ARTICLE

Disappearance of Vesicoureteral Reflux in Children

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Objective: To describe the disappearance of reflux in children with vesicoureteral reflux, in whom there are presently no population-based long-term studies.

Design: An unselected cohort of children with reflux detected after their first known symptomatic urinary tract infection was followed up prospectively for up to 15 years.

Setting: A single children's hospital in a distinct geographical area at which most children with symptomatic urinary tract infection were treated.

Patients: Two hundred thirty children—173 girls and 57 boys—with unilateral (n=130) and bilateral (n=100) reflux. Dilated reflux (grades III-V) was found in 54 patients (23.5%). The frequency of reflux was 34% in girls and 31% in boys who were examined after urinary tract infection.

Main Outcome Measure: Disappearance of reflux.

Results: The probability of spontaneous disappearance of reflux was estimated using Kaplan-Meier survival curves based on 164 children who underwent multiple voiding cystourethrographies. There was a marked tendency for disappearance of reflux, with 73% of children with dilated reflux having no or only grade I reflux after 10 years. Shorter persistence of reflux was found in children with undilated reflux at the initial investigation and in boys compared with girls. However, age at first investigation was not related to the rate of disappearance, and there was no difference between children with bilateral compared with unilateral reflux.

Conclusions: This study of an unselected group of children with urinary tract infection shows a favorable long-term outcome concerning disappearance of reflux. In children with dilated reflux, this tendency was more pronounced than previously reported.

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Editor's Note: This long-term study not only provides valuable and positive natural history information but points out the importance of long-term follow-up for anyone with a significant problem.

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URINARY TRACT infection (UTI) is one of the most common bacterial infections during childhood. In a study from Göteborg, Sweden, 7.8% of the girls and 1.6% of the boys at age 7 years had had at least 1 symptomatic UTI verified by urinary culture.[1] Vesicoureteral reflux is the most common pathologic finding in children examined after UTI, occurring in about one third of patients.[2,3] In children with febrile UTI, the overall risk of renal scarring according to urography is approximately 10%.[2,4] The term *reflux nephropathy* was introduced by Bailey[5] in 1973 to emphasize the relation between reflux and renal scarring.

Most reports on reflux in children have been retrospective, and the studied patients have been selected in various ways. Data on disappearance of reflux are limited, and to our knowledge there is no long-term study focusing on this aspect in a population-based cohort.

In this article, we describe an unselected group of children followed up prospectively from the first recognized symptomatic UTI until 16 years of age, at most. The aim is to describe the disappearance of reflux and to find factors affecting this course.

RESULTS

Of the 1221 children, 653 had febrile and 568 had nonfebrile first-time UTI. The age

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PATIENTS AND METHODS

In Göteborg, there is only 1 children's hospital. During the 1970s, this distinct geographical area had a population of approximately 430 000 people, of whom 80 000 were younger than 16 years. Few children with acute diseases were handled at outpatient clinics elsewhere, and most children with symptomatic UTI were taken care of at the hospital; 90% of children diagnosed as having febrile UTI were cared for at the children's hospital.[6] The children were followed up at a UTI clinic that provides continuity and uniform follow-up.

PATIENTS

From January 1970 through December 1979, 1221 children, aged birth to 15 years and residents of the city, with the first recognized symptomatic UTI and without previously recognized malformations or neurogenic bladder dysfunction were registered. There were 989 girls and 232 boys. Two boys with urethral valves were excluded from further analysis. All the children attended the hospital because of symptoms. Also, infants with symptoms such as irritability, loss of appetite, or poor weight gain were regarded as having symptomatic UTI. The children were followed up prospectively using a standardized protocol. Detailed clinical data and results of urinary cultures, laboratory tests, and imaging investigations were registered in a database.[7]

DEFINITIONS

A diagnosis of UTI required significant bacteriuria, ie, at least 10^5 colony-forming units per milliliter in 1 midstream or 2 bag urine samples and any growth of bacteria in urine samples obtained by suprapubic bladder aspiration. A child with a temperature of 38.5°C or higher was considered to have a febrile infection.

RADIOLOGICAL INVESTIGATIONS

The general policy was to perform radiological investigations in all children younger than 2 years and in all children with febrile infections. Imaging investigations included voiding cystourethrography (VCU) and urography within 1 to 3 months. Follow-up included urography 1 to 3 years later and, in those with reflux, another VCU. In children with renal scarring or persisting reflux, further investigations were performed at increasing intervals. Resolution of reflux was considered to have occurred at the time between the first VCU with no reflux and the preceding examination.

Reflux was classified into 5 grades according to the International Reflux Study.[8] Renal scarring on urography was defined as localized or generalized reduction of parenchymal thickness with adjacent caliceal deformity according to Hodson.[9]

ANTIBIOTIC TREATMENT

All children with UTI were treated for 10 days. A policy to give children with dilated reflux (grades III-V) or recurrent febrile infections long-term, low-dose antibacterial prophylaxis was gradually introduced during the first half of the 1970s; the drugs used were nitrofurantoin, 1 mg/kg per day, or trimethoprim, 0.5 to 1 mg/kg per day, with or without sulfamethoxazole.

STATISTICAL METHODS

For comparison of proportions, the Fisher exact test was used. Kaplan-Meier survival curves were used to estimate the spontaneous disappearance of reflux. When comparing survival of different groups of reflux grade, the nonparametric log-rank test was used. The Cox proportional hazards regression model was used to analyze several predictors at the same time and to estimate the relative risk (RR) with 95% confidence intervals (CIs), both univariate and adjusted for other predictors.

distribution at the first UTI is shown in **Figure 1**. The highest incidence was noted during the first year of life in both sexes. There were few boys with first-time UTI after infancy, whereas many girls were identified also after 1 year of age.

A total of 688 patients underwent VCU. Among children younger than 2 years, 297 (87.8%) of 338 febrile and 55 (74%) of 74 nonfebrile children were examined. Among children aged 2 years and older, the corresponding numbers were 216 (68.6%) of 315 and 121 (24.5%) of 494, respectively. Reflux was found in 230 children: 173 (34.3%) of 505 girls and 57 (31.1%) of 183 boys. Within this group, the median age at the first UTI was 2.2 years (range, 26 days to 12.0 years) in girls and 0.3 years (range, 4 days to 8.9 years) in boys. Unilateral reflux was found in 130 children (26 boys and 104 girls), and bilateral reflux was found in 100 children (31 boys and 69 girls). This difference between boys and girls did not reach significance (P=.06, Fisher exact test).

Grade of reflux at the first VCU is shown in **Table 1**. In children with bilateral reflux, the most severe grade was used for classification. Fifty-four children with reflux (23%) had dilation (grades III-V), which was significantly more common in boys than in girls (32% vs 21%; $P<.05$).

RENAL SCARRING

Of the 688 children who underwent VCU, all but 1 underwent urography. Renal scarring was ultimately found in 74 patients at follow-up, of whom 60 (81%) had reflux at the first VCU.

SURGICAL GROUP

Twenty-one patients underwent surgery. Neoimplantation of the ureter was performed in 16 patients (**Table 2**). The median time between the first UTI and neoimplantation was 5.9 years (range, 0.4-13.8 years). The main indications were persistence of reflux in combination with renal scarring and recurrent UTI. Two more patients underwent neoimplantation because reflux was complicated by obstruction. Nephrectomy was performed primarily in 2 children and heminephrectomy was performed in 1 child because of severe renal damage.

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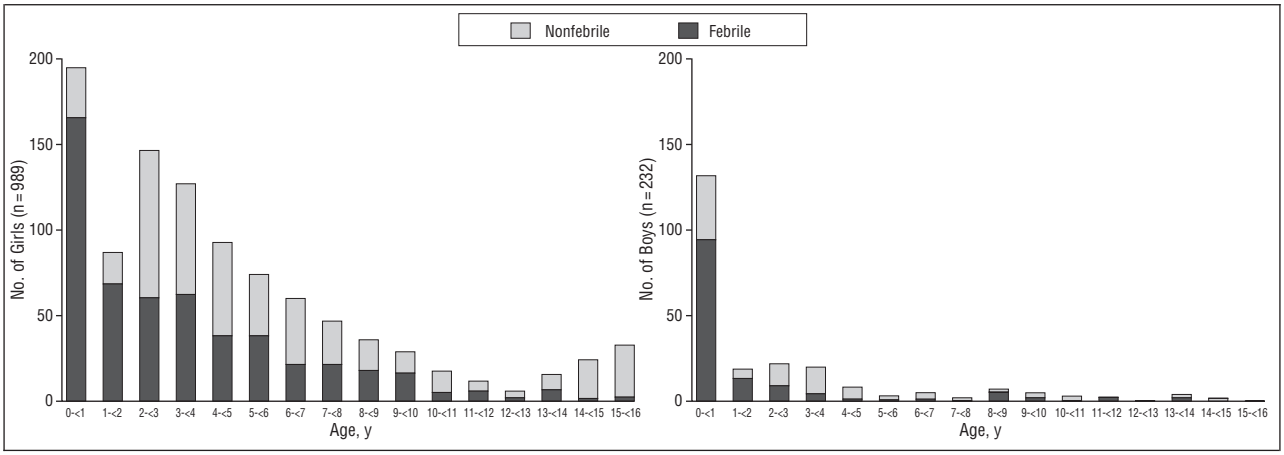

Figure 1. *Age distribution at first symptomatic urinary tract infection. The mean and median ages were 4.7 and 3.6 years, respectively, in girls (left) and 2.3 and 0.6 years, respectively, in boys (right).*

Table 1. Reflux Grade at the First Voiding Cystourethrography

Reflux Grade	No. (%) Boys (n = 183)	No. (%) Girls (n = 505)
0	126 (68.8)	332 (65.7)
I	8 (4.4)	36 (7.1)
II	31 (16.9)	101 (20.0)
III	14 (7.6)	33 (6.5)
IV	2 (1.1)	2 (0.4)
V	2 (1.1)	1 (0.2)

Table 2. Characteristics of the 16 Children Treated With Neoimplantation*

Sex	Age at First UTI	Initial VUR Grade	Renal Scarring Before Surgery	Indication for Surgery†	Time From First UTI to Surgery
F	1 mo	III	0	1	10 mo
M	1 mo	III	1	2	1 y 3 mo
F	2 mo	II	1	1, 3	13 y 10 mo
F	2 mo	III	1	1, 2	5 y 8 mo
F	8 mo	II	1	2, 3	6 y 11 mo
F	11 mo	III	1	1, 3, 4	2 y
F	1 y 2 mo	II	1	1, 2	8 y 2 mo
F	1 y 9 mo	II	0	1, 3	2 y 7 mo
F	2 y 2 mo	III	1	1, 2, 3	7 y 11 mo
F	2 y 2 mo	IV	1	2, 3	7 y 11 mo
F	2 y 5 mo	II	1	2	4 y 9 mo
F	3 y 1 mo	II	1	2, 3	8 y 7 mo
F	3 y 6 mo	II	1	1, 2, 3, 4	7 y 9 mo
F	3 y 9 mo	III	0	1, 3	6 y 1 mo
M	4 y 3 mo	V	1	2	5 mo
F	5 y 3 mo	III	1	1, 2	1 y 4 mo

**UTI indicates urinary tract infection; VUR, vesicoureteral reflux.*
†1 indicates recurrent UTI; 2, new or progressive renal damage; 3, golf-hole ostium[10]; and 4, poor compliance.

CONSERVATIVE GROUP

Of the 210 children with reflux managed conservatively, VCU was performed again in 164—119 girls and 45 boys; in 46 children, VCU was not repeated (**Table 3**). It was decided not to perform a second VCU in 24 patients with reflux grade I. Follow-up was discontinued after the first VCU in 17 children (15 with grade II and 2 with grade III) because the families moved. In 5 cases (4 with grade II and 1 with grade III), the child or parents denied a second investigation because of discomfort.

Figure 2 shows the probability of complete spontaneous disappearance of reflux by Kaplan-Meier survival curves. Children with reflux grades III through V were included in the same group. The tendency for disappearance of reflux was more pronounced for the lower grades of reflux. In the group with reflux grade I at detection, 50% were free of reflux after 2.5 years. In the group with reflux grade II, the corresponding time was 5 years, and in those with reflux grades III through V, the corresponding time was 8 years. Reflux grade I resolved significantly faster than reflux grades III through V ($P<.05$, RR=0.69; 95% CI, 0.48-0.99). However, comparing all 3 groups in order (Cox regression model), the difference in the disappearance rate did not reach statistical significance ($P=.06$).

The same statistical analysis was made using reflux grade I as well as no reflux as end points; this left 144 children with reflux grade II or higher at the first VCU for analysis (**Figure 3**). The median survival time was 2.5 years for reflux grade II and 4.5 years for reflux with dilation. Of children with reflux grade II, 83% reached end point, and of children with dilated reflux, 73% reached end point.

Persistence of reflux was significantly longer in girls compared with boys, both unadjusted ($P=.008$, RR=0.55; 95% CI, 0.36-0.86) and adjusted for reflux grade, unilateral reflux, and duplex-single system ($P=.003$, RR=0.51; 95% CI, 0.32-0.80). Median persistence time for boys was 2 years compared with 6.5 years for girls.

There were 11 children with duplex kidneys within the conservatively treated group (7%). The rate of reflux disappearance was slower in duplex systems, although statistical significance was not reached ($P=.14$, RR=0.47; 95% CI, 0.17-1.29).

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Table 3. Grade of Reflux at First Voiding Cystourethrography (VCU) in the Conservatively Treated Group

Reflux Grade	No. With Repeated VCU	No. Without Repeated VCU
I	20	24
II	107	18
III	32	4
IV	3	0
V	2	0
Total	**164**	**46**

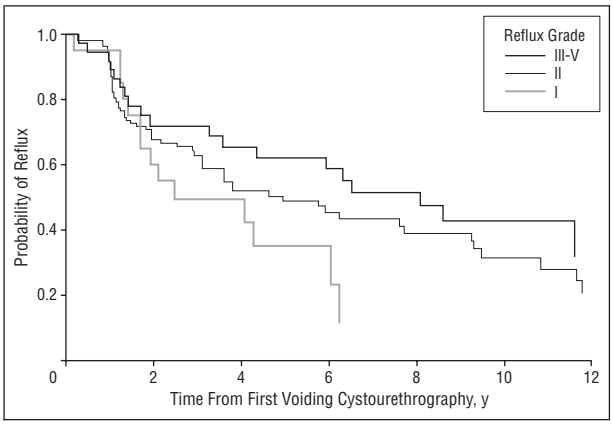

Figure 2. *Kaplan-Meier survival curves showing probability of persistence of any grade of reflux. At baseline, 20 children with grade I, 107 children with grade II, and 37 children with grades III through V were at risk. The corresponding numbers at 4 years were 7, 37, and 20; at 8 years were 1, 18, and 13; and at 10 years were 0, 10, and 5.*

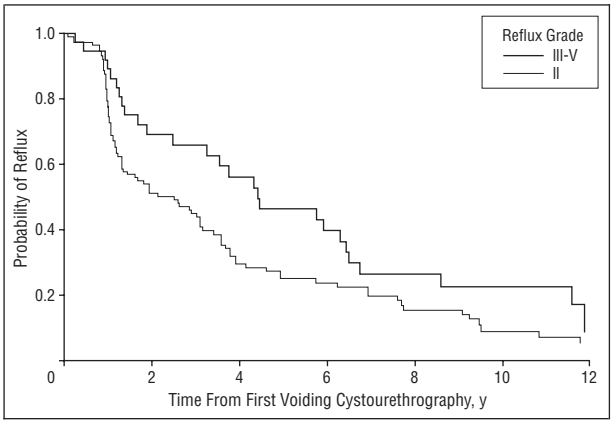

Figure 3. *Kaplan-Meier survival curves showing probability of persistence of reflux grade II or more. At baseline, 107 children with grade II and 37 children with grades III through V were at risk. The corresponding numbers at 4 years were 26 and 17; at 8 years were 11 and 7; and at 10 years were 5 and 4.*

The rate of disappearance was not different in children with unilateral vs bilateral reflux and was not affected by age at first investigation.

COMMENT

To study the natural history of vesicoureteral reflux, frequent cystographic investigations would be of value. However, the VCU is unpleasant because of the need to use a bladder catheter, and the radiation dose is not negligible. This explains the long interval between the investigations in our study, in many cases several years. More frequent investigations will be possible when a noninvasive method with good sensitivity is developed. Even with frequent investigations, an exact time of reflux disappearance will be difficult to establish because there is probably a period of intermittent reflux before a stable, nonrefluxing situation is reached. Our choice of time of resolution or reaching grade I as the halfway mark between 2 VCUs seems to be a reasonable approximation.

Our findings of a high probability of reflux disappearance or of reaching the end point of grade II or less in children with reflux without dilation corroborates previous studies.[11-15] For dilated reflux, comparison is more difficult. In different studies, the follow-up time varies and is given either from the first investigation or according to chronological age. Most authors describe complete disappearance of reflux, whereas diminished reflux is not subdivided so that our end point using grade I can be identified. In the early studies by Edwards et al,[11] 9 (53%) of 17 ureters with dilated reflux reached the end point of reflux grade II or less after 7 to 15 years. In the Birmingham study of children with dilated reflux,[16] 37 (49%) of 75 children randomly allocated to nonoperative treatment were free of reflux at the 5-year investigation. In the International Reflux Study in Children,[17] the corresponding numbers were 57 (25.0%) of 228. Goldraich and Goldraich[14] described disappearance of reflux at age 5 years in 42% to 48% of patients and at age 10 years in 55% to 60% of children with dilated reflux. In the study by Huang and Tsai,[15] reflux disappeared in 58 (54.7%) of 106 ureters with dilating reflux after a mean of 2.4 years. In our study, the end point of reflux grade I or less was reached in 50% of children after 5 years and in approximately 75% of children after 10 years.

We decided to include not only no reflux but also grade I as end points in our results because grade I, in clinical practice, is generally regarded as an innocent finding not requiring reinvestigation.[18]

An unexpected finding was that reflux persisted significantly longer in girls than in boys. In contrast, Goldraich and Goldraich[14] noted a longer persistence of reflux in boys than in girls, although the difference was not statistically significant. The tendency for longer persistence in children with duplex systems was expected, but an important improvement of the reflux status also can occur in these patients. In the International Reflux Study in Children,[17] there was a markedly better reflux improvement in children with unilateral compared with bilateral reflux. This difference was not seen in our study.

These inconsistencies in results may be explained by differences in the patient materials. Whereas our study was population based, followed up children from their first UTI, and included all grades of reflux as well as children with duplex kidneys, the other studies used more or less selected materials. Another problem is that the reflux status is often given for ureters in other studies, whereas we consider patients to be of main interest.

We described patients who underwent neoimplantation in Table 2; such information has often been lacking in previous reports. Of these 16 patients, 7 had re-

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flux grade III and 7 had grade II at the initial VCU. In general, a more conservative regimen is currently used. These patients were not included in the survival curves.

In conclusion, this study of an unselected group of children with reflux after UTI shows a favorable long-term outcome concerning disappearance of reflux, especially when considering grade I or less as the end point. Even children with dilated reflux had a high probability of resolution or marked improvement. Grade of reflux and sex had an impact on rate of disappearance, whereas age at detection or whether reflux was unilateral or bilateral did not affect the rate of disappearance.

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REFERENCES

1. Hellström A, Hanson E, Hansson S, Hjälmås K, Jodal U. Association between urinary symptoms at 7 years old and previous urinary tract infection. *Arch Dis Child*. 1991;66:232-234.
2. Winberg J, Andersson HJ, Bergström T. Epidemiology of symptomatic urinary tract infection in childhood. *Acta Paediatr Scand Suppl*. 1974;252:1-20.
3. Blickman J, Taylor G, Lebowitz R. Voiding cystourethrography: the initial radiologic study in children with urinary tract infection. *Radiology*. 1985;156:659-662.
4. Pylkkänen J, Vilska J, Koskimies O. The value of level diagnosis of childhood urinary tract infection in predicting renal injury. *Acta Paediatr Scand*. 1981;70:879-883.
5. Bailey RR. The relationship of vesicoureteral reflux to urinary tract infections and chronic pyelonephritis: reflux nephropathy. *Clin Nephrol*. 1973;1:132-141.
6. Hansson S, Martinell J, Stokland E, Jodal U. The natural history of bacteriuria in childhood. *Infect Dis Clin North Am*. 1997;3:499-512.
7. Jodal U. The natural history of urinary tract infection in childhood. *Infect Dis Clin North Am*. 1987;1:713-729.
8. Report of the International Reflux Study Committee. Medical versus surgical treatment of primary vesicoureteric reflux: a prospective international reflux study in children. *J Urol*. 1981;125:277-283.
9. Hodson CJ. The radiological contribution toward the diagnosis of chronic pyelonephritis. *Radiology*. 1967;88:857-871.
10. Lyon RP, Marshall S, Tanagho EA. The ureteral orifice: its configuration and competency. *J Urol*. 1969;102:504-509.
11. Edwards D, Normand ICS, Prescod N, Smellie JM. Disappearance of vesicoureteric reflux during long-term prophylaxis of urinary tract infection in children. *BMJ*. 1977;2:285-288.
12. Skoog SJ, Belman AB, Majd M. A nonsurgical approach to the management of primary vesicoureteral reflux. *J Urol*. 1987;138:941-946.
13. Arant BS. Medical management of mild and moderate vesicoureteral reflux: followup studies of infants and young children: a preliminary report of the Southwest Pediatric Nephrology Study Group. *J Urol*. 1992;148:1683-1687.
14. Goldraich NP, Goldraich IH. Followup of conservatively treated children with high and low grade vesicoureteral reflux: a prospective study. *J Urol*. 1992;148:1688-1692.
15. Huang F-Y, Tsai T-C. Resolution of vesicoureteral reflux during medical management in children. *Pediatr Nephrol*. 1995;9:715-717.
16. Birmingham Reflux Study Group. Prospective trial of operative versus nonoperative treatment of severe vesicoureteric reflux in children: five years' observation. *BMJ*. 1987;295:237-241.
17. Tamminen-Möbius T, Brunier E, Ebel KO, et al. Cessation of vesicoureteral reflux for 5 years in infants and children allocated to medical treatment. *J Urol*. 1992;148:1662-1666.
18. Bailey RR. Commentary: the management of grades I and II (nondilating) vesicoureteral reflux. *J Urol*. 1992;148:1693-1695.

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