

Subclinical acute kidney injury: a novel biomarker-defined syndrome

Sean M Bagshaw

Acute kidney injury (AKI) is an undeniable clinical problem. Its incidence among critically ill patients is remarkably high, and it consistently forecasts increased complexity of care, negatively modifies both short- and long-term outcomes, and greatly intensifies the associated health costs for patients in whom it develops.^{1,2} Hence, considerable research effort is focused on understanding the pathobiology and improving the outcomes associated with AKI.

The term AKI broadly defines a wide spectrum of abrupt changes to kidney function, encompassing mild elevations in serum creatinine (sCr) levels to overt kidney failure requiring support with renal replacement therapy (RRT). Historically, inferences on the epidemiological burden of AKI have been imprecise due to the lack of agreement on an acceptable clinical and academic definition. However, in 2004, the Acute Dialysis Quality Initiative (ADQI) workgroup proposed the consensus-driven Risk–Injury–Failure–Loss–End-stage (RIFLE) classification scheme.³ The RIFLE criteria define three grades of AKI severity (Risk of renal dysfunction, Injury to the kidney and Failure of kidney function) based on detected changes to sCr levels from a known baseline and changes to urine output, along with two clinical outcomes (Loss of kidney function, End-stage kidney disease). Since this publication, AKI has been largely defined according to these criteria (or the proposed modifications presented by Acute Kidney Injury Network [AKIN]).⁴

These consensus criteria represent the current diagnostic paradigm in AKI, and have clearly been a monumental advance in the field.⁵ However, the RIFLE (and AKIN) criteria are not without significant shortcomings. For example, sCr concentration is a poor surrogate marker of changes to glomerular filtration rate (GFR), so its use is immensely problematic. Serum creatinine can require hours and/or days to accumulate after acute declines to GFR, and may only show significant increases after loss of about 50% of GFR. The volume of distribution of sCr can be inconsistent and heavily modified by critical illness and fluid resuscitation.⁶ Finally, experimental data have shown the expression of creatinine from muscle may be suppressed in septic states.⁷ Consequently, the use of sCr as the principal marker of AKI is highly prone to delayed detection and missed episodes of important declines in GFR. This is clearly inadequate when the timely diagnosis of AKI among critically ill patients is a major clinical priority, given the prognostic repercussions associated with kidney failure.

Several promising novel biomarkers specific to kidney injury have recently been characterised, validated, and are increasingly available in clinical practice for the early detection and diagnosis of AKI. Importantly, these biomarkers better reflect real-time injury to renal tubular epithelial tissue and provide considerable lead time in the detection of the potential for overt AKI compared with sCr levels.⁸

Neutrophil gelatinase-associated lipocalin (NGAL) is one such promising biomarker. NGAL is a 25 kD polypeptide that is rapidly up-regulated in renal tubular epithelial tissue in response to distal nephron injury.⁹ NGAL levels are easily measured in urine and plasma, where its concentration increases in a dose-dependent relationship with the severity and duration of acute tubular injury.^{10,11} Several observational studies have suggested NGAL is a sensitive biomarker for anticipating (by 24–48 hours) the occurrence of conventionally diagnosed AKI.^{12–14} Moreover, NGAL may provide important prognostic information on the risk of worsening AKI, need for RRT and mortality.^{10,11} Although encouraging, these findings have not been universally consistent.^{15,16} Interestingly, however, it has been speculated that the observed uncertainty on the performance of NGAL, particularly among critically ill patients, may be more specifically related to the use of a suboptimal surrogate marker (ie, sCr) as the diagnostic “gold standard” for AKI.¹¹

This is perhaps best demonstrated by the recent observation of a subgroup of patients who were exposed to a kidney injury stimulus, such as cardiopulmonary bypass, and who clearly developed increased detectable levels of kidney injury-specific biomarkers, such as elevated NGAL, yet did not overtly manifest changes to sCr levels. Thus, despite detectable organ injury, these patients did not satisfy the conventional consensus definition for AKI. These patients have a syndrome best characterised as “subclinical” AKI.¹¹

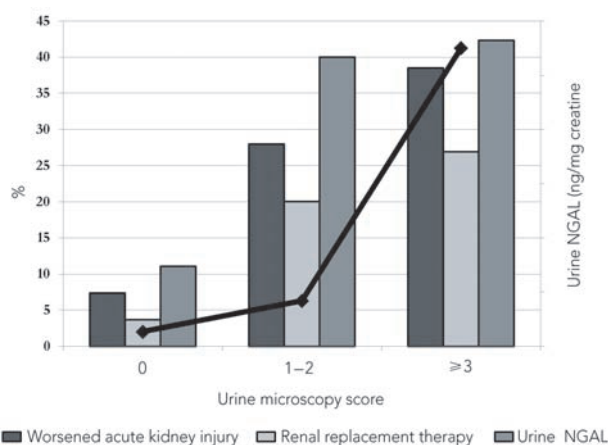
Recently, Haase and colleagues investigated the hypothesis that elevated NGAL levels, in the absence of detectable increases in sCr concentration that would fulfil the conventional diagnosis of AKI, would identify a unique cohort of patients with subclinical AKI whose clinical course would be more complicated and whose prognosis would be poorer.¹¹ These investigators performed a pooled analysis of aggregate data from 10 prospective observational studies, comprising a total of 2322 critically ill patients, that evaluated the value of NGAL for the early diagnosis of AKI. The patients were classified into four discrete groups for analysis: NGAL(–)/sCr(–),

Table 1. Summary of outcomes stratified by aggregate subgroups of NGAL and sCr¹¹

	NGAL(-)/sCr(-)	NGAL(+)/sCr(-)	NGAL(-)/sCr(+)	NGAL(+)/sCr(+)
No. (%)	1296 (55.8%)	445 (19.2%)	107 (4.6%)	474 (20.4%)
Median peak NGAL, ng/mL (IQR)	59 (20–97)	213 (117–1124)	69 (21–118)	354 (208–1888)
RRT, no. (%)	2 (0.015%)	11 (2.5%)	8 (7.5%)	38 (8.0%)
Composite,* no. (%)	63 (4.9)	69 (15.5)	10 (9.3)	84 (17.7)
Median ICU stay, days (IQR)	4.2 (2.2–6.4)	7.1 (5.4–10.3)	6.5 (3.0–11.7)	9.0 (8.0–14.0)
Median hospital stay, days (IQR)	8.8 (7.7–19.0)	17 (8.4–24.2)	17.8 (5.1–26.4)	21.9 (15.8–29.9)

ICU = intensive care unit. IQR = interquartile range. NGAL = neutrophil gelatinase-associated lipocalin. RRT = renal replacement therapy. sCr = serum creatinine. * Composite = RRT or death.

Figure 1. Summary of clinical outcomes* and urine NGAL stratified by worsening urine microscopy score²¹



NGAL = neutrophil gelatinase-associated lipocalin. *Worsening acute kidney injury, renal replacement therapy, or death.

NGAL(+)/sCr(-), NGAL(-)/sCr(+), and NGAL(+)/sCr(+). In all, 19% of these patients were classified as NGAL(+)/sCr(-), consistent with proposed syndrome of subclinical AKI (Table 1). The identification of this subgroup by NGAL only would have resulted in an additional 43% of patients being diagnosed with AKI, rather than being missed and classified as non-AKI by sCr levels alone. More importantly, the subclinical AKI subgroup showed significantly higher use of RRT, greater mortality, and longer durations of stay in the intensive care unit and hospital than the NGAL(-)/sCr(-) subgroup. This finding was consistent regardless of whether NGAL levels were measured from the urine or plasma. Haase and colleagues further speculate that their data support their hypothesis of a state of subclinical injury detectable only by novel injury-specific biomarkers, such as NGAL, that occurs without significant loss to GFR and is effectively missed by the current AKI diagnostic paradigm.¹¹

How can the biological plausibility of this hypothesis be further proven? There is an additional method for detection of renal tubular injury that can be readily performed as a simple bedside test — urine microscopy. An examination of the urine sediment, a time-honoured practice in clinical nephrology, may represent an additional surrogate for structural injury to renal tubular epithelial tissue. Moreover, such an assessment of the urine sediment may provide additional lead time in the diagnosis of AKI along with prognostic information about the severity of injury and/or its expected clinical course.¹⁷⁻²⁰ Perazella and colleagues recently reported two prospective observational studies evaluating the diagnostic value of a novel urine microscopy score (UMS) among non-ICU hospitalised patients with AKI to predict the occurrence of a composite of “worsening AKI”, defined as an increase in AKIN stage, need for RRT and/or hospital death.^{19,20} They observed that a higher UMS, suggestive of greater detectable structural tubular injury, was associated with an increased adjusted risk for worsening AKI.

More recently, my colleagues and I reported a prospective observational study examining the urine microscopy profile in a cohort of critically ill patients with AKI and its association with urine and plasma NGAL levels, worsening AKI, need for RRT initiation and hospital mortality.²¹ This study found that a higher UMS, implying a greater degree of structural renal tubular injury, correlated significantly with higher urine NGAL concentration (this correlation was less robust for plasma NGAL concentration), and was associated with higher adjusted odds ratio of worsening AKI, defined as a progression in AKI to a higher RIFLE category or need for RRT support (Figure 1).²¹

Interestingly, our study also demonstrated that commonly used urine biochemical indices (ie, fractional excretion of sodium [FeNa] and fractional excretion of urea) correlated poorly with UMS and failed to discriminate reliably whether patients would develop worsening AKI. In fact, a significant proportion of patients with an elevated UMS had relatively preserved global tubular function when expressed as a

capacity to generate a FeNa <1%. This is an important observation, and would suggest the association between true structural tubular injury, detected by either urine microscopy or NGAL concentration, and tubular function is more complex than often appreciated. Traditionally, patients who fulfil the conventional RIFLE definition for AKI and have evidence of preserved tubular function (ie, FeNa <1%) would be classified as having functional AKI (ie, prerenal azotaemia). Clearly, this notion can now be challenged by observations suggesting that structural tubular injury, independent of detectable declines in tubular function and/or glomerular filtration, conveys an increased risk for worse outcome.^{11,21} Moreover, these data further support the hypothesis of the existence of a syndrome of subclinical AKI, again characterised by detectable structural tubular injury but relative preservation of global kidney function.

The implication of these observations, and the next logical step, would be to integrate these measures of structural injury (ie, NGAL levels, urine microscopy) into the next iteration of a consensus definition for AKI, so as to ensure this novel subgroup of subclinical AKI is appropriately identified and captured. This would certainly translate into an improvement in the diagnostic performance of current consensus criteria, but also have far-reaching implications for providing earlier opportunity for therapeutic interventions that may limit ongoing injury, promote renal repair, and improve the outcomes for these patients who have previously fared poorly.

Competing interests

None declared.

Author details

Sean M Bagshaw, Assistant Professor

Division of Critical Care Medicine, University of Alberta Hospital, University of Alberta, Edmonton, Alberta, Canada.

Correspondence: bagshaw@ualberta.ca

References

- Ishani A, Xue JL, Himmelfarb J, et al. Acute kidney injury increases risk of ESRD among elderly. *J Am Soc Nephrol* 2009; 20: 223-8.
- Wald R, Quinn RR, Luo J, et al. Chronic dialysis and death among survivors of acute kidney injury requiring dialysis. *JAMA* 2009; 302: 1179-85.
- Bellomo R, Ronco C, Kellum JA, et al. 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: R204-12.
- Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; 11: R31.
- Ricci Z, Cruz D, Ronco C. The RIFLE criteria and mortality in acute kidney injury: a systematic review. *Kidney Int* 2008; 73: 538-46.
- Macedo E, Bouchard J, Soroko SH, et al. Fluid accumulation, recognition and staging of acute kidney injury in critically-ill patients. *Crit Care* 2010; 14: R82.
- Doi K, Yuen PS, Eisner C, et al. Reduced production of creatinine limits its use as marker of kidney injury in sepsis. *J Am Soc Nephrol* 2009; 20: 1217-1221.
- Paragas N, Qiu A, Zhang Q, et al. The *Ngal* reporter mouse detects the response of the kidney to injury in real time. *Nat Med* 2011; 17: 216-22.
- Mishra J, Dent C, Tarabishi R, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. *Lancet* 2005; 365: 1231-8.
- Haase M, Bellomo R, Devarajan P, et al. 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* 2009; 54: 1012-24.
- Haase M, Devarajan P, Haase-Fielitz A, et al. The outcome of neutrophil gelatinase-associated lipocalin-positive subclinical acute kidney injury: a multicenter pooled analysis of prospective studies. *J Am Coll Cardiol* 2011; 57: 1752-61.
- Bennett M, Dent CL, Ma Q, et al. Urine NGAL predicts severity of acute kidney injury after cardiac surgery: a prospective study. *Clin J Am Soc Nephrol* 2008; 3: 665-73.
- Cruz DN, de Cal M, Garzotto F, et al. Plasma neutrophil gelatinase-associated lipocalin is an early biomarker for acute kidney injury in an adult ICU population. *Intensive Care Med* 2010; 36: 444-51.
- Zappitelli M, Washburn KK, Arikian AA, et al. Urine neutrophil gelatinase-associated lipocalin is an early marker of acute kidney injury in critically ill children: a prospective cohort study. *Crit Care* 2007; 11: R84.
- Siew ED, Ware LB, Gebretsadik T, et al. Urine neutrophil gelatinase-associated lipocalin moderately predicts acute kidney injury in critically ill adults. *J Am Soc Nephrol* 2009; 20: 1823-32.
- Wagener G, Gubitosa G, Wang S, et al. Urinary neutrophil gelatinase-associated lipocalin and acute kidney injury after cardiac surgery. *Am J Kidney Dis* 2008; 52: 425-33.
- Chawla LS, Domm A, Berger A, et al. Urinary sediment cast scoring index for acute kidney injury: a pilot study. *Nephron Clin Pract* 2008; 110: c145-50.
- Marcussen N, Schumann J, Campbell P, Kjellstrand C. Cytodiagnostic urinalysis is very useful in the differential diagnosis of acute renal failure and can predict the severity. *Ren Fail* 1995; 17: 721-9.
- Perazella MA, Coca SG, Hall IE, et al. Urine microscopy is associated with severity and worsening of acute kidney injury in hospitalized patients. *Clin J Am Soc Nephrol* 2010; 5: 402-8.
- Perazella MA, Coca SG, Kanbay M, et al. Diagnostic value of urine microscopy for differential diagnosis of acute kidney injury in hospitalized patients. *Clin J Am Soc Nephrol* 2008; 3: 1615-9.
- Bagshaw SM, Haase M, Haase-Fielitz A, et al. A prospective evaluation of urine microscopy in septic and non-septic acute kidney injury. *Nephrol Dial Transplant* 2011; Jun 9. [Epub ahead of print] □