© 2008 Órgano Oficial de la Sociedad Española de Nefrología

Can vesicoureteral reflux be predicted in infants with urinary infection?

M. Sánchez Bayle, G. Yep Chullen, E. de La Torre Montes de Neira, J. Cano Fernández and B. Rabadán Sanz

Sección de Lactantes. Hospital Niño Jesús. Madrid.

Nefrología 2008; 28 **(3)** 283-286

SUMMARY

Aims To look forward for a formulae able to predict the presence of vesicoureteral reflux (VUR) in the first urinary tract infection (UTI) in infants.

Subjects and Methods: *We had studied all the diagnosticated first UTI in breast-fed babies in our hospital along 2 1/2 years. All had been subjects of a renal ultrasound scan, VCUG and CRP test. We have analyzed the result by diagnosis test and logistic regression.*

Results: *We have studied 267 infants aged between 2 days and 24 months old.17,33% manifested UTI caused by germs different than E Coli, 40 subjects presented anomalies in the ultrasound scan and 108 manifested VUR. Oostenbruck´s score had been useless in detecting VUR subjects. In the multivariable analysis the two variables of anomalies in the ultrasonographic scan and non E Coli caused UIT were the only ones to presented statistical significance to sign the presence of VUR and of the likeness of VUR of grade ≥ 3. The negative probability coefficients for infants with ultrasonographics anomalies and/or UTI non E Coli produced were of 0,78 (IC 0,67-0,90) for all degrees of VUR, 0,25 (IC 0,10-0,52) for VUR with degree ≥ 3 and 0 (IC 0-0,67) for VUR with degree ≥ 4.*

Conclusions: *We deduced that in children younger of 24 months old that suffer their first UTI the indication to proceeded with a VCUG could be limited to the subjects with present anomalies in the renal ultrasound scan and/or UTI non E Coli, thought there will précised more studies to confirm this findings.*

Key words: *Vesicoureteral reflux. UTI non-E Coli. Ultrasonographic anomalies. VCUG.*

RESUMEN

Objetivos: **Buscar fórmulas para predecir la presencia de reflujo vesicuoureteral (RUV) en la primera infección urinaria (ITU) en la infancia.**

Sujetos y métodos: **Se han estudiado todos los niños diagnosticados de la primera ITU en la Sección de Lactantes de nuestro hospital durante 2 1/2 años. A todos ellos se les realizó ecografía renal, cistografía miccional (CUMS) y determinación de PCR. Se analizaron los resultados mediante regresión logística y los test para pruebas diagnósticas.**

Resultados: **Se estudiaron 267 niños de edades comprendidas entre los 2 días y los 24 meses. El 17,33% presentaron ITU por gérmenes distintos al E Coli, 40 tenían anomalías en la ecografía renal y 108 RUV. La fórmula de Oostenbrink no demostró utilidad para identificar los RUV. En el análisis multivariante la presencia de UTI no E Coli y de anomalías ecográficas fueron las únicas variables que presentaron significación estadística tanto para la presencia de cualquier tipo de RUV como para RUV de grado ≥ 3. Los coeficientes de probabilidad negativos para niños con anomalías ecográficas y/o ITU no E Coli fueron de 0,78 (IC 0,67-0,90) para cualquier grado de RUV, 0,25 (IC 0,10-0,52) para RUV con grado ≥ 3 y de 0 (IC 0-0,67) para RUV con grado ≥ 4.**

Conclusiones: **De nuestro estudio parece deducirse que en los niños menores de 24 meses con una primera ITU, la indicación de realización de un CUMS podría limitarse a los casos con presencia de anomalías en la ecografía renal y/o de ITU no E Coli, aunque son precisos estudios más amplios para confirmar estos hallazgos.**

Palabras clave: Reflujo vesicoureteral. ITU no E Coli. Anomalías ecográficas renales. CUMS.

INTRODUCTION

Urinary tract infection (UTI) is a common condition in infancy, and is commonly associated to urinary tract abnormalities, particularly to the vesicoureteral reflux (VUR) existing in 30%-40% of infants with UTI.[1,2]

Indication of imaging studies in infants with UTIs is controversial. The most recent guidelines of the American Association of Pediatrics[2] recommend performing a SVCU in all infants under 2 years of age with UTI, but widely different

Correspondence: *Marciano Sánchez Bayle*
Hospital Niño Jesús
Avda. Menéndez Pelayo, 65
28009 Madrid. España
msanba@teleline.es

opinions exist about what subsequent examinations are indicated and when they should be done.[3-9]

In this setting, a formula has recently been proposed to predict the presence of VUR and avoid unnecessary SVCUs.[10] Other authors have questioned the validity of this formula.[11] The purpose of our study was to assess this formula and propose alternatives to it.

PATIENTS AND METHODS

Infants diagnosed of their first urinary tract infection (UTI) at the infant section, either in the outpatient clinic or the hospital ward, from January 2005 to June 2007 were studied.

All infants having positive urine cultures, CRP values at diagnosis, an ultrasonography performed during the UTI episode, and a serial voiding cystoureterography (SVCU) within 1 month of UTI diagnosis were enrolled into the study. Fifteen infants were excluded from the study due to lack of any of the variables analyzed.

Risk was calculated using the Oostenbrink score (score = 6 * male gender + 7 * positive family history – 1 * age + 1*CRP + 14 for dilation in renal ultrasonography).[10]

Sensitivity, specificity, and positive and negative odds ratios, with their 95% CIs, were also calculated using the statistical page 2-way Contingency Table Analysis available in the Internet.[12]

A multivariate study was performed by binary logistic regression using commercial SPSS 11.0© software,[13] starting from the maximum model including all variables in the Oostenbrink formula plus the presence of urine cultures positive for pathogens other than *E. coli.* Variables not achieving a significance value of $p < 0.05$ were removed from the model one by one.

RESULTS

A total of 267 infants were enrolled into the study. Age ranged from 2 days to 24 months, with a mean of 4.2 months (standard deviation 4.79 months, median 2.50 months). One hundred and sixty infants (59.5%) were males. The clinical history showed that 4 infants (1.5%) had a family history of VUR, and 137 (51.3%) were being breastfed, or had been breastfed for at least 3 months.

Pathogens responsible for UTIs were divided into two groups, *E. coli* (82.67%) and non *E. coli* (17.33%). The most common pathogen in the latter group was *Klebsiella* (22 cases), followed by enterococci (14 cases), *Proteus*, *Citrobacter*, and *Streptococcus agalactiae*.

A total of 40 infants (14.98%) had abnormalities in the kidneys and/or urinary tract in ultrasonography, in most cases dilations of the pyelocalycial and pyeloureteral system (pyelic and ureteral dilations were defined as values greater than 18 mm and 10 mm in the transverse axis and distal ureter respectively), and 108 infants had a pathological SVCU (40.44%), with a total of 175 kidneys with VUR. The probability of VUR was calculated using the Oostenbrink formula.[10] Table 1 shows the cases with scores greater and lower than 0 (the advocated cut-off point) and VUR. As shown, this value was exceeded in most cases and only 14 infants had this value, 8 of whom had VUR.

Table 2 gives the distribution of VUR presence and grade according to the International Study Classification[14] (the maximum grade was considered in bilateral VURs), depending on whether an abnormal ultrasonography and/or UTI by pathogens other than *E. coli* had been seen, and Table 3 shows the results of logistic regression for the presence of VUR and grade ≥ 3 VUR. Statistical significance was only found with the presence of abnormalities in ultrasonography and non-*E. coli* UTI in both cases.

Table 3 shows the sensitivity, specificity, and positive and negative odds ratios for the presence of non-*E. coli* urine cultures and/or ultrasonographic abnormalities for the presence of VUR, grade ≥ 3 VUR, and grade ≥ 4 VUR. The negative odds ratio was 0 for VUR ≥ 4 and 0.25 for VUR ≥ 3.

DISCUSSION

The cumulative incidence of UTIs in children under 6 years of age has been estimated at 3%-7% in females and 1%-2% in males. Imaging tests have been recommended after the first UTI to assess VUR presence and grade. SVCU has an essential place among these tests because it allows for identifying the presence of VUR and its grade.[2-4,6] Therapeutic decisions deriving from the presence of VUR are related to its grade and include surgical correction, prophylactic treatment, and follow-up without treatment. A wide controversy exists about the most appropriate treatment, but most recent studies appear to suggest that the course is similar in patients with VUR regardless of whether or not they receive prophylactic treatment, at least in cases with less severe VUR (grades I-II), which are a majority.[15-17]

Table I. VUR classification according to the Oostenbrink score[10]

Score	No VUR	VUR
0	6	8
> 0	153	100

Table II. Patient distribution by tipe of VUR and urine culture

VUR type	non-*E. Coli* urine culture	Pathological ultrasonography	Culture + US	Total
No	14	14	28	159
Grade 1	0	0	0	6
Grade 2	24	12	33	81
Grade 3	5	10	13	17
Grade 4	2	3	3	3
Grade 5	1	1	1	1
Total	46	40	78	267

Table III. Results of logistic regression for the presence of VUR and grade ≥ 3 VUR

		Exp Beta	95% CI	P
VUR	Non-*E. Coli* urine culture	4.11	2.03-8.29	< 0.0001
	Abnormal ultrasonography	2.20	1.07-4.54	0.032
VUR Grade ≥ 3	Abnormal ultrasonography	7.07	2.75-18.16	< 0.0001
	Non-E. Coli urine culture	2.08	1.01-3.58	0.041

EXP Beta = exponential beta.

Table IV. Diagnostic test of the presence of pathological ultrasonography and/or non-*E. Coli* urine culture for different types of VUR

	VUR	Grade ≥ 3 VUR	Grade ≥ 4 VUR
Sensitivity	0.36 (0.31-0.41)	0.81 (0.61-0.92)	1 (0.51-1)
Specificity	0.81 (0.77-0.85)	0.75 (0.73-0.76)	0.73 (0.72-0.73)
OR+	1.98 (1.31-2.98)	3.26 (2.30-3.86)	3.70 (1.85-3.70)
OR–	0.78 (0.67-0.90)	0.25 (0.10-0.52)	0 (0-0.67)

OR = Odds ratio.

VUR is found in 30%-40% of children with UTIs.[2] The proportion of children with VUR in our study was 40.44%. In order to avoid performance of SVCU, a traumatic examination exposing to a high amount of radiation, in the 60%-70% of children showing no VUR, Oostenbrink proposed use of a formula that considered age, family history, dilations in renal ultrasonography, and CRP values. Using this formula, only one case of VUR was excluded from diagnosis in his study.[10] Other authors have questioned this formula, pointing out that it only had a 3% specificity for any type of VUR, and a 13% specificity for grade ≥ 3 VUR.[11] Application of the Oostenbrink formula in our study was shown to be of little help, first because it would only exclude performance of SVCU in 12 cases (5.24%), but also because VUR was found in 8 of these patients.

The presence of UTIs caused by pathogens other than *E. coli* has also been reported to be a risk factor for the presence of urinary tract abnormalities, including VUR (OR, 8.16; 95% CI, 1.88-35.48).[18] This was also seen in our study for the presence of VUR (OR, 3.98; 95% CI, 1.99-7.95).

In the calculation performed using logistic regression for the presence of both any VUR and grade ≥ 3 VUR, both the variables in the Oostenbrink formula and the existence of an urine culture revealing a pathogen other than *E. coli* were introduced. The result showed that only the presence of abnormalities in ultrasonography and the existence of positive non-*E. coli* urine cultures maintained statistical significance. All grade ≥ 4 VURs, 80.6% of grade ≥ 3 VURs, and 57.47% of all VURs were detected under these conditions, but it should be noted that only four cases with grades higher than 4 were found.

It should also be noted that the need for detecting grade I-II VURs has been questioned because of their good course without treatment. The proposed indication for SVCU in all cases of UTI is therefore not clear.[2,15-17,19]

The main limitation of our study was that it only enrolled children under 24 months of age referred to a hospital, who are supposed to have the most severe symptoms, though most infants with a febrile syndrome are usually referred for hospital diagnosis and management.

The conclusion drawn from our study is that it appears reasonable to advocate that SVCU is only performed in the first UTI episode in children under 2 years of age having abnormalities in renal ultrasonography and/or urine cultures revealing pathogens other than *E. coli*. In any case, the conduct of larger studies to confirm these findings would be appropriate.

REFERENCES

1. Larcombe J. Urinary tract infection in children. *BMJ* 1999; 319: 1173-5.
2. Americam Academic of Pediatrics: Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. *Pediatrics* 1999; 103: 843-52.
3. Dick PT, Feldman W. Routine diagnostic imaging for childhood urinary tract infections: a systematic overview. *J Pedaitr* 1996; 128: 15-22.
4. Hoberman A, Charron M, Hickey RW, Baskin M, Kearney DH, Wald ER. Imaging studies after a first febrile urinary tract infection in young children. *N Engl J Med* 2003; 348: 195-202.
5. Zamir G, Sakran W, Horowitz Y, Koren A, Miron D. Urinary tract infection: is there a need for routine renal ultrasonography? *Arch Dis Child* 2004; 89: 466-8.
6. Sathapornwajana P, Dissaneewate P, McNeil E, Vachvanichsanong P. Timing of voiding cystourethrogram after urinary tract infection. *Arch Dis Child.* Published online 11 Jul 2007; doi:10.1136/adc. 2007: 116392.
7. Mc Donald A, Sacranton M, Gillespie R, Mahajan V, Edwards GA. Voiding cystourethrogram and urinary tract infection: how long to wait? *Pediatrics* 2000; 105:e50.
8. Johnson CE. New advances in childhood urinary tract infections. *Pediatrics in Review* 1999; 20: 335-42.
9. Cohen AL, Rivara FP, Davis R, Christakis DA. Compliance with guidelines for the medical care of first urinary tract infections in infants: a population – based study. *Pediatrics* 2005; 115: 1474-8.
10. Oostenbrink R, Van der Heijden AJ, Moons KGM, Moll HA. Prediction of vesicoureteric refleux in childhood urinary tract infection: a multivariate approach. *Acta Paeditr* 2000; 89: 806-10.
11. Leroy S, Marc E, Adamsbaum D, Gendrel D, Breart G, Chalumeau M. Prediction of vesicoureteral reflux after a first febrile urinary tract infection in children: validation of a clinical decision rule. *Arch Dis Child* 2006; 91: 241-244.
12. 2-way Contingency Table Analysis: http://statpages.org/ ctab2x2.html (Fecha de consulta: 14/8/2007).
13. Pérez López C. Métodos estadísticos avanzados con SPSS. Thompson. Madrid 2005.
14. Lebowitz RL, Olbing H, Parkkulainen KV, Tamminen-Mobius T. Internacional reflux study in children writing committee: international system of radiographic granding of vesicoureteral reflux. *Pediatr Radiol* 1985; 15: 105-9.
15. Wald ER. vesicoureteral reflux: the role of antibiotic prophylaxis. *Pediatrics* 2006; 117: 919-22.

16. Garín EH, Olavarría F, García Nieto V, Valenciano B, Campos A, Young L. Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. *Pediatrics*. 2006 Mar; 117(3): 626-32.
17. Conway PH, Cnaan A, Zaoutis T, Henry BV, Grundmeier RW, Keren R. Recurrent urinary tract infections in children: risk factors and association with prophylactic antimicrobials. *JAMA* 2007; 298: 179-86.
18. Friedman S, Reif S, Assia A, Levy I. Clinical and laboratory characteristics of non-E Coli urinary tract infections. *Arch Dis Child* 2006; 91: 845-6.
19. Tseng MH, Lin WJ, Lo WT, Wang SR, Chu ML, Wang CC. Does a normal DMSA obviate the performance of voiding cystourethrography in evaluation of young children after their first urinary tract infection? *J Pediatr* 2007; 150: 96-9.