ADQI

Acute Dialysis Quality Initiative

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Workgroup 1

Definition for Acute Renal Failure

Catherine Bouman

*John A. Kellum**

Norbert Lamiere

Nathan Levin

Defining Acute Renal Failure

The clinical condition of acute renal failure (ARF) is said to occur in anywhere from 1 to 25% of critically ill patients (1,2) depending on the population being studied and the criteria used to define its presence. Furthermore, mortality in these populations ranges from 28 to 90% (3-5). Clearly, trials of prevention and therapy are not comparable because widely disparate definitions have been used. A standardized case definition is necessary for comparisons of outcome across studies, for development of prognostic scoring systems, for interpretation of dialytic and non-dialytic therapeutic interventions, and for design of multicenter studies. Depending on the population studied the same noxious stimuli may result in impairment in renal function over a wide range.

Classically, acute renal failure (ARF) is defined an "abrupt and sustained decrease in renal function". Different authors have chosen different methods of accessing renal function and have chosen different degrees of abnormality as cutoffs for the diagnosis. Even the degrees to which the process is "abrupt" or "sustained" have varied between study such that there are now more than 30 definitions of ARF in the literature (see appendix 1). This situation has impaired the study of ARF as well as its possible treatments (6).

What functions of the kidney should be assessed in definition of ARF?

Although the kidney has numerous functions (*e.g.,* fluid and solute excretion, electrolyte and acid--base regulation, endocrine functions, and so forth), in clinical practice, we accept the argument that the only functions that are routinely and easily measured and that are unique to the kidney are the production of urine and the excretion of waste products of nitrogen metabolism (6). This is not to say that the other functions of the kidney are less important, only that they are less verifiable, at least for now.
Recommendation: for clinical research, ARF can be defined as an "abrupt and sustained decrease in glomerular filtration, urine output, or both."

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*Authors are listed in alphabetic order. *Denotes group facilitator.*

What are the ideal features of a definition for ARF (e.g. sensitive vs. specific, prognostic value, grades of dysfunction, research/clinical standardization etc.)?

We feel that the following features are important in any definition of ARF.

a. Considers change from baseline.

A serum creatinine of 1.5 mg/dL (133 mcmol/L), at steady-state, corresponds to a GFR of 36 ml/min in an 80 y/o white female, but 77 ml/min in a 20 y/o black male. Similarly, a serum creatinine of 3.0 mg/dL (265 mcmol/L) in a patient suspected of having renal impairment would reflect a GFR of 16 ml/min in the elderly female but 35 ml/min in the young male. In both cases, a doubling of serum creatinine cosrresponds to an approximate decrease in GFR by 50% (exactly a 55% decrease in the above example) because there is a linear relationship between GFR and 1/Cr. While every classification of ARF in the literature relies on some threshold value for serum creatinine concentration, no single creatinine value corresponds to a given GFR across all patients. Thus it is the change in creatinine that determines ARF. One useful approach is to estimate a steady-state baseline GFR so that a magnitude of change can be calculated. Importantly, an estimate of GFR based on serum creatinine is only valid during steady state, which by definition, is not the case in ARF. Finally, since ARF is an "abrupt" decrease in GFR, a classification system must be bounded by time. While renal dysfunction occurring over even 1 month might be considered "acute", under most conditions ARF will evolve over 1-7 days (7).

b. Includes classification for acute on chronic (ARF)

Virtually all definitions for ARF have distinguished between patients with normal and abnormal baseline renal function. When ARF becomes superimposed on chronic renal disease, so-called "acute-on-chronic" renal failure, there are important diagnostic and prognostic differences that distinguish these patients from those with normal baseline renal function. Some authors have chose to exclude such patients but because pre-existing renal disease is an important risk factor for ARF, these patients represent a substantial portion of the at risk population. More commonly, authors have chosen to use different criteria for ARF in patients with baseline abnormal renal function (see below).

c. Easy to use and Clinically Applicable across different centers

Importantly, the purpose of developing standard criteria for the diagnosis and classification of ARF is to allow different centers to report findings that can be compared to other centers. Standardization for the purpose of research may eventually form the platform for a standard clinical classification system, particularly if clinical trials produce positive results. However, at this time, consensus criteria for ARF are **not intended to guide clinical management of individual patients**. Nonetheless, criteria for ARF should be easy to use and based on standard clinical variables. Until such time as a specific diagnostic marker (urine or blood) has been developed to detect patients with ARF, the criteria should utilize existing clinical variables.

d. Needs to consider BOTH sensitivity and specificity because of different populations and research questions.

For some research questions, early and or mild tubular injury will be important to include even when function is relatively intact whereas for others only significant renal dysfunction will be the focus. Thus, if one set of criteria is to be used for ARF, it will need to include different levels of dysfunction. Furthermore, by its very nature, a classification system that includes both mild (or early) and severe (or late) cases will include varying degrees of sensitivity and specificity—being more sensitive at one end and more specific at the other (8). Accordingly we advocate a multi-level classification system where a wide range of disease spectra can be included.

Recommendations: 1. ARF should be defined in terms of a change from baseline. It should be abrupt (1-7 days) and be sustained (>24 hrs). 2. Criteria for ARF should include "acute-on-chronic" disease but modifications to the criteria will be required. 3. Though not intended for individual patient management, ARF criteria should be based on clinically available data that are consistent across centers. 4. A multi-level classification system is desirable.

What clinical/biochemical markers are useful in defining ARF?

In keeping with the recommendations above, clinically available variables that are potentially useful in defining ARF include Creatinine clearance; Serum creatinine; Urea or Blood Urea Nitrogen (BUN); Urine output; and markers of tubular injury.

a. Creatinine clearance

Once glomerular filtration has reached a steady state it can be quantified by measuring a 24h creatinine clearance. Unfortunately, the accuracy of a creatinine clearance (even when collection is complete) is limited because as GFR falls creatinine secretion is increased and thus the rise in serum creatinine (S_{Crt}) is less (9,10). Thus, creatinine excretion is much greater than the filtered load, resulting in a potentially large overestimation of the GFR (as much as a two-fold difference) (10). Therefore creatinine clearance represents the upper limit of what the true GFR is under steady-state conditions. A more accurate determination of GFR requires measurement of the clearance of inulin or a radiolabeled compound such as iothalamate, DTPA, or EDTA (11). Unfortunately, these tests are not routinely available. However, for clinical purposes, determining the exact GFR is rarely necessary. Instead, it is important to determine whether renal function is stable or getting worse or better. This can usually be determined by monitoring S_{Crt} alone (12). Furthermore, since patients with ARF are not in steady state, creatinine clearance will not accurately reflect GFR.

b. Serum creatinine

Like creatinine clearance, the S_{Crt} will not be an accurate reflection of GFR in the non-steady state condition of ARF. During the evolution of dysfunction, S_{Crt} will under-estimate the degree of dysfunction

while the opposite will be true as renal function recovers. Nonetheless, the degree to which S_{Crt} changes from baseline (and perhaps the rate of change as well) will, to some degree, reflect the change in GFR. S_{Crt} is readily and easily measured and it is specific for renal function. However, in patients without renal disease there is a fundamental assumption that creatinine is in steady state where production equals excretion. Thus, S_{Crt} (or creatinine clearance) is a reasonable approximation of GFR in most patients with normal renal function (13). Creatinine is formed from non-enzymatic dehydration of creatine in liver and 98% of creatine pool is in muscle. Critically ill patients may have abnormalities in liver function and markedly decreased muscle mass; hence altering creatinine metabolism significantly. Additional factors influencing creatinine production include conditions of increased production such as trauma, fever, and immobilization; and conditions of decreased production including liver disease, decreased muscle mass, and aging. In addition, tubular reabsorption ("backleak") may occur in conditions associated with low urine flow rate. Finally, the volume of distribution (V_D) for creatinine (total body water) influences S_{Cr} and may be dramatically increased in criticially ill patients. There is currently no information on extrarenal creatinine clearance in ARF and a non-steady state condition often exists (14).

Importantly, several studies have shown an inverse relationship between the level of S_{Crt} and outcome in ARF (15-18). Liano et al. reported that ICU patients with ARF had much lower S_{Crt} at admission compared to non-ICU patients with ARF (15). Similarly, Brivet and colleagues noted that patients who were begun on renal replacement therapy later in the course of ARF tended to have lower S_{Crt} but higher mortality (71% vs 50%) (17). Paganini et al. found a similar relationship whereby patients started on renal replacement therapy with $S_{Crt} \leq 2$ mg/dL had an odds ratio for mortality of 4.8 compared to patients with $S_{Crt} \geq 5$ mg/dL (18). Perhaps most convincingly, Mehta has shown recently in an observational cohort that S_{Crt} is positively correlated with survival within the ARF population—odds ratio 0.71 (0.63-0.81) (16). Thus, within groups of patients with ARF, S_{Crt} is not correlated with worse outcome; indeed the opposite appears to be true. This may reflect less underlying severity of illness manifest in less affect on creatinine metabolism as discussed above. However, clearly S_{Crt} should be interpreted cautiously when used as a marker of severity of renal dysfunction.

c. Urea

Urea or BUN, is a non-specific marker of renal function. High levels of urea reflect renal dysfunction but a variety of non-renal conditions dramatically influence the levels (12) of urea making it a poor marker relative to creatinine.

d. Urine output

Urine output is more sensitive to changes in renal function than biochemical markers. However, it is far less specific except when severely decreased or absent. Severe ARF can exist despite normal urine output (i.e. non-oliguric) but changes in urine output often occur long before biochemical changes are apparent.

e. Other markers

Some authors advocate the examination of the urine in all cases of ARF (19) although the practice does not often lead to a change in diagnosis or management. The main role of urine analysis is to look for evidence of glomerular nephritis (e.g. red cell casts) or allergic interstitial nephritis (urine eosinophils). When present, these findings are important since they lead to specific treatment or avoidance of the causative agent etc. However, the urine sediment in acute tubular necrosis is non-specific. The classic finding of muddy brown casts is neither specific nor sensitive (20).

Markers of tubular injury would be a great advantage since traditional blood and urine markers for the diagnosis of various renal diseases are insensitive and nonspecific. Kidney Injury Molecule-1 (KIM-1), expression is markedly up-regulated in the proximal tubule in the post-ischemic rat kidney (21). A soluble form of human KIM-1 can be detected in the urine of patients with ATN and may serve as a useful biomarker for renal proximal tubule injury, possibly facilitating the early diagnosis of the disease and serving to discriminate between different forms of renal dysfunction (21). Similarly, Cyr61, a renally secreted, cysteine-rich, heparin binding protein, is markedly up-regulated early in the course of ischemia in the kidney but not in other organs. In situ hybridization studies suggest that Cyr61 is synthesized in the proximal tubule. In one resent study, Cyr61 was rapidly induced in proximal tubules following renal ischemia, and was excreted in the urine where it might serve as an early biomarker of renal injury (22).

Recommendations: S_{Crt} and urine output provide the best existing markers of ARF. Care should be taken when interpreting S_{Crt} especially within the subgroup of patients with ARF. Urine analysis should be undertaken in cases of ARF primarily to exclude glomerular disease or allergic interstitial nephritis.

How should oliguria/non-oliguria be incorporated in a classification system for ARF?

Given the observed differences in mortality and renal recovery between oliguric and non-oliguric ARF, it would seem appropriate to differentiate these conditions in an ARF classification system. Definitions of oliuria vary somewhat in the literature as well, especially between adult medicine and pediatrics. Classically, oliguria is defined (approximately) as urine output < 5ml/kg/day.

Recommendation: Classification of ARF should include a designation for oliguria and non-oliguria.

How can ARF be defined when baseline renal function is unknown?

One option is to calculate a theoretical baseline serum creatinine value for a given patient assuming a normal GFR of approximately 95 ± 20 mL/min in women and 120 ± 25 mL/min in men (9). By normalizing the GFR to the body surface are a normal GFR of approximately 75-100 ml/min/1.73m^2 can be assumed (23) and thus a change from baseline can be estimated for a given patient. The simplified "modification of diet in renal disease" (MDRD) formula provides a robust estimate of GFR relative to serum creatinine based on age, race, and sex (24). This estimate could then be used to calculate the relative change in GFR in a given patient. The application of the MDRD equation to estimate baseline creatinine requires a simple table with age, race and gender. Table 1 solves the MDRD equation for the lower end of the normal range, (i.e. 75 ml/min/1.73m^2). Note, the MDRD formula is used only to estimate the baseline

when it is not known. For example, a 50-year-old black female would be expected to have a baseline creatinine of 1.0 mg/dL (88 mcmol/L).

Table 1: Estimated baseline creatinine

Age (years)	Black Males (mg/dL | mcmol/L)	While Males (mg/dL | mcmol/L)	Black Females (mg/dL | mcmol/L)	While Females (mg/dL | mcmol/L)
20-24	1.5 | 133	1.3 | 115	1.2 | 106	1.0 | 88
25-29	1.5 | 133	1.2 | 106	1.1 | 97	1.0 | 88
30-39	1.4 | 124	1.2 | 106	1.1 | 97	0.9 | 80
40-54	1.3 | 115	1.1 | 97	1.0 | 88	0.9 | 80
55-65	1.3 | 115	1.1 | 97	1.0 | 88	0.8 | 71
>65	1.2 | 106	1.0 | 88	0.9 | 80	0.8 | 71

Estimated GFR = 75 (ml/min/1.73m2) = 186 x (SCr)–1.154 x (Age)-0.203 x (0.742 if female) x (1.210 if African-American) = exp(5.228 – 1.154xln(SCr)–0.203x ln(Age) – (0.299 if female) + (0.192 if African – American))

Recommendation: When baseline creatinine is unknown, it should be estimated from the MDRD equation.

How should "acute on chronic" renal failure be handled?

One basic assumption in most definitions of ARF is that the patient's baseline renal function was normal before the current insult. Estimation of GFR in ARF is easy if the serum creatinine is known before the level began to increase. In the absence of this information, although the current GFR can be estimated once the level has stabilized, it will be impossible to exclude accurately "acute on chronic" renal failure. When the patient has pre-existing renal disease, there are two important differences in the way ARF is classified. First, the patient's baseline GFR and, hence, serum creatinine will be different from those predicted by the MDRD equation. Second, the patient's starting position in the spectrum and progression of renal dysfunction will be more advanced. The implication of this latter difference is that the relative decrease in renal function required to reach a level consistent with the diagnosis of ARF will be less than that of a patient without pre-existing disease. For example, a patient with a serum creatinine of 1 mg/dL (88 mcmol/L) will have a steady-state serum creatinine of 3 mg/dL (229 mcmol/L) when 75% of GFR is lost. By contrast, a mere 50% decrease in GFR in a perfectly matched patient for age, race, and sex with a baseline creatinine of 2.5 mg/dL (221 mcmol/L) corresponds to a creatinine of 5 mg/dL (442 mcmol/L). The problem with these criteria is that the former patient may have had a baseline GFR of 120 mL/min decreasing to 30, whereas the latter patient has a GFR of 40 mL/min decreasing to 20. It would be difficult to consider the first patient with a GFR of 30 mL/min as having ARF whereas the patient with a GFR of 20 mL/min does not. Thus, it seems that either a different set of criteria will be needed in patients with pre-existing disease or some absolute creatinine criteria will need to be integrated into the classification system. One possible approach would be to use a relative change in creatinine (e.g. threefold) as the primary criterion, with an absolute cutoff (e.g. 4 mg/dL or about 350 mcmol/L) as a secondary criterion when baseline creatinine is abnormal. Similar approaches have been used in the literature (25,26).

Recommendation: Separate criteria should be used for the diagnosis of ARF superimposed on chronic renal disease. An acute rise in S_{Crt} (of at least 0.5 mg/dL or 44 mcmol/L) to more than 4 mg/dL (350 mcmol/L) will serve to identify most patients with ARF when their baseline S_{Crt} is abnormal.

How can a definition for ARF be evaluated/tested?

The ultimate value of a definition for ARF will be determined by its utility. A classification scheme for ARF should be sensitive and specific and also predictive of relevant clinical outcomes such as mortality and length of hospital stay. These are testable hypotheses. Large, population-based studies have already collected the necessary data to analyze the predictive value of any classification system using serum creatinine or urine output (2,25,27). These datasets can be used to validate the classification system for ARF and such criteria can be applied prospectively. Analytical methods for validating and refining classification systems have been developed for other diseases, such as chronic fatigue syndrome (28), breast cancer (29), and neuropsychiatric systemic lupus erythematosus (30). These approaches have used artificial neural networks (28,29) or conditional logistic regression methods (30) that could be applied here. ARF is similar to systemic lupus erythematosus and many other syndromes in medicine that lack a gold standard for diagnosis. Clinical-pathologic correlation is often impossible in cases of ARF because specimens are usually not available for analysis, and pathology is generally nondiagnostic anyway (31). Final disposition of cases cannot be used as endpoints because relatively few survivors of ARF go on to develop end-stage renal failure. Thus, nonspecific clinical endpoints such as all-cause mortality will probably be the only variables that can be used to test the validity of ARF classification systems.

Recommendation: ARF criteria should be tested prospectively in large clinical datasets. Nonspecific clinical endpoints such as all-cause mortality should be used for validation.

How might treatment decisions influence or be influenced by the definitions? (In other words, dialysis will affect the clinical/biochemical markers and so how should this be integrated into the definitions so as not to make them confusing or circular)? Should we attempt to define ARF in terms of indications for RRT? (i.e. a level of ARF that is likely to require RRT).

It is understood that therapeutic maneuvers can influence the primary criteria for the diagnosis of ARF. For example hydration status will influence urine output, and even to some degree, by altering V_D, S_{Crt}. Such influences are unavoidable and analogous to other disease processes, which require clinical classification. For example, positive end-expiratory pressure (PEEP) will influence arterial oxygenation and hence alter the PaO_2:FIO_2 ratio. In theory a marginal case might be considered to "have" or "not have" acute lung injury depending on the level of PEEP applied. A similar situation could occur with ARF, for example, when large dose diuretics are used to force a urine output when it would otherwise fall into a category consistent with a diagnosis of ARF. Ultimately these cases will generally sort out but they may cause confusion in the acute situation. In the end, it must be assumed that patients are adequately hydrated, not

treated with diuretics except in the case of volume overload and treated with renal replacement therapy when clinically indicated.

Recommendation: ARF criteria should assume a clinical state that is as close to "natural" as possible. In other words, the criteria assume "adequate" hydration and no diuretics. In practice the use of diuretics may precede evaluation of renal function and extrapolation may be necessary. Patients treated with renal replacement therapy for "renal" indications should be considered to have ARF regardless of their S_{Crt} or urine output.

How does etiology impact definitions and should etiology be considered in the definition?

The consensus criteria developed for ARF are meant to be applied in the case of critical illness and will usually be in the setting of acute tubular necrosis (ATN). Occasionally other forms of ARF occur in thus setting (e.g. interstitial nephritis) and not all forms of ATN have similar epidemiology (*eg*, radiocontrast vs. sepsis). The present criteria are intended to be applied across these various etiologies. However, primary renal diseases such as glomerulonephritis are sufficiently different in terms of there natural history and management that they should be excluded from this classification system.

Recommendation: ARF criteria should be applied to all forms of ARF in the critically ill except for primary renal disease such as glomerulonephritis. In general most cases will have ATN.

How should recovery be defined?

The issue of renal recovery, as a clinical endpoint, is addressed by work group 2. A working definition of renal recovery is a return to near baseline GFR (complete recovery) or if failure to return to baseline but without the need for chronic renal replacement (partial recovery).

Recommendation: Complete renal recovery is defined by a convalescent S_{Crt} not more than 50% increased from baseline (e.g. if baseline S_{Crt} is 1.0 mg/dL, (88 mcmol/L) complete recovery is said to occur if the new steady state S_{Crt} is < 1.5 mg/dL (133 mcmol/L)). Partial renal recovery is said to occur if the above condition for complete recovery is not met but the patient does not require chronic dialysis (i.e. renal "loss" has not occurred).

Proposed ARF Criteria: The RIFLE Classification

Figure 1 summarizes the ADQI consensus criteria for ARF based on the recommendations outlined above. The classification of ARF is divided into 3 levels, "risk", "injury" and "failure" based on either GFR or urine output criteria whichever is more severe. Thus a patient with no urine output for 12 hrs has RIFLE-F regardless of the S_{Crt}. Conversely, a patient with a baseline S_{Crt} of 0.5 mg/dL (44 mcmol/L) that increases to 1.5 mg/dL (133 mcmol/L) has RIFLE-F even if UO is > 0.5ml/kg/h. We would further distinguish these two conditions as being oliguric (first example) and designate this as RIFLE-F_O or non-oliguric (second example) and simply designate this as RIFLE-F. The designation is not needed for RIFLE-R or I because any oliguric patient would be classified as RIFLE-F. It should be noted that we define oliguria under this

criteria as 0.3ml/kg/h for 24 hrs or anuria for 12 hrs. A second distinction for RIFLE-F is for "acute-on-chronic" disease. In this case any acute (1-7 days) increase in S_{Crt} by at least 0.5 mg/dL (44 mcmol/L) such that the new S_{Crt} is ≥ 4.0 mg/dL (350 mcmol/L) is considered to be RIFLE-F and designated as RIFLE-F_C. Combinations could also occur such that an oliguric patient with acute-on-chronic disease would be designated as RIFLE-F_{CO}. There is no need to designate acute-on-chronic disease for RIFLE-R or I since these conditions can only occur in the setting of normal baseline function (i.e. acute renal insufficiency cannot occur if there is already chronic renal insufficiency). Table 2 provides a breakdown of the criteria based on different starting S_{Crt} levels.

The RIFLE criteria also include two clinical outcomes "loss" and "end-stage renal disease" (ESRD). These are separated to acknowledge the important adaptations that occur in ESRD that are not seen in persistent ARF. Persistent ARF (loss) is defined as need for RRT for > 4 weeks; while ESRD is defined by need for dialysis > 3 months.

Table 2. Serum creatinine values and corresponding RIFLE classification

Baseline	0.5 (44)	1.0 (88)	1.5 (133)	2.0 (177)	2.5 (221)	3.0 (265)
Risk	0.75 (66)	1.5 (133)	2.25 (200)	3.0 (265)	3.75 (332)	---
Injury	1.0 (88)	2.0 (177)	3.0 (265)	---	---	---
Failure	1.5 (133)	3.0 (265)	4.0 (350)	4.0 (350)	4.0 (350)	4.0 (350)

Creatinine is expressed in mg/dL and (mcmol/L).

Authors:

In alphabetic order.

Catherine Bouman: Department of Intensive Care Academic Medical Center, Amsterdam, The Netherlands

John A. Kellum: University of Pittsburgh, School of Medicine, Department of Critical Care Medicine, Pittsburgh, PA, USA

Norbert Lamiere: Renal Division, University Hospital, Ghent, Belgium

Nathan Levin: Renal Research Institute, New York, NY, USA

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Figure 1.

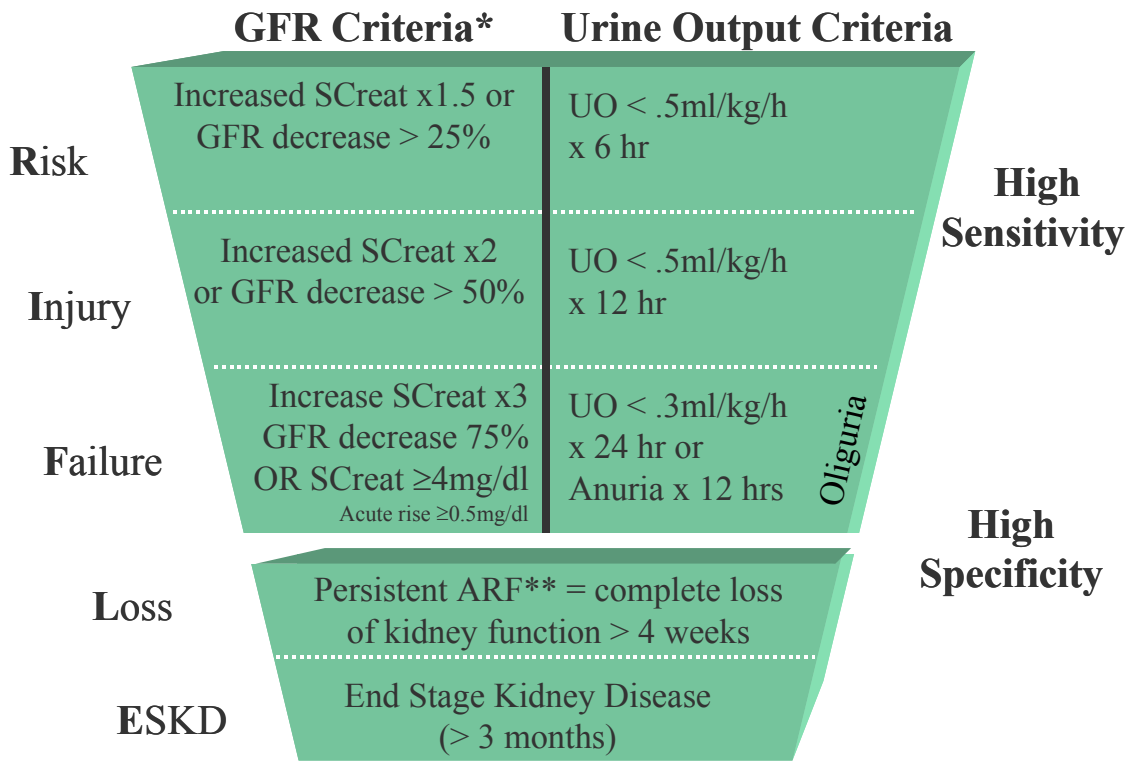

Figure 1. Proposed classification scheme for acute renal failure. The classification system includes separate criteria for creatinine and urine output. The criteria that leads to the worst classification should be used. Note that RIFLE-F is present even if the increase in S_{Crt} is < 3 fold so long as the new S_{Crt} is ≥ 4.0 mg/dL (350 mcmol/L) in the setting of an acute increase of at least 0.5 mg/dL (44 mcmol/L). The designation RIFLE-F_C should be used in this case to denote "acute-on-chronic" disease. Similarly when RIFLE-F classification is reached by urine output criteria, a designation of RIFLE-F_O should be used to denote oliguria. The shape the figure denotes the fact that more patients (high sensitivity) will be included in the mild category, including some without actually having renal failure (less specificity). In contrast, at the bottom, the criteria are strict and therefore specific, but some patients will be missed.