CHAPTER 216

Diagnosis and Management of Acute Kidney Injury in the Emergency Department

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OBJECTIVES

This chapter will:

1. Describe the importance of timely acute kidney injury (AKI) diagnosis according to available guidelines.
2. Discuss the importance of early diagnosis of AKI in the emergency department (ED) and how physicians should manage the patients with AKI in the ED properly.

The diagnosis of acute kidney injury includes an acute and broad condition of kidney dysfunction detected by serum creatinine (SCr) modification, estimated glomerular filtrate (eGFR) change, or urine output decrease in a given time frame, as recommended by the Acute Dialysis Quality Initiative group (ADQI). On the basis of impairment of kidney function the same group developed the so-called Risk, Injury, Failure, Loss and End-stage kidney (RIFLE) criteria.[1] More recently, the Acute Kidney Injury Network

TABLE 216.1

Acute Kidney Injury Criteria: KDIGO Criteria Classification, AKIN Criteria Classification, RIFLE Criteria Classification

CLASSIFICATION*	SERUM CREATININE, GFR, OR OTHER CRITERIA	URINE OUTPUT CRITERIA
KDIGO		
Stage 1	1.5- to 1.9-fold increase in serum creatinine level from baseline or ≥0.3 mg/dL (26.5 μmol/L) increase in serum creatinine level	<0.5 mL/kg per hr for 6–12 hr
Stage 2	2.0- to 2.9-fold increase in serum creatinine level from baseline	<0.5 mL/kg per hr for 2:12 hr
Stage 3	Threefold increase in serum creatinine level from baseline or increase in serum creatinine level to ≥4.0 mg/dL (≥353.6 μmol/L) or initiation of renal replacement therapy or, in patients aged <18 years, decrease in eGFR to <35 mL/min/1.73 m^2	<0.3 mg/kg per hr for ≥24 hr or anuria for ≥12 hr
AKIN[15]		
Stage 1	Increase in serum creatinine level of >0.3 mg/dL (≥26.4 μmol/L) or increase to ≥150%–200% (1.5- to 2.0-fold) from baseline	<0.5 mL/kg per hr for >6 hr
Stage 2	Increase in serum creatinine level to >200%–300% (>2- to 3-fold) from baseline	<0.5 mL/kg per hr for >12 hr
Stage 3	Increase in serum creatinine level to >300% (>3-fold) from baseline (or serum creatinine level of >4.0 mg/dL [≥354 μmol/L] with an acute increase of at least 0.5 mg/dL [44 μmol/L])	<0.3 mL/kg per hr for 24 hr or anuria for 12 hr
RIFLE[13]		
Risk	1.5-fold increase in serum creatinine level or >25% decrease in GFR	<0.5 mL/kg per hr for 6 hr
Injury	Twofold increase in serum creatinine level or >50% decrease in GFR	<0.5 mL/kg per hr for 12 hr
Failure	Threefold increase in serum creatinine level or 75% decrease in GFR or increase in serum creatinine level to ≥4 mg/dL (≥354 μmol/L) with an acute increase ≥0.5 mg/dL (≥44 μmol/l)	<0.3 mg/kg per hr for 24 hr or anuria for 12 hr
Loss	Persistent AKI with complete loss of renal function (>4 weeks)	N/A
End-stage renal disease	ESRD (>3 months)	N/A

*In AKIN stage and RIFLE criteria. AKI classification is based on the more severe of urine output serum creatinine or eGFR criteria. In the KDIGO classification, AKI is defined as an increase in serum creatinine level of ≥0.3 mg/dL (≥26.5 μmol/L) within 48 hr or ≥1.5 times baseline within the prior 7 days or urine volume <0.5 mL/kg per hr for 6 hr. For AKIN criteria, the diagnosis of AKI is based on changes occurring during a 48-hr time period, staging may occur over a longer time frame. For RIFLE classification. AKI diagnosis is based on changes occurring during a period of 1–7 days, which must be sustained for more than 24 hr.

AKI, Acute kidney injury, *AKIN,* Acute Kidney Injury Network; *eGFR,* estimated glomerular filtration rate; *ESRD,* end-stage renal disease; *GFR,* glomerular filtration rate; *KDIGO,* Kidney Disease Improving Global Outcomes; *RIFLE,* risk, injury, failure, loss, end-stage renal disease. KDIGO criteria permission obtained from Nature Publishing Group Kidney Disease Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. *Kidney Int Suppl. 2.*1–138 (2012). AKIN criteria reproduced from Metha, R. L. et al. *Crit Care.* 11, R31 (2007), which is published under an open access license by Biomed Central.

(AKIN) approved a slightly modified set of criteria with a modification to include small changes in SCr (≥0.3 mg/dL or 26.5 μmol/L) when they occur within a 48-hour period.[2] These criteria have been reconciled in the definitive scoring system called Kidney Disease: Improving Global Outcomes (KDIGO) (Table 216.1).[1,3–4] Despite the fact that the existing criteria are standardized, they appear as limited and imperfect methods to detect the development of early AKI in the emergency department (ED).[5] Because clinical signs and symptoms of acute renal damage are not specific,[3,6,7] it is difficult to promptly distinguish AKI at the time of patient ED presentation. The missing early diagnosis of kidney injury leads to a higher risk of death during hospitalization[8–9] as consequence of a delay in prompt AKI treatment. A report by the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) found that 30% of AKI cases occurring during hospital admission were avoidable and that only 50% of patients with AKI received a timely standard of care.[10] The limitation of current criteria for diagnosis of AKI are related to the nonspecific sign of oliguria, imprecise evaluation of eGFR in the context of an acute dynamic condition, and to the wide spectrum of mechanisms and conditions of AKI that actually start from a subclinical form of kidney dysfunction and damage. The subclinical form of AKI often is unrecognized because no evident symptoms can be present in this phase. However, subclinical AKI could be the prelude to the progression of an established AKI, and eventually to a chronic kidney dysfunction (CKD), risk for need of renal replacement therapy (RRT), and risk of death. The limitations of SCr are related to (1) creatinine metabolism, which is influenced a variety of nonrenal factors such as age, gender, muscle mass, diet (particularly protein intake), and (2) nutritional status. Although some equations for eGFR calculation take into account some of these variables (i.e., age and gender in the Modification of Diet in Renal Diseases [MDRD] equation), muscle mass and nutritional considerations are not reflected by these equations.[11] Tubular secretion of creatinine also can vary and cause error in creatinine-derived estimates of GFR. Under normal conditions, tubular secretion of creatinine accounts for roughly 10% of creatinine clearance, but this secretion is inhibited by certain medications such as trimethoprim and cimetidine, leading to elevations in serum creatinine that do not reflect true decrements in GFR.[11] SCr finally is influenced by its volume of distribution, which can be altered significantly by volume overload (a condition commonly present in acute and chronic renal insufficiency).[11] Most important, the temporal gap between decreases in GFR and resultant elevations in SCr precludes early recognition of significant GFR loss. Substantial loss of GFR (up to 50%) may not manifest with elevations in SCr, and this condition may last over a prolonged period of time.[11] In addition, during non-steady-state conditions, creatinine-based estimates of GFR are inaccurate, making

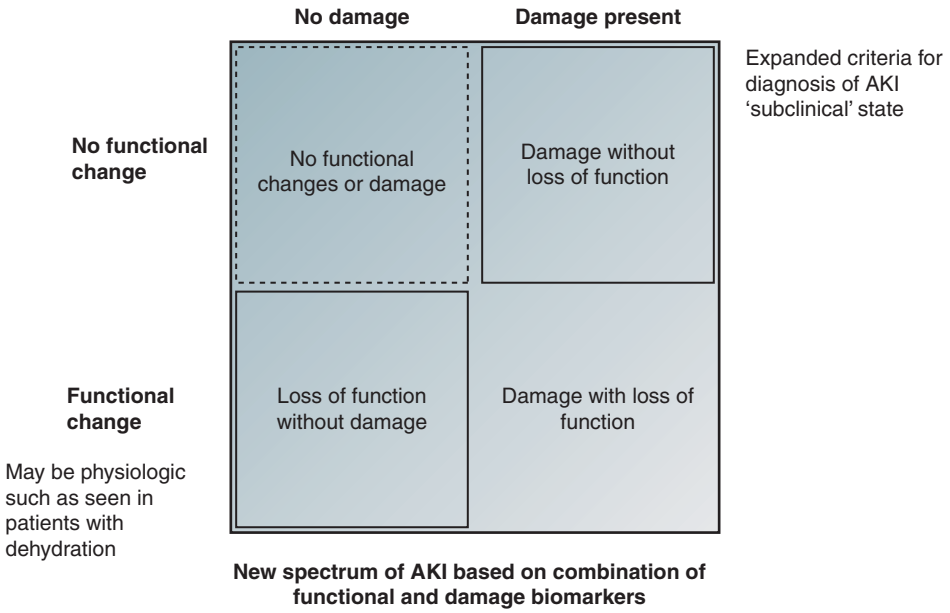

FIGURE 216.1 Revision of acute kidney injury criteria, including novel biomarkers into the diagnostic flow chart, and separating functional criteria (according to traditional biomarkers) and damage criteria (identified by novel biomarkers).

assessment of true renal function difficult. Furthermore, when GFR is reduced significantly, the proportion of creatinine cleared by tubular secretion proportionally increases, with a substantial overestimation of GFR until the level of 15 mL/min is reached.[11] A false elevation of creatinine levels may be due to Jaffe assay interference, secondary to hyperglycemia, delayed centrifugation, and hemolysis.[12]

DIAGNOSTIC UTILITY OF BIOMARKERS

Similarly to what happened with troponin for acute myocardial infarction diagnosis, in recent years eager research has been conducted to identify a biomarker for timely AKI diagnosis. Renal biomarkers levels, once elevated beyond a specific cutoff value or when changing over time, can detect a risk of AKI or subclinical kidney damage, allowing development of a new conceptual model for AKI. A continuum exists from initial kidney stress, susceptibility to insult and early injury to advanced kidney damage.[13] Such acute early phase has also been defined "kidney attack,"[14] whereas the subsequent phases in the time window of 90 days are described as acute kidney disease (AKD). In such conditions, a biomarker may trigger early preventive and protective measures before clinical AKI becomes manifest.[15] The ADQI consensus group proposed the use of biomarkers to diagnose AKI with kidney damage even in the absence of renal dysfunction.[16] Subclinical AKI may be diagnosed only with the use of biomarkers, when classic criteria are still within normal range showing the presence of reduced nephron mass.[17–18] AKI implies injury or damage but not necessarily dysfunction in subclinical status. SCr and urine output only modify late with respect to the beginning of kidney injury.[19] A recent revision of AKI criteria has been proposed recently, including novel biomarkers into the diagnostic flow chart and separating functional criteria (according to traditional biomarkers) and damage criteria (identified by novel biomarkers) (Fig. 216.1).[16] An ideal biomarker of AKI would be a substance that the kidney releases immediately in response to injury, not influenced by other clinical parameters or patient's characteristics and that can be detected in the blood or urine without significant metabolism. Biomarkers of kidney damage could result of great utility in emergency room to identify in a timely manner patients with high risk to develop AKI. Most clinical biomarkers were identified for early diagnosis of AKI, but the field is still developing.

Cystatin C

Cystatin C or cystatin 3 (formerly gamma trace, post-gamma-globulin, or neuroendocrine basic polypeptide) has been proposed as a valuable alternative marker tested in urine and in blood, particularly in situations in which creatinine-based estimates of GFR fail to provide an accurate estimate.[20–21] If kidney function and glomerular filtration rate decline, the blood levels of cystatin C rise. Serum levels of cystatin C are a more precise test of kidney function (as represented by the glomerular filtration rate, GFR) than serum creatinine levels.[22–23]

Neutrophil Gelatinase-Associated Lipocalin

Neutrophil gelatinase-associated lipocalin (NGAL) is an independent biologic marker able to detect earlier AKI than SCr.[24] In fact SCr is a marker of kidney function, whereas NGAL is a marker of kidney injury.[25] Moreover, NGAL levels are useful to quantify the degree of tubular damage to establish the stratification of AKI. The clinical use of NGAL in ED to clinical judgement in acute kidney injury diagnosis is recognized largely in the scientific community.[26] NGAL seems to be even a good marker in detecting AKI after cardiac surgery, and its concentration is related to risk to develop a tubular damage according a score

(Fig. 216.2).[27] The limitations of using NGAL in ED seem to be related to the false-positive levels in septic patients or in chronic kidney diseases.

Proenkephalin

Proenkephalin (PenKid) is associated with diagnosis and severity of acute kidney injury not being elevated by inflammation in patient with sepsis admitted in the ED.[28] The majority of patients without kidney failure are within normal range, despite inflammation, whereas NGAL, as one example of an inflammation-dependent marker, is elevated above the normal range for almost all patients.[28] Biomarkers, alone or in combination, can be used as a discriminating test to alert physicians, for high risk (patient who develops AKI during hospitalization in the ED).

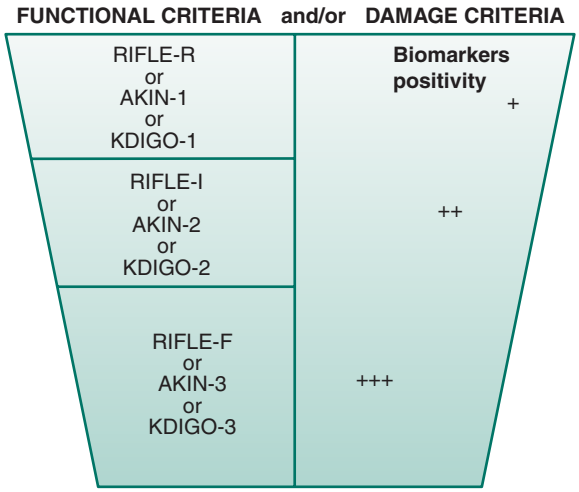

FIGURE 216.2 Neutrophil gelatinase-associated lipocalin concentration score according to tubular damage in detecting acute kidney injury after cardiac surgery.

Tissue Inhibitor of Metalloproteinase-2 and Insulin-Like Growth Factor Binding Protein-7

The use of tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein-7 (IGFBP7) as markers for risk assessment are approved in a clinical setting in the intensive care unit (ICU); unfortunately, they are not yet approved in the ED.[29] On the basis of the biologic characteristics of these biomarkers a laboratory test was performed that combines both biomarkers (Nephrocheck test); it is a rapid test that allows a quantitative measurement of biormarkers.[30] On the basis of combined value by formula was performed a score that identifies the high risk to develop AKI. A value of at least 0.3 identifies positive patients (Fig. 216.3).[30] A high-specificity cutoff (2.0) identifies the subgroup of patients who are at the highest risk of AKI and who therefore may be appropriate for more active interventions.[30] Actually the use of biomarkers should be applied in appropriate population: ICU patients older than 21 years, with one other risk factor for AKI, after CABG or other major high-risk surgery or with sepsis.[30] The appropriate use is at ICU admittance or sudden deterioration of a critically ill patient.[30] Even if there are a lot of proposed biomarkers for diagnosis of AKI, only some of these had a worldwide clinical approvation for their use in the ED (Fig. 216.4).[31]

MANAGEMENT OF ACUTE KIDNEY INJURY IN THE EMERGENCY DEPARTMENT

Risk Assessment

It is important to screen patients promptly who have undergone an exposure to a potential renal harm and to

Cardiac surgery associated (CSA) acute kidney tubular damage

Concentration Sample	(ng/mL)	Delta (Δ) NGAL at following measurement	CSA-NGAL Score
uNGAL	50		0 Tubular damage unlikely
pNGAL	<100		
uNGAL	50 – <150		1 Tubular damage possible
pNGAL	100 – <200		
uNGAL	150 – <1000 or	Δ >100+ second value ≥125	2 Tubular damage
pNGAL	200 – <1000 or	Δ >100+ second value ≥150	
uNGAL / pNGAL	>1000		3 Severe tubular damage

FIGURE 216.3 A score of combination 2 (tissue inhibitor of metalloproteinase-2) and – 7 (insulin-like growth factor binding protein-7) that identifies the high risk to develop acute kidney injury. A value of at least 0.3 identifies positive patients.

AKIRISK™ Score* = (TIMP-2) × (IGFBP-7)

AKIRISK™ Score	WHAT IT MEANS
>0.3†	Positive: Patient could develop moderate to severe acute kidney injury within 12 hours of testing
≤0.3	Negative: Patient may not develop moderate to severe acute kidney injury within 12 hours of testing

FIGURE 216.4 Worldwide clinical approval of biomarkers for diagnosis of acute kidney injury.

	Clinical trial setting						
Biomarker	**ICU**	**CPB surgery**	**Kidney Tx**	**IV contrast**	**ED**	**SEPSIS**	**Acute heart failure**
NGAL	+	+	+	+	+	–	+
IL-18	+	+	+	?	?	?	?
L-FABP	+	+	?	?	+	?	?
KIM-1	?	+	–	?	+	+	?
(TIMP-2) x (OGFBP7)	+	+	?	?	?	+	?
PRO-ENKEFALIN	+	+	?	?	+	+	+

FIGURE 216.5 Clinical actions according to Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.

continue monitoring high-risk patients. Physicians should investigate carefully the clinical history of patients and their home therapies for potential toxicity of drugs and hydration status. The presence sepsis or acute heart failure often is associated strongly with the development of AKI.[26] Risk assessment of an acute renal insult at the moment of emergency admission may include the dosage of biomarkers levels. Regardless of timely diagnosis, the early identification of patients as being at high risk of AKI may allow eventual strict monitoring of renal function and to include all possible preventive measures to reduce the occurrence of an established renal injury. Furosemide stress test (FST) also has been proposed to predict the onset of advanced AKI within the ICU or ED, where urine output can be monitored continuously. FST could help to select patients suitable at risk of advanced tubular injury.[30] With FST the kidney is challenged with a single, standardized furosemide bolus (1 to 1.5 mg/kg). In case of intact kidney function, with preserved GFR and tubular function, FST should imply a brisk diuresis. On the other hand, tubular injury can be associated with urine output that fails to significantly augment after the diuretic challenge,[30] although it is apparently normal in basal conditions.

General Management of Acute Kidney Injury in the Emergency Department

In patients admitted to ED, once the diagnosis of (1) established AKI, (2) high risk of AKI, and (3) subclinical AKI is performed, several actions could be initiated according to KDIGO guidelines (Fig. 216.5). Urine analysis and microscopic examination as well as urinary chemistries should be performed to identify potential causes of AKI.[32] Imaging tests, especially ultrasound, must be ordered for the complete evaluation of patients with AKI.[33] A nephrologist consultation in ED should be requested to select the appropriate critical ill patients with AKI candidate for renal replacement therapy (RRT).[34]

Prognostic Evaluation of Acute Kidney Injury in the Emergency Department

After ED admission and discharge AKI detection has a great impact on mortality. Three months after resolving an AKI episode, patients may be at risk of developing chronic kidney disease (CKD).[35] AKI biomarkers in the ED, such as NGAL and PENKID, have been demonstrated to also have prognostic value for mortality. The admission NGAL value at cutoff of 400 ng/mL showed a relationship with in-hospital mortality.[26] Pro-ENK is highly predictive of short-term mortality and could be able in early identification of patients admitted to the ED for sepsis at risk of death.[28] Further serial measurement of pro-ENK improved its predictive performance in the ED. All of these considerations may suggest a remarkable advantage justifying the use of expensive biomarkers in selected population with high risk of AKI in the ED.

Treatment of Acute Kidney Injury in the Emergency Department General Considerations

The usefulness of serial measurement of AKI biomarkers could allow an individualized therapy for these patients. Either the efficacy of pharmacologic management or the need for timely RRT may be established based on this initial evaluation.[36] It has been shown that NGAL positivity may predict the need for RRT in septic patients.[37] Patients' volume status is an important clinical feature to be established in the ED. Fluid resuscitation in dehydrated patients is the first-line treatment in patients with kidney dysfunction,

but an excessively positive fluid balance could be associated with increased short-term mortality.[38–39] The use of balanced crystalloids for intravascular volume expansion are recommended strongly compared with colloids to avoid starch-associated AKI.[40–42] As far as the use of vasoactive drugs is concerned (norepinephrine), current clinical data are insufficient to recommend their routine use for AKI prevention, but the appropriate use in volume-resuscitated patients with vasomotor septic shock to improve kidney perfusion together fluid can be considered appropriate.[43] Adrenomedullin could be a useful marker in the ED to indicate the correct timing for vasopressor administration in patients with septic shock to prevent kidney injury and mortality.[44] Loop diuretics can be prescribed surely in the acute care setting as in the ED for the management of fluid overload and pulmonary edema in patients with AKI.[45–47] Controversial data cannot associate the use of loop diuretics definitely with increased mortality, but they have been deemed as ineffective in critically ill patients for the treatment of nonoliguric AKI.[35,48–50] Contrasting data suggest that loop diuretics are not dangerous in AKI.[51] RRT should not be delayed when established AKI has been identified. The use of biomarkers could be useful for timing the start of RRT.

Other Emergency Department Acute Kidney Injury Presentations

If a patient is presented at the ED with an acute infection the use of aminoglycosides should be discouraged because of their nephrotoxicity.[35] The use of topical or local applications of aminoglycosides (e.g., respiratory aerosols, instilled antibiotic beads), rather than intravenous application, when feasible, could be attempted.[35] Glycemic control is desirable with insulin therapy targeting plasma glucose from 110 to 149 mg/dL: such strategy should be conducted with great attention, especially in the ED setting[35]: definitive data relatively to accurate glycemic control and AKI prevention in the acute AKI patient are not available so far. Nutritional control should be achieved with a total energy intake of 20 to 30 kcal/kg/day in patients with any stage of AKI.[35] Restriction of protein intake should not be performed to delay the initiation of RRT that, instead, should be considered at an early stage.[35] Administration of RRT in the ED has not been described, but it is possible that improved overall expertise and technique safety, in major hospitals could be considered in the next years.

Key Points

1. The incidence of AKI in the ED currently may be overlooked by clinicians, and after careful observation it is significantly higher than expected.
2. The diagnosis of AKI in the ED is very important. Several novel diagnostic tools and renal biomarkers play a crucial role in timely diagnosis of renal failure. It is also possible that subclinical AKI, evidenced in the ED, could result as established AKI during successive hospitalization.
3. The management of AKI in the ED, and the prevention of further renal damage if subclinical forms are evidenced, eventually can be started promptly directly in the ED. Biomarkers positivity in the ED also showed prognostic value to guide eventual management of renal care in the ward and intensive care unit.

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