Acute kidney injury

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Diagnosis and classification of acute pathology in the kidney are major clinical problems. Azotemia and oliguria represent not only disease but normal responses of the kidney to extracellular volume depletion or decreased renal blood flow. Changes in urine output and glomerular filtration rate are therefore neither necessary nor sufficient for the diagnosis of renal pathology. However, no simple alternative for the diagnosis currently exists. By examining both glomerular and tubular function, clinicians routinely make inferences not only on the presence of renal dysfunction but also on its cause. However, pure prerenal physiology is unusual in hospitalized patients, and its effects are not necessary benign. Sepsis, the most common condition associated with acute renal failure in the intensive care unit, may alter renal function without any characteristic changes in urine indices, and classification of these abnormalities as prerenal will undoubtedly lead to incorrect management decisions. The clinical syndrome known as *acute tubular necrosis* does not actually manifest the morphologic changes that the name implies. A precise biochemical definition of acute renal failure has never been proposed, and until recently, there has been no consensus on the diagnostic criteria or clinical definition. Depending on the definition used, acute renal failure has been reported to affect from 1% to 25% of intensive care unit patients and has led to mortality rates ranging from 15% to 60%. From this chaos, two principles emerged: first, the need for a standard definition and, second, the need to classify the severity of the syndrome rather than only consider its most severe form. The RIFLE criteria were developed to achieve these goals, and the term *acute kidney injury* has been proposed to encompass the entire spectrum of the syndrome, from minor changes in renal function to requirement for renal replacement therapy. Thus, acute kidney injury is not acute tubular necrosis, nor is it renal failure. Small changes in kidney function in hospitalized patients are important and are associated with significant changes in short-term and possibly long-term outcomes. The RIFLE criteria provide a uniform definition of acute kidney injury and have now been validated in numerous studies. (Crit Care Med 2008; 36[Suppl.]:S141–S145)

KEY WORDS: acute kidney injury; acute renal failure; RIFLE criteria; epidemiology; hemodialysis; hemofiltration; kidney disease; critical illness

It's 2:45 am, and Angela Johnson, MD, is on call for the intensive care unit (ICU). Her pager jumped to life moments ago as she was just drifting off to sleep in the on-call room some 20 yd from the entrance to the unit. She exhaled audibly and sat up, noting the number on the pager without actually lifting it. She pushed the speaker button on the phone next to the pager and punched in the number. On the second ring, Thomas Becker, RN, answered and apologized for waking her. His patient in bed 5, Mr. Colombo, had been making reasonable amounts of urine all day, but for the last 2 hrs, he only produced 20 mL. An experienced ICU nurse, Becker had already checked the Foley catheter's position and patency before calling. Dr. Johnson was surprised at this development. Mr. Colombo was her most stable patient. She had even considered transferring him to the ward last night to make room for a patient from the emergency department, but that had proved unnecessary. Now she had no idea what the problem was. Mr. Colombo was recovering from severe bacterial pneumonia. He had been quite ill and had even been intubated briefly. Now, 4 days later, his fever was gone and his breathing was significantly improved. He was somewhat volume overloaded from all the fluid he had received in the ICU, and Dr. Johnson had considered giving him Lasix (furosemide). Did he need Lasix now? Or was he becoming volume depleted? Or was his volume status fine but his kidneys the problem? How would she be able to find out?

What Is Acute Kidney Injury?

Abnormalities in fluid and electrolyte balance are some of the most common problems faced by practitioners in modern ICUs. Urine output is an important physiologic sign, and fluid imbalance is common in the critically ill due to the inability to drink, excess fluid losses, large obligatory fluid input, and not the least, renal dysfunction. Furthermore, measurements of blood urea nitrogen and serum creatinine to assess glomerular filtration rate (GFR) are done routinely in the ICU. Increases is the blood urea nitrogen and serum creatinine are known as *azotemia* (*azote* is a very old name for nitrogen). Azotemia will result from reductions in GFR and, together with oliguria ("small" urine) or anuria (no urine), form the cardinal features of kidney failure. However, azotemia and oliguria represent not only disease but also a normal response of the kidney to extracellular volume depletion or a decreased renal blood flow. Conversely, a "normal" urine output and GFR in the face of volume depletion could only be viewed as renal dysfunction. Thus, changes in urine output and GFR are neither necessary nor sufficient for the diagnosis of renal pathology. However, as we shall see, no simple alternative for the diagnosis currently exists.

Acute Renal Success? Before examining pathologic states further, it will be useful to review normal renal physiology. The normal kidney functions to remove nitrogenous waste and other solutes and

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to regulate fluid, electrolyte, and acid–base balance. Although it does each of these tasks with remarkable efficiency, there are limits to what the kidney can do when stressed. For example, in the face of severe extracellular fluid depletion, GFR is reduced. This reduction is sometimes called *single-nephron* GFR to distinguish it from the loss of nephrons that occurs in renal disease (e.g., diabetic nephropathy), but it actually refers to all nephrons. The reduced GFR means that a greater fraction of salt and water can be absorbed, and thus, less will enter the tubules. Of course, less tubular filtrate means less urine and less nitrogen excretion. This azotemia is commonly called *prerenal* to indicate that the cause lies outside, specifically "before," the kidney. The physiology has also given rise to the observation that some cases of azotemia and oliguria actually represent a perfectly normal response and thus "acute renal success" (1). Although the prerenal concept may be useful to understand the physiology, it may also be problematic clinically. Indeed, it is quite tempting to extrapolate the prerenal/renal paradigm to a benign and malignant azotemia. As I (2) and others (3, 4) have argued elsewhere, pure prerenal physiology is unusual in hospitalized patients, and its effects are not necessary benign.

Oliguria and Anuria. Although urine output is both a reasonably sensitive functional index for the kidney and a biomarker of tubular injury, the relationship between urine output and renal function/injury is complex. For example, oliguria may be more profound when tubular function is intact. Volume depletion and hypotension are profound stimuli for vasopressin secretion. As a consequence, the distal tubules and collecting ducts become fully permeable to water. Concentrating mechanisms in the inner medulla are also aided by low flow through the loops of Henle, and thus, urine volume is minimized and urine concentration maximized (>500 mOsm/kg). Conversely, when the tubules are injured, maximal concentrating ability is impaired, and urine volume may even be normal (i.e., nonoliguric renal failure). Analysis of the urine to determine tubular function has a long history in clinical medicine. Indeed, a high urine osmolality coupled with a low urine sodium in the face of oliguria and azotemia is strong evidence of intact tubular function. However, this should not be interpreted as "benign" or even prerenal azotemia. Intact tubular function, particularly early on, may be seen with various forms of renal disease (e.g., glomerulonephritis). Sepsis, the most common condition associated with acute renal failure in the ICU (5), may alter renal function without any characteristic changes in urine indices (3, 4). Classification of these abnormalities as prerenal will undoubtedly lead to incorrect management decisions. Classification as benign azotemia or acute renal success is not, as we will see, consistent with available evidence. Finally, although severe oliguria and even anuria may result from renal tubular damage, it can also be caused by urinary tract obstruction and by total arterial or venous occlusion. These conditions will result in rapid and irreversible damage to the kidney and require prompt recognition and management.

Acute Tubular Necrosis. When mammalian kidneys are subjected to prolonged (most studies use >1 hr) warm ischemia followed by reperfusion, there is extensive necrosis, destroying the proximal tubules of the outer stripe of the medulla, and the proximal convoluted tubules become necrotic as well (6). Distal nephron involvement in these animal experiments is minimal, unless medullary oxygenation is specifically targeted (7). Although these animals develop severe acute renal failure, as noted by Rosen and Heymen (8), not much else resembles the clinical syndrome in humans. Indeed, these authors correctly point out, the term *acute tubular necrosis* (ATN) "does not accurately reflect the morphologic changes in this condition" (8). Instead, ATN is used to describe a clinical situation in which there is adequate renal perfusion to largely maintain tubular integrity but not to sustain glomerular filtration. Data from renal biopsies in patients with ATN dating back to the 1950s (9) confirm the limited parenchymal compromise, despite severe organ dysfunction (8). Thus, the syndrome of ATN has very little to do with the animal models traditionally used to study it. More recently, investigators have emphasized the role of endothelial dysfunction, coagulation abnormalities, systemic inflammation, endothelial dysfunction, and oxidative stress in causing renal injury, particularly in the setting of sepsis (10, 11). True ATN does, in fact, occur. Patients with arterial catastrophes (ruptured aneurysms, acute dissection) can have prolonged periods of warm ischemia, just like animal models. However, these cases comprise <1%, and ironically, these patients are often excluded from studies seeking to enroll patients with the more common clinical syndrome known as ATN.

Acute Renal Failure. In a recent review, Eknoyan (12) noted that the first description of acute renal failure, then termed *ischuria renalis*, was by William Heberden in 1802. At the beginning of the 20th century, acute renal failure, then named *acute Bright's disease*, was well described in William Osler's *Textbook for Medicine* (1909) as a consequence of toxic agents, pregnancy, burns, trauma, or operations on the kidneys. During World War I, the syndrome was named *war nephritis* (13) and was reported in several publications. The syndrome was forgotten until World War II, when Bywaters and Beall (14) published their classic article on crush syndrome. However, it is Homer W. Smith who is credited for the introduction of the term *acute renal failure* in the chapter "Acute renal failure related to traumatic injuries" in his textbook, *The Kidney–Structure and Function in Health and Disease* (1951). Unfortunately, a precise biochemical definition of acute renal failure was never proposed, and until recently, there was no consensus on the diagnostic criteria or clinical definition of acute renal failure, resulting in multiple different definitions. A recent survey revealed the use of ≥35 definitions in literature (15). This state of confusion has given rise to wide variation in reported prevalence and clinical significance of acute renal failure. Depending on the definition used, acute renal failure has been reported to affect from 1% to 25% of ICU patients and has led to mortality rates from 15% to 60% (5, 16, 17).

RIFLE Criteria. In the last few years, the case for a consensus definition and a classification system for acute renal failure has been repeatedly made (18, 19). The major aim of such a system would be to bring one of the major intensive care syndromes to a standard of definition and a level of classification similar to that achieved by two other common ICU syndromes: sepsis and acute respiratory distress syndrome. Furthermore, the need to classify the severity of the syndrome, rather than only consider the most severe form, was emphasized. Following such advocacy and through the persistent work of the Acute Dialysis Quality Initiative (ADQI) group, such a system was developed through a broad consensus of

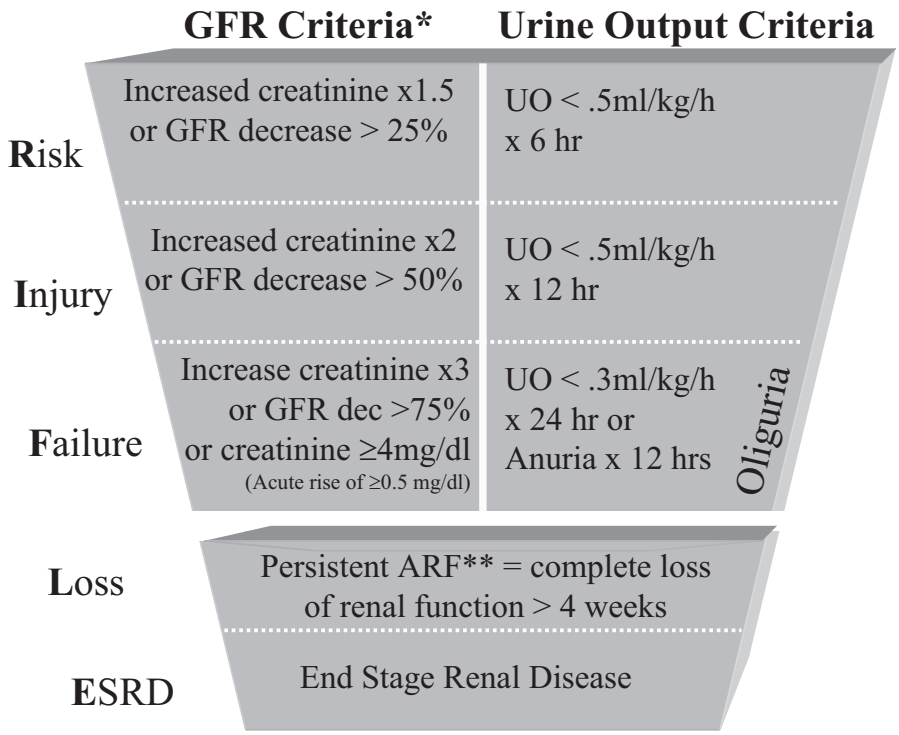

Figure 1. RIFLE criteria for acute kidney injury. *GFR*, glomerular filtration rate; *UO*, urine output; *dec*, decrease; *ARF*, acute renal failure; *ESRD*, end-stage renal disease. Used with permission from Bellomo et al (20). *GFR changes are shown for general reference only. The criteria fulfilled by changes in serum creatinine relative to baseline.

experts (20). The characteristics of this system are summarized in Figure 1. The acronym *RIFLE* stands for the increasing severity classes, risk (R), injury (I), and failure (F), and the two outcome classes, loss (L) and end-stage kidney disease (E). The three severity grades are defined on the basis of the changes in serum creatinine or urine output, in which the worst of each criterion is used. The two outcome criteria, loss and end-stage kidney disease, are defined by the duration of loss of kidney function. Since its publication, the RIFLE classification system has received much attention, with >100,000 electronic hits for its publication site and >80 citations in 2 yrs. It has also spawned several investigations of its predictive ability, internal validity, robustness, and clinical relevance in a variety of settings.

Acute Kidney Injury. Importantly, by defining the syndrome of acute changes in renal function more broadly, RIFLE criteria move beyond acute renal failure. The term *acute kidney injury* (AKI) has been proposed to encompass the entire spectrum of the syndrome, from minor changes in renal function to requirement for renal replacement therapy (21). Thus, the concept of AKI, as defined by RIFLE, creates a new paradigm. AKI is not ATN, nor is it renal failure. Instead, it encompasses both and also includes other, less severe conditions. Rather than focusing exclusively on patients with renal failure, those who receive dialysis, or those who have a clinical syndrome defined by pathology, which is usually absent (ATN), the strong association of AKI with hospital mortality demands that we change the way we think about this disorder. In a study by Hoste et al. (22), only 14% of patients reaching RIFLE class F received renal replacement therapy, yet these patients experienced a hospital mortality more than five times that of the same ICU population without AKI. Is renal support underutilized or delayed? Are there other supportive measures that should be employed for these patients? Sustained AKI leads to profound alterations in fluid, electrolyte, acid–base, and hormonal regulation. AKI results in abnormalities in the central nervous system, immune system, and coagulation system. Many patients with AKI already have multisystem organ failure. What is the incremental influence of AKI on remote organ function and how does it affect outcome? A recent study by Levy et al. (23) examined outcomes for >1,000 patients enrolled in the control arms of two large sepsis trials. Early improvement (<24 hrs) in cardiovascular ($p = .0010$), renal ($p < .0001$), or respiratory ($p = .0469$) function was significantly related to survival. This study suggests that outcomes for patients with severe sepsis in the ICU are closely related to early resolution of AKI. Although rapid resolution of AKI may simply be a marker of a good prognosis, it may also indicate a window of therapeutic opportunity to improve outcome in such patients.

Validation Studies Using RIFLE

More than 76,000 patients have now been enrolled in studies to evaluate the RIFLE criteria as a means of classifying patients with AKI (editorial). One of the earliest studies by Abosaif et al. (24) studied 247 patients admitted to the ICU with a serum creatinine of >150 μmol/L. The investigators found that the ICU mortality was greatest among patients classified as RIFLE F, with a 74.5% mortality, compared with 50% among those classified as I and 38.3% among those classified as RIFLE R. In a significantly larger single-center multi-ICU study, Hoste et al. (22) evaluated RIFLE as an epidemiologic and predictive tool in 5,383 critically ill patients. They found that AKI occurred in a staggering 67% of patients, with 12% achieving a maximum class of R, 27% I, and 28% F. Of the 1,510 patients who reached R, 56% progressed to either I or F. Patients with a maximum score of R had a mortality rate of 8.8%, compared with 11.4% for I and 26.3% for F. On the other hand, patients who had no evidence of AKI had a mortality rate of 5.5%. Furthermore, RIFLE I (hazard ratio of 1.4) and RIFLE F (hazard ratio of 2.7) were independent predictors of hospital mortality after controlling for other variables known to predict outcome in critically ill patients.

Uchino et al. (25) focused on the predictive ability of the RIFLE classification in a cohort of 20,126 patients admitted to a teaching hospital for >24 hrs during a 3-yr period. The authors used the electronic laboratory database to classify patients into RIFLE R, I, and F and observed them to hospital discharge or death. Nearly 10% of patients achieved a maximum RIFLE R, 5% I, and 3.5% F. There was a nearly linear increase in hospital mortality with increasing RIFLE class, with patients at R having more than three times the mortality rate of patients with-

out AKI. Patients with class I had close to twice the mortality of those with R, and patients with RIFLE F had ten times the mortality rate of hospitalized patients without AKI. The investigators performed multivariate logistic regression analysis to test whether RIFLE classification was an independent predictor of hospital mortality. They found that class R carried an odds ratio of hospital mortality of 2.5, I of 5.4, and F of 10.1.

Ali et al. (26) studied the incidence of AKI in northern Scotland, a geographical population base of 523,390. The incidence of AKI was 2,147 per million population. Sepsis was a precipitating factor in 47% of patients. RIFLE classification was useful for predicting recovery of renal function ($p < .001$), requirement for renal replacement therapy ($p < .001$), length of hospital stay for survivors ($p < .001$), and in-hospital mortality ($p = .035$). Although not statistically significant, subjects with AKI had high mortality at 3 and 6 months as well.

Finally, a recent study by Ostermann and Chang (27) analyzed 41,972 patients admitted to 22 ICUs in the United Kingdom and Germany between 1989 and 1999 as part of the Riyadh Intensive Care Program database. AKI defined by RIFLE occurred in 15,019 patients (35.8%): 7,207 (17.2%) with class R, 4,613 (11%) with I, and 3,199 (7.6%) with F. Hospital mortality rates were 20.9% for RIFLE class R, 45.6% for I, and 56.8% for F, compared with 8.4% among patients without AKI. Independent risk factors for hospital mortality were age (odds ratio, 1.02); APACHE II score at admission to ICU (odds ratio, 1.10); presence of preexisting end-stage disease (odds ratio, 1.17); mechanical ventilation (odds ratio, 1.52); RIFLE classes R (odds ratio, 1.40), I (odds ratio, 1.96), and F (odds ratio, 1.59); maximum number of failed organs (odds ratio, 2.13); admission after emergency surgery (odds ratio, 3.08); and nonsurgical admission (odds ratio, 3.92). Interestingly, renal replacement therapy for AKI was not an independent risk factor for hospital mortality.

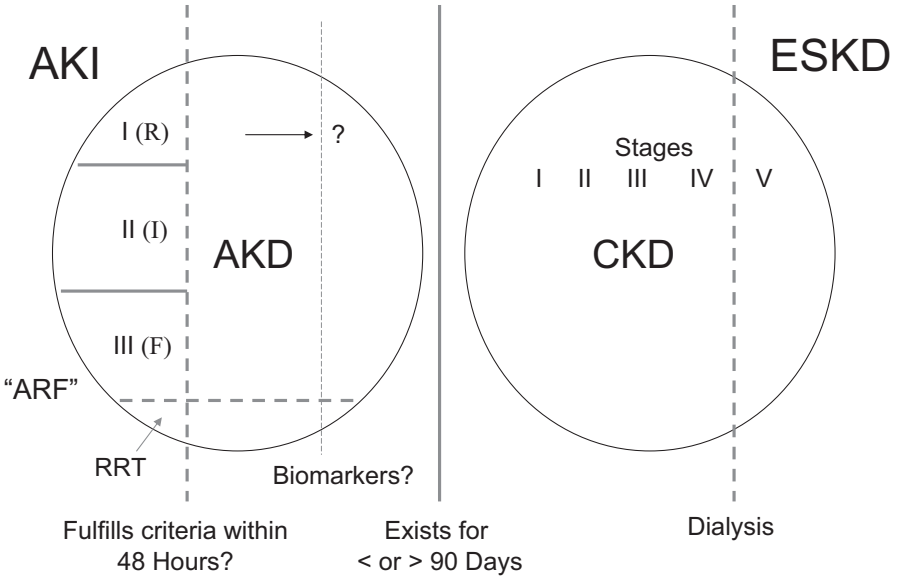

Figure 2. Renal disease landscape developed at the 2006 Acute Kidney Injury Network Congress in Vancouver, British Columbia, Canada. *AKI*, acute kidney injury; *R*, RIFLE risk (AKI stage I); *I*, RIFLE injury (AKI stage II); *F*, RIFLE failure (AKI stage III); *AKD*, acute kidney disease; *ARF*, acute renal failure; *RRT*, renal replacement therapy; *CKD*, chronic kidney disease; *ESKD*, end-stage kidney disease.

Future Steps

The goal of standardizing a definition and classification system for one of the most common ICU syndromes would seem to have been realized. However, standards do not mean complacency, and efforts to include more recent evidence have led to proposals to set a 48-hr window on the first documentation of criteria and broaden the risk category of RIFLE to include an increase in serum creatinine of ≥0.3 mg/dL, even if this does not reach the 50% cutoff (21). The Acute Kidney Injury Network, an interdisciplinary, international group, has also attempted to integrate AKI classification with chronic kidney disease staging (Fig. 2). Indeed this may be very important if AKI has the potential to accelerate the progression of chronic kidney disease (28). However, although such proposals are useful in theory, validation is needed before use, and they do not yet have the evidence base that the original RIFLE criteria now enjoy.

It is hoped that the use of functional markers (urine output and serum creatinine) will be replaced or augmented in the near future by injury biomarkers. Several potential serum and urinary markers have been identified and reviewed elsewhere (29). These markers include neutrophil gelatinase–associated lipocalin (30), kidney injury molecule-1 (31), cysteine-rich protein 61 (32), spermidine/spermine N(1)-acetyltransferase (33), cystatin C (34), and urine interleukin-18 (IL-18) (35, 36). In the future, markers of cellular injury in the kidney will likely define AKI and offer the potential to diagnose the disorder before functional decline. Until then, the "tried and true" markers of urine output and serum creatinine, disciplined by RIFLE criteria, will be the best we can provide.

CONCLUSION

Small changes in kidney function in hospitalized patients are important and associated with significant changes in short-term and possibly long-term outcomes. The shift of terminology from ATN and acute renal failure to AKI has been well received by the research and clinical communities. RIFLE criteria provide a uniform definition of AKI, and are increasingly used in the literature. RIFLE severity grades represent patient groups with increasing severity of illness, as illustrated by an increasing proportion of patients treated with renal replacement therapy and increasing mortality. Thus, AKI, as defined by RIFLE criteria, is now recognized as an important ICU syndrome alongside other syndromes used in ICU patients for the purpose of epidemiology and trial execution, such as the acute lung injury/acute respiratory distress syndrome consensus criteria (37) and the consensus definitions for systemic inflammatory response syndrome/sepsis/severe sepsis and septic shock (38). The RIFLE classification for AKI is quite analogous to the Kidney Disease Outcomes Quality Initiative for chronic kidney disease staging, which is well known to correlate disease severity with cardio-

vascular complications and other morbidities (39). Chronic kidney disease stages also have been linked to specific treatment recommendations, which have proved extremely useful in managing this disease (39). As the epidemiology of AKI becomes clearer and as treatments emerge (both made all the more possible by standard criteria for diagnosis and classification), RIFLE classifications will undoubtedly be used to reference recommendations for prevention and treatment. Indeed, this is the ultimate purpose that RIFLE criteria were intended to serve.

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