Acute kidney injury (AKI) is a widespread problem in the intensive care unit (ICU) that heralds increased morbidity, mortality, and ICU length and cost of stay, independent of other factors (1–3). Unfortunately, there are few, if any, specific interventions proven to prevent or treat AKI. Renal replacement therapy is a reactionary, supportive therapy that almost by definition is started long after the inciting process and well into the pathophysiologic cascade of AKI. Although renal replacement therapy is effective at treating the sequelae of AKI such as electrolyte, fluid, and acid-base disorders, it does not address the underlying disease and is rather a bridge to hoped-for spontaneous renal recovery. Although many interventions have been studied to treat AKI and prevent its progression (4), nothing has been clearly beneficial, and we are left with the obvious yet nonspecific interventions: Maintain renal perfusion, avoid nephrotoxic drugs, and correct the underlying process (sepsis, hypovolemic).

Many have suggested that at least one reason for the futility of interventions for AKI is late disease detection using conventional markers of renal function (4–7). That is, by the time azotemia and its sequelae are detected, renal injury is well established and may be outside the window for mitigation by an intervention (8). Part of the problem is that in contrast to many other acute disease states in which patients present with acute symptoms, patients with AKI are relatively asymptomatic until the disease is advanced. For example, in the case of acute myocardial infarction, patients typically present with symptoms of disease (chest pain, shortness of breath) that precipitate a workup including electrocardiogram and testing for relatively sensitive and early biomarkers such as troponin and CK-MB; however, what if acute myocardial infarction were a painless process? Myocardial ischemia would likely go undetected until perhaps several hours or even days after the initial event, when the patient presented with late signs and symptoms of the (now) irreversible infarction, such as new congestive heart failure or arrhythmia. In this scenario of late detection, it is easy to imagine that coronary angioplasty and stenting might be found to be ineffective therapies for myocardial injury.

This problem of late detection of AKI is not new. In a classic example, multiple animal studies demonstrated that atrial natriuretic peptide was an effective treatment for AKI (9,10), yet atrial natriuretic peptide had no benefit in a well-performed large, randomized clinical trial (11). Despite the efforts of study investigators to identify patients early in the course of AKI, patients were enrolled relatively late, with a mean serum creatinine level of 4.5 mg/dl. Consequently, many investigators have explored the use of novel blood markers as sensitive and early biomarkers for AKI (12,13), arguing that the standard tests for AKI are late indicators with imperfect sensitivity and specificity, because they are altered under common clinical conditions such as trimethoprim and diuretic administration, sepsis, and fluid resuscitation. Although some of these new markers, including neutrophil gelatinase-associated lipocalin and kidney injury molecule 1 (14,15), are rapidly gaining approval by regulatory agencies for use in the clinical and preclinical settings, for the most part, these markers have not yet been broadly validated, are expensive, and are not widely available; however, there is increasing hope that these novel AKI biomarkers will soon be readily available in clinical practice.

With the routine clinical use of novel biomarkers on the horizon, the question arises of how to use these biomarkers. Biomarkers, no matter how sensitive or well validated, will detect renal injury only when they are ordered as either widespread screening tests or, better yet, when renal injury is suspected. Widespread diagnostic testing may yield an unacceptable number of false-positive results. Thus, testing when renal injury is suspected may increase test specificity and be useful to trigger a therapy for AKI, because it is likely that such therapies need to be delivered early to be effective. The question becomes, “How can we suspect renal injury early enough to trigger biomarker testing and subsequent intervention aimed at the underlying pathophysiology of AKI?: Again, the acute coronary syndrome analogy seems useful: Because patients do not complain of an “anginal equivalent” with AKI, we are currently unable to identify...
patients who are at risk for early AKI and are candidates for further diagnostic testing.

In this month’s issue of CJASN, Goldstein and Chawla (16) address the dilemma of silent AKI by proposing a renal angina syndrome for critically ill adult and pediatric patients. Furthermore, they propose that AKI biomarkers used in conjunction with a renal angina syndrome will improve their performance as specific and sensitive indicators of AKI.

The first step in the analogy to acute coronary syndrome is risk factor assessment. Just as there are well-established risk factors for coronary artery disease, the authors suggest that there are known risk factors for AKI that clinicians should consider as they risk-stratify patients for AKI, including age >65 years, diabetes, liver failure, congestive heart failure, chronic kidney disease, and cardiopulmonary bypass, among others.

The authors suggest that in patients with risk factors for AKI, clinicians should be vigilant for “renal angina.” The authors propose that anginal equivalents include oliguria, small increases in serum creatinine, and volume overload. In the current environment, where novel biomarkers are not widely available, the presence of any of these anginal equivalents should trigger a more intensive investigation for early signs and symptoms of AKI, including urine microscopy and chemistries, as well as more frequent serum creatinine measurements and consideration of cystatin C measurements. In the future and where currently available, these patients would be excellent candidates for measurements of novel AKI biomarkers. A similar conceptual framework for AKI risk assessment and detection for pediatric patients uses slightly different risk factors and a slightly different definition for the syndrome itself and is based on the current pediatric literature.

At present, AKI management remains the usual: Evaluation of treatable causes of AKI, optimizing renal perfusion, minimizing exposure to nephrotoxins, and management of fluid overload. However, the important hope is that identifying these patients on the basis of renal anginal equivalents and novel biomarkers will allow us to test novel therapies for AKI early in the course of the disease. Thus, what is novel about the conceptual framework proposed by Goldstein and Chawla is not the specific components of the approach, which if they are to be applied to current clinical practice are necessarily bound by the limitations of our current knowledge and capabilities, but rather the conceptual framework they present that will support the future of AKI assessment and treatment. Furthermore, the framework as proposed can now be tested by investigators to determine, for example, whether there are specific cutoffs that are useful for the proposed anginal equivalents, as well as to understand the risk for developing severe AKI (say, a doubling of serum creatinine) on the basis of a patient’s constellation of risk factors and renal angina symptoms. Along the same lines, a goal of future biomarker studies may be to develop cut points that are useful in a population with renal angina—for example, a cut point above which patients with renal angina are extremely likely to develop severe AKI. This might in turn allow targeted delivery of novel therapies to those individuals with the goal of preventing or mitigating severe AKI.

As our knowledge of AKI evolves, so will the definitions, criteria, and tools that compose this approach. Nonetheless, the underlying structure of a systematic risk assessment, early investigation, and prompt therapy provides a useful and testable framework for future study and clinical management of AKI that will allow the field to move forward.

Disclosures
None.

References

