The AKIN group sought to change the acute kidney injury (AKI) definition through a reappraisal of the barriers to progress. Investigators began a more coordinated effort at reappraising the barriers to progress, and consensus guidelines to standardize the definition of AKI, iv) identified a “silver bullet,” or even a bronze one, in the prevention and treatment of AKI. The answer may be simply that these therapeutic agents may be effective, but a number of barriers exist that preclude favorable outcomes. Thus a large number of investigators began a more coordinated effort at reappraising the barriers to progress in human AKI.

**A reappraisal of the field of acute kidney injury**

Recently, concerted effort has been made to determine and understand gaps in our knowledge. With better understanding of these deficiencies, progress might be made in reducing the morbidity and mortality of AKI. There have been a number of consensus conferences from different groups, including the Acute Dialysis Quality Initiative (ADQI), the Acute Kidney Injury Network (AKIN), the Acute Kidney Injury Advisory groups to the American Society of Nephrology, and the International Society of Nephrology, as well as the National Kidney Foundation and Kidney Disease: Improving Global Outcomes (KDIGO) groups. Two important barriers to advancement are: i) lack of a definition of AKI and ii) lack of an accurate way to detect AKI early in its course. This recognition has inspired leaders in the field of AKI. As a result, major advances have been made in classification of AKI, biomarkers, epidemiology, pathophysiology, and drug development. These new drugs on the horizon have led to a tremendous effort in the translational research arena in AKI.

**Why we need a definition of AKI**

The AKIN group sought to change the name from ARF to AKI given the fact that ARF includes a spectrum of clinical conditions from subclinical injury and prerenal azotemia to acute tubular necrosis. This all-inclusive terminology of AKI has been adapted and has been used with increasing acceptance worldwide.

The literature indicates that for a single procedure such as cardiac surgery, there are over 30 definitions for AKI leading to highly variable incidence of AKI of 1-31 percent. With such high variability one cannot compare studies to determine whether drugs are efficacious or not. Severity of injury may be highly variable between studies.

Recently, two classification schemes have been described: RIFLE (Risk, Injury and Failure) and Acute Kidney Injury Network (AKIN) Staging (I, II, III). Based upon graded levels of rise in serum creatinine and/or decrease in urine output (4,10). In 2000, the ADQI was established to develop an evidence-based framework and consensus guidelines to standardize care and direct further research (11). The ADQI group classified ARF based upon creatinine and urine output. A growing number of studies have validated this classification scheme of AKI (12,13).

In light of recent studies indicating that even a small rise in creatinine was associated with an increase in mortality, the AKIN group proposed the AKIN staging (I, II, III). These studies highlight the importance of a small decline in GFR on the overall outcome of critically ill patients. Even the least severe category of RIFLE, “R,” or AKIN stage I, was associated with a mortality rate of 30.9 percent or 30.7 percent, respectively (14). Recent studies indicate that both classification systems perform well. Thus, these new classification systems will allow future studies to be done using a single definition of AKI.

**Chronic kidney disease increases risk of AKI**

Most recently, in population-based studies, there is evidence that strongly suggests an important and growing role of AKI in the global epidemiology of chronic kidney disease (CKD) and end stage renal disease (ESRD). A recent study highlights this important association between baseline kidney function and the risk of hospital-acquired AKI (15). In this study they found that in cases of dialysis-requiring AKI, 74 percent occurred among patients with an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m². There was a graded association between baseline eGFR and the risk of AKI, ranging from a twofold increase among patients with eGFR <15 mL/min/1.73 m² to a 40-fold increase among patients with eGFR <15 mL/min/1.73 m². Although no drug has been shown to be beneficial in the prevention of AKI, understanding that CKD increases the risk of AKI should lead physicians to use caution in this high risk group. Avoidance of non-steroidal anti-inflammatory drugs, avoidance of contrast imaging studies, and using isomolar contrast agents or avoiding invasive procedures are critical measures in the prevention of AKI.

**Acute kidney injury increases risk of chronic kidney disease and ESRD**

Although the high mortality associated with AKI has long been recognized, only recently have the long-term effects of AKI on renal outcomes been demonstrated. Ishani et al. demonstrated for the first time that patients with AKI and preexisting CKD had an increased risk for progression to ESRD, an observation that was not previously demonstrated (16). In this study, a 5 percent random sample of Medicare beneficiary claims data from the Centers for Medicare and Medicaid Services (CMS) and the ESRD incidence database from the United States Renal Data System (USRDS) was used. Risk developing ESRD was greatest in patients with AKI and CKD with a hazard ratio of 41.2 (95% confidence interval (CI) 34.6 to 49.1) compared to AKI without CKD, 15.0 (95% CI 10.6 to 16.0) and with CKD without AKI, 8.4 (95% CI 7.4 to 9.5). In another study, AKI in patients with CKD poses a significantly increased risk for ESRD, and AKI may accelerate a progressive decline in renal function.

**Distant organ effects of AKI**

Recent studies have focused on the observation that a small increase in creatinine is an independent predictor of increased mortality. What is becoming increasingly evident is that AKI is a complex and multisystemic condition, which is thought to lead to a distant organ dysfunction syndrome contributing to fatal injury in such patients. Experimental studies provide some insight into the mechanism by which isolated events leading to the loss of GFR can lead to distant organ effects, including circulating factors such as cytokines and chemokines, activated leukocytes, and adhesion molecules leading to immune cell infiltration. One such injury, apoptosis, and cellular necrosis contributes to the final pathway of organ dysfunction (17). Thus the ability of kidney dysfunction to affect other organs likely contributes to the high mortality associated with AKI. This concept implies that future drugs for the treatment of AKI should have broad effects that may ameliorate damage to multiple organs.

**Biomarkers of AKI**

Serum creatinine is a poor biomarker of AKI. Although both the RIFLE and AKIN criteria use serum creatinine in their staging, it is hoped that sensitive biomarkers will be employed in the future. There is a considerable amount of injury that may occur without a change in GFR. At the same time there may be changes in GFR without a change in tubular injury (pree-nal). Furthermore, there is a delay in the rise in serum creatinine so that by the time a change is observed, intervention may be too late. Lastly, a number of factors affect serum creatinine independent of a change in GFR, including but not limited to nutrition, muscle mass, infection, edema (which affects the volume of distribution), and drugs such as n-acetyl cysteine, which may alter the metabolism of creatinine. Over the past several years, a concerted effort has been made to identify the “kidney biomarker.” Biomarkers must be able to identify, early in the course of AKI, different forms of AKI, and they may predict the severity and prognosis of patients with AKI. A number of biomarkers have been identified, and prominent among these are kidney injury molecule 1 (KIM-1), neutrophil gelatine associated lipocan (NGAL), interleukin-18 (IL-18), and liver fatty acid binding protein (LFABP) to name a few. The value of biomarkers as diagnostic tools and predictors of clinical course will depend on their individual performance. Given the heterogeneity of causes of AKI, background conditions, and age, it is likely that a panel of biomarkers will be most effective. A highly sensitive, high-throughput method that can be performed within 3-4 h has been developed by Bonventre’s group and uses a multiplex micro bead technology capable of simultaneously measuring multiple biomarkers within a single well (18). Another high-throughput, easy to use immunochromatographic assay developed for KIM-1 is sensitive and specific and will permit rapid (within minutes) point-of-care detection of urinary biomarkers in humans with AKI (19). We are hopeful that a rapid “diystick” method or multiplex technology will lead to early diagnosis of AKI where therapies may be instituted early in the course of disease to minimize the extent of injury.

In the end, one must ask, why do we not have drugs to treat AKI? Clearly the disease is complex, but over the past five years there has been a reappraisal of the field of AKI that has led to intense investigation. Significant progress has been made to; i) understand the epidemiology of the disease, ii) understand the pathophysiology and multisystemic nature of AKI, iii) standardize the definition of AKI, iv) identify new biomarkers to diagnose patients.
with AKI early in the course of the disease, and v) develop novel compounds through advanced drug discovery programs and innovative translational sciences.

Further initiatives are underway to rapidly synthesize new knowledge in the field of AKI. In sequential and complementary fashion, the AKIN group is planning a summit focused on defining appropriate clinical endpoints for outcomes in AKI research in San Diego February 27–28, 2010, and the National Institute of Diabetes and Digestive and Kidney Diseases/ National Institutes of Health is planning a conference focused on current opportunities of clinical trials in AKI, October 2010, in Bethesda, Md. Leading investigators in the field of AKI from around the world will gather and finalize important guidelines and therapeutic opportunities in AKI.

We are now ready to implement newly acquired knowledge and develop well-designed clinical trials of promising new drugs as well as re-evaluation of older drugs that have failed in past studies. We anxiously await clinical trials in AKI in the next five years as the results of these trials should finally lead to new treatments for a devastating disease. The fruits of these studies should justify the time spent in reappraising the field of AKI.

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References