



## Review Article

# Diagnostic Approach for Acute Kidney Injury and Renal Functions: An Update

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## ABSTRACT

Acute kidney injury (AKI) is characterized by a sudden impairment of kidney function occurring over a period of hours to days. The diagnosis for AKI is currently made on the basis of the presence of increased serum creatinine and/or blood urea nitrogen (BUN) levels and/or a decreased urine output, despite their well-known limitations. It should be noted that changes in BUN and serum creatinine may represent not only renal injury, but also normal responses of the kidney to extracellular volume depletion or decreased renal blood flow. The presence of proteinuria predicts the development of AKI independently of estimated Glomerular Filtration Rate (eGFR). Initial results from a large prospective study of AKI biomarkers in cardiac surgery indicate lower agreement with serum creatinine as an AKI standard than observed in early studies. AKI severity and duration are important predictors of chronic kidney disease (CKD) and long-term mortality. A minority of patients surviving AKI with decreased kidney function is seen by a nephrologist. Expanding rates of AKI coupled with increasing awareness of its short and long-term sequelae have focused efforts to identify patients at risk for developing this disease and its complications. This review details recent attempts to identify novel risk factors for AKI, describe further refinements in the diagnostic and prognostic approach to this disease using biological markers of injury.

## Keywords

AKI,  
ARF,  
RIFLE,  
ATN,  
AGAL

## Introduction

Acute Kidney Injury (AKI) is an increasingly common disease that strongly associates with poor short- and long-term morbidity and mortality. Disappointingly, only marginal improvements in the survival

have been observed with little evidence supporting the use of tested pharmacotherapies in established disease. With recent well-executed trials also indicating a therapeutic ceiling in

conventional renal replacement therapies may have been achieved, emphasis on developing strategies to prevent AKI and its long-term consequences has grown. In this review, we discuss recent additions to the AKI literature focusing on novel risk factors for developing AKI, ongoing efforts to refine the diagnostic and prognostic approach to this disease with emerging biomarkers of injury, and attempts to better identify survivors at risk for poor longitudinal outcomes.

Prompt recognition and treatment of AKI remain the cornerstone of clinical management for this high-mortality, high-cost syndrome. The most recent updates in the definition, diagnosis, pathophysiology, and treatment options for patients with AKI, providing a stepwise approach to clinical evaluation for use in all fields of medical practice (Lattanzio *et al.*, 2009). AKI is not acute renal failure (ARF) but a more general description. Small changes in kidney function in hospitalized patients are important and are associated with significant changes in short and possibly long-term outcomes. The RIFLE [R-renal risk, I-injury, F-failure, L-loss of kidney function, E-end stage kidney disease (ESKD)] and AKIN (Acute Kidney Injury Network) criteria and use of biomarkers of AKI.

Criteria provide a uniform definition of AKI and have now been validated in numerous studies (Kellum *et al.*, 2008). A precise biochemical definition of acute renal failure has never been proposed, and until recently, there has been no consensus on the diagnostic criteria or clinical definition. Depending on the definition used, acute

renal failure has been reported to affect from 1% to 25% of intensive care unit patients and has led to mortality rates ranging from 15% to 60%. Small changes in kidney function in hospitalized patients are important and are associated with significant changes in short-term and possibly long-term outcomes. The RIFLE criteria provide a uniform definition of AKI and have now been validated in numerous studies (Kellum, 2008). Acute tubular necrosis (ATN) is the most common cause of intrinsic ARF and is responsible for over 50% of ARF in hospitalized patients, and up to 76% of cases in patients in intensive care units.

ATN usually occurs after an acute ischaemic or toxic event. The pathogenesis of ATN involves interplay of processes that include endothelial injury, microvascular flow disruption, tubular hypoxia, dysfunction and apoptosis, tubular obstruction and trans-tubular back-leak. Vasculitis causing ARF should not be missed as this condition is potentially life threatening (Cheung *et al.*, 2008). In critically ill patients continuous venovenous hemo (dia) filtration is the first choice because it provides more hemodynamic and metabolic stability than intermittent therapy. Acute life-threatening hyperkalemia is an indication for intermittent hemodialysis because of the higher efficacy of dialysis in the clearance of low molecular weight substances (Haller *et al.*, 2000).

Recent developments in the diagnosis of AKI include the use of the RIFLE, ESKD, AKIN (Acute Kidney Injury Network) criteria and use of biomarkers of AKI.

RIFLE and AKIN criteria for diagnosis of AKI

**RIFLE criteria (within 7 days)**

Class	GFR criteria	Urine output criteria
R-Risk	Creatinine increase x 1.5 or GFR loss > 25%	0.5 < mL/kg/hour x > 6 hours
I-Injury	Creatinine increase x 2 or GFR loss > 50%	0.5 < mL/kg/hour x > 12 hours
F-Failure	Creatinine increase x 3 or GFR loss > 75% or Creatinine increase > 4 mg/dL (acute increase > 0.5 mg/dL)	0.3 < mL/kg/hour x > 24 hours or anuria > 12 hours
L-Loss	Persistent loss of kidney function > 4 weeks	
E-ESKD	ESKD > 3 months	

**AKIN criteria (within 48 hours)**

Stage	Serum creatinine criteria	Urine output criteria
1	Creatinine increase x 1.5 or creatinine increase > 0.3 mg/dL	0.5 < mL/kg/hour x > 6 hours
2	Creatinine increase x 2	0.5 < mL/kg/hour x > 12 hours
3	Creatinine increase x 3 or creatinine increase > 4 mg/dL (acute increase > 0.5 mg/dL)	0.3 < mL/kg/hour x > 24 hours or anuria > 12 hours

The aetiology of ARF is classically grouped into three categories: prerenal, intrinsic and postrenal. Prerenal ARF is the second most common cause of ARF in the elderly, accounting for nearly one-third of all hospitalized cases. Common causes can be grouped into true volume depletion (e.g. decreased fluid intake), decreased effective blood volume (e.g. systemic vasodilation) and haemodynamic (e.g. renal artery stenosis, NSAID use). ATN is the most common cause of intrinsic ARF and is responsible for over 50% of ARF in hospitalized patients. The treatment of prerenal and ATN ARF is largely supportive with little evidence of benefit from current pharmacological therapies. Despite advances in critical care medicine and renal replacement therapy, the mortality of ARF has not changed significantly over the last 40 years, with current mortality rates being up to 75% (Cheung *et al.*, 2006). A large number of patients with ischaemic

ARF pass through a phase of potentially reversible pre-renal oliguria; early recognition and prompt, appropriate treatment of these pre-renal factors can prevent progression to established ARF, with the genuine prospect of improved patient morbidity and mortality. Early diagnosis in other patients with ARF, such as those with acute inflammatory renal disease (e.g. vasculitis) or urinary tract obstruction, will allow appropriate prompt treatment and the possibility for reversal of the ARF (Kalra *et al.*, 2002). Patients with ATN or rapidly progressive glomerulonephritis may not recover, or may only partially recover, their renal function. Haemodialysis and nutritional support are common measures for patients with severe ATN and a highly catabolic state. Corticosteroids and immunosuppressive therapy should be instituted for rapidly progressive glomerulonephritis, in addition to haemodialysis, haemodiafiltration instead

of haemodialysis is recommended for patients who are haemodynamically unstable [i.e., with a persistently low blood pressure (systolic  $<$  or  $=$  100 mm Hg)]. Haemodiafiltration has been shown to improve acid-base balance and uraemia better than standard haemodialysis. However, despite dialysis, mortality in patients with ARF associated with ischaemic ATN remains high (Mandal *et al.*, 1996). Nutrition must be implemented and an adequate protein and calorie intake must be obtained, through spontaneous oral route and, whenever required, enteral and parenteral nutrition. In conclusion, patients with mild-degree, mostly of prerenal origin, ARF represent a common finding in hospital practice. Identification and prompt treatment of the underlying cause is the best prevention of acute tubular necrosis. Patients with ARF of renal origin require, in particular, daily nutritional assessment and dietary treatment to delay the onset of dialysis (Edefonti *et al.*, 1997). Babies with ARF have to be monitored for several metabolic derangements like hyponatremia, hyperkalemia, hypocalcemia, and acidosis and have to be managed accordingly. Fluid balance should be precise in order to avoid fluid overload.

It is difficult to provide adequate calories due to fluid restriction. Dialysis has to be instituted to preempt complications. Peritoneal dialysis is the easiest and safest modality. These babies need long term follow up as they are prone for long term complications (Subramanian *et al.*, 2008). Peritoneal dialysis or hemodialysis should be prepared for whenever severe hypertension, pulmonary edema or worsening biochemistry occurs. Acute renal failure has a generally good prognosis if properly treated (Guignard *et al.*, 1984). Although the importance of fluid management is generally recognized, the

choice of fluid, the amount, and assessment of fluid status are controversial. As the choice of fluids become wider and monitoring devices become more sophisticated, the controversy increases. This article provides an overview of the concept of fluid management in the critically ill patient with acute renal failure (Mehta *et al.*, 2002). Acute renal failure (ARF) is a common problem in critical care; therefore, nurses should consider it to be a potential issue for all of their patients. Fluid management and diuretic therapy are important in these patients (Sumnall, 2007). The use of diuretic agents can be harmful, as indicated by observational and cohort studies. Although mannitol flushes out intratubular casts and increases tubular flow, which is favorable in myoglobinuria or hemoglobinuria, so far no well-designed clinical studies have demonstrated its efficacy in ARF. In conclusion, there is currently no convincing evidence for any benefit from diuretic agents and/or (low dose) dopamine in the prevention of ARF. High quality intensive care and avoidance of harm is, therefore, the current standard of the prevention of ARF (Girbes, 2004). Research efforts over the last decade have focused on the discovery and validation of novel urinary biomarkers to detect AKI prior to a change in kidney function and to aid in the differential diagnosis of AKI. The optimal and appropriate utilization of AKI biomarkers will only be realized by understanding their characteristics and placing reasonable expectations on their performance in the clinical arena (Goldstein, 2011). Promising diagnostic injury markers include neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), interleukin 18 (IL-18) and liver-type fatty acid binding protein (L-FABP). However, there are currently insufficient data on damage biomarkers to support their use for AKI staging. Rigorous validation

studies measuring the association between the novel damage biomarker(s) and clinically relevant outcomes are needed.

The presence of underlying CKD or of sepsis poses additional challenges in differential diagnosis, since these conditions alter both baseline biomarker excretion and biomarker performance. We recommend that biomarkers be validated within the clinical context in which they are to be used. Within that context, combinations of biomarkers may, in the future, allow differentiation of the site, mechanism and phase of injury (Endre *et al.*, 2013).

Currently, the place of biomarkers in this decision-making process is still uncertain. Indiscriminate use of various biomarkers may distract clinicians from adequate clinical evaluation, may result in worse instead of better patient outcomes, and may waste money. Future large randomized studies are necessary to demonstrate the association between biomarker levels and clinical outcomes, such as dialysis, clinical events, or death. It needs to be shown whether assignment to earlier treatment for AKI on the basis of generally accepted biomarker cut-off levels results in a reduction in mortality and an improvement in recovery of renal function (Schiffel *et al.*, 2012). Novel biomarkers appear capable of offering a more sensitive means of detecting acute kidney injury than existing approaches. Certain of these allow discrimination between the various mechanisms and anatomical site of acute injury. Ultimately, clinical assessment might incorporate a panel of different biomarkers, each informing on the integrated aspects of glomerular, tubular and interstitial function. Presence of biomarkers may in some cases detect mild or transient renal dysfunction that is presently undetected, and the clinical relevance needs further exploration. Whilst

many potentially useful biomarkers have been proposed, comparatively few clinical data exist to support their validity in routine practice. Further prospective clinical studies are required to examine the validity of biomarkers after acute drug or toxin exposure, and to establish whether they might offer improved clinical outcomes in the setting of clinical toxicology (Waring *et al.*, 2011). Conversely, based on its early and time-dependent increase, its large magnitude of alteration and its high accuracy and sensitivity of detection (KIM-1) in urine appeared to be the best biomarker for detection of CDDP-induced proximal tubular injury. Moreover, LDH was considered useful for broad detection of damaged nephrons, because of its broad distribution along the nephron. Therefore, combinatorial measurement of these biomarkers may be a powerful tool for highly effective screening of nephrotoxicity (Tonomura *et al.*, 2010).

By Receiver Operating Characteristic analysis, urinary kidney injury molecule-1 was the best marker at predicting histological changes, with areas under the Receiver Operating Characteristic curve of 0.81 and 0.98 at 8 and 24h (best cut-off value >0.000326µg/ml), respectively. Urinary kidney injury molecule-1, urinary albumin and urinary Cystatin-C elevations correlated with the degree of renal damage and injury development. Further study is required to compare biomarkers changes in rats with those seen in human poisoning (Wunnapuk *et al.*, 2013). This study suggests a temporal hierarchy in the ability of certain urinary protein-based biomarkers to detect AKI after a well-defined tubular injury. Comparative analyses of urinary biomarkers are warranted in clinical settings such as patients receiving CP to discern the time course and pattern of expression (Sinha *et al.*, 2013). Early diagnosing of AKI in



clinical conditions by using new serum and urinary biomarkers remains cumbersome, especially in those settings where timing and aetiology of AKI are not well defined. Putting too much emphasis on markers that have not convincingly proven reliability might lead to incorrect interpretation of clinical trials. Further research in this field is warranted before biomarkers can be introduced in clinical practice (Vanmassenhove *et al.*, 2013).

New molecules such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), N-acetyl- $\beta$ -D-glucosaminidase (NAG), monocyte chemotactic peptide (MCP-1), IL-18, liver-type fatty acid-binding protein (L-FABP) and Netrin-1 are available and represent promising new markers that, however, need to be further evaluated in the clinical setting for suitability. In clinical settings with incipient AKI, not only the development and the implementation of more sensitive, practicable and accurate biomarkers are required for well-timed treatment initiation. Just as important is a substantial improvement of refined and applicable prophylactic therapeutic options in these situations. Before full adoption in clinical practice can be accomplished, adequately powered clinical trials testing a row of biomarkers are strongly warranted (Obermüller *et al.*, 2014). It is vital that additional large future studies demonstrate the association between biomarkers and hard clinical outcomes independent of serum creatinine concentrations and that randomization to a treatment for AKI based on high biomarker levels results in an improvement in clinical outcomes (Nguyen *et al.*, 2008). Neutrophil gelatinase-associated lipocalin is emerging as an excellent standalone troponin-like biomarker in the plasma and urine for the prediction of AKI, monitoring clinical trials in AKI and

for the prognosis of AKI in several common clinical scenarios (Devarajan, 2010).

The most promising of biomarkers in AKI for clinical use include a plasma panel consisting of (NGAL and Cystatin C and a urine panel including NGAL, IL-18 and (KIM-1. Most of these biomarkers were developed in non-transplant AKI, yet their role in clinical transplantation has to be identified (Halawa, 2011). As they represent tandem biomarkers, it is likely that the AKI panels will be useful for timing the initial insult and assessing the duration and severity of AKI. Based on the differential expression of the biomarkers, it is also likely that the AKI panels will distinguish between the various types and etiologies of AKI. It will be important in future studies to validate the sensitivity and specificity of these biomarker panels in clinical samples from large cohorts and from multiple clinical situations (Devarajan, 2007a,b,c). These include the identification of biomarker panels in plasma (neutrophil gelatinase-associated lipocalin and cystatin C) and urine (neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, interleukin-18, cystatin C, alpha1-microglobulin, Fetuin-A, Gro-alpha, and meprin). It is likely that the AKI panels will be useful for timing the initial insult, and assessing the duration and severity of AKI. It is also probable that the AKI panels will distinguish between the various etiologies of AKI and predict clinical outcomes. It will be important in future studies to validate the sensitivity and specificity of these biomarker panels in clinical samples from large cohorts and from multiple clinical situations. Such studies will be facilitated markedly by the development of commercial tools for the reproducible measurement of biomarkers across different laboratories (Devarajan, 2007a,b,c).

Recent advances in proteomics that hold promise in ischemic AKI, the most common and serious subtype of ARF, are chronicled in this article. These include the identification of biomarkers in the plasma (NGAL and cystatin C) and urine (NGAL, KIM-1, IL-18, cystatin C, alpha 1-microglobulin, fetuin-A, Gro-alpha, and meprin) for the investigation of AKI. It is likely that the AKI panels will be useful for timing the initial insult and assessing the duration of AKI. Based on the differential expression of the biomarkers, it is also likely that the AKI panels will distinguish between the various etiologies of AKI, and predict clinical outcomes ((Devarajan, 2007a,b,c).

Based on the differential expression of the biomarkers, it is also likely that the AKI panels will distinguish between the various types and etiologies of AKI. It will be important in future studies to validate the sensitivity and specificity of these biomarker panels in clinical samples from large cohorts and from multiple clinical situations (Nguyen *et al.*, 2008). Immediately postoperatively, NGAL and cystatin C correlated with and were independent predictors of duration and severity of AKI and duration of intensive care stay after adult cardiac surgery. The combination of both renal biomarkers did not add predictive value (Haase *et al.*, 2009). Accurate measurements of plasma NGAL are obtained using the point-of-care Triage(R) NGAL device. Plasma NGAL is an early predictive biomarker of AKI, morbidity, and mortality after pediatric CPB (Dent *et al.*, 2007).

Cardiopulmonary bypass (CPB) is associated with a significant risk of postoperative renal dysfunction. A study of the utility of a novel biomarker in predicting acute kidney injury (AKI) in adult patients undergoing cardiac surgery indicated the

measurement of this novel biomarker in the urine or plasma of patients in the first hours after CPB is predictive of subsequent renal injury. Although the AUC for plasma NGAL seemed inferior to urine, even an AUC of 0.8 as reported compares very favorably to that for other "outstanding" biomarkers (eg, AUCs in the 0.7 range for troponin) (Tuladhar *et al.*, 2009). Early postoperative measurement of plasma NGAL was of good value in identifying patients who developed AKI after adult cardiac surgery. Plasma NGAL and serum cystatin C were superior to conventional biomarkers in the prediction of AKI and were also of prognostic value in this setting (Haase-Fielitz *et al.*, 2009). The use of serum and urinary biomarkers for the prediction of AKI in patients undergoing cardiac surgery is highly dependent on the sampling time. Of the evaluated markers urinary NGAL had the best predictive profile. The previously unstudied marker of urinary RBP showed similar predictive power as more established markers (Che *et al.*, 2010).

uNGAL was useful in the early diagnosis of postoperative AKI as well as in predicting the 6 months renal outcome after hepatobiliary surgery. A considerable proportion of patients developed subclinical AKI, and these patients showed worse renal outcome compared with the non-AKI group (Cho *et al.*, 2014). The difference between the NGAL concentration 2 hours after reperfusion and the baseline NGAL concentration was predictive of AKI in all patients, including patients with preexisting renal dysfunction. In patients with creatinine concentrations less than 1.5 mg/dL, a single NGAL determination 2 hours after reperfusion of the liver was associated with the development of AKI. Total occlusion of the inferior vena cava was associated with AKI. In conclusion, NGAL concentrations

obtained during surgery were highly associated with postoperative AKI in patients undergoing liver transplantation. These findings will allow the design of larger interventional studies. Our findings regarding the impact of surgical techniques and glucose require validation in larger studies (Niemann *et al.*, 2009). Urinary NGAL can be used from the 1st day of injury as a reliable predictor of early AKI in multi-trauma patients (Makris *et al.*, 2009). uNGAL is an early marker of acute kidney injury in critically ill children: a prospective cohort study (Ronco, 2007). The parameter uNGAL was a good diagnostic marker for AKI development (area under the receiver operating characteristic curve [AUC] 0.78, 95% confidence interval [CI] 0.62 to 0.95) and persistent AKI for 48 hours or longer (AUC 0.79, 95% CI 0.61 to 0.98), but not for AKI severity, when it was recorded after a rise in serum creatinine had occurred (AUC 0.63, 95% CI 0.44 to 0.82).

We found uNGAL to be a useful early AKI marker that predicted development of severe AKI in a heterogeneous group of patients with unknown timing of kidney injury (Zappitelli *et al.*, 2007). uNGAL, serum cystatin C (sCysC) and uCysC were not altered by sepsis and were good predictors of AKI. In a septic state, sNGAL alone did not discriminate patients with AKI from those without AKI (Di Nardo *et al.*, 2013). To improve the effectiveness of therapeutic treatment in septic newborns with AKI, there is the need to accurately distinguish NGAL molecular forms originating within the distal nephron from those originating from neutrophils. This concise review summarizes properties and perspectives of uNGAL and Netrin-1 for their appropriate clinical utilization (Mussap *et al.*, 2011). The annual incidence of dialysis-requiring AKI among critically ill patients increased from 0.8% in 1996 to 3.0% in 2010 (P for

trend < 0.001). 90-day mortality declined from 50% in 1996 to 2000 to 45% in 2006 to 2010 (adjusted HR, 0.83 [95% CI, 0.79-0.87] compared to 1996-2000). Dialysis dependence among surviving patients at 90 days was marginally lower in 2006 to 2010 (25.1%) compared to 1996 to 2000 (27.2%), but after adjustment for confounding factors, was not significantly different (adjusted OR, 0.91; 95% CI, 0.80-1.03). The incidence proportion of dialysis-requiring AKI among critically ill patients increased by almost 4-fold between 1996 and 2010. This was accompanied by a significant decline in mortality, but the risk of long-term dialysis dependence continues to affect a substantial minority of surviving patients with no clear evidence of improvement over time (Wald *et al.*, 2015). uNGAL, serum CysC (sCysC), and urinary CysC (uCysC) levels were significantly increased in patients with septic AKI compared with septic patients without AKI, while sNGAL levels were not significantly different between septic patients with and without AKI. Median serum creatinine levels did not show significant differences between AKI and non-AKI patients. uNGAL, sCysC and uCysC were not altered by sepsis and were good predictors of AKI. In a septic state, sNGAL alone did not discriminate patients with AKI from those without AKI (Di Nardo *et al.*, 2013). Plasma and urinary Cystatin C and urinary NGAL are useful markers in predicting AKI in septic critically ill patients. Plasma NGAL raises in patients with sepsis in the absence of AKI and should be used with caution as a marker of AKI in septic ICU patients (Aydođdu *et al.*, 2013).

Recent work has helped to reinforce the link between CKD as a risk factor for AKI by uncovering proteinuria as a novel risk factor not routinely assessed, further examined the ability of novel markers of injury to provide



important diagnostic and prognostic information beyond creatinine alone in larger. Successful management of AKI requires early recognition of the diagnosis, investigation of the causes of AKI, management of complications, timely RRT, prevention of ongoing kidney injury, aggressive supportive care, and correction of the primary disorders. Despite many advances in the therapy of AKI, mortality rates remain constant at about 50–80%. This review article will certainly help researchers to establish simple and cost effective laboratory diagnostic markers so that AKI management may be made possible in a cost effect manner. Further research studies on hospitalized patients affected with AKI are recommended.

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