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# EXPERIENCE WITH VESICOURETERAL REFLUX IN CHILDREN: CLINICAL CHARACTERISTICS

SAUL P. GREENFIELD, MANYAN NG AND JULIAN WAN

*From the Department of Pediatric Urology, Children's Hospital of Buffalo and State University of New York at Buffalo, School of Medicine, Buffalo, New York*

ABSTRACT

Purpose: We reviewed our 9-year experience with a large population of children with vesicoureteral reflux who were evaluated and treated according to contemporary concepts.

Materials and Methods: From 1985 to 1993 we followed 288 boys and 752 girls with vesicoureteral reflux. If surgery was not performed, patients were on antibiotic prophylaxis and evaluation was done every 18 months with contrast voiding cystography and radionuclide renal imaging. Urine cultures were obtained every 4 months. Two negative voiding cystourethrograms 1 year apart were required to discontinue prophylaxis.

Results: The major reasons for initial evaluation were urinary tract infection in 560 children (54%), voiding dysfunction without urinary tract infection in 156 (15%), sibling surveys in 122 (12%) and prenatal hydronephrosis in 23 (2%). In 150 kidneys (10%) in 132 children scarring at presentation was grade 0 in 10 (7%), I in 18 (12%), II in 27 (18%), III in 30 (20%), IV in 48 (32%) and V in 17 (11%). Of these 132 patients 17 presented at ages less than 1 year (13%), 29 at ages 1 to 3 (22%), 50 at ages 4 to 6 (38%), 24 at ages 7 to 9 (18%) and 12 at ages greater than 10 (9%). No new scars were seen in children on prophylaxis without breakthrough infection. After 1 negative voiding cystourethrogram reflux was noted again in 27% of the cases. Breakthrough infections developed in 62 children of whom a third were older than 7 years. Reimplantation in 205 children (20%) was performed for grade IV to V reflux (101), breakthrough infection (62), advanced age (18), large periureteral diverticulum (12) and noncompliance (3). Five boys and 57 girls (30% of all children) had urinary tract infections after successful reimplantation.

Conclusions: Almost half of the children with vesicoureteral reflux have no history of culture proved urinary tract infection. Scarring may be associated with any reflux grade and it may be initially diagnosed at any age. Only half of the scars are noted with higher grades of reflux (IV and V). Continuous prophylaxis prevents new scarring. Breakthrough infections are rare but they can occur at ages greater than 7 years. Two consecutive negative cystograms are necessary before discontinuing prophylaxis. Children should be monitored after reimplantation for recurrent urinary tract infection.

KEY WORDS: vesico-ureteral reflux, kidney, urinary tract infections

As a clinicopathological entity, vesicoureteral reflux was first identified in children in conjunction with urinary tract infection.[1] The major morbidity of vesicoureteral reflux, that is reflux nephropathy, may result in hypertension and various degrees of renal insufficiency in the minority of patients most significantly affected.[2,3] It is now established that ongoing renal scarring does not usually occur in the presence of vesicoureteral reflux unless there are intercurrent infections.[4–9] Except in certain experimental animal models, sterile reflux does not appear to cause any meaningful alterations in renal function or development.[10–12] This observation has been confirmed by a number of large prospective clinical trials that exclusively enrolled children who initially presented with a urinary tract infection. This information with the observation that much low grade vesicoureteral reflux spontaneously resolves with somatic growth has led to continuous antibiotic prophylaxis therapy for most children rather than immediate surgical correction.

More recently vesicoureteral reflux has been identified in populations without a history of urinary tract infection. These children are brought to medical attention because of prenatal ultrasound, voiding dysfunction and prospective sibling screening.[13–15] A number of these children are found to have scarring immediately after birth, and so urinary tract infection was not the cause.[16] These scars are thought to be congenital or dysplastic and not secondary to episodes of pyelonephritis.

Regardless of the underlying diagnosis, most children with vesicoureteral reflux are placed on antibiotic prophylactic regimens. Surgery is reserved for patients with higher reflux grades and breakthrough infection, lack of compliance, and those who have reached an end point age after which resolution is unlikely. Given the change in demographics in contemporary populations of children with reflux, we reviewed our 9-year experience. We closely evaluated reasons for presentation and subsequent clinical course based on current concepts of management.

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## MATERIALS AND METHODS

We prospectively monitored 1,040 children (1,463 ureters) with vesicoureteral reflux who were enrolled from 1985 through 1993, including 288 boys (28%) and 752 girls (72%). All patients were evaluated using contrast voiding cystography and technetium stannous glucoheptonate or technetium dimercapto-succinic acid renal scans initially and every 18 months thereafter. Unless early surgery was performed, all patients were placed on continuous low dose antibiotic prophylaxis regimens with trimethoprim-sulfamethoxazole or

nitrofurantoin. Urine cultures were obtained every 4 months at office visits. Breakthrough infection was defined as an infection with an organism resistant to the prophylactic antibiotic, as documented by the hospital bacteriology laboratory. Infections with organisms sensitive to the prophylactic antibiotic were attributed to a lapse in compliance. Two negative voiding cystourethrograms 1 year apart were required to discontinue prophylaxis. Patients who failed to return to an office visit were contacted by mail. In addition to office counseling, all families received written materials describing reflux, its management and its clinical importance. All children who underwent surgery were monitored an additional 2 years with periodic urine cultures.

## RESULTS

The major reasons for initial evaluation were urinary tract infection in 560 cases (54%), voiding dysfunction without infection in 156 (15%), sibling screening in 122 (12%), prenatal ultrasound in 23 (2%) and other in 179 (17%). Reflux was grade I in 296 ureters (20%), II in 676 (46%), III in 317 (22%), IV in 124 (9%) and V in 50 (3%). A total of 211 children was initially diagnosed at ages less than 1 year (20%), 320 at ages 1 to 3 (31%), 304 at ages 4 to 6 (29%), 135 at ages 7 to 9 (13%) and 70 at ages greater than 10 (7%). In 150 kidneys (10%) in 132 children (13%) scarring at presentation was grade 0 in 10, I in 18 (12%), II in 27 (18%), III in 30 (20%), IV in 48 (32%) and V in 17 (11%) (table 1). Of these 132 patients 17 presented at ages less than 1 year (13%), 29 at ages 1 to 3 (22%), 50 at ages 4 to 6 (38%), 24 at ages 7 to 9 (18%) and 12 at ages greater than 10 (9%). Of all children who presented with scars 103 (78%) had a history of infection.

In the children followed on prophylaxis without breakthrough infection no new scars were seen. Of the entire group 354 patients (34%) were lost to followup. A total of 481 children (46%) was monitored on prophylaxis, including 193 with 1 negative voiding cystourethrogram during observation. Of these 193 children repeat voiding cystography was positive in 53 (27%), necessitating continued prophylaxis, while 2 consecutive voiding cystourethrograms were negative in 140. Reimplantation was done in 205 children (20%) for grade IV to V reflux (63 girls and 38 boys), breakthrough infection (60 girls and 2 boys), older age (14 girls and 4 boys), large periureteral diverticulum (4 girls and 8 boys) and noncompliance (3). Of the 62 children with breakthrough infection reflux was grade I in 2, II in 19, III in 24, IV in 14 and V in 3 with the higher grade noted in the presence of bilateral disease (table 2). Breakthrough infection was present in 3 patients at ages less than 1 year, 14 at ages 1 to 3, 24 at ages 4 to 6, 15 at ages 7 to 9 and 6 at ages greater than 10, including 49 (80%) who initially presented with a urinary tract infection.

Five boys and 57 girls who underwent reimplantation (30% of the total) had recurrent urinary tract infection (episodes of cystitis without clinical pyelonephritis) even after successful surgery, including 11 who underwent surgery at ages less than 1 year, 10 at ages 1 to 3, 26 at ages 4 to 6, 9 at ages 7 to 9 and 6 at ages greater than 10. The major initial presenting diagnoses were urinary tract infection in 52 patients, voiding dysfunction without urinary tract infection in 3 and sibling screening in 5. Initial operations were performed at ages less than 1 year in 11 children, ages 1 to 3 in 10, ages 4 to 6 in 26, ages 7 to 9 in 9 and ages greater than 10 in 6. The major reasons for initial reimplantation in these children were high grade reflux in 24, breakthrough infection in 27, advancing age in 7 and periureteral diverticulum in 3.

TABLE 1. *Scarring in 150 kidneys at presentation*

| | No. Kidneys (%) |
|---|---|
| Reflux grade: | |
| I | 18 (12) |
| II | 27 (18) |
| III | 30 (20) |
| IV | 48 (32) |
| V | 17 (11) |
| Scars and no reflux | 10 (7) |
| Pt. age at diagnosis (yrs.): | |
| Younger than 1 | 17 (13) |
| 1–3 | 29 (22) |
| 4–6 | 50 (38) |
| 7–9 | 24 (18) |
| Older than 10 | 12 (9) |
| Diagnosis: | |
| Urinary tract infection | 103 (78) |
| Voiding dysfunction | 9 (7) |
| Sibling | 9 (7) |
| Hematuria | 6 (5) |
| Prenatal | 2 (2) |
| Other | 3 (2) |

TABLE 2. *Children with breakthrough urinary tract infections*

| | No. Pts. |
|---|---|
| Grade:* | |
| I | 2 |
| II | 19 |
| III | 24 |
| IV | 14 |
| V | 3 |
| Pt. age (yrs.): | |
| Younger than 1 | 3 |
| 1–3 | 14 |
| 4–6 | 24 |
| 7–9 | 15 |
| Older than 10 | 6 |

* Higher grades noted when reflux was bilateral.

## DISCUSSION

The management of vesicoureteral reflux in children has not been standardized but certain basic principles can be derived from the literature. Large scale prospective studies have shown that reflux of any grade or at any patient age can be well tolerated as long as there are no urinary tract infections.[5–8] These studies were based on populations that initially presented with urinary tract infection. More recently, other populations at risk but without a history of infection have been identified, such as asymptomatic siblings of children with reflux, children with voiding dysfunction and no history of infection, and infants diagnosed prenatally.[13–16] In our experience these individuals comprise almost half (46%) of all children with reflux whom we follow.

Only 13% of our entire population presented with a renal scar. Renal scarring was most often seen in those with a prior infection (78%) but 22% of our patients in whom scars were noted at diagnosis had no history of infection. Previous studies have shown that up to 30% of children diagnosed because of an infection have scars at presentation and up to 50% have scars if the reflux is high grade.[9,17,18] Observed scarring in populations without a history of infection is presumably congenital or secondary to an unrecognized infection. In our series scarred kidneys were associated with any reflux grade or patient age. Only half of the scarred kidneys were associated with grades IV and V reflux. Infants and older children, even those older than 10 years, had scars at diagnosis. This distribution and incidence has been corroborated by others in noninfected populations. Scott noted that up to 45% of newborns discovered to have reflux prenatally had congenital scars.[13] Scars have also been found in up to 14% of asymptomatic siblings, many of whom were older than 10 years at the initial diagnosis.[14] Of older children with voiding dysfunction and no history of infection 20% also had scars at presentation.[15]

If surgery is not performed, we routinely place all children with reflux on antibiotic prophylaxis regardless of the underlying presenting diagnosis. Prophylaxis is continued until

resolution has been documented. As demonstrated by others, new scars are successfully prevented by this approach and none of our patients on prophylaxis had new scars on radionuclide imaging unless they also had a breakthrough infection. Breakthrough infection is rare and it only occurred in 62 children or 13% of those followed long term.

Breakthrough infection rates have been previously reported but only in children who initially presented with infection. In children with higher grades of reflux breakthrough infection rates have varied from 4 to 38%.[5,6,19] Arant monitored children with nondilating, low grade reflux and noted a breakthrough infection rate of 18%.[20] A third of our patients in whom breakthrough infection developed were 7 years old or more and 73% had low grade (I to III) reflux. Most but not all of these children were initially diagnosed with reflux because of a presenting urinary tract infection. Belman suggested that prophylaxis should be discontinued in children older than 7 years.[1] However, Smellie et al showed that older children with reflux have new scarring with infection,[21] which agrees with our data that prophylaxis must be continued until resolution, no matter what the age. Two consecutive negative cystograms are necessary before releasing a patient from care, since a quarter have reflux again after a single negative study.

Unfortunately, a third of the children in this series were lost to followup, and so remained untreated despite a program of written materials and aggressive attempts to contact those who missed appointments. Previously reported compliance rates have ranged widely from 12 to 90%.[6,20] This large variation is difficult to explain and it may reflect cultural, regional or socioeconomic differences. A detailed analysis of our experience revealed that there were no socioeconomic factors that enabled the clinician to predict who would not remain on prophylaxis until resolution.[22] Therefore, it must be emphasized that a sizable untreated population results from the blanket recommendation of nonoperative therapy. While noncompliance with a medical regimen is said to be an indication for earlier surgery, this situation rarely occurred in our experience. Only 3 children underwent surgery for this reason, since poorly compliant families did not return to discuss options.

Of our population 205 children (20%) underwent surgery, mainly for high grade reflux or breakthrough infection. Skoog et al reported a 14% rate of surgery in a group with all grades of reflux using similar but not identical indications.[6] Rates of antireflux surgery vary among regions and referral centers, and so they remain largely unknown. Furthermore, the introduction of regional anesthesia, shorter hospital stays and closed cystoscopic techniques may make surgical intervention more common with time. Almost a third of our patients had documented urinary infections after successful reimplantation surgery. Jodal et al reported infection rates as high as 39% after reimplantation surgery in the European arm of the International Reflux Study.[19] However, a number of those patients had ureteral obstruction postoperatively as well as pyelonephritis. Many but not all of our patients who had postoperative infections had had a breakthrough infection on prophylaxis and most initially presented due to infection, which suggests that these populations are especially infection prone. It may also help to explain the relatively high incidence of urinary infection in pregnant women who previously underwent successful reimplantation surgery.[23] Therefore, surgeons should follow these patients for a period after surgery. In addition, families should be made aware that urinary infections are not eradicated by antireflux surgery.

## CONCLUSIONS

Almost half of the children with reflux have no history of culture proved urinary tract infection in contemporary populations. Renal scarring can occur with any grade of reflux or at any time in childhood and only half of the cases associated with higher reflux grades (IV or V). Most but not all children who have renal scarring at diagnosis present with infection. Continuous prophylaxis prevents renal scarring and breakthrough infection is rare. Many breakthrough infections develop in children older than 7 years, and so prophylaxis should be continued until resolution is documented. Two consecutive negative cystograms are necessary before discontinuing prophylaxis. A third of families remain noncompliant with long-term prophylaxis and, thus, children remain untreated. Few children actually undergo surgery due to lack of compliance with a medical regimen, since these families do not return to the urologist. While often successful for eliminating reflux, reimplantation surgery does not eradicate infection in these children and almost a third have urinary tract infections postoperatively.

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