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Acute kidney injury in children: Enhancing diagnosis with novel biomarkers

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ABSTRACT

This narrative review aims to appraise the sensitivity and specificity of novel biomarkers in identifying acute kidney injury (AKI) in children. Serum creatinine represents a poor traditional biomarker for AKI due to some limitations. Although alternative reliable biomarkers that would better identify individuals at high risk for developing AKI, identify AKI early enough, monitor its progression and patients' recovery, as well as identify those patients at higher risk for poor outcomes are not yet available in renal care, the search-light has recently been focused on various novel biomarkers, some of which could provide this information in time ahead. Several studies have established their predictive value. However, none of them could solely fulfill all the criteria of the ideal biomarker. Therefore, to increase their sensitivity and specificity and enhance the diagnosis of AKI, constellations of different biomarkers with specific features are probably required. In future, the diagnostic evaluation of AKI in intensive care units will have to undergo a paradigm shift from serum creatinine as the traditional biomarker to tissue-specific injury biomarkers. A panel of these novel biomarkers employed at the bedside setting will ultimately revolutionize the diagnosis and prognostication of AKI in children.

1. Introduction

Acute kidney injury (AKI) is defined as a sudden and rapid decline in renal excretory function within hours to days, accompanied by an accumulation of nitrogenous waste products such as creatinine, urea and other clinically unmeasured products[1]. In routine clinical practice, serum creatinine is used to estimate renal function and thus as a marker for the diagnosis and staging of AKI[1,2]. The risk, injury, failure, loss of function, end-stage renal disease (RIFLE), as well as the Acute Kidney Injury Network criteria provide a consistent definition for AKI and have become the standard criteria for diagnosis[3–5].

Although serum creatinine is regarded as a traditional biomarker for AKI, it is essentially a renal performance indicator rather than a pathology indicator because its level changes only when renal function is reduced by about 50%[6]. Besides, it varies with muscle size, chronologic age, gender, drugs and state of hydration[7]. A sudden reduction in renal function may not be evidenced by an elevation in serum creatinine until after 24–48 h. Secondly, it provides scanty information about the underlying cause and nature of renal injury and is less accurate for patients with small muscle mass and unusual diets. These limitations have led to the search for alternative biomarkers. Unfortunately, reliable biomarkers that would better identify individuals at high risk for developing AKI, identify AKI early enough, monitor its progression and patients' recovery, and identify those patients at higher risk for poor outcomes are not yet available in renal care. Investigations have recently focused on several new biomarkers, some of which could provide this information in future. Proteomic biomarkers hold prospects for improving the management of patients with kidney diseases by enabling more accurate and earlier detection of renal disease than is possible with currently available biomarkers such as serum creatinine and urinary albumin[8]. Biomarkers under investigation include neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18), and cystatin C[9–12]. Others include hepatocyte growth

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factor (HGF), N-acetyl-β-D-glucosaminidase (NAG), vascular endothelial growth factor (VEGF), chemokine interferon-inducible protein 10 and total protein[13].

Despite the dearth of global data on the incidence of hospital or community-acquired AKI, reports indicate that mortality rates range from 10% in uncomplicated cases[14] to as high as 80% in complicated cases that require renal replacement therapy (RRT)[15]. AKI has indeed been shown to be an independent risk factor for mortality especially in intensive care settings[16–18]. AKI used to be considered as an acute disease, from which the pediatric patient generally recovers, but it has now been reported to be a major risk factor for the occurrence and exacerbation of chronic kidney disease (CKD). Moreover, once a patient develops AKI, the therapeutic options are limited since RRT is the main stay of treatment. Remarkably, RRT remains inaccessible and unaffordable for the majority of pediatric patients in resource-poor countries[19,20]. For these reasons, highly sensitive and specific diagnostic tests for AKI remain a priority in the management algorithm of the acutely ill child since this will help to improve survival outcomes. Early recognition and treatment of AKI will obviously reduce mortality rates. Any delay in diagnosis means a missed opportunity to minimize renal injury. The patient incurs more severe AKI with subsequent greater risk of developing CKD and the attendant cardiovascular sequels such as myocardial infarction and stroke. Thus, a paradigm shift from the old to the new biomarkers may improve the management of AKI through enhanced diagnosis.

This narrative review aims to appraise the sensitivity and specificity of these novel biomarkers in identifying AKI in children.

2. AKI and the novel biomarkers: pathophysiological mechanisms

The common triggers of AKI include ischemia, nephrotoxins, radiocontrast and bacterial endotoxins[7]. Although community-acquired pediatric AKI is common in developing countries, hospital-acquired AKI frequently occurs in children managed in the intensive care unit (ICU) or those who have undergone cardiac surgery. For the identification of more biomarkers of renal injury, the typical features of an ideal biomarker include elaboration by the injured cells and organ specificity, concentration equivalent to the degree of injury, early expression after a potentially reversible organ injury, prompt post-injury reduction in concentration to enable its utilization as a monitoring parameter for treatment and lastly, its quick and reliable measurability[21]. Generally, there are two major types of biomarkers: biomarkers of renal function and biomarkers of renal injury. Irrespective of the type of renal injury and the clinical scenario, an inflammatory response appears to play a prominent role in the genesis of AKI[7]. The triggers of AKI (ischemia, nephrotoxins, and bacterial endotoxins) stimulate the release of inflammatory mediators from renal endothelial and tubular cells. Early in the post-injury period, inflammatory cells migrate and marginate along the peritubular capillary wall and indeed, data from animal models support the concept that cardiogenic pulmonary edema (from volume overload) and non-cardiogenic pulmonary edema (from endothelial injury due to inflammation and apoptosis) can occur in AKI[22]. Endothelial inflammatory injury makes the vessels more permeable which in turn helps to bring about the migration of neutrophils into the renal interstitium and the luminal space of the tubules within a 24-h period. The subsequent tubular response to AKI is characterized by a disruption of the cytoskeletal architecture resulting in shedding of living cells, as well as apoptosis and necrosis[23]. The proposed mechanisms for the reduced glomerular filtration rate (GFR) in AKI include tubular blockage from shed cells, renal vasoconstriction induced by vasoactive mediators, and direct action on the glomerulus[7]. During the evolution of AKI, a number of etiologic factors result in the accumulation of biomarkers in plasma and urine and possibly indicate varied pathophysiological events during the process of renal damage and repair. For instance, biomarkers accumulate in urine due to an induced tubular epithelial synthesis in different parts of the nephron (NGAL, IL-18, NAG, KIM-1) and as a sequel of diminished reabsorption of the filtered load in the proximal tubule (NGAL, cystatin C)[7]. Again, production of biomarkers from transmigrated, activated immune cells into the tubular lumen may also be contributory (NGAL, IL-18), while increased production of some biomarkers in other tissues has been demonstrated, thereby raising concerns about their diagnostic value in AKI (NGAL, IL-18)[24]. This extra-renal synthesis will definitely increase circulating biomarker levels and a reduction in GFR will aggravate this elevation.

3. The novel biomarkers: how sensitive and specific?

The paucity of reliable biomarkers has significantly hindered the evolution of treatment strategies aimed at improving the prognosis of AKI. A single biomarker may not be sufficient enough to establish AKI given the intrinsic structural diversity of the kidney and the different settings which renal injury occurs[8]. Interestingly, one study has demonstrated the comparative value of multiple biomarkers in the diagnosis and prognosis of AKI[13]. In a cross-sectional comparative study of 204 patients with AKI and their non-AKI controls, the investigators specifically evaluated the diagnostic value of nine urinary biomarkers, namely, KIM-1, NGAL, IL-18, HGF, cystatin C, NAG, VEGF, chemokine interferon-inducible protein 10 and total protein. The major finding of this study was that the median urinary concentrations of each biomarker in patients with AKI was significantly higher than that in their non-AKI controls[13]. Using the logistic regression analysis, the researchers noted that the four best performers independently and in combination were KIM-1, NGAL, HGF, and total protein[13]. The study represents an important milestone in the authentication of these biomarkers as it has demonstrated that clearly defined AKI can be differentiated from non-AKI controls. Furthermore, a recent review has highlighted in detail the subclasses and additional examples of the biomarkers[25]. These include functional markers (serum cystatin C, urine albumin and NGAL), up-regulated proteins (KIM-1, liver-type fatty-acid binding protein, IL-18, β-trace protein and asymmetric dimethylarginine), low-molecular weight proteins [urine cystatin C, NAG, glutathione *S*-transferase, γ-glutamyl-transpeptidase (γGT)] and enzymes (alanine amino-peptidase and lactate dehydrogenase).

The sensitivity of these biomarkers refers to their ability to correctly detect patients who have AKI (*i.e.* the proportion of the patients who test positive for AKI among those who have the disease) while their specificity relates to their ability to correctly detect patients without AKI (*i.e.* the proportion of healthy children known not to have AKI who will test negative for it).

For instance, KIM-1 (a transmembrane tubular glycoprotein which is up-regulated approximately 50–100 fold in the kidney) is shed into the urine following proximal tubular injury and urinary KIM-1 constitutes a promising biomarker for early detection of AKI with considerable predictive value[26]. In addition, KIM-1 and its soluble ectodomain in urine (90 kDa) are thought to be involved in the regeneration processes after epithelial damage. It is thus highly predictive of tubular injury as it may be the most useful in combination with other biomarkers, including NGAL, to show not only the kidney injury and predict who may develop it, but also the most prominent location of the injury. Nevertheless, a drug-safety study indicates that KIM-1 may also be useful in determining drug toxicity[27]. In comparison to other biomarkers used as indicators of drug toxicity, KIM-1 significantly outperformed serum creatinine and blood urea nitrogen at detecting renal tubular injury in rats and it was actually the first injury biomarker of renal toxicity approved by the US Food and Drug Administration for pre-clinical toxicity testing and drug development[27].

Furthermore, a combination of some urinary biomarkers (liver-type fatty acid-binding protein and NGAL) may allow for the early detection of AKI after cardiac surgery before an elevation in serum creatinine[28]. Similarly, NGAL has been shown to be a sensitive, specific, and highly predictive early biomarker of AKI superimposed on CKD following cardiac surgery, albeit in adult subjects[29]. This biomarker is a universal iron-carrying protein expressed in the tubular epithelium of the distal nephron and released into the blood and urine following tubular damage. It was first identified as a 25 kDa protein in the secondary granules of human neutrophils which is released into the bloodstream in response to bacterial infection and its elevated level in urine may be diagnostic of AKI using the Acute Kidney Injury Network criteria though the predictive value was reported to be only moderate[30,31]. Nevertheless, the novel biomarkers of AKI, NGAL were identified as the most speedily induced proteins in rat models of ischemic and toxic AKI and their levels were raised in multiple folds in both serum and urine within hours of the insult[11]. Another biomarker of kidney injury worthy of mention is NAG, a large (>130 kDa) lysosomal enzyme which is located in several human cells including the renal tubules[7]. Its size makes glomerular filtration impossible, and increased urinary levels are therefore presumed to emanate from the tubules. The elevated NAG levels indicate tubular injury, but probably result from increased lysosomal activity without cell damage as well. Notably, urinary NAG activity has been shown to be high during active renal disease[32]. In a prospective study of 61 patients over a 1-year period, the authors comparatively evaluated the accuracy of several biomarkers (urinary tubular enzymes such as γGT, alkaline phosphatase, and urinary lactate dehydrogenase and urinary NGAL) on predicting AKI episode after liver transplantation[33]. From the findings, it was concluded that the absolute value of urinary γGT evaluated at the end of liver transplantation was the most accurate parameter to predict AKI in the study cohort. Urinary NGAL was conclusively found to be less accurate.

Some of the biomarkers are non-specific for AKI as they have also been discovered to be useful for the diagnosis of CKD and for monitoring its progression including NGAL, and KIM-1. NGAL has diagnostic and prognostic value for CKD as well as other renal diseases such as acute pyelonephritis[34,35]. According to one study conducted among 3 386 CKD patients, urine NGAL was an independent risk factor of CKD progression though it did not substantially improve the prediction of outcome events[26]. Furthermore, specific novel biomarkers are significantly elevated during kidney allograft rejection while urinary levels of VEGF, cytokines, chemokines and cell adhesion molecules are raised in diabetic nephropathy as VEGF is known to drive the associated increased angiogenesis, underscoring their non-specificity for AKI diagnosis[36–40]. This equally applies to urinary cystatin C. Although it is used as a biomarker for AKI, its level is elevated when the re-absorptive capacity of the cells of the proximal tubules is diminished and thus, the level has been found to be high in subjects with known tubulopathy[41]. This finding can be explained by the fact that cystatin C is a low-molecular weight protein produced by all nucleated cells in the body at a constant rate, freely filtered by the glomeruli but completely reabsorbed and catabolized by the renal tubules[42]. In one report, urinary cystatin C correctly predicted that ICU patients with established AKI would require dialysis[43]. Furthermore, in another study that aimed to determine if early cystatin C levels could predict AKI in pediatric patients undergoing cardiac surgery, as well as predict pediatric-modified RIFLE grouping and kidney injury as determined by estimated GFR, the researchers reported that the biomarker was not only an early predictor of AKI in children after cardiopulmonary bypass but also a good predictor of pediatric RIFLE classification and decreased estimated GFR after the same surgical procedure[44]. Finally, in a similar prospective study which evaluated the use of serum cystatin C for the early and accurate diagnosis of AKI in patients hospitalized from the emergency setting, the investigators concluded that serum cystatin C estimated on admission, either alone or in combination with serum creatinine and estimated GFR, could be considered a reliable armamentarium for the prediction of AKI in patients at the emergency department[45]. They also established that serial assessment of serum cystatin C did not rank higher than serum creatinine and estimated GFR in discriminating AKI from non-AKI subjects.

4. Conclusions

The discriminative and predictive abilities of these novel biomarkers of AKI have been evaluated by several studies and are currently still being evaluated. Given the characteristics of an ideal biomarker, it is difficult to find one marker which can solely fulfill all the criteria. Rather, constellations of different biomarkers with specific features are probably required to increase their sensitivity and specificity in order to enhance the diagnosis of AKI. In future, the diagnostic evaluation of AKI in ICU will have to undergo a paradigm shift from serum creatinine as the traditional biomarker to tissue-specific injury biomarkers[7]. A panel of these novel biomarkers employed at the bedside setting will ultimately revolutionize the diagnosis and prognostication of AKI in children.

Conflict of interest statement

The author reports no conflict of interest.

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