternatives or adjuncts to serum creatinine for the diagnosis and staging of CKD (9). Increasingly, clinical laboratories report eGFR simultaneously with the corresponding serum creatinine value. Moreover, the rate and magnitude of change of eGFR provide similar information as changes in serum creatinine about the level of GFR and, in addition, may simplify clinical interpretation of acute *versus* chronic kidney disease. This derived variable should also be tested for utility as predictor of AKI stage and outcome. Existing retrospective data may already be used to determine cutoff values of these markers for the definition and staging of AKI. This information may then be used in one or several prospective multicenter studies involving diverse patient cohorts (*e.g.*, pediatric, elderly) and risk groups. Because serum creatinine has numerous limitations as a diagnostic marker of GFR, current and emerging alternative GFR markers routinely should be tested within the staged AKIN definition framework. These multicenter studies should measure and test all available GFR markers in parallel, and additional samples should be stored in a repository for the measurement of future markers. Studies of other GFR markers may eventually improve the sensitivity and specificity of AKI diagnosis and staging and could even lead to changes in the classification system. This again may aid in future therapeutic studies to determine the optimal time points for interventions.

Question 2: Should emerging biomarkers of AKI be included in the AKI criteria?

Question 2a: What are the markers of kidney damage that predict the development and severity of AKI, as defined by low GFR with or without oliguria?

Developing the Answer. Emerging technologies such as functional genomics and proteomics have identified novel promising biomarkers for the early detection of AKI. Markers of tubular damage such as kidney injury molecule-1 (KIM-1), IL-18, and neutrophil gelatinase-associated lipocalin (NGAL) have been detected in the urine (and serum in the case of NGAL) several hours to days preceding the rise in serum creatinine in select clinical situations, including cardiac surgery, intensive care, and kidney transplantation (10–14). The pattern of biomarker expression may allow for timing as well as etiologic identification of the initial insult. For example, NGAL is markedly induced within 2 to 6 h after initiation of cardiopulmonary bypass in patients destined for AKI but declines after 12 h, when IL-18 and KIM-1 are easily detectable (13). Moreover, NGAL and KIM-1 are induced in nephrotoxic AKI, whereas IL-18 is not.

Several key questions remained unanswered, however. First, the published AKI biomarker studies have enrolled only small numbers of patients, and the findings will need to be confirmed in large multicenter studies involving a variety of clinical situations (the clinical situations proposed here should mirror what we are proposing in question 1). Second, in analogy with cardiac markers, the utility of biomarker expression patterns in determining the timing and characterization of the initiating insult will need to be determined. Third, detailed biomarker characteristics such as sensitivities, specificities, and area under the curve will need to be determined. Fourth, the ability of early biomarkers to predict severity of the ensuing AKI will need to be ascertained. Fifth, the role of biomarkers for the prediction of other renal and nonrenal outcomes of AKI will need to be established. Sixth, the utility of biomarkers to guide response to therapies will need to be gauged. Seventh, standardized and validated commercial tests to translate current and future biomarkers from their current status in select laboratory benches to widespread availability at the bedside will need to be developed.

Question 2b: Do markers of kidney damage predict other (nonrenal) clinical outcomes in the absence of AKI?

Developing the Answer. Recent findings suggest that even small increases in serum creatinine are predictive of nonrenal outcomes; however, it is widely known that serum creatinine remains an insensitive and delayed marker of AKI. A key unanswered question is whether sensitive early biomarkers of "subclinical" kidney damage can predict nonrenal complications in the absence of changes in serum creatinine. A corollary question is whether these biomarkers can guide therapy to

prevent nonrenal complications. To answer this question, prospective studies to evaluate the utility of putative AKI biomarkers should routinely collect complete information to assess the full array of nonrenal outcomes.

Conclusions

AKI is defined on the basis of a reduction in kidney function, in the presence or absence of oliguria. The utility of a definition is that it informs clinical practice, clinical research, and clinical care. The proposed conceptual framework of disease describes a series of stages or conditions and allows a description of research recommendations on the basis of transition between AKI stages. It is imperative that methods for testing of the definition and developing research questions that establish the utility of new biomarkers for the diagnosis and staging of AKI and associated illnesses be developed. Retrospective studies should be conducted to initiate the validation process, followed by comprehensive prospective studies that incorporate sampling for emerging AKI biomarkers.

Disclosures

P.T.M.: none; P.D.: licensing agreements with Abbott Diagnostics and Biosite, Inc. for developing NGAL as a biomarker of acute renal failure; A.S.L.: none; K.U.E.: none; J.V.B. has patents on KIM-1 (a kidney injury biomarker); R.L.: none; S.H.-R. has received honoraria from Dade-Behring, Marburg, Germany, for lectures regarding cystatin C in kidney disease; A.L.: none.

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