

Defining, Quantifying, and Classifying Acute Renal Failure

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The syndrome of so-called “acute renal failure” (ARF) is common in the intensive care unit (ICU) and may affect from 1% to 25% of patients [1–6], depending on the population and the criteria that are used to define its presence. In many ways, its nature and epidemiology resemble those of other ICU syndromes, such as severe sepsis, septic shock [7], or acute respiratory distress syndrome (ARDS) [8]. Like any other clinical entity, it is an invention of man. There is no such thing as ARF like there is a table or a chair; there are only people who have malfunction of the kidney for several reasons.

Because it is an artificial concept, it can neither be proven nor denied that someone has ARF unless one agrees ahead of time on what the term means. It is a bit like saying that a person is Chinese. Unless one agrees on what Chinese means, one cannot say that a given person is or is not Chinese (born in China? has a People’s Republic of China passport? has a particular phenotype?). Although these “philosophical” observations might seem to be futile, unnecessary, and even counterproductive to the clinician who “knows” what a patient who has ARF is “when he/she sees one,” they might be important to the researcher. The researcher needs clear consensus definitions to describe and understand epidemiology, to randomize patients in controlled trials, to test therapies in similar groups of patients, to develop animal models, to validate diagnostic tests and so on, including subdividing patients into objective types of ARF. Furthermore, if research is to generate evidence to change clinical practice, practitioners will need to adopt definitions from studies to apply their results.

Definitions cannot be arbitrary (the researcher likes them but other researchers do not). They need to be based on at least some widely accepted foundations of

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physiology, clinical behavior, response to treatment, histopathologic features, and prognosis. They need to be the same worldwide: a concept that moves the issue of definition from the scientific or clinical world to the political (“my definition is better than yours syndrome”).

In this regard, ARF is no different from ARDS, systemic inflammatory response syndrome, severe sepsis, or septic shock [7,8]. All of these syndromes have no gold standards of diagnosis, no specific histopathologic confirmation, and no uniform clinical behavior, just like ARF, because they do not “exist.”

What exists are patients who have a spectrum of conditions that we choose to lump together for operative purposes until further information emerges that allows us to be more specific and to create other useful artificial entities. Yet, these imperfect, highly flawed, man-made definitions are useful. This usefulness is demonstrated nicely by the ability to conduct trials in patients who have sepsis or ARDS that would be impossible without definitions.

Thus, patients can and should be lumped together as having “ARF” for operative purposes. Such “lumping” of patients is done to facilitate the diagnostic process, clinical assessment, and, hopefully, therapeutic intervention. Once this cognitive process is accepted as useful, then it becomes necessary to define what ARF actually is and when someone does or does not have ARF. After a definition is provided, it also becomes necessary to quantify and classify the entity that is created by such a definition for the same utilitarian principles of diagnostic and therapeutic usefulness.

In this article, these issues are discussed in detail with a particular focus on the critically ill patient.

Approaching the issue of definition

A logical approach to organ “failure” is to start by defining what an organ does. In the case of the kidney, the list is long; however, many of its functions are shared with other organs (eg, acid-base control with lung) or require complex neuro-hormonal interactions, which also involve other organs (renin-angiotensin-aldosterone or vitamin D-calcium-calcitonin-parathyroid hormone axis). Other functions, which are not shared, are not measured routinely (small peptide excretion, tubular metabolism, hormonal production) in the ICU.

Accordingly, the kidney may “fail” in several of these tasks (eg, erythropoietin release may fail before changes in glomerular filtration rate [GFR] are detected); however, the clinician may be unable to detect such failure because of lack of measurement or because of compensation by other organs. Thus, the intensivist is left with limited information to help him/her assess renal function in the critically ill patient.

Only two “functions” that are “unique” to the kidney are measured routinely and easily in the ICU: the excretion of water-soluble waste products of nitrogen metabolism (of which we routinely measure only urea and creatinine) and the production of urine. Thus, clinicians have focused on these two aspects of renal

function to help them define the presence of so-called “ARF.” To understand these surrogates of GFR, itself a surrogate of global renal failure, one needs to reflect on some important aspects of renal physiology.

Solute excretion and glomerular filtration rate

Solute excretion by the kidney involves water-soluble molecules and is the result of glomerular filtration. The GFR is a convenient and time-honored way of quantifying this function of the kidney; however, GFR varies dynamically and markedly as a function of normal physiology and disease. For example, subjects who are on a vegetarian diet may have a GFR of 45 mL/min to 50 mL/min, whereas subjects who have a large intake of animal protein may have a GFR of 140 mL/min to 150 mL/min, both with the same normal nephron mass [9–12].

Baseline GFR can be incremented by efferent arteriolar vasoconstriction, afferent arteriolar vasodilatation, or both. Angiotensin-converting enzyme inhibitors induce the opposite effect and reduce filtration fraction and GFR by inducing greater efferent arteriolar vasodilatation. It is not clear what the maximum GFR value can be but it can be approached with an acute animal protein or amino acid load. The concept of a baseline and maximal GFR in humans has been defined as the “renal functional reserve”. Fig. 1 displays a series of examples that describe the GFR/functional nephron mass domain graph.

For the purposes of this illustration, GFR can be considered to be a continuous function, which is maximal in subjects who have 100% nephron mass, absent in anephric patients, and 50% in subjects who have undergone a unilateral nephrectomy.

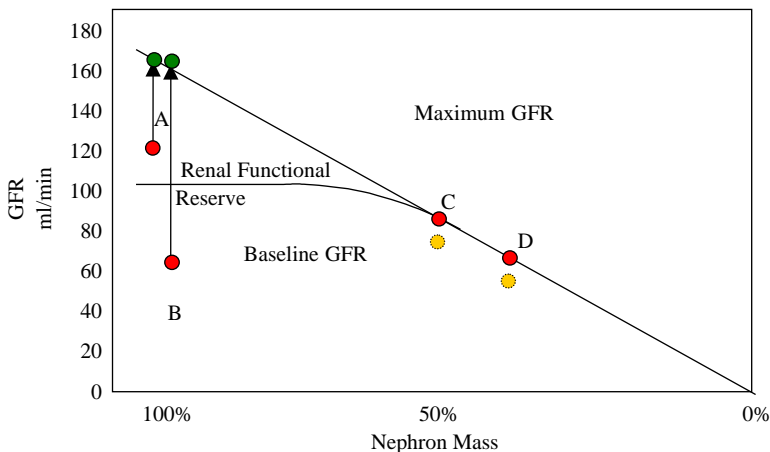


Fig. 1. Diagram illustrating the concepts of renal functional reserve and the limitations of creatinine measurements to assess the dynamic aspects of GFR.

Patients A and B have the same nephron mass but different baseline GFRs owing to different basal protein intakes levels. Subject A has a GFR of 120 mL/min that can be stimulated to 170 mL/min [9–12]. Patient B is a vegetarian and has a baseline GFR of 65 mL/min that also can be stimulated to 170 mL/min. In other words, the renal functional reserve in these two patients is different because they are using their GFR capacity at a different level.

Patient C has undergone a unilateral nephrectomy. His baseline GFR corresponds to his maximal GFR under unrestricted dietary conditions. If a moderate protein restriction is applied to his diet, his baseline GFR may decrease and some degree of renal functional reserve becomes evident. The same concept is true for patient D; however, to restore some functional reserve, severe protein restriction is needed.

Thus, baseline GFR does not correspond necessarily with the extent of functioning nephron mass; even careful measurements of GFR will not allow us to define renal function without placing it in the context of maximal capacity. Serial measurements of GFR may be impractical but surrogates are readily available. Because urea or blood urea nitrogen (BUN) is such a nonspecific indicator of renal function, it is a poor surrogate for GFR and will not be discussed further.

Serum creatinine, its physiology, and defining acute renal failure

Creatinine is more specific at assessing renal function than BUN but it corresponds only loosely to GFR [13–15]. For example, a serum creatinine (S_{Cr}) of 1.5 mg/dL (133 μ mol/L), at steady-state, corresponds to a GFR of approximately 36 mL/min in an 80-year-old white woman, but approximately 77 mL/min in a 20-year-old black man.

Similarly, an S_{Cr} of 3.0 mg/dL (265 μ mol/L) in a patient who is suspected of having renal impairment would reflect a GFR of 16 mL/min in the elderly woman but 35 mL/min in the young man. In both cases, a doubling of S_{Cr} corresponds 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 $1/Cr$. Thus, although every classification of ARF in the literature relies on some threshold value for S_{Cr} concentration, no single creatinine value corresponds to a given GFR across all patients. Therefore, the change in creatinine is clinically and physiologically useful in determining the presence of ARF.

Like all estimates of GFR (including creatinine clearance), the S_{Cr} is not an accurate reflection of GFR in the nonsteady state condition of ARF. During the evolution of dysfunction, S_{Cr} will underestimate the degree of dysfunction. Nonetheless, in populations, the degree to which S_{Cr} changes from baseline (and perhaps the rate of change as well) reflects the change in GFR. S_{Cr} is measured easily and it is reasonably specific for renal function. Thus, S_{Cr} is a reasonable approximation of GFR in most patients who have normal renal function [13–15].

Creatinine is formed from nonenzymatic dehydration of creatine in the liver; 98% of the creatine pool is in muscle. Critically ill patients may have abnormalities in liver function and markedly decreased muscle mass. Additional factors that influence creatinine production include conditions of increased production (eg, trauma, fever, immobilization) and conditions of decreased production (eg, liver disease, decreased muscle mass, aging). In addition, tubular reabsorption (“back-leak”) may occur in conditions that are associated with decreased urine flow rate. Finally, the volume of distribution (V_D) for creatinine (total body water) influences S_{Cr} and may be increased dramatically in critically ill patients; in the short term, its concentration in plasma can be altered dramatically by rapid plasma volume expansion.

Creatinine clearance

After GFR has reached a steady state it can be quantified by measuring a 24-hour creatinine clearance. The accuracy of creatinine clearance (even when collection is complete) is limited because as GFR decreases, creatinine secretion increases; therefore, the increase in S_{Cr} is less [15].

Accordingly, creatinine excretion is much greater than the filtered load which causes overestimation of the GFR [13–15]. Therefore, creatinine clearance represents the upper limit of true GFR. A more accurate determination of GFR requires measurement of the clearance of insulin or radio-labeled compounds [16]. These tests are not routinely available; however, for clinical purposes, determining the exact GFR rarely is necessary. Instead, it is important to determine whether renal function is stable or getting worse or better. This usually can be determined by monitoring S_{Cr} alone.

Other markers of renal failure

Urine output

Urine output is the commonly measured parameter of renal function in the ICU and is more sensitive to changes in renal hemodynamics than biochemical markers of solute clearance; however, it is far less specific except when severely reduced or absent. Severe ARF can exist despite normal urine output (ie, nonoliguric ARF) but changes in urine output often occur long before biochemical changes are apparent. Because nonoliguric ARF has a lower mortality rate than oliguric ARF, urine output is used to differentiate ARF conditions. Classically, oliguria is defined (approximately) as urine output of less than 5mL/kg/d or 0.5 mL/kg/h; however, no study exists to diagnose when oliguria is a true early marker of developing renal failure.

Another marker of potential importance is cystatin C (cysC). CysC is a cysteine proteinase inhibitor of low molecular weight that is produced constantly

by nucleated cells (apparently independently of pathologic states) and is excreted by the glomerulus, and thus, closely reflects GFR. Therefore, *cysC* may be a better marker of GFR than creatinine [17]. Little information exists on the usefulness of *cysC* in ARF. A recent pilot study suggested that it might be superior to S_{Cr} and the modification of diet in renal disease (MDRD) equation in the detection of ARF [18].

Defining acute renal failure when baseline renal function is unknown

In some patients, premorbid renal function is unknown; this makes it more difficult to know the meaning of a given S_{Cr} concentration. One option is to calculate a theoretic baseline S_{Cr} value for a given patient assuming a normal GFR of approximately 95 mL/min ± 20 mL/min in women and 120 mL/min ± 25 mL/min in men. A normal GFR of approximately 75 mL/min/1.73 m² to 100 mL/min/1.73 m² can be assumed by normalizing the GFR to body surface area; thus, a change from baseline can be estimated for a given patient. The simplified MDRD formula provides a robust estimate of GFR relative to S_{Cr} based on age, race, and sex [19,20]. This estimate can 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 (ie, 75 mL/min/1.73m²). The MDRD formula is used to estimate the baseline only when it is not known. For example, a 50-year-old black woman would be expected to have a baseline creatinine of 1.0 mg/dL (88 μmol/L).

Defining acute renal failure in the setting of known renal dysfunction

If the patient has pre-existing renal disease, the baseline GFR and S_{Cr} will be different from those that are predicted by the MDRD equation. Also, the relative

Table 1
Estimated baseline creatinine

Age (years)	Black men (mg/dL μmol/L)	White men (mg/dL μmol/L)	Black women (mg/dL μmol/L)	White women (mg/dL μmol/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/1.73 m²) = 186 × (S_{Cr})^{-1.154} × (Age)^{-0.203} × (0.742 if female) × (1.210 if African American) = exponent (exp)(5.228 – 1.154 × ln(S_{Cr}) – 0.203 × ln(Age) – (0.299 if female) + (0.192 if African American)).

decrease in renal function that is required to reach a given level of S_{Cr} will be less than that of a patient who does not have pre-existing disease. For example, a patient who has a S_{Cr} of 1 mg/dL (88 μ mol/L) will have a steady-state S_{Cr} of 3 mg/dL (229 μ mol/L) when 75% of GFR is lost. By contrast, when only 50% of GFR is lost in a patient who is matched perfectly for age, race, and sex and who has a baseline S_{Cr} of 2.5 mg/dL (221 μ mol/L), the S_{Cr} will be 5 mg/dL (442 μ mol/L).

These S_{Cr} change criteria fail to convey accurately the degree of loss of renal function and the severity of injury. Thus, separate criteria should be used for the diagnosis of ARF that is superimposed on chronic renal disease. One possible approach is to use a relative change in S_{Cr} (eg, three-fold) as the primary criterion for ARF, with an absolute cut-off (eg, 4 mg/dL or \sim 350 μ mol/L) as a secondary criterion, when baseline S_{Cr} is abnormal. For example, an acute increase in S_{Cr} (of at least 0.5 mg/dL or 44 μ mol/L) to more than 4 mg/dL (350 μ mol/L) will identify most patients who have ARF when their baseline S_{Cr} is abnormal.

Testing a definition of acute renal failure

The ultimate value of a definition for ARF is determined by its usefulness. A classification scheme for ARF should be sensitive, specific and predictive of relevant clinical outcomes, such as mortality, use of dialysis, and length of hospital stay. These are testable hypotheses, despite the lack of renal specificity for such end points.

It also is understood that therapy can influence the primary criteria for the diagnosis of ARF. For example, volume status will influence urine output, and even to some degree, by altering V_D and S_{Cr} . Large-dosage diuretics may be used to force a urine output when it otherwise would fall into a category that is consistent with a diagnosis of ARF. Ultimately, these cases generally fall into defined criteria; however, they may cause confusion in the early acute situation. In the end, for operative purposes, it must be assumed that patients are hydrated adequately; not treated with diuretics, except in the case of volume overload; and treated with renal replacement therapy when clinically indicated. Although this may not always be true for individuals, it should be broadly true for populations.

Thus, there are no perfect ways to measure renal function. Even precise measures of GFR will fail to distinguish mild to moderate functional loss from normal function. Renal function reserve is important but cumbersome to measure. Surrogate measures, such as S_{Cr} —although available routinely at the bedside—show limited correlation to GFR, especially in the setting of critical illness. Nonetheless, the lessons of physiology can be used to guide the development of definitions for ARF. All of the above physiologic considerations have played an important role in guiding the members of the Acute Dialysis Quality Initiative (ADQI) [21] in the formulation of a consensus set of criteria to define ARF (www.ADQI.net).

Why develop a consensus definition for acute renal failure?

A consensus definition seems to be possible and desirable, despite the limitations that were outlined above and the lack of validated ways of selecting cut-off points of S_{Cr} for defining when a patient does or does not have ARF. This difficulty in finding a rational way of picking such a cut-off point, given the nonlinear relationship between S_{Cr} and GFR, does not seem to have inhibited investigators from making choices.

We now have too many essentially arbitrary biochemical “cut-off values” for the definition of ARF, all of which have been used in clinical studies. This point was highlighted in a recent review of 28 studies of postoperative ARF; each one used a different definition [22]. The way forward must surely be the development of consensus criteria for the definition of ARF [23].

The case for and against consensus criteria

The strongest case against developing consensus criteria for ARF is that we have no scientific basis for them. Urine output is affected by fluid loading and by the use and dose of diuretics. The plasma urea level is modulated by many nonrenal factors. The S_{Cr} is modulated by muscle bulk, gender, age and body size. Typically, the “normal” value for S_{Cr} is not adjusted automatically for age, body size, and ethnicity, and frequently, is loosely and similarly applied to a 100-kg young man and a 45-kg octogenarian woman. Other factors, such as rhabdomyolysis and analyte dilution that is due to fluid resuscitation, can alter creatinine values markedly within minutes in the absence of any changes in GFR. Further, the frequency of biochemical measurements can affect the recorded peak value. How do we choose the value by which we define the presence or absence of ARF? Should it be a creatinine value of greater than $150\mu\text{mol/L}$ [4], greater than $177\mu\text{mol/L}$ [5], or greater than $310\mu\text{mol/L}$ [6]? If so, why? Why not some other number? The relationship between such values and outcome is unknown, so why should we choose one instead of another? Furthermore, it is absurd to argue that if the patient’s creatinine peaks at $309\mu\text{mol/L}$, he/she does not have ARF; however, if it reaches $311\mu\text{mol/L}$, he/she does have ARF.

These are powerful and logical arguments, but they do not hold sway in the real world. If they did, there would be a deafening silence on the subject in the literature. The opposite is true; there is a cacophony of views. This is because human beings are practical. To use a metaphor, nobody can define what justice is; however, all countries have laws. Laws are operative consensus definitions of justice in particular areas of human activity. They are terribly flawed but are much better than the alternative—lawlessness. The same is true for ARF; any consensus definition will be terribly flawed, but the alternative is much worse. The power of operative definitions in critical care medicine is highlighted clearly by the enormous impact that consensus criteria for sepsis and ARDS have made on randomized, clinical research and patient care. ARF lags at least 10 years

behind. These observations constitute the strongest case in favor of developing working consensus criteria [23].

The lessons from acute respiratory distress syndrome

The consensus criteria for acute lung injury (ALI) and ARDS are simplistic and flawed [8]; however, they are extremely valuable. How can we argue both points simultaneously? Easily.

The ALI/ARDS criteria have created two tiers of lung injury. Is there evidence that they are different in outcome? Not yet. The division is simplistic; however, it is useful to have a way of recruiting patients who have early lung injury into trials. These are the patients who are most likely to respond to novel therapies because their disease may not be so advanced. The ALI/ARDS criteria use the PaO₂/FiO₂ ratio. They ignore positive end-expiratory pressure (PEEP), even though it might affect such a ratio significantly. Yet, this is still acceptable because the amount of PEEP may shift some patients from ALI to ARDS but really will not change the kind of population that is under study by a significant amount. We study populations in randomized, controlled studies, not individuals. It is possible to go on *ad nauseam* about each and every aspect (eg, need to know oncotic pressure, frequency of measurements, effect of medications on pulmonary artery occlusion pressure [PAOP], effect of PEEP on PAOP) but that is unnecessary. The consensus criteria need not be “right.” They just need to be simple, clear, easily defined, and routinely measured in all ICUs. They should also be “research friendly.”

In response to all of these issues, the ADQI group considered that, in the end, most definitions of ARF have common elements, including the use of S_{Crit}, and often, urine output. It also considered that the following features would be important in any consensus definition of ARF: (1) it should consider change from baseline; (2) it should include classifications for acute or chronic renal disease; (3) it should be easy to use and clinically applicable across different centers; and (4) it should consider sensitivity and specificity because of different populations and research questions. A classification system that includes mild (or early) and severe (or late) cases will include varying degrees of sensitivity and specificity; it is more sensitive at one end and more specific at the other. Accordingly, the ADQI group advocated a multi-level classification system in which a wide range of disease spectra can be included.

The resulting classification scheme, based on the above considerations, is shown in Fig. 2. In addition to the three levels of renal dysfunction, the risk injury failure loss end stage criteria 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 the need for renal replacement therapy for longer than 4 weeks, whereas ESRD is defined by the need for dialysis for longer than 3 months. This consensus definition of ARF, therefore, defines its presence

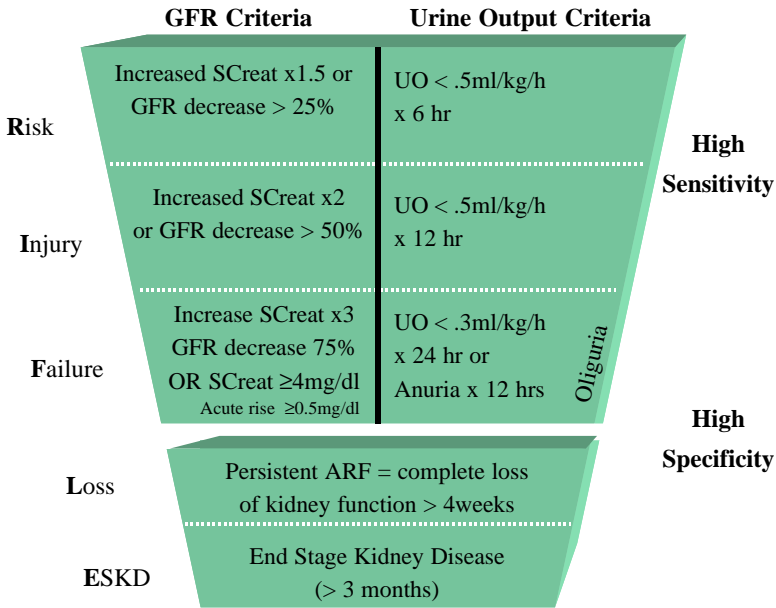


Fig. 2. Illustration summarizing the salient aspects of the risk injury failure loss end stage consensus definition of acute renal failure. SCreat, serum creatinine; UO, urine output.

and quantifies the degree of dysfunction in a way that is simple, easily reproduced everywhere, and, it is hoped, likely to reflect different prognostic categories.

Finally, many patients may present with acute renal dysfunction without any baseline measure of renal function. The simplified MDRD formula provides a robust estimate of GFR relative to S_{Cr} that is based on age, race, and sex. The ADQI consensus definition was published recently [24] and is being tested in a variety of settings.

Classifying acute renal failure

Clearly, if we cannot define ARF, we can hardly define ways to separate different types of ARF objectively. Once we have defined ARF, however, the questions come thick and fast:

- When is ARF prerenal (functional)?
- When is it renal (structural)?
- If prerenal ARF (functional loss with no structural damage) causes acute tubular necrosis (ATN) (functional loss with structural damage), where does prerenal ARF end and where does ATN begin? Who decides? How?

- What is ATN? Does a patient have ATN if one tubular cell is necrotic on biopsy? Or do we need 10? 100? 1000?
- Given that a biopsy sample approximately only 1/100,000th of the kidney, how can we make comments about structural changes being present or absent?
- How do we know that a given patient has ATN (however defined) when ATN is a histologic diagnosis and we essentially never biopsy patients in western ICUs?
- What is the relationship between histology (which we never have) and function? How many patients that clinicians agree, on whatever clinical and biochemical criteria, have so-called “prerenal azotemia” actually have tubular necrosis on biopsy?
- Is ATN the actual histopathologic substrate of septic ARF in modern ICUs given that no biopsies have ever been done in such patients and the cardiac output is high? Or is it acute tubular apoptosis [25]?

One could go on with a hundred more questions for which we have limited and grossly inaccurate and inadequately tested answers; however, they would simply describe the gigantic research agenda that surrounds ARF in modern medicine.

For the ICU clinician, it might be instructive, useful, and amusing to note that time-honored tests (eg, presence of casts, decreased specific gravity, increased urinary sodium, increased fractional excretion of sodium, decreased urinary osmolarity) that are reproduced obsequiously in textbooks year after year after year may be no more than tautologies.

They were not “validated” against a gold standard or accepted definition, not blinded, not tested in patients in the ICU, obtained at variable and non-standardized “moments in time” in the course of the patient’s illness, performed almost 25 years ago, never repeated, and never shown to alter management or outcome [26]. What is their specificity or sensitivity in an ICU patient who is in septic shock, has received 2 L of colloid resuscitation in the operating theater, is now fluid overloaded, has a cardiac index of 4.5 L/m²/min, and is on a furosemide infusion and a norepinephrine infusion?

One still sees clinicians performing such tests, almost like a ritual and making pronouncements about likely outcome and histopathology. Such is the impact of history and mentorship in medicine.

Finally, in any given patient, even if all of the tests were just like in the textbooks, if the ultrasound clearly showed obstruction, or if the renal biopsy clearly showed crescentic glomerulonephritis (GN), it is naïve to think that only one mechanism is at work. Patients who have obstruction almost always have a degree of sepsis, often have hypotension, and may be underresuscitated. Patients who have crescentic GN often are systemically unwell, may have pulmonary disease with hypoxemia or volume depletion from inadequate oral intake or hypotension from volume depletion or the vasodilatory effect of inflammation, and so on.

Where do we go from here?

The above problems of classification do not have an easy solution. Much more research needs to be done before we can understand ARF and create more objective subdivisions like we have done for pneumonia. The ADQI group has started a process in this direction [24], which slowly might yield better and more objective criteria to guide our understanding, classification, and treatment of ARF. Only time will tell whether objective classification criteria for different types of ARF can be developed.

Despite the above major caveats, some practically useful approaches to the classification of ARF remain and relate to dividing its causes according to the probable source of renal injury—prerenal, renal (parenchymal), and postrenal.

Prerenal acute renal failure

So-called “prerenal ARF” is by far the most common cause of ARF in ICUs. The term typically indicates that the kidney malfunctions predominantly because of systemic factors, which, through variable mechanisms, decrease GFR. By far, the most common systemic factors that cause ARF in ICUs from developed countries are sepsis and septic shock. They account for close to 50% of all cases. Other common systemic causes of ARF include a low cardiac output state (myocardial infarction, tamponade, valvular disease), cardiac surgery, major vascular surgery, trauma with hypovolemia, any cause of shock (anaphylactic, hemorrhagic, hypovolemic), hemodynamic instability in association with surgery, liver failure, increased intra-abdominal pressure, and rhabdomyolysis. The mechanisms by which these events induce ARF are variable according to the causative trigger and are poorly understood, and are likely to be complex and to involve multiple pathways of renal injury.

If the systemic cause of prerenal ARF is removed rapidly or corrected, renal function usually improves and, over a period time (days), returns to near normal levels; however, if intervention is delayed or unsuccessful, renal injury becomes established, dialytic therapy may become necessary, and, if the patient survives, several days or weeks are needed for recovery. Clinicians, however, also loosely use terms, such as “prerenal azotemia” or “prerenal ARF” to indicate that the cause or trigger of ARF is outside the renal parenchyma and that a given patient has “functional” loss of GFR (no structural cell injury) as opposed to “structural” loss of GFR. Such suspected structural injury to the kidney typically is labeled acute tubular necrosis (ATN).

It is likely that this clinical subdivision does not reflect a true separation of pathophysiologic states, which are much more likely to lead to a continuum of renal injury. Furthermore, no biopsy studies of ARF in patients who were treated in the ICU have been conducted to demonstrate that so-called “ATN” is the histopathologic substrate of prolonged renal dysfunction.

Parenchymal renal failure

The term “parenchymal renal failure” is used to define a syndrome in which the principal source of damage is within the kidney and typical structural changes can be seen on microscopy. Disorders that affect the glomerulus or the tubule can be responsible. Among these, nephrotoxins are particularly important, especially in hospitalized patients. Many cases of drug-induced ARF rapidly improve upon removal of the offending agent. Accordingly, a careful history of drug administration is mandatory in all patients who have ARF. In some cases of parenchymal ARF, a correct working diagnosis can be obtained from history, physical examination, and radiologic and laboratory investigations. In such patients, one can proceed to a therapeutic trial without the need to resort to renal biopsy; however, before aggressive immunosuppressive therapy, renal biopsy is recommended to allow histologic confirmation of the etiology of ARF. Renal biopsy in ventilated patients under ultrasound guidance does not carry additional risks compared with standard conditions.

In this context, it is useful to note that more than one third of patients who develop ARF have chronic renal dysfunction with chronic parenchymal changes that are due to factors, such as age-related changes, long-standing hypertension, diabetes, or atheromatous disease of the renal vessels. They may have an increased premorbid S_{Cr} ; however, this is not always the case. Often, what may seem to the clinician to be a trivial insult that does not explain fully the onset of ARF in a normal patient, is sufficient to unmask the lack of renal functional reserve in another.

Postrenal acute renal failure

Obstruction to urine outflow causes so-called “postrenal renal failure,” which is the most common cause of functional renal impairment in the community (nonhospitalized patients) and is secondary to prostatic hypertrophy. Typical causes of obstructive ARF include bladder neck obstruction from an enlarged prostate, ureteric obstruction from pelvic tumors or retroperitoneal fibrosis, papillary necrosis, or large calculi. The clinical presentation of obstruction may be acute or acute-on-chronic in patients who have long-standing renal calculi. It may not always be associated with oliguria. If obstruction is suspected, ultrasonography can be performed easily at the bedside. Not all cases of acute obstruction have an abnormal ultrasound and, in many cases, obstruction occurs in conjunction with other renal insults (eg, staghorn calculi, severe sepsis of renal origin) such that the cause of renal dysfunction is a combination of factors.

Summary

There is now a consensus definition of ARF that also quantifies the degree of dysfunction. This definition represents a major step forward in our ability to

conduct studies of this condition. Although the condition is common in the ICU, we understand little about its pathogenesis and histopathology. Accordingly, accurate classification is difficult. A practical approach that seeks to identify extrarenal causes, parenchymal disease, or obstruction remains clinically useful. Much research still needs to be done because our understanding of what happens to the kidney in ARF in critically ill patients is poor.

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