42 Traditional and Novel Tools for Diagnosis of Acute Kidney Injury

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Case Presentation

A 58-year-old male with unknown past medical history was admitted to the intensive care unit after he had a witnessed seizure in a parking lot. When paramedics arrived, his blood pressure was 213/115 mmHg. He was unresponsive. CT scan of the head without IV contrast showed a large right parietal lobe hemorrhage with mild midline shift. Laboratory exam revealed a WBC count of 13.2×10^9/L, Hemoglobin 10.2 g/dL, Platelets $178{,}000 \times 10^6$/L. Serum creatinine was 1.8 mg/dL and blood urea nitrogen (BUN) 41 mg/dL. Baseline serum creatinine was unknown. BMI was 27.3. An indwelling urinary catheter was placed and yielded 50 cc of urine. He was intubated and treated with calcium channel blockers, anti-seizure medications and intravenous fluid resuscitation. Twelve hours after admission, he had produced 150 cc of urine, and his repeat labs showed a serum creatinine of 2.2 mg/dL and a BUN of 47 mg/dL. A renal ultrasound showed normal sized kidneys, with increase in echogenicity of the renal cortex compared to the liver parenchyma, but no hydronephrosis. Urinalysis and urine microscopy revealed 1+ protein, no blood or cellular casts.

Question What establishes the diagnosis of Acute Kidney Injury in this case?

Answer Increase in serum creatinine and oliguria.

Criteria for diagnosis of acute kidney injury (AKI) include a 1.5 fold increase in serum creatinine compared to baseline (within the prior 7 days), an absolute increase in serum creatinine (SCr) by 0.3 mg/dL (26.5 μmol/L) or more (within 48 h) or a decrease in urine output to less than 0.5 cc/Kg/h for 6–12 h. In this case, SCr was elevated on admission (1.8 mg/dL), but it was not clear whether this represented acute kidney injury or Chronic Kidney Disease (CKD). Low urine output through the indwelling urinary catheter initially and over the next few hours after admission was an important first clue to the diagnosis of AKI. Subsequent increase in SCr by ≥0.3 mg/dL (from 1.8 to 2.2 mg/dL) confirmed the diagnosis. When baseline creatinine is not known, both renal ultrasonography and urine sediment examination can provide useful clues on the acuity of kidney injury. In this case, the increase in renal cortex echogenicity and presence of mild proteinuria suggested the presence of some

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degree of chronic kidney dysfunction prior to admission. Therefore, this patient probably had acute kidney injury superimposed on CKD.

Principles of Management

Serum Creatinine and Urine Output

Despite having several limitations, changes in serum creatinine and urine output remain the backbone of diagnosis of acute kidney injury. In 2004, the RIFLE (Risk Injury Failure Loss End-stage renal disease) criteria were published [1], and included either change in serum creatinine (1.5 fold increase or more) or urine output (less than 0.5 mL/Kg/h for 6 h) as diagnostic criteria for AKI. Including both urine output and SCr in the definition of AKI increased the sensitivity of AKI diagnosis [2] but also recognized that AKI can be non-oliguric in 40–60 % of cases [3, 4]. Whether actual body weight or ideal body weight should be used to judge urine output is a subject of debate. Using actual body weight does increase the sensitivity of AKI diagnosis but will decrease specificity [5]. One shortcoming of the RIFLE classification was its inaccuracy in patients with preexisting CKD: a patient with a baseline SCr of 2.2 mg/dL would require an increase in SCr to 3.3 mg/dL in order to be at risk for AKI (RIFLE-R). For this reason, the AKI Network (AKIN) proposed a modification to RIFLE in 2007 that would also classify AKI when a small increase in creatinine (0.3 mg/dl or greater) is observed in a short period of time (48 h or less) [6]. The AKIN group indicated two important caveats: excluding urinary obstruction when urine output is the sole criteria used to define AKI, and application of diagnostic criteria only after volume status has been optimized [6]. In 2012, in an effort to harmonize RIFLE, AKIN and pRIFLE (a modification for pediatrics), Kidney Disease Improving Global Outcomes (KDIGO) proposed a unified version of these rules [7] (Table 42.1).

Blood Urea Nitrogen (BUN) is commonly used as a marker for AKI, despite being affected by many non-renal factors (protein intake, catabolic state, volume status etc.). The ratio of BUN to SCr, similarly to urine chemistry (fractional excretion of sodium and urea) and urine microscopy are useful tools for workup of AKI. Nonetheless, BUN, urine studies and kidney biopsy are rarely helpful in establishing the diagnosis of AKI in clinical practice.

Table 42.1 Definition of AKI per KDIGO guidelines

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 years, decrease in eGFR to <35 ml/min per 1.73 m²*	<0.3 ml/kg/h for ≥24 h OR Anuria for ≥12 h

Minimum criteria for Acute Kidney Injury include an Increase in SCr by ≥0.3 mg/dl (>26.5 μmol/l) observed within 48 h; or an Increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or Urine volume <0.5 ml/kg/h for 6 h

Despite the usefulness of RIFLE, AKIN and KDIGO criteria, clinical judgment remains a key component of AKI diagnosis. Diagnostic criteria provide a "frame of reference" for the clinician and are essential for large epidemiological studies and quality improvement projects. Nevertheless, those criteria do not take into account the patient's clinical course and response to therapy, which are often key to establishing or refuting the diagnosis of AKI.

Relationship Between Serum Creatinine and Urine Output

Several studies have demonstrated that oliguric AKI carries a worse prognosis compared to non-oliguric AKI. In other words, the presence of the two components of the definition of AKI is

Table 42.2 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	8,179	3,158	5,421	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	1,889	1,262	3,485	842	7,478
	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	1,533	831	3,458
	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	1,019	2,200	3,911
	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	5,217	11,458	4,313	32,045
	Dead	5.6%	10.5%	13.0%	42.6%	14.0%
	RRT	0.3%	1.4%	1.7%	34.6%	5.6%

Source: Kellum et al. [8]
Shown are the number of patients, % hospital mortality, and % renal replacement therapy (RRT) for patients by maximum acute kidney injury (AKI) criteria (UO, SC, or both). Colors denote similar outcome patterns

associated with worse outcomes [3, 8]. Isolated oliguria without subsequent increase in SCr still appears to be associated with a decrease in 1-year survival [8]. These results further validate the role of urine output in diagnosing and staging of AKI (Table 42.2).

Differentiating Between AKI and CKD

Renal ultrasonography is a useful tool for differentiation of CKD from AKI. When no information about baseline renal function is available, findings such as a small kidney size and an

increased echogenicity of the renal cortex compared to the liver parenchyma are good surrogates of chronic irreversible kidney disease [9]. The caveat here is that one cannot rule out superimposed AKI on CKD. Nevertheless, this remains useful information in diagnosing and classifying the severity of AKI. Oliguria and anuria are suggestive of AKI. Other parameters such as serum calcium and phosphorus, intact parathyroid hormone (iPTH) levels and hemoglobin are less helpful for differentiation between AKI and CKD. A group in Turkey suggested that setting the cutoff for intact PTH as 170 pg/mL or more could be a sensitive and specific way to distinguish CKD from AKI [10].

Clinical Use of Novel Biomarkers

There is currently a multitude of well-validated biomarkers that are able to predict, diagnose early, differentiate the severity and provide information on the course and outcomes of AKI. Despite reasonable performance, these biomarkers have yet to become established in clinical practice, despite their availability in certain regions of the world [11, 12]. The 10th Acute Dialysis Quality Initiative (ADQI) meeting in 2014 examined the discrepancy between the number of biomarkers that have been validated and their limited clinical application till this moment [13]. Ideally, "damage biomarkers" should be incorporated with "functional biomarkers" (such as urine output, SCr) to improve management of AKI. Incorporation of AKI biomarkers, or possibly a combination of those biomarkers, into clinical tools (such as the incorporation of cardiac troponins in the TIMI risk score for unstable angina and non-ST elevation myocardial infarction) that will guide management of AKI is the next step for those biomarkers. Cost is also a consideration, but the costs associated with current practice, which often includes testing such as urine chemistries, must also be considered. Finally, the costs associated with delayed recognition of AKI are also likely to be considerable. In late 2014, the US Food and Drug Administration announced the clearance of the first biomarker for AKI, urine [TIMP-2] [IGFBP7] (trade name NephroCheck™). The extent to which this test changes the existing paradigm is still unknown but the test characteristics are superior to previous markers [10].

Evidence Contour

Some questions surrounding the diagnosis of AKI remain subject for debate and for further investigation.

Determining Baseline Serum Creatinine

KDIGO guidelines emphasize the use of relative changes in SCr rather than absolute numbers for diagnosis and classification of AKI. Determining baseline SCr is therefore a necessary step to the diagnosis of AKI. It is not uncommon that information about baseline renal function is not available, especially upon initial evaluation of critically ill patients. The ADQI group suggested that an estimated glomerular filtration rate (eGFR) of 75 ml/mn/1.73 m^2 be assumed for such patients and calculating their baseline SCr using the Modification of Diet in Renal Disease (MDRD) formula [6]. The problem with this method is that CKD is one of the most important risk factors for AKI [14], and assuming that patients with AKI have a near-normal baseline eGFR will under-estimate their baseline SCr and therefore over-estimate the incidence of AKI [15]. Using this method in the case example would have resulted in overestimation of the severity of AKI by assuming a normal eGFR at baseline. Thus, this method should be avoided in patients with a suspicion of CKD. Conversely, using the minimum inpatient SCr or the admission SCr tends to underdiagnose AKI and is also suboptimal [15]. Multiple imputation is a commonly used method in statistical analyses that uses known patient characteristics to estimate

missing data points. This method has shown promise in its ability to determine baseline SCr in a more accurate way [16], but is not widely used in clinical practice to this date. Currently the best method will depend on the patient in question and require clinical judgment.

Imaging Techniques for Diagnosis of AKI

Several studies have examined the utility of resistive indices (RI) through renal Doppler ultrasonography in diagnosing or predicting AKI prior to alteration of functional markers such as urine output and SCr [17–19]. Unfortunately, resistive indices are affected by a wide variety of factors [20, 21], which limits their specificity and usefulness in the clinical setting. Assessing kidney function or GFR through imaging is also an appealing idea, as information about the structure, perfusion and differential function of both kidneys may also be obtained. Functional magnetic resonance (functional MR) imaging is a promising tool for evaluation of glomerular filtration rate and renal oxygenation but is limited by need for exogenous contrast media and is still largely experimental [22]. Real-time GFR measurement using fluorescent markers is also a promising method but is still limited to animal models of AKI [23–25]. Contrast-enhanced ultrasonography (CEUS) is a new technique that can identify alterations in renal perfusion and has been applied in renal transplantation to differentiate between rejection and acute tubular necrosis. CEUS has yet to be validated for AKI in the ICU setting [26].

Emerging Role for Novel Biomarkers

Recognizing the poor sensitivity of functional markers (urine output and SCr) for early diagnosis of AKI, there has been a growing interest in identifying better biomarkers of AKI. Biomarkers can be divided into three categories: those that detect "functional changes" (SCr, urine output or serum cystatin C), those that detect "kidney damage" (urine and serum neutrophil gelatinase-associated lipocalin [NGAL], kidney injury molecule 1 [KIM-1] and liver-type fatty-acid binding protein [LFABP] among others), and those that detect "kidney stress" (urinary insulin-like growth factor-binding protein 7 [IGFBP7] and tissue inhibitor of metalloproteinases-2 [TIMP-2]). Measuring "kidney damage" while urine output and SCr (functional markers) are still within normal ranges allows detection of "subclinical AKI". On the other side, "functional AKI" is when there is oliguria or elevation in SCr, but damage markers have not risen yet. This could well represent a normal adaptive mechanism by the kidneys in response to a certain stressor, such as hypotension, hypovolemia or changes in renal blood flow. Cell cycle arrest biomarkers (such as TIMP-2 and IGFBP7) have been suggested to detect "kidney stress" prior to the incurrence of "damage". Cell cycle arrest is a protective mechanism that eukaryotic cells use in response to injury and stress to halt cell division. TIMP-2 and IGFBP7 are expressed in tubular cells in response to DNA and other signals, increasing the expression of p proteins, which block the effect of cyclin-dependent protein kinase complexes, thereby resulting in G1 cycle arrest. Prediction of moderate to severe AKI (KDIGO stage 2–3) 12 h after the sample was better using the [TIMP-2] [IGFBP7] product compared to previously described markers [27]. The "ideal biomarker" would be one that will rise very shortly after the episode of AKI, improve rapidly with resolution of AKI, have a high sensitivity and specificity, be highly reproducible, easily obtainable and most importantly be able to predict severity and affect management and outcomes. Since one single biomarker is unlikely to provide all this information, a combination of biomarkers has often been used in clinical trials [27, 28]. The extent of which current and future biomarkers will improve the existing algorithm for diagnosis of AKI has yet to be determined (Fig. 42.1).

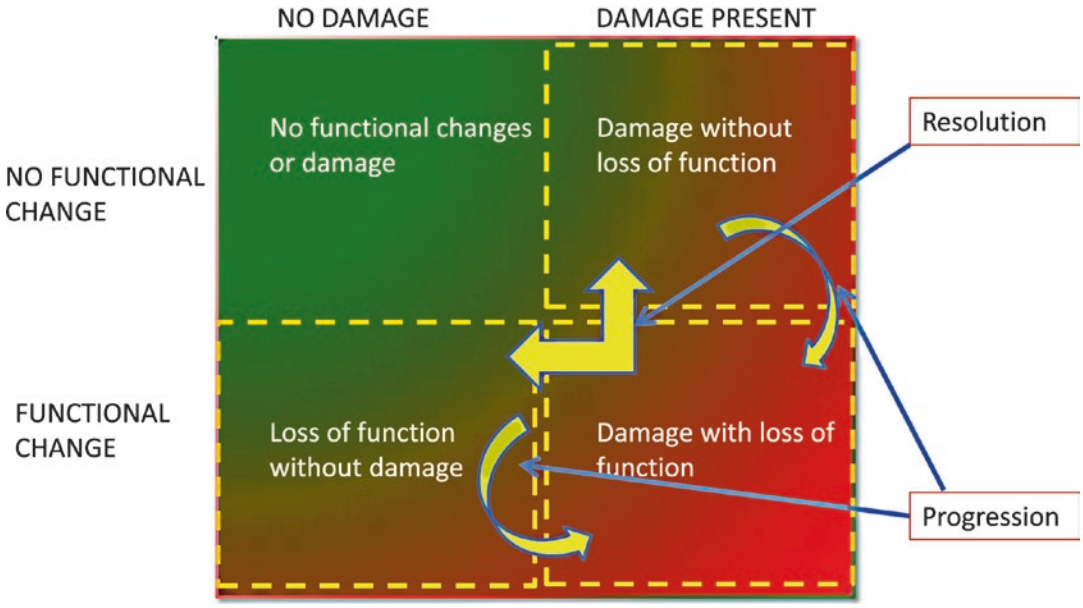

Fig. 42.1 Proposed framework for evaluating AKI based on Biomarkers. A combination of kidney functional and damage markers simultaneously provides a simple method to stratify patients with AKI. At initial presentation, patients would be evaluated in terms of these two domains, and then could be assessed over time to monitor their transitions across the domains (Adapted from the 10th ADQI meeting report)

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