Acute Renal Failure Definitions and Classification: Time for Change?

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Epidemiology of Acute Renal Failure

The development of acute renal failure (ARF) in the hospital setting continues to be associated with poor outcomes (1–7). Over the last three decades, several experimental models have identified pathophysiologic mechanisms associated with ARF and have enhanced our understanding of the disease (8–10). It is evident that ARF can result from alterations in renal perfusion, changes in glomerular filtration, and tubular dysfunction, and that correction of these factors can ameliorate the effects of ARF (11,12). On the basis of the identification of the underlying mechanisms, several new potential interventions have been developed that have been shown to alter the course of incipient and established ARF in experimental models (13–15). Application of these findings has resulted in improvements in the prevention of ARF due to radiocontrast agents, aminoglycoside antibiotics, and rhabdomyolysis (16,17). Several other agents are now in advanced stages of development or initial phases of clinical trials (18,19). In concert, advances in dialysis have occurred with the availability of continuous renal replacement therapies in addition to intermittent hemodialysis and acute peritoneal dialysis (20–22).

It is well recognized that uncomplicated ARF can usually be managed outside the intensive care unit (ICU) setting and carries a good prognosis, with mortality rates less than 5% to 10% (23,24). In contrast, ARF complicating nonrenal organ system failure in the ICU setting is associated with mortality rates of 50% to 70%, which has not changed for several decades (6,25–30). These figures are in sharp contrast to the experience with acute myocardial infarction (AMI), where in-hospital mortality rates have declined from the range of 50% to approximately 6% over the past 25 to 30 yr. Much of the credit for improved AMI outcomes has been attributed to the use of coronary care units, cardiac catheterization, aspirin, β-adrenergic antagonists, thrombolytic therapy, and, more recently, specialized percutaneous coronary interventions and glycoprotein IIb–IIIa inhibitors (31–34). In spite of improved dialytic technology, including the development and refinement of continuous renal replacement therapies for the most critically ill patients, we have seen no material change in the high mortality rates associated with ARF. Indeed, we have not demonstrated any pharmacologic or other intervention effective in the early management of ARF. Interventions that have been deemed ineffective (or potentially harmful) include the following: loop and osmotic diuretic agents (35,36), “renal dose” dopamine (37,38), atrial natriuretic peptide (39,40), insulin-like growth factor-1 (41), and endothelin receptor antagonists (42).

Although ARF may develop in 5% or more of hospitalized patients, the heterogeneity of ARF and associated comorbidity make its study more difficult than AMI and other, more discrete conditions. Among the impediments to progress in ARF research is the lack of a uniform definition of ARF that might be used to compare and contrast observational studies, and to allow for rational design of clinical trials.

Relatively few studies have examined the incidence of hospital-acquired ARF. The oft-cited study by Hou et al. (23) reported an ARF incidence estimate of 4.9%. Shusterman et al. (24) conducted a similar study identifying ARF in 1.9% of hospitalized patients. A follow-up study recently published by Hou and colleagues (43) showed an increase in incidence (7%), but a similar spectrum of risk factors.

ARF in the ICU setting has also been characterized in the last two decades. Líñño et al. (6) found ICU patients with ARF to have associated organ failure, sepsis, and other complications. It is well recognized that the development of ARF is associated with an increase in mortality (22,25,26,44,45). It is also known that patients with ARF as part of multiorgan failure have the highest mortality rates. In several studies, sepsis-related ARF had a significantly worse prognosis than ARF in the absence of sepsis (46,47). It is also recognized that untreated ARF may contribute to a higher incidence of new-onset sepsis (48).

Definition of ARF

The spectrum of definitions in published studies of ARF is striking, ranging from severe (e.g., ARF requiring dialysis) to relatively modest observable increases in serum creatinine concentration (e.g., increase in serum creatinine of 0.3 to 0.5 mg/dl above baseline). Solomon et al. (36) used the definition of an increase in serum creatinine of 0.5 mg/dl within 48 h of radiocontrast exposure in a widely cited study that showed a borderline significant difference in ARF among individuals...
given saline infusion versus furosemide or mannitol before radiocontrast exposure. However, neither the Solomon et al. study nor others that use this ARF definition (including the Tepel et al. (49) and Kay et al. (50) publications on N-acetyl cysteine) have shown an association between a transient change in serum creatinine and morbidity, or the likelihood of long-term recovery of renal function. Many other definitions of ARF have been applied; some are outlined in Table 1. The most liberal of definitions have been used in intervention studies aimed at ARF prevention, usually in the context of radiocontrast exposure, one of the few instances in which ARF can be anticipated.

Several of the definitions are extremely complex (see Liaño et al. (6) and others) and could allow excessive subjectivity in ARF determination. These would likely be impractical for prospective, multicenter investigations. Moreover, none of the definitions used to date take into account the modifying effects of age, gender, and race on creatinine generation (and thereby serum creatinine concentration in ARF). It is noteworthy that creatinine generation is typically higher among individuals who are younger, male, and African American (51). Therefore, at the same decrement in GFR, persons with different demographic characteristics may be more likely to “qualify” with ARF diagnoses, particularly those definitions that require a minimum peak creatinine (e.g., 50% increase, to at least 2.0 mg/dl). By use of this definition, we found a twofold increase in the incidence of amphotericin B–associated ARF among men (52). Whether male gender is a true risk for ARF or simply a risk for being diagnosed with ARF is unclear. Regardless, the association of ARF with male gender highlights one of the limitations of the use of a definition of ARF that is creatinine based and not age, gender, and race adjusted.

Changes in serum creatinine are not specific and do not discriminate the nature and type of renal insult (e.g., ischemic, nephrotoxic) or the site and extent of glomerular or tubular injury, and levels are relatively insensitive to small changes in GFR (53). Moreover, changes in serum creatinine may lag behind changes (decline or recovery) in GFR by several days. Finally, because serum creatinine is influenced by one of the potential interventions for ARF (e.g., creatinine is removed by dialysis), its specificity for renal recovery is even more problematic.

Empiric Evidence of the Focus on Creatinine and Urine Output

We recently completed an analysis focusing on correlates of timing of nephrology consultation for ARF in the ICU (54). To avoid the complexities of comparing individuals whose ARF developed during a complicated ICU stay, we restricted our analysis to those patients with evidence of ARF at ICU admission and excluded individuals designated as “do not resuscitate.” We considered a wide array of demographic, clinical, laboratory, and physiologic variables (including pulmonary artery catheter data in some patients). The serum creatinine concentration and urine output (either as a continuous variable or the dichotomous “oliguria”) (<400 ml/d) were associated with the timing of consultation. There was no relation between the timing of consultation and hospital service, medical history, physiologic parameters, other laboratory studies, or the presence or absence of organ system failure, despite the fact that many of these factors have been shown to predict mortality in ARF in other studies. In other words, empiric evidence demonstrates that the definitions used in published reports are operative in practice, with little attention to risk profiles or associated nonrenal organ system failure.

Analogous Definitions in Other Conditions

Conceptual Framework for Other Disease Definitions. Disease definitions may be used to ascertain the presence of a disease in an individual or a population, guide the nature and timing of diagnostic and therapeutic interventions, and, in individual patients, help determine prognosis. The presence of any disease is inferred from a combination of clinical symptoms and signs, and alterations in biologic markers that can be reproducibly measured. Measures defining a disease should be responsive to change, track the natural history of the disease, and provide an assessment of the severity of injury. Consequences of the untreated disease and its response to specific interventions are additional criteria that might be considered when evaluating the choice of variables to define and classify a disease. Most disease definitions rely on the presence of specific markers that are measurably altered in response to an injury, and the sensitivity and specificity of any definition depends on the criteria used. These “response variables” may appear at varying time points in the disease and help define the course of the disease. Ideally, the magnitude and pattern of change of the response variable correlate with disease outcomes.

For instance, AMI can be diagnosed with the combination of chest pain and elevated cardiac troponins or creatine phosphokinase. Gradations in the severity of signs (including electrocardiography) and symptoms and the levels of troponin and creatine phosphokinase profile allow further classification of the disease spectrum (e.g., angina, unstable angina, demand ischemia, silent ischemia, myocardial infarction). A key feature for AMI is that the clinical presentation is directly related to an underlying event (i.e., coronary thrombosis). Moreover, the markers are sensitive, specific, and correlate with the severity of injury, even in the absence of typical clinical features.

In contrast, sepsis is heterogeneous in its presentation and affects multiple organs, so no single marker can be used to define the presence or absence of disease. Recognizing this limitation, a functional definition for sepsis has been based on events in the natural history of the sepsis syndrome: systemic inflammatory response syndrome, sepsis, severe sepsis, and septic shock (55).

In the absence of specific markers, effective definitions for a disease rely on multiple parameters, some of which represent the specific response to the disease, whereas others reflect nonspecific consequences of the disease. Disease severity is graded on the basis of the presence of specific parameters. For instance, the transition from sepsis to severe sepsis requires the presence of sepsis-related organ dysfunction. These graded...
<table>
<thead>
<tr>
<th>Author</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Solomon et al. (36),</td>
<td>0.5 mg/dl increase in (SCr&lt;sup&gt;a&lt;/sup&gt;) within 48 h</td>
</tr>
<tr>
<td>Tepel et al. (49),</td>
<td></td>
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<tr>
<td>Schwab et al. (81),</td>
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<tr>
<td>Weisberg et al. (82),</td>
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<tr>
<td>Stevens et al. (83),</td>
<td></td>
</tr>
<tr>
<td>and others</td>
<td></td>
</tr>
<tr>
<td>Hou et al. (23)</td>
<td>0.5 mg/dl increase in SCr if baseline SCr ( \leq 1.9 \text{ mg/dl} ), or 1.0 mg/dl increase in SCr if baseline SCr 2.0 to 4.9 mg/dl, or 1.5 mg/dl increase in SCr if baseline SCr ( \geq 5.0 \text{ mg/dl} )</td>
</tr>
<tr>
<td>Shusterman et al. (24)</td>
<td>0.9 mg/dl increase in SCr if baseline SCr &lt;2.0 mg/dl, or 1.5 mg/dl increase in SCr if baseline SCr ( \geq 2.0 \text{ mg/dl} ), and “remained elevated for at least one additional consecutive determination”</td>
</tr>
<tr>
<td>Liaño and Pascual (84)</td>
<td>“Sudden” rise of ( &gt;2 \text{ mg/dl} ) in subjects with prior “normal” renal function, or “sudden” increase in SCr of ( \geq 50% ) with “mild to moderate” basal chronic renal failure with SCr &lt;3.0 mg/dl, or “elevation of SCr at admission with normal or increased renal size (except with myeloma or hydronephrosis with cortical atrophy)”</td>
</tr>
<tr>
<td>Bates et al. (52)</td>
<td>50% increase in SCr to at least SCr of 2.0 mg/dl (“ARF”)</td>
</tr>
<tr>
<td></td>
<td>100% increase in SCr to at least SCr of 3.0 mg/dl (“severe ARF”)</td>
</tr>
<tr>
<td>Levy et al. (48)</td>
<td>25% increase in SCr to at least SCr of 2.0 mg/dl within two days</td>
</tr>
<tr>
<td>Behrend and Miller (1)</td>
<td>0.9 mg/dl increase in SCr if baseline SCr &lt;2.0 mg/dl to at least 2.0 mg/dl, or 1.5 mg/dl increase in SCr if baseline SCr ( \geq 2.0 \text{ mg/dl} ) (baseline defined as lower of most recent SCr in past 3 mo or lowest value during hospitalization)</td>
</tr>
<tr>
<td>Obialo et al. (51)</td>
<td>0.5 mg/dl increase in SCr to at least 2.0 mg/dl, or admission SCr ( \geq 2.0 \text{ mg/dl} ) with no history of renal disease</td>
</tr>
<tr>
<td>Kurnik et al. (85)</td>
<td>0.5 mg/dl increase in SCr or 25% increase from baseline within 48 h</td>
</tr>
<tr>
<td>Wang et al. (42)</td>
<td></td>
</tr>
<tr>
<td>Hirschberg et al. (41)</td>
<td>SCr ( \geq 3.0 \text{ mg/dl} ) with baseline SCr &lt;1.8 mg/dl, or “acute decrease” in creatinine clearance to ( \leq 25 \text{ mL/min} ) after surgery, trauma, hypotension, or sepsis</td>
</tr>
<tr>
<td>Allgren et al. (39)</td>
<td>1.0 mg/dl increase in SCr over 2 days</td>
</tr>
<tr>
<td>Parfrey et al. (86)</td>
<td>( &gt;50% ) increase in SCr to at least 1.4 mg/dl</td>
</tr>
<tr>
<td>Cochran et al. (87)</td>
<td>( &gt;0.3 \text{ mg/dl} ) and ( &gt;20% ) increase in SCr</td>
</tr>
<tr>
<td>Eisenberg et al. (88)</td>
<td>( \geq 1.0 \text{ mg/dl} ) increase in SCr, or ( \geq 20 \text{ mg/dl} ) or ( 50% ) increase in BUN</td>
</tr>
<tr>
<td>Lautin et al. (89)</td>
<td>6 graded criteria</td>
</tr>
<tr>
<td></td>
<td>( &gt;0.3 \text{ mg/dl} ) and ( &gt;20% ) increase in SCr on day 1, 2, 3, and day 5, 6, or 7, or ( &gt;0.3 \text{ mg/dl} ) increase in SCr on day 1, 2, 3, or ( &gt;0.3 \text{ mg/dl} ) and ( &gt;20% ) increase in SCr on day 1 or 2, or ( \geq 2.0 \text{ mg/dl} ) increase in SCr on day 1 or 2, or ( \geq 1.0 \text{ mg/dl} ) increase in SCr on day 1, or ( \geq 20 \text{ mg/dl} ) or ( \geq 50% ) increase in BUN on day 1</td>
</tr>
<tr>
<td>Fiaccadori et al. (90)</td>
<td>( &gt;50% ) increase in SCr in absence of “volume responsive prerenal status,” or ( &gt;1 \text{ mg/dl} ) increase in SCr with known renal insufficiency</td>
</tr>
<tr>
<td>Taylor et al. (91)</td>
<td>( \geq 0.3 \text{ mg/dl} ) increase in SCr</td>
</tr>
</tbody>
</table>

\* ARF, acute renal failure; SCr, serum creatinine.
definitions are more readily applied to classify populations, although they have also been used to guide interventions in individual patients and research subjects (56,57).

The multidimensional definition and classification construct has been applied to several diseases where a single specific diagnostic criterion is not available or is otherwise unsuitable. For example, the Ranson criteria enable early classification of severe acute pancreatitis (58). These criteria rely on the presence of three or more of the 11 criteria evident within 48 h of admission. Criteria include age and a series of laboratory parameters that reflect consequences of disordered pancreatic function (i.e., hyperglycemia in absence of diabetes, hypocalcemia, azotemia, anemia, hypoalbuminemia, leukocytosis, elevations of the hepatic enzymes lactate dehydrogenase and aspartate aminotransferase) and physiologic variables (i.e., metabolic acidosis, hypoxia) to grade the response. Interestingly, serum amylase and lipase, enzymes directly related to pancreatic injury (and analogous to creatinine in ARF), are not included in the scoring system. The number of positive criteria are associated with mortality ranging from <5% for zero to two criteria to 100% for seven to eight criteria (58). Similarly, the Child-Pugh classification is a means of assessing the severity of hepatic cirrhosis (59). It assigns scores for each of three laboratory parameters (bilirubin, albumin, and prothrombin time) and two clinical criteria representing the consequences of liver failure (encephalopathy and ascites). The individual scores are summed and then grouped as <7 (A), 7 to 9 (B), and >9 (C). A Child-Pugh “C” classification forecasts survival of less than 12 mo. Cancer staging similarly uses the tumor node metastasis grading system to classify malignant disease. Common to all of these classification systems is the lack of any single criterion to diagnose the disease and reliance on the consequences of the disease and on other factors influencing the course of the disease for classification. We propose that ARF be viewed in a similar manner; in terms of complexity of diagnosis and subsequent organ effects, ARF has more in common with sepsis or pancreatitis than with AMI.

What Are Desired Characteristics of Disease-Defining Variables in ARF? For any condition, the clinician needs to know whether the disease is present, and where and when the patient falls in the natural history of the disease. The former facilitates recognition, whereas the latter could identify time points for intervention. Thus, disease-defining variables should allow recognition of the disease and provide a mechanism to determine the time course of the disease. Renal functional alterations encompass many dimensions (e.g., vascular, endothelial, tubular, glomerular), and markers specific for the site and pattern of injury are lacking. Several new techniques are emerging to study ARF and are poised to be adapted for human studies (60). Recently, Ichimura et al. (61) and Han et al. (62) demonstrated that KIM-1 may be an early marker for renal injury specific for the renal tubule. Star et al. (63) and Muramatsu et al. (64) have described new markers for kidney disease, including a new cysteine-rich protein (CYP61) that is found in urine after ischemia-reperfusion injury. Other studies have utilized a spectrum of markers for renal injury but none have been tested in a large number of patients (65). Recent advances in proteomics will likely provide new targets for assessment (66).

Several methods exist for estimating changes in GFR (Table 2); however, each technique has limitations. Urinary markers may be the most practical, and techniques for rapid assessment of changes in GFR and these markers are being validated (60,67). Cystatin C appears to be a promising marker for changes in GFR but requires validation in the ICU and other settings (68). Magnetic resonance imaging methods that use newer contrast agents are being tested in experimental models of ARF and could provide information on intrarenal hemodynamics (69), the level and extent of proximal tubule dysfunction (70), and the presence of renal inflammation (71). It is evident that knowledge of the site and extent of injury would permit a precise determination of the underlying severity of renal dysfunction, could facilitate clinicopathologic correlations, and could help guide specific therapeutic interventions.

### Applying Lessons from Other Diseases to ARF

**Why Change?** It is evident that current definitions of ARF that rely on serum creatinine and urine output do not adequately characterize the spectrum of ARF observed in clinical practice. Additionally, in their current form, they do not support the clinical need to inform decisions for therapeutic interventions. Indeed, variation in the timing of drug delivery relative to renal injury has contributed to heterogeneity in intervention studies in ARF and may be partly responsible for the lack of demonstrable benefit. It is also recognized that processes of care (including the timing of initiation of dialysis, provision of nutrition, and the use of diuretics) likely influence the course of, and outcomes from, ARF. Simply put, better diagnostic and classification tools are required to allow for advances in ARF research and clinical practice.

**What Is Required?** We must focus on two separate but related issues. First, we need to expand the repertoire of sensitive and specific markers to quantify the site and severity of renal injury and to track functional change over time. Second, we need to more clearly define the course of ARF in a variety of settings and identify factors that condition the renal response to injury and influence outcomes from ARF. Gaining this knowledge will increase diagnostic specificity and allow for more appropriate evaluation of interventions. For instance, the

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**Table 2. Comparison of methods for determination of GFR**

<table>
<thead>
<tr>
<th>Clearance Method</th>
<th>Testing Complexity</th>
<th>Accuracy</th>
<th>Clinical Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic inulin clearance</td>
<td>++ ++</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Radioisotope clearance</td>
<td>++</td>
<td>++ +1/2</td>
<td>++</td>
</tr>
<tr>
<td>Radioisotope plasma disappearance</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Nomogram creatinine clearance</td>
<td>+1/2</td>
<td>+1/2</td>
<td>+++</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
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dose of radiocontrast agent and underlying renal function determine the trajectory of creatinine elevation and incidence of radiocontrast-associated nephropathy (72). In most circumstances, elevations in serum creatinine are seen within 48 h after radiocontrast exposure, so that the efficacy of a preventive therapy or early therapeutic intervention can be assessed peri-event (50). In contrast, when the nature and timing of insult are less well characterized (e.g., episodes of hypotension in a postoperative patient with sepsis), trends in serum creatinine and urine output are less predictable (73–75). Comparison of the actual pattern of illness with the predicted response could help to guide the timing of specific interventions, and ultimately compare two or more interventions in clinical trials.

**How Can We Do It?** Given the heterogeneity of ARF and the absence of specific markers for renal injury, an effective diagnostic and classification scheme should consider parameters other than the renal response to injury. Nonrenal organ system dysfunction also affects the ARF episode. For instance, serum creatinine levels may underestimate the severity of renal dysfunction in hepatic failure with elevated bilirubin levels (53) and the requirement for mechanical ventilation may further reduce GFR (76). In other diseases, susceptibility and response factors have been incorporated in the definition and classification of disease (see above, and the recent Predisposition, Infection, Response, Organ Failure [PIRO] classification for sepsis (77)).

**Defining ARF: Multidimensional Criteria**

To optimize the approach to ARF, we should gain insight into several domains: factors that predispose to injury, the nature and timing of the inciting event, the response of the kidney to the insult, and the later consequences of the ARF episode. We propose that a new definition for ARF should incorporate elements from each of these domains. This approach would lead to a more robust definition for the “ARF syndrome” and would facilitate the assessment of future interventions in this field. Table 3 describes a proposed definition for ARF that incorporates variables from each of the four domains noted above. Each domain is graded. An increasing grade reflects an increased risk of adverse outcomes.

We propose a framework for staging ARF that is based on the criteria within each domain. We based “susceptibility” grade roughly on the risk of ARF derived from epidemiologic studies. We grade the nature and timing of the insult on the basis of knowledge of the specific insult and the time interval from the insult to the point of evaluation. We grade the response variables after the RIFLE (Risk, Injury, Function, Loss, End Stage) criteria suggested by the Acute Dialysis Quality

### Table 3. Proposed classification of acute renal dysfunction

<table>
<thead>
<tr>
<th>Domain (44, 54, 92)</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Susceptibility</strong></td>
<td>None</td>
<td>Known pre-existing kidney disease (CKD stage 2)</td>
<td>Pre-existing chronic kidney disease (CKD stages 3 and above); baseline GFR &lt;60 mL/min/1.73 m²</td>
<td>Pre-existing kidney disease (CKD stage 2 or 3 or above) GFR &lt;89 mL/min/1.73 m² + presence of one risk factor</td>
</tr>
<tr>
<td>Baseline GFR &gt; 90 mL/min/1.73 m²</td>
<td>Baseline GFR 60 to 89 mL/min/1.73 m²</td>
<td>Baseline GFR &lt;60 mL/min/1.73 m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Insult</strong></td>
<td>Known</td>
<td>Known</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>nature</strong></td>
<td>Within 24 h</td>
<td>24 to 48 h</td>
<td>&gt;48 h</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Response</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Increase 0.5 to 1 mg, GFR decrease 25 to 49%</td>
<td>Increase 1 to 2 mg, GFR decrease by 50 to 74%</td>
<td>Increase &gt;2.0 mg/dl, GFR decrease &gt;75%</td>
<td>Increase &gt;3.0 mg/dl, GFR &lt;10 mL/min/1.73 m²</td>
</tr>
<tr>
<td><strong>physiologic urine output</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>UO &lt;0.5 mL/kg/h for 3 h</td>
<td>UO &lt;0.5 mL/kg/h for 12 to 23 h</td>
<td>UO 0.3 mL/kg/h for 24 h or anuria for 12 h</td>
<td>Anuria</td>
</tr>
<tr>
<td><strong>End-organ consequences</strong></td>
<td>None</td>
<td>Single organ</td>
<td>Two organs</td>
<td>&gt; 2 organs</td>
</tr>
</tbody>
</table>

<sup>a</sup> K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease (CKD) (93).
<sup>b</sup> Risk factors include diabetes mellitus with microalbuminuria, dehydration, multiple myeloma, congestive heart failure, and decompensated cirrhosis.
<sup>c</sup> Based on consensus RIFLE criteria proposed by ADQI (78).
<sup>d</sup> Respiratory, CV, neurological, hematological, liver, based on organ system failure criteria (44).
Initiative (ADQI) consensus conference (78). We define nonrenal organ dysfunction by using standardized organ failure scores (44). Gradations in the "susceptibility" and "insult" domains reflect increasing levels of risk for an adverse outcome, whereas those in the "response" and "end-organ" domains reflect an increasing severity of illness. We anticipate that at each point of assessment, individual patients would be graded within each domain. On the basis of the overall status in the four domains, patients would be categorized into the stage of ARF and would move through various stages during the course of the disease (Table 3).

Past and Present Constructs in ARF

Myers et al. (75) demonstrated three distinct patterns of ARF after surgery. On the basis of these observations, it is widely taught that clinical ARF has three phases: initiation, maintenance, and recovery. The duration of each phase varies on the basis of the presence of pre-existing kidney disease and the nature and type of insult. Sutton et al. (12) and Molitoris (79) have recently proposed a mechanistic classification for ischemic ARF that delineates four distinct phases for this disease: initiation, extension, maintenance, and recovery (Figure 1). Variability in response has also been established in experimental ARF wherein the response can be graded on the basis of preconditioning for the model, and this variability is being explored as a therapeutic strategy (e.g., ischemic preconditioning may reduce the response to subsequent insults) (80). Multifactorial insults accelerate the decline in renal function in ARF. For any given patient, the pattern of ARF will depend on his or her susceptibility to injury and the nature (type, site) and severity (single or multiple, duration) of injury. The renal response is likely to be dependent on these two factors and may in turn determine nonrenal organ dysfunction. If the course is prolonged, nonrenal organ dysfunction will further affect the renal response.

By characterizing individuals on the basis of four domains, it may be possible to more accurately define the time course of disease and consequently detect distinct time points for intervention (79). This approach is similar in concept to sepsis syndrome, where distinct windows of opportunity have been defined for targeted therapeutic intervention. The multicenter trial of recombinant activated protein C required the drug to be initiated within 24 h of the first sepsis-induced organ system failure (57). If the nature and timing of the insult in ARF were clearly defined, one could select a specific therapeutic agent directed to ameliorate the injury and deliver the agent within a known therapeutic window. If the renal response can be characterized, supportive therapy can be instituted, and depending on the presence or absence of the underlying nonrenal organ dysfunction, specific interventions, such as dialysis support, could be optimized.

**How Could the Clinician Use These Definitions?**

The proposed definitions could be used to establish the presence of disease by using the response variable graded for the susceptibility for ARF and knowledge of the insult. An increase in serum creatinine of 0.7 mg/dl with a susceptibility grade of 4 and an insult grade of 3 is more likely to represent significant injury (and to be accompanied by more dire consequences) than if the susceptibility and insult grades were 1 and 1, respectively. With an end-organ grade of 3, a similar increase in serum creatinine might require dialytic intervention.

A comparison of patients’ actual versus predicted course could be useful in refining diagnostic and classification criteria—and ultimately in efforts aimed at quality assurance and improvement. The multidimensional approach can be illustrated with hypothetical cases. A patient with diabetes mellitus, baseline creatinine 1.2 mg/dl, and no proteinuria (susceptibility grade 2) seen 36 h after a contrast load (insult grade 2) with a urine output of 2 L/d and a follow-up serum creatinine of 2.5 mg/dl (response grade 2) with no nonrenal end-organ damage (end-organ grade 1) would be classified “S2-I2-R2-E1.” A reevaluation 48 h later shows a change in serum creatinine to 3.5 mg/dl and a decrease in urine output to 400 ml/d without evidence of end-organ dysfunction (now stage S2-N2-R3-E1). On the basis of these two time points, it is evident that this hypothetical patient has experienced a continued decline in renal function, representing either an extension phase from the original injury or ongoing injury. Because the expected trajectory for change in renal function based on the timing of the contrast load would have been a return to baseline creatinine within roughly 96 h, the deviation from the predicted response would suggest an extension of the initial injury (Figure 1). A targeted therapeutic intervention with a molecule that could ameliorate injury or promote repair could then be timed for this phase.

In a second example, a postcardiac surgery patient who required emergency coronary artery bypass grafting and aortic valve replacement is evaluated 5 d after surgery. The patient is 80 yr old with a baseline creatinine of 2.0 mg/dl and a history of hypertension. Postoperatively, his serum creatinine increased slowly from 1.8 to 3.5 mg/dl with adequate urine output (900 ml/d) on an intravenous bumetanide drip. There

![Figure 1. Phases of ischemic acute renal failure (ARF). Therapies aimed at (A) preventing, (B) limiting the extension phase, and (C) treating established ARF. Reprinted from reference 79, with permission.](image-url)
was no decline in blood pressure during surgery or postoperatively, and he has not received any nephrotoxic agents. There was no evidence for infection or sepsis. At evaluation on postoperative day 5, he is mechanically ventilated with satisfactory oxygenation on supplemental oxygen and requires two vasopressors to maintain a mean arterial blood pressure of 60 mmHg. His total bilirubin is 7 mg/dl and serum albumin 2.8 g/dl. On the basis of records of daily fluid balance, he is estimated to have 6 L of extracellular volume excess. According to current nomenclature and diagnostic methods, he would be considered to be nonoliguric, acute on chronic renal failure. Many internal medicine and critical care physicians (and nephrologists) would not intervene with dialysis or hemodialfiltration in this case because the patient is still making urine and has no life-threatening biochemical abnormalities. By use of the proposed classification scheme, this patient would be S3-I4-R3-E3. Given the presence of end-organ damage and ongoing reduction in renal function, a case could be made to institute dialytic support, although currently there is no evidence base on which to make this recommendation. Certainly, providing detailed data on outcomes associated with S3-I4-R3-E3 patients (not unusual in clinical practice) would be more valuable to decision making than data on all patients classified as “nonoliguric, acute on chronic renal failure.”

Providing a Framework for Experimental and Clinical Research

Although a more detailed diagnostic and classification system would be valuable to clinicians, it could also be used to rationalize certain aspects of research. For example, in a trial comparing dialysis modality or intensity, one could specify that dialysis should begin for “S2-I3” subjects with “R3 regardless of E,” or “R2 with E stage of 2 or greater.” A more comprehensive and flexible classification scheme could accommodate new and improving markers derived from genomic and proteomics investigations. For instance, if susceptibility genes were discovered that predict the renal response, these could be included as new criteria in the susceptibility domain. Similarly, new injury markers could be included in the insult domain and provide more specific information on the nature and severity of disease. Other markers of renal function (e.g., cystatin C) or of organ dysfunction (e.g., cytokines) could be included to enhance other domains.

Advantages and Limitations

The proposed definitions are based on concepts tested in other settings such as acute pancreatitis, liver disease, and sepsis. The suggested criteria are universally applicable and easy to obtain. The schema could be applied to describe a population or for individual bedside decision making. The schema proposed could also facilitate and accommodate future discoveries. However, there are several limitations to (and concerns with) our proposal. First, we believe that the four domains described are important, but the performance and relative contribution of each domain to the definition and classification scheme has not been tested. We do not know whether these domains are the correct ones or whether there are others that need to be identified. We do not have sensitive markers for defining the consequences of renal dysfunction. We need to define the nature and severity of underlying disease with the markers at hand. We need proof that the cutoffs established for response variables are related to outcomes and are appropriate ones. We must explore the interactions of the variables to determine whether additional conditional definitions would be preferred. It is evident that future studies need to evaluate the utility of the proposed definition in several settings. However, we propose a new diagnostic and classification scheme to help rationalize bedside management and intellectual inquiry into this condition.

Summary

ARF continues to be a vexing problem occupying a significant amount of time for clinicians and offering numerous challenges to investigators. Despite the recognition that ARF contributes to adverse outcomes in the critically ill, little progress has been made in managing this condition. One of the key impediments to progress is the lack of a uniform definition for this disease. Current definitions that rely on changes in serum creatinine and urine output are neither sensitive nor specific. We propose a new classification for ARF that incorporates information from other domains in an effort to enhance descriptive data and, we hope, improve decision making. Future studies will need to validate the “multidimensional diagnosis of ARF” construct and to improve the content and precision of components within each domain. What we present here (or a variation thereof) is not definitive, just a necessary first step. On the frontier, we see much more precision in ARF definitions, effective interventions, and, ultimately, mortality rates in the single digits.

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