Published in final edited form as:
Semin Nephrol. 2008 September ; 28(5): 493–498. doi:10.1016/j.semnephrol.2008.05.010.

THE FUTURE OF PEDIATRIC AKI MANAGEMENT BIOMARKERS

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Abstract

Acute kidney injury (AKI) represents a common and devastating problem in clinical medicine. A major reason for is the lack of early biomarkers for AKI, and hence an unacceptable delay in initiating therapy. Fortunately, the application of innovative technologies has uncovered several novel biomarkers. The most promising of these are included in a putative AKI Biomarker Panel, consisting of neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), and kidney injury molecule-1 (KIM-1). These biomarkers have completed initial validation, and have entered the prospective screening stage in the biomarker development process, facilitated by the development of commercial tools for their reproducible measurement across laboratories. The availability of a panel of validated biomarkers will revolutionize renal and critical care, and enable the practice of personalized and predictive medicine at an unprecedented level.

Keywords

acute kidney injury; acute renal failure; biomarker; interleukin-18; kidney injury molecule-1; nephrotoxicity; neutrophil gelatinase-associated lipocalin; personalized medicine

Why Do We Need AKI Biomarkers?

Dr. McCoy:: "What's the matter with you?"

Patient:: "Kidney failure – I'm waiting for dialysis"

Dr. McCoy:: "Dialysis? What is this, the Dark Ages?"

From Star Trek IV – The Voyage Home (1986).

As illustrated by the clinical examples in this issue, acute kidney injury (AKI) represents a complex disorder, which occurs in a wide variety of settings. The incidence of AKI is rising globally, and the associated mortality and morbidity remain unacceptably high [1]. Once established, there is no effective treatment for human AKI, and dialysis merely provides supportive care. Ironically, even tragically, animal studies have shown that AKI can be prevented or treated by several maneuvers, but these must be initiated within a narrow window of opportunity. Therein lies the Achilles' heel of AKI management - the paucity of early

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biomarkers has lead to an unacceptable delay in initiating therapy in humans [2, 3]. In current clinical practice, AKI is diagnosed by a rise in serum creatinine, which is a notoriously unreliable indicator during acute changes in kidney function [4]. Not surprisingly, the use of serum creatinine as a therapeutic trigger has resulted in the failure of landmark clinical trials of interventions for AKI in humans [5].

In addition to early diagnosis, biomarkers may serve several other purposes in AKI [6], such as (a) identifying the primary location of injury (proximal tubule, distal tubule, interstitium, or vasculature); (b) discerning AKI subtypes (pre-renal, intrinsic renal, or post-renal); (c) identifying AKI etiologies (ischemia, toxins, sepsis, or a combination); (d) predicting outcomes (duration and severity of AKI, need for dialysis, length of hospital stay, mortality); and (e) monitoring the response to therapy.

Desirable characteristics of clinically applicable AKI biomarkers include (a) they should be rapid, non-invasive and easy to perform using easily accessible samples such as blood or urine; (b) they should be sensitive to facilitate early detection, and have a wide dynamic range and cut-off values that allow for risk stratification; (c) they should be specific for AKI, and enable the identification of AKI sub-types; and (d) they should exhibit strong biomarker properties with an area under the receiver-operating characteristic curve (AUC) of >0.90 [6].

Conventional urinary biomarkers such as casts, fractional excretion of sodium, filtered high molecular weight proteins and tubular proteins or enzymes have been insensitive and non-specific for the early recognition of AKI. Fortunately, the application of functional genomics and proteomics to human and animal models of kidney disease has uncovered several novel candidates that are emerging as biomarkers of AKI. Several of these candidates have now progressed through the pre-clinical stages of the biomarker development process. This review will focus on those that hold the greatest promise to reach clinical application in the near future, namely neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), and kidney injury molecule-1 (KIM-1).

NGAL As An AKI Biomarker

Mouse kidney microarray analysis revealed NGAL as one of the most upregulated genes at early time points after AKI [7]. Downstream proteomic studies showed NGAL to be one of the most rapidly and robustly induced proteins in the kidney after ischemic or nephrotoxic AKI in animal models, and NGAL protein was easily detected in the blood and urine very early in the course of AKI [8, 9]. These findings generated several translational studies to evaluate NGAL as a novel biomarker in human AKI. In a prospective study of children undergoing cardiopulmonary bypass (CPB), the diagnosis of AKI (defined as a 50% increase in serum creatinine) was only possible 1–3 days after surgery [10]. In contrast, NGAL measurements by ELISA revealed a marked increase in the urine and plasma within 2–6 hours of the surgery in patients who subsequently developed AKI. Using a cut-off of 50 ng/ml, both urine and plasma NGAL were independent predictors of AKI, with an outstanding AUC of 0.99 for the 2 hour urine NGAL and 0.91 for the 2 hour plasma NGAL measurement [10]. The 2 hour urine NGAL level also represented an independent predictor of duration of AKI among cases [11]. In a subsequent study, urine NGAL measured at 4 hours after initiation of CPB in children showed an AUC of 1.000 [12]. For an NGAL cut-point concentration of 100 ng/mg creatinine, both sensitivity (1.000) and specificity (1.000) were perfect for the prediction of AKI. Thus, NGAL has emerged as a sensitive, specific, and highly predictive early biomarker of AKI in the urine and plasma, after CPB in children.

NGAL has also been evaluated in pediatric kidney transplantation. Biopsies of kidneys obtained 1 hour after vascular anastomosis revealed a significant correlation between NGAL staining intensity and the subsequent development of delayed graft function [13]. In a prospective

multicenter study of children and adults, urine NGAL levels in samples collected on the day of transplant predicted subsequent delayed graft function and dialysis requirement (which typically occurred 2–4 days later) with an AUC of 0.9 [14]. In a retrospective study of kidney transplant patients undergoing either protocol biopsies or clinically indicated biopsies, urine NGAL measurements were found to be significantly increased in subjects with tubulitis or other tubular pathologies, suggesting NGAL as a non-invasive screening tool [15].

Several investigators have examined the role of NGAL as a predictive biomarker of nephrotoxicity following contrast administration, with promising results. 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 [16]. Using a cut-off value of 100 ng/ml, the AUC for prediction of contrast nephropathy was excellent for the 2 hour urine NGAL (0.92) as well as the 2 hour plasma NGAL (0.91). By multivariate analysis, the 2 hour NGAL concentrations in the urine and plasma were found to be powerful independent predictors of contrast nephropathy [16].

Urine NGAL has also been shown to predict the severity of AKI and dialysis requirement in a multicenter study of children with diarrhea-associated hemolytic uremic syndrome, with high sensitivity but low specificity [17]. Using a cut-off of 200 ng/ml, NGAL in urine obtained soon after hospitalization was significantly increased in those children who subsequently developed severe AKI requiring dialysis. Urine NGAL 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 [18]. Early urine NGAL measurements were also predictive of duration of AKI as well as worsening of AKI in critically ill subjects. Thus, NGAL may represent an early diagnostic and prognostic AKI marker even in a heterogeneous group of children with unknown timing of kidney injury.

All results described thus far have been obtained using research-based assays. The availability of validated clinical tools for NGAL measurements could revolutionize renal diagnostics. In this regard, a standardized point-of-care kit is under development for the measurement of plasma NGAL (Triage® NGAL Device, Biosite Incorporated). The assay is easy to perform, with quantitative results available in15 minutes, and requires only microliter quantities of whole blood. In a pilot study with 120 children undergoing CPB, plasma NGAL levels measured by Triage® NGAL Device increased three-fold within 2 hours of CPB in those who subsequently developed AKI [19]. By multivariate analysis, plasma NGAL at 2 hours post-CPB was the most powerful independent predictor of AKI. For the 2 hour plasma NGAL measurement, the AUC was 0.96, sensitivity was 0.84, and the specificity was 0.94 for prediction of AKI using a cutoff value of 150 ng/ml. The early plasma NGAL levels strongly correlated with change in creatinine, duration of AKI, length of hospital stay, and mortality.

In addition, a urine NGAL immunoassay is being developed for a standardized clinical platform (ARCHITECT® analyzer, Abbott Diagnostics). This assay is also easy to perform, with a first result available within 35 minutes, and it requires only 150 μl of urine. In a pilot study of 196 children undergoing CPB, urine NGAL measured by ARCHITECT® analyzer increased 15-fold within 2 hours, in those who subsequently developed AKI [20]. For the 2 hour urine NGAL measurement, the AUC was 0.95, sensitivity was 0.82, and the specificity was 0.90 for prediction of AKI using a cutoff value of 100 mg/ml. The 2 hour urine NGAL levels highly correlated with severity of AKI, duration of AKI, length of hospital stay, dialysis requirement, and death.

In summary, NGAL is emerging as a center-stage player in the AKI field, as a novel predictive biomarker, for prominent inclusion in the urinary “AKI Biomarker Panel”. However, NGAL

measurements may be influenced by a number of coexisting variables such as systemic infections, inflammatory conditions, and malignancies [21]. There is also an emerging literature suggesting that NGAL is a marker of chronic kidney disease severity [22].

IL-18 As An AKI Biomarker

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 [23]. In a cross-sectional study, urine IL-18 levels measured by ELISA were markedly elevated in patients with established AKI, but not in subjects with urinary tract infection, chronic kidney disease, nephrotic syndrome, or prerenal azotemia [24]. In a subsequent study, urinary IL-18 was found to be significantly upregulated prior to the increase in serum creatinine in patients with acute respiratory distress syndrome who developed AKI [25]. On multivariate analysis, urine IL-18 levels > 100 pg/mg creatinine predicted the development of AKI 24 hours before the rise in serum creatinine, with an AUC of 0.73. Urine IL-18 on the day of initiation of mechanical ventilation was also predictive of mortality in these patients, independent of severity scores and serum creatinine.

Urinary IL-18 and NGAL were shown to represent sequential AKI biomarkers in children undergoing cardiac surgery [11]. In patients who developed AKI 2–3 days after surgery, urinary NGAL was induced within 2 hours and peaked at 6 hours whereas urine IL-18 levels increased around 6 hours and peaked at over 25-fold at 12 hours post surgery (AUC 0.75). Both IL-18 and NGAL were independently associated with duration of AKI among cases. In addition, both IL-18 and NGAL in urine samples collected on the day of kidney transplant predicted subsequent delayed graft function and dialysis requirement with an AUC of 0.9 [13]. By multivariate analysis, both urine IL-18 and NGAL predicted the trend in serum creatinine in the post-transplant period after adjusting for age, gender, race, urine output, and ischemia time.

Urine IL-18 measurements also represent early biomarkers of AKI in the intensive care setting, being able to predict this complication about 2 days prior to the rise in serum creatinine [26]. Urinary IL-18 rose prior to serum creatinine in non-septic critically ill children, predicted severity of AKI, and was an independent predictor of mortality in this heterogeneous group of patients with unknown timing of kidney injury.

Thus, IL-18 may represent a promising candidate for inclusion in the urinary “AKI Biomarker Panel”. IL-18 is more specific to ischemic AKI, and is affected by chronic kidney disease or urinary tract infections. It is likely that NGAL and IL-18 will emerge as sequential urinary biomarkers of AKI. However, urinary IL-18 measurements may also be influenced by a number of variables, such as endotoxemia, immunologic injury and cisplatin toxicity [27].

KIM-1 As An AKI Biomarker

KIM-1 was first identified by subtractive hybridization screening as a gene that is markedly up-regulated in ischemic rat kidneys [28]. KIM-1 is one of the most highly induced proteins in the kidney after AKI in animal models, and a proteolytically processed domain of KIM-1 is easily detected in the urine soon after AKI [29, 30]. Assays for KIM-1 (ELISA and microbead-based) have been developed in research laboratories [31], but are not commercially available. In a small human cross-sectional study, KIM-1 expression was markedly induced in proximal tubules in kidney biopsies from patients with established AKI (primarily ischemic), and urinary KIM-1 measured by ELISA distinguished ischemic AKI from prerenal azotemia and chronic renal disease [32]. Patients with AKI induced by contrast did not have increased urinary KIM-1.

Recent studies have expanded the potential clinical utility of KIM-1 as a predictive AKI biomarker. In a case-control study of children undergoing CPB, urinary KIM-1 levels were

markedly enhanced in subjects who subsequently developed AKI, with an AUC of 0.83 at the 12 hour time point 33. In a larger prospective cohort study of 201 hospitalized patients with established AKI, both urinary KIM-1 as well as urinary N-Acetyl-β-(D)-Glucosaminidase (NAG) were associated with adverse clinical outcomes, including dialysis requirement and death [34].

Thus, KIM-1 represents a promising candidate for inclusion in the urinary "AKI Biomarker Panel". It is likely that NGAL and KIM-1 will emerge as tandem biomarkers of AKI, with NGAL being most sensitive at the earliest time points and KIM-1 potentially adding specificity at slightly later time points. One advantage of KIM-1 as a urinary biomarker is the fact that its expression seems to be limited to the injured or diseased kidney, and no systemic source of KIM-1 has been described. However, urinary KIM-1 measurements may be influenced by a number of other confounding variables. KIM-1 is induced in the kidney and upregulated in the urine by a large number of nephrotoxins, including cyclosporine, cisplatin, cadmium, gentamicin, mercury, and chromium [35]. KIM-1 in the kidney and urine is also induced in a variety of chronic proteinuric, inflammatory, and fibrotic disease states in humans [36].

Future Perspectives

It is instructive to consider a clinical situation that is analogous to AKI, namely acute myocardial infarction, the medical evaluation of which has progressed over the past few decades from detection of Q-waves by EKG through a series of serum biomarkers with increasing sensitivity and predictive value. Now widely available to the clinician is a panel of tandem serum biomarkers such as troponins and CPK, for the timely and accurate diagnosis. This has allowed for timely institution of a number of therapeutic interventions, with a resultant 50% or so reduction in mortality rate. In stark comparison, the diagnosis, treatment, and prognosis have not changed appreciably in the last five decades. Utilizing serum creatinine measurements to institute promising interventions for AKI is analogous to waiting 2–3 days before intervening in patients with acute myocardial infarction or acute neurologic stroke.

Fortunately, we are closing in on the "kidney troponins" and the "AKI Biomarker Panel". Incredibly, much of the confusion surrounding the early diagnosis of AKI is being solved by the adaptive response of the stressed kidney itself, with the rapid and robust induction of select genes whose protein products have provided us with highly promising biomarkers [37]. These include NGAL, IL-18, and KIM-1. All of these may now be considered to have completed initial validation, and have entered the prospective screening stage in the biomarker development process. Each individual biomarker in the putative AKI panel has merits and demerits. It is doubtful that any single biomarker will suffice. The reason for this is evident from the complex and heterogeneous nature of AKI, occurring in a wide variety of clinical settings with multiple pathophysiologic mechanisms that interplay with and amplify each other.

The availability of a panel of validated biomarkers will revolutionize renal and critical care, and allow for the practice of personalized and predictive medicine at an unprecedented level. An early elevation in AKI biomarkers would trigger an immediate paradigm shift in the clinical management of almost every patient described in the clinical vignettes. At the very least, the future physician would monitor AKI biomarker levels in every child undergoing cardiac surgery, abdominal surgery, nephrotoxin administration, kidney or bone marrow transplantation, and ICU admission for shock, sepsis, or trauma. Clinicians informed of an ominous change in biomarker levels would be aware of the potential for development of full-blown AKI, and biomarkers may add substantively to existing clinical scoring systems for AKI prediction. Such patients would deserve closer monitoring with respect to blood pressure, urine output and renal perfusion. Every effort to monitor intravascular status and to optimize hydration and renal perfusion would be deployed. These subjects would benefit from the

diligent avoidance of additional nephrotoxins. The ability to predict which patients will develop AKI could enable early initiation of therapies. For example, earlier intervention with renal replacement therapy may be strongly considered for subjects with elevated biomarker levels who are developing fluid overload but will not display increased serum creatinine for several days due to hemodilution and time required for re-establishment of a steady state. The availability of promising early biomarkers may enable the timely initiation of interventions such as atrial natriuretic peptide and insulin-like growth factor that have been successful in smaller, phase II-level efficacy studies but not in larger phase III trials. In addition, animal studies continue to reveal novel therapies such as growth factors, anti-apoptotic, anti-inflammatory, and anti-oxidant approaches that are effective in early AKI, prior to the rise in serum creatinine [5]. The availability of standardized clinical platforms for AKI biomarker determination will enable these and other highly promising agents to be systematically investigated in humans with AKI, to change the dismal outcomes associated with this all-too-common clinical problem.

Acknowledgements

Studies cited in this review that were performed in the author's laboratory were supported by grants from the NIH (R01 DK53289, RO1 DK069749, RO1 HL08676, and R21 DK070163).

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