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Original Article

Urine interleukin-1β in children with acute pyelonephritis and renal scarring

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SUMMARY:

Aim: Acute pyelonephritis is a common infectious disease in children and can result in permanent renal damage. Interleukin (IL)-1β is an important inflammatory mediator that appears early during bacterial infection. This prospective study examined urine IL-1β levels in children with acute pyelonephritis documented by ^{99m}Tc-dimercaptosuccinic acid (DMSA) scan, and also evaluated whether this cytokine correlated with renal scarring.

Methods: A total of 75 children aged 1–121 months with a diagnosis of first-time febrile urinary tract infection (UTI) were studied. The following inflammatory markers were assessed: fever, white blood cell (WBC), neutrophil, C-reactive protein (CRP) and urine IL-1β. Urine samples were collected for IL-1β measurement by enzyme-linked immunosorbent assay before and after antibiotic treatment of the infection. Follow-up DMSA scan was performed at 6–12 months after the acute pyelonephritis to detect renal scarring. Twenty children with other febrile illnesses served as non-renal febrile controls.

Results: The 75 children were divided into acute pyelonephritis ($n = 41$) and lower UTI ($n = 34$) groups according to the findings of DMSA scans. Fever, WBC count, neutrophil count and CRP were significantly higher in the children with acute pyelonephritis than in those with lower UTI (all $P < 0.001$). The initial urine IL-1β levels of children with acute pyelonephritis were significantly higher when compared with lower UTI and non-renal febrile controls ($P < 0.001$). Urine IL-1β in children with acute pyelonephritis was positively correlated with fever, CRP, WBC, neutrophil and leucocyturia. Renal scarring was found in 12 (29.3%) of the 41 children with acute pyelonephritis. The mean age was significantly lower in the children with renal scarring compared with those without ($P < 0.05$).

Conclusion: These results have shown that urine IL-1β level may serve as a useful marker for the early detection of acute pyelonephritis in febrile children. Young children are at a risk of the development of renal scarring following acute pyelonephritis.

KEY WORDS: **acute pyelonephritis, child, interleukin-1β, renal scarring, ^{99m}Tc-dimercaptosuccinic acid scan.**

Acute pyelonephritis is one of the most common serious bacterial infections in infancy and childhood. Without early diagnosis and rapid treatment of children with acute pyelonephritis, the progression of renal inflammation can result in renal scarring and permanent kidney damage. Postinfectious renal scarring is the most important complication after acute pyelonephritis in children, with an estimated incidence of 10–65% of cases.[1,2] Renal scarring later in life may lead to the subsequent development of hypertension, proteinuria and even loss of renal function that is one of the major causes of end-stage renal disease in many countries.[3,4] Differentiation of acute pyelonephritis from lower urinary tract infection (UTI) and follow up to identify renal scarring after the first infection in febrile children are thus very important.

Cytokines are small soluble proteins, which play a major role in mediating the inflammatory response to various infectious and inflammatory diseases.[5,6] The analysis of serum and urine cytokines is emerging as an important area of urological research. Elevated levels of the proinflammatory cytokines

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interleukin (IL)-1α, IL-6 and IL-8 have recently been reported in the serum and urine of children with UTI.[7–11] These cytokines are thought to be prime initiators of the immune response inducing the further cascade of cytokines. IL-6 and IL-8 are also known to be produced after the stimulation by the most-potent proinflammatory cytokines, IL-1 and tumour necrosis factor (TNF)-α.[6,12] IL-1 is the first cytokine produced in the antigen recognition immune cascade and exists in two distinct forms: IL-1α and IL-1β.[13] IL-1α is predominantly a membrane- and cell-associated cytokine, while IL-1β is found free in biological fluids, including serum, urine and synovial fluid. The basic biological difference between the two forms made IL-1β the more logical choice for study in human urine. IL-1β was originally described as a fever-producing endogenous pyrogen that appears early during the inflammatory processes, which are responsible for acute-phase reactions, including fever production, increased secretion of acute-phase reactants such as C-reactive protein (CRP), and peripheral neutrophilia.[13] IL-1β was chosen for investigation in this study over other urinary markers because it appears early in the immune response cascade. The assessment of IL-1β in urine is both clinically feasible and potentially useful in acute pyelonephritis due to its role in systemic inflammation.

^{99m}Tc-dimercaptosuccinic acid (DMSA) uptake reflects the functional integrity of renal parenchyma, especially as it relates to the renal cortex. DMSA scan is a widely accepted standard method for the diagnosis of acute pyelonephritis and for the follow-up detection of renal cortical scars.[14,15] DMSA scintigraphy, therefore, offers great value in distinguishing pyelonephritis from lower UTI and in evaluating persistent DMSA uptake defects after the initial infection in children.

The aims of this prospective study were to investigate the role of urine IL-1β in children with a first-time acute pyelonephritis confirmed by acute-phase DMSA scan, and also to examine the correlations of urine IL-β level with inflammatory markers, vesicoureteral reflux (VUR) and renal scarring.

PATIENTS AND METHODS

Subjects and study design

A total of 75 children (aged from 1 month to 10 years) with a first-time febrile UTI were enrolled into this prospective study during a 2.5-year period. The diagnosis of febrile UTI was based on the following criteria: fever ≥38°C (axillary temperature); leucocyturia, defined as ≥5 white blood cell (WBC) per high-power field; and a positive urine culture, defined as growth of a single organism $\geq 10^5$ colony-forming units per mL collected from clean midstream urine or $\geq 10^4$ colony-forming units per mL collected from a catheter. Children were excluded if they had a history of previous UTI, renal or bladder disease, immunodeficiency or ongoing antibiotic treatment. All children were treated empirically with broad-spectrum antibiotics, and the regimen was later adjusted according to the results of antibiotic susceptibility testing of the isolates. A total of 20 age- and sex-matched children with various febrile illnesses (fever ≥38°C) having a normal urinalysis and a negative urine culture and no history of UTI served as the non-renal febrile controls. Informed consent was given by all parents of children participating in the study. The protocol was approved by the Institutional Review Board of the Chung Shan Medical University Hospital.

Laboratory analysis

Serum and urine samples were collected from all febrile children. Laboratory tests routinely performed for the identification of infection in all cases included peripheral WBC count and differential, platelet count, CRP, urinalysis, urine culture and routine biochemistry. CRP was measured by a nephelometry (Dade Behring Marburg GmbH, Marburg, Germany). Urinalysis was carried out using the dipstick analysis (Bayer Diagnostics Manufacturing Limited, Bridgend, UK). Urine leucocytes were microscopically counted in centrifuged urine. For urine cultures, an aliquot (1 μL) of urine was inoculated into the appropriate medium (BD BBL plate; Becton, Dickinsen and Company, Sparks, MD, USA), and colonies were counted 24 and 48 h later. Urine creatinine was determined by a photometric assay (Daiichi Pure Chemicals, Ibaraki, Japan). In all episodes of febrile UTI, a subsequent urine culture was performed after 3 days of antibiotic treatment.

Radiological studies

All children underwent renal ultrasound examination for detection of anomalies of the urinary tract within the first 3 days of hospitalization. DMSA scan was routinely performed within the first 7 days of hospitalization to verify the presence of pyelonephritic lesions on the renal parenchyma. A normal scan was defined as normal radioisotope uptake within the kidneys, and an abnormal scan was defined as the presence of areas of impaired uptake (focal or multifocal) with preservation of the renal contour.[15] Based on the findings of DMSA scan, children were divided into groups according to the diagnosis of acute pyelonephritis or lower UTI. If the result of the initial DMSA scan was abnormal, another follow-up DMSA scan was performed again 6–12 months after the episode to detect renal scarring. Renal scarring was defined as the presence of focal or generalized areas of persistent diminished uptake of radioisotope associated with loss or contraction of functioning renal cortex at 6 months after the initial DMSA scan.[15] Voiding cystourethrography (VCUG) examination was performed 1–2 weeks after completion of the treatment for infection (negative urine culture). The presence of VUR was graded from 0-V using an international classification scheme.[16]

Measurement of IL-1β

Urine samples were collected for IL-1β measurement from all children before and approximately 2 weeks after the initiation of antibiotic treatment. Urine samples for IL-1β assay were immediately centrifuged, separated, frozen and stored at −70°C until they were tested in batches. IL-1β levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN, USA), which uses the quantitative sandwich enzyme immunoassay technique following the manufacturer's instructions. The ELISA protocol included the following steps. A 200 μL aliquot of the urine samples was added to the microtiter well coated with IL-1β monoclonal antibody. The plate was covered with an adhesive strip to prevent sample evaporation. The samples were incubated for 2 h at room temperature. After incubation, the microtiter wells were washed three times using an automated plate washer and washed buffer. Another horseradish peroxidase-conjugated polyclonal antibody directed against IL-1β was added (200 μL), and the specimens were incubated for 1 h at room temperature. The microtiter wells were then repeatedly washed three times with buffer solution. Colour developing reagent (200 μL)

Table 1 Clinical characteristics of children with acute pyelonephritis and lower UTI

Variable	Acute pyelonephritis ($n = 41$)	Lower UTI ($n = 34$)	P value
Age (months)	30.8 ± 27.5	40.3 ± 31.4	NS
Sex (boy/girl)	18/23	11/23	NS
Fever (≥38°C)	39.2 ± 0.8	38.4 ± 0.3	<0.001
CRP (mg/dL)	9.2 ± 5.9	1.8 ± 1.1	<0.001
WBC count (per mm^3)	18 671 ± 8 687	12 060 ± 4332	<0.001
Neutrophil count (per mm^3)	13 578 ± 6 916	6 316 ± 2 941	<0.001
Vesicoureteral reflux	16/38 (42.1%)	5/31 (16.1%)	0.02
Grade ≥3	10/16 (62.5%)	1/5 (20%)	NS
Grade 1–2	6/16 (37.5%)	4/5 (80%)	NS

CRP, C-reactive protein; NS, not significant; UTI, urinary tract infection; WBC, white blood cell.

was added and incubated for 20 min at room temperature. A stop solution was then added, and the plates were read 30 min later on a dual wavelength ELISA reader at 450 and 540 nm, respectively, which corrected optical density $(OD)_{450}$ reading by subtracting OD_{540}. IL-1β (pg/mL) levels were calculated using a standard curve generated with recombinant cytokine supplied in the kit. All measurements were performed in duplicate. The differences between duplicate wells were consistently less than 10% of the mean values. The cost of a commercially available kit for IL-1β assay was US$630 per kit. The total expense of IL-1β measurements in this study was about US$2000. The lower limit of detection in urine IL-1β was 1.0 pg/mL. To standardize the measurements of different urine samples and avoid dilutional effects of varying urine output, urinary levels of cytokine were expressed as the ratio of urine IL-1β to urine creatinine (pg/mg).

Statistical analysis

All tests were performed using SPSS for Windows, version 10.0 (SPSS Inc., Chicago, IL, USA). The data were expressed as mean ± SD. Mann–Whitney *U*-test was used for intergroup comparisons. Wilcoxon's rank-sum test was used for comparisons of paired data within the same group. Chi-square test or Fisher's exact test was used for comparisons of group proportions with qualitative data. The data among groups were assessed by the Kruskal–Wallis one-way analysis, with adjustment for multiple comparisons. Correlations between variables were assessed using the Spearman rank correlation test. Multiple linear regression analysis was performed to determine significant association of urine IL-1β levels and independent variables. Sensitivity and specificity of inflammatory markers and urine IL-1β were calculated. Optimal cut-off values of inflammatory markers and urine IL-1β for diagnosing acute pyelonephritis were determined. For all tests, a P value of <0.05 was considered statistically significant.

RESULTS

Patient characteristics and laboratory tests

Seventy-five children with a first-time febrile UTI, including 29 boys and 46 girls, aged from 1 to 121 months (mean age 35.1 ± 29.5 months), were studied. Among them, 41 children (18 boys and 23 girls) had acute pyelonephritis, and 34 (11 boys and 23 girls) had lower UTI. The median age at the time of diagnosis of acute pyelonephritis was 24.0 months (range 1–120 months), and for lower UTI was 34.6 months (range 3.6–121 months). The 20 non-renal febrile control children had the following diagnoses: acute tonsillitis ($n = 6$), acute pharyngitis ($n = 4$), acute otitis media ($n = 4$), pneumonia ($n = 3$) and gastroenteritis ($n = 3$). The median age of the 20 febrile controls (11 boys and 9 girls) was 26.2 months (range 3–90 months). There were no significant differences in the sex and age among the children with acute pyelonephritis and lower UTI and febrile controls. The characteristics of the children with acute pyelonephritis and lower UTI are summarized in Table 1. Inflammatory markers, including fever, CRP, WBC count and neutrophil count, were significantly higher in the children with acute pyelonephritis when compared with lower UTI (all $P < 0.001$). The isolated microorganisms of children with febrile UTI were *Escherichia coli* (74.7%) and other bacteria (*Klebsiella*, *Proteus*, *Citrobacter*, *Enterobacter*, *Pseudomonas* and *Enterococcus*). There were no significant differences in the aetiological agents identified between the children with acute pyelonephritis and lower UTI. Follow-up urine cultures were negative in all febrile UTI.

Radiological findings

Renal ultrasound revealed the following findings: mild to moderate hydronephrosis in three children; duplex kidney in one child; and ureterocele in one child. All of the children with positive renal ultrasound findings belonged to the acute pyelonephritis group. Of the 69 children who underwent VCUG studies, 21 (30.4%) had VUR (1 with grade I, 9 with grade II, 7 with grade III, 2 with grade IV and 2 with grade V, maximum degree of reflux given if bilateral). The prevalence of VUR in the children with acute pyelonephritis was significantly higher compared with lower UTI ($P = 0.02$).

Urine IL-1β levels and urine IL-1β/creatinine ratio in children with acute pyelonephritis and lower UTI

IL-1β was detected in the urine in 93% of the children with acute pyelonephritis and in 74% of the children with lower UTI, compared with that in 30% of the febrile controls; the

Table 2 Cytokine levels expressed both as the urine IL-1β levels and as the urine IL-1β/creatinine ratio in children with acute pyelonephritis and lower UTI and non-renal febrile controls

Urine cytokine	Acute pyelonephritis ($n = 41$)	Lower UTI ($n = 34$)	Febrile controls ($n = 20$)	P value (across groups)
IL-1β (pg/mL)				
Initial measurement	172.0 ± 263.3*,**	20.4 ± 41.2*,***	4.6 ± 14.0†	<0.001
Follow-up measurement	0.9 ± 2.4	0.4 ± 1.0	0.2 ± 0.7	NS
IL-1β/creatinine (pg/mg)				
Initial measurement	1115.5 ± 1689.6*,**	113.5 ± 230.1*, ***	30.6 ± 88.8†	<0.001
Follow-up measurement	4.4 ± 12.1	2.4 ± 6.3	1.4 ± 4.4	NS

*$P < 0.001$ *versus* follow-up measurement; **$P < 0.001$ *versus* initial measurement of lower UTI and febrile controls; ***$P < 0.01$ *versus* initial measurement of febrile controls. †$P < 0.05$ *versus* follow-up measurement. IL, interleukin; NS, not significant; UTI, urinary tract infection.

Table 3 Initial urine IL-1β levels and urine IL-1β/creatinine ratio in children with VUR and renal scarring

	VCUG ($n = 69$)		DMSA ($n = 41$)	
Urine cytokine	VUR (+)	VUR (–)	Renal scarring (+)	Renal scarring (–)
Number of children	21	48	12	29
IL-1β (pg/mL)	128.9 ± 182.5*	101.3 ± 232.5	40.2 ± 50.8**	226.6 ± 295.8
IL-1β/creatinine (pg/mg)	879.6 ± 1144.7*	639.6 ± 1561.4	328.3 ± 378.4**	1441.2 ± 1909.5

*P = not significant *versus* VUR (–); **$P < 0.01$ *versus* renal scarring (–). DMSA, ^{99m}Tc-dimercaptosuccinic acid; IL, interleukin; VCUG, voiding cystourethrography; VUR, vesicoureteral reflux.

differences were highly significant ($P < 0.001$ and $P < 0.005$, respectively). Cytokine levels were expressed both as the urine IL-1β levels and as the urine IL-1β/creatinine ratio in the children with acute pyelonephritis and lower UTI and non-renal febrile controls (Table 2). The reported data were analysed using the urine IL-1β level as well as the urine IL-1β/creatinine ratio. There were no differences in the results regardless of the form in which they were expressed. The children with acute pyelonephritis had significantly higher initial urine IL-1β levels than after appropriate antibiotic treatment ($P < 0.001$). The children with lower UTI also had significantly higher initial urine IL-1β levels than at follow up ($P < 0.001$). There was a significant difference in the initial urine levels of IL-1β among the children with acute pyelonephritis and lower UTI and febrile controls ($P < 0.001$). The initial urine IL-1β levels were significantly higher in the children with acute pyelonephritis than in the lower UTI ($P < 0.001$) and the febrile controls ($P < 0.001$). The initial urine IL-1β levels of children with lower UTI were also significantly higher when compared with febrile controls ($P < 0.01$). At follow up after the treatment, there was no significant difference in the urine IL-1β levels among the children with acute pyelonephritis and lower UTI and febrile controls.

Urine IL-1β levels and urine IL-1β/creatinine ratio in children with VUR and renal scarring

Initial urine IL-1β levels and urine IL-1β/creatinine ratio in children with VUR and renal scarring are shown in Table 3. No differences were noted in the results in both the expressed data. The initial urine IL-1β levels were not significantly different between the children with ($n = 21$) and without VUR ($n = 48$). Follow-up DMSA scan was performed in 41 children with initially abnormal DMSA scans, and showed that 12 children (29.3%) had renal scarring. The initial urine IL-1β levels were significantly lower ($P < 0.01$) in children with renal scarring ($n = 12$) compared with those without ($n = 29$). The median age of the 12 children with renal scarring was 9.0 months (range 1.2–44 months). The mean age was significantly lower in the children with renal scarring compared with those without (15.8 ± 14.8 *vs* 36.2 ± 29.0 months, $P < 0.05$).

Correlations of urine IL-1β level with inflammatory markers and age in children with acute pyelonephritis

The correlation and multiple linear regression of urine IL-1β level with inflammatory markers and age in the children with acute pyelonephritis are shown in Table 4. There was no association of age with urine IL-1β level. When a multiple linear regression analysis was performed with a stepwise method, a significant positive correlation was found between urine IL-1β level and neutrophil ($P < 0.001$). Urine IL-1β in the children with lower UTI was only significantly correlated with leucocyturia ($r = 0.414$, $P < 0.05$).

Optimal cut-off values of inflammatory markers and urine IL-1β for the diagnosis of acute pyelonephritis

Optimal cut-off values of inflammatory markers and urine IL-1β for the diagnosis of acute pyelonephritis in children

Table 4 Correlation and multiple linear regression of urine IL-1β with inflammatory markers and age in children with acute pyelonephritis

	Urine IL-1β/creatinine (pg/mg)			
	Multiple linear regression		Correlation	
Variable	Beta†	*P* value	*r*‡	*P* value
Enter method				
Fever	0.004	0.978	0.460	0.002
CRP	0.224	0.134	0.580	<0.001
WBC	–0.663	0.300	0.641	<0.001
Neutrophil	1.246	0.052	0.593	<0.001
Leucocyturia	0.156	0.226	0.504	0.001
Age	0.163	0.162	0.116	0.471
Stepwise method				
Neutrophil	0.690	<0.001		

†Standardized coefficients. ‡Spearman rank correlation coefficients. CRP, C-reactive protein; IL, interleukin; WBC, white blood cell.

Table 5 Sensitivity and specificity of inflammatory markers and urine IL-1β for the diagnosis of acute pyelonephritis

Variable (cut-off value)	Sensitivity (%)	Specificity (%)
Fever (>39°C)	59	68
CRP (>4 mg/dL)	80	91
WBC count (>15 000/mm^3)	61	76
Neutrophil count (>9000/mm^3)	71	82
Urine IL-1β/creatinine (>150 pg/mg)	88	79

CRP, C-reactive protein; IL, interleukin; WBC, white blood cell.

are shown in Table 5. Using a cut-off value of 39°C for fever and 4 mg/dL for CRP, the sensitivity and specificity in distinguishing acute pyelonephritis from lower UTI were 59% and 68% respectively for fever, and 80% and 91% respectively for CRP. In addition, using a cut-off value of 15 000/mm^3 for WBC count and 9000/mm^3 for neutrophil count, the sensitivity and specificity in distinguishing between acute pyelonephritis and lower UTI were 61% and 76% respectively for WBC count, and 71% and 82% respectively for neutrophil count. With an optimal cut-off level of urine IL-1β/creatinine at 150 pg/mg, the sensitivity of this marker in diagnosing acute pyelonephritis was 88%, and the specificity was 79%.

DISCUSSION

The clinical spectrum of UTI in paediatric patients ranges from asymptomatic bacteriuria to acute pyelonephritis. In the absence of any specific symptomatology, especially in younger infants, early diagnosis of acute pyelonephritis is problematic and challenging. Despite the fact that even though children with fever and systemic clinical symptoms or signs are consistent with a diagnosis of acute pyelonephritis, there is still a high false-positive and/or false-negative rate based on clinical manifestations and laboratory tests.[17,18] The detection of cytokines in the urine has been used in the diagnosis and monitoring of various urological diseases. However, there have been relatively few studies of the role of urine IL-1 in children with UTI.[10,11,19] IL-1β is a preferred investigative focus over IL-1α because it is predominantly secreted into body fluids and, therefore, more likely to play a role in systemic inflammation.

In our study, urine IL-1β levels were elevated in the children with febrile UTI. Urine IL-1β was detected in 84% of children with febrile UTI compared with in 30% of non-renal febrile controls ($P < 0.001$). These findings suggest that the release of urine IL-1β is especially related to infection of the urinary tract. In the study, urine IL-1β levels increased significantly more in the children with acute pyelonephritis than in the other groups studied. Our data are in agreement with previous studies[10,19] which found that IL-1β levels were significantly raised in the urine of children with acute pyelonephritis. Our results also demonstrated that urine IL-1β was significantly elevated at the time of diagnosis of acute pyelonephritis and returned to normal levels after appropriate antibiotic treatment. These suggest that a significant inflammatory process begins early in renal infection and is then blunted after treatment is initiated.

This study showed a positive correlation of urine IL-1β with fever, WBC, CRP, leucocyturia, and especially neutrophil, in the children with acute pyelonephrits. These findings are in agreement with a study by Tullus *et al.* in children with acute pyelonephritis,[11] which showed that urine levels of IL-1α and IL-1 receptor antagonist (IL-1ra) were significantly associated with local inflammatory responses as indicated by the presence of leucocyturia and erythrocyturia. Our results also agree with Gürgöze *et al.*,[7] who found a positive association between serum IL-1β and systemic inflammatory response indicated by the elevation of procalcitonin in the children with acute pyelonephritis. The release of IL-1β from the site of infection causes both local and systemic inflammatory responses, suggesting that IL-1β is an important mediator of early renal inflammation in children.

Only two published studies in the English literature have assessed the correlation between IL-1 and acute

pyelonephritis confirmed by acute-phase DMSA scan in children.[7,11] Gürgöze *et al.* reported that children with acute pyelonephritis documented by DMSA scan had significantly higher serum levels of IL-1β, IL-6 and TNF-α than those with lower UTI.[7] Tullus *et al.*'s study of urine cytokines levels in children with a first-time acute pyelonephritis detected by DMSA scintigraphy found significantly increased urine levels for both IL-1α and IL-1ra.[11] To our knowledge, the present study is the first to demonstrate a significant elevation of IL-1β levels in the urine during the acute phase of first-time pyelonephritis confirmed by DMSA scan in febrile children. Our results are consistent with the findings of Gürgöze *et al.*[7] on serum IL-1β levels, and are also similar to the observations of Tullus *et al.*[11] on urine IL-1α levels in the children with acute pyelonephritis. These findings demonstrate that IL-1β is secreted during the acute phase of renal infection, leading to its release into the serum and urine.

It was found in previous studies that IL-1β is rapidly induced by experimental *E. coli* pyelonephritis and plays an important role in both inflammatory and anti-inflammatory responses.[20,21] IL-1β also activates chemokines secretion and may be involved in the pathogenesis of scar formation.[22] In this study, the results of follow-up DMSA scans showed that renal scarring developed in 12 children (29.3%). The finding is well within the range of previously reported incidence (10–65%) of renal scarring following acute pyelonephritis in paediatric patients.[1,2,7,11] We also noted that the initial urine IL-1β levels were significantly lower in the children with renal scarring. These data are consistent with the findings of Tullus *et al.*[11] that urine levels of both IL-1α and IL-1ra were significantly higher in children with first-time acute pyelonephritis, and that urine IL-1α levels were lowest in the children with renal scarring. Based on these results, they concluded that persistent high urine levels of IL-1α were associated with less renal inflammation and scarring. All these findings support that increased IL-1α or IL-1β levels during the acute phase of renal inflammation may be protective against scar formation. A study of experimentally induced acute *E. coli* pyelonephritis in IL-1β-deficient mice by Hertting *et al.*[23] also supported the potential involvement of IL-1β in the scarring process. They found that IL-1β knockout mice developed more severe and widespread renal inflammation changes than wild-type mice. Their results indicated that the main function of IL-1β in the renal inflammation is anti-inflammatory. Thus, increased urine IL-1β during the acute phase of pyelonephritis in children may have a protective effect against the progression of renal inflammation. In this study, we also observed that renal scarring was more likely to occur at a younger age, suggesting that young children who have a tendency to respond with low IL-1β levels may be at greatest risk of renal scarring.

Our results showed that an optimal cut-off level of 150 pg/mg for urine IL-1β is of high sensitivity and adequate specificity for diagnosing acute pyelonephritis in children. Our data are in agreement with the findings of Gürgöze *et al.*[7] that serum IL-β levels increased significantly in the children with acute pyelonephritis (97% sensitivity and 59% specificity). Tullus *et al.* have demonstrated that acute urine levels of IL-6 and IL-1α can be used to predict later renal scarring.[11,24] In this study, lower initial urine IL-1β levels were found in the children with renal scarring compared with children without. This finding suggests that the initial urine IL-1β levels may be used as another indicator of risk for subsequent development of renal scarring in acute pyelonephritis in children.

In conclusion, this study has demonstrated that urine IL-1β level was markedly elevated during the acute phase of a first-time pyelonephritis in children and it was also significant in distinguishing acute pyelonephritis from lower UTI. Young age at the time of first acute pyelonephritis has an increased risk of postinfectious renal scarring. This study supports a role for urine IL-1β in the pathophysiology of acute pyelonephritis and renal scarring in children. IL-1β level may, therefore, be used as a reliable urinary marker for early identification of acute pyelonephritis in febrile children.

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