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)*

See related article, p 96

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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

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]

All risk factors for VUR previously described in the literature were used as cofactors of interest: family history of uropathy,[29] young age,[2,30] male sex,[2] high serum CRP at admission,[17] and urinary tract dilation (defined as renal pelvic and/or ureteral dilation) on ultrasonography[17] identified by a senior pediatric radiologist. The urine collection technique used in each center was also considered as a cofactor.[25] The cofactors were dichotomized according to previously proposed thresholds, as follows: first-degree family history of uropathy coded as (1), no such history (0)[29]; age ≤1 year (1), >1 year (0)[2,30]; boys (1), girls (0)[2]; urinary tract dilation on ultrasonography (1), or not (0)[17]; and sterile bags or clean-voided midstream for urine collection (1), or suprapubic aspiration, transurethral catheterization or clean-voided midstream (0). CRP values were dichotomized and the cutoff point set at the median of the distribution among patients without VUR, rounded to the nearest multiple of 10, which is consistent within values previously suggested in the literature: CRP ≥40 mg/L (1), CRP <40 mg/L (0).[31-34]

Statistical analyses were performed with the use of EPI INFO software (Centers for Disease Control and Prevention, Atlanta, Ga) and Stata/SE 8 software (StataCorp, College Station, Tex). We first analyzed the distribution of PCT according to VUR grade. These distributions were compared with the Mann-Whitney or Kruskall-Wallis nonparametric test. Second, a univariate analysis used the odds ratio (OR) and the χ^2 test to evaluate the relation between VUR and either high PCT (≥0.5 ng/mL) or all cofactors. The relation between VUR and high PCT was determined for all children and then for the subgroup for whom urine specimens were collected by suprapubic aspiration or catheterization. If the 2 × 2 table contained a zero cell, we calculated a corrected OR by adding 0.5 in each cell of the table.[35] Third, the Breslow-Day test assessed the potential interaction of the cofactors in the relation between VUR and high PCT. Fourth, the independence of the relation between VUR and high PCT was assessed after adjustment for all cofactors and for center, with a logistic regression model. Adjustments for urine collection technique and for center were performed in two different logistic regression models because of a strong colinearity between these variables. Fifth, the relation between the different VUR grades and high PCT was examined with the χ^2 test for trend. Sixth, we determined the discriminating power of high PCT by calculating its sensitivity, specificity, and negative and positive predictive values for VUR according to grade. Finally, likelihood ratios were used to analyze the relation between VUR and high PCT.

Patients with a PCT-Q semiquantitative rapid test were not included in the analyses of PCT as a continuous variable. Patients for whom direct radionuclide cystography was used to identify VUR were not included in the analyses by VUR grade.

RESULTS

Recruitment

The search strategy described above identified 9 centers.[21-23,31-34,36-39] All agreed to participate in the study, and 8 centers provided complete data files. Centers varied widely for inclusion dates, urine collection techniques, UTI diagnostic criteria, and prevalence of VUR (Table I). The prevalence of VUR did not statistically differ (P = .9) according to urine collection technique: it was 26% for the centers using suprapubic aspiration, transurethral catheterization, or clean-voided midstream versus 25% for the centers using sterile bags or clean-voided midstream.

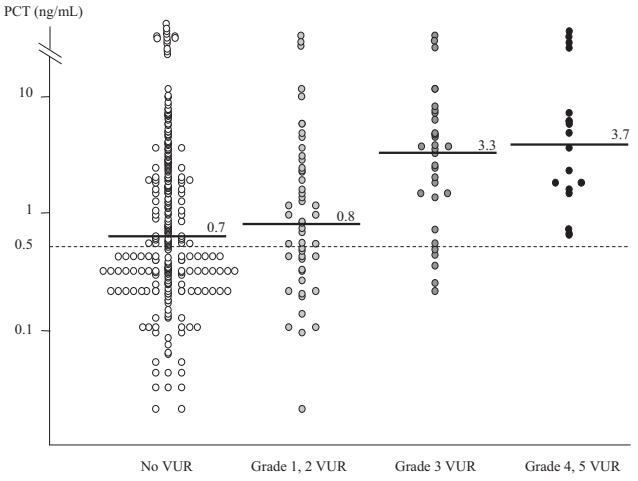

Figure. Distribution of PCT values according to VUR grade. *Dashed horizontal line* is the dichotomization threshold; *short, bold, horizontal lines* are the median for each group. n = 369. See text.

Four hundred thirty-six patients met the inclusion criteria. Because 36 (8%) were lost to follow-up before cystography could be performed and PCT values on admission were unavailable for 2 (0.5%) others, the analysis was based on 398 (91%) patients. Analysis of PCT as a continuous variable involved only 374 (94%) patients because PCT was measured by the PCT-Q semiquantitative test for 24 patients. VUR was identified by direct radionuclide cystography for 5 patients and thus analyses by VUR grades concerned 393 (99%) patients. Analyses of PCT as a continuous variable by VUR grades involved only 369 (93%) patients.

Population Characteristics

The mean age of the children was 13.1 months (standard deviation [SD]: 12.0; median, 9.0; interquartile, 4.0 to 18.0); 154 (39%) were boys. Thirty-six (10%) patients had a family history of uropathy. Ultrasonography showed urinary tract dilation in 81 (21%). VUR was diagnosed in 101 (25%) children, and it was grade ≥3 in 46 (12%) (Table I).

Procalcitonin

The median PCT concentration was significantly higher in children with VUR than in those without: 1.6 versus 0.7 ng/mL ($P = 10^{-4}$). The median PCT value increased significantly ($P = 10^{-5}$) with the VUR grade (Figure). A 0.5 ng/mL PCT concentration was used as the threshold definition of high PCT for the dichotomization in the subsequent

Table II. Crude relations between VUR and high PCT

VUR grade	n (%)	PCT (ng/mL) n (%)		OR* (95% CI)	*P* value	Likelihood ratio positive (95% CI)	Likelihood negative (95% CI)
		<0.5	≥0.5				
None	297 (75)	127 (43)	170 (57)	1			
All-grade VUR†.	101 (25)	25 (25)	76 (75)	2.3 (1.3–3.9)	.001	1.3 (1.1–1.5)	0.6 (0.4–0.8)
Grade 1, 2 VUR	50 (13)	19 (38)	31 (62)	1.2 (0.6–2.4)	.5	1.1 (0.9–1.4)	0.9 (0.6–1.3)
Grade 3 VUR	30 (8)	5 (17)	25 (83)	3.7 (1.4–12.8)	.005	1.5 (1.2–1.8)	0.4 (0.2–0.9)
Grade 4, 5 VUR	16 (4)	0 (0)	16 (100)	24.7‡ (1.5–415)	.0007	1.7 (1.6–1.9)	0.0 (–)§

*OR for VUR of patients with high PCT levels.
†n = 398 for all-grade VUR, n = 393 for VUR in grade (see text).
‡Corrected OR.[38]
§95% Confidence interval not calculable.

analyses (Table II). At this threshold, the OR between VUR and high PCT was 2.3 (95% confidence interval [CI], 1.3 to 3.9; P = 10^{-3}) and 1.9 (95% CI, 1.0 to 3.6; P = .03) for the children for whom urine specimens were collected by suprapubic aspiration or urethral catheterization. VUR was not significantly related to any cofactors (Table III). Neither any of these cofactors nor the center interacted significantly in the relation between VUR and high PCT (P >.1). Logistic regression analysis used the data of only 368 (92%) patients, including 93 (25%) with VUR, because of missing data for cofactors for 30 patients. Adjustment for all cofactors and urine collection technique yielded an adjusted OR of 2.5 (95% CI, 1.4 to 4.4; P = 10^{-3}). Adjustment for all cofactors and center yielded an adjusted OR of 2.6 (95% CI, 1.4 to 4.9; P = 10^{-3}). The strength of the association increased significantly (P = 10^{-5}) with the grade of VUR (Table II).

Of 101 patients with VUR, 25 (25%) had low PCT levels, so that high PCT had a sensitivity for all-grade VUR of 75% (95% CI, 66 to 83), a positive predictive value of 31% (95% CI, 25 to 37), and a negative predictive value of 84% (95% CI, 77 to 89). Five (11%) of the 46 patients with grade ≥3 VUR had low PCT concentrations, so that high PCT had a sensitivity for grade ≥3 VUR of 89% (95% CI, 77 to 95), a positive predictive value of 19% (95% CI, 14 to 25), and a negative predictive value of 96% (95% CI, 91 to 99). Among these 5 patients, 3 had urinary tract dilation on ultrasonography. Four of these 5 patients underwent renal scintigraphy, which was normal for three and showed antenatal dysplasia for one. None of the 16 patients with grade 4 or 5 VUR had a low PCT concentration. The sensitivity of high PCT was 100% (95% CI, 81 to 100) for grade 4 or 5 VUR. Its positive and negative predictive values were, respectively, 9% (95% CI, 5 to 14) and 100% (95% CI, 97 to 100). Specificity was 43% (95% CI, 37 to 48), regardless of VUR grade.

Positive and negative likelihood ratios were, respectively, 1.3 (95% CI, 1.1 to 1.5) and 0.6 (95% CI, 0.4 to 0.8) for all-grade VUR and, respectively, 1.5 (95% CI, 1.2 to 1.8) and 0.4 (95% CI, 0.2 to 0.9) for grade ≥3 VUR (Table II).

DISCUSSION

We confirmed that a high serum PCT concentration (≥0.5 ng/mL) is a strong and independent predictor of VUR in children with a first febrile UTI diagnosed with different urine collection techniques. Moreover, the relation grew significantly stronger as VUR grade increased. The discriminating power of a high PCT level was consistent with the findings from the single-center study.[24] A high PCT level predicted VUR with high sensitivity: 75% (95% CI, 66 to 83) for all-grade VUR and 100% (95% CI, 81 to 100) for grade 4 or 5 VUR. Its specificity was 43% (95% CI, 37 to 48). A PCT-based strategy could thus have been used to avoid 152 cystourethrographies, including 127 that turned out to be unnecessary, and it would have misdiagnosed only 5 children with a grade 3 VUR.

This study evaluated the geographic, historic, and methodologic transportability of the relation between VUR and PCT.[26] Geographic transportability was tested by the multicenter international study design. The wide range of VUR prevalence values (19% to 38%) attested to the different recruitment patterns. Historic transportability was assessed by including patients from 1997 through 2004. Validity across various methods was shown with the different urine collection techniques (suprapubic aspiration, urethral catheterization, clean-voided midstream, or sterile bag), diagnostic criteria thresholds for positive bacteriuria, PCT measurement techniques (immunoluminometric quantitative assay or PCT-Q semiquantitative rapid test), and cystography techniques (voiding cystourethrography or direct radionuclide cystography).

PCT, the prohormone of calcitonin, is an early, sensitive, and specific marker of bacterial infection.[19,20] 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 (confirmed by early renal scintigraphy)[22,23,31,36] and for late renal scars.[21-23] The risk of renal scarring also increases with VUR grade.[3] The probably greater frequency of retrograde renal inoculation during UTI in cases of VUR[2] explains the association between VUR (especially high-grade VUR) and high PCT.

The main limitation of this study is its design, a secondary analysis of prospective cohort studies, which may have led to several biases. We searched only published reports and congress abstracts. It is possible that this approach led to a

Table III. Crude relations between VUR and potential confounders

Variables*	None VUR n (%)	All-grade VUR n (%)	OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Family history of uropathy (n = 374)						
Yes	24 (9)	12 (13)	1.6 (0.7–3.5)	.2	1.6 (0.7–3.4)	.2
No	256 (91)	82 (87)	1		1	
Sex (n = 398)						
Male	118 (40)	36 (36)	0.8 (0.5–1.4)	.5	0.9 (0.5–1.6)	.8
Female	179 (60)	65 (64)	1		1	
Age (n = 398)						
≤1 year	191 (64)	57 (56)	0.7 (0.4–1.2)	.2	0.8 (0.4–1.3)	.3
>1 year	106 (36)	44 (44)	1		1	
Urinary tract dilation on US† (n = 393)						
Yes	56 (19)	25 (25)	1.4 (0.8–2.5)	.2	1.6 (0.9–3.0)	.1
No	237 (81)	75 (75)	1		1	
CRP (n = 397)						
≥40 mg/L	207 (70)	77 (76)	1.4 (0.8–2.4)	.2	0.9 (0.5–1.7)	.8
<40 mg/L	89 (30)	24 (24)	1		1	
Urine collection technique (n = 398)						
SB‡ or CVM§	84 (28)	28 (28)	1.0 (0.6–1.7)	.9	1.0 (0.5–1.7)	.9
SA‖, UC¶ or CVM	213 (72)	73 (72)	1		1	

*The sample sizes for each variable differed because of missing data for few of them (see text).
†Ultrasonography.
‡Sterile bag.
§Clean-voided midstream.
‖Suprapubic aspiration.
¶Urethral catheterization.

publication bias insofar as studies with null findings were less likely to have been reported. Nonetheless, one of the studies included in this analysis found negative results for the relation between renal involvement and PCT.[33] Publication bias is thus unlikely. Another limitation is that center selection was based on voluntary participation. One center did not complete the study. The authors of this study had shown in a prospective multicenter cohort study of 445 patients that PCT was a sensitive and specific marker for distinguishing viral and bacterial infections in the emergency room.[39] The mean PCT concentration among the 92 patients with a febrile UTI was higher in the children with than without renal parenchymal involvement, evaluated by early DMSA scintigraphy: 4.9 ng/mL (SD: 13.2) versus 0.3 ng/mL (SD: 0.2).[39] These findings are similar to those reported in the four studies we included that examined the relation between renal involvement in febrile UTI and PCT.[22,23,31,36] Thus, participation bias is also unlikely. Pooling data from different centers may have induced heterogeneity. However, there was no significant interaction with the center in the relation between VUR and high PCT. Furthermore, the relation between VUR and high PCT remained strong and statistically significant after adjustment for all cofactors, including the center.

The use of sterile bags for urine collection in several centers could have introduced a selection bias,[25] as this technique is less specific than suprapubic aspiration or transurethral catheterization and not recommended by the American Academy of Pediatrics.[5] Our study did indeed include some patients who would not have had a diagnosis of UTI if suprapubic aspiration or transurethral catheterization had been used. Had the specificity of sterile bags been truly poor, the prevalence of VUR in our study would have been higher in children with UTI diagnosed by suprapubic aspiration or transurethral catheterization than by sterile bags. However, it did not differ significantly according to the urine collection technique used (26% for the centers using suprapubic aspiration, transurethral catheterization, or clean-voided midstream versus 25% for those using sterile bags or clean-voided midstream, $P = .9$). Furthermore, the OR between VUR and high PCT was still significant in the subgroup for whom urine specimens were collected by suprapubic aspiration, catheterization, or clean-voided midstream. Moreover, the urine collection technique did not significantly interact in the relation between VUR and high PCT. Finally, the relation between VUR and high PCT remained strong and statistically significant after adjustment for all cofactors, including the urine collection technique used in each center. We therefore think that such a selection bias cannot explain our results. Moreover, sterile bags are routinely used by 25% of North American pediatricians[40] and in many European countries.[17,24,37,38]

We propose to replace the current systematic screening strategy for VUR by a PCT-based selective approach, even though high PCT did not offer 100% sensitivity for the prediction of all-grade or grade ≥3 VUR. One way to deal

with this lack of sensitivity is to accept that VUR will remain undiagnosed for some patients after a first febrile UTI. The potential adverse consequences of this practice should be balanced against the debatable efficacy of treatments (secondary antibiotic prophylaxis and surgery) for children with VUR[4,41] and the possibility that low-grade VUR and even high-grade VUR can spontaneously disappear.[42] These reasons have led some authors[43] to propose waiting for the second febrile UTI, if any, for screening VUR. Moreover, of the 4 patients with grade 3 VUR, a PCT concentration <0.5 ng/mL and renal scintigraphy, 3 had normal findings and 1 had antenatal dysplasia. Waiting for a second febrile UTI, if any, for screening VUR in patients with low PCT would thus not have exposed these patients to important renal damage.[22,23,31,36]

There is a current debate on the a priori recommendation for a voiding cystourethrography as the first study to be done after a first febrile UTI, contrary to the alternative recommendation to look for damaged kidneys by a renal scintigraphy.[44] Because high PCT levels also predict the presence of acute pyelonephritis[22] and renal scarring,[20] a PCT-based strategy could identify patients who need either voiding cystourethrography or renal scintigraphy.

The cost of a voiding cystourethrography (≈$150) is 10 times that of PCT (≈$15). PCT makes it possible to avert 38% of the routine cystourethrographies. A PCT-based strategy versus a systematic approach thus reduces costs by 30%.

In conclusion, high PCT is a strong, independent and now validated predictor of vesicoureteral reflux and can be used to identify low-risk patients to avoid unnecessary cystourethrographies.

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Fifty Years Ago in *The Journal of Pediatrics*

Medical progress: The abnormal hemoglobins: Clinical and hematologic aspects

Smith, CH. J Pediatr 1957;50:91-113

Linus Pauling et al reported in 1949[1] that an abnormal hemoglobin molecule was present in persons with sickle cell anemia, and presumably it was responsible for the manifestations of this disorder. Additional hemoglobin variants were subsequently identified and reported in persons with other disease states and of different ancestries. Using gel electrophoresis to distinguish these abnormal hemoglobins, variants were initially designated by letters of the alphabet (eg, HbC, HbD, HbE, etc.).

In this 1957 Medical Progress article, Smith describes in great detail the then-current state of the art in terms of laboratory methodology, nomenclature, erythrocyte morphology, and clinical correlation with known diseases. The article provides a readable snapshot into a rapidly developing area of research. At that point in time, the abnormal hemoglobins had proceeded up through HbJ, but the author accurately predicted that more variants would likely follow.

Indeed that has occurred! Now 50 years later, there are more than 500 beta globin variants reported, and almost 500 additional alpha and gamma globin variants, according to the Hemoglobin Variant (HbVar) Database maintained at http://globin.cs.epsu/edu. Alphabetic nomenclature has long since been abandoned, as has the use of city/hospital names, and now the variants are designated by their specific nucleotide sequence mutations. Molecular diagnostic methodology, including direct DNA sequencing, has replaced gel electrophoresis and other older techniques. Our understanding of these abnormal hemoglobin variants has also evolved considerably.

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