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Biomarkers of Acute Kidney Injury

An Evolving Domain

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DESPITE more than half a century of investigation, acute kidney injury (AKI) remains a major healthcare issue in medicine today. Reported to occur in 1–32% of all hospital admissions and 10–90% of intensive care unit admissions, the wide variation reflects different criteria used to define AKI. However, independent of definition, a diagnosis of AKI is consistently associated with an increase in both short- and long-term morbidity and mortality. Even the mildest forms of AKI are independently associated with increased early as well as long-term mortality, the risk increasing as severity of renal injury increases.^{1,2} Furthermore, the incidence of AKI is increasing. Based on a large administrative database study of hospital admissions from 1992 to 2001, Xue *et al.*³ estimated an 11% increase per year in the incidence of AKI. However, of even greater concern is the failure to develop effective interventions to prevent or treat AKI, meaning that the current management remains directed toward supportive therapy while awaiting recovery of renal function.

A major impediment to developing effective therapeutic interventions to combat AKI has been the limited ability to accurately detect significant renal injury in a timely manner. Serum creatinine has been the predominant marker of renal function in clinical practice for more than half a century and

its limitations are well documented. As a marker of renal function rather than injury, the nonlinear relationship between glomerular filtration rate and serum creatinine means glomerular filtration rate may decrease by more than 50% from normal before a significant rise in serum creatinine occurs, making creatinine insensitive to small but significant reductions in glomerular filtration rate. Furthermore, serum concentration is influenced by numerous nonrenal factors including age, race, gender, and muscle mass as well as factors such as drug metabolism, protein intake, perioperative fluid administration and hydration status. Consequently, it has proven difficult to define what change in creatinine constitutes significant AKI. The RIFLE criteria (an acronym of the sequentially graded Risk, Injury, Failure, Loss and End-stage classification system for AKI) and more recently the AKIN (Acute Kidney Injury Network classification of AKI) criteria represent attempts by international bodies of experts to standardize definitions and improve the understanding of the epidemiology of AKI. In validating these criteria, the significance of small changes in creatinine has been confirmed, emphasizing the enormous disease burden that AKI represents.

However, a further limitation in the use of creatinine to diagnose AKI is the inevitable delay between injury and the subsequent rise in serum creatinine. Although serum creatinine may begin to increase on postoperative day 1 after cardiac surgery, the majority of patients who develop AKI do not meet diagnostic criteria until postoperative day 2 or beyond.^{4,5} Consequently, by the time serum creatinine can identify AKI, the inciting injury may be days old. Animal models of AKI consistently indicate that the window of opportunity for effective intervention to prevent or attenuate AKI is limited to within just a few hours of injury.

The Urgent Need for Biomarkers

Acknowledging the inherent deficiencies of serum creatinine to diagnose AKI, the American Society of Nephrology in 2005 designated identification, characterization, and development of new AKI biomarkers as a key research area for

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Table 1. Characteristics of an Ideal Biomarker for Acute Kidney Injury

Biologic Properties	Physicochemical Properties
Rapid and reliable increase in response to injury	Stable across a wide range of temperature and pH environments
Highly sensitive for AKI with a wide dynamic range and cutoff values	Easily measured in urine or serum
Highly specific for AKI	Rapid, reliable, and inexpensive measurement using standardized assay platforms
Etiologic specificity (given multifactorial etiology of AKI)	Levels unaffected by drugs or other endogenous substances
Level should correlate with injury severity	
Level should provide prognostic information	
Applicable across a range of different populations	

AKI = acute kidney injury.

the next 5 yr.⁶ An ideal biomarker would identify patients at highest risk for AKI in a timely manner, thus allowing early and potentially effective intervention. Characteristics of the ideal AKI biomarker have been described and include early identification of injury, stratification according to injury severity, etiologic specificity for the injury, and providing valuable prognostic information (table 1). However, the wide

spectrum of pathophysiology leading to AKI makes it unlikely that any single biomarker will achieve all these aims. Several promising biomarkers of AKI have been identified, both in urine and plasma, and are currently the subject of ongoing studies defining their clinical utility (fig. 1). However, the translational process from bench to bedside is complicated. Interpretation of novel biomarkers to detect minor but significant renal injury undetected by serum creatinine proved difficult in the 1990s as anesthesiologists investigated potential nephrotoxicity associated with sevoflurane. Although insensitive and slow to respond, creatinine remains the only marker validated against clinically relevant outcomes. Any potential replacement must therefore demonstrate the ability to identify clinically meaningful injury and be useful in guiding suitable interventions or other management decisions. Although the molecular pathways mediating renal injury are increasingly understood, with potential to quantify individual components of these pathways in the laboratory,⁷ the focus of this clinical commentary is on biomarkers that reflect renal injury, which is frequently the result of multiple contemporaneous mechanisms in clinical practice.

Current Biomarkers under Investigation

Neutrophil Gelatinase-associated Lipocalin

DNA microarray techniques searching for candidate biomarkers of AKI found neutrophil gelatinase-associated lipocalin (NGAL) as one of the maximally induced genes in a murine model of renal ischemia-reperfusion injury. A 25-kDa glycoprotein covalently bound to gelatinase, its resistance to proteolysis further enhanced potential suitability as a clinical biomarker. It is synthesized and secreted by tubular

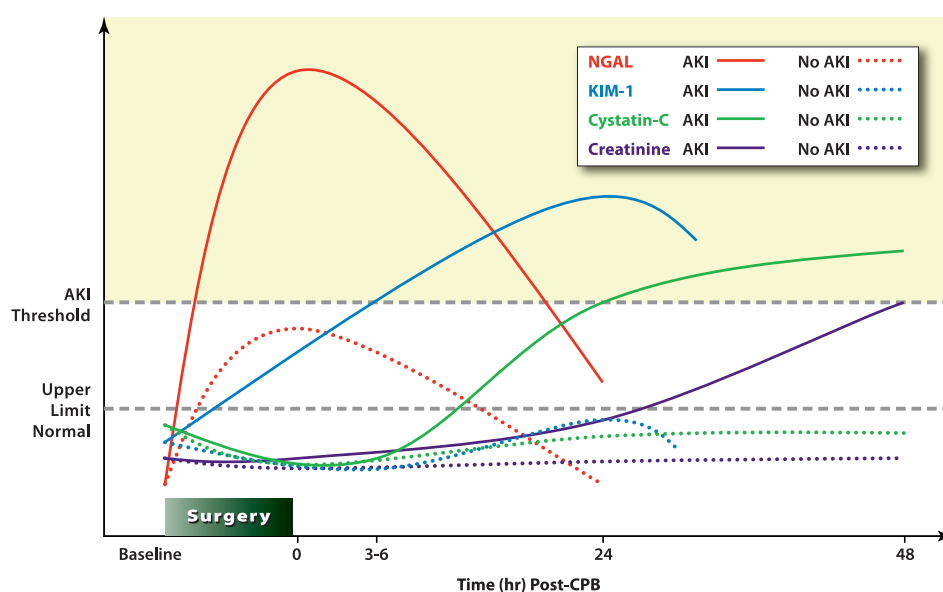


Fig. 1. Schematic representation of the predicted time course of change in biomarker levels for the detection of AKI after cardiac surgery in adults. Patterns of change represent ideal circumstances, which have not been consistently demonstrated in clinical studies. AKI = acute kidney injury; CPB = cardiopulmonary bypass; creatinine = serum creatinine; cystatin-C = serum cystatin-C; KIM-1 = urinary kidney injury molecule-1; NGAL = urinary neutrophil gelatinase-associated lipocalin.

epithelial cells of the proximal and distal segment. It is freely filtered by the glomerulus, undergoing rapid clearance by the proximal tubule *via* receptor binding and endocytosis. In healthy kidneys, it is barely detectable in either plasma or urine. However, in the setting of acute tubular injury, NGAL undergoes rapid and profound upregulation with large increases in both urine and plasma. Distinct from traditional markers of function such as creatinine, this rapid response enables NGAL to potentially identify injured kidney much earlier than was previously possible. The endogenous role of NGAL remains unclear. It seems to be involved with iron transportation to and from the proximal tubular epithelial cells, and animal studies demonstrate a renoprotective effect of exogenously administered NGAL in the setting of acute ischemic injury.

NGAL demonstrated a near-perfect performance for identifying AKI after pediatric cardiac surgery with an area under the receiver operator characteristic curve (AUC_{ROC}) of 0.99 and 1.0 at 2 and 4 h after cardiopulmonary bypass (CPB), respectively.⁸ Subsequent studies of both urinary and plasma NGAL in pediatric cardiac surgery support this, further demonstrating it to be an independent predictor of AKI severity and duration as well as hospital length of stay. However, results in adult cardiac surgery have been mixed, with different studies reporting widely varying diagnostic characteristics for NGAL. The AUC_{ROC} for early diagnosis of AKI by urinary NGAL has varied from 0.61 at 18 h post-CPB⁵ to 0.96 at 2 h post-CPB.⁹ Similarly, performance of plasma NGAL for the diagnosis of AKI has varied from an AUC_{ROC} of 0.54 within 6 h of CPB¹⁰ to 0.87 at 24 h post-CPB.¹¹ Although specificity was consistently 70–80% in these studies, sensitivity has varied greatly, ranging from 40 to 90%. The reason for such widely discrepant findings is unclear. Studies reporting poorer diagnostic performance of NGAL have typically included patients with a wide spectrum of baseline renal function, and it is unknown whether this impacts the diagnostic performance of NGAL. The additional comorbidities typical of an adult cardiac surgical population may also introduce potential confounding variables, thus increasing the etiologic heterogeneity of AKI in this population. Furthermore, it is uncertain whether age itself modifies NGAL synthesis in AKI. Recently, urinary NGAL at hospital admission in multitrauma patients provided excellent early identification of AKI developing during the subsequent 5 days (AUC_{ROC} 0.98) with both sensitivity and specificity greater than 90%.¹² NGAL has also been demonstrated to identify delayed graft function within hours of kidney transplantation,¹³ and ongoing studies are exploring its utility for early identification of renal injury in liver transplantation.

The biologic rationale for NGAL as an early AKI biomarker is strong. However, a number of key issues, including the wide variability in reported diagnostic performance, require clarification before adoption into clinical practice. Although a rapid point-of-care test is available, experience is limited

and its reliability remains to be confirmed with most studies to date using a research-based enzyme-linked immunosorbent assay technique for NGAL quantification.

Cystatin-C

A small cysteine proteinase inhibitor, cystatin-C, has many features of an ideal glomerular filtration marker. Synthesized and released into plasma by all nucleated cells at a constant rate, its small size (13 kDa) and positive charge at physiologic pH makes it freely filtered at the glomerulus. It is neither secreted nor reabsorbed by renal tubules but undergoes almost complete catabolism by proximal tubular cells, and thus little, if any, appears in the urine. With a half-life of about 2 h, serum cystatin-C reflects glomerular filtration rate better than creatinine. Although it is generally considered less subject to the nonrenal variables that impact creatinine, recent studies suggest that cystatin-C levels may in fact be affected by various anthropometric measures as well as inflammatory processes, use of corticosteroids, and changes in thyroid function, thereby potentially confounding perioperative interpretation.¹⁴

Although increasingly reported as an endpoint in clinical studies, the diagnostic and prognostic characteristics of cystatin-C for AKI remain incompletely defined. In a mixed critical care population, cystatin-C enabled a diagnosis of AKI 1.5 days earlier than plasma creatinine, with moderate ability to predict dialysis requirement.¹⁵ However, a similar repeat study found that cystatin-C identified AKI no earlier than creatinine and did not predict mortality.¹⁶ Results in adult cardiac surgery are similarly mixed, with one study reporting good discrimination for AKI within 6 h of surgery (AUC_{ROC} 0.83, sensitivity 77%, specificity 86%),¹¹ whereas a further study of similar size found serum cystatin-C no better than chance for identifying AKI.¹⁰ However, the latter study did find that urinary cystatin-C identified AKI within 6 h of surgery (AUC_{ROC} 0.72, sensitivity 94%, specificity 40%), suggesting that tubular injury may impair the usual catabolism of cystatin-C, leading to its appearance in urine. Several studies report a rise in cystatin-C within 8 h of exposure to radiocontrast agents but without adequate description of the diagnostic characteristics for contrast-induced nephropathy. Although a commercial platform for rapid and reliable cystatin-C measurement is available, the total number of patients studied remains small and with inconsistencies in results that are not well understood.

Interleukin-18

Interleukin (IL)-18 is synthesized as an inactive 23 kDa precursor by several tissues including monocytes, macrophages, and proximal tubular epithelial cells. Ischemia-reperfusion injury of the proximal tubules as well as other more generalized inflammatory states induces intracellular cleavage, producing the active mature form of IL-18. Animal studies indicate that IL-18 is a mediator of acute tubular necrosis, inducing both neutrophil and monocyte infiltration of the renal parenchyma.

Cross-sectional studies indicate that urinary IL-18 levels are markedly elevated in patients with acute tubular necrosis compared with healthy controls and a variety of other renal pathologies, including urinary tract infection, chronic renal insufficiency, and prerenal azotemia.¹⁷ At renal transplantation, IL-18 accurately identified delayed graft function (AUC_{ROC} 0.90) as well as predicted the rate of decline in serum creatinine over the ensuing days.¹⁸ A study of critically ill patients found a urinary IL-18 level of more than 100 pg/ml as an independent risk factor for AKI during the subsequent 24–48 h, with no evidence that sepsis affected levels, suggesting that most measured IL-18 was of renal origin.¹⁹ However, despite the association between IL-18 and AKI diagnostic utility was only fair 24 h before the rise in creatinine (AUC_{ROC} 0.73) with sensitivity and specificity of 74% and 66%, respectively. In a pediatric critical care population, elevated IL-18 levels were associated with a fivefold increase in odds of AKI developing during the subsequent 48 h but diagnostic utility for AKI was poor (AUC_{ROC} 0.54), limited by a sensitivity of less than 40%.²⁰ Results in contrast-induced nephropathy are similarly mixed. Although one study reported fair ability for the early identification of AKI by IL-18 (AUC_{ROC} 0.75) with sensitivity and specificity close to 70% as well as a further association with late cardiovascular events,²¹ another similar study found no association between IL-18 levels and subsequent contrast-induced nephropathy after angiography.²²

IL-18 levels increased within 4 h of cardiac surgery in children who developed AKI, peaking 12 h postoperatively.²³ Optimal diagnostic performance occurred 12 h postoperatively (AUC_{ROC} 0.75) and although sensitivity for AKI was poor (50%), specificity and positive predictive value were good across a range of threshold values (94 and 83%, respectively), and IL-18 was independently associated with AKI duration. Another study of adults and children undergoing cardiac surgery supported the potential for diagnosis of AKI within 2 h of surgery (AUC_{ROC} 0.89), with sensitivity and specificity both in the excess of 80%.²⁴ However, in a further study in adult cardiac surgery, IL-18 levels increased in all patients postoperatively with no relationship between IL-18 and any creatinine-based measure of renal injury.²⁵ The strong correlation between IL-18 and CPB duration may suggest that IL-18 better represents a nonspecific inflammatory marker rather than a specific marker of AKI.

Although easily and reliably measured in the urine by commercially available enzyme-linked immunosorbent assay, the pathophysiology of IL-18 remains incompletely understood and its true role may be as a mediator of specific injury subtypes rather than as a marker of injury. Current clinical experience is limited and inconsistent with further studies required to understand these differences.

Kidney Injury Molecule-1

Kidney Injury Molecule (KIM)-1 is a type I membrane glycoprotein not detectable in healthy kidneys but dramatically upregulated in dedifferentiated, regenerating proximal

tubular epithelial cells after a variety of injuries including ischemia–reperfusion and nephrotoxic exposure. Increased expression is seen in several malignancies including renal cell carcinoma and clear-cell ovarian carcinoma. The ectodomain of KIM-1 undergoes regulated cleavage, appearing in the urine where it is stable and readily detected by commercially available enzyme-linked immunosorbent assay. It is believed to function as a cell adhesion molecule in the process of regenerating and reconstructing damaged proximal tubules.

The presence of KIM-1 has been demonstrated in renal biopsy specimens of patients with proven acute tubular necrosis. Similarly, urinary KIM-1 was significantly elevated in patients with a clinical diagnosis of acute tubular necrosis compared with patients with normal renal function, chronic renal disease, or acute renal failure of other etiologies including contrast nephropathy.²⁶ A similar study demonstrated excellent diagnostic characteristics (AUC_{ROC} 0.90) for established AKI by urinary KIM-1 across a broad range of etiologies.²⁷ In a hospital population referred for nephrology consultation for acute renal failure, patients with urinary KIM-1 values in the upper quartile had 3.2-fold higher odds for the composite outcome of in-hospital mortality or dialysis. However, after adjusting for other established comorbidities, the association became nonsignificant.²⁸ Urinary KIM-1 increased 6–12 h after cardiac surgery in children who developed AKI and demonstrated good discriminant utility for AKI (AUC_{ROC} 0.83) 12 h postoperatively with sensitivity and specificity of 74 and 90%, respectively.²⁷ However, despite KIM-1 levels being higher in adult cardiac surgery patients who developed AKI, it provided only modest ability to identify AKI (AUC_{ROC} 0.59–0.68) within 24 h of surgery, limited by poor sensitivity (< 50%), despite a specificity greater than 80%.⁴ Subgroup analysis indicated improved diagnostic utility within 3 h of surgery for “early AKI” (AUC_{ROC} 0.73–0.79), defined as AKI occurring within 24 h of surgery. However, it is unknown whether early AKI represents a distinct biologic entity or merely the vagaries of subgroup analysis. The authors further assessed the value of combining biomarkers to enable early diagnosis of AKI, observing a small improvement with the combination of urinary NGAL, KIM-1, and *N*-acetyl- β -D-glucosaminidase (NAG) compared with either marker in isolation.

***N*-Acetyl- β -D-Glucosaminidase**

Although several enzymes present in tubular epithelial cells have been investigated as potential markers of renal injury, NAG remains the most extensively investigated to date. A lysosomal enzyme, it is abundantly present in proximal tubular epithelial cells and its relatively large size (130 kDa) prevents glomerular filtration with the result that urinary NAG represents enzyme leakage from proximal tubular cells into the tubular lumen. It is stable in urine across a range of pH and temperature, and it is easily quantified by com-

mercially available colorimetric or spectrophotometric methods.

Although a large number of studies have profiled the release of NAG across a diverse range of clinicopathologic conditions, each purporting to demonstrate subtle proximal renal tubular damage, few studies address either the diagnostic capability for AKI or a direct link with clinical outcomes. NAG was used extensively through the 1990s by anesthesiologists investigating the potential nephrotoxicity of compound A, a degradation product of sevoflurane. Despite several studies indicating increases in urinary NAG with sevoflurane exposure, as well as other potential markers of renal injury, such as albumin, microglobulins, glutathione-S-transferase, and glucose, a link with histopathologic changes, increasing serum creatinine, or adverse clinical outcomes was unable to be established, thus leaving the interpretation of these transient perioperative changes unclear. However, in a cross-sectional study, urinary NAG provided excellent discrimination of patients with established AKI from a control group including both normal individuals and patients with urinary tract infection (AUC_{ROC} 0.97)²⁷ and in a hospital population referred for nephrology consultation for acute renal failure, increasing urinary NAG was associated with a 3.0-, 3.7-, and 9.1-fold higher odds for the composite outcome of in-hospital mortality or dialysis with each increasing quartile relative to the first, a relationship maintained despite adjusting for multiple comorbidities.²⁸ NAG levels increased within 6 h of pediatric cardiac surgery, remaining elevated through 48 h. Although higher in patients who developed AKI, diagnostic utility was modest 12 h post-CPB (AUC_{ROC} 0.69) and despite sensitivity greater than 80%, specificity remained poor across a range of potential threshold values.²⁷ In contrast, urinary NAG levels were not consistently different between patients with or without AKI after cardiac surgery in adults,⁴ and a single study in liver transplant recipients failed to show a difference in postoperative urinary NAG levels between patients with or without AKI.²⁹

Other Candidate Biomarkers

Several other candidate biomarkers for AKI have been identified, including proatrial natriuretic peptide, neutrophil CD11b and IL-6, -8, and -10 in serum as well as matrix metalloproteinase-9, multiple forms of glutathione-S-transferase, microglobulins, retinol binding protein, and more recently liver fatty acid-binding protein in urine. However, existing studies are small and restricted to limited patient cohorts, and it remains unknown what role, if any, these markers may play in detecting and monitoring AKI in the future.

Clinical Perspective and Future Directions

The emerging field of biomarkers for early detection of AKI is an area of intense ongoing research with significant clinical potential. Novel tools such as gene chip array analysis allow selection of potential markers with a precision and

specificity not possible previously. However, despite the enthusiasm and the recognized need for a new generation of AKI biomarkers, all of those currently under investigation remain experimental and not yet ready for routine clinical practice. The widely varying diagnostic characteristics in current studies remain largely unexplained, and studies to identify and explain clinically relevant factors that may confound biomarker performance in the perioperative period are urgently required. With the exception of NAG, any potential effect of anesthetic agents or other commonly used drugs in the perioperative period on biomarker response remains unknown. Aprotinin use in cardiac surgery is associated with a 20-fold increase in urinary NGAL, which is disproportionately greater than the twofold increase in the risk of AKI associated with aprotinin use in the same study,³⁰ indicating possible confounding of urinary NGAL by aprotinin, which competitively blocks megalin, the protein responsible for tubular reuptake of NGAL. Many studies assessing the early diagnostic performance of biomarkers for AKI have excluded patients with baseline renal dysfunction, a group consistently demonstrated to be at greatest risk for perioperative AKI.² Although a significant reduction in functional reserve may not be apparent in many of these patients under normal circumstances, relatively minor perioperative renal injury may be sufficient to produce AKI with its associated increase in morbidity and mortality.³¹ The performance of novel biomarkers must therefore be characterized across a range of baseline renal function before widespread clinical use. Optimal timing of biomarker measurement also remains uncertain, and many of the current studies use serial measurements through the early postoperative period to define the typical pattern of biomarker increase and decrease. However, such repeated measures are expensive in comparison with a daily measure of creatinine, and the wide variation reported in the performance characteristics of spot biomarker samples over the course of just a few hours may ultimately limit clinical applicability. Although the diagnostic characteristics of these novel biomarkers are generally compared against creatinine-based measures of AKI as the existing gold standard, a creatinine-based diagnosis of AKI is itself imperfect, potentially contributing to apparent limitations of new biomarkers and necessitating other means of evaluating the accuracy and clinical implications of a new test.³² In fact, a new biomarker with perfect sensitivity and specificity when compared with creatinine would simply replicate the inaccuracies of creatinine, perhaps a little earlier in the clinical course.³³ However, studies thus far have not been powered to address outcomes such as mortality or other creatinine-independent outcomes.

The total number of patients in which any one of these biomarkers has been studied remains relatively small, further limiting the generalizability of results, and few studies have been reported according to the recommendations of the Standards for Reporting of Diagnostic Accuracy.³⁴ It is generally accepted that no single biomarker will perform sufficiently to stand alone as a diagnostic, injury severity, and prognostic marker. More likely, a panel of biomarkers will

emerge combining to optimize the features of each marker. However, the complicated process of how to combine biomarkers for optimal clinical utility remains a hurdle. Recently, Haase *et al.*³⁵ used a process of simple multiplication, combining NGAL and cystatin-c, whereas Han *et al.*⁴ used logistic regression modeling to combine multiple biomarkers and generate an odds ratio for AKI. Whether this process is best used as a diagnostic tool or perhaps part of a larger risk scoring system requires further investigation.

Importantly, it must be remembered that biomarkers are not an end in themselves but rather a means to an end. Although clinical trials of interventions to prevent or reduce AKI have generally been disappointing, new interventions targeting novel aspects of AKI pathophysiology such as specific components of the inflammatory and oxidative stress response, endothelial dysfunction, RNA inhibitors, as well as renal-specific vasodilators are currently being studied at both the preclinical and clinical level. To fulfil their promise, biomarkers will need to enable sufficiently early diagnosis of AKI to permit effective intervention, monitoring response to intervention, allow accurate risk stratification to guide clinical trial recruitment, and provide accurate prognostic information, thus guiding clinical decision-making and resource utilization.

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