The evaluation and initial management of patients with acute kidney injury (AKI) should include: 1) an assessment of the contributing causes of the kidney injury, 2) an assessment of the clinical course including comorbidities, 3) a careful assessment of volume status, and 4) the institution of appropriate therapeutic measures designed to reverse or prevent worsening of functional or structural kidney abnormalities. The initial assessment of patients with AKI classically includes the differentiation between prerenal, renal, and postrenal causes. The differentiation between so-called “prerenal” and “renal” causes is more difficult, especially because renal hypoperfusion may coexist with any stage of AKI. Using a modified Delphi approach, the multidisciplinary international working group, generated a set of testable research questions. Key questions included the following: Is there a difference in prognosis between volume-responsive and volume-unresponsive AKI? Are there biomarkers whose patterns (dynamic changes) predict the severity and recovery of AKI (maximal stage of AKI, need for RRT, renal recovery, mortality) and guide therapy? What is the best biomarker to assess prospectively whether AKI is volume responsive? What is the best biomarker to assess the optimal volume status in AKI patients? In evaluating the current literature and ongoing studies, it was thought that the answers to the questions posed herein would improve the understanding of AKI, and ultimately patient outcomes.

The evaluation and Initial Management of Acute Kidney Injury


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Received November 14, 2007. Accepted February 4, 2008.


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ISSN: 1555-9041/304–0962
sion (prerenal component) and injury (renal component) often exist at the same time, decreasing the predictive value of traditional “renal failure indices” for evaluation of volume status. Moreover, because reversibility can only be determined by the response to fluid administration over time, the current “gold standard” means of diagnosing prerenal azotemia is necessarily a retrospective diagnosis. Volume resuscitation can correct pre-renal conditions resulting from absolute or relative hypovolemia. In contrast, renal hypoperfusion resulting from low cardiac output (e.g., end-stage congestive heart failure) and reduced renal perfusion pressure (e.g., sepsis, or liver failure) cannot always be corrected by fluid administration. Prospectively detecting a prerenal component in the evaluation and initial management of AKI would permit improved classification of the incidence, prevalence, and prognostication of AKI, potentially leading to important therapeutic decisions.

Materials and Methods
An international multidisciplinary group participated in a modified Delphi process, which included a literature review phase, development of research questions within smaller groups, interaction with the entire group, and refinement of the research questions.

Literature Review of AKI and Synthesis
We conducted a systematic review of the literature, in all languages, using the following databases: MEDLINE (1966 through August 2006), EMBASE (1980 through 2006, week 36), CINAHL (1982 through August 2006), and PubMed to identify key unanswered questions in AKI. A secure internet website was setup with FTP capability to permit access by group members of uploaded full text articles. Through a number of iterative steps, a series of clinical questions were developed.

Key Research Questions
Research questions developed by the AKIN Working Group on Evaluation and Initial Management of AKI are presented in Table 1. They are focused on two pivotal issues related to AKI evaluation and initial management: 1) differentiating between volume-responsive and volume-unresponsive AKI and 2) the use of sensitive biomarkers to facilitate this differentiation, as well as prognosticate. Volume-responsive AKI can be operationally defined when volume administration clearly results in improved kidney function. Key research questions are conceptually focused on whether volume-responsive AKI is associated with complete or partial improvement in kidney perfusion (oxygenation, urinary indices, or biomarkers) or attenuation of specific measures of kidney injury (AKI biomarkers).

Table 1. Research questions

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<th>Question</th>
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<td>1. Is there a difference in prognosis between volume-responsive and volume-unresponsive AKI?</td>
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<tr>
<td>2. Are there biomarkers whose patterns (dynamic changes) predict the severity and recovery of AKI (maximal stage of AKI, need for RRT, renal recovery, mortality) and guide therapy?</td>
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<td>3. What is the best biomarker to assess prospectively whether AKI is volume responsive?</td>
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<td>4. What is the best biomarker to assess the optimal volume status in AKI patients?</td>
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The following sections describe the key areas of discussion and literature review, thus ensuring appropriate background and rationale for the itemization of the key research questions.

Results
Initial Consideration: Pharmacologic Interventions for Early Management of AKI
The efficacy of a number of pharmacologic interventions has been evaluated in the early management of AKI (8,9). These interventions can be separated into measures designed to improve kidney perfusion and/or glomerular function or to modulate intrarenal pathophysiology. In sepsis-associated AKI, small and uncontrolled studies have shown that vasopressors can improve glomerular filtration (10,11). Renal-dose ("low-dose") dopamine, once widely used, is ineffective in improving kidney function in AKI, with the possible exception of increasing diuresis on the first day of use (12,13). In addition, renal-dose dopamine may even worsen kidney perfusion as reflected by renal resistive indices in patients with established AKI (14). Despite early promise in pilot studies of contrast nephropathy (15,16) and sepsis-associated AKI (17,18), the selective dopamine A1 agonist, fenoldopam, did not improve or protect kidney function in larger studies of early AKI (19) nor in contrast nephropathy (20). Low doses of atrial natriuretic peptide attenuate the rise in serum creatinine in postoperative ischemic renal failure (21) and increase urine flow rates after liver transplantation (22,23). Larger doses, however, have not been effective in large randomized clinical trials of both nonoliguric (24) and oliguric acute tubular necrosis (25). Several preliminary reports suggest beneficial effects of the adenosine antagonist, theophylline, in the management of contrast nephropathy (26,27) and in some forms of nephrotoxic AKI (28), but adequately powered, controlled studies are lacking. More advanced selective adenosine AR 1 receptor agonists showing proximal tubule diuretic effects and inhibition of tubuloglomerular feedback induced kidney vasoconstriction appear to be effective in certain clinical situations, such as decompensated heart failure (29).

Loop diuretics (30,31) and osmotic diuretics (32,33) have failed to successfully prevent AKI in humans despite their ability to decrease tubular oxygen demand and relieve intratubular obstruction in animal models of AKI (34). Diuretics do not have any significant effect on progression or outcome of AKI (35) and could be harmful (31,32). Finally, N-acetylcysteine, a thiol-containing antioxidant has been investigated in multiple trials, primarily in the setting of contrast nephropathy. Despite several positive reports (36,37), the prophylactic efficacy of N-acetylcysteine for contrast nephropathy remains controversial (38), and in other settings of AKI it appears to be ineffective (39–41). Although bicarbonate and mannitol have lost favor in the early treatment of AKI in the setting of rhabdomyolysis (42), there may be an effect of bicarbonate administration to prevent or lessen contrast nephropathy (43–45).

The AKIN Working Group on Evaluation and Initial Management of AKI recognizes that, in the future, it is likely that many additional pharmacologic agents worthy of evaluation in
the initial management of AKI will be developed and tested. Prototypical agents for evaluation include, but are not limited to, agents designed to increase large vessel kidney blood flow, improve kidney microvascular blood flow, attenuate inflammation, limit renal tubular epithelial cell injury, necrosis and apoptosis, and enhance renal tubular epithelial cell recovery after acute injury. Cell therapies using renal progenitor cells and/or mesenchymal stem cells to promote recovery or replace damaged renal tubular epithelium are novel therapeutic strategies under consideration. The working group reasons that these studies will require availability of an optimal classification system for AKI that encompasses risk stratification, and includes an assessment of hemodynamic management. Within the spectrum of hemodynamic interventions in the early management of AKI, assessing and monitoring volume status remain persistently challenging for the clinician and an area of highest priority for research. Thus, the working group prioritized the critical research questions involved in optimal volume management of early AKI as being “upstream” of almost every other conceivable intervention and therefore of most immediate importance.

**Volume-Responsive and Volume-Unresponsive AKI**

Given the theoretical and practical difficulties in the usage of the historical terms “prerenal azotemia” and “acute tubular necrosis,” we propose that these terms be discarded and replaced with “volume-responsive AKI” and “volume-unresponsive AKI.” Use of this terminology would have a number of clinical and research advantages:

1. Recognition that there may be variable and graded responses to volume administration over time.
2. Subclassification of presumed causes of AKI for epidemiologic studies.
3. Development of severity scores or staging to facilitate risk stratification for clinical trials of interventions in early AKI.

Volume-responsive AKI describes a functional impairment that can be improved by fluid administration. Many patients with volume-responsive AKI and overall lesser severity of illness may be managed in a standard clinical setting and may not require an intensive care setting with invasive hemodynamic monitoring to optimize fluid status and maintain kidney perfusion. In some clinical situations, vigorous initial volume resuscitation should be followed by continuous fluid administration: major burns, massive secretory diarrhea, active gastrointestinal bleeding, loss of effective intravascular volume because of “third-spacing” in trauma, major surgery, catabolic states, and sepsis. The optimal method to determine a patient’s fluid-responsiveness remains a matter of debate and is an important priority for future research (46). In addition, a clear distinction should be made between volume-responsiveness of the kidney and of the patient. In most circumstances, a volume-responsive kidney will occur in a volume-responsive patient; in other words, hypovolemia is the most important cause of volume-responsive AKI. A patient with severe renal damage may be volume-responsive (i.e., cardiac output will increase with volume administration), whereas kidney function is not volume-responsive. Alternatively, kidney function may be volume-responsive (i.e., kidney function will improve when perfusion is increased) in clinical states, such as congestive heart failure and liver failure, which are associated with severe total extracellular volume overload with peripheral edema but compromised effective circulating arterial volume. Although kidney perfusion is not optimal and these patients would previously be classified as a “prerenal state,” AKI may not be volume responsive in this setting because of the difficulty of restoring effective arterial volume when fluid is avidly accumulating in the extravascular space. In conclusion, the term volume-responsive AKI should be reserved for patients in whom volume administration results in improved kidney function.

**Discussion**

**Hemodynamic and Volume Status and Kidney Function**

We hypothesize that, early in the course of AKI, optimization of the hemodynamic status and correction of any volume deficit will have a salutary effect on kidney function, will help minimize further extension of the kidney injury, and will potentially facilitate recovery from AKI with minimization of any residual chronic impairment of kidney function. AKI is characterized by a continuum of volume responsiveness and/or unresponsiveness (Figure 1). We further speculate that the timing of volume replacement to facilitate early restoration of kidney perfusion may be a critical determinant in the prevention of progression and facilitate recovery of AKI, which should, in turn, improve survival, especially in critically ill patients. This second assertion is supported by a recent analysis by Levy et al. (47), in which data were analyzed from more than 1000 patients from two severe sepsis trials (PROWESS and secretory phospholipase A2 inhibitor). Early (baseline to day 1 of study) improve-
ment in cardiovascular ($P = 0.0010$), renal ($P < 0.0001$), or respiratory ($P = 0.0469$) function was significantly related to 28-d survival (47). These analyses suggest that outcomes for patients with severe sepsis in the ICU may be closely related to early interventions that improve kidney function.

Assessment of Volume Therapy

We further hypothesize that the required precision for assessment of volume therapy in AKI increases as the severity of illness increases. For example, in noncritically ill patients without cardiac disease, there is proportionately less risk associated with initial vigorous volume therapy, and simple clinical monitoring (e.g., blood pressure, heart rate, physical examination, and urine output) may initially be sufficient. At the extreme end of the spectrum is the patient with AKI and multiorgan dysfunction syndrome, including acute lung injury. In this setting, insufficient volume therapy exposes the patient to the risk of underperfusion of vital organs, including the kidneys, whereas excess volume therapy may increase lung water, worsen lung mechanics, worsen gas exchange, and may even hinder the recovery of lung function (48).

The ARDS Network has described a number of trials assessing the effects of goal-directed therapy in the setting of acute lung injury. Most recently, the ARDS Network compared a conservative approach to fluid administration (net positive fluid balance over 7 d of 136 ml) to a more liberal approach to fluid administration (net positive fluid balance over 7 d of 6992 ml). The conservative approach permitted more rapid weaning from mechanical ventilation with a decrease in the number of intensive care unit days, and no proven adverse effect of conservative fluid management on kidney function or on kidney outcomes (although in the conservative approach group, creatinine tended to be greater than in the liberal group, $P = 0.07$). This study was limited by the exclusion of patients with more severe kidney dysfunction and by the use of serum creatinine as the marker of kidney function. Further studies are needed to assess whether the fluid restriction approach in the conservative arm of the ARDS Network trial would compromise kidney recovery in the setting of AKI, especially in patients who had some degree of chronic kidney disease at baseline.

Validation of Biomarkers for Hypoperfusion and Severity of AKI

Physiologic markers of kidney underperfusion, such as the fractional excretion of urea and sodium, have been demonstrated to have some utility but to lack adequate discrimination in clinical practice (49–51). The AKIN Working Group assumes that the use of additional validated markers for the degree of kidney hypoperfusion and severity of AKI will facilitate initial management, improve stratification for clinical studies, and enhance the ability to prognosticate for patients with AKI. Patients with early AKI could represent a group that demonstrates a graded increase in tubular enzynuria and other biomarkers that suggest the earliest evidence of epithelial cell injury (Figure 1). Current available "traditional" biomarkers, such as plasma creatinine, blood urea nitrogen, urine electrolytes, urinalysis, and ultrasound, may not discriminate between patients with and without evidence of tubular injury despite early volume-responsive AKI. The identification of sensitive and specific biomarkers of early tubular injury in the setting of volume-responsive AKI may have significant therapeutic implications for several reasons. First, if a biomarker can identify patients with volume-unresponsive AKI, then specific pharmacologic therapy could be initiated early in the course of AKI when the therapeutic window may be broad and simple volume replacement will not provide adequate therapy. Second, an equally important consideration is whether a biomarker can identify patients with volume-responsive AKI for whom other drug therapies will not be necessary. The avoidance of unnecessary treatment will reduce the incidence of potential side effects and improve the likelihood of a beneficial outcome. Finally, the use of a classification system to stratify the severity of early AKI, based on the hemodynamic response to volume administration, may well facilitate clinical and epidemiologic studies designed to determine whether volume-responsive AKI affects prognosis and overall patient outcomes.

Disclosures

None.

References

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See related editorial, “Setting the Agenda,” on pages 933-934.