USEFULNESS OF SERUM PROCALCITONIN AND URINARY INTERLEUKIN-8 IN PEDIATRIC URINARY TRACT INFECTION

By
Gamal T Soliman*, Mohamed Abdel Maboud*, Ashraf M Osman**, and Sabry N Ali*
Departments of *Pediatrics and **Clinical Pathology, El-Minia Faculty of Medicine

ABSTRACT:
Background: The distinction between lower and upper urinary tract infection (UTI) is important because renal involvement can induce parenchymal scarring that may lead to arterial hypertension and chronic renal failure. Dimercaptosuccinic acid (DMSA) scintigraphy is considered the reference method for diagnosis of renal parenchymal involvement. However, scintigraphy is an expensive examination that is not readily accessible in all centers, and it exposes the patient to radiation.
Objective: This study aimed to assess the value of measuring serum procalcitonin (PCT) and urinary interleukin-8 (IL-8) concentrations in diagnosis of UTI and in distinguishing between lower UTI and acute pyelonephritis in children.
Methods: We studied 40 infants and children (14 males and 26 females) with manifestations suggestive of UTI, their ages ranged from 6 months to 8 years, in addition to 40 apparently healthy children of matched age and sex as a control group. Serum PCT, urinary IL-8, C-reactive protein (CRP), and total leukocytic count were measured in all patients and controls. In cases with positive urine culture, renal parenchymal involvement was assessed by $^{99m}$Tc-DMSA renal scan in the first 5 days after admission.
Results: Patients with UTI had significantly higher levels of serum PCT (3.09±1.01 µg/l), urinary IL-8 (1545±38.2 pg/ml), and CRP (52.1±26.2 mg/L) compared with controls (0.32±0.15 µg/l, 117±26 pg/ml, and 6.1±1.2 mg/L respectively) (p< 0.001 for all). Similarly, patients with acute pyelonephritis (n=23) had significantly higher levels of PCT (5.54±1.18 µg/l), urinary IL-8 (1642 ± 354 pg/ml), and CRP (68.2 ± 8.89 mg/L) compared with cases with lower UTI (n=17), (0.39±0.12 µg/l, 1416 ± 256 pg/ml, and 6.91±4.5 mg/L); p< 0.001, p<0.01, and p<0.01 respectively). Serum PCT correlated positively with urinary IL-8, total leukocytic count and CRP.
Conclusion: in infants and children with suspected UTI, serum PCT and urinary IL-8 may be used as markers of infection, their levels vary with the severity of infection and are increased significantly when renal parenchymal involvement is present. Taking the appropriate clinical situations into account, their measurement might be a useful and practical tool for differentiating acute pyelonephritis from lower UTI.

KEY WORDS:
Procalcitonin, IL-8, Urinary tract infection, Pyelonephritis, DMSA scintigraphy

INTRODUCTION:
Febrile urinary tract infection (UTI) is a frequent pediatric pathology. Commonly used clinical parameters such as fever or flank pain and laboratory markers such as white cell count and C-reactive protein (CRP) cannot differentiate acute pyelonephritis reliably from lower UTI, especially in young children. This distinction, however, is essential because
the risk of renal parenchymal damage in pyelonephritis requires more aggressive therapy, investigation, and follow-up than does lower UTI\textsuperscript{1}.

A high value of \(^{99m}\text{Tc}\)-dimercapto-succinic acid (DMSA) scintigraphy in distinguishing pyelonephritis from lower UTI has been recognized, and it is considered the reference method for diagnosis of renal involvement. However, scintigraphy is an expensive examination that is not readily accessible in all centers, exposes the patient to radiation, and it also may not differentiate between old scarring and acute parenchymal involvement unless a follow-up scan is performed\textsuperscript{2}.

Procalcitonin (PCT) is the prohormone of calcitonin and has been reported to be a specific marker of UTI in adults and infants. Previous studies also suggested that PCT might have a high sensitivity for bacterial infection in infants\textsuperscript{3}. PCT levels offer a better sensitivity and specificity than other markers, such as CRP for the diagnosis of children with bacterial infection\textsuperscript{4,5}. Serum PCT levels appeared to correlate with the severity of infection and decreased rapidly after appropriate antibiotic therapy. Some patients with localized bacterial or viral infection had a slight rise in PCT\textsuperscript{6,7}.

Interleukin-8 (IL-8) is an interleukin that belongs to an ever expanding family of proteins that exert chemoattraction activity to leukocytes and fibroblasts\textsuperscript{8}. It is a chemoattractant for neutrophils, basophils, and T-cells and it stimulates neutrophils and T lymphocytes to invade injured and inflamed tissues\textsuperscript{9}. Given its role in mediating inflammation, the use of urinary IL-8 was assessed and found to be helpful in the non-invasive diagnosis of some common acute and chronic inflammatory diseases\textsuperscript{10}.

This study aimed to assess the value of measuring serum PCT and urinary IL-8 concentrations in diagnosis of UTI and in distinguishing between lower UTI and acute pyelonephritis in infants and children.

**PATIENTS AND METHODS:**

This study was carried out at EL-Minya University Hospital from November 2002 to May 2003, and included 40 infants and children with fever (rectal temperature \textgreater 38.0\(^\circ\)C) and symptoms suggestive of UTI (abdominal or flank pain, nausea and vomiting, non specific symptoms as poor feeding, irritability and weight loss, suprapubic pain and tenderness, dysuria, urgency, frequency, incontinence and nocturnal enuresis), and/or a positive urine analysis (pyuria \textgreater 5 pus cells/HPF \pm positive nitrite). They were 14 males and 26 females and their ages ranged from 6 months to 8 years. Children who received antibiotics in the previous week and those known to have recurrent UTI or urinary tract abnormalities were excluded from the study. In addition, 40 apparently healthy children of matched age and sex were included as a control group.

On admission, blood was sampled for routine laboratory investigations, including complete blood picture, CRP, erythrocyte sedimentation rate, blood urea, and serum creatinine. Serum PCT and its related peptide was measured via a competitive radioimmunoassay. This assay was based on the competition of labeled I\textsuperscript{125}–peptide (either standard or unknown) binding to a limited quantity of specific antibodies. The kits supplied from Peninsula laboratories Inc. Pennsylvania 415-592-5392.

Routine urine analysis was done to detect pus cells or red blood cells in the sediment of a centrifuged urine sample. CRP was determined by latex agglutination test for the qualitative and semiquantitative measurement of CRP in non diluted serum.
Urine samples were obtained before the first antibiotic dose by suprapubic aspiration, clean-void midstream catch, or sterile collection bag and sent for analysis and culture within 1 hour after standard procedures. Urine cultures were considered positive if >\(10^3\), \(10^4\), \(10^5\) colony-forming units/ml of a urinary tract pathogen for suprapubic aspiration, midstream catch, and collection bag samples, respectively.

Measurement of IL-8 in urine was performed using commercially available enzyme linked immunosorbent assay (ELISA). Expected values of IL-8 in fresh serum, plasma, and urine samples of healthy individuals are below 10 pg/ml supplied from BioSource International Inc. 542 Flynn Road, Camarillo, CA93012 USA.

At days 3 to 5 children with positive urine culture were subjected to renal cortical scintigraphy (CS), which was considered to be abnormal if a focal or diffuse decrease or absence of \(^{99m}\)Tc-dimercaptosuccinic acid (DMSA) uptake was noted on at least two projections.

The data of the study were tabulated and analyzed by SPSS (Statistical Package for Social Science) under windows (version 11). Specificity and sensitivity of CRP, PCT and IL-8 were calculated and a comparison between groups was carried out using the Mann-whitney, Kruskal Wallis one-way analysis of variance, and \(t\) test. The level of statistically significant difference was defined as \(p<0.01\).

RESULTS:

This study included 40 infants and children (14 males and 26 females) with febrile UTI, their ages ranged from 6 months to 8 years (4.7±2.2 years). Among them, 23 children (57.5%) were found to have abnormal CS and were considered to have pyelonephritis. The remaining 17 children (42.5%) with normal CS were diagnosed as having lower UTI. Escherichia coli was the causative organism in 85% of cases and other organisms in the remaining 15%.

Table (1) revealed that pus cells in urine, total leukocytic count, and serum creatinine were significantly higher in infants and children with UTI compared with controls. Serum levels of PCT, urinary IL-8 and CRP were significantly higher in cases compared with controls, \(p<0.001\) for all.

Table (2) revealed the differences between cases with upper and lower UTI regarding laboratory data. Cases with pyelonephritis had significantly higher levels of serum PCT, urinary IL-8, and CRP compared with patients with cystitis respectively. \(P<0.001\), <0.01, and <0.01 respectively).

Table (3) revealed specificity and sensitivity of PCT, IL-8 and CRP. PCT had a sensitivity of 72.5% and a specificity of 79.7%. IL-8 had a sensitivity of 90% and a specificity of 92%. CRP had a sensitivity of 100% and a specificity of 23.6%.

Figure (1) revealed significant positive correlation between urinary IL-8 and serum PCT in patients with UTI (\(r=0.71\) and \(p=0.001\)), figure (2) revealed significant positive correlation between urinary IL-8 and pus cells in urine in patients with UTI (\(r=0.59\) and \(p=0.001\)), figure (3) revealed significant positive correlation between serum PCT and WBCs count in patients with UTI (\(r=0.62\) and \(p=0.001\)), and figure (4) revealed significant positive correlation between serum PCT and CRP in patients with UTI (\(r=0.72\) and \(p=0.001\)).
**Table (1):** Comparison between cases and controls regarding laboratory data.

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pus cells in urine</td>
<td>24.8±19.2</td>
<td>4.4±0.8</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>(cells/HPF)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBCs/mm$^3$</td>
<td>12.30±8.0</td>
<td>7.210±2.950</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>S. Creatinine (mg/dl)</td>
<td>0.83±0.82</td>
<td>0.41±0.32</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Serum PCT (µg/L)</td>
<td>3.09±1.01</td>
<td>0.32±0.15</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Urinary IL-8 (pg/ml)</td>
<td>1545±38.2</td>
<td>117±26</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>52.1±26.2</td>
<td>6.1±1.2</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

**Table (2):** Comparison between upper and lower UTI regarding laboratory data.

<table>
<thead>
<tr>
<th></th>
<th>Pyelonephritis (N=23)</th>
<th>Cystitis (N=17)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pus cells in urine</td>
<td>16.5±15.9</td>
<td>32.6±28.9</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>(cells/HPF)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBCs/mm$^3$</td>
<td>17.400±0.649</td>
<td>14.200±1.620</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>S. Creatinine (mg/dl)</td>
<td>1.44±1.12</td>
<td>0.71±0.04</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Serum PCT(µg/L)</td>
<td>5.54±1.18</td>
<td>0.39±0.12</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Urinary IL-8 (pg/ml)</td>
<td>1642±354</td>
<td>1416±256</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>68.2±8.89</td>
<td>6.91±4.5</td>
<td>&lt;0.01*</td>
</tr>
</tbody>
</table>

**Table (3):** Sensitivity and specificity of PCT, IL-8 and CRP.

<table>
<thead>
<tr>
<th></th>
<th>PCT (≥0.5µG/L)*</th>
<th>IL-8 (≥200PG/ML)*</th>
<th>CRP (≥6 MG/L)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>72.5%</td>
<td>90%</td>
<td>100%</td>
</tr>
<tr>
<td>Specificity</td>
<td>79.7%</td>
<td>92%</td>
<td>23.6%</td>
</tr>
</tbody>
</table>

* Cutoff point
Figure (1): Correlation between urinary IL-8 and serum PCT in patients with UTI

Figure (3): Correlation between Serum PCT and WBCs in patients with UTI

Figure (2): Correlation between urinary IL-8 and pus cells in urine in patients with UTI

Figure (4): Correlation between serum PCT and CRP in patients with UTI
DISCUSSION:

UTI in young children carries the risk of parenchymal damage and sequelae. The location of the infection within the urinary tract influences decisions regarding both therapeutics and follow-up. Because clinical features and laboratory markers of infection at an early age are not specific, it is difficult to make a distinction between lower UTI and acute pyelonephritis. Until now, 99m Tc DMSA scintigraphy has been the most sensitive tool for detection of acute pyelonephritis among children. Because DMSA scintigraphy can demonstrate anatomic and functional changes in renal parenchyma, it was believed that DMSA scintigrams could be used to predict renal scarring. The relationship between the area of renal parenchymal involvement and the risk of subsequent renal scarring has been roughly estimated by using DMSA scintigraphy. We studied 40 infants and children with symptomatic UTI, among them, 23 children (57.5%) were found to have abnormal CS and were considered to have pyelonephritis. The remaining 17 children (42.5%) with normal CS were diagnosed as having lower UTI. Animal models have confirmed that the lesions observed on DMSA scans correlate with areas of renal inflammation. Our results are in accordance with Chon et al., who reported that when DMSA lesions are used as the standard, 50% to 86% of children with febrile UTI and other clinical signs were found to have pyelonephritis. Benador et al., and Merrick et al., found that 67% and 61.9% of infants and children with symptomatic febrile UTI had renal involvement, respectively.

PCT was initially described as a potential marker of bacterial disease by Assicote et al., can help in the early diagnosis of bacterial neonatal infection, and contributes to the differentiation of bacterial versus viral meningitis in children. Dandona et al., reported that plasma concentrations of PCT are very low in healthy individuals and increase markedly in response to bacterial endotoxins. Serum PCT supplies very rapid information in children with sepsis that is already available at admission in a critical care unit. Results are similar in both sex and age groups, from 1 month to adolescence. The measurement of PCT gives information about the severity of bacterial infection in all pediatric ages and may help the physician to choose the appropriate therapeutic procedure.

In our study, serum levels of PCT were significantly higher in cases compared with controls and also were significantly higher in cases with pyelonephritis compared with those with lower UTI, and the sensitivity and specificity of PCT were 72.5% and 79.7% respectively. Benador et al., Gervaix et al., and Smoklin et al., have shown that PCT, determined by either an immunoluminometric quantitative or a rapid semiquantitative test, was elevated in children with acute pyelonephritis and often normal in lower UTI, with a sensitivity of 70.3%, 74%, 94.1%, and a specificity of 82.6%, 85%, 89.7% respectively. In Smoklin et al., study, DMSA scan was performed within the first week after admission and repeated 6 months later, and the diagnosis of acute pyelonephritis was confirmed only in patients with totally or partially reversible lesions on scintigraphy, which may explain the higher sensitivity and specificity of PCT compared to our results.

In the present study elevated CRP was highly sensitive in diagnosing acute pyelonephritis (100%), but was poorly specific (23.6%), and these results were nearly similar to that of Benador et al.. Thus, most children with normal CRP...
values probably could be safely considered not suffering from acute pyelonephritis and could not require either DMSA scintigraphy or early parenteral antibiotic therapy. However the lower specificity of this test limits its clinical usefulness, as a number of children with elevated CRP values show no renal lesions. The higher sensitivity and specificity of serum PCT compared to CRP noticed in our study was consistent with the results of Benador et al., who found a borderline correlation of the severity of renal involvement to CRP that contrasted with a highly significant correlation to elevated PCT values. The superior sensitivity and specificity of PCT compared to CRP as a diagnostic marker was reported also by Hatherill et al., who attributed this to the wide range of CRP concentrations in all categories of infection. The best advantage over serum CRP is the association of high PCT levels with the severity of the disease and bad prognosis.

Rodrigo et al., reported that white cell count, CRP and PCT were significantly higher in patients with febrile UTI with renal scars at late gammography compared to the group with febrile UTI without renal scars and with patients having lower UTI (absence of fever and absence of renal lesions in acute and late explorations), this is in agreement with our results.

UTI activate local and systemic cytokine responses. Release of cytokines from the site of infection precedes the onset of fever, acute phase responses, and neutrophil responses. IL-8 is an important early mediator of inflammation and a chemoattractant for neutrophils. However, IL-8 can be produced by epithelial cells of the renal tract in response to a variety of inflammatory stimuli. IL-8 has been reported in the urine of patients with inflammatory renal disorders including pyelonephritis, and glomerulonephritis. IL-8 is found in urine of patients with urinary tract infection, including neonates.

In this study, levels of IL-8 in urine were significantly higher in cases with UTI compared with controls, and in patients with acute pyelonephritis compared to those with lower UTI and this was in agreement with Taha et al., Roilides et al., and Olszyna et al.,. Jantausch et al., found that urinary IL-8 concentrations were significantly higher in febrile patients with UTI at the time of admission compared with age, race, and sex-matched febrile control children with negative urine culture. They also found that urinary IL-8 concentrations were lower in follow-up urine samples from UTI patients, obtained 48 hr after the initiation of antibiotic therapy.

Ko et al., stated that elevated levels of IL-8 were found in urine of 112/113 patients with UTI (1078.0 +/- 181.5 pg/ml), regardless of whether they had an upper or lower UTI, in contrast to undetectable levels (<16 pg/ml) in urine of the 20 normal individuals and 74 control patients without UTI. This is in agreement with our results comparing patients and controls.

Our results showed that urinary IL-8 had a sensitivity of 90% and a specificity of 92% in diagnosing UTI. This is in agreement with the results of Rao et al., who reported that using a cut-off of 200 pg/ml, urine IL-8 had a sensitivity of 93% and a specificity of 90% for diagnosing UTI, and concluded that this cytokine is a sensitive test for UTI, but is poorly specific as it is also present in a variety of other infectious and inflammatory disorders.

In conclusion, these data indicate that, in infants and children with suspected UTI, serum PCT and urinary IL-8 are useful markers of infection, their levels vary with the severity of infection and are increased significantly when renal
parenchymal involvement is present. Taking the appropriate clinical situations into account, their measurement might be a useful and practical tool for differentiating acute pyelonephritis from lower UTI. Accurate diagnosis allows informed decisions about intravenous or oral antibiotic treatment in these patients. Further and larger studies should be performed to corroborate this statement.

**Abbreviations:** CT: cortical scintigraphy, DMSA: dimercaptosuccinic acid, IL-8: interleukin-8, PCT: procalcitonin, UTI: urinary tract infection.

**REFERENCES:**


the early diagnosis of neonatal infection. J Pediatr; 128: 570-573


تهدف هذه الدراسة لمعرفة دور كل من مستوى مادة البروكالسيتونين في مصل الدم ومستوى مادة الأنتريلوكيون-8 في البول، في تشخيص الالتهاب البكتيري في مجرى البول وكذلك في الفرق بين الالتهاب البكتيري في كل من الجهاز البولي العلوي والجهاز البولي السفلي.

استمرت هذه الدراسة على مجموعتين من الأطفال وهم:
المجموعة الأولى تتكون من أربعين طفل مصاب بالتهاب في مجرى البول (اربعة عشر ذكر وستة وعشرون أنثى) تتراوح أعمارهم بين ستة أشهر وثمانية سنوات وقد قسمت هذه المجموعة إلى مجموعتين فرعية: ثلاثة وعشرون طفل مصابون بالتهاب بكتيري في الجهاز البولي العلوي وسبعة عشر طفل مصابون بالتهاب بكتيري في الجهاز البولي السفلي.

المجموعة الثانية تتكون من أربعين طفل أصحاء كمجموعة عمرية ونوعية مطابقة لمجموعة المرضى.

وقد خضع أطفال المجموعتين للأتي:

- صورة دم كاملة
- بروتين سم النشط وسرعة ترسيب
- مزرعة بول
- مستوى البولينا في الدم ومستوى الكراتينين في مصل الدم
- قياس نسبة البروكالسيتونين في مصل الدم
- قياس نسبة الأنتريلوكيون-8 في البول.

خضع الأطفال المرضى أصحاب مزرعة البول الإيجابية للتشخيص بالأشعة الدمسية.

أظهرت هذه الدراسة ارتفاع نسبة البروكالسيتونين في مصل الدم ونسبة الأنتريلوكيون-8 في البول وكذلك بروتين سم النشط في الأطفال المرضى عنهم في أطفال المجموعة الضابطة كما وجد ارتفاع الدلالات الثلاثة في الأطفال المصابين بالتهاب في الجهاز البولي العلوي عنه في الأطفال المصابين بالتهاب في الجهاز البولي السفلي. كما وجد أن حساسية اختبار بروتين سم النشط (100%) أعلى من حساسية الأنتريلوكيون-8 في البول (90%) وكلاهما أعلى من حساسية البروكالسيتونين في مصل الدم (72.5%) في البول (69.2%) أعلى من حساسية البروكالسيتونين في مصل الدم (79.7%) وكلاهما أعلى من حساسية بروتين سم النشط (23.6%), كذلك وجدنا علاقة طردية بين مستوى الأنتريلوكيون-8 في البول وكل من مستوى البروكالسيتونين في مصل الدم وكذلك عدد الخلايا الصدغية في البول كما وجدنا علاقة طردية بين مستوى مادة البروكالسيتونين في مصل الدم وكل من عدد كرات الدم البيضاء وبروتين سم النشط.

نستنتج من هذه الدراسة أن مستوى مادة البروكالسيتونين في مصل الدم ومواد الأنتريلوكيون-8 في البول يعتبرا دلائلًا لالتهاب مجرى البول وخاصة في الأطفال الذين أصيبوا بالتهاب في الجهاز البولي العلوي.