Review

Novel Urinary Biomarkers for Diagnosis of Acute Pyelonephritis in Children

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Urinary tract infection (UTI) is common among pediatric population. Pyelonephritis, especially in young infants, is associated with a significant morbidity. Usually, clinical manifestations, laboratory findings, and imaging are used to differentiate between lower and upper UTI. Lack of specific clinical findings and commonly used nonspecific blood indices are important hamper differentiation between lower and upper UTI in early stages. Imaging techniques are neither cost benefit nor safe for detection of UTI. Recent efforts have focused on characterization of novel serum and urinary biomarkers for early detection of acute pyelonephritis in children. It seems that urinary NGAL, NAG, TNF-α and IL-8 may be used as novel markers for early diagnosis of acute pyelonephritis in children.

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INTRODUCTION

Urinary tract infection (UTI) is a very common pediatric infection. Acute pyelonephritis is associated with significant complications and morbidity, especially in neonates and young infants.[1] Prompt and accurate diagnosis of pyelonephritis and differentiation between lower and upper UTI are very important in this regard. In infants, approximately 60% of febrile UTI episodes will result in renal scarring, which increases the risk of secondary hypertension and chronic kidney diseases.[2] For better diagnosis and differentiation, specialists usually rely on clinical manifestations, laboratory findings and DMSA scintigraphy.[3] Because clinical findings and commonly used blood tests are not specific, it is challenging to differentiate lower UTI from pyelonephritis. Hospitalization, intravenous antibiotic administration and extensive evaluations and detection of the risk factors like urological and bowel habit abnormalities and voiding dysfunction are important factors to achieve better results in treatment of a child with upper pyelonephritis.[4-7]

The results of previous researches on pyelonephritic patients confirmed that kidney ultrasonography is helpful in predicting development of inflammation and renal cortical scar.[8,9]

Although renal scintigraphy using technetium-99m–labeled dimercaptosuccinic acid can be used to confirm acute kidney infection, document renal damage, and predict vesicoureteral reflux[10-13] as a valid diagnostic tool, using this imaging method routinely during an acute illness does not affect the choice of treatment modalities in most of the patients.[2,14] According to previous studies, imaging techniques are not usually cost benefit in acute phase and they expose children to radiation too.

Recent efforts have focused on the characterization of novel serum and urinary biomarkers for the early detection of acute pyelonephritis. The most important biomarkers in this regard are urinary markers, NGAL (Neutrophil gelatinase associated lipocalin), interleukins, NAG (N-acetyl-β- (D) -glucosaminidase) and TNF-α (Tumor necrosis factor-alpha). In this article the author tried to highlight the diagnostic significance and practical aspects of urinary levels of these biomarkers in pediatrics.

URINE SEDIMENT AS A BIOMARKER OF KIDNEY DISEASES

Urine microscopy has many ideal qualities as a good urinary biomarker for early detection of kidney diseases like acute urinary tract infection. It is fast, easy, available, noninvasive, and inexpensive. Moreover, most studies have shown its acceptable sensitivity and specificity. In addition, urine microscopy findings change following specific therapy with kidney recovery.[15]

Although urine microscopic examination suffers some shortcomings that prevent its use as an ideal biomarker, in practical terms, urine sediment findings may provide more information about the site of renal infection or injury. Urine sediment examination, especially together with dipstick urinalysis, can indicate the involvement of different kidney compartments like the glomerules, tubules, or interstitium.[16,17]

For example, urinary acanthocytes and red blood cell casts plus albuminuria detected by dipstick suggest glomerular injury. The results of our study confirm the assumption that during an acute pyelonephritis, proteinuria is frequent and occasionally in nephrotic range.[18] Finding renal tubular epithelial cell and muddy brown casts point toward tubular injury. The presence of leukocyturia, renal tubular epithelial cells, white blood cell and granular casts strongly indicates an acute or chronic tubulointerstitial disease in a consistent clinical setting, such as infection, drug toxicity, or an underlying systemic illness. For prompt detection of pyelonephritis, one of the most useful and practical tests is leukocyte cast. It provides plenty of information about kidney problems and is a valuable urinary biomarker. It warns the clinician of the kidney involvement, provides diagnostic information, guides treatment, and may help determine the prognosis of pediatric UTIs.[19] Regardless of all these advantages, urine sediment seems to be operator dependent with low degree of sensitivity and specificity in some situations.

NEUTROPHIL GELATINASE ASSOCIATED LIPOCALIN

Neutrophil gelatinase associated lipocalin (NGAL) is a novel iron-carrier protein identified in human neutrophil granules. It is believed to be a component of the innate immune system and plays a key role in response to bacterial infection. Animal studies have shown that NGAL-deficient mice are very susceptible to infection with *Escherichia coli* and died with sepsis.[20,21] Some studies have shown that the serum level of NGAL (sNGAL) serves as a useful marker for differentiation between acute bacterial infections with viral infections in newborns, children, and adults.[22] Ichino *et al.* conducted an experimental study in pyelonephritic rats and reported an increase in urine NGAL level (uNGAL) at the early stages of UTI, indicating the value of uNGAL in prediction of UTI in humans as well.[23]

The positive and negative predictive values of the urinary NGAL/Cr ratio were 89% and 92%, respectively. When the urinary NGAL/Cr ratio is higher than this cutoff value, the likelihood of UTI increases by four times (positive likelihood ratio = 4.07 and negative likelihood ratio = 0.02). The sensitivity of uNGAL/Cr (98%) is higher than leukocyte esterase or nitrite test, while its specificity (76%) is lower than urinalysis. So urinary NGAL/Cr ratio was excellent marker to predict inflammation like UTI in children and optimal cutoff value could be used for initiation of treatment before urine culture results are obtained.[24] Since increased level of urinary NGAL are reported in patients with acute kidney injury and chronic kidney diseases, it should be kept in mind that uNGAL can potentially be used for early detection of UTI in children, but only if there is no acute kidney injury and chronic kidney disease.[25,26]

In a recent study, Krzemień G *et al.* evaluated serum and urinary levels of NGAL and showed that NGAL and uNGAL levels were both significantly higher in febrile versus non-febrile UTI and control groups. The receiver operating curves (ROC) showed an optimum cut-off of 76.2 ng/mL for sNGAL with a sensitivity of 92.9%, specificity of 94.4%, and the AUC of 0.98, and an optimum cut-off of 42.2 ng/mL for uNGAL with a sensitivity of 73.8%, specificity of 72.2%, and AUC of 0.76 for diagnosis of febrile UTI in children.[27] Recently, Lubell TR *et al.* reported 97.1% sensitivity and 95.6% specificity of uNGAL for diagnosis of urinary tract infections (UTIs) in febrile infants and children.[28]

INTERLEUKIN-8

There is a lipid component in the endotoxin and P fimbriae of Escherichia coli and other gram

negative bacteria that has been shown to cause an inflammatory reaction in association with kidney damage. Previous studies have demonstrated that Interleukin-1β (IL-1β), Interleukin-6 (IL-6), and Interleukin- 8 (IL-8) have a role in this response and their levels increase in the urine of patients suffering from bacterial UTI.[29-30] IL-8 acts as a neutrophilic chemotactic factor. It has been shown that mesangial cells produce IL-8 in response to IL-1β and tumor necrosis factor-α. IL-8 is a neutrophil-activation protein excreted from the renal tubules following acute inflammation. Previous studies have shown significantly higher initial levels of IL-8 in the serum and urine of children with acute pyelonephritis.[29-31] However, IL-6 and IL-8 levels cannot differentiate acute pyelonephritis from cystitis in children aged less than 24 months.[30]

It seems that kidney damage due to inflammation begins early in the course of acute pyelonephritis and usage of antibiotics combined with dexamethasone significantly decreased urinary IL-8 level in patients with pyelonephritis.[32]

Tullus *et al.* reported detectable levels of IL-8 in 98% of children with pyelonephritis and 42% of other children. They showed higher levels of urinary IL-8 in children less than 1 year of age.[33]

Sheu *et al* reported that serum or urine levels of IL-6 andIL-8 had a direct correlation with fever, CRP, leukocytes, and leucocyturia in children with acute pyelonephritis, indicating that bacterial invasion can activate both local and systemic inflammatory responses in pediatric patients with acute pyelonephritis.[29]

In the acute phase of UTI, IL-8 is produced in the urine by gram-negative bacteria and a wide spectrum of microorganisms. The urine level of IL-8 is higher than its serum level in patients with UTI, suggesting local production of IL-8 in the urinary tract. There is a correlation between the urine level of IL-8 and the number of PMNs in the urine, suggesting that IL-8 has a role in PMN migration into the urinary tract.[34]

W H Rao *et al.* showed a sensitivity of 93% for urine IL-8 as a marker of UTI with a cutoff value of 200 pg/mL, indicating that the test correctly identifies 93% of the patients with UTI, but fails to detect the disease in 7% of the cases. In addition, they reported a specificity of 90% for the test, i.e. it can correctly identify 90% of the subjects without a UTI but is positive in 10% of these cases.[35]

N-ACETYL-BETA-GLUCOSAMINIDASE

N-acetyl-beta-glucosaminidase (NAG) is a lysosomal enzyme presents in the proximal convoluted tubule. It can be used as a marker of proximal tubular damage and nephrotoxicity.[36] It is a relatively high-weight molecule (approximately 130000-140000 Da) and therefore cannot filtrate through the glomerular basement membrane. Moreover, NAG has a rapid clearance from the circulation by the liver. Urinary NAG can be checked by noninvasive techniques and it can be used in a clinical setting to detect acute kidney injury and other functional disorders of the kidneys.[37]

Regardless of acute kidney injury, an abnormal urinary NAG excretion is also reported in different kind of renal disorders such as UTI, vesicoureteral reflux, nephrotoxic drugs, renal allograft rejection, diabetes mellitus, nephrotic syndrome, glomerulonephritis, nephrocalcinosis, hypercalciuria, urolithiasis, hypertension, perinatal asphyxia, heavy metals poisoning, and heart failure.[38-43]

There is a circadian variation in the urinary NAG excretion in healthy children. According to previous studies, urinary NAG values are high in 2-3 years old children and then decrease with the lowest levels seen in children six to eight years old.[44]

Urinary tract infections are associated with an increase in urinary excretion of NAG. Hence, urinary NAG may serve as an additional criterion for diagnosis of upper UTI. It can potentially be used as an additional marker to diagnose pyelonephritis and interstitial tubular damage.[39-44] Therefore, urinary NAG is an indicator of kidney damage, such as injury or dysfunction due to infection, inflammation, and nephrotoxic drugs.[41,46]

Some studies have shown significantly higher levels of urinary NAG in patients with upper UTI compared with lower UTI.[36] According to a study by Cottone, target chemo-antibiotic treatment causes a reduction in inflammation, urinary NAG level and hence the tubular distress in all patients.[47] Belli *et al.* reported elevated urinary NAG levels in children with pyelonephritis with or without urinary tract abnormality.[37]

Jantausch BA reported a sensitivity and specificity of 88% for NAG ≥ 40 μmol/h/mg of creatinine in predicting UTI in febrile infants, regardless of the site of infection. There is an association between increased urinary NAG and UTI in febrile patients

Table. The Sensitivity and Specificity of Urinary Biomarkers for Detection of UTI

Urinary Biomarkers	Sensitivity	Specificity	Study	Year of Publication	Country
IL-8	93%	90%	W H Rao et al.[35]	2001	UK
TNF-α	91%	-	Mohkam et al.[63]	2009	Iran
NAG	73.6%	77.3%	Mohkam et al.[40]	2008	Iran
NGAL	97.1%	95.6%	Lubell T R et al.[28]	2018	USA
NGAL	73.8%	72.2%	Krzemień G[27]	2018	Poland

regardless of the level of infection, and therefore urinary NAG may be an informative indicator of UTI.[48] The results of our study in this regard showed that urinary NAG/creatinine ratio is 73.6% sensitive and 77.3% specific for diagnosis of pyelonephritis with a cutoff point of 10.16 U/g.[40]

TUMOR NECROSIS FACTOR-ALPHA

Tumor necrosis factor-alpha (TNF-α) is one of the most potent pro-inflammatory cytokines. In fact, TNF-α induces a potent inflammatory response involving macrophages and neutrophils.

Previous studies have revealed the role of TNF-α in monitoring therapeutic response to BCG in bladder cancer,[49] other febrile infections in children,[50] Schistosoma hematobium-induced urinary tract morbidity,[51,52] glomerulonephritis,[53,54] and pathogenesis of allograft rejection.[55] According to recent studies, TNF- α also plays a role in apoptosis and pathogenesis of pediatric renal diseases,[56,57] acute pyelonephritis,[58,59] and pathogenesis of renal injury in diabetes mellitus. It is also a pathogenic indicator of multidrug resistant E. coli in urosepsis.[60]

Engel *et al.* found increased level of TNF-α in the bladder during UTI, which may play a key role in defining pyelonephritis.[61] In an animal study, Biyikli *et al.* showed elevated serum levels of TNF-α, kidney tissue malondialdehyde, and myeloperoxidase in acute and chronic phases of pyelonephritis.[62] The results of our study on pediatric patients confirmed significantly higher levels of TNF-α in the acute phase of pyelonephritis that decreased after appropriate antibiotic treatment. Based on our study, urinary TNF-α is 91.0% sensitive for diagnosis of acute pyelonephritis in comparison with the results of DMSA scan as the gold standard test with an AUC of 0.919.[63,64] Furthermore, Sadeghi and Davidoff reported that the levels of urinary cytokines including TNF-α were elevated during bacteriuria in kidney transplant patients and in patients with cystitis[65,66] and again we showed TNF-α as a predictor of urological abnormality in pediatric patients with UTI as well.[67]

CONCLUSION

Based on upper mentioned studies for prompt diagnosis of pyelonephritis especially in young infants and for prevention of renal damage and the other complications of upper UTI in pediatric group the clinicians need fast, available, cost benefit and non-invasive methods with no radiation. Using urinary biomarkers help us to detect UTI and confirm the levels of UTI in most situations especially in first 48 hours.

Although urinary biomarkers are not highly specific for diagnosis of UTI, some of them have enough sensitivity for detection of UTI. Table demonstrates the sensitivity and specificity of these laboratory tests for detection of UTI in pediatric group. According to Table, NAG and IL-8 are the most sensitive and specific urinary biomarkers for detection of UTI.[28,35]

Early recognition and awareness of UTI by urinary biomarkers can help appropriate treatment and reduce frequent laboratory tests, imaging and expenses, prevent family anxiety and agitation and finally can lessen duration of hospitalization.

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