Diagnostic Criteria for Acute Kidney Injury

Present and Future

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KEYWORDS

• Acute kidney injury • Renal-replacement therapy • Dialysis • Clinical trials
• Biomarkers • Renal recovery • Mortality

KEY POINTS

- The criteria for acute kidney are based on changes in serum creatinine and urine output. Standardized criteria, such as KDIGO criteria, allow for uniform implementation of guidelines and reliable estimates of incidence and outcomes.
- However, acute kidney injury (AKI) remains a clinical diagnosis and clinical judgment is necessary to apply diagnostic criteria and to evaluate the changing clinical status of the patient.
- Baseline renal function is also based on clinical judgment and is best determined by prior serum creatinine measurements; when none are available estimating equations can be used with caution.
- Both serum creatinine and urine output provide independent and complementary information on renal function. Novel biomarkers can provide information on kidney damage and the latest markers can assess kidney stress.
- In the near future, function, damage, and stress may all be used to define AKI.

INTRODUCTION

Acute kidney injury (AKI) is a clinical diagnosis. Already in ancient times it was noted that the failure to pass urine was lethal if untreated and might be caused by either "an

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empty bladder" or an obstruction. Indeed, urinary catheters were used as early as 3000 BC. It was Galen who first established the kidneys as the source of urine and as organs that "filtered the blood."[1] Before this, it was generally believed that urine was made in the bladder from food and drink. Progress in the clinical assessment of renal function was quite limited from the time of Galen until the eighteenth century when urea was discovered. However, it would be more than a century later before increases in blood urea and serum creatinine would be used to quantify azotemia ("azote" is a very old name for nitrogen). Azotemia results from reductions in glomerular filtration rate (GFR) and together with oliguria ("small" urine) or anuria (no urine) form the cardinal features of kidney failure.

However, azotemia and oliguria represent not only disease but a normal response of the kidney to extracellular volume depletion or a decreased renal blood flow. Conversely, a "normal" urine output and GFR in the face of volume depletion could only be viewed as renal dysfunction. Thus, changes in urine output and GFR are neither necessary nor sufficient for the diagnosis of renal pathology.[2] Still, they serve as the backbone for the existing diagnostic criteria.[3]

CRITERIA FOR ACUTE KIDNEY INJURY

Little progress was made in the understanding of AKI throughout the first two millennia AD. Although the term nephritis dates back to the sixteenth century it was not really until the late nineteenth century that Bright described renal failure (Bright disease) and included acute and chronic forms.[4] A century later Bywaters and Beall described "acute renal failure" following crush injury.[5] Throughout the remainder of the twentieth century, however, acute renal failure had no widely accepted biochemical definition. As many as 60 different definitions littered the field. In 2004 the RIFLE criteria (Risk Injury Failure Loss End-stage renal disease) were put forth by the Acute Dialysis Quality Initiative.[6] RIFLE included either change in serum creatinine or urine output as criteria recognizing that AKI could be nonoliguric but at the same time creatinine may not increase as rapidly as urine output falls and it is therefore better to have both criteria available. It was not understood at the time, the degree to which urine output and creatinine criteria interact (discussed later in the section on creatinine and urine output). One shortcoming of the RIFLE criteria was its application in patients with preexisting chronic kidney disease (CKD). In patients with elevated baseline creatinines, the proportional changes required by RIFLE seemed excessive. For example, although a patient with a baseline creatinine of 1.0 mg/dL would fulfill criteria for AKI with an increase to 1.5, a patient with a baseline of 2.0 mg/dL would need to reach 3.0. Furthermore, the higher the baseline creatinine the longer the time required to reach a 50% increase. In essence it does not seem credible that a patient with a baseline of 2.6 mg/dL would need to increase to 3.9 and take 3 days to do it just to get to RIFLE-R. For this reason the AKI Network proposed a modification to RIFLE that would also classify AKI when only a small increase in creatinine (0.3 mg/dL or greater) is observed in a short period of time (48 hours or less).[7] Finally, to harmonize RIFLE, AKI Network, and pRIFLE (a modification for pediatrics), the Kidney Disease Improving Global Outcomes (KDIGO) proposed a unified version of these rules (**Table 1**).[3]

THE PURPOSE OF STANDARDIZED CRITERIA FOR ACUTE KIDNEY INJURY

If AKI is clinical diagnosis, why are standard criteria desirable? The answer to this question comes in two parts. First, even though clinical judgment is required, a framework for the clinical diagnosis is needed. In general diagnoses are not based on pure

Table 1
Criteria and staging for acute kidney injury

Stage	Serum Creatinine	Urine Output
1	1.5–1.9 times baseline OR ≥0.3 mg/dL (>26.5 μmol/L) increase	<0.5 mL/kg/h for 6–12 h
2	2.0–2.9 times baseline	<0.5 mL/kg/h for ≥12 h
3	3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dL (353.6 μmol/L) OR Initiation of renal-replacement therapy OR In patients <18 y, decrease in eGFR to <35 mL/min per 1.73 m^2	<0.3 mL/kg/h for ≥24 h OR Anuria for ≥12 h

Minimum criteria for acute kidney injury include an increase in serum creatinine by ≥0.3 mg/dL (>26.5 μmol/L) observed within 48 hours; or an increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume less than 0.5 mL/kg/h for 6 hours.

speculation; clinicians consider a set of diagnostic features and use these to guide their judgment. These criteria are not "cook book" but they do serve as a frame of reference so that the average patient with the disease in question fulfills the criteria put forth. Second, standardized criteria for diagnosis of AKI serve multiple purposes (Fig. 1) and it is neither feasible nor desirable to have a clinical adjudication for all of these. For example, in large epidemiologic studies it is not practical to examine each patient. In these studies clinicians accept diagnostic constructs as long as

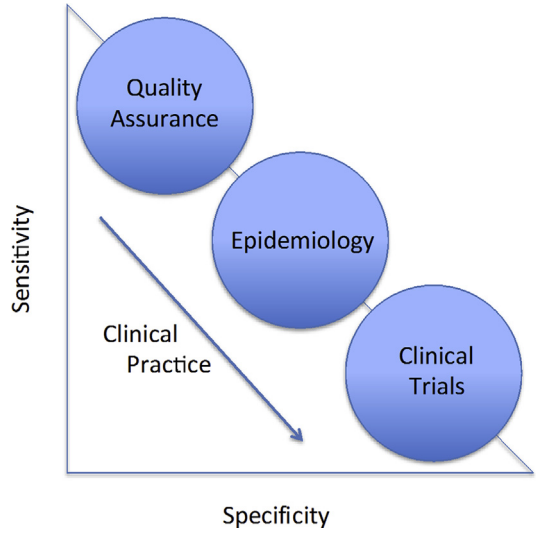

Fig. 1. Sensitivity/specificity tradeoffs for various applications of clinical definitions. For research and quality improvement, fixed thresholds are usually needed, whereas for clinical application diagnoses can be more flexible depending on the actions they elicit.

they achieve reasonable sensitivity and specificity for the disease in question. However, diagnostic criteria, just like a diagnostic test, have test characteristics and specific "cut points" are chosen to maximize sensitivity, specificity, or some degree of both. For quality improvement one might be interested in casting the widest possible net, maximizing sensitivity. If certain things can be done for all patients with "possible AKI," such as avoiding unnecessary nephrotoxic medications, clinicians would want to identify these patients. Conversely, for ascertaining outcomes in clinical trials clinicians tend to favor specificity over sensitivity.

For clinical use, the preference for maximizing sensitivity or specificity depends on the clinical actions intended to be taken. The decision to admit a patient with chest pain to the hospital is best supported by tests that are highly sensitive because the chief concern is about missing a myocardial infarction. Giving that same patient thrombolytic therapy calls for higher specificity. Importantly, however, there is another feature that exists in clinical practice that clinical studies or quality improvement projects usual do not enjoy: time. For clinical studies and for most quality improvement projects, a diagnosis is fixed. A patient either has AKI or they do not. For clinical purposes there is the luxury of provisional diagnoses. As more information becomes available clinicians can and do change their diagnoses. Thus, it may be very appropriate to use a set of diagnostic criteria that are very sensitive for initial evaluation and to require greater specificity for final diagnosis. Over time one can include the patient's clinical course and response to therapy in the assessment (Fig. 2).

BASELINE RENAL FUNCTION

A reference serum creatinine is used to apply the diagnostic criteria shown in Table 1 and to stage patients. When determining the most suitable reference creatinine, the first consideration is the timing of the acute illness believed to be the cause of the AKI. For example, in a patient admitted on Friday with unstable angina who then

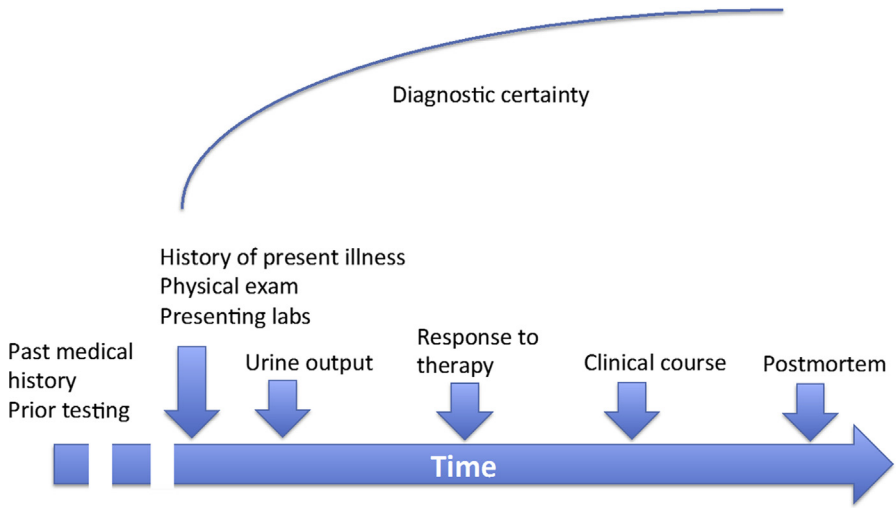

Fig. 2. Diagnostic certainty. Diagnostic certainty is usually low at the outset of a clinical evaluation but improves with time as more information and diagnostic testing results become available.

has three daily serum creatinine measures, all essentially the same, before undergoing cardiac surgery on Monday, there is a need to have a historical baseline to evaluate the serum creatinine on postoperative Day 1. In this example, the preoperative serum creatinine is a suitable reference. By contrast, consider the patient who presents with a 2-day history of fever and cough and an elevated creatinine. Let us say the creatinine continues to increase after admission. If there is an increase of at least 0.3 mg/dL over a period of 48 hours or less (any 48-hour period not only the first 48 hours), the patient meets criteria for AKI. However, assume that the patient's creatinine reaches 2.2 mg/dL. What stage is the AKI? Staging is important because the stage correlates with clinical outcomes, such as receipt of renal-replacement therapy (RRT) and mortality.[8–10] A serum creatinine might mean stage 3 AKI, for example, in a patient with a reference creatinine of 0.7 mg/dL, or it could be stage 1 in a patient with a reference creatinine of 1.4 mg/dL. Thus, the reference is extremely important. The best reference creatinine for a patient presenting with AKI is not the admission value because it is likely already abnormal (unless the patient presented only with oliguria). Therefore a baseline creatinine obtained before the current illness but still recent is ideal. Unfortunately, patients rarely have the intuition to get their creatinine checked just before developing AKI. As such one is left with deciding between various less ideal baseline values or no value at all. Various studies have shown that even an old baseline (up to 1 year prior) is better than nothing.[11,12] When multiple baseline values are available, particularly when no clear pattern is discernable, a median is probably the most representative.[11] However, even here, judgment can be important. In a patient whose last six serum creatinines (one each month for the last 6 months) have been slowly rising, the most recent creatinine is probably the best reference. Similarly, some prior baselines might have been in the setting of prior episodes of AKI and it might be possible to select a more representative value out of the series of prior values if the history is known. The best reference creatinine is the one that the clinician believes is most representative of the patient's premorbid renal function.

One of the most difficult clinical problems is the assessment of a patient with abnormal renal function and an uncertain past medical history. The problem is not dissimilar to the cardiac patient with an abnormal but nondiagnostic electrocardiogram (eg, nonspecific T-wave abnormalities) and no prior electrocardiogram on record for comparison. Importantly, a patient presenting with previously unknown kidney disease might have CKD, AKI, or both. In any case, the patient does have "something" and it is incumbent on the heath care system to determine what and to manage it appropriately. Ancillary tests, such as renal ultrasound, can be helpful to determine kidney size and examination of the urine can provide other clues. For example, a 40-year-old white woman presenting with an acute illness and a serum creatinine of 2.0 mg/dL who has normal kidney size on ultrasound and unremarkable urine sediment has AKI until proved otherwise. Conversely, a similar patient with small kidneys and albuminuria has some element of CKD; however, she may well have AKI on CKD. Obviously clinical judgment is required in these cases and what might serve as a provisional diagnosis might well change over time.[3]

If a patient presents with a clinical history compatible with AKI and an abnormal creatinine with no evidence of CKD by history or examination, the best reference creatinine may be a derived one. Because a normal creatinine may vary by more than two-fold based on demographics (especially age, race, and sex) it is not appropriate to use a single normal value for all patients. Instead, the patient's demographics can be fitted into the estimated GFR equations, such as the Modification of Diet in Renal Diseases equation using a GFR of 75 mL/min/1.73 m^2 (**Table 2**).[6] This approach has been validated in multiple studies; one shows that it tends to overestimate the

Table 2
Estimated baseline creatinine

Age (y)	Black Men (mg/dL [μmol/L])	Other Men (mg/dL [μmol/L])	Black Women (mg/dL [μmol/L])	Other Women (mg/dL [μmol/L])
20–24	1.5 (133)	1.0 (88)	1.3 (115)	1.2 (106)
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 glomerular filtration rate = 75 (mL/min per 1.73 m^2) = 186 × (serum creatinine) − 1.154 × (age) − 0.203 × (0.742 if female) × (1.210 if black) = exp(5.228 − 1.154 × ln [serum creatinine]) − 0.203 × ln(age) − (0.299 if female) + (0.192 if black).

From Bellomo R, Ronco C, Kellum JA, et al, Acute Dialysis Quality Initiative Workgroup. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8:R207; with permission.

severity of AKI,[11] whereas another shows just the opposite.[12] Differences are likely the result of the frequency of undetected CKD in the population.

SERUM CREATININE AND URINE OUTPUT

Older systems to classify AKI and non–renal-specific organ failure scores, such as the Sepsis-related Organ Failure Assessment,[13] use fixed thresholds for serum creatinine (eg, 2.0 mg/dL) to classify renal "organ failure." This approach is not appropriate for AKI for two reasons. First, normal creatinine may vary by two-fold depending on age, race, and sex (see **Table 2**). Second, a fixed creatinine does not distinguish between acute and chronic abnormalities. Thus, modern methods to quantify severity of AKI are based on relative azotemia, defined by an increase in serum creatinine, or oliguria defined by a decrease in urine output (see **Table 1**). However, patients manifesting both oliguria and azotemia and those in which these impairments are persistent are more likely to have worse disease and therefore worse outcomes.[14]

Recently, using a large heterogeneous series of patients cared for over an 8-year period, we examined the associations between AKI and short- and long-term outcomes as functions of serum creatinine and urine output criteria alone and in combination.[14] Our results demonstrated that despite relatively minor differences in baseline characteristics, patients meeting both serum creatinine and urine output criteria for AKI have dramatically worse outcomes compared with patients who manifest AKI solely or predominantly by one criterion. Indeed as seen in **Table 3**, hospital mortality was less than 18% and RRT was less than 3.5% for the 11,897 (37.1%) patients manifesting AKI by only one parameter. Meanwhile, mortality reached 51.1% and RRT 55.3% for the 2200 (6.9%) patients meeting stage 3 criteria by both serum creatinine and urine output. Even stage 3 criteria in one domain with stage 1 criteria in another was associated with greater than 30% hospital mortality and greater than 10% use of RRT.[14] These results establish the absolute necessity for urine output assessment for staging of AKI. They also seem to contrast with prior work by Ralib and colleagues[15] who found that the oliguria threshold of 0.5 mL/kg/h was not predictive of survival, whereas 0.3 mL/kg/h was. These authors did not examine the effects of serum creatinine and urine output together and their sample size was only 725

Table 3
Relationship between urine output and serum creatinine criteria and clinical outcomes

KDIGO Stage		Urine Output Only				
		No AKI	Stage 1	Stage 2	Stage 3	Total
Serum Creatinine Only	**No AKI**	8179	3158	5421	440	17,198
	Dead	4.3%	5.3%	7.9%	17.7%	5.9%
	RRT	0.0%	0.0%	0.1%	1.1%	0.1%
	Stage 1	1889	1262	3485	842	7478
	Dead	8.0%	11.3%	13.0%	32.1%	13.6%
	RRT	0.3%	0.7%	0.6%	10.9%	1.7%
	Stage 2	618	476	1533	831	3458
	Dead	11.3%	23.9%	21.5%	44.2%	25.5%
	RRT	1.0%	1.3%	1.7%	21.7%	6.3%
	Stage 3	371	321	1019	2200	3911
	Dead	11.6%	38.6%	28.0%	51.1%	40.3%
	RRT	3.2%	17.8%	14.2%	55.3%	36.6%
	Total	11,057	5217	11,458	4313	32,045
	Dead	5.6%	10.5%	13.0%	42.6%	14.0%
	RRT	0.3%	1.4%	1.7%	34.6%	5.6%

Shown are the number of patients, % hospital mortality, and % RRT for patients by maximum AKI criteria (urine output, serum creatinine, or both). Colors denote similar outcome patterns.

Data from Kellum JA, Sileanu FE, Murugan R, et al. Classifying AKI by urine output versus serum creatinine level. J Am Soc Nephrol 2015. [Epub ahead of print].

patients, limiting their statistical power. Other investigators have found urine output to be a sensitive and early marker for AKI and to be associated with adverse outcomes in critically ill patients.[16] Urine output is also affected by renal tubular function as evidenced by response to a "furosemide stress test."[17] Importantly, 1-year outcomes parallel hospital outcomes for the various combinations of serum creatinine and urine output criteria. Indeed the survival curves continue to separate for much of the year following an AKI event.[14]

In addition, isolated oliguria (no creatinine criteria present) is surprisingly frequent and seems to be associated with a long-term hazard. Stage 2 and 3 AKI by urine output criteria alone are associated with decreased 1-year survival. Several studies have emphasized the importance of fluid overload in terms of its effect on clinical outcomes[18–20] and on serum creatinine measurements.[21] It is likely that most patients with oliguria are volume overloaded and it is reasonable to deduce that this represents an adverse effect on survival. It is also conceivable that volume overload masks some degree of azotemia and thus profound oliguria is not just an early indicator of AKI but may be the only indicator.

It is also clear that AKI persistence has a substantial influence on outcome. For example, we found that 4 days at stage 3 AKI results in an approximately 30% rate of death or dialysis at 1 year, whereas it requires more than a week at stage 1 to incur the same hazard.[14] Similarly, Coca and colleagues[22] demonstrated that duration of AKI based on creatinine following surgery was independently associated with subsequent outcome. Thus, risk for death or dialysis following AKI is greatest for patients that meet both serum creatinine and urine output criteria and for those in whom the abnormalities persist longer. However, even a brief episode of isolated oliguria without subsequent azotemia seems to be associated with decreased 1-year survival.

Apart from clinical use, trials of diagnostics and therapeutics for AKI are challenging for several reasons.[23–25] The selection of short-term AKI end points requires an

understanding of the relationship between AKI severity and duration and long-term outcomes. In the critically ill, AKI is very common; upward of 75% of patients manifest the syndrome when defined by the full KDIGO criteria.[26] However, spontaneous resolution (or rapid response to treatment) occurs in some patients. Such patients may be less appropriate for enrollment in clinical trials of novel therapeutics. Similarly, for various clinical trial applications, it may be important to select end points that are more closely tied to clinical outcomes.

NOVEL BIOMARKERS

Over the last decade several novel biomarkers have been evaluated for their capacity to detect kidney damage and predict the development of AKI.[27] Most novel markers were developed for their capacity to detect damage and as such they can provide additional insight into AKI, complementary to functional tests, such as serum creatinine and urine output.[28] Note that the relationship between decreasing function and increasing damage is not as straightforward as might be assumed (**Fig. 3**). The characteristic pattern whereby damage proceeds loss of function (**Fig. 3**A) may be seen in some cases of AKI and affords an opportunity to detect "subclinical" AKI before function starts to fall. The problem is that other patterns also occur. For example, functional decline may start to occur alongside damage (**Fig. 3**B) or in some cases

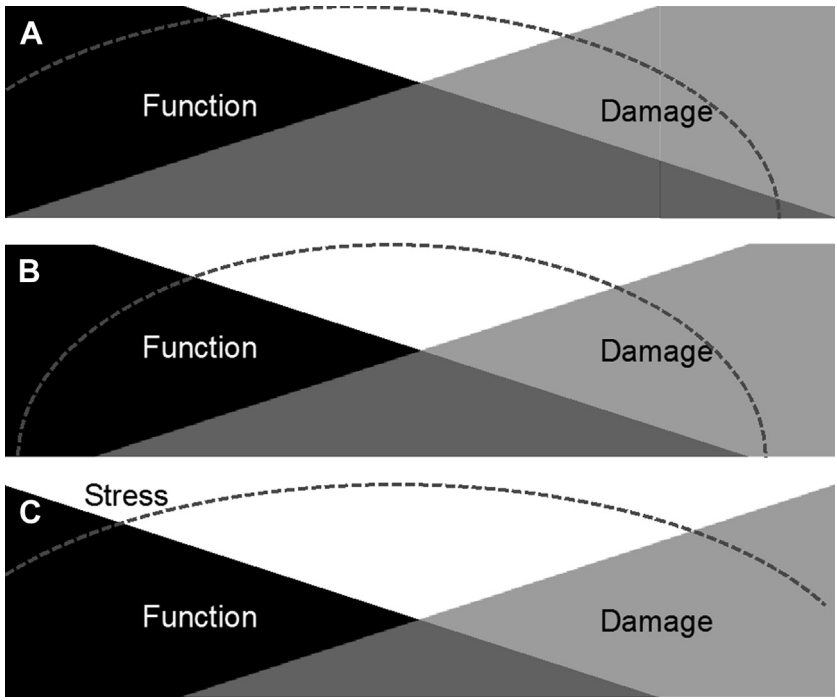

Fig. 3. Various clinical scenarios of acute kidney injury based in function, damage, and stress. The change in kidney function (eg, glomerular filtration rate) is shown in *black* and damage is shown in *gray*. (*A*) Classic case where damage increases and is followed by a decline in function only after some time (time shown on the x-axis). (*B, C*) Alternate scenarios where function may change coincidental to or even before damage. The *dashed arc* represents renal cell stress.

function may start to decline even before damage (Fig. 3C). This makes damage markers hard to use to forecast AKI. However, other markers might actually measure "stress" occurring at the cellular level before damage or loss of function.

In 2013 we reported the results of a prospective, observational, international investigation (Sapphire study) of tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) in a heterogeneous group of critically ill patients.[29] In the validation phase we enrolled 744 adults without evidence of AKI. The primary end point was moderate-severe AKI (KDIGO stage 2–3)[3] within 12 hours of sample. The area under the receiver operating characteristic curve was 0.80 for [TIMP-2]•[IGFBP7] and these markers were significantly superior to all previously described markers of AKI ($P<.002$) including neutrophil gelatinase-associated lipocalin and kidney injury molecule-1, none of which achieved an area under the receiver operating characteristic curve greater than 0.72.[29] Two subsequent studies, Opal[30] and Topaz,[31] using the same end point in new cohorts confirmed the test characteristics for predicting AKI.

One of the reasons that [TIMP-2]•[IGFBP7] works for predicting AKI is that the markers relate to a cellular defense mechanism known as cell-cycle arrest. Each phase of the cell cycle has a specific function that is required for appropriate cell proliferation. Quiescent cells are normally in G_0. For cells to divide and begin the process of repair, they must enter and exit each phase of the cell cycle on schedule.[32–34] If the cell exits a phase too soon, or stays in a phase too long, the normal repair and recovery process can become maladaptive.[33] For instance, if epithelial cells remain arrested in G_1 or G_2, it favors a hypertrophic and fibrotic phenotype.[32,34] Conversely, exit from cell cycle in late G_1 leads to apoptosis.[35] Cyclins, cyclin-dependent kinases, and cyclin-dependent kinase inhibitors control each phase of the cell cycle.[33] The cell uses cell-cycle arrest as a protective mechanism to avoid cell-division when potentially damaged.[33,36] By initiating cell-cycle arrest, cells can thus avoid cell division during stress and injury, which is protective. However, if the cells do not reinitiate the cell-cycle and remain arrested at G_1 or G_2 (or possibly other phases of cell cycle), a fibrotic phenotype can ensue. By detecting cell-cycle arrest markers in the urine one may actually be detecting cell stress (depicted as the *dashed lines* in Fig. 3). This stress may or may not lead to damage and functional decline but it is the earliest possible point the process can be detected.

DIAGNOSTIC UNCERTAINTY AND FUTURE CLASSIFICATION SYSTEMS

No diagnostic criteria based on serum creatinine and urine output will ever be perfect. Some patients will meet these criteria and not have AKI. For example, a vegetarian with a baseline serum creatinine of 0.4 mg/dL who develops a creatinine of 0.6 after a large protein load may not have any kidney abnormality at all. A patient with short-term dehydration will experience oliguria and yet kidney injury is unlikely in absence of underlying disease or acute nephrotoxic exposures (eg, myoglobin, radiocontrast). A fairly common scenario in hospitalized patients is to see the serum creatinine fall sharply on the first hospital day. Then over the next 48 hours the creatinine rebounds to baseline value. The increase in serum creatinine over the 48 hours may reach 0.3 mg/dL and thus meet AKI criteria. AKI should not be diagnosed in a vacuum and clinical context should always be considered. Conversely, some patients with AKI may not fulfill the diagnostic criteria. A patient receiving large-volume resuscitation or massive transfusion may not achieve the changes in serum creatinine especially early on. Similarly, patients receiving large amounts of diuretics may maintain urine output at least for a time. Clinical judgment works both ways and should always be exercised

in evaluating a patient with suspected AKI. Importantly, some investigators have shown that small absolute changes in serum creatinine in patients with low baseline creatinine are less significant than larger changes in the same relative magnitude in patients with high baseline levels.[37] However, our study in critically ill patients found that in those with very low baseline creatinine AKI is nevertheless associated with adverse long-term outcomes.[14]

Novel biomarkers of kidney damage or stress add information to help clinicians arrive at prompt and accurate diagnoses. In the future clinicians may well talk not just about the stage of AKI but the associated biomarker pattern. Patients with the same stage of AKI but with very different urinary [TIMP-2]•[IGFBP7] levels have different long-term outcomes (death or dialysis).[38] In the future clinicians may well speak of "stress positive/damage negative" AKI the way they currently speak of non–ST elevation myocardial infarction or "BRCA1-positive breast cancer."[26,39]

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