NGAL in Acute Kidney Injury

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Introduction

Acute kidney injury (AKI) represents an abrupt deterioration in kidney function and is a frequently encountered phenomenon in hospitalized patients [1, 2]. The impact of AKI is most profound among patients admitted to intensive care units (ICU). The incidence of AKI among hospitalized and critically ill patients appears to be increasing. This is likely attributable to demographic transition (i. e., older patients; more comorbid illness; greater prevalence of chronic kidney disease) coupled with admissions associated with increasingly complex medical and/or surgical diseases and the need for multi-faceted diagnostic and therapeutic interventions. The development of AKI now complicates the course in an estimated two-thirds of critically ill patients [3–5]. For those with more severe forms of AKI, an estimated 50–70 % will require support with acute renal replacement therapy (RRT), which represents a small, but important subgroup of all critically ill patients (4–8 %) [6]. The initiation of RRT can contribute to a considerable escalation in both the complexity of illness and associated costs of care. Indeed, these critically ill patients experience substantial morbidity, including non-recovery of kidney function and long-term chronic kidney disease or dialysis dependence [7–9] as well as excess mortality, with hospital mortality rates commonly exceeding 60 % [6, 8].

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Classification of AKI

The diagnostic classification of AKI has evolved considerably in the last several years. In 2004, a consensus definition, the RIFLE classification scheme (Acronym: Risk, Injury, Failure, Loss and End-stage renal disease), was published by the Acute Dialysis Quality Initiative (ADQI) group [10]. This classification defined three grades of severity of AKI (Risk, Injury, Failure), based on relative changes to serum creatinine (sCr) and changes in urine output, and two outcome categories (Loss and End-Stage Kidney Disease) based on the duration of RRT. This novel classification scheme has been validated and widely integrated into the medical literature. The RIFLE classification was later refined by the Acute Kidney Injury Network (AKIN), a consortium uniting representatives from all major nephrology and critical care societies. This adaption specified a 48-hour timeline during which the acute changes in kidney function had to occur to fulfill the definition of AKI. The AKIN modification also simplified the stages of severity of AKI, with the first two representing worsening renal dysfunction and the third stage characterized by kidney failure and encompassing any patients initiated on RRT. The RIFLE/AKIN classification schemes have now been consolidated into the KDIGO Clinical Practice Guidelines for Acute Kidney Injury definition for AKI [11] (Table 1).

Although the development of this consensus classification scheme has been an important landmark for clinical care and research in AKI, it has recognized limitations. The integration of urine output criteria may be confounded by numerous factors unrelated to the severity of underlying kidney injury (e.g., inability to measure outside of intensive monitoring settings; diuretic therapy). In addition, the stages associated with severity of urine output and sCr criteria may not be aligned in terms of prognosis (e.g., Stage 2 by sCr criteria associated with higher mortality

Table 1 Acute kidney injury (AKI) definition (KDIGO Clinical Practice Guidelines for Acute Kidney Injury) [11]

Stage	Serum creatinine criteria	Urine output criteria
1	Increase in sCr ≥ 26.4 μmol/l or Increase in sCr to 1.5–1.9 times baseline	< 0.5 ml/kg/h for 6–12 hours
2	Increase in sCr to 2.0–2.9 times baseline	< 0.5 ml/kg/h for ≥ 12 hours
3	Increase in sCr ≥ 3 times baseline or Increase in sCr ≥ 354 μmol/l or Initiation of RRT or For patients < 18 years, decrease in eGFR to < 35 ml/min per 1.73 m^2	< 0.3 ml/kg/h for ≥ 24 hours or anuria ≥ 12 hours

sCr: serum creatinine; RRT: renal replacement therapy; eGFR:

than Stage 2 by urine output criteria). Likewise, the use of sCr has limitations. Because sCr is a surrogate marker of kidney function and not a biomarker of kidney damage, changes to sCr may occur long after the injury stimulus has occurred (i. e., changes in sCr after injury may not rise significantly until there is a 50 % decline in glomerular filtration rate [GFR]) [12]. Serum creatinine is known to be influenced by a number of non-renal factors including patient age, sex, muscle mass, nutritional status and metabolism, medications, and extravascular fluid balance. Finally, baseline sCr values are often unknown (in ~ 30 % of ICU patients). This presents challenges for interpretation and attributing an elevated sCr solely to AKI rather than representing pre-existing chronic kidney disease or a combination of both.

Accordingly, the integration of novel biomarkers that may be sensitive and specific to the detection of early and acute kidney damage would be welcome and are likely essential to appropriately identify, triage and intervene in patients with AKI at increased risk for less favorable outcomes. Similar to conventional markers, such as sCr, these novel biomarkers need to be minimally invasive, easily detectable, reliable and inexpensive, but also need to be a direct biomarker of kidney damage (not a surrogate for function) and show correlation with clinically meaningful and potentially actionable outcomes, such as worsening AKI, need for initiation of RRT, non-recovery of function or a composite of these [13].

Biomarkers in AKI

The concept of novel biomarkers for the accurate and timely diagnosis of AKI brings much promise. However, as with any new information available to the clinician, we must ensure that it will positively inform our decision making process, and not simply provide more 'noise' for the clinician to sift through when trying to reach a diagnostic conclusion. For example, when deciding on whether to initiate RRT, the decision is rarely made based solely on biochemical grounds and rather is more likely to be the integration of a number of variables in the setting of a deteriorating clinical picture. It is with all likelihood that biomarkers will eventually play an increasing role in the diagnosis and management of AKI, but integrated into existing decision-making tools and clinical judgment (Table 2). In August 2011, the Acute Dialysis Quality Initiative (ADQI) held a multi-disciplinary consensus conference specifically focused on the evaluation of biomarkers in acute kidney injury (http://www.adqi.net/).

Neutrophil Gelatinase-Associated Lipocalin

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25 kDa protein bound to gelatinase and is typically expressed in several human tissues including the kidney, trachea, lungs, stomach and colon [13, 14]. NGAL is one of the first and most

Table 2 A summary of potential actions that clinicians could take in response to elevated kidney-damage biomarkers, such as NGAL

Action/Decision	Description
Triage	Longer observation in the ED; transition to higher acuity monitoring unit (i. e., HDU or ICU)
Consultation/Referral	Nephrology; intensive care
Diagnostic evaluation	Further evaluation for diagnosis, etiology, reversible contributing factors (e.g., renal ultrasound; urine microscopy; nephrotoxin exposure)
Initiate renal protective strategies	Restore arterial filling; hemodynamic optimization; discontinue or dose-adjust nephrotoxic medications
Monitoring	Surveillance for development of AKI; worsening AKI; complications of AKI and overt renal failure; RRT planning
Context-specific interventions	Dependent on the key contributing factor for AKI
Follow-up	Surveillance for longer-term decline in kidney function and development of CKD

ED: emergency department; HDU: high dependency unit; ICU: intensive care unit; AKI: acute kidney injury; CKD: chronic kidney disease; RRT: renal replacement therapy

rapidly upregulated transcripts in renal tubular epithelial cells following acute injury [14–16]. The protein by-product of this gene upregulation, NGAL, is easily measured in the urine and plasma, where its concentration increases in a dose-dependent relationship with the severity and duration of acute tubular injury. Numerous observational studies have evaluated urine and serum NGAL for the diagnosis and prognosis of AKI in adult critically ill patients and will be the primary focus of this review (Table 3).

Diagnosis of AKI

In pediatric populations, NGAL has been shown to be an early marker of kidney damage, rising significantly as early as two hours after cardiac surgery with cardiopulmonary bypass (CPB) and predictive of development of conventionally defined AKI [17, 18]. However, translation of these findings to adult populations has been variable [12]. This is likely attributable to the added confounding influences in adult patients, such as burden of comorbid illness (e.g., cardiovascular disease, chronic kidney disease) and the multiple heterogeneous contributing factors for AKI [14]. Several studies have examined the validity of NGAL for the diagnosis of AKI in adult critically ill patients [19–23]. Cruz et al. evaluated serum NGAL in 301 consecutive patients admitted to a general medical/surgical ICU. AKI, defined by the RIFLE criteria, occurred in 133 patients (44 %). NGAL was higher in those developing AKI (185 ng/ml vs. 82 ng/ml, $p < 0.001$) and had good

Table 3 Selected prospective cohort studies examining NGAL in adult patients (studies inclusive of > 100 patients).

Author	Year	Design	Patient Population	N	NGAL	Outcome	AUC ROC
Doi et al [30]	2011	Single center	Mixed	339	Urine	AKI Death	0.70 0.83
de Geus et al [20]	2011	Single center	Mixed	632	Urine and Serum	AKI RRT	0.77 0.88
Endre et al [21]	2011	Multicenter	Mixed	529	Urine	AKI RRT Death	0.66 0.79 0.66
Cruz et al [19]	2010	Single center	Mixed	307	Serum	AKI RRT	0.78 0.82
Kumpers et al [31]	2010	Single center	Mixed + RRT	109	Serum	Death	0.74
Parikh et al [35]	2011	Multicenter	Post-CPB	1,219	Urine and Serum	AKI LOS Death	0.67 and 0.70
Koyner et al [36]	2010	Single center	Post-CPB	123	Urine and Serum	AKI	0.69 and 0.69
Haase-Fieltz [12]	2009	Single center	Post-CPB	100	Serum	AKI RRT	0.79 0.83
Liangos et al [37]	2009	Multicenter	Post-CPB	103	Urine	–	–
Wagener et al [38]	2008	Single center	Post-CPB	426	Urine	AKI	0.60
Torregrosa et al [39]	2012	Single center	Cardiac ICU	135	Urine	AKI	0.98
Shapiro et al [22]	2011	Multicenter	ED + Sepsis	661	Serum	AKI	0.96; 0.51‡
Nickolas et al [29]	2008	Single center	ED	635	Urine	AKI Composite†	0.90; 0.99‡

ICU: intensive care unit; mixed: medical/surgical ICU; ED: emergency department; CPB: cardiopulmonary bypass; AUROC: area under the receiving operator characteristic curve; AKI: acute kidney injury; †Nephrology consultation, RRT initiation, ICU admission; ‡ Sensitivity and specificity.

discrimination for predicting AKI in the subsequent 48 hours (area under receiver operative characteristic curve [AUROC] 0.78), implying a lead-time benefit for the diagnosis of those at elevated risk for AKI [19]. In another large single-center prospective observational study, de Geus et al. [20] measured urine and serum NGAL

at ICU admission in 632 consecutive critically ill patients to evaluate its utility to predict development of AKI, defined by the RIFLE criteria, within 1 week. In this study, the discrimination of urine and serum NGAL were higher for more severe AKI (AUROC for RIFLE – Failure 0.88 and 0.86, respectively). Whereas crude prediction was similar to that of admission estimated GFR (eGFR, AUROC 0.84), the integration of urine and serum NGAL in the best clinical prediction model improved discrimination. In addition, urine NGAL was superior to serum NGAL for discriminating between the development of transient and sustained AKI (AUROC 0.80) and added net discrimination improvement to the best clinical prediction model [24]. In another prospective observational study of several novel biomarkers including urine NGAL, in which 529 critically ill patients admitted to two ICUs were enrolled, the diagnostic performance of urine NGAL was improved when stratified by baseline kidney function and time from onset of injury [21].

Subclinical AKI

In a recent pooled analysis of 10 prospective observational studies, detectable elevations in urine and/or plasma NGAL, in the absence of detectable changes in sCr fulfilling the conventional diagnosis of AKI, identified a unique cohort of patients with 'subclinical AKI' [25]. These patients were at greater risk of adverse events, a more complicated clinical course and less favorable clinical outcome, including RRT initiation, higher mortality, longer durations of stay in the ICU and hospital when compared to those without evidence of detectable elevations in NGAL. These findings were consistent regardless of whether NGAL was measured in the urine or serum. It has also recently been suggested that NGAL be used as a marker of kidney damage without evident dysfunction and concomitant elevations in sCr in patients undergoing radiographical procedures involving contrast dyes to better define and treat contrast-induced nephropathy [26]. These observations imply the existence of a clinically important state of subclinical kidney 'damage' detectable only by injury-specific biomarkers, such as NGAL, that occurs without significant loss to GFR and that may be completely missed by our current diagnostic paradigm for AKI [27].

Prognosis in AKI

NGAL has been investigated in numerous studies across a range of clinical settings (e.g., ICU, emergency department [ED], postoperative) as a prognostic biomarker to discriminate and predict clinically important outcomes. A large systematic review and meta-analysis showed that NGAL had value for predicting not only the development of AKI, but also RRT initiation and mortality [28]. Two studies have recently shown that urine NGAL has high predictive value for the diagnosis of AKI

within 72 hours for patients presenting to the ED [22, 29]. Indeed, a single elevated urine NGAL > 130 ng/mg was associated with a 24-fold increased risk of treatment escalation, including nephrology consultation, RRT initiation or ICU admission [29]. In the critically ill, several studies have shown that an elevated NGAL at the time of ICU admission predicts RRT initiation (AUROC 0.82–0.88); prolonged stay in ICU and hospital; and/or increased risk of death; however, prediction of mortality was only fair (AUROC 0.68) [19, 20, 30]. Plasma NGAL has also been shown to correlate with the severity and duration of AKI, as well as overall illness severity (e.g., Acute Physiology and Chronic Health Evaluation II [APACHE II] score), implying it may have value as a valuable global biomarker of prognosis [19]. In addition, when measured in critically ill patients with severe AKI started on RRT, serum NGAL concentrations at the time of RRT initiation were higher in non-survivors compared to survivors, and independently predicted 28-day survival [31]. Elevated NGAL after cardiac surgery not only predicts the development of AKI, but is also associated with improved discrimination for hospital stay, RRT initiation or death (AUROC 0.75). Serum NGAL has also been shown to have value for prediction of worsening or progressing of AKI in the postoperative period [32]. Recently, two studies have shown that NGAL may have value for predicting kidney recovery after an episode of severe AKI [33, 34]. Recovery may depend on a number of independent factors, including baseline kidney function, the severity of the initial insult and whether there are ongoing insults. In a small substudy of critically ill patients from the ATN trial, serial measures of a composite of biomarkers, including NGAL, cystatin C, and hepatocyte growth factor (HGF), when integrated with the best clinical prediction model, showed excellent discrimination for recovery to dialysis independence (AUROC 0.90), implying incremental value for integrating a panel of biomarkers for predicting renal recovery [34].

Conclusion

AKI remains a common and challenging clinical problem for clinicians. Indeed, AKI may be largely iatrogenic and may be partly attributable to the advent of modern ICU support. Importantly, its incidence continues to rise, its associated outcomes are poor, and there are currently few, if any, preventative and/or therapeutic interventions that can modify this prognosis once established. Currently, the standard tools we have to diagnose and monitor AKI (i. e., sCr and urine output) have remained unchanged for several decades and are clearly suboptimal. There are now numerous conventional and novel kidney-injury specific biomarkers that have been characterized and are undergoing clinical validation for the diagnosis and clinical outcome prediction across a spectrum of at-risk patients. This list also includes a reappraisal of conventional measures of kidney function, such as urine output, sCr, and urine microscopy; but also importantly highlights a growing list of novel biomarkers, such as interleukin-18, kidney injury molecule-1, L-type fatty acid binding protein, HGF, *N*-acetyl-β-D-glucosaminidase, α-glutathione S-transferase,

π-glutathione S-transferase and matrix metalloproteinase-9. NGAL remains one of the most well-described biomarkers of kidney damage. While numerous ongoing clinical studies are pursuing further clinical validation, available data imply that this biomarker holds promise to better inform on the early diagnosis and provide important prognostic information (e.g., worsening AKI, need for RRT, renal recovery), in particular when integrated with clinical prediction models.

References

1. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW (2005) Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol 16:3365–3370
2. Liangos O, Wald R, O'Bell JW, Price L, Pereira BJ, Jaber BL (2006) Epidemiology and outcomes of acute renal failure in hospitalized patients: a national survey. Clin J Am Soc Nephrol 1:43–51
3. Bagshaw SM, George C, Bellomo R (2007) Changes in the incidence and outcome for early acute kidney injury in a cohort of Australian intensive care units. Crit Care 11:R68
4. Bagshaw SM, George C, Dinu I, Bellomo R (2008) A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients. Nephrol Dial Transplant 23:1203–1210
5. Hoste EA, Clermont G, Kersten A et al (2006) RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care 10:R73
6. Uchino S, Kellum JA, Bellomo R et al (2005) Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 294:813–818
7. Ahlstrom A, Tallgren M, Peltonen S, Rasanen P, Pettila V (2005) Survival and quality of life of patients requiring acute renal replacement therapy. Intensive Care Med 31:1222–1228
8. Bagshaw SM, Laupland KB, Doig CJ et al (2005) Prognosis for long-term survival and renal recovery in critically ill patients with severe acute renal failure: a population-based study. Crit Care 9:R700–R709
9. Wald R, Quinn RR, Luo J et al (2009) Chronic dialysis and death among survivors of acute kidney injury requiring dialysis. JAMA 302:1179–1185
10. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P (2004) 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 8:R204–R212
11. Kidney Disease: Improving Global Outcomes (2012) KDIGO Clinical Practice Guidelines for Acute Kidney Injury. Kidney Int(Suppl 2):1–138
12. Haase-Fielitz A, Bellomo R, Devarajan P et al (2009) Novel and conventional serum biomarkers predicting acute kidney injury in adult cardiac surgery – a prospective cohort study. Crit Care Med 37:553–560
13. Cowland JB, Borregaard N (1997) Molecular characterization and pattern of tissue expression of the gene for neutrophil gelatinase-associated lipocalin from humans. Genomics 45:17–23
14. Devarajan P (2008) NGAL in acute kidney injury: from serendipity to utility. Am J Kidney Dis 52:395–399
15. Bolignano D, Coppolino G, Campo S et al (2008) Urinary neutrophil gelatinase-associated lipocalin (NGAL) is associated with severity of renal disease in proteinuric patients. Nephrol Dial Transplant 23:414–416

16. Bolignano D, Donato V, Coppolino G et al (2008) Neutrophil gelatinase-associated lipocalin (NGAL) as a marker of kidney damage. Am J Kidney Dis 52:595–605
17. Dent CL, Ma Q, Dastrala S et al (2007) Plasma neutrophil gelatinase-associated lipocalin predicts acute kidney injury, morbidity and mortality after pediatric cardiac surgery: a prospective uncontrolled cohort study. Crit Care 11:R127
18. Mishra J, Dent C, Tarabishi R et al (2005) Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet 365:1231–1238
19. Cruz DN, de Cal M, Garzotto F et al (2010) Plasma neutrophil gelatinase-associated lipocalin is an early biomarker for acute kidney injury in an adult ICU population. Intensive Care Med 36:444–451
20. de Geus HR, Bakker J, Lesaffre EM, le Noble JL (2011) Neutrophil gelatinase-associated lipocalin at ICU admission predicts for acute kidney injury in adult patients. Am J Respir Crit Care Med 183:907–914
21. Endre ZH, Pickering JW, Walker RJ et al (2011) Improved performance of urinary biomarkers of acute kidney injury in the critically ill by stratification for injury duration and baseline renal function. Kidney Int 79:1119–1130
22. Shapiro NI, Trzeciak S, Hollander JE et al (2010) The diagnostic accuracy of plasma neutrophil gelatinase-associated lipocalin in the prediction of acute kidney injury in emergency department patients with suspected sepsis. Ann Emerg Med 56:52–59
23. Soni SS, Ronco C, Katz N, Cruz DN (2009) Early diagnosis of acute kidney injury: the promise of novel biomarkers. Blood Purif 28:165–174
24. de Geus HR, Woo JG, Wang Y et al (2011) Urinary neutrophil gelatinase-associated lipocalin measured on admission to the intensive care unit accurately discriminates between sustained and transient acute kidney injury in adult critically ill patients. Nephron Extra 1:9–23
25. Haase M, Devarajan P, Haase-Fielitz A et al (2011) The outcome of neutrophil gelatinase-associated lipocalin-positive subclinical acute kidney injury: a multicenter pooled analysis of prospective studies. J Am Coll Cardiol 57:1752–1761
26. Ronco C, Stacul F, McCullough PA (2013) Subclinical acute kidney injury (AKI) due to iodine-based contrast media. Eur Radiol 23:319–323
27. Ronco C, Kellum JA, Haase M (2012) Subclinical AKI is still AKI. Crit Care 16:313
28. Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A (2009) Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis 54:1012–1024
29. Nickolas TL, O'Rourke MJ, Yang J et al (2008) Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury. Ann Intern Med 148:810–819
30. Doi K, Negishi K, Ishizu T et al (2011) Evaluation of new acute kidney injury biomarkers in a mixed intensive care unit. Crit Care Med 39:2464–2469
31. Kumpers P, Hafer C, Lukasz A et al (2010) Serum neutrophil gelatinase-associated lipocalin at inception of renal replacement therapy predicts survival in critically ill patients with acute kidney injury. Crit Care 14:R9
32. Koyner JL, Garg AX, Coca SG et al (2012) Biomarkers predict progression of acute kidney injury after cardiac surgery. J Am Soc Nephrol 23:905–914
33. Srisawat N, Murugan R, Lee M et al (2011) Plasma neutrophil gelatinase-associated lipocalin predicts recovery from acute kidney injury following community-acquired pneumonia. Kidney Int 80:545–552
34. Srisawat N, Wen X, Lee M et al (2011) Urinary biomarkers and renal recovery in critically ill patients with renal support. Clin J Am Soc Nephrol 6:1815–1823
35. Parikh CR, Coca SG, Thiessen-Philbrook H et al (2011) Postoperative biomarkers predict acute kidney injury and poor outcomes after adult cardiac surgery. J Am Soc Nephrol 22:1748–1757
36. Koyner JL, Vaidya VS, Bennett MR et al (2010) Urinary biomarkers in the clinical prognosis and early detection of acute kidney injury. Clin J Am Soc Nephrol 5:2154–2165

37. Liangos O, Perianayagam MC, Vaidya VS et al (2007) Urinary N-acetyl-beta-(D)-glucosaminidase activity and kidney injury molecule-1 level are associated with adverse outcomes in acute renal failure. J Am Soc Nephrol 18:904–912
38. Wagener G, Gubitosa G, Wang S, Borregaard N, Kim M, Lee HT (2008) Urinary neutrophil gelatinase-associated lipocalin and acute kidney injury after cardiac surgery. Am J Kidney Dis 52:425–433
39. Torregrosa I, Montoliu C, Urios A et al (2012) Early biomarkers of acute kidney failure after heart angiography or heart surgery in patients with acute coronary syndrome or acute heart failure. Nefrologia 32:44–52