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Elevated serum procalcitonin values correlate with renal scarring in children with urinary tract infection

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Background. **Urinary tract infection (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. Procalcitonin (PCT) has been studied as a marker of severe bacterial infection. The aim of this study was to test the usefulness of PCT concentration in serum to distinguish between uncomplicated UTI and severe acute pyelonephritis with renal scars.**

Methods. **PCT was measured by immunoluminometric assay in serum samples from children with microbiologically documented infection. Severe renal involvement was assessed by ^{99m}Tc-dimercaptosuccinic acid gammagraphy done 5 to 6 months after the episode to check for the presence of parenchymal scars. C-reactive protein (CRP) and leukocyte count were also measured.**

Results. **PCT at presentation showed a significant correlation ($P < 0.001$) with the presence of renal scars in children with UTI. Using a cutoff of 1 ng/ml for PCT and 20 mg/l for CRP, sensitivity and specificity in distinguishing between urinary tract infection with and without renal damage were 92.3 and 61.9%, respectively, for PCT and 92.3 and 34.4% for CRP. Positive and negative predictive values were 32 and 97.5%, respectively, for PCT and 23 and 95%, respectively, for CRP.**

Conclusions. **A low PCT value at admission indicates a low risk of long term renal scarring. Increased PCT values at admission correlate with the presence of scars. PCT values have proved to be more specific than CRP and leukocyte count for identifying patients who might develop renal damage.**

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INTRODUCTION

Young children are at higher risk than older children to incur acute renal injury after an urinary tract

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infection (UTI)[1, 2] and thus subsequent renal scarring. That leads to long term medical problems such as uremia, arterial hypertension and end stage renal disease.[3] Location of the site of infection within the urinary tract influences decisions regarding the choice, duration and route of administration of antimicrobial therapy. It also influences the decision of hospitalization as well as the follow-up needed.[4–6] During the acute phase the distinction between lower UTI and acute pyelonephritis is difficult. Symptoms and signs in infants are nonspecific; failure to thrive, irritability, vomiting and fever are the most frequent. Because young children usually have a febrile illness with no localizing findings, delay in diagnosis and treatment is bound to happen. Children older than 2 years of age are more likely to display localizing symptoms such as increased urinary frequency, dysuria and abdominal or flank pain. Urinalysis is useful in detecting infection and also for urine culture, but not for location of the disease within the urinary tract.[1] Indicators of inflammation in febrile infants such as leukocyte count or C-reactive protein (CRP) can suggest the infection but do not provide confirmatory evidence that they have pyelonephritis.[7, 8] Bacteremia during pyelonephritis is uncommon in children.[9]

The radionuclide renal scan helps to distinguish cystitis from pyelonephritis. ^{99m}Tc-dimercaptosuccinic acid (DMSA) gammagraphy is the reference method for identification of renal lesions secondary to acute inflammation of parenchyma.[10–12] Its performance 5 to 6 months after the infection episode detects the presence of renal scarring. Imaging techniques are not cost-effective methods for acute UTI diagnosis, and they expose the patient to radiation. A test that distinguishes lower UTI from acute pyelonephritis at the time of diagnosis would help to guide its management.

Procalcitonin (PCT) is a 116-amino acid propeptide of calcitonin.[13] In healthy humans it is produced in the C cells of the thyroid gland, and during severe infections it is produced by the monocyte-macrophage system.[14] Since its original description in children, many series have shown the importance of procalcitonin as an indicator of systemic bacterial infection,[15] distinguishing it from organ-confined bacterial infection, viral infection and fever of noninfectious origin.

The aim of our study was to test the usefulness of PCT concentration in serum as a discriminator between uncomplicated UTI and severe acute pyelonephritis with renal scars. The PCT results were compared with other inflammatory markers: leukocyte count and CRP.

MATERIALS AND METHODS

Study population. We studied children 1 month to 12 years old who were admitted to the Pediatric Emergency Department with clinical signs (fever and abdominal pain in older children and non specific signs of irritability or vomiting in young children) and abnormal urinalysis. Blood was sampled for routine laboratory investigations (leukocyte count and CRP) at the time of admission. A serum sample was also collected for PCT measurement and stored at −20°C. A second sample was taken 24 h later when possible. After blood and urine cultures were performed, antibiotic therapy was started. Urine specimens were obtained by suprapubic aspiration or transurethral bladder catheterization in incontinent infants and by midstream collection in continent children.

Patients were eligible for the study entry when microbiologically confirmed infection was achieved (positive urine culture, defined by $\geq 10^5$ colony-forming units/ml in midstream clean void urine, $\geq 10^4$ in transurethral catheterization specimens and $\geq 10^2$ in suprapubic aspiration specimens).[1] Children with known previous UTI were not enrolled in the study, because scars could have resulted from the previous episode. Patients with recurrent UTI after the first episode were also excluded for the same reason. Imaging techniques were performed in all children with confirmed UTI. During the acute phase, within the first days of admission, abdominal sonography was conducted to detect urinary tract abnormalities or urinary flow obstruction. After 4 to 6 weeks, direct cystography was performed to rule out the presence of vesicoureteral reflux. Five to six months after the episode, DMSA gammagraphy was done to demonstrate the presence of renal scars.

We used the presence of scars as evidence of severe renal involvement. Acute pyelonephritis does not necessarily lead to parenchymal damage, but the presence of kidney scars after an episode of UTI confirms localization of infection within the renal parenchyma and its severity. To establish the range of normal PCT values in our pediatric population, we obtained serum samples from a control group of 38 healthy children without infection, from the same range of age, who were admitted to the hospital for elective surgery.

PCT detection. PCT was measured by immunoluminometric assay (Lumitest PCT; Brahms Diagnostica, Hennigsdorf/Berlin, Germany) following the manufacturer's instructions. Luminescence was measured by luminometer Leader 50i (Gen-Probe; San Diego, CA).

Statistical analysis. The Kolmogorov-Smirnov test with Lilliefors correction was used to check the data for parametric distribution. Differences between medians of the groups were evaluated by the nonparametric Mann-Whitney test. Differences were considered statistically significant when P was <0.05. Data were analyzed by sensitivity, specificity and positive and negative predictive values derived from the receiver operating characteristics (ROC) curve. Data are expressed on median, range and 5 to 95 percentiles. The

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commercial statistical software package used was SPSS 11.0 (SPSS, Inc., Chicago, IL).

RESULTS

Seventy-seven patients diagnosed with UTI were included in the study. *Escherichia coli* was isolated in urine culture in 72 patients, *Klebsiella pneumoniae* in 3, *Proteus mirabilis* in 1 and *Enterococcus faecalis* in 1.

Sixty-four children had no renal damage by DMSA gammagraphy. Of those, 19 patients had low fever (<38°C) and no clinical signs of systemic involvement. They were clinically considered to have a lower UTI. Only one of them showed vesicoureteral reflux on cystography. Clinical findings for the other 45 patients suggested systemic involvement, including high fever (38°C or more), and the patients were clinically diagnosed with acute pyelonephritis. In this group abnormal sonography was found in 7 patients, and vesicoureteral reflux on cystography was found in another 7 patients.

Thirteen children showed the presence of renal parenchymal damage by DMSA gammagraphy, confirming severe renal involvement. All had been clinically diagnosed with acute pyelonephritis. For three of them DMSA gammagraphy was also performed during the acute phase and was abnormal. *E. coli* was also isolated in the blood culture in another two patients. All of these patients had pathologic findings on ecography (hydronephrosis) and/or cystography (vesicoureteral reflux) except one.

Age groups presented equal variances ($P = 0.082$). Table 1 shows the median, range and 5 to 95 percentiles for PCT, CRP and leukocyte count at the time of admission in subjects with and without renal damage. In those without renal damage, we distinguish the subjects clinically diagnosed as having lower UTI and those clinically diagnosed as having acute pyelonephritis. These data are also shown in Figures 1 to 3. Control group showed a median PCT value of 0.363 ng/ml (SD 0.29). When comparing subjects having UTI with renal damage *vs.* UTI without renal damage, median PCT and CRP values yielded significant differences ($P < 0.0001$ and $P = 0.002$, respectively), but no significance was found for the leukocyte count ($P = 0.174$). Median values were also compared between clinically diagnosed pyelonephritis without scars and pyelonephritis with scars, and significant differences were also found for PCT and CRP ($P = 0.003$ and $P = 0.026$, respectively), but not for leukocyte count ($P = 0.544$).

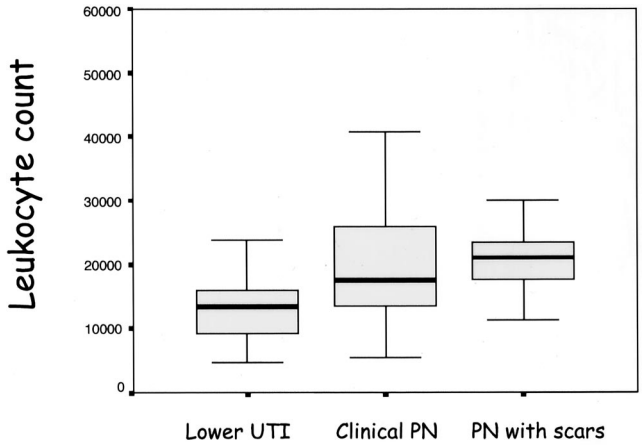

FIG. 1. Leukocyte count/mm^3 (median, range, 5 to 95 percentiles) at the time of admission in clinically diagnosed lower urinary tract infection (*Lower UTI*), clinically diagnosed acute pyelonephritis without scars (*Clinical PN*) and pyelonephritis with scars on DMSA gammagraphy (*PN with scars*).

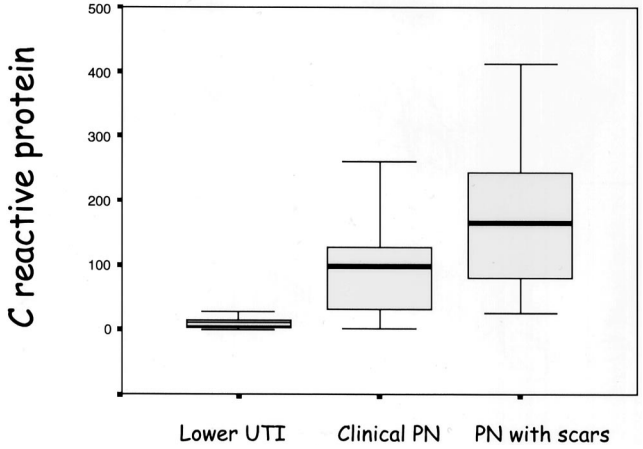

FIG. 2. C-reactive protein concentrations (median, range, 5 to 95 percentiles) at the time of admission in clinically diagnosed lower urinary tract infection (*Lower UTI*), clinically diagnosed acute pyelonephritis without scars (*Clinical PN*) and pyelonephritis with scars on DMSA gammagraphy (*PN with scars*).

The area under the ROC curve obtained for PCT in distinguishing between UTI with and without renal

TABLE 1. Laboratory parameters at time of admission

	Procalcitonin (ng/ml)			C-reactive Protein (mg/l)			Leukocyte Count/mm^3		
	Median	Range	5–95 percentiles	Median	Range	5–95 percentiles	Median	Range	5–95 percentiles
UTI without renal damage									
Clinical lower UTI	0.312	0.79	0.0033–0.7610	7.20	59	0.0001–46.68	12 100	19 300	4600–21 620
Clinical PN	1.16	191.94	0.125–77.53	97.0	325.5	4.98–250.98	18 000	25 900	8100–32 680
UTI with renal damage	9.28	61.52	0.68–48.36	162.2	412	0.001–350.4	21 000	35 300	5000–40 260

PN, pyelonephritis.

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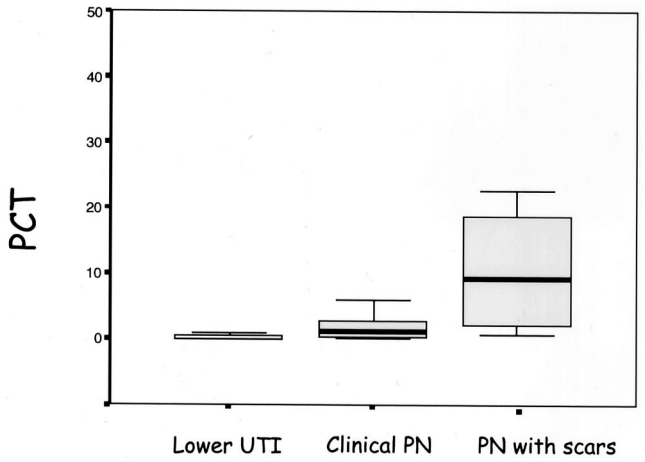

FIG. 3. Procalcitonin concentrations (median, range, 5 to 95 percentiles) at the time of admission in clinically diagnosed lower urinary tract infection (*Lower UTI*), clinically diagnosed acute pyelonephritis without scars (*Clinical PN*) and pyelonephritis with scars on DMSA gammagraphy (*PN with scars*).-

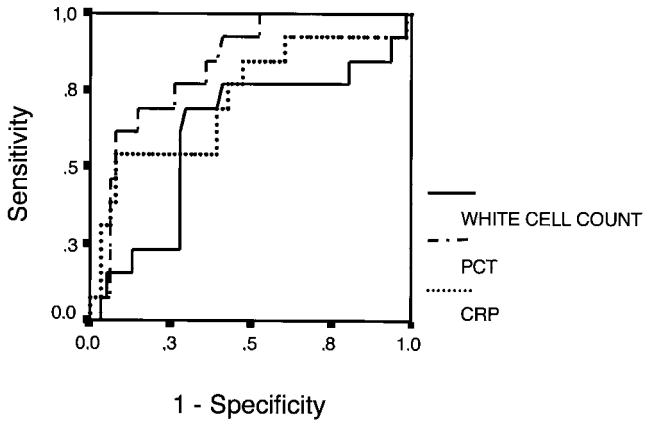

FIG. 4. ROC curve of PCT, CRP and white blood cell count in predicting renal parenchymal damage in children with UTI.

damage was 0.83, for CRP it was 0.72 and for leukocyte count it was 0.62 (Fig. 4). Using a cutoff value of 1 ng/ml for PCT and 20 mg/l for CRP, sensitivity and specificity were 92.3 and 61.9% for PCT, and for CRP they were 92.3 and 34.4%, respectively. Positive and negative predictive values for PCT were 32 and 97.5%, respectively, and for CRP they were 23 and 95%.

To evaluate whether PCT values were influenced by factors other than the urinary tract infection that is bound to develop renal scarring, correlation with presence of vesicoureteral reflux and with early age was also analyzed. Of 61 patients without reflux, 5 developed scars; 8 of 16 patients with reflux developed scars. There was no significant correlation between PCT values and vesicoureteral reflux ($P = 0.192$). The influence of an early age on PCT values was also evaluated, and no correlation was found ($P = 0.659$).

A second sample of serum was obtained within the first 24 h in 42 patients. Median, range and 5 to 95 percentiles for PCT and CRP of the second sample are shown in Table 2. Eight of 19 patients with clinical lower UTI had a second determination, and the value remained <1 ng/ml. Twenty-seven of 45 patients with clinical pyelonephritis without scars had a second determination. In 14 of them the second PCT value was higher than the first. In 3 of these cases the first measurement was normal, and the second was high. Nine of 13 patients with renal scars had a second determination, and all had a high PCT value but lower than the first one.

DISCUSSION

The aim of our study was to evaluate the usefulness of PCT measurement in distinguishing between uncomplicated UTI and pyelonephritis with renal scarring, comparing the results with other inflammatory markers.

The leukocyte count did not correlate with the severity of UTI, as previously reported in other studies.[16] Also CRP alone is not a risk predictor for serious renal damage and in combination with fever does not improve the predictive value of fever alone.[7] In our study low specificity of CRP was confirmed.

Many clinical studies have confirmed PCT as a specific marker of bacterial infection and as a good predictor of disease severity and efficacy of antibiotic therapy.[15, 17, 18] PCT values might help to distinguish severe bacterial infection from localized and viral disease in febrile children.[19] Furthermore PCT values are related to the anatomical extent of the inflamed tissue involved. Benador et al.[20] demonstrated a highly significant correlation between elevated PCT values and

TABLE 2. Laboratory parameters 24 h after admission

	Procalcitonin (ng/ml)			C-reactive Protein (mg/l)		
	Median	Range	5–95 percentiles	Median	Range	5–95 percentiles
UTI without renal damage						
Clinical lower UTI	0.4995	0.92	0.1270–0.5742	6.0	22.0	1.0–21.5
Clinical PN	1.31	58.52	0.3664–39.6	105	222.2	4.5–203.15
UTI with renal damage	2.80	8.74	0.5770–7.50	206.0	259.6	3.0–240.25

PN, pyelonephritis.

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the severity of renal involvement assessed by DMSA scintigraphy done within the first 5 days of admission and ranked according to the extent of the lesions. This correlation was reported in other studies.[21, 22] The results of our study show a significant correlation between high PCT values at the time of admission and renal damage. When scars are present, severity and parenchymal location of the UTI are the most likely.

Serum PCT values at the time of admission are influenced by the severity of infection as well as by its kinetics in serum, which depends on the lapse of time taken by the bacteria to trigger the inflammatory response.[23, 24] Serial measurements reflect the course of this inflammatory activity. In our study PCT values in clinical lower UTI were very low or not detectable and remained low on a second determination 24 h later. Alternatively PCT values in pyelonephritis with scars were elevated at the time of admission and still high 24 h later, but lower than initially. Some of the patients (14) clinically diagnosed with acute pyelonephritis showed low values at admission but increased PCT values on the second determination. Nevertheless none of them developed renal scars. All these patients had received one injection of gentamicin (once daily dose of 5 to 6 mg/kg) within the first hours. PCT has a half-life of ~25 to 30 h after a single stimulus.[24] When the bacteria have triggered a systemic response, high levels can still be in serum within the first day although effective antibiotic therapy has been started. Therefore a second measurement can help to identify patients at risk of severe pyelonephritis but who reach the Emergency Department early in the inflammatory response.

We can conclude that PCT yields a high negative predictive value of renal damage. Therefore a low PCT value at the time of admission, in spite of clinical signs of pyelonephritis, points out a low risk of renal scarring. PCT measurement can be useful to identify patients at risk of developing renal parenchymal damage who would then benefit from additional therapies.

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