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Biomarkers for the Early Detection of Acute Kidney Injury

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Abstract

Purpose of review—Acute kidney injury (AKI) is a common and serious condition, the diagnosis of which depends on serum creatinine, which is a delayed and unreliable indicator of AKI. Fortunately, understanding the early stress response of the kidney to acute injuries has revealed a number of potential biomarkers. The current status of the most promising of these novel AKI biomarkers, including NGAL, KIM-1, L-FABP and IL-18, is reviewed.

Recent findings—In particular, NGAL is emerging as an excellent biomarker in the urine and plasma, for the early prediction of AKI, for monitoring clinical trials in AKI, and for the prognosis of AKI in several common clinical scenarios. However, biomarker combinations may be required to improve our ability to predict AKI and its outcomes in a context-specific manner.

Summary—It is vital that additional large future studies demonstrate (a) the association between biomarkers and hard clinical outcomes independent of serum creatinine concentrations, and (b) that randomization to a treatment for AKI based on high biomarker levels results in an improvement in clinical outcomes.

Keywords

Acute kidney injury; acute renal failure; biomarker; neutrophil gelatinase-associated lipocalin; kidney injury molecule-1; interleukin-18; liver-type fatty acid binding protein

Introduction

Acute kidney injury (AKI) is largely asymptomatic, and establishing the diagnosis in this increasingly common disorder currently hinges on functional biomarkers such as serum creatinine. Unfortunately, serum creatinine is a delayed and unreliable indicator of AKI for a variety of reasons (1–4). This is a problem, because animal studies have identified several interventions that can prevent and/or treat AKI if instituted early in the disease course, well before the serum creatinine begins to rise (2). The paucity of early structural injury biomarkers has hampered our ability to translate these promising therapies to human AKI, which now complicates about 5% of all hospitalizations (2–6). The incidence of AKI in the pediatric intensive care unit (PICU) is even higher, afflicting about 10% in all children admitted to a PICU (7) to 82% of the most severely ill children (8). AKI on admission to the PICU is associated with a >5-fold increased risk of mortality, and development of AKI

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Statement of disclosure: Dr. Devarajan is a co-inventor on NGAL patents. Abbott Diagnostics has signed an exclusive licensing agreement with Cincinnati Children's Hospital for developing urine NGAL as a biomarker of acute renal failure. Biosite(R) Incorporated has signed an exclusive licensing agreement with Cincinnati Children's Hospital for developing plasma NGAL as a biomarker of acute renal failure. Dr. Devarajan has received honoraria for speaking assignments from Biosite(R) Incorporated and Abbott Diagnostics.

during a PICU stay is associated with a 9-fold increase in mortality and a 4-fold increase in length of hospital stay (7, 9). Biomarkers of AKI that are capable of early detection, risk stratification, and prognostication would represent a tremendous advance in the care of this highly vulnerable population.

Clinically applicable AKI biomarkers should be (a) non-invasive, using easily accessible samples such as blood or urine; (b) rapidly measurable using standardized clinical assay platforms; (c) sensitive to facilitate early detection, with a wide dynamic range and cut-off values that allow for risk stratification; (d) specific for AKI, to differentiate intrinsic AKI from pre-renal azotemia and chronic kidney disease; (e) predictive of clinical outcomes such as need for dialysis, length of hospital stay, and mortality; (f) able to guide initiation of therapies; and (g) facilitate monitoring the response to interventions (10–13). Fortunately, understanding the early stress response of the kidney to acute injuries has revealed a number of proteins that inform early pathophysiology, and serendipitously, represent potential biomarkers (14, 15). The current status of the most promising of these novel AKI biomarkers, including NGAL, KIM-1, L-FABP and IL-18, is appraised in this review.

Neutrophil Gelatinase-Associated Lipocalin (NGAL)

Preclinical transcriptome profiling studies identified *Ngal* (also known as lipocalin 2 or *lcn2*) to be one of the most upregulated genes in the kidney very early after acute injury in animal models (16). Downstream proteomic analyses also revealed NGAL to be one of the most highly induced proteins in the kidney after ischemic or nephrotoxic AKI in animal models (17–19). The serendipitous finding that NGAL protein was easily detected in the urine soon after AKI in animal studies has prompted an explosion of translational studies to evaluate NGAL as a non-invasive biomarker in human AKI. In several small prospective single center studies of children undergoing cardiopulmonary bypass (CPB), AKI defined as a 50% increase in serum creatinine occurred 1–3 days after surgery (20–24). In contrast, NGAL concentrations increased in the urine and plasma within 2–6 hours of the surgery in those who subsequently developed AKI. Both urine and plasma NGAL were excellent independent predictors of AKI, with an area under the receiver-operating characteristic curve (AUC) of > 0.9 for the 2–6 hour measurements (20–24). In a recent validation study of 374 children undergoing CPB, plasma and urine NGAL significantly increased in AKI patients at 2h after CPB and remained elevated for at least 48 hours, with the 2h NGAL being the earliest and strongest independent predictor of AKI (25). The 2h plasma and urine NGAL also strongly correlated with length of hospital stay and severity of AKI. The AUC for plasma and urine NGAL at various time-points (2–48 hours) after CPB ranged from 0.88 to 0.97 indicating that both are excellent predictors of AKI. These findings have now been confirmed in prospective studies of adults undergoing cardiac surgery, in whom urinary and/or plasma NGAL was significantly elevated by 1–3 hours after the operation, and this was independently associated with post-operative AKI (26–32). However, the AUCs for the prediction of AKI have ranged widely from 0.61 to 0.96. The somewhat inferior performance in adult populations may be reflective of confounding variables such as older age groups, pre-existing kidney disease, prolonged bypass times, chronic illness, and diabetes (15). The predictive performance of NGAL also depends on the severity of AKI as classified by RIFLE critieria (31, 33). Furthermore, the predictive power of NGAL for AKI after cardiac surgery varied with baseline renal function, with optimal discriminatory performance in patients with normal preoperative renal function (34). Despite these numerous potential variables, a meta-analysis of published studies in the setting of cardiac surgery revealed an overall AUC of 0.78 for prediction of AKI, when NGAL was measured within 6 hours of initiation of CPB and AKI was defined as a >50% increase in serum creatinine (35).

NGAL has been evaluated as a biomarker of delayed graft function (DGF, defined as dialysis requirement within the first post-operative week) in patients undergoing kidney transplantation. Protocol biopsies of kidneys obtained 1 hour after vascular anastomosis revealed a significant correlation between NGAL staining intensity in the allograft and the subsequent development of DGF (36). In prospective multicenter studies, urine NGAL levels in samples collected on the day of transplant identified those who subsequently developed DGF with an AUC of 0.8–0.9 (37, 38). A recent study of serial urine NGAL measurements after deceased donor kidney transplants demonstrated that day 1 urine NGAL levels predicted DGF with an AUC of 0.75 even in a subset of patients with good urine output and decreasing serum creatinine values, in whom DGF was not clinically expected (39).

An emerging application of NGAL is in the arena of human nephrotoxicities. For example, NGAL is a predictor of AKI following contrast administration. In a prospective study of children undergoing elective cardiac catheterization with contrast administration, both urine and plasma NGAL predicted contrast-induced nephropathy (defined as a 50% increase in serum creatinine from baseline) within 2 hours after contrast administration, with an AUC of 0.91–0.92 (40). A meta-analysis of pediatric and adult studies revealed an overall AUC of 0.894 for prediction of AKI, when NGAL was measured within 6 hours after contrast administration (35). With respect to other common nephrotoxins, early urinary NGAL measurements may be useful for the prediction of cisplatin-induced AKI (41) and early cyclosporine-associated nephrotoxicity (42).

Urine and plasma NGAL measurements also represent early biomarkers of AKI in a heterogeneous pediatric intensive care setting, being able to predict this complication about 1–2 days prior to the rise in serum creatinine, with high sensitivity and AUCs of 0.68–0.78 (43, 44). Several studies have also examined NGAL levels in critically ill adult patients (45–52). In these mixed populations, the NGAL level on admission has been predictive of AKI, with an AUC ranging from 0.71–0.92. In a study of adults in the emergency department setting, a single measurement of urine NGAL at the time of initial presentation predicted AKI with an AUC of 0.95, and reliably distinguished prerenal azotemia from intrinsic AKI and from chronic kidney disease (53). Thus, NGAL is a useful early AKI marker that predicts development of AKI even in heterogeneous groups of patients with unknown timing of kidney injury. Despite limitations inherent to a diverse critical care setting, a meta-analysis revealed an overall AUC-ROC of 0.73 for prediction of AKI, when NGAL was measured within 6 hours of clinical contact with critically ill subjects and AKI was defined as a >50% increase in serum creatinine (35).

NGAL is also emerging as an early biomarker in interventional trials. For example, a reduction in urine NGAL has been employed as an outcome variable in clinical trials demonstrating the improved efficacy of a modern hydroxyethylstarch preparation over albumin in maintaining renal function in cardiac surgery patients (54). Similarly, the response of urine NGAL was attenuated in adult cardiac surgery patients who experienced a lower incidence of AKI after sodium bicarbonate therapy when compared to sodium chloride (55). In addition, urinary NGAL levels have been utilized to document the efficacy of a miniaturized CPB system in the preservation of kidney function when compared to standard CPB (56). The approach of using NGAL as a trigger to initiate and monitor AKI therapies, and as a safety biomarker when using potentially nephrotoxic agents, is a logical next step. It is also hoped that the use of predictive and sensitive biomarkers such as NGAL as endpoints in clinical trials will result in a reduction in required sample sizes, and hence the cost incurred.

Beyond the prediction of creatinine-based AKI, it is highly desirable of biomarkers to provide an early warning signal for impending adverse outcomes. In a multicenter study of children with diarrhea-associated hemolytic uremic syndrome, urine NGAL obtained early during the hospitalization predicted the severity of AKI and subsequent dialysis requirement with high sensitivity (57). Early urine NGAL levels were also predictive of duration of AKI in a heterogeneous cohort of critically ill pediatric subjects (43). In the adult critical care setting, those who subsequently required renal replacement therapy were found to have the highest early NGAL values (45–52). Collectively, the published studies in critically ill subjects revealed an overall AUC of 0.78 for prediction of subsequent dialysis requirement, when NGAL was measured within 6 hours of clinical contact (35). In addition, early NGAL measurements serve as a mortality marker, with an overall AUC of 0.71 in these heterogeneous populations (35). Furthermore, there is now evidence for the utility of subsequent NGAL determinations in critically ill adults with severe AKI. Serum NGAL measured at the inception of renal replacement therapy was an independent predictor of 28-day mortality, with an AUC of 0.74 (58). The finding that plasma NGAL is not substantially cleared by continuous veno-venous hemofiltration (59), combined with the documented "real-time" response of NGAL to kidney injury and recovery, support the use of NGAL as an early indicator of renal recovery in critically ill patients supported by renal replacement therapy.

A major advance in the field has been the development of standardized clinical platforms for the measurement of NGAL. A point-of-care kit for plasma NGAL (Triage® NGAL Device, Biosite Incorporated, San Diego, USA) has been tested in children undergoing cardiac surgery (23, 60), and is currently being validated in multicenter trials. In addition, a chemiluminescent microparticle immunoassay has been developed for urine NGAL (ARCHITECT® analyzer, Abbott Diagnostics, Abbott Park USA), tested in children (24, 60, 61) and also currently undergoing multicenter validation. The global deployment of these clinical assays is highly promising for uniform interpretation of research studies as well as clinical care.

Clearly, NGAL represents a novel predictive biomarker for AKI and its outcomes. However, reported values of NGAL concentrations have been highly variable, and may depend on the clinical context leading to the AKI. Plasma NGAL measurements may be influenced by a number of coexisting variables such as chronic kidney disease (CKD), chronic hypertension, systemic infections, and inflammatory conditions (62, 63). However, the increase in plasma NGAL in these situations is generally much less than those typically encountered in intrinsic AKI. Urine NGAL is also emerging as a marker of chronic kidney disease and its severity (64–67). Urine NGAL may also represent an early biomarker for the degree of chronic injury in patients with IgA nephropathy (68) and lupus nephritis (69–71), and may be increased in urinary tract infections (72). However, the levels of urine NGAL in these situations are typically significantly blunted compared to those measured in true AKI.

Kidney Injury Molecule-1 (KIM-1)

Preclinical subtractive hybridization screens identified kidney injury molecule 1 (*Kim-1*) as a gene that is markedly up-regulated in ischemic rat kidneys (73). Downstream proteomic studies have also shown KIM-1 to be one of the most highly induced proteins in the kidney after AKI in animal models. KIM-1 is a transmembrane protein that is specifically upregulated in dedifferentiated proximal tubule cells after ischemic or nephrotoxic AKI. An extracellular domain of KIM-1 is detectable in the urine soon after AKI (74). KIM-1 represents a promising biomarker for the early diagnosis of AKI and its clinical outcomes (75–77). In hospitalized patients with established AKI, urinary KIM-1 levels predicted adverse clinical outcomes such as dialysis requirement and mortality (75). In children

undergoing CPB who developed AKI 1–3 days post surgery, urine KIM-1 concentrations were significantly increased within 12 hours. The AUC for AKI prediction at 12 hours was 0.83 (76). KIM-1 is also an excellent marker of nephrotoxicity in preclinical studies (78). The recent availability of a rapid urine dipstick test for KIM-1 will facilitate its further evaluation in preclinical and clinical studies (79). Urinary KIM-1 is also increased in a number of chronic kidney diseases (80–82).

Liver-type Fatty Acid Binding Protein (L-FABP)

L-FABP is a protein expressed in the proximal tubule of the kidney. Increased expression and urinary excretion have been described in animal models of AKI (83–85). In children undergoing CPB who subsequently developed AKI, urine L-FABP concentrations were significantly increased within 4 hours of the surgery (86). The urinary L-FABP level at 4 hours was an independent risk factor for the development of AKI, with an AUC of 0.81 (86). In hospitalized patients with established AKI, the AUC of urinary L-FABP for prediction of AKI was 0.93 (87). Urinary L-FABP levels in this cohort were significantly higher in patients with poor outcome, defined as the requirement for renal replacement therapy or the composite end point of death or renal replacement therapy (87). In patients with septic shock and AKI, urinary L-FABP measured at admission was significantly higher in the non-survivors than in the survivors, with an AUC for mortality prediction of 0.99 (88). Thus, emerging data point to L-FABP as a promising urinary biomarker of AKI and its outcomes. However, the urinary excretion of L-FABP is also increased in the setting of CKD (89, 90). Standardized clinical platforms for the measurement of urinary L-FABP are not currently available.

Interleukin-18 (IL-18)

IL-18 is a pro-inflammatory cytokine that is induced and cleaved in the proximal tubule, and subsequently easily detected in the urine following ischemic AKI in animal models (91). In a cross-sectional study, urine IL-18 levels were markedly elevated in patients with established AKI, but not in subjects with urinary tract infection, chronic kidney disease, nephrotic syndrome, or prerenal azotemia (92). Urinary IL-18 was significantly upregulated prior to the increase in serum creatinine in patients with acute respiratory distress syndrome who develop AKI (93). On multivariate analysis, urine IL-18 levels predicted the development of AKI 24 hours before the rise in serum creatinine, with an AUC of 0.73 (93). In children undergoing CPB who developed AKI, urinary IL-18 levels increased around 6 hours and peaked at over 25-fold at 12 hours post CPB (AUC 0.75) (21). In kidney transplantation, urine IL-18 is a predictive biomarker for DGF (37, 38). Urine IL-18 measurements also represent early biomarkers of AKI in the pediatric intensive care setting, being able to predict this complication about 2 days prior to the rise in serum creatinine (94). Early urine IL-18 measurements correlated with the severity of AKI as well as mortality. Overall, IL-18 appears to be more specific to ischemic AKI, and largely unaffected by chronic kidney disease or urinary tract infections. However, IL-18 measurements may also be influenced by a number of coexisting variables, such as endotoxemia, immunologic injury and cisplatin toxicity. Furthermore, plasma IL-18 levels are known to be increased in various pathophysiologic states, such as inflammatory arthritis, inflammatory bowel disease, and systemic lupus erythematosus. Standardized platforms for the clinical measurement of urinary IL-18 remain to be developed and validated.

AKI Biomarker Combinations

From the above, it is apparent that there is no single perfect AKI biomarker. A combination of biomarkers may be necessary to provide the best diagnostic and prognostic information in a context-specific manner. Recent studies have explored this possibility. In a large

prospective multicenter study of a panel of nine biomarkers to predict clinical outcomes in 971 emergency department patients with suspected sepsis, plasma NGAL emerged as the strongest predictor of shock and death (95). In a secondary analysis of this cohort, an elevated plasma NGAL level at the time of presentation to the emergency department predicted severe AKI with an AUC of 0.82 (96). In a study examining biomarkers for the prediction of AKI following elective cardiac surgery, urinary NGAL concentrations measured at the time of admission to the ICU predicted the subsequent development of AKI with an AUC of 0.773, and outperformed other biomarkers including α1-microglobulin and cystatin C (97). In a similar analysis of multiple urinary biomarkers following cardiac surgery, the 6-hour post-operative NGAL best predicted severe AKI with an AUC of 0.88 (98). Serial measurements of multiple urinary biomarkers after pediatric cardiac surgery have revealed a sequential pattern for the appearance of AKI biomarkers (60), with NGAL and L-FABP being the earliest responders (with 2–4 hours after initiation of cardiopulmonary bypass) and KIM-1 and IL-18 representing the intermediate responders (increased 6–12 hours after surgery). Current multicenter studies of multiple biomarkers will help determine which combinations best predict AKI and its outcomes in a context-dependent manner. In this rapidly evolving area of study, ongoing functional genomic and proteomic analyses may also reveal additional biomarkers that further advance this field in the near future (99).

Conclusions

Despite the optimism in the field, there are important limitations that exist in the published AKI biomarker literature that must be acknowledged. First, majority of studies reported were from single centers. Second, most studies did not include patients with chronic kidney disease. Third, only a few studies have investigated biomarkers for the prediction of AKI severity, morbidity, and mortality. Fourth, biomarker combinations are likely to improve our ability to predict AKI and its outcomes, and these studies are only beginning to surface.

Finally, and perhaps most importantly, the definition of AKI in the published studies was based largely on elevations in serum creatinine, which raises the challenge of using a flawed outcome variable to analyze the performance of a novel assay. This definition of AKI sets up the biomarker assay for lack of accuracy due to either false positives (true tubular injury but no significant change in serum creatinine) or false negatives (absence of true tubular injury, but elevations in serum creatinine due to pre-renal causes or any of a number of confounding variables that plague this measurement). Indeed, a recent multicenter pooled analysis of published data on 2322 critically ill children and adults revealed the surprising finding that approximately 20% of patients display early elevations in NGAL concentrations but never develop increases in serum creatinine (100). Importantly, this sub-group of “NGAL-positive creatinine-negative” subjects encountered a substantial increase in adverse clinical outcomes, including mortality, dialysis requirement, ICU stay, and overall hospital stay (100). Thus, early NGAL measurements can identify patients with sub-clinical AKI who have an increased risk of adverse outcomes, even in the absence of diagnostic increases in serum creatinine. Since the gold standard for true AKI (tissue biopsy) is highly unlikely to be feasible in humans, it is vital that additional future studies demonstrate (a) the association between biomarkers and hard outcomes such as dialysis, cardiovascular events, hospital stay and death, independent of serum creatinine concentrations, and (b) that randomization to a treatment for AKI based on high biomarker levels results in an improvement in kidney function and reduction of clinical outcomes. These should be the next challenges to overcome, in order to firmly establish the clinical utility of AKI biomarkers, and to dramatically improve the outcome of AKI.

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Bullet Points

- AKI is a common and serious condition in critically ill children
- Novel biomarkers are dramatically improving our ability to predict AKI
- In particular, urine and plasma NGAL are emerging as powerful biomarkers for the early detection of AKI and prediction of adverse clinical outcomes
- Biomarker combinations may further improve our ability to predict AKI in a context-specific manner