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ORIGINAL ARTICLE

Procalcitonin as a predictor of renal scarring in infants and young children

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Abstract The aim of this study was to evaluate the usefulness of procalcitonin (PCT) as a marker of renal scars in infants and young children with a first episode of acute pyelonephritis. Children aged 7 days to 36 months admitted for first febrile urinary tract infection (UTI) to a pediatric emergency department were prospectively enrolled. The PCT concentration was determined at admission. Acute ^{99m}Tc-dimercaptosuccinic acid (DMSA) scintigraphy was performed within 7 days of admission and repeated 12 months later when abnormal findings were obtained on the first scan. Of the 72 children enrolled in the study, 52 showed signs of acute pyelonephritis (APN) on the first DMSA scan. A follow-up scintigraphy at the 12-month follow-up performed on 41 patients revealed that 14 (34%) patients had developed renal scars; these patients also presented significantly higher PCT values than those without permanent renal lesions [2.3 (interquartile range 1–11.6) vs. 0.5 (0.2–1.4) ng/mL; p=0.007]. A comparison of the PCT concentration in patients with febrile UTI without renal involvement, with APN without scar development and with APN with subsequent renal scarring revealed a significant increasing trend (p=0.006, Kruskal–Wallis test). The area under the ROC curve for scar prediction was 0.74 (95% confidence interval 0.61–0.85), with an optimum statistical cut-off value of 1 ng/mL (sensitivity 78.6%; specificity 63.8%). Based on these results, we suggest that serum PCT concentration at admission is a useful predictive tool of renal scarring in infants and young children with acute pyelonephritis.

Keywords Children · DMSA scan · Procalcitonin · Renal scar · Urinary tract infection

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Introduction

Urinary tract infection (UTI) is one of the most frequently occurring bacterial infections in pediatric patients, especially among the age group <3 years [1, 2], with the prevalence being 6.5 and 3.3% in girls and boys <1 year of age, respectively. Approximately 60% of those with a febrile UTI will develop an infection of the renal parenchyma or acute pyelonephritis (APN) [3]. The identification of children with APN who may develop permanent renal scarring is a major challenge to healthcare providers as the kidneys of these children have a high risk of being damaged. Scarring secondary to APN is a common event, occurring in approximately 30% of all cases [4].

Commonly used clinical and laboratory parameters have been shown to be poor diagnostic tools in terms of identifying those children with UTI at risk for renal scars [5, 6]. Of the instrument-based approaches, Tc-99 m dimercaptosuccinic acid (DMSA) renal scintigraphy is currently the most sensitive test available for the diagnosis of APN and plays an undisputed important role in the detection and characterization of renal scarring when performed at least 6 months after the acute infection.

However, it is not readily accessible in every setting and radiation exposure, albeit small, is unavoidable [7–11].

Procalcitonin (PCT), a prohormone of calcitonin that lacks hormonal activity, was initially reported to be a potential marker of bacterial infections [12], but more recent reports suggest that PCT levels are correlated with the presence of renal scarring after a first UTI episode in febrile children [5, 6]. To date, however, only limited evidence exists on this correlation in very young children, i.e. the ones at higher risk for UTI.

The primary aim of this study was to evaluate the usefulness of PCT as a marker of renal scars in children younger <3 years at the time of a first episode of APN.

Materials and methods

Patient characteristics and inclusion criteria

This prospective observational study was conducted in the Emergency Department (ED) of the Children's Hospital, Padova (Italy) between 1 January 2005 and 30 September 2006. Patients included in the study were children 7 days to 3 years of age who presented with a first episode of febrile UTI and no other focus of infection (based on the results of a complete physical examination) and who were at risk for pyelonephritis based on traditional inflammatory markers values [C-reactive protein (CRP) ≥15 mg/L or white blood cell (WBC) count ≥15,000/mm^3]. Febrile UTI was defined as a body temperature >38°C, associated with positive urinalysis (two concordant consecutive tests with white cell counts ≥25/μL; =1+ with the dipstick) and positive urine cultures (two concordant consecutive tests with the growth of only one micro-organism showing ≥100,000 colony forming units/ml) [13]. Urine was collected in sterile bags changed every 30 min (two concordant consecutive urinalysis and cultures were required to minimize the risk of false positive tests) or, in older toilet-trained children, by the midstream clean-void technique. Patients with congenital or acquired urinary tract abnormality at the time of the UTI diagnosis were excluded from the study. Children who had received antibiotics in the previous week were also excluded.

Clinical and diagnostic evaluations

Patients were eligible for the study when the urine culture confirmed the infection. All children were hospitalized and treated with antibiotics. Complete history, demographic information, body temperature, physical examination and clinical evaluation using the Yale Observation Score [14] were recorded at the time of the initial evaluation. According to the guidelines in use at the time of the study in our department, WBC count, absolute neutrophil count (ANC) and CRP concentration were obtained in all patients, along with the results of a urine analysis; in addition, a blood sample was also collected and serum was stored at −20°C for later determination of the PCT level.

Laboratory assessments

Quantitative measurements of PCT levels were performed using a sandwich immunoluminometric method (detection limit 0.04 ng/mL) employing two monoclonal antibodies: one against the catacalcin region of procalcitonin and the other against calcitonin (Liason Brahms; Brahms Diagnostica, Henningdorf, Berlin, Germany).

Imaging techniques

At the time of the study, an acute DMSA scan was routinely performed on all children within 7 days of the initiation of antibiotic therapy. A weight-scaled dose of ^{99m}Tc-DMSA was administered (reference adult dose 110 MBq; minimal dose 40 MBq) [8]. Three hours after injection, three views (one posterior and two posterior oblique) were obtained, using a low-energy high-resolution collimator and a pixel dimension of 1.0–1.8 mm. The presence and the severity of renal lesions was determined by two nuclear medicine physicians unaware of the patient's clinical or laboratory data.

Pyelonephritis was defined as focal or diffuse areas of decreased cortical uptake, without evidence of cortical loss. If the child had a positive result on scintigraphy for APN, we scheduled a repeat scan after 12 months to detect any renal scarring at the site of the original pyelonephritis. Scars were defined according to the guidelines of the European Association of Nuclear Medicine [15].

A voiding cystourethrography (VCUG) was also performed 4–8 weeks after the acute infection to detect vesicoureteral reflux (VUR). This exam was part of the follow-up for children with a first febrile UTI at the time of the study. The VUR was classified according to the International System of Radiologic Grading of Vesicoureteric Reflux [16].

Clinical follow-up and data collection were carried out by the two of the authors (BA and SB). Informed consent was obtained from the parents or legal guardians. The study protocol was approved by the hospital Ethics Committee.

Statistical analysis

Normally distributed data were expressed as mean ± standard deviation (SD); non-normally distributed data were expressed as median and interquartile range; categorical variables were reported as percentages. For non-normally distributed data, comparisons were performed using the Mann–Whitney *U* or Kruskal–Wallis test when

Table 1 Clinical characteristics and laboratory parameters at admission for patients with and without renal scar development

Clinical characteristics/laboratory parameters	UTI with renal scars (n=14)	UTI without renal scars[a] (n=47)	p
Age (months)	4 (0.9–6.7)	3.7 (1–7.4)	0.972
Sex (M/F)	7/7	24/23	0.815
Fever duration (h)			0.249
<8	6	8	
8–24	3	20	
>24	5	17	
Maximum temperature (°C)	39±0.6	39±0.8	0.974
Yale score (n)			0.534
<10	11	35	
10–16	3	9	
>16	0	3	
PCT (ng/mL)	2.3 (1–11.6)	0.5 (0.2–1.4)	0.007
CRP (mg/L)	62 (40–111)	50 (33.25–88.25)	0.425
WBC (/mm^3)	15000 (12200–22200)	50 (33.25–88.25)	0.773
ANC (/mm^3)	12000 (8000–14700)	9700 (7300–13200)	0.465

UTI, Urinary tract infection; PCT, procalcitonin; CRP, C-reactive protein; WBC, white blood cell; ANC, absolute neutrophil count
For continuous variables, data are expressed as median and interquartile range (in parenthesis), except for temperature values which are mean ± SD.
[a] Twenty patients with negative acute Tc-99 m dimercaptosuccinic acid (DMSA) scan + 27 patients with APN but no scars on follow up DMSA scan

appropriate; comparison of normally distributed data were performed with the independent-samples t test. For categorical data, the χ^2 test with Yates correction for 2×2 tables was used. Parameters for which p values < 0.05 were considered to be statistically significant.

The diagnostic performance of PCT was investigated by receiver operating characteristic (ROC) analysis, which was used to calculate the best statistical cut-off value (the point at which the sum of false-positives and false-negatives is less than that at any other point).

The commercial statistical software package used was Stata ver. 10 (Stata Corp, College Station, TX).

Results

The patient cohort comprised 72 children, aged 7 days to 3 years (median age 4.5 months; range 1–10 months), with a first episode of febrile UTI. Fifty-eight (80.5%) patients were infants younger than 12 months, and 31 (43%) were males (all non-circumcised). Mean body temperature before admission was 39.0±0.8°C, with 41 patients (58.6%) presenting fever for less than 24 h.

Escherichia coli was cultured as a single pathogen in 69 children, *Enterococcus fecalis* in two children and *Klebsiella penumoniae* in one patient.

The median interval between admission and acute DMSA scan was 4 days; 75% of the scans were performed within 5 days.

The results of the DMSA scan for 52 children (72%) were consistent with an APN; the remaining 20 children (28%) showed a normal DMSA scan and were diagnosed as having a febrile UTI without renal involvement.

Of the 52 patients subjected to further study, 41 (78.8%) underwent repeated scintigraphy after 12 months, at which time 27 showed total regression of their initial lesions, and 14 (34%) had an irreversible defect. The 11 patients on whom a follow-up DMSA scan was not performed were excluded from analysis.

Clinical characteristics and laboratory findings of the patients with and without scars are presented in Table 1.

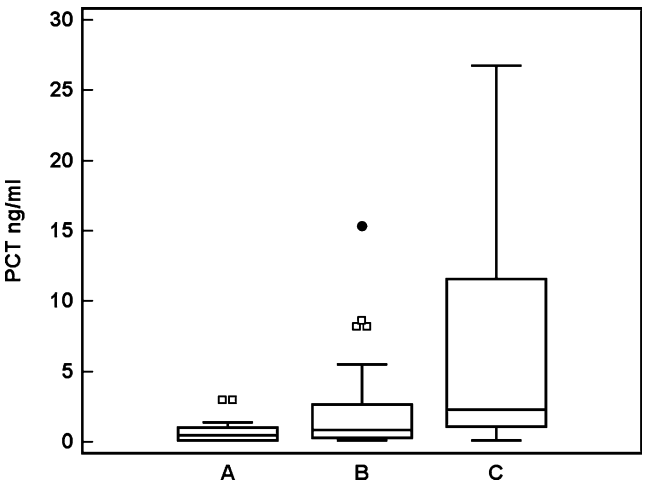

Fig. 1 Plasma procalcitonin (*PCT*) levels at admission in febrile urinary tract infection (UTI) without renal involvement (*A*), acute pyelonephritis (APN) without scar development (*B*) and APN with subsequent renal scarring (*C*) The box-whisker plots show the median (horizontal line), the interquartile range (IQR, margins of box), and outlier values (small box indicates values >1.5 IQR and filled circle indicates values >3 IQR) (Kruskal–Wallis test, p=0.006)

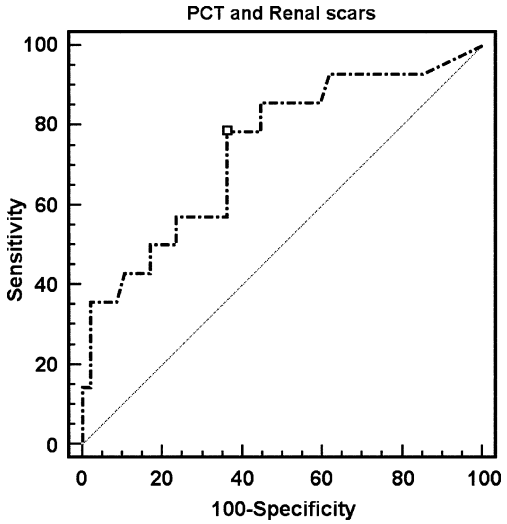

Fig. 2 Receiver operating characteristic of PCT values for the prediction of renal scarring

The two groups were comparable in terms of age, sex, duration of fever before admission, body temperature and Yale score. Of the laboratory parameters, only PCT levels were statistically different between children with and without permanent lesions on the follow-up scintigraphy [2.3 (interquartile range 1–11.6) vs. 0.5 (0.2–1.4) ng/mL; $p=0.007$]. In 85% of the patients with a scar, PCT values were >0.5 ng/mL. When children with febrile UTI without renal involvement, with APN without scar development and with APN with subsequent renal scarring were compared, the PCT values showed a significant increasing trend with median values and interquartile ranges of 0.49 (0.12–1), 0.83 (0.3–2.6) and 2.3 (1–11.6) ng/ml, respectively ($p=0.006$, Kruskal–Wallis test) (Fig. 1). The area under the ROC curve for scar prediction was 0.74 (95% confidence interval: 0.61–0.85), with an optimum statistical cut-off value of 1 ng/mL (sensitivity 78.6%; specificity 63.8%) (Fig. 2).

Table 2 shows the sensitivity, specificity and likelihood ratios for different PCT cut-offs for the prediction of scars.

Sixty-one children (49/52 of patients with APN and 12/20 of patients with normal acute renal scan) underwent a VCUG 4–8 weeks after the acute infection. A VCUG was not performed in 11 children because of parents' refusal. Vesicoureteral reflux was detected in 13 children (21.3%), 12 of whom were in the APN group (two patients had grade I reflux, seven had grade II, three had grade III and one had grade IV). The only patient with VUR and no renal involvement, as revealed by the acute scan, showed a grade II reflux. Vesicoureteral reflux was detected in seven of 13 (54%) patients with renal scar who had a VCUG performed; four patients had grade II reflux, two had grade III and one grade IV.

A comparison of the PCT concentration in children with and without VUR revealed significantly higher PCT values in the former group of patients [1.9 (1–7.8) vs. 0.5 (0.2–2.2) ng/mL; $p=0.027$] but there was no significant correlation to VUR grade ($p=0.08$, Kruskal–Wallis test).

Discussion

Febrile UTIs are the most common serious bacterial infections of infancy and early childhood. Several studies have reported that the development of renal scarring subsequent to parenchymal localization of the infection ranges from 10 to 30 % of all cases of UTI [3–6, 17–20]. As permanent renal lesions can lead to long-term adverse outcomes, such as arterial hypertension and chronic kidney damage, pediatricians have the important task of identifying those pediatric patients with UTI who are at a higher risk of developing renal scars. Clinical signs and symptoms and commonly used laboratory markers have been found to be poor diagnostic tools for distinguishing such patients at the time of the acute infection [5, 6, 21], especially when the patients are infants and very young children.

The frequency of scintigraphy-confirmed APN (72%) found in our study is high but quite similar to the value reported by other authors [7, 13, 17, 20, 22] in different age groups.

We focused our attention on infants and children <3 years of age (80.5% of the patients included were <12 months), which is the age group most frequently affected by UTI. Clinical signs and symptoms in this age group are particularly non-specific and of little value, even for distinguishing between pyelonephritis and lower UTI. Of the studies investigating the role of PCT in UTIs in pediatric patients [5, 6, 17, 20, 22–24], only Smolkin and colleagues [25] selectively included very young children aged 2 weeks to 3 years. The prevalence of APN reported

Table 2 Sensitivity, specificity, positive and negative likelihood ratio values of PCT for prediction of scars on follow-up scan

PCT (ng/mL)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	LR+, % (95% CI)	LR-, % (95% CI)
>0.5	85.7 (60.1–96.0)	51.1 (37.2–64.7)	1.75 (1.565–1.96)	0.28 (0.10–0.80)
>1	78.6 (49.2–95.1)	63.8 (48.5–77.3)	2.17 (1.75–2.40)	0.34 (0.17– 0.70)
>2	50.0 (26.8–73.2)	78.7 (65.1–88.0)	2.35 (1.46–3.78)	0.64 (0.47–0.85)

LR, Likelihood ratio; CI, confidence interval

in their study was lower than that in our study, but the inclusion criteria of the studies were different.

We found an occurrence of 34% renal scarring in patients with APN, which is similar to that reported in other studies, although in different age groups [4–6, 26, 27]. Our results show that PCT concentration was significantly higher in infants and children who developed renal scars, as evidenced on follow-up scintigraphy, compared to the values of the commonly used laboratory parameters. In addition, PCT values showed a significant correlation with the severity of renal damage that had been graded according to the results of the acute scan as no renal involvement, APN without subsequent renal scarring and APN with renal scar development. Previous studies [5, 23] have demonstrated a significant increase in PCT values with increasing severity of renal involvement, as assessed according to the extent of renal lesions on acute DMSA scan.

Although there have been very few reports on the correlation between PCT and renal scarring [5, 6], those available have obtained results similar to our study. In our population, 85% of the patients with a scar on repeated DMSA scan presented a PCT value > 0.5 ng/mL. These findings suggest that PCT has the potential as a diagnostic tool for selecting those previously healthy infants who may not require a follow-up scintigraphy after their first UTI, thereby reserving a follow-up DMSA scan to those with a PCT concentration >0.5 ng/mL.

The use of PCT as a non-invasive tool for predicting VUR has received much attention in recent years. Vesicoureteral reflux is a recognized risk factor for scar development, even though renal scarring can also be observed in the absence of VUR [28], as shown also by our results. In the recently published studies by Leroy et al. [29, 30], PCT emerged as a strong and independent predictor of VUR. We found significantly higher PCT values in children with VUR but no correlation between PCT concentration and VUR grade. However, the small number of patients with significant reflux in our study does not allow us to draw definitive conclusions on this subject. In addition, it should be mentioned that the single patient presenting a grade IV VUR and who developed a scar had a relatively low PCT concentration (0.46 ng/mL). Clearly, further investigation is required to determine the role of PCT as a predictor of VUR and its implications for clinical practice.

This study has a number limitations. Firstly, urine samples were collected mainly by sterile bags. This technique is considered to be less specific than suprapubic aspiration or bladder catheterization, but it reduces the discomfort experienced by the patients and their family, which is why it is still used in daily practice both in primary care and in emergency department settings by many European and some North American pediatricians [13, 22, 24, 29–33]. As already stated by Leroy et al. [32], the range of specificity related to bag urine collection varies widely across studies, and the low specificity reported by some authors is supported by a questionable level of evidence. In our experience, the increased risk of contamination was accounted for by collecting the urine twice: two consecutive concordant urinalyses and cultures minimized the risk of contamination and false positive tests; furthermore, urine collection was performed following a standardized protocol, which required changing the bag every 30 min. In an earlier larger study [13] carried out by our group, urine was also collected in this way, and the DMSA scan confirmed that pyelonephritis was similar to that reported by Pecile et al. [5] and Hobermann et al. [3, 18] who collected urine by catheterization or midstream clean void.

Another limitation of the study is that the selection of patients based on CRP and WBC values could represent a bias. During the study period, this was the standard practice of our department for selecting those children at higher risk of pyelonephritis who had to receive a DMSA scan, sparing unnecessary examinations to children unlikely to have APN. As many studies have demonstrated, CRP has a very high sensitivity (ranging from 94 to 100% for a cut-off of 20 mg/L) for predicting acute renal damage [5, 20–22, 24–26], suggesting that children with normal CRP values could be considered to have a high probability of having no renal involvement.

Conclusion

In conclusion, our data show that, in the very young children of our study with a first febrile UTI, serum PCT concentration at admission was a good predictor of permanent renal lesions. Even though it has not yet been determined whether PCT could be a reliable replacement of the DMSA scan, it can be considered to be a useful non-invasive tool for identifying those children who, despite having no previous history of urinary tract abnormalities, are at risk of complications and who need further assessment and a closer follow-up as early as their first febrile UTI. However, more and larger studies are needed to better assess the role of PCT as a predictor of renal scarring.

Conflict of interests/ sources of support The authors state that they have no financial relationships with commercial companies pertaining to this topic.

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