Procalcitonin is a Predictor for High-Grade Vesicoureteral Reflux in Children: Meta-Analysis of Individual Patient Data

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Objective To assess the predictive value of procalcitonin, a serum inflammatory marker, in the identification of children with first urinary tract infection (UTI) who might have high-grade (≥3) vesicoureteral reflux (VUR).

Study design We conducted a meta-analysis of individual data, including all series of children aged 1 month to 4 years with a first UTI, a procalcitonin (PCT) level measurement, cystograms, and an early dimercaptosuccinic acid scan.

Results Of the 152 relevant identified articles, 12 studies representing 526 patients (10% with VUR ≥3) were included. PCT level was associated with VUR ≥3 as a continuous ($P = .001$), and as a binary variable, with a 0.5 ng/mL preferred threshold (adjusted OR, 2.5; 95% CI, 1.1 to 5.4). The sensitivity of PCT ≥0.5 ng/mL was 83% (95% CI, 71 to 91) with 43% specificity rate (95% CI, 38 to 47). In the subgroup of children with a positive results on dimercaptosuccinic acid scan, PCT ≥0.5 ng/mL was also associated with high-grade VUR (adjusted OR, 4.8; 95% CI, 1.3 to 17.6).

Conclusions We confirmed that PCT is a sensitive and validated predictor strongly associated with VUR ≥3, regardless of the presence of early renal parenchymal involvement in children with a first UTI. *(J Pediatr 2011;159:644-51)*.

Approximately 30% of children with urinary tract infections (UTIs) will be diagnosed with vesicoureteral reflux (VUR), which is thought to result in recurring UTIs, renal scarring, hypertension, and renal failure.[1,2] Accordingly, in the past decade, European and American pediatric societies have recommended cystography after a first febrile UTI.[3-7] However, this strategy is truly non-selective, painful,[8] irradiating,[9] and expensive,[10] with a risk of iatrogenic UTI.[11] Moreover, recent publications report the absence of any real benefit to treating low-grade VUR (grade ≤2)[12-15] and its high rate of spontaneous resolution.[16] Newer guidelines have thus recommended that cystography never be performed after a first febrile UTI,[17] raising some concerns[18] on the basis of the risks of diagnosis delay of high-grade VUR, which is more particularly related to recurring UTI.[2]

An intermediate evidence-based strategy thus could be useful for predicting high-grade VUR (grade ≥3) and make it possible to avoid cystograms that are a posteriori unnecessary, because they are without any therapeutic consequences, while missing the fewest possible patients.[19] Procalcitonin (PCT), a sensitive and specific marker of bacterial infections,[20] has been found to be and validated as a strong and sensitive predictor of high-grade VUR.[21,22] However, PCT was also found to be associated with renal parenchymal involvement,[23-26] and the relationship between high-grade VUR and PCT level might be biased by the results of an early dimercaptosuccinic acid (DMSA) scan, which is considered the gold standard for diagnosing acute pyelonephritis.[27] Therefore, we set out to validate the predictive ability of high serum PCT for high-grade VUR when taking early renal parenchymal involvement into account. We performed such a validation conducting a systematic review and meta-analysis of individual patient data to gather the published data on UTI, VUR,

DMSA	Dimercaptosuccinic acid
PCT	Procalcitonin
ROC	Receiver operating characteristic
UTI	Urinary tract infection
VUR	Vesicoureteral reflux

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PCT, and renal parenchymal involvement in children in the largest existing dataset and address our research question.

Methods

We performed a systematic review and meta-analysis of individual patient data on the basis of published cohort studies of children with UTI and a PCT level measurement, in accordance with the Centre for Reviews and Dissemination guidelines for undertaking systematic reviews.[28]

Data Source

We searched Medline for all studies published from January 1993 through May 2008 of first febrile UTI with a PCT level measurement in children. The search strategy used medical subject heading terms and text words, including "procalcitonin" and "child." This computerized search was supplemented by a manual review of the reference lists of all papers and review articles included and a separate search for any papers thus identified, a manual review of abstracts from the Interscience Conference on Antimicrobial Agents and Chemotherapy, the Infectious Diseases Society of America, the European Society for Paediatric Nephrology, and the International Congress of Pediatrics from 1994 to 2008, a manual revision of abstracts of Pediatrics Academic Societies, American Society of Nephrology from 2002 and 2008, and by discussion with 3 experts in the field. No language restriction was used. One reviewer (S.L.) screened the titles and abstracts from the electronic searches against the inclusion and exclusion criteria. In case of insufficient information to make a decision, the full article was read and, when necessary, discussed with a second reviewer (M.C.) until a decision was reached.

Eligibility of Studies and Patients

We included all articles that met these criteria: a cohort of consecutively included children with a first febrile UTI, a PCT measurement, and an early renal DMSA scintigraphy performed within 7 days after diagnosis of febrile UTI. The corresponding authors of each article were contacted first with e-mail (twice when necessary) and with a phone call. We asked the authors to send us the data files of their already published study (and we discarded duplicates in cases of double publication). The analysis was based on the data of all consecutive children aged 1 month to 4 years admitted with a first febrile UTI and an early DMSA scintigraphy performed. Febrile UTI was defined as a rectal temperature $\geq$38°C associated with a positive results on a bacterial urine culture the thresholds used by each center to define a positive bacterial urine culture according to the collection method chosen are given in (Table I). Children with a known uropathy at the time of the UTI diagnosis and children who had received antibiotics in the 48 hours before diagnosis were not included.

Data Collection

Information was collected about each center's techniques for urine collection, PCT measurement, and cystography. Each center sent an electronic file containing the data of patients in their published study, from which we extracted the clinical (sex, age, and first-degree family history of uropathy), laboratory (C-reactive protein level, PCT level), and radiological data (urinary tract dilation on ultrasound scanning, parenchymal involvement on the DMSA scintigraphy, and presence and grade of VUR on fluoroscopic cystography) for this study.

Quality Assessment

The methodological quality of each study was assessed with a checklist, adapted from the criteria in the Douglas Altman framework and the quality assessment tool for diagnostic studies.[29] Details of the methodological assessment are shown in Table II (available at www.jpeds.com).

Outcome Definition

All patients underwent a voiding cystogram, the gold-standard examination for the diagnosis and classification of VUR. Cystogram results were read according to the International System of Radiological Grading of Vesicoureteric Reflux[30] by a senior radiologist blinded to PCT level and renal ultrasound scanning findings. High-grade VUR was defined as a VUR grade $\geq$3.[31]

Definition of the Potential Predictor and Other Variables

The predictive variable was PCT level, both considered as a continuous variable, and dichotomized (by using the previously proposed cutoff points of 0.5 ng/mL[22,32] 1 ng/mL,[24-26] and 2 ng/mL[25,26,33]). PCT level was measured at admission for febrile UTI. All risk factors for VUR previously described in the literature were considered to be potential confounders: family history of uropathy (obstructive uropathy or vesicoureteral reflux of febrile UTI in parents or siblings[2]), young age,[2] male sex,[2] serum C-reactive protein level at admission,[34] and urinary tract dilation[34] (defined as renal pelvic dilation, ureteral dilation, or both) on ultrasound scanning and identified by a senior pediatric radiologist. The binary variables were coded as: first-degree family history of uropathy (coded as 1), no such history (coded as 0)[2]; boy (coded as 1), girl (coded as 0)[2]; presence of urinary tract dilation on renal ultrasound scanning (coded as 1), no such dilation (coded as 0)[34]; and the presence or absence of renal parenchymal involvement on DMSA scans performed in the 7 days after admission and analyzed according to Benador's classification.[35] The other variables (age and C-reactive protein level) were considered to be continuous, as recommended.[36]

Statistical Analysis

We first described the general characteristics of the population and compared them in centers with a χ^2 test or a nonparametric Kruskal-Wallis test. We then analyzed the relationship of high-grade VUR to PCT and to all the other co-variables in turn, by using a multilevel logistic-regression model (with centers as the group level variable). When the relationship between high-grade VUR and continuous variables

Table I. Population characteristics according to center

Center*	Urine collection techniques (threshold of the positive bacteriuria)†	n	Male	Age	CRP	VUR	VUR ≥3	DMSA lesions
Centres using SA or UC								
Afula-Israel [10]	SA (10^1), UC (10^3)	56	16 (29)	15.0 (7.0-25.5)	86 (58-124)	14 (25)	6 (11)	15 (27)
Athens-Greece [11]	SA (10^3), UC (10^4), CVM (10^5)	36	15 (42)	7.2 (3.6-10.7)	66 (28-135)	6 (17)	5 (14)	16 (44)
Barcelona-Sp. [4,5]	UC (5.10^4)	58	23 (40)	5.0 (3.0-9.0)	40 (13-62)	14 (24)	4 (7)	35 (60)
Firat-Turkey [8]	UC (10^3), CVM (10^5)	52	25 (48)	16.0 (10.0-30.0)	13 (4-40)	3 (6)	0 (0)	20 (38)
Geneva-Switz [6,7]	SA (10^1), UC (10^3), CVM (10^5)	77	29 (38)	10.2 (4.7-16.5)	71 (30-152)	22 (29)	10 (13)	58 (75)
Udine-Italy [9]	UC (5.10^4), CVM (10^5)	80	27 (34)	7.0 (3.5-5.0)	61 (32-100)	15 (19)	9 (11)	55 (69)
Yvoir-Belgium[12]	SA (10^3), UC (5.10^4), CVM (10^5)	33	9 (27)	19.0 (7.0-24.0)	130 (79-196)	7 (21)	4 (12)	24 (73)
Total for those centers		392	144 (37)	9.5 (4.3-19.2)	60 (25-115)	81 (21)	38 (10)	223 (57)
Centres using SB								
Lille-Fance [3]	SB (10^5), CVM (10^5)	24	7 (29)	8.5 (4.0-19.0)	53 (19-83)	14 (58)	3 (13)	14 (58)
Padova-Italy [1]	SB (10^5), CVM (10^5)	50	18 (36)	6.4 (3.5-11.4)	61 (37-120)	11 (22)	2 (4)	41 (82)
Toulouse-Fr. [2]	SB (10^5), CVM (10^5)	60	15 (25)	10.6 (5.8-20.1)	98 (59-133)	26 (43)	10 (17)	44 (73)
Total for those centers		134	40 (30)	8.7 (4.4-15.8)	70 (37-120)	51 (38)	15 (11)	99 (73)
Between-center variability *(P)*			.3	<.001	<.001	<.001	<.001	<.001
Between-urine collection technique variability *(P)*‡			.1	.5	.02	<.001	.6	<.001
Total		526	184 (35)	9.0 (4.4-18.0)	62 (30-115)	132 (25)	53 (10)	322 (61)

CRP, C-reactive protein; *CVM,* clean-voided midstream; *SA,* suprapubic aspiration; *SB,* sterile bag; *UC,* urethral catheterization; *UT,* urinary tract.
Values are expressed as n (%) for all binary variables, and as median (25th-75th percentiles) for continuous variables (age, CRP). Age was expressed in months, and CRP in mg/L. *P* values were calculated with the χ^2 test for binary variables and with the non-parametric Kruskal-Wallis test for continuous variables (age, CRP). The references were those corresponding to the publication of each study center, provided in the supplementary (**Appendix**).
*Classified according to the urine collection technique in non-toilet-trained children.
†In colony-forming units/mL.
‡Comparison between centers using UC, SA, or CVM and centers using SB or CVM.

(PCT, C-reactive protein, and age) was not linear, these variables were transformed into a fractional polynomial of the lowest degree possible. Variables were entered into the multivariate model, after checking for potential co-linearity. Variables for which >10% of the data was missing were not entered in the multivariate model. A backward stepwise elimination modeling technique was used, with a significance limit for removal from the model of a *P* value >.05 and maximum likelihood ratio estimates. Several separate models were built, depending on whether PCT was considered to be a continuous or a binary variable (one model for each of the previously defined thresholds). The analyses were performed for all patients and then for the subgroup of children with a positive results on an early DMSA scan. The final accuracy of PCT level as a continuous variable to discriminate patients with and without high-grade VUR was evaluated by the area under the receiver operating characteristic (ROC) curve. The accuracy of PCT considered to be a binary variable dichotomized according to previously defined thresholds was determined by calculating sensitivity, specificity, positive and negative predictive values, and positive and negative LRs. Post-test probabilities were evaluated on the basis of LR, and VUR prevalences were evaluated with the Fagan diagram. Statistical analysis was performed with Stata/SE software version 10 (StataCorp, College Station, Texas) and Confidence Interval Analysis software (British Medical Association, London, United Kingdom).[37]

Results

Study Characteristics

We retrieved 149 abstracts by electronic-searching; 19 were considered potentially suitable, as shown in the flow chart (**Figure 1**; available at www.jpeds.com). We found one more study by hand-searching and two others by asking experts. After full text review, 8 studies were not included: 5 because there was no early DMSA scan and 3 because the data were not original. Fourteen articles were considered for inclusion, and the 12 corresponding study centers were contacted; 11 agreed to participate, and one did not meet the criterion of consecutiveness (references are available in the **Appendix**; available at www.jpeds.com). In the end, 10 centers including 656 patients who fully met our inclusion criteria (children aged 1 month to 4 years, first febrile UTI), participated in the study. All centers had a high methodological quality (**Table II**). Seven of the 10 centers collected urine samples with gold standard methods (suprapubic aspiration, urethral catheterization for non-toilet–trained children, and clean-voided midstream for the other patients). All centers measured PCT level with the LUMItest PCT immunoluminometric assay or the BRAHMS PCT-Q semiquantitative rapid test (BRAHMS, Hennigsdorf, Germany) and used fluoroscopic cystography to diagnose VUR. All centers included hospitalized children with UTI. **Table I** provides details on the characteristics of the population at each center.

The first multicenter study included 8 centers and 398 patients.[22] Part of this study was included again in this meta-analysis on individual patient data (4 centers, 246 patients) because these centers performed early DMSA scan.[22] Six centers were newly included, representing 280 patients (53% of the included patients).

Of the 656 children (**Figure 2**; available at www.jpeds.com), 53 (8%) were lost to follow-up before cystography and 51 (8%) were lost to follow-up before the early DMSA scan, and PCT values on admission were unavailable for 26

Table III. Relationships between high-grade vesicoureteral reflux and variables

Variable	VUR < 3 n (%)	VUR ≥ 3 n (%)	OR (95% CI)	P	Adjusted OR (95% CI)†	P†
PCT as a dichotomized variable with a threshold of 0.5 ng/mL (n = 526)*						
≥0.5	272 (58)	44 (83)	3.6 (1.7-7.9)	.001	2.5 (1.1-5.4)	.03
<0.5	201 (42)	9 (17)	1		1	
PCT as a dichotomized variable with a threshold of 1.0 ng/mL (n = 519)*						
≥1	201 (43)	39 (74)	3.7 (1.6-8.6)	.03	3.5 (1.4-8.3)	.005
<1	265 (57)	14 (26)	1		1	
PCT as a dichotomized variable with a threshold of 2.0 ng/mL (n = 526)*						
≥2	134 (28)	31 (58)	3.6 (1.8-7.0)	<.001	2.5 (1.1-5.5)	.02
<2	339 (72)	22 (42)	1		1	
PCT as a continuous variable (transformed in FP1–n = 485)*‡			−0.24(−0.36-−0.12)	.001	−0.23(−0.35-−0.11)	.001
Family history of uropathy (n = 363)						
Yes	20 (6)	1 (2)	0.4 (0.0-1.4)	.4	–§	
No	302 (94)	40 (98)	1			
Sex (n = 526)						
Boy	168 (36)	16 (30)	0.8 (0.4-1.4)	.4	0.7 (0.4-1.6)¶	.4
Girl	305 (64)	37 (70)	1			
Urinary tract dilation on ultrasound scanning (n = 512)						
Yes	60 (13)	19 (38)	4.1 (1.6-10.2)	.002	4.3 (1.8-9.8)¶	.001
No	402 (87)	31 (62)	1			
Positive early DMSA scan results (n = 526)						
Yes	277 (59)	45 (85)	4.0 (1.6-9.8)	.003	2.6 (1.2-5.6)¶	.01
No	196 (41)	8 (15)	1			
Age** (n = 526)			0.02 (−0.05-0.004)	.1	−0.02 (−0.04-0.01)¶	.2
CRP** (n = 517)			0.004 (0.000-0.008)	.04	0.001 (−0.002-0.006)¶	.4

FP, Fractional polynomial; *CRP*, C-reactive protein.
PCT is expressed in ng/mL; CRP is expressed in mg/L.
*The sample sizes for each variable differed because PCT measurement was not available for all thresholds (see text).
†Adjusted OR was calculated for each variable from the full multivariate logistic-regression model (including PCT—one model was built for each different threshold or as a continuous variable, sex, urinary tract dilation on renal ultrasound scanning, the presence of early DMSA renal parenchymal lesions, age, and CRP). The sample size for each multivariate logistic regression model differed: n = 512 for PCT as a dichotomized variable with a threshold of 0.5 ng/mL, n = 497 for PCT as a dichotomized variable with a threshold of 1 ng/mL, n = 504 for PCT as a dichotomized variable with a threshold of 2 ng/mL, and n = 481 for PCT as a continuous variable.
‡Coefficient for PCT, calculated from the logistic regression equation. The FP1 transformation used for PCT was: (PCT/100)^(-0.38) − 3.37.
§This variable was dropped from the model because >10% of data was missing.
¶For variables different from PCT (ie, sex, urinary tract dilation on ultrasound scanning, the presence of early DMSA renal parenchymal lesions, age, and CRP), the adjusted OR came from the full multivariate logistic-regression model including PCT as a dichotomized variable at 0.5 ng/mL threshold.
**These variables are continuous, results are given as mean (± SD) for the two first columns, and then as regression coefficients (with 95% CI). Because the relationships between high-grade VUR and those variables were linear, no transformation was needed.

other children (4%); the analysis was therefore based on 526 patients (80%). Analysis of PCT as a continuous variable involved only 495 patients (94%), however, because PCT level was measured with the PCT-Q semiquantitative test for 31 patients. For the same reason, analysis of PCT level at the 1 ng/mL threshold covered only 519 patients (99%).

Population Characteristics

The children's mean age was 13.0 months (SD, 11.2; median, 9.0; IQR, 4.4 to 18.0); 184 children (35%) were boys. A family history of uropathy was reported for 21 of the 363 patients (6%) for whom this information was available, and with ultrasound scanning, urinary tract dilation was shown in 79 patients (15%). Lesions on early DMSA scintigraphy were found in 322 patients (61%). VUR was diagnosed in 132 children (25%) and was high-grade in 53 children (10%). The characteristics of the 130 children not included because they were lost to follow-up before examinations (cytography, DMSA scan, or PCT) were: 62 (48%) were boys, the mean age was 9.3 months (SD, 9.6 months; median, 5.5 months; IQR, 3.1 to 11.0 months).

Procalcitonin

Table III shows the crude and adjusted relationships between high-grade VUR and PCT. Because the relationship between high-grade VUR and PCT as a continuous variable was not linear ($P < .001$), it was transformed into a first-degree fractional polynomial and was significantly associated with high-grade VUR, as was PCT as a binary variable according to the defined thresholds (Table III). Urinary tract dilation on renal ultrasound scanning, early renal parenchymal involvement on DMSA scan, and C-reactive protien level

Table IV. Discriminative ability of procalcitonin for high-grade vesicoureteral reflux prediction

	PCT ≥0.5 ng/mL	PCT ≥1.0 ng/mL	PCT ≥2.0 ng/mL
Overall study population*			
Sensitivity	83 (71-91)	74 (60-84)	59 (45-71)
Specificity	43 (38-47)	57 (52-61)	72 (67-76)
PPV	14 (11-18)	16 (12-21)	19 (14-25)
NPV	96 (92-98)	95 (92-97)	94 (91-96)
Positive LR	1.4 (1.3-1.7)	1.7 (1.4-2.1)	2.1 (1.6-2.7)
Negative LR	0.4 (0.2-0.7)	0.5 (0.3-0.7)	0.6 (0.4-0.8)
Subgroup of children with early renal parenchymal involvement†			
Sensitivity	93 (82-98)	82 (69-91)	67 (52-79)
Specificity	27 (22-33)	39 (33-45)	57 (52-63)
PPV	17 (13-22)	18 (13-24)	20 (15-28)
NPV	96 (89-99)	93 (87-96)	91 (86-95)
Positive LR	1.3 (1.2-1.4)	1.3 (1.1-1.6)	1.6 (1.2-2.0)
Negative LR	0.4 (0.1-0.7)	0.5 (0.2-0.9)	0.6 (0.4-0.9)

All discriminative values are expressed in percentages (95% CI).
NPV, negative predictive value; *PPV*, positive predictive value.
*The sample size was n = 526 (high-grade VUR prevalence = 10%) for PCT ≥0.5 ng/mL and for PCT ≥2.0 ng/mL, n = 519 (high-grade VUR prevalence = 10%) for PCT≥ 1.0 ng/mL.
†The sample size was n = 322 (high-grade VUR prevalence = 14%) for PCT ≥0.5 ng/mL and for PCT ≥2.0 ng/mL, n = 321 (high-grade VUR prevalence = 14%) for PCT≥1.0 ng/mL.

(for which no transformation was needed) were also related to high-grade VUR in the univariate analysis (Table III). Because there was no co-linearity, all co-variables (except family history, because data were missing for 31% of patients) were entered in the multivariate logistic regression model. After a stepwise reduction procedure, PCT remained significantly associated with high-grade VUR, as both a continuous and a binary variable and regardless of the threshold (Table III). Urinary tract dilation on renal ultrasound scanning and early renal parenchymal involvement were also independently related to high-grade VUR, whereas C-reactive protein level was not (Table III). The area under the ROC curve for PCT was 0.71 (95% CI, 0.64 to 0.78). The accuracy of PCT as a binary variable according to thresholds is presented in Table IV. A PCT level ≥0.5 ng/mL had a sensitivity of 83% (95% CI, 71 to 91) and a specificity of 43% (95% CI, 38 to 47) for the prediction of high-grade VUR. The negative predictive values were high regardless of the threshold (94% to 96%), indicating that approximately 5% of patients with a low PCT level (depending on the threshold used) would have had a misdiagnosis when they actually had high-grade VUR (Table IV). Eight patients with high-grade VUR had a misdiagnosis with a PCT level <0.5 ng/mL (Figure 3): 7 had grade 3 VUR, including two with grade 2 DMSA lesions according to Benador's classification,[35] and one with grade 4 VUR and grade 3 DMSA lesions. The negative LRs ranged from 0.4 to 0.6 (Table IV), meaning that the pre-test probability (10%) decreased to approximately 4% post-test probability. Urinary tract dilation on renal ultrasound scanning had a sensitivity rate of 38% (95% CI, 26 to 52), and a specificity rate of 87% (95% CI, 84 to 90).

In the subgroup of children with positive results on early DMSA scan (n = 322), 97 (30%) had VUR of any grade, including 45 (14%) with high-grade VUR. PCT was significantly associated with high-grade VUR as a continuous variable after transformation into a second-degree fractional polynomial ($P = .009$) and as a binary variable regardless of threshold (Table V; available at www.jpeds.com). PCT remained significantly associated with high-grade VUR after adjustment for all co-variables (except family history, which was not entered in the multivariate model because of missing data; Table V). Urinary tract dilation on renal ultrasound scanning was related to high-grade VUR in the univariate and multivariate analyses (Table V). The sensitivity rate of PCT in this subgroup was higher than that in the overall population, and the specificity rate was lower (Table IV). The negative predictive values remained high regardless of the threshold (91% to 96%; Table IV). The negative LRs ranged from 0.4 to 0.6 (Table IV), meaning that the pre-test probability (14%) decreased to approximately 5% post-test probability. Three children with high-grade VUR had a misdiagnosis with a PCT level <0.5 ng/mL: two had grade 3 VUR, including one with grade 2 DMSA lesions, and the third was the same child previously missed in the overall population with grade 4 VUR.

Discussion

Serum PCT concentration is a sensitive predictor strongly and independently associated with high-grade VUR, even after consideration of early renal parenchymal involvement, taking into account as a potential confounder in the multivariate analysis and in the subgroup analysis of children with acute pyelonephritis proven with DMSA. This adds evidence to earlier findings from a multicenter study, in which DMSA was not performed in all patients,[22] and definitively demonstrated that PCT is a predictor of VUR independently of its relationship with early parenchymal involvement, contrary to the concerns raised by Chevalier et al.[27]

The best threshold for the fewest possible misdiagnoses appeared to be 0.5 ng/mL, which is also the previously defined threshold.[21,22] The discriminating power of a serum PCT level ≥0.5 ng/mL was consistent with the findings from earlier single-center and multicenter studies.[22,32] It offered a sensitivity rate of 83% (95% CI, 71 to 91) and a specificity rate of 43% (95% CI, 38 to 47) for high-grade VUR. The high negative predictive value indicates that approximately 5% of patients with a PCT level <0.5 ng/mL would have been misdiagnosed and actually had high-grade VUR. The design of the study, a meta-analysis of individual patient data, allowed us to draw conclusions without the usual threshold effect that affects diagnostic accuracy meta-analysis and confuses results.

PCT, the prohormone of calcitonin, is an early, sensitive, and specific marker of bacterial infection.[20] However, its role in inflammatory response and in the cytokine cascade remains unknown.[20] In febrile UTI, a high PCT concentration is a validated predictor of acute pyelonephritis[23-26,38] and of late renal scarring.[23,24] This strong relationship made it important to take early renal parenchymal involvement into account in studying the association between high-grade

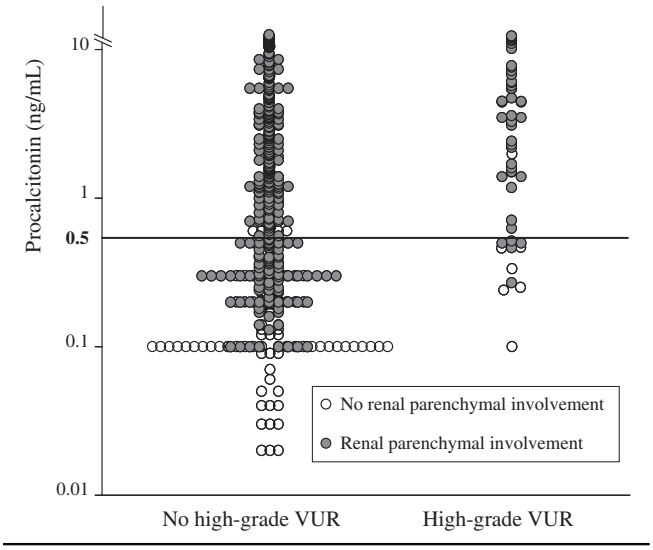

Figure 3. Distribution of PCT values according to the presence of high-grade VUR. The *horizontal line* corresponds to the proposed best threshold.

VUR and PCT to reach a definitive conclusion about this association in patients with DMSA-proven acute pyelonephritis, especially after the association was questioned.[27]

However, several limitations in this study must be addressed. First, the study design, a systematic review and meta-analysis, might have led to several biases. Despite the extensive electronic and hand-searches performed, completed by a hand-search of the gray literature, a publication bias is possible because test accuracy studies, because they are more easily conducted and abandoned than randomized controlled trials, may be particularly susceptible to publication bias.[39] However, because of the limitations of current knowledge about the precise effects of publication bias on meta-analytic estimates and how to measure it,[40] its assessment in reviews of test accuracy is complex, and we provide no estimates of the effect of a probable publication bias. Second, another limitation is that center inclusion was based on voluntary participation. One center did not respond to our request, possibly because their data had not yet been published, but their findings were consistent with those of the studies included here; the authors demonstrated in a prospective cohort study of 57 children that PCT was a specific and sensitive predictor of early renal parenchymal involvement and correlated with its grade (**Appendix**). Another study was not included because children did not undergo systematic cystography, but those authors demonstrated in a prospective cohort study of 33 patients that the mean PCT concentration was higher in the children with early renal parenchymal involvement than children without it (1.2 ng/mL; SD, 1.2 versus 0.8 ng/mL, SD, 0.8; **Appendix**). Participation bias thus seems unlikely. Third, in our meta-analysis of individual patient data, 104 patients (16%) were lost to follow-up before early DMSA or cystography could be performed, and PCT values at admission were unavailable for 26 patients (4%). This rate is close to that reported in other studies.[31] Fourth, classification bias seems unlikely because PCT was measured with validated techniques (immunoluminometric assay or semi-quantitative PCT-Q assay), while blinded to the outcome. Fifth, we took into account the potential heterogeneity caused by pooling data from different centers by analyzing the data as hierarchical. We chose to analyze the dataset as a meta-analysis of individual patient data, because this provides the least biased and most reliable means of addressing the questions.[41] Finally, we did not comply with the standard rule of 10 outcome events per predictor variable (we had 53 events for 7 variables). However, recent publications indicate that this rule can be relaxed to 7 outcome events per variable without a major effect on CI coverage, type I error, relative bias, or measurement of model performance.[42]

Three centers used sterile bags to collect urine in non-toilet trained children, which is not the recommended method.[3] This could have led to selection bias, increasing the number of false-positive results for UTI and overestimating in particular the relationship between high-grade VUR and PCT. However, the percents of VUR and early parenchymal lesions on DMSA were significantly higher in children for whom urine was collected by using sterile bags than in children for whom urine was collected with a proper technique (**Table I**). Moreover, the relationship between high-grade VUR and PCT remained significant, with a higher sensitivity in the subgroup of children for whom acute pyelonephritis was confirmed with early DMSA. In addition, the inclusion of only hospitalized children by the centers might have led to a selection bias, because they included only the sickest children. However, children aged 1 month to 4 years with a first febrile UTI were systematically hospitalized in the centers included. So selection biases seem unlikely. The absence of earlier negative results of DMSA scintigraphy might also have introduced a selection bias. There is a strong association between urinary tract malformations and dysplastic kidneys, known as CAKUT (Congenital Anomalies of the Kidney and Urinary Tract),[43] caused by a single disorder of the embryonic development of the kidney and urinary tract. Thus, these patients, in whom acute pyelonephritis would not have been diagnosed if the DMSA scintigraphy results would have been the same at the time of the febrile UTI as the earlier results, were included in our study. However, we probably did not include such patients because they had markedly decreased renal function that was not reported in any of the centers. Lastly, the time from the beginning of the infectious signs that PCT level had been measured was not taken into account, and this might have introduced a bias in the results, more by underestimating the relationship between high-grade VUR and PCT, and thus overestimating the number of children who were thought to have high-grade VUR, because this marker increases from the sixth hour after the beginning of the infectious process and decreases as quickly at the end.

We validate PCT as a predictor for high-grade VUR for an evidence-based strategy between the cystography recommended[3-7] in the past decade and a wait-and-see policy for recurrent UTI proposed in the National Institute for Clinical Excellence guidelines.[17] This marker could misdiagnose high-grade VUR in a very few children, who could thus have cystography at the time of the second UTI. Considering that even high-grade VUR can spontaneously disappear in some cases[44] and that most clinicians do not make any decision about surgery to treat high-grade VUR after the first UTI,[2] very little renal damage is likely before the second UTI. We focus only on high-grade VUR, meaning that cystography should not be performed to diagnose low-grade VUR. The diagnosis of low-grade VUR serves no therapeutic purpose, because its antibiotic prophylaxis has been demonstrated to be equivalent to no treatment.[12-15] Urinary tract dilation was also strongly and independently associated with high-grade VUR, but with a lower sensitivity rate than PCT, as previously demonstrated,[45] meaning that many children with a disease would have received a misdiagnosis. However, the higher specificity rate of this variable could make it an interesting variable for a combination with PCT to increase the global specificity.

PCT thus has a place in an intermediate evidence-based strategy, apart from the current debate over tests for predicting high-grade VUR, and makes it possible to avoid cystographies that have no therapeutic consequences. Combining PCT with other variables, such as ultrasound scanning criteria, might also be pertinent and play a role in a clinical decision rule that allows the prescription of fewer cystographies without misdiagnosis in any patients with high-grade VUR. ■

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Appendix

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Reference of the article whose authors did not respond to the request that they participate in the systematic review.

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Reference of the study that did not met the criterion of consecutive examinations:

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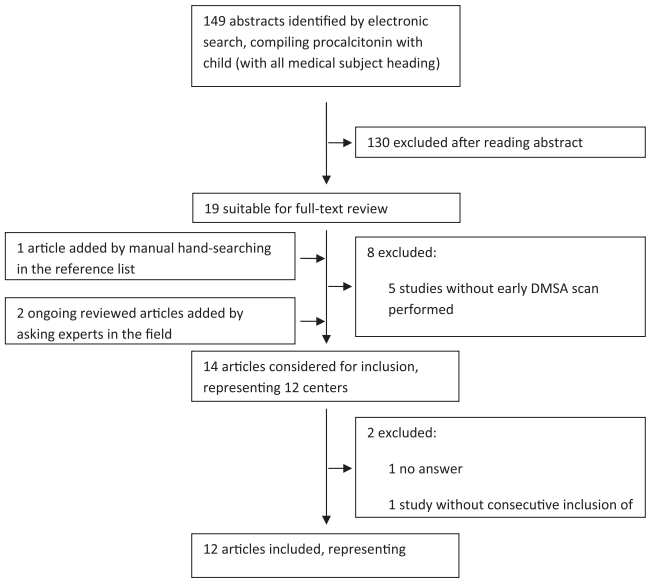

Figure 1. Flow diagram of processes used to select the articles used in this systematic review.

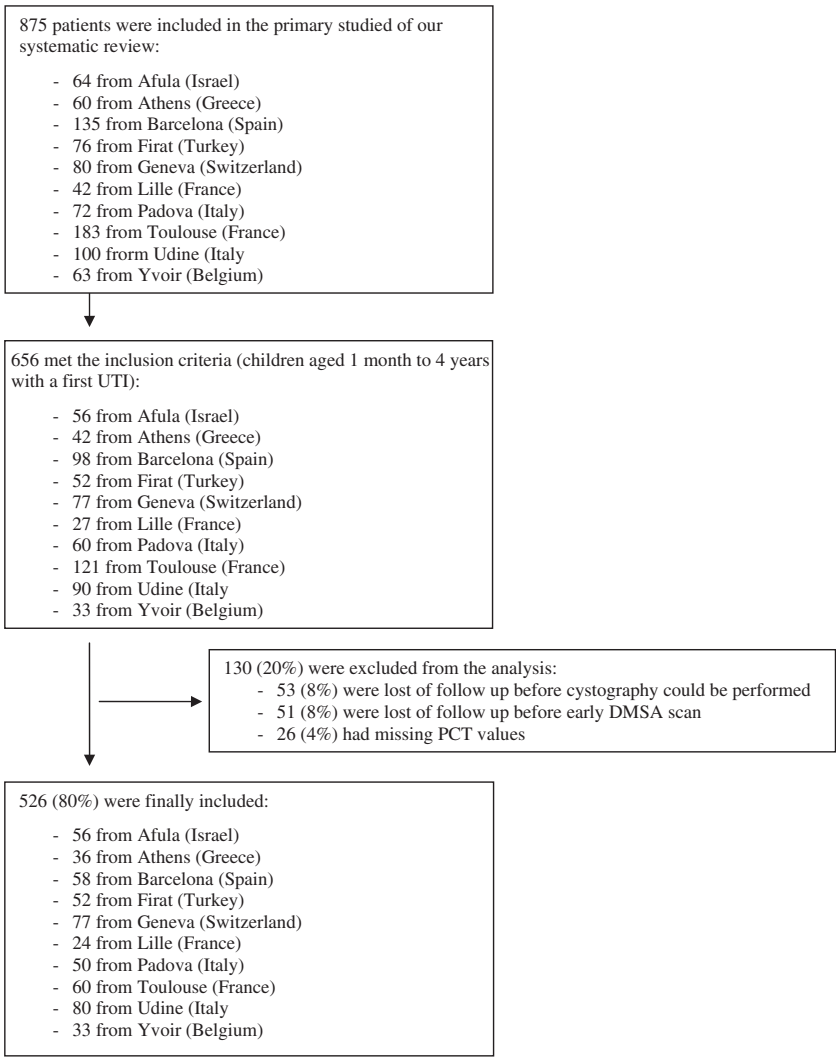

Figure 2. Flow diagram of included patients.

Table II. Quality assessment of the 10 cohort series (from the 12 included studies), by methodological variable

Methodological variable	Information required in each study
Did the result of index test influence whether patients received the reference test (work-up bias)?	All patients should receive reference test regardless of PCT test results
Was the interpretation of the reference test made blinded to the index test?	Diagnosis of VUR was made independent of the result of the PCT test
Description of the reference test	Sufficient details provided in how reflux was diagnosed and classified
	The reference test was objective, unbiased, appropriate and available for all or a high proportion of patients
Description of the index test	Sufficient details provided about how PCT was measured
	PCT was precisely measured and available for all or a high proportion of patients
Description of study population	Sufficient details were provided about the characteristics of the patients included
Method of recruitment	Patients were prospectively or consecutively recruited
	The sample was representative and patients were at a common point of their disease

Table V. Relationship between high-grade vesicoureteral reflux and variables in the subgroup of children with early renal parenchymal involvement

Variable	VUR <3 n (%)	VUR ≥3 n (%)	OR (95% CI)	*P* value	aOR (95% CI)†	*P* value†
PCT as a binary variable with a threshold of 0.5 ng/mL (n = 322)*						
≥0.5	202 (73)	42 (93)	5.2 (1.5-17.9)	.009	4.8 (1.3-17.6)	.02
<0.5	75 (27)	3 (7)	1		1	
PCT as a binary variable with a threshold of 1.0 ng/mL (n = 321)*						
≥1	169 (61)	37 (82)	2.9 (1.0-8.3)	.04	2.7 (1.0-7.6)	.05
<1	107 (39)	8 (18)	1		1	
PCT as a binary variable with a threshold of 2.0 ng/mL (n = 322)*						
≥2	118 (43)	30 (67)	2.7 (1.3-5.5)	.006	2.5 (1.2-5.2)	.02
<2	159 (57)	15 (33)	1		1	
Sex (n = 322)						
Male	86 (31)	14 (31)	1.0 (0.5-1.9)	1.0	0.9 (0.4-1.8)‡	.7
Female	191 (69)	31 (69)	1		1	
UT dilation on renal ultrasound scanning (n = 314)						
Yes	34 (13)	16 (38)	4.3 (1.8-10.2)	.001	4.8 (1.3-17.6)‡	.02
No	238 (87)	26 (62)	1		1	
Age§ (n = 322)			0.001 (−0.002-0.005)	.6	−0.03 (−0.07-0.02)‡	.2
CRP§ (n = 316)			0.001 (−0.07-0.0004)	.5	−0.0006 (−0.004-0.002)‡	.7

aOR, Adjusted OR; *CRP*, C-reactive protein.

PCT is expressed in ng/mL; CRP is expressed in mg/L.

*The sample sizes for each variable differed because PCT measurement was not available for all thresholds (see text).

†aOR was calculated for each variable from the full multivariate logistic-regression model (including PCT—one model was built for each different threshold or as a continuous variable, sex, urinary tract dilation on renal ultrasound scanning, the presence of early DMSA renal parenchymal lesions, age, and CRP). The sample size for each multivariate logistic regression model differed: n = 314 for PCT as a dichotomized variable with a threshold of 0.5 ng/mL, n = 313 for PCT as a dichotomized variable with a threshold of 1 ng/mL, and n = 314 for PCT as a dichotomized variable with a threshold of 2 ng/mL.

‡For variables different from PCT (ie, sex, urinary tract dilation on ultrasound scanning, the presence of early DMSA renal parenchymal lesions, age, and CRP), the aOR came from the full multivariate logistic-regression model including PCT as a dichotomized variable at 0.5 ng/mL threshold.

§These variables are continuous, results are given as mean (± SD) for the two first columns, and then as regression coefficients (with 95% CI). Because the relationships between high-grade VUR and those variables were linear, no transformation was needed.