Defining Acute Renal Failure: RIFLE and Beyond

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The introduction of the RIFLE classification has increased the conceptual understanding of the acute kidney injury (AKI) syndrome, and this classification has been successfully tested in a number of clinical studies. This review discusses the strengths and weaknesses of the RIFLE classification and suggests additional parameters to broaden future definitions of AKI. These definitions should not only focus on kidney function alone, but also include parameters describing the origin of the patient, the most important causal factors responsible for AKI and information on the pre-existing kidney function. This more complete definition should lead to a decrease in the variability of the results of epidemiological studies and of future clinical trials in AKI populations.

Defining Patients at Risk for Acute Renal Injury

The first stratum of the RIFLE criteria (risk) might be the most important one, because at this stage, a positive test should increase the physician’s awareness of the presence of risk for renal injury, at a moment when the situation still is reversible by preventive or therapeutic intervention. This screening parameter should have a high sensitivity and a low cost and be easily accessible. Risk is defined as an increase of serum creatinine with 50% corresponding to a decrease in GFR, relative to baseline, of \( \frac{1}{2} \) or a urine output of \( \frac{1}{2} \) ml/kg per h for \( \geq 6 \) h. Recently, the definition of risk was expanded to include an absolute increase in serum creatinine of 0.3 mg/dl (26.5 \( \mu \)mol/L) or more (R. Mehta, personal communication, October 2005).

Despite its limitations, as outlined next, a recent analysis (13) of the RIFLE criteria in 5383 critically ill patients revealed that of the 1510 (28%) patients who were admitted in the risk stage, 840 (56%) progressed further to more severe RIFLE strata, suggesting that these criteria have a reasonable specificity to detect the difference between functional (vasoconstriction because of renal hypoperfusion) and structural (acute tubular necrosis [ATN]) alterations.

Serum creatinine is the most widely used parameter for everyday assessment of GFR, but it has poor sensitivity and specificity in AKI because serum creatinine lags behind both renal injury and renal recovery (16). In addition, even its determination is not standardized, and a variety of methods are used worldwide, making direct comparison between studies problematic (17).

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Hoste et al. (18) reported that 25% of patients who were in the ICU and had a normal serum creatinine value (<1.5 mg/dl) had an estimated GFR <60 ml/min per 1.73 m\(^2\) as measured with a 1-h creatinine clearance. Of interest, the patients with the low creatinine clearance had a low creatinine generation and were more likely to be ventilated and on vasopressors. Serious critical illness modifies the value of serum creatinine as marker of GFR. It therefore is no surprise that already small increments in serum creatinine levels are associated with an increased mortality risk (3,4). Furthermore, modest changes in serum creatinine not only may reflect changes in filtration but also could reflect subtle derangements in the plasma flow–dependent component of active creatinine secretion by the organic ion transport systems in the proximal tubule. From this perspective, serum creatinine becomes more than a marker for glomerular filtration—it then can be viewed as a biomarker for acute tubular injury (19). The definition of AKI, if based only on cutoff values of serum creatinine, therefore is far from perfect and probably slows the recognition of AKI, particularly in critically ill patients.

The widely known formulas, such as the Modification of Diet in Renal Disease (MDRD) and Cockroft-Gault, to estimate GFR or creatinine clearance on the basis of gender, body weight, age, and ethnicity have been developed in patients with chronic renal failure and assume a stable serum creatinine level (20,21). The rapidly changing creatinine kinetics of critically ill patients with AKI therefore cannot be captured by these formulas. However, they might be valuable to alert the physician of a preexisting chronic decline in GFR, which in many instances is an
enhanced risk for additional AKI (e.g., postsurgery AKI, acute toxic AKI, notably acute contrast nephropathy) (22–24).

Another alternative for “early” detection of a fall in GFR is the monitoring of serum levels of cystatin C, a 13-kD endogenous cysteine proteinase housekeeping protein. This compound is produced at a constant rate by all nucleated cells and is filtered freely at the glomerulus and reabsorbed and catabolized but not secreted by the tubules. Cystatin C detects the development of AKI 1 to 2 d earlier than graded changes in serum creatinine as based on the ADQI/RIFLE criteria (25) and increases more rapidly than serum creatinine after administration of radiocontrast media (26). Although the accuracy of cystatin C as marker of GFR was questioned recently, particularly in inflammation (27) and patients with liver cirrhosis (28), from a pragmatic point of view, it can be supposed that if a cystatin C–based definition should be used, then physicians would be alerted 1 to 2 d earlier for the risk for AKI than by serum creatinine. However, cystatin C is not widely used and is expensive, and cutoff values for detection of AKI are lacking at this stage. It seems unavoidable that now that different analytical kits for routine determination are available, the bias between measurements in different laboratories will increase.

Some of the problems that are encountered with serum creatinine can be avoided by the use of clearance determinations that are based on timed urinary collections over 1 or 2 h, with blood sampling in the middle to cover potential changes in serum creatinine (18,29,30). This method can be performed accurately only when urine collections occur with an indwelling bladder catheter, but the “GFR” that is based on this measurement still can be inserted into the RIFLE criteria, because a GFR decrease of >25% meets the criteria for a risk classification. Even when the GFR falls to a very low level, this will be detected by a 1- to 2-h urine collection, because the creatinine urine concentration will decline to zero, so even small increments in serum creatinine will yield very low calculated GFR values.

The difficulties that are associated with the use of serum creatinine as the sole parameter for risk in a patient with AKI explain why the inclusion of changes in urine output in RIFLE is valid. A decreased diuresis, particularly in critically ill patients, might be one of the first signs that draw attention to a decrease in filtration is associated with enhanced tubular so-

by the lack of consistent and convenient markers of early kidney damage. Because in the future more drugs probably will become available, the development of either an individual marker or a panel of markers to detect early kidney injury is of utmost importance.

There might be room for improvement by the implementation of markers that really can detect early injury of the tubular cells before the filtration capacity of the kidney is decreased (37,38). Several biomarkers of renal tubular injury have been proposed, the most promising of which seem to be kidney injury molecule 1, neutrophil gelatinase–associated lipocalin, IL-18, sodium/hydrogen exchanger isoform 3, N-acetyl-β-D-glucosaminidase, and matrix metalloproteinase 9 (for review, see reference [38]). As biomarkers for early detection of AKI, neutrophil gelatinase–associated lipocalin and kidney injury molecule 3 are already increased in urine very early (2 h) after injury, followed by IL-18 at 12 h, and hence may serve as early detection biomarkers, at least in well-defined clinical settings (38). Although all of these molecules have shown great promise in experimental settings, their use in everyday clinical practice is hampered by the lack of standardized assays, clear cutoff values, and lack of sufficient validation of their specificity for types of AKI and other renal and nonrenal diseases in large cohorts. These are conditio sine qua non if these markers are to be used for screening, diagnosis, and evaluation of severity and of therapy.

Despite the limitations of the actually proposed definitions of AKI, some dialytic interventions already have been performed with apparent success in the strata defined by risk or injury in the RIFLE criteria, on the basis of the changes in urine output. These studies (39,40) started “early” dialysis when a urine output of <100 ml during the first 8 h after bypass surgery was observed, regardless of solute clearance; in both studies, the patients with early dialysis showed a better outcome compared with the patients who began dialysis at more conventional indications. However, the relevance of these data to nonpostoperative patients or to patients with nonoliguric AKI is unclear.

Defining Renal Injury

In the RIFLE criteria, the stratum of injury is defined by a doubling of serum creatinine or a reduction of urinary output below 0.5 ml/kg per h during at least 12 h. Importantly, of the patients who develop injury, >50% later will develop established renal failure (13). In this stage, the differential diagnosis between prerenal AKI and renal AKI, particularly ATN, becomes crucial. The RIFLE criteria give no guidance on how to discriminate between prerenal and renal causes of deterioration of kidney function. This discrimination is of utmost importance, because it is widely accepted that long-term hyperperfusion of the kidney will result in established tubular necrosis, whereas timely restoration of circulating volume might prevent further negative evolution (41).

Besides a thorough clinical evaluation and an examination of the urine sediment, determination of urinary indices can be useful (41). In prerenal ARF, tubular function is intact and the decrease in filtration is associated with enhanced tubular so-
dium reabsorption. Therefore, when creatinine accumulates in the blood as a result of a fall in GFR with intact tubular function, the fractional excretion of filtered sodium \( (\text{FE}\_{\text{Na}}) \) is 
\[ (\text{urine sodium} \times \text{plasma creatinine})/(\text{plasma sodium} \times \text{urine creatinine}) \]
declines below 1%, at least with a previously undamaged kidney. A paradoxically high \( \text{FE}\_{\text{Na}} \) despite the presence of prerenal azotemia occurs during diuretic treatment, including mannitol, within the preceding 24 h in the presence of glucosuria or excretion of an alkaline urine, which decreases tubular sodium reabsorption. Also, renal vasocostriction in patients with advanced chronic renal failure may not be associated with an \( \text{FE}\_{\text{Na}} \) below 1% because of chronic adaptation to an increased single-nephron GFR. A reduced effective circulating volume also stimulates antidiuretic hormone (ADH) release. ADH results in increased distal water and urea reabsorption, and it was found that a low \( \text{FE}\_{\text{urea}} \) (<35%) is more sensitive and specific than \( \text{FE}\_{\text{Na}} \) in differentiating between prerenal and renal causes of ARF, especially when diuretics have been administered (42).

Conversely, a low \( \text{FE}\_{\text{Na}} \) does not always indicate prerenal azotemia and can be observed in the early stages of obstruction, acute glomerulonephritis, pigment nephropathy, and intrinsic ARF, induced by radiographic contrast agents. The approximately 80% diagnostic specificity of \( \text{FE}\_{\text{Na}} \) in distinguishing “prerenal” azotemia from established ARF with tubular dysfunction may result from limited sensitivity of this parameter or, perhaps more likely, from the fact that the patient actually may be progressing from a prerenal azotemic state to established ARF. It also is hoped that in this RIFLE stratum the determination of serum and/or urinary biomarkers may become useful to differentiate between the “prerenal” and “renal” types of AKI.

**Defining Kidney Failure**

In some studies, ARF is defined as the need for RRT. Although this seems to be a clearcut definition at first glance, it is far from an objective one. Because the decision to start RRT is to some extent subjective. In RIFLE, failure is defined as a threefold increase of serum creatinine or decrease in GFR of >75% or a urine output of <0.3 ml/kg per h for >24 h or anuria for >12 h. Alternatively, failure also is defined by a serum creatinine of >4 mg/dl (353.6 \( \mu \)mol/L) with an acute rise of 0.5 mg/dl (42.2 \( \mu \)mol/L).

The generally accepted indications for initiation of RRT in AKI include volume overload, hyperkalemia, metabolic acidosis, and overt uremic symptoms. In addition, renal “support” often is initiated in the management of progressive azotemia in the absence of these specific indications, on the basis of the “belief” that early or so-called prophylactic dialysis decreases morbidity and improves survival, although there is no consensus on the degree of azotemia that warrants initiation of therapy (43). Starting supportive RRT and, of course, the selection of these patients with large differences in comorbidity and “lead-time bias” will have a serious impact on the outcome.

In addition, there is a growing interest in indications for RRT in nonazotemic/nonrenal conditions (44). The most spectacular indication is early isovolemic hemofiltration in patients who have septic shock (45,46). Most of the still uncontrolled and preliminary studies describing this dialysis modality only use outcomes on “crude mortality” and surrogate end points, such as need for vasopressors (47,48). One retrospective study (49) compared two groups of oliguric septic patients (before and after introduction of early short-term isovolemic hemofiltration). Group 1 received conventional extracorporeal support, and group 2 received hemofiltration at 45 ml/kg per h over 6 h, followed by conventional continuous venovenous hemofiltration. Despite that the serum creatinine levels (1.7 ± 2 [150 ± 177 \( \mu \)mol/L] and 1.8 ± 2 mg/dl [159 ± 177 \( \mu \)mol/L], respectively) were similar and apparently indicated acute renal injury, 28-d survival was 55% in group 2 and only 27.5% in group 1. If these results are confirmed, then they would indicate that other indications for RRT, beyond renal function, should be included in the definition of AKI.

**Defining Loss of Renal Function and ESRD**

An old paradigm states that patients with ARF either die or survive and that those who survive recover their renal function almost completely. A recent study confirmed that if critically ill patients with normal renal function before the renal insults survive the precipitating cause of ATN, then the overwhelming majority will recover sufficient renal function to obviate the need for RRT (50). In contrast, a recent multicenter analysis included 1260 of 29269 critically ill patients who needed RRT at hospital discharge, 13.8% remained dialysis dependent, particularly those who had preexisting chronic renal dysfunction (51). Because this segment of the patient population will continue to grow, the RIFLE criteria for AKI correctly include indices for longstanding need for RRT (>4 wk), represented by L, and for nonrecovery of renal function, resulting in ESRD, represented by E.

**Additional Specifications**

Whereas the RIFLE criteria already allow diversification in the definition of AKI, making it possible to identify more exactly than before the degree of renal injury, it is clear that other important variables that describe the type of patient are not included. As pointed out before, Mehta and Chertow (2) correctly proposed to add parameters to describe the susceptibility of the patient for AKI and to stage the course of the disease. However, before such parameters can be defined, common criteria will be needed to allow the collection of the data to feed the epidemiologic databases that support the definitions. In this way, circular reasoning, whereby definitions are used on the basis of data that are collected in patient groups that are not well defined, can be avoided.

Like in oncology, in which the anatopathologic diagnosis is elaborated further with a Tumor, Nodule, M (Tumor) classification, some terminology that indicates the origin of the patient and the cause of AKI should be elaborated. For this patient-oriented classification, one might propose the introduction of a three-digit indication: The geographic background underlying the pathology (P) of the patient with AKI can be indicated by using 0 (ambulatory patient), 1 (hospital-acquired AKI), or 2 (ICU patient). In addition, an underlying causal
factor (C) for the AKI can be indicated by using 0 or 1 to indicate the absence of presence of preexisting renal failure (chronic kidney disease stage number) (52).

A patient who has preexisting normal renal function and develops AKI after trauma with a decrease of GFR of 50% in a setting of sepsis then would be indicated as RIFLE I P (2)C (0). Conversely, a patient who has a preoperative GFR of 50 ml/min per 1.73 m² and develops AKI with anuria after cardiac surgery would be indicated by RIFLE F P (1)C (1).3. It is evident from this labeling that the prognosis for survival and for recovery of renal function is different in the two cases. Of course, this classification can be implemented only after careful testing in the clinical field. In our opinion, these additions to RIFLE would add further clarification in the international reporting of patients with AKI.

Conclusions

The introduction of the RIFLE classification certainly has increased our conceptual understanding of the AKI syndrome, and this classification already has been tested successfully in a number of clinical studies. The RIFLE criteria will have to be refined in the future, when other parameters that allow earlier detection of AKI will become available. These parameters will reflect not only the declined excretory function of the injured kidney but also the underlying tubular damage.

In view of the rapidly changing epidemiology of AKI as a result of the aging population and the more aggressive medical and surgical diagnostic and therapeutic interventions, a future definition of AKI that focuses on kidney function alone is not sufficient. This review proposes that additional parameters that describe the origin of the patient, the most important causal factors that are responsible for AKI, and, importantly, the preexisting kidney function should be added to the actually used RIFLE system. It is hoped that by this more complete definition, the variability in the definitions used in epidemiologic studies and clinical trials, which until now confound their interpretation and limit their comparisons, will decrease (22–24).

References
22. Dangas G, Iakovou I, Nikolsky E, Aymong ED, Mintz GS,