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Procalcitonin: A Marker of Severity of Acute Pyelonephritis Among Children

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ABSTRACT. *Objective.* **Febrile urinary tract infection (UTI) is a common problem among children. The diagnosis and management of acute pyelonephritis is a challenge, particularly during infancy. The distinction between acute pyelonephritis and UTI without renal involvement is very important, because renal infection may cause parenchymal scarring and thus requires more aggressive investigation and follow-up monitoring. However, this distinction is not easy among children, because common clinical findings and laboratory parameters are nonspecific, especially among young children. In an attempt to differentiate acute pyelonephritis from febrile UTI without renal lesions in a group of 100 children, we measured serum levels of procalcitonin (PCT), a new marker of infection. The objective of the study was to determine the accuracy of PCT measurements, compared with C-reactive protein (CRP) measurements, in diagnosing acute renal involvement during febrile UTI and in predicting subsequent scars, as assessed with ^{99m}Tc-dimercaptosuccinic acid (DMSA) scintigraphy.**

Design. **Serum CRP levels, erythrocyte sedimentation rates, leukocyte counts, and PCT levels were measured for 100 children, 1 month to 13 years of age, admitted for suspected febrile UTI (first episode). Renal parenchymal involvement was evaluated with DMSA scintigraphy within 5 days after admission. The DMSA study was repeated 6 months later if the initial results were abnormal.**

Results. **The mean PCT level was significantly higher in acute pyelonephritis than in UTI without renal lesions (4.48 ± 5.84 ng/mL vs 0.44 ± 0.30 ng/mL). In these 2 groups, the mean CRP levels were 106 ± 68.8 mg/L and 36.4 ± 26 mg/L, mean erythrocyte sedimentation rates were 79.1 ± 33 mm/hour and 58.5 ± 33 mm/hour, and leukocyte counts were 18 492 ± 6839 cells/mm^3 and 16 741 ± 5302 cells/mm^3, respectively. For the prediction of acute pyelonephritis, the sensitivity and specificity of PCT measurements were 83.3% and 93.6%, respectively; CRP measurements had a sensitivity of 94.4% but a specificity of only 31.9%. Positive and negative predictive values for prediction of renal involvement with PCT measurements were 93.7% and 83% and those with CRP measurements were 61.4% and 83.3%, respectively. When inflammatory markers were correlated with the severity of the renal lesions, as assessed with DMSA scintigraphy, a highly significant correlation with both PCT and CRP levels was found. However, when the 2 parameters were correlated with renal scarring in follow-up scans, a significant positive association was found only for PCT levels.**

Conclusions. **Serum PCT levels may be a sensitive and specific measure for early diagnosis of acute pyelonephritis and determination of the severity of renal parenchymal involvement. Therefore, this measurement could be useful for the treatment of children with febrile UTIs, allowing prediction of patients at risk of permanent parenchymal renal lesions.** *Pediatrics* **2004; 114:e249–e254. URL: http://www.pediatrics.org/cgi/content/full/114/2/e249; *procalcitonin, pyelonephritis, renal scar, children.***

ABBREVIATIONS. PCT, procalcitonin; UTI, urinary tract infection; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; DMSA, ^{99m}Tc-dimercaptosuccinic acid; VUR, vesicoureteral reflux.

Febrile urinary tract infection (UTI) is a frequent problem among infants and children.[1] The clinical differentiation between acute pyelonephritis and UTI without renal involvement is often difficult, because symptoms among febrile infants and children are not specific. Commonly used laboratory markers, such as erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP) levels, and leukocyte counts, cannot reliably differentiate acute pyelonephritis from lower UTI, especially among young children. Although CRP measurement has a better predictive value for the presence of renal involvement, compared with other parameters,[2] it has low specificity, which limits its clinical usefulness.[3,4]

Accurate diagnosis and early treatment of acute pyelonephritis are important because of the risk of renal scarring and subsequent secondary hypertension and renal failure.[5] At present, ^{99m}Tc-dimercaptosuccinic acid (DMSA) scintigraphy is considered the standard method for diagnosis of acute pyelonephritis and assessment of the extent and progression of renal parenchymal damage.[2,6–9] However, factors that limit the widespread use of DMSA scintigraphy include the fact that the test is not readily accessible in all centers, it exposes patients to radiation, and it is expensive.

The levels of procalcitonin (PCT), a 116-amino acid propeptide of calcitonin that is devoid of hormonal activity, are elevated among patients with severe infections such as septic shock but are normal among

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patients with noninfectious inflammatory conditions of viral origin.[10–12] Plasma concentrations of PCT are very low (<0.1 ng/mL) among healthy individuals and increase to very high values in response to bacterial endotoxins.[13] This increase seems to be correlated with the severity of microbial invasion.[12]

Recent studies proposed PCT as a marker of acute pyelonephritis among infants and children. PCT measurements have been performed either with a quantitative immunoluminometric assay with 2 monoclonal antibodies[3,4,14] or with a rapid, semiquantitative, immunochromatographic test.[15] The purpose of this prospective study was to determine the ability of PCT measurements, compared with CRP measurements, to predict the severity of renal involvement among children in the acute phase of febrile UTI and to predict the risk of subsequent renal scarring.

METHODS

Patient Characteristics and Inclusion Criteria

This prospective study included 100 children (69 girls and 31 boys), 1 month to 13 years of age, who were admitted to the Pediatric Department of the University of Udine, between January 2000 and January 2002, with a first episode of febrile UTI. Criteria used for inclusion of patients in the study included fever (temperature of ≥38°C) and/or symptoms suggesting UTI, abdominal or flank pain among older children, and nonspecific signs, such as irritability, vomiting, difficulties with feeding, or failure to thrive, among children <5 months of age. Inclusion of patients in the study was confirmed with a diagnosis of UTI based on a positive urine culture, with a single microorganism at $\geq 10^5$ colony-forming units/mL, from either a catheterized or midstream, clean-void, urine sample. Patients with documented or suspected previous febrile UTI and/or with known abnormalities or malformation of the urinary tract were excluded from the study. Children who had received antibiotics in the previous week were also excluded. All children were given antibiotics intravenously (ceftriaxone, 75 mg/kg per day) for 1 to 5 days, followed by orally administered antibiotics chosen according to bacterial susceptibility tests, for a total duration of treatment of 10 days.

Clinical and Laboratory Assessments

Clinical assessments included recording of body temperature and duration of symptoms (duration of fever) before diagnosis and treatment. At the time of admission, white blood cell count, CRP level, ESR, and PCT level were determined for all children. For determination of PCT levels, blood samples (1 mL) were centrifuged and the serum was separated and frozen at −20°C before analysis. Quantitative measurement of PCT levels was performed with an immunoluminometric assay with 2 monoclonal antibodies (LUMI test PCT; Brahms Diagnostica, Henningdorf BEI, Berlin), as described previously.[16] Values of ≥0.8 ng/mL was considered abnormal. CRP levels were determined with an immunometric test, and values of ≥20 mg/L were considered abnormal.

Imaging Studies

Renal ultrasonography was performed within the first 3 days after admission, and voiding cystourethrography was performed 1 month after the infection, for detection of vesicoureteral reflux (VUR). Renal DMSA scintigraphy was performed within the first 5 days after admission, as previously described,[8] for all children. The presence and extent of renal lesions were evaluated independently by 2 investigators, who were blinded with respect to CRP and PCT levels and the clinical status of the patient. The scintigraphy results were considered to be positive for renal involvement (acute pyelonephritis) if a focal, multifocal, or diffuse decrease or absence of DMSA uptake was noted.

The renal lesions were graded as previously described by Benador et al,[3] with the following scores: 0, absence of lesion; 1, uncertain or very mild lesion (defect covering <5% of the surface area); 2, mild lesion (defect covering 5% to 10% of the surface area); 3, moderate lesion (defect covering 10% to 30% of the surface area); 4, severe renal parenchymal lesion (defect covering >30% of the surface area). The patients were divided in 2 groups; group 1 included patients with scintigraphic scores of 0 or 1, with nonsignificant risk of developing subsequent permanent renal damage, and group 2 included patients with scores of 2, 3, or 4, with significant risk of renal scarring.

If the first scintigraphic result was abnormal, then a repeat examination was planned 6 months after the initial study, to assess the presence of permanent renal lesions or scars. In the period between the 2 scintigraphic studies, no child experienced a relapse of UTI. Only children with VUR received antibiotic prophylaxis during this 6-month period. Parents were informed of the potential risks and benefits of DMSA scanning and cystourethrography and gave their consent before enrollment in the study.

Study Design

Sensitivity and specificity for the detection of acute pyelonephritis (scores of 2–4, as assessed with DMSA scans) were determined for CRP and PCT measurements. Positive and negative predictive values of PCT and CRP measurements for renal involvement in the course of febrile UTI were determined. The relationship between PCT and CRP levels and the severity of acute renal damage, as assessed with early DMSA scintigraphy, was evaluated. Finally, PCT and CRP levels were related to the risk of permanent renal involvement, as assessed with follow-up DMSA scans.

Statistical Analyses

Data are expressed as the mean ± SE. Comparisons between groups were conducted by using the χ^2 test, Mann-Whitney test, *t* test, and Kruskal-Wallis test (1-way analysis of variance) as appropriate. The level of statistical significance was defined as $P < .05$.

RESULTS

Patient Characteristics for Groups 1 and 2

One hundred children (69 girls and 31 boys) with a diagnosis of a first episode of febrile UTI were consecutively enrolled in the study. Although the ages of the patients ranged from 1 month to 13 years (mean: 19 months), 66% were <1 year of age. Forty-seven children (47%) exhibited normal scintigraphic results or uncertain/very mild renal involvement (scores of 0 or 1, group 1). Among the children in this group, 37 had scores of 0 and 10 had scores of 1 in the first scintigraphic study. As noted, group 1 was considered to have a nonsignificant risk of permanent renal sequelae.

Fifty-three children (53%) demonstrated significant positive scintigraphic results, corresponding to scores between 2 and 4 (group 2). This group of children was considered to have a significant risk of scar formation. Among the children in group 2, 12 had scores of 2, 24 had scores of 3, and 18 had scores of 4 in the first study.

Clinical Data and Mean PCT Levels, CRP Levels, ESR Values, and Leukocyte Counts for the 2 Groups of Patients

Comparisons between group 1 and group 2 showed no statistically significant differences in mean age or gender. The duration of fever before admission was found to be significantly longer among children in group 2 (2.3 ± 1.5 days), compared with those in group 1 (1.5 ± 1.0 days, $P = .0015$) (Table 1).

The mean PCT level was significantly higher in group 2 than in group 1 (4.48 ± 5.84 ng/mL vs 0.44

TABLE 1. Clinical and Laboratory Data for Groups 1 and 2

	Group 1 (Scores of 0 or 1) (n = 47)	Group 2 (Scores of 2–4) (n = 53)	P
Age, mo	16.7 ± 24.5	21.4 ± 32.8	.4025, NS
Gender, female/male	28/19	41/12	.0781, NS
Days of fever	1.5 ± 1.0	2.3 ± 1.5	.0015
PCT level, ng/mL	0.44 ± 0.30	4.48 ± 5.84	<.0001
CRP level, mg/L	36.4 ± 26.0	106.0 ± 68.8	<.0001
ESR, mm/h	58.5 ± 33.1	79.1 ± 33.0	.0025
Leukocyte count, cells/mm^3	16 741 ± 5302	18 492 ± 6839	.1512, NS

P values were analyzed with the Mann-Whitney test (for age, days of fever, ESR, CRP level, and PCT level), χ^2 test (for gender), and t test (for leukocyte count). NS indicates not significant.

± 0.30 ng/mL, $P < .0001$). Furthermore, the mean CRP level (106.0 ± 68.8 mg/L) and ESR (79.1 ± 33.0 mm/hour) for group 2 were significantly higher than the values for group 1 (CRP: 36.4 ± 26.0 mg/L, $P < .001$; ESR: 58.5 ± 33.1 mm/hour, $P < .025$). Therefore, there were significant differences between the groups in the values for the 3 inflammatory markers. No significant difference in median leukocyte counts for the 2 groups was observed ($P = .1512$) (Table 1).

Sensitivity and Specificity of PCT and CRP Measurements for Prediction of Renal Lesions in Acute Scans

In the acute phase of UTI, the prediction of significant renal lesions among patients in group 2 (scores of 2–4) with the use of a CRP cutoff value of 20 mg/L showed a sensitivity of 94.4% but a specificity of only 31.9%. The sensitivity and specificity of PCT measurements (cutoff: 0.8 ng/mL) were 83.3% and 93.6%, respectively (Table 2). The sensitivity of PCT levels increased to 100% for the prediction of severe renal lesions (scores of 4), as ranked with DMSA scintigraphy. Positive and negative predictive values for the prediction of renal involvement were 93.7% and 83% for PCT measurements and 61.4% and 83.3% for CRP measurements, respectively (Table 2).

Table 2 also shows sensitivity, specificity, positive predictive values, and negative predictive values for serum PCT levels with other cutoff values (0.5 and 1 ng/mL). We also used receiver operating characteristic curves to establish the cutoff points (Fig 1).

Relationship Between PCT and CRP Levels and Extent of Acute Renal Lesions

When levels of inflammatory markers (PCT and CRP) were correlated with the severity of renal lesions, as assessed with DMSA scintigraphy, a highly significant correlation only with plasma levels of PCT was found. Mean PCT levels increased proportionally with the extent of renal involvement ($P <$ .0001) (Fig 2). Furthermore, for CRP levels, a trend toward a positive correlation with the severity of renal lesions was found ($P < .0001$). Distributions of PCT and CRP levels for single patients are shown in Figs 3 and 4.

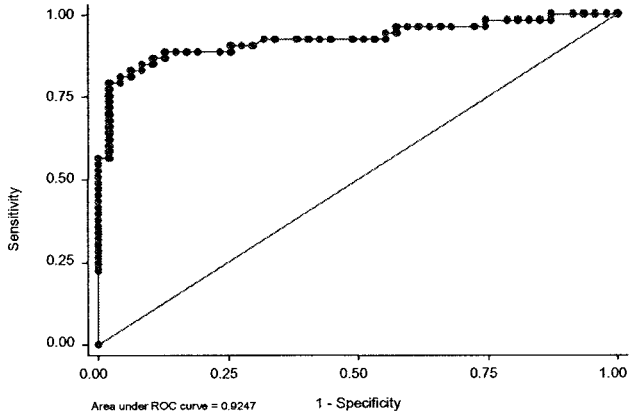

Fig 1. Receiver operating characteristic curve for specificity and sensitivity of PCT measurements.

Relationship Between VUR and Appearance of Acute Scans

Ninety children underwent voiding cystourethrography 1 month after the acute infection. Of these, 16 (18%) had VUR; 7 patients had grade II reflux, 6 had grade III reflux, and 3 had grade IV reflux. Ten children did not undergo cystourethrography because the parents refused consent. Of these, 9 children demonstrated normal DMSA scintigraphy results and 1 had mild renal involvement (score of 2) during the acute phase of infection. Among children in group 2 with significant renal lesions (scores of 2–4), as assessed with acute DMSA scans, VUR was found for 21% of patients, compared with 13% of patients with negative or very mild renal involvement (scores of 0 or 1, group 1; $P = .1684$).

TABLE 2. Sensitivity, Specificity, PPV, and NPV of PCT and CRP Measurements for Prediction of Acute Pyelonephritis (Cutoff Values of 0.8, 0.5, or 1 ng/mL for PCT and 20 or 50 mg/L for CRP)

	Sensitivity, %	Specificity, %	LR+	LR-
PCT, ≥0.8 ng/mL	83.3	93.6	13.0	0.18
PCT, ≥0.5 ng/mL	90.7	70.2	3.0	0.13
PCT, ≥1 ng/mL	81.4	93.6	12.7	0.2
CRP, ≥20 mg/L	94.4	31.9	1.4	0.18
CRP, ≥50 mg/mL	74.0	76.6	3.16	0.34

PPV, positive predictive value; NPV, negative predictive value.

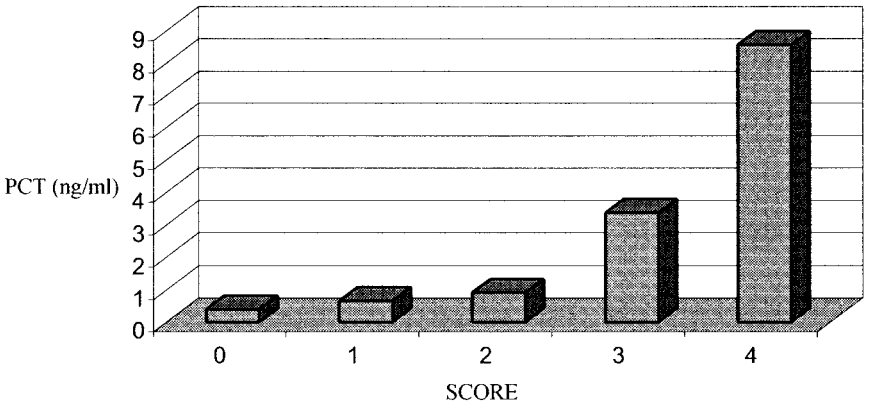

Fig 2. Mean PCT values for the 5 groups of patients with increasing scintigraphic scores for renal damage (Kruskal-Wallis test, $P < .0001$).

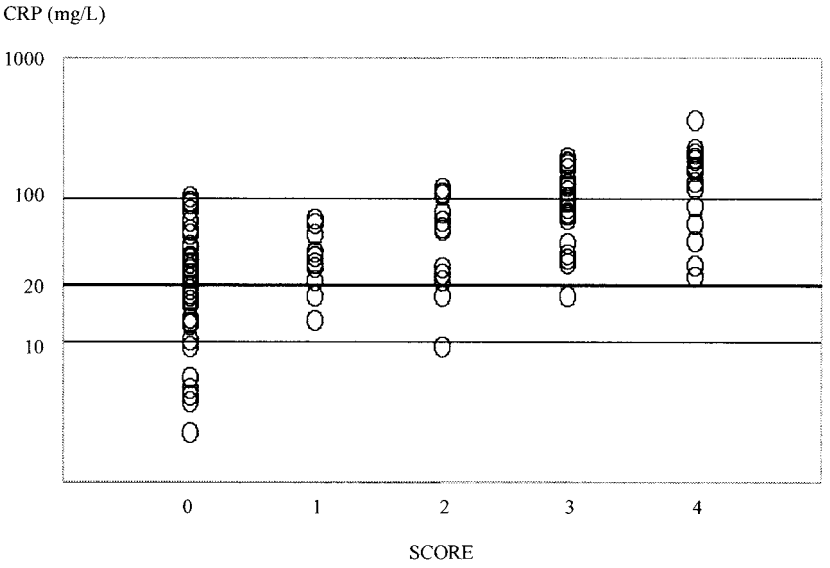

Fig 3. Plasma CRP levels (cutoff: 20 mg/L) in relation to the severity of DMSA scintigraphy-assessed lesions graded 0 to 4 (Kruskal-Wallis test, $P < .0001$).

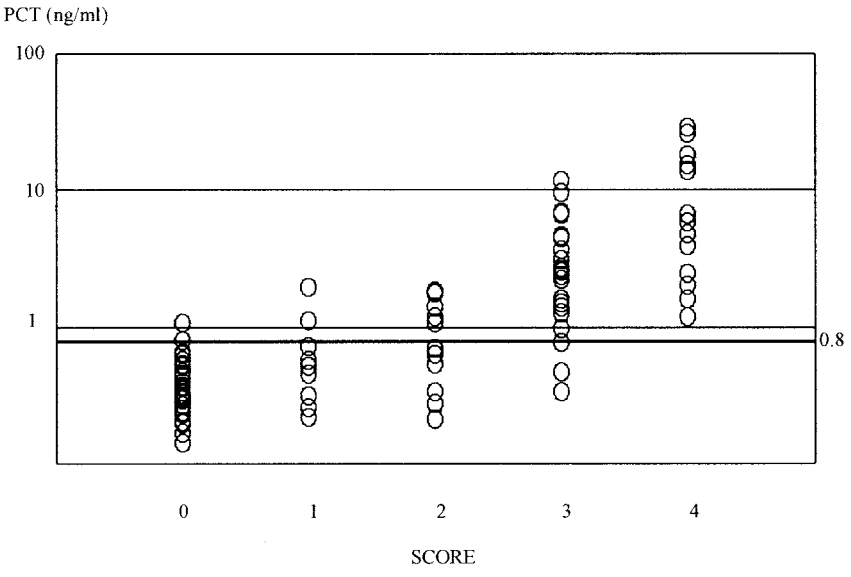

Fig 4. Plasma PCT levels (cutoff: 0.8 ng/mL) in relation to the severity of DMSA scintigraphy-assessed lesions graded 0 to 4 (Kruskal-Wallis test, $P < .0001$).

Results of Follow-Up DMSA Scans, Indicating Frequency of Reversible and Persistent Renal Lesions (Scars)

Of the 53 children included in group 2, 40 underwent follow-up scanning 6 months after UTI. Among these, all children with severe renal involvement (scores of 4) in the first scans were included. All patients who underwent repeat scans exhibited totally or partially reversible renal lesions. Therefore, all renal lesions on the first scans represented acute pyelonephritis and not preexisting scars.

Follow-up scintigraphy showed persistent lesions at the sites of initial lesions (scars) in 18 cases (45%), whereas 22 children (55%) exhibited total regression

of their initial lesions. Of the 18 children with renal scars on follow-up scans, 1 patient (5.5%) had a score of 2, 5 (27%) had scores of 3, and 12 (66%) had scores of 4 in the first DMSA scintigraphic study. Among these children, 6 patients (33%) had VUR (bilateral in 3 cases). Of the 22 children who demonstrated complete regression of their initial renal lesions on follow-up scans, 2 had VUR (bilateral in 1 case) and 20 had no VUR.

Relationship Between PCT and CRP Levels and Renal Scars in Follow-Up DMSA Scans

The PCT levels at admission for children with totally reversible lesions on follow-up scans (3.25 ± 3.5 ng/mL) were lower than the PCT values for children with only partially reversible lesions or renal scars (7.48 ± 8.4 ng/mL; $P = .0428$, Wilcoxon test). In contrast, there was no significant difference between CRP levels at admission for children with negative follow-up scintigraphy results (103.0 ± 93.3 mg/L) and those with renal scars (116.8 ± 64.0 mg/L; $P = .384$).

DISCUSSION

The distinction between acute pyelonephritis and lower UTI is very important, because renal parenchymal involvement can induce permanent renal damage (scars), which may lead to arterial hypertension and chronic renal failure.[17] Previous studies noted that even children with unilateral renal disease are at risk for long-term complications.[18] Therefore, accurate rapid diagnosis of acute pyelonephritis would be valuable, because early aggressive treatment reduces the risk of renal scarring.[19]

It is well known that DMSA scintigraphy performed during the acute phase of infection is very sensitive in assessment of renal parenchymal involvement; it is considered the standard method for the diagnosis of acute pyelonephritis.[6,7,20] However, scintigraphy is an expensive technique, is not readily available in all centers, and exposes the patients to radiation. Moreover, it may not differentiate old scarring from acute renal involvement unless follow-up scanning is performed.

In the present study, significant renal lesions were observed for 53% of children in the acute phase of febrile UTI. The duration of fever before diagnosis was longer for children with renal lesions, compared with those with no or very mild/uncertain renal involvement on DMSA scans. These findings emphasize the importance of early diagnosis and treatment of infection for prevention of parenchymal renal damage.

It is well known that VUR is not a prerequisite for renal involvement among children with febrile UTIs and that renal scarring can be observed even without VUR.[2,9] In this study, only 21% of children with significant positive renal scans were found to have VUR. Furthermore, there was no significant difference in the incidences of VUR among children with and without renal lesions.

It is well recognized that the nonspecific nature of symptoms among febrile infants and small children makes the clinical differentiation of acute pyelonephritis and lower UTI difficult. Furthermore, even the commonly used laboratory markers cannot reliably indicate the diagnosis of acute pyelonephritis, especially among young children.

As in other studies,[4,15] the present data indicate that leukocyte counts have no value in differentiating acute pyelonephritis from lower UTI. In this study, high ESR values and CRP levels were correlated with abnormal results on DMSA scans. In particular, a highly significant correlation for CRP measurements for prediction of acute positive scintigraphy findings, with a sensitivity of 94.4%, was observed. These results were also reported in recent studies.[2–4,15]

Furthermore, when the severity of renal involvement was analyzed, a positive correlation with CRP levels was found. This correlation was also found in the study by Benador et al,[3] which noted only borderline significance for this marker. However, as reported in other studies,[3,4,15] the present data indicate that elevated CRP levels have a very low specificity (31.9%), which limits the clinical usefulness in current practice. In fact, a large number of children with elevated CRP levels exhibited no renal lesions and would have undergone unnecessary tests, treatment, and follow-up monitoring. Furthermore, when the association with subsequent scarring was analyzed, no correlation with high levels of CRP during the acute phase of infection was found. Therefore, CRP is not a good predictive marker of renal permanent scarring.

Since Assicot et al[12] first proposed PCT as an early accurate marker of bacterial infection that seems to be correlated with the severity of microbial invasion, interesting studies among children have been published.[11,13,21,22] Recently, a few studies with small numbers of patients evaluated the accuracy of PCT levels, compared with CRP levels, to predict renal involvement among children with febrile UTIs.[3,4,14,15] Those previous studies found that serum PCT concentrations, measured with either an immunoluminometric quantitative test or a rapid semiquantitative test, diagnosed acute pyelonephritis with a sensitivity of 70.3% to 94.1% and a specificity of 82.65% and 89.7%.

By using a PCT cutoff value of 0.8 ng/mL in the present study, a sensitivity and specificity of 83.3% and 93.6%, respectively, were obtained. In accordance with recent studies,[3,4,15] the specificity of PCT measurements was much higher than that of CRP measurements. The present data indicate that PCT could be a more useful parameter for the treatment of children with febrile UTIs. Furthermore, high positive and negative predictive values for PCT measurements (93.7% and 83%, respectively) for prediction of renal involvement were found. When the sensitivity, specificity, negative predictive value, and positive predictive value were calculated with different cutoff values (0.5, 0.8, and 1.0 ng/mL), it was found that a cutoff value of 0.8 ng/mL yielded the best performance.

Like the study by Benador et al,[3] this study indicated a highly significant correlation between elevated PCT levels and the severity of renal involve-

ment, as graded with scintigraphic scores. Furthermore, there was a positive correlation between high PCT levels at admission and the development of long-term renal scarring. This positive correlation was reported in 2 previous studies.[3,14]

CONCLUSIONS

These data indicate that PCT is an accurate biological marker with high sensitivity and specificity for the prediction of acute pyelonephritis among infants and children, compared with the low specificity of CRP measurements. This parameter is correlated with the severity of renal involvement at the time of diagnosis of febrile UTI and also with the risk of permanent scarring. Therefore, PCT measurements could be a valuable tool for the treatment of children with febrile UTIs.

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