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NEPHROLOGY-ORIGINAL PAPER

Procalcitonin for the early prediction of renal parenchymal involvement in children with UTI: preliminary results

Aggeliki Kotoula · Stefanos Gardikis · Aggelos Tsalkidis · Elpis Mantadakis · Athanassios Zissimopoulos · Katerina Kambouri · Savvas Deftereos · Gregorios Tripsianis · Konstantinos Manolas · Athanassios Chatzimichael · George Vaos

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Abstract In order to establish the most reliable marker for distinguishing urinary tract infections (UTI) with and without renal parenchymal involvement (RPI), we recorded the clinical features and admission leukocyte count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum procalcitonin (PCT) in 57 children (including 43 girls) aged 2–108 months admitted with a first episode of UTI. RPI was evaluated by Tc-99m dimercaptosuccinic acid (DMSA) scintigraphy within 7 days of admission. To establish cut-off points for ESR, CRP, and PCT, we used receiver operating characteristics curves and compared the area under the curve for ESR, CRP, and PCT. Twenty-seven children were diagnosed as having RPI based on positive renal scintigraphy. A body temperature of >38°C, a history of diarrhea, and poor oral intake were more common in patients with RPI. ESR, CRP, and PCT, but not leukocyte count, were significantly higher in patients with RPI ($P < 0.001$). PCT was more sensitive and specific for the diagnosis of upper versus lower UTI than ESR and CRP. Using a cut-off value of 0.85 ng/ml, PCT had the best performance, with sensitivity, specificity, and positive and negative predictive values of 89%, 97%, 96%, and 91% respectively. Serum PCT is a better marker than ESR, CRP, and leukocyte count for the early prediction of RPI in children with a first episode of UTI.

Keywords Urinary tract infections · Renal parenchymal involvement · Procalcitonin · C-reactive protein · Children

A. Kotoula · A. Tsalkidis · E. Mantadakis · A. Chatzimichael
Department of Pediatrics, Alexandroupolis University Hospital, Democritus University of Thrace School of Medicine, 68100 Alexandroupolis, Greece

S. Gardikis (✉) · K. Kambouri · G. Vaos
Department of Pediatric Surgery, Alexandroupolis University Hospital, Democritus University of Thrace School of Medicine, 68100 Alexandroupolis, Greece
e-mail: sgardik@med.duth.gr

A. Zissimopoulos
Department of Nuclear Medicine, Alexandroupolis University Hospital, Democritus University of Thrace School of Medicine, 68100 Alexandroupolis, Greece

S. Deftereos
Department of Radiology, Alexandroupolis University Hospital, Democritus University of Thrace School of Medicine, 68100 Alexandroupolis, Greece

G. Tripsianis
Department of Medical Statistics, Alexandroupolis University Hospital, Democritus University of Thrace School of Medicine, 68100 Alexandroupolis, Greece

K. Manolas
Department of Surgery, Alexandroupolis University Hospital, Democritus University of Thrace School of Medicine, 68100 Alexandroupolis, Greece

Introduction

Urinary tract infections (UTI) are frequent in children, occuring in 3.3–5.3% of febrile infants [1, 2]. UTI are especially common in Caucasian girls, with no definite source of fever [2]. The nonspecific nature of the symptoms among febrile infants and small children makes it difficult to differentiate clinically between upper UTI (UUTI) with renal parenchymal involvement (RPI) and lower UTI (LUTI), i.e., UTI without RPI [1–3]. Although UUTI is frequently referred to as acute pyelonephritis (APN), we refrain from using this term because it is a clinical description that can not be accurately used in infants or young children.

The accurate diagnosis and early treatment of UUTI are important because of its association with renal scarring [4, 5]. Therefore, a quick and readily available diagnostic test would be of value for the early diagnosis of RPI, which requires more aggressive therapy than LUTI and meticulous patient follow-up.

At present, renal scintigraphy with Tc-99m dimercaptosuccinic acid (DMSA) is considered the gold standard for the diagnosis of RPI and for assessing the extent and progression of renal parenchymal damage [6].

Procalcitonin (PCT), a 116-amino acid propeptide of calcitonin that is devoid of hormonal activity, was initially described as a potential marker of bacterial infections [7, 8]. PCT is almost undetectable (<0.5 μg/l) under physiological conditions, but rises to very high values in response to bacterial endotoxins, and this rise appears to be related to the severity of infection. Sequential measurements of PCT in patients with bacteremia have shown a rapid fall within 48 h of antibiotic administration. In the first 2 days of life, PCT can be physiologically elevated without evidence of an underlying neonatal infection. From the third day of life onward, the same reference values are applied for children and adults.

The primary goal of the present study was to record the clinical features of children with a first episode of UTI and to compare the diagnostic value of admission leukocyte count, erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP), and PCT in these children, in order to establish the most reliable marker in distinguishing upper from lower UTI.

Patients and methods

We prospectively studied children who were hospitalized in the Department of Pediatrics of Alexandroupolis University Hospital between 1 September 2006 and 31 May 2007 because of a first episode of proven UTI. Children with a history of prior UTI were excluded. Urine specimens were obtained, mainly by supra-pubic aspiration (SPA) and urethral catheterization. In a few cases the urine specimens were collected by urine bags in infants and toddlers, while in older children by midstream clean-voided catch. A urine bag specimen with no bacterial growth was considered sterile, but a positive culture result was always confirmed by a second sample. All urine samples were cultured by standard microbiological techniques.

Urinary tract infection was defined as any growth of a single bacterial pathogen from SPA or >104 colony-forming units (cfu) per ml from a catheterized specimen or >105 cfu per ml in samples collected by midstream clean-voided urine and by urine bags.

On admission and before the initiation of antibiotic treatment, all patients underwent clinical evaluation and routine laboratory investigations, including leukocyte count, ESR, serum CRP, and PCT determination. Regarding clinical evaluation, the following data were recorded on admission: temperature (≥38°C), presence of vomiting or diarrhea, or decreased oral intake prior to admission.

Leukocyte counts were measured by the hospital's automated blood cell counter (XE 2100; SYSMEX Corporation, Kobe, Japan). CRP measurements were carried out with an Olympus System autoanalyzer (model AU 640; Medicon Hellas, Gerakas, Greece). CRP was measured quantitatively by means of an immunoturbidimetric assay (Reagent 800; Lismeehan, Clare, Ireland). In this assay, CRP reacts specifically with anti-human CRP antibodies to yield insoluble aggregates, with absorbance proportional to the CRP concentration. For PCT determination, 2 ml of blood was centrifuged, the serum separated, frozen at −70°C, and measured with a rapid, semi-quantitative immunochromatographic test (Brahms Diagnostica; Henningdorf BEI, Berlin, Germany). Once the diagnosis of UTI was confirmed, DMSA scintigraphy was performed within the first 7 days. DMSA studies with a gamma camera (GE Millenium MPR, USA) were performed 4 h after the intravenous injection of an

age-adjusted dose of Tc-DMSA (minimum dose 40 MBq, maximum dose 100 MBq). Anterior and posterior planar views using a high-resolution parallel hole collimator were collected for 5 min each for the evaluation of differential renal function, using a geometric mean method to compensate for differences in the position of each kidney. These views were also used for the evaluation of the relative size and cortical uptake of the kidneys. In addition, magnified posterior and posterior oblique views of each kidney were obtained and acquired for 100,000 counts per kidney. Moreover, according to recommended guidelines, a renal ultrasonogram was obtained within the first 48 h after diagnosis.

The study was approved by the hospital ethics committee and consent was obtained from the parents of all participating children.

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 13.0 (SPSS, Chicago, IL, USA). Quantitative variables are expressed as medians with ranges. Qualitative variables are expressed as frequencies and percentages. Differences in demographic and laboratory characteristics between children with upper and lower UTI were compared using the Mann–Whitney *U* test. Chi-squared and Fisher's exact tests were used to evaluate potential associations between qualitative variables. In order to evaluate the diagnostic significance of the parameters tested, the area under the receiver operating characteristics (ROC) curve was calculated. Specificity, sensitivity, and positive and negative predictive values were estimated for the cut-off points established by the ROC curves, while Cohen's kappa coefficient was used to evaluate agreement. All tests were two-tailed and statistical significance was set at $P < 0.05$.

Results

Fifty-seven children, 14 boys and 43 girls, were consecutively enrolled in the study. Demographic and some clinical characteristics of the participating children are shown in Table 1. The median age of all participating children was 12 months (range 2–108 months). The median age of boys was 12 months (range 2–50 months), while that of girls was 14 months (range 3.5–108 months). This difference was not significant ($P = 0.0505$). The age of boys with upper versus lower UTI was not significantly different ($P = 0.5481$), while girls with LUTI were significantly older than girls with UUTI ($P = 0.0129$). Thirty-five children (61.4%) were ≤15 months of age, 7 (12.3%) were between 16 and 30 months, 7 (12.3%) between 31 and 48 months, and 8 (14%) were >48 months of age (Fig. 1). Twenty-seven children (47%) were diagnosed as having UUTI based on positive renal scintigraphy (Group 1). The remaining 30 (53%) exhibited normal scintigraphic results and thus were considered as having LUTI (Group 2). Among children ≤15 months old, 20 (57%) had UUTI.

Table 1 Clinical data of 57 children with documented urinary tract infection (UTI)

	Group 1 ($n = 27$)	Group 2 ($n = 30$)
Sex (male/female)	6/21	8/22
Age (months)	Median 11, range (3–108)	Median 17.5, range (2–105)
Temperature ≥ 38°C	27	21
Vomiting	4	3
Diarrhea	9	2
Decreased feeding	12	3

Group 1: children with upper urinary tract infection; Group 2: children with lower urinary tract infection

The median age between the two groups was not significantly different and the majority of patients in Groups 1 and 2 were girls (21 and 22 respectively). Although there was a trend toward higher leukocyte counts on admission in children with UUTI,

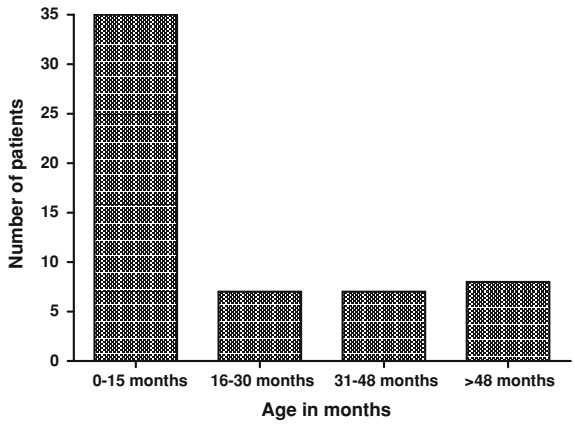

Fig. 1 Age distribution of 57 children with urinary tract infection (UTI)

Table 2 Laboratory data of 57 children with documented UTI

	Group 1 ($n = 27$) median (range)	Group 2 ($n = 30$) median (range)	P value
Leukocyte count (/μl)	19,000 (8,000–27,000)	12,750/(4,500–23,500)	0.056
ESR (mm/h)	40 (27–98)	17.5 (2–75)	<0.001
CRP (mg/dl)	9 (1.9–35)	0.5 (0.1–6.5)	<0.001
PCT (ng/ml)	4.8 (0.5–13.2)	0.3 (0.1–0.9)	<0.001

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; PCT, procalcitonin

Data are expressed as medians with ranges for quantitative variables and as frequencies and percentages for qualitative variables

statistical significance was not reached (median 19,000 vs. 12,750/μl; $P = 0.056$). On the other hand, ESR was significantly higher in children with UUTI (median 40 vs. 17.5 mm/h; $P < 0.001$). CRP serum concentrations were also significantly higher in children with UUTI (median 9 vs. 0.5 mg/dl; $P < 0.001$) respectively. Finally, PCT serum concentrations were significantly higher in children with UUTI (median 4.8 vs. 0.3 ng/ml; $P < 0.001$) respectively (Table 2).

Figure 2 shows the ROC curves for the sensitivity and specificity of ESR, CRP, and PCT measurements. The area under the ROC curve for ESR was 0.883 (95% CI, 0.797–0.969; $P < 0.001$), for CRP it was 0.957 (95% CI 0.914–1; $P < 0.001$), and for PCT it was 0.988 (95% CI 0.969–1; $P < 0.001$). The characteristics of ESR, CRP, and PCT measurements for the prediction of UUTI are summarized in Table 3. A combined analysis of PCT and CRP revealed that the simultaneous presence of PCT ≥ 0.85 ng/ml and CRP ≥ 3.50 mg/dl had a sensitivity of 78% (95% CI: 57–91%), specificity 100% (95% CI: 88–100%), PPV 100%, NPV 83%, and accuracy 89.5% (51 out of 57 patients) in predicting RPI, i.e., UUTI.

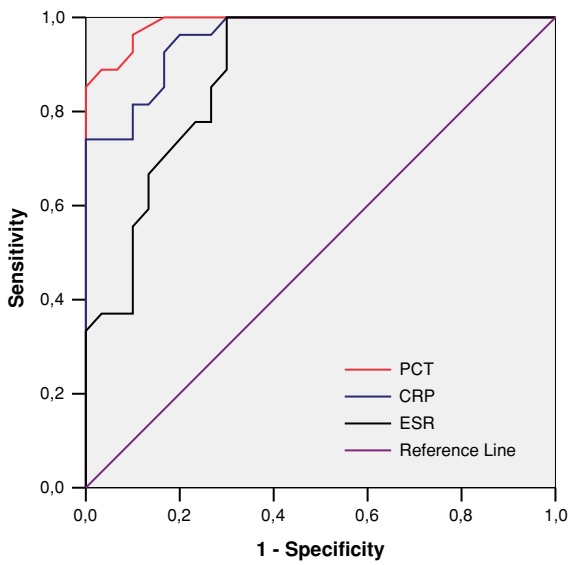

Fig. 2 Receiver operating characteristic (ROC) curve for the specificity and sensitivity of the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and procalcitonin (PCT) measurements. *ESR* area under ROC curve = 0.883 (95% CI, 0.797–0.969), $P < 0.001$;*CRP* area under ROC curve = 0.957 (95% CI, 0.914–1.000), $P < 0.001$; *PCT*area under ROC curve = 0.988 (95% CI, 0.969–1.000),$P < 0.001$

Among the 27 children with UUTI based on abnormal DMSA scans, 15 (55.6%) had an abnormal renal ultrasonogram. Ultasonographic findings suggestive of RPI included hypoechoic and often heterogeneous renal parenchyma, most often unilateral. Interestingly, all children with abnormal renal ultrasonograms were girls, except one. In other words, 14 out of 21 girls with UUTI (66.7%) had an abnormal renal ultrasonogram, while only 1 out of 6 boys with UUTI (16.7%) had an abnormal renal ultrasonogram ($P = 0.026$).

Discussion

In the absence of specific symptomatology, early diagnosis of UUTI is a challenge, particularly during infancy [1–3]. The distinction between upper and lower UTI is necessary, because RPI can induce permanent renal scarring, which may lead to arterial hypertension and chronic renal failure [4, 5]. Therefore, accurate diagnosis of RPI and early treatment is important.

Tc-99m dimercaptosuccinic acid (DMSA) scintigraphy performed during the acute phase of the infection is very sensitive in assessing RPI, with a sensitivity of approximately 93% [6]. However,

Table 3 Characteristics of ESR, CRP, and PCT measurements for the prediction of renal parenchymal involvement (RPI)

	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Overall agreement	Kappa	*P* value
ESR	≥25	100 (87–100)	70 (51–85)	75	100	84.2	0.689	<0.001
	≥30	85 (66–95)	73 (54–87)	74	85	79	0.581	<0.001
	≥35	67 (46–83)	87 (69–96)	82	74	77.2	0.538	<0.001
	≥75	33 (17–54)	100 (88–100)	100	63	68.4	0.345	0.001
CRP	≥1.85	100 (87–100)	70 (51–85)	75	100	84.2	0.689	<0.001
	≥3.50	81 (61–93)	90 (72–97)	88	84	85.9	0.717	<0.001
	≥6.60	74 (54–88)	100 (88–100)	100	81	87.7	0.750	<0.001
PCT	≥0.50	100 (87–100)	83 (65–94)	84	100	91.2	0.826	<0.001
	≥0.85	89 (70–97)	97 (81–100)	96	91	92.9	0.859	<0.001
	≥1.20	85 (65–95)	100 (88–100)	100	88	93	0.858	<0.001

ESR, erythrocyte sedimentation rate in mm/h; CRP, C-reactive protein in mg/dl; PCT, procalcitonin in ng/ml; PPV, positive predictive value; NPV, negative predictive value

factors limiting the widespread use of DMSA scintigraphy include its cost, limited availability, exposure of patients to radiation, and inability to differentiate old scarring from acute RPI unless follow-up DMSA scanning is performed. Follow-up DMSA scintigraphy will be repeated in all our patients 6 months after the first DMSA study. The results will be evaluated and presented in the near future.

In the present study, renal lesions of various sizes were observed on the DMSA scans in 47% of children with a first episode of UTI in the acute phase. The majority in this group of children with presumed UUTI consisted of girls (77.8%). The overall prevalence of UUTI in our study and its higher incidence in girls are in agreement with the literature available [4].

Our results showed that leukocytosis was more prominent in children with RPI, although this did not reach statistical significance. On the other hand, ESR was significantly higher in children with RPI than in children without RPI. However, using ESR as a possible indicator of UUTI was inadequate, since the best performance for all statistical parameters calculated did not exceed >80% for any of the four cut-off values tested. The biochemical markers CRP and PCT correlated well with abnormal results on DMSA scans. More specifically, using three different cut-off values for CRP, the calculated sensitivity, specificity, PPV, and NPV were quite good; the cut-off of 3.5 mg/dl was the best, with values of >80% for all statistical parameters. Regarding PCT, using cut-off values of 0.5, 0.85, and 1.2 ng/ml showed excellent calculated sensitivity, specificity, PPV, and NPV. The cut-off value of 0.85 ng/ml gave the best performance, with values of >88% for all statistical parameters. PCT was superior to CRP as an indicator of RPI, since the ROC curve for the specificity and sensitivity of PCT was higher than that for CRP. Moreover, combining the highest cut-off values for PCT and CRP was not superior to PCT alone in predicting RPI.

We agree with other studies showing the superiority of PCT as an indicator of RPI over CRP [9], although in our study CRP performed better than suggested by published studies. Furthermore, the results of previous studies are consistent with our findings, suggesting that PCT is a reliable marker for detecting RPI during UTI in children [10–16]. However, two studies showed that PCT is not a sensitive and specific measure for the early diagnosis of UUTI (Table 4) [17, 18].

The seemingly dissimilar results among different studies dealing with the same issue may be due to age and sex differences in the underlying populations studied and/or the techniques used to diagnose a UTI. For this reason, it is essential for future studies to consistently utilize the best available technique to diagnose UTI, i.e., SPA or bladder catheterization, as recommended by the American Academy of Pediatrics [19]. This would minimize diagnostic biases. Another reason for the discrepancies between the various studies is that the methodologies used to choose different cut-off values for PCT and/or CRP

Table 4 Parameters of procalcitonin for predicting renal parenchymal involvement in children with a first episode of UTI, as assessed by DMSA scintigraphy

References	Number of patients	Cut-off (ng/ml)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
[12]	80	0.5	70.3	82.6	85.7	97.6
[10]	54	0.5	74	85	89	
[13]	64	0.5	94.1	89.7		
[14]	77	1.0	92.3	61.9	32	97.5
[11]	100	0.8	83.3	93.6	93.7	83.0
[16]	42	0.5	100	87	86	100
[15]	76	0.5	58	76		
Present study	57	0.85	89	97	56	91
[17][a]	63	0.5	68	23		
[18][a]	33	0.96	86.4	36.4	47.6	75.0

[a] Studies that have shown PCT to have low accuracy in detecting RPI

PPV, positive predictive value; NPV, negative predictive value

are not always clearly mentioned. Hence, the sensitivity, specificity, and predictive values of PCT and/or CRP among similar studies appear different, when in fact the results are comparable [20]. Keeping these in mind, we do acknowledge that the serum CRP performed better in our study than previously described as a marker for differentiating upper from lower UTI, showing a specificity of $\geq$70%, which has not previously been seen.

The majority of patients with UUTI in our study (55.6%) had an abnormal renal DMSA cortical scan and in detecting obstructive uropathy that may be associated with UTI, renal sonography has low sensitivity for the detection of acute inflammatory changes of the renal cortex. In a study of 52 children with a first-time documented RPI, cortical scintigraphy showed renal lesions in 41 children (78.8%), while ultrasonography was normal in all children with normal renal scintigraphy and detected renal abnormalities in only 16 out of 41 children (39%) with abnormal scintigraphy ($P < 0.0001$) [21]. In another study the sensitivity of ultrasonography for detecting APN, as identified by DMSA renal scans, was 49.2% [22]. Hence, our results are comparable to the published experience, showing that renal ultrasonography is relatively insensitive in documenting RPI in UTI and is inadequate for the detection of renal scars [23].

In conclusion, although our study is in progress, it indicates that PCT is a reliable biological marker, with higher sensitivity and specificity than CRP for the prediction of RPI after a first episode of UTI in infants and children. However, in our study CRP performed quite well, showing higher specificity and predictive values than in previous studies. Nevertheless, serum PCT appears to be the most valuable marker for the accurate diagnosis of UUTI in infants and children.

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