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Pediatrics 2005;115:e706-e709; originally published online May 2, 2005;

DOI: 10.1542/peds.2004-1631

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American Academy of Pediatrics

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Procalcitonin as a Predictor of Vesicoureteral Reflux in Children With a First Febrile Urinary Tract Infection

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ABSTRACT. *Objective.* A first febrile urinary tract infection leads to the diagnosis of vesicoureteral reflux in 20% to 40% of children. Systematic voiding cystourethrography then is recommended. However, for 60% to 80% of the children, voiding cystourethrography is a posteriori normal. Moreover, it is irradiating, painful, and expensive. Thus, selective approaches are needed. Because procalcitonin has been shown to be associated with severe pyelonephritis and renal scars, which are correlated to vesicoureteral reflux, we analyzed its relationship with vesicoureteral reflux.

Methods. A retrospective hospital-based cohort study included all children who were 1 month to 4 years of age and had a first febrile urinary tract infection. Univariate and multivariate analyses were performed.

Results. Among 136 patients included, 25% had vesicoureteral reflux. The median procalcitonin concentration was significantly higher in children with reflux than in those without (1.2 vs 0.6 ng/mL). High procalcitonin (≥ 0.5 ng/mL) was associated with reflux (odds ratio [OR]: 4.6; 95% confidence interval [CI]: 1.6–16.2). After logistic-regression adjustment for all potential confounders, the association remained significant (OR: 4.9; 95% CI: 1.7–14.0). The relationship was stronger for high-grade (≥ 3) reflux (OR: 8.7; 95% CI: 1.2–382) than low-grade reflux (OR: 3.6; 95% CI: 1.1–15.3). High procalcitonin sensitivities were 85% (95% CI: 70–94) and 92% (95% CI: 65–99) for all-grade and high-grade reflux, respectively, with 44% specificity (95% CI: 35–54).

Conclusion. High procalcitonin is a strong and independent predictor of vesicoureteral reflux and could be used to identify low-risk patients to avoid unnecessary voiding cystourethrography. *Pediatrics* 2005;115:e706–e709. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-1631; children, prediction, procalcitonin, urinary tract infection, vesicoureteral reflux.

ABBREVIATIONS. UTI, urinary tract infection; VUR, vesicoureteral reflux; PCT, procalcitonin; OR, odds ratio; CI, confidence interval.

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Accepted for publication Dec 21, 2004.

doi:10.1542/peds.2004-1631

No conflict of interest declared.

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Urinary tract infection (UTI) is one of the most frequent bacterial infections in children.¹ It has been estimated that 7% of girls and 2% of boys will have a UTI before 6 years of age.² Vesicoureteral reflux (VUR) is diagnosed at the time of the first febrile UTI in 20% to 40% of children.³ VUR is a risk factor for relapsing UTI, renal scarring, hypertension, and renal failure.³ Thus, pediatric societies^{4–6} have recommended systematic voiding cystourethrography after the first febrile UTI in children. However, for 60% to 80% of the children, voiding cystourethrography is a posteriori normal. Moreover, this procedure has been associated with a risk for iatrogenic UTI⁷ and is irradiating, particularly for gonads,⁸ painful,⁹ and expensive.¹⁰ Therefore, it would be useful to be able to predict the absence of VUR so as to avoid unnecessary voiding cystourethrography.⁸

Two predictive tools have been proposed to define selective approaches for voiding cystourethrography. Renal ultrasonography alone, regardless of the criteria chosen, was shown to be poorly sensitive for VUR prediction.^{11–14} A highly sensitive VUR risk score, combining clinical, biological, and radiologic variables, was also proposed,¹⁵ but we have shown that this score was poorly reproducible.¹⁶

Thus, new predictors of VUR after a first febrile UTI are needed to define selective approaches for voiding cystourethrography. Procalcitonin (PCT), a recently identified marker of inflammation,¹⁷ is a candidate because it was shown to be associated with renal scars,^{18,19} which are correlated with VUR.²⁰ The aim of the present study was to analyze the relationship between PCT and VUR at the first febrile UTI in children.

METHODS

Study Design

We conducted a retrospective hospital-based cohort study in the Department of Pediatrics of a Parisian teaching hospital, from January 2000 to September 2003. Data were extracted from medical files by using a standardized data form.

Patients

All patients with UTI as a discharge code or a text word in their computerized hospital records were considered for inclusion. All children who were 1 month to 4 years of age and admitted with a first episode of community-acquired febrile UTI were included. Febrile UTI was defined as a rectal temperature $\geq 38^\circ\text{C}$ associated with a positive bacterial urine monoculture ($\geq 10^5$ colony-forming units per mL in urine collected in sterile bags changed every 30

minutes or by midstream clean-void sample for older toilet-trained children) and a biological inflammatory syndrome (leukocyte count $\geq 15\,000/\text{mm}^3$ and/or C-reactive protein $\geq 15\text{ mg/L}$). Patients with a known uropathy at the time of diagnosis were not included.

Outcome Definition

During the study period, all patients had undergone voiding cystourethrography, performed by a senior pediatric radiologist, who had been blinded to PCT results and potential confounders, and graded from 0 to 5, according to the International System of Radiologic Grading of Vesicoureteric Reflux.²¹ VUR then was classified as no VUR (grade 0), low-grade VUR (grades 1 and 2), and high-grade VUR (grade ≥ 3).^{12,13,20,22}

PCT

At admission, the patient's serum PCT was measured prospectively using the LUMitest PCT immunoluminometric assay (BRAHMS, Hennigsdorf, Germany).

Potential Confounders

All risk factors for VUR previously described in the literature were a priori considered to be potential confounders: family history of uropathy,^{23,24} young age,³ male gender,³ and urinary tract dilation on renal ultrasonography,¹⁴ performed by a senior pediatric radiologist. The variables were dichotomized using previously proposed thresholds, as follows: ≤ 1 year 1, >1 year 0; boys 1, girls 0; first-degree family history of uropathy 1, no such history 0; and urinary tract dilation on renal ultrasonography 1, otherwise 0.

Statistical Analysis

Statistical analyses were performed using EPI INFO software (Centers for Disease Control and Prevention, Atlanta, GA) and Statview software (SAS Institute Inc, Cary, NC). First, we analyzed the distribution of PCT concentrations according to VUR grade. These distributions were compared using the Mann-Whitney non-parametric test. Second, PCT values were dichotomized using as

the threshold the median of the distribution among patients without VUR, rounded off to the nearest half integer. Third, univariate analysis was conducted using the odds ratio (OR) and the χ^2 or Fisher's exact test to evaluate the relationship between high PCT ($\geq 0.5\text{ ng/mL}$) and VUR for all patients and only girls. Fourth, the independence of this relationship was assessed after adjustment for all potential confounders using a logistic-regression model. Fifth, the relationship between high PCT and low-grade or high-grade VUR was examined using the χ^2 test for trend. Sixth, the discriminating power of a high PCT was determined by calculating its sensitivity and specificity for VUR.

RESULTS

A total of 159 patients fulfilled the inclusion criteria. Ten (6%) were lost to follow-up before voiding cystourethrography could be performed. For 13 (8%) others, PCT values at admission were not available. Thus, the analysis was based on 136 (86%) patients.

The median age of the included children was 9.7 months (SD: 8.2); 63 (46%) patients were male. Thirty-two (24%) patients had a family history of uropathy; renal ultrasonography detected a urinary tract dilation in 26 (19%) patients. VUR was diagnosed in 34 (25%) children, including 12 (9%) with high-grade VUR.

The median PCT concentration was significantly higher in children with VUR than in those without (1.2 vs 0.6 ng/mL; $P = .02$; Fig 1). A PCT concentration of 0.5 ng/mL was selected as the threshold for dichotomization for the subsequent analyses (Table 1). Using this PCT threshold ($\geq 0.5\text{ ng/mL}$), the OR between high PCT and VUR was 4.6 (95% confidence interval [CI]: 1.6–16.2; $P = .002$) for the entire population and 3.4 (95% CI: 1.0–13.1; $P = .04$) for female

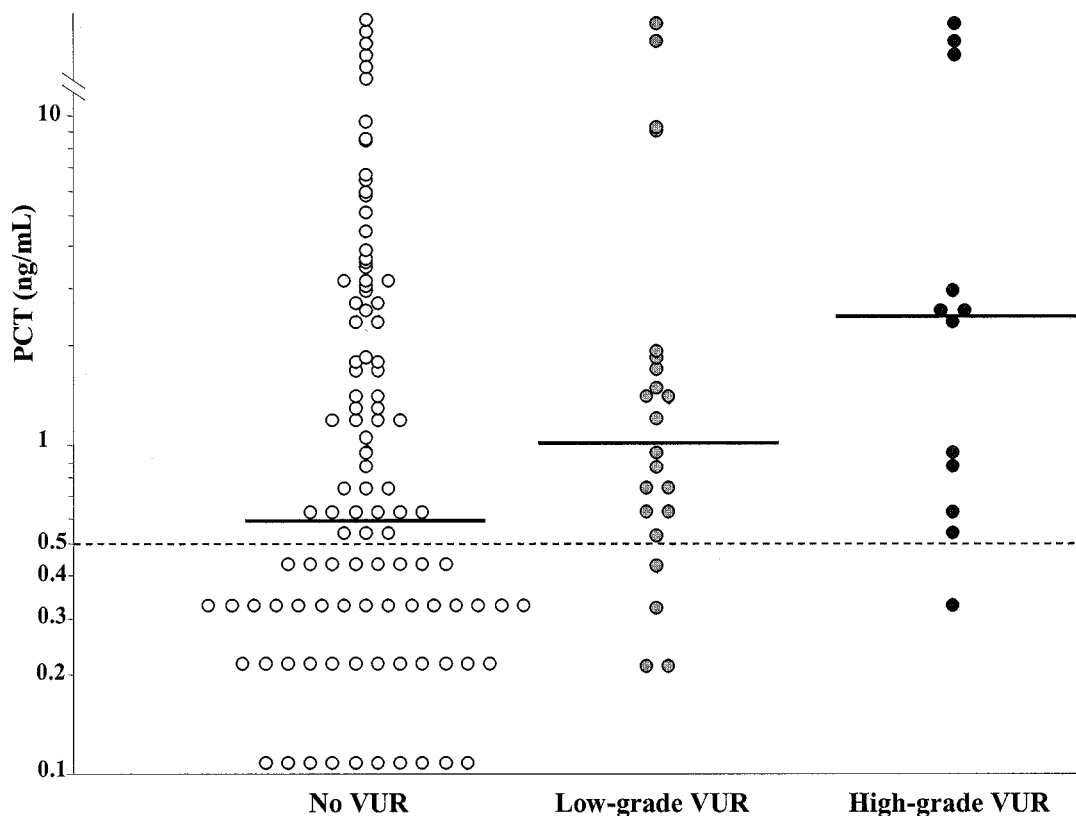


Fig 1. Distribution of PCT values according to VUR grade. The discontinuous horizontal line is the dichotomization threshold. The short, bold, horizontal lines are the median for each group.

TABLE 1. Crude Relationships Between High PCT and VUR

VUR Grade	n	PCT (ng/mL), n (%)		OR (95% CI)*	P
		<0.5	≥0.5		
		None	102		
All grades	34	5 (15)	29 (85)	4.6 (1.6–16.2)	.002
Low grade	22	4 (18)	18 (82)	3.6 (1.1–15.3)	.02
High grade	12	1 (8)	11 (92)	8.7 (1.2–382)	.03

* OR for VUR of patients with high PCT levels.

patients. Logistic-regression analysis was performed with the data of 131 (96%) patients, including 32 with VUR. Adjustment for all potential confounders yielded an OR of 4.9 (95% CI: 1.7–14.0; $P = .003$). The strength of the association increased significantly ($P = .02$) with the grade of VUR (Table 1), with the OR rising from 3.6 for low-grade VUR to 8.7 for high-grade VUR.

Among the 34 patients with VUR, 5 (15%) had low PCT levels. High PCT had a sensitivity of 85% (95% CI: 70–94) for all-grade VUR and 44% specificity (95% CI: 35–54). For the 12 patients with high-grade VUR, 1 (8%) had a low PCT concentration, giving high PCT a sensitivity of 92% (95% CI: 65–99) for high-grade VUR and a specificity of 44% (95% CI: 35–54). The patient with a low PCT concentration and grade 3 VUR was a 6-month-old girl, who had been febrile for 24 hours and had not received any antibiotics at the time of diagnosis. She had no family history of uropathy, and her renal ultrasonography was normal.

DISCUSSION

We identified a new predictor of VUR in children with a first febrile UTI: a high serum PCT concentration (≥ 0.5 ng/mL) at admission. The association between high PCT and VUR was strong and remained so after adjustment for all potential confounders. Moreover, the relationship increased significantly and almost linearly with the VUR grade. A high PCT level predicted VUR with high sensitivity: $>80\%$ for all-grade VUR and $>90\%$ for high-grade VUR. In light of its specificity, this could avoid 44% of a posteriori normal voiding cystourethrographies.

PCT, the prohormone of calcitonin, is an early, sensitive, and specific marker of bacterial infection.^{17,25} However, its role in the inflammatory response and in the cytokine cascade remains unknown.²⁵ In febrile UTI, a high PCT concentration is a validated predictor of acute pyelonephritis²⁶ (confirmed by early renal scintigraphy) and for late renal scars.^{18,19} The association between high PCT and VUR, especially high-grade VUR, could be explained by the risk for renal scarring that also increases with the VUR grade.²⁰

In our retrospective study, 10 (6%) patients were lost to follow-up before voiding cystourethrography could be performed. This rate is close to that reported in other studies.^{14,20} Among the 13 (8%) patients for whom admission PCT values were not available, 3 had VUR (including 2 high-grade VUR). These missing data may have biased our results. However, even when we considered that those with

VUR had low PCT concentrations and those without VUR had high PCT levels, the OR between a high PCT and VUR still would have been significant (2.4; 95% CI: 1.0–6.7; $P = .04$).

The use of sterile bags for urine collection introduced a selection bias, as this technique is less specific than suprapubic aspiration and not recommended by the American Academy of Pediatrics.⁴ Indeed, some patients who would not have had a diagnosis of UTI if suprapubic aspiration or catheterization had been used were included in our study. This bias explains the higher prevalence of boys in our study (46%) compared with other studies that use suprapubic aspiration or catheterization to diagnose UTI (11%, 28%).^{20,26} However, among female patients, the OR between a high PCT and VUR still was significant. Therefore, we considered that the selection bias could not explain our results. Moreover, sterile bags are used in routine practice by 25% of North American pediatricians²⁷ and in many European countries.^{6,15}

The PCT threshold of 0.5 ng/mL was used to dichotomize the variable. It was the same as that applied in previous studies on PCT as a predictor of renal scarring,^{18,26} and it is the lower limit of PCT in the semiquantitative doctor's bedside test.²⁸

CONCLUSIONS

In our study, a high PCT concentration was a strong and independent predictor of VUR. These results need to be confirmed by prospective multicenter studies. If the high sensitivity is confirmed, then it could be used to define selective strategies for voiding cystourethrography after a first febrile UTI in children. Its specificity (44%) means that approximately one third to one half of a posteriori normal voiding cystourethrographies could be avoided. Both sensitivity and specificity perhaps could be improved by combining a high PCT with other VUR predictors in clinical decision rule, as has been proposed in other situations to avoid unnecessary imaging in children.²⁹

ACKNOWLEDGMENTS

Dr Leroy was financially supported by a grant from the Association des Juniors en Pédiatrie and Laboratoire Gallia and from the Fondation pour la Recherche Médicale. We acknowledge the financial support provided by Délégation à la Recherche Clinique, Assistance Publique-Hôpitaux de Paris (contract de recherche clinique 03154).

We thank Drs Ekindjan and Guérin for procalcitonin determinations. We also thank Maria Gonzales, Jennifer Renard, and Patricia Noble for technical support.

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