Procalcitonin to Reduce the Number of Unnecessary Cystographies in Children with a Urinary Tract Infection: A European Validation Study

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Objective To validate high serum procalcitonin (PCT) as a predictor of vesicoureteral reflux (VUR) in children with a first febrile urinary tract infection (UTI).

Study design This secondary analysis of prospective hospital-based cohort studies included children ages 1 month to 4 years with a first febrile UTI.

Results Of the 398 patients included in 8 centers in 7 European countries, 25% had VUR. The median PCT concentration was significantly higher in children with VUR than in those without: 1.6 versus 0.7 ng/mL ($P = 10^{-4}$). High PCT (≥0.5 ng/mL) was associated with VUR (OR: 2.3; 95% CI, 1.3 to 3.9; $P = 10^{-3}$). After adjustment for all cofactors, the association remained significant (OR: 2.5; 95% CI, 1.4 to 4.4; $P = 10^{-3}$). The strength of the relation increased with the grade of reflux ($P = 10^{-5}$). The sensitivity of procalcitonin was 75% (95% CI, 66 to 83) for all-grade VUR and 100% (95% CI, 81 to 100) for grade ≥4 VUR, both with 43% specificity (95% CI, 37 to 48).

Conclusions High PCT is a strong, independent and now validated predictor of VUR that can be used to identify low-risk patients and thus avoid one third of the unnecessary cystourethrographies in children with a first febrile UTI. *(J Pediatr 2007;150:89-95)*

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It has been estimated that 7% of girls and 2% of boys will have a urinary tract infection (UTI) before 6 years of age.[1] Among those with a first febrile UTI, 20% to 40% are diagnosed with vesicoureteral reflux (VUR).[2] VUR is a risk factor for recurring UTI, renal scarring, hypertension, and renal failure,[2] and the risk is correlated to VUR grade.[3] Antimicrobial prophylaxis and surgical correction are therefore recommended for low-grade and high-grade VUR, respectively.[4] Thus, pediatric societies[5-9] recommend routine voiding cystourethrography for all children with a first febrile UTI. The results of this procedure are normal, however, for 60% to 80% of these children. Voiding cystourethrography has been associated with a risk of iatrogenic UTI,[10] exposes children to radiation, especially of the gonads,[11] and is both painful[12] and expensive.[13] Moreover, a recent study of 780 patients with a first UTI during their first year of life found that only 40% underwent this screening.[14] These results mean that pediatricians are applying implicit criteria to select patients for cystography and may indicate a place for a selective evidence-based approach that uses a validated predictor. Ability to predict the absence of VUR would help to avoid unnecessary cystography.[15]

Three predictive tools have been proposed as selective approaches for cystography. Ultrasonography alone, regardless of the criteria chosen, has poor sensitivity for VUR prediction.[3,16] A highly sensitive VUR risk score,[17] combining clinical, laboratory, and radiological variables, was also proposed, but some of us have shown that its reproduc-

CRP	C-reactive protein	UTI	Urinary tract infection
PCT	Procalcitonin	VUR	Vesicoureteral reflux

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Table I. Population characteristics in each center

Center*	n (398)	Inclusion dates	Urine collection techniques (threshold of the positive bacteriuria)†	All-grade VUR, %	Grade ≥3 VUR, %
Centers using SA‡ or UC§					
Afula	56	1999–2000	SA (10^1), UC (10^3)	25	11
Badalona	40	1998–2001	SA (10^2), UC (10^4), CVM‖ (10^5)	38	29
Geneva	77	1998–2002	SA (10^3), UC (10^4), CVM (10^5)	29	13
Udine	80	2000–2002	UC (5 10^4), CVM (10^5)	19	11
Yvoir	33	1999–2003	SA (10^3), UC (5 10^4), CVM (10^5)	21	12
Centers using SB¶					
Clamart	23	2001–2002	SB (10^5)	30	4
Paris	40	2003–2004	SB (10^5), CVM (10^5)	25	5
Rzeszow	49	1997–1998; 2001–2004	SB (10^5), CVM (10^5)	22	8
Mean				25	12

*Classified according to the urine collection technique in non–toilet-trained children.
†In colony-forming units/mL.
‡Suprapubic aspiration.
§Urethral catheterization.
‖Clean-voided midstream.
¶Sterile bag.

ibility is poor.[18] Thus, new predictors of VUR in children with a first febrile UTI are needed to define selective approaches for cystography. Procalcitonin (PCT), a recently identified marker of bacterial infection,[19,20] is a candidate because it was shown to be associated with renal scars,[21-23] which, in turn, are correlated with VUR, especially high-grade VUR.[3] Some of us showed in a single-center study that a high serum PCT level at the time of the UTI diagnosis was a strong and independent predictor of VUR.[24] Its sensitivity was 85% for all-grade VUR and 92% for high-grade VUR, with a specificity of 44% in both cases. Because single-center results may be subject to both selection and measurement biases (and, indeed, Chevalier et al[25] recently argued that the use of sterile bags for urine collection in the single-center study[24] may have introduced a strong bias), they should be validated by multicenter studies.[26]

The aim of the current work was to validate in a multicenter study, including centers that collected urine by suprapubic aspiration or urethral catheterization, the use of high serum PCT as a predictor of VUR in children with a first febrile UTI.

METHODS

We conducted a secondary analysis of prospective hospital-based cohort studies. Potential investigating centers were contacted if they had reported a cohort of patients with a first febrile UTI and a PCT measurement. Publications were identified by a MEDLINE search from 1993 to 2004 with the key words procalcitonin and child and by a review of abstract books from the Interscience Conference on Antimicrobial Agents and Chemotherapy, the Infectious Diseases Society of America, and the European Society for Paediatric Infectious Diseases from 1995 to 2004. Each center selected one or several study periods during which all children with a first febrile UTI routinely had PCT measurement and cystography.

The study included all consecutive children ages 1 month to 4 years and admitted with a first febrile UTI, defined according to the criteria used in each center (Table I). Children with a known uropathy at the time of the UTI diagnosis, those who had received antibiotics in the 48 hours before diagnosis, and patients already included in the previous single-center study[24] were not included.

Information was collected about each center's techniques for urine collection, PCT measurement, and cystography. Each participating center sent an electronic file containing the data of its previous prospective study. We extracted from files the clinical (sex, age, first-degree family history of uropathy), laboratory (C-reactive protein [CRP], PCT), and radiological data (urinary tract dilation on ultrasonography, presence and grade of VUR on cystography) needed from each patient for the current study.

VUR was identified by a senior pediatric radiologist (blinded to PCT) from the voiding cystourethrographies or direct radionuclide cystographies in each center. VUR was graded from 0 to 5, according to the International System of Radiological Grading of Vesicoureteric Reflux[27] only from the voiding cystourethrographies, because precise grading is not possible with direct radionuclide cystographies.[28]

At admission, each patient's serum PCT was prospectively measured with the LUMItest PCT immunoluminometric assay or the BRAHMS PCT-Q semiquantitative rapid test (BRAHMS, Hennigsdorf, Germany). The PCT variable was dichotomized for some analyses at the previously proposed cutoff point of 0.5 ng/mL, which corresponded to the median of the distribution (rounded to the nearest half integer) among patients without VUR included in the previous single-center study.[24]