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Clinical Outcomes and Long-Term Resolution in Patients with Persistent Vesicoureteral Reflux after Open Ureteral Reimplantation

Katherine C. Hubert¹, Paul J. Kokorowski¹, Lin Huang², Michaela M. Prasad¹, Ilina Rosoklija¹, Alan B. Retik¹, and Caleb P. Nelson¹

¹Department of Urology, Children's Hospital Boston, Boston, MA

²Clinical Research Program, Children's Hospital Boston, Boston, MA

Abstract

Purpose—Success rates of ureteral reimplantation for primary vesicoureteral reflux (VUR) are high. Few studies document the natural history of children with persistent VUR. We reviewed their clinical outcomes and long-term resolution.

Materials and Methods—We performed a retrospective review of all children with persistent VUR (grade 1) into the reimplanted ureter(s) on initial cystogram after reimplantation for primary VUR at our institution from January 1990 - December 2002. We evaluated subsequent cystograms (graded on the 3-point radionuclide cystogram scale), surgery, and urinary tract infection (UTI). We performed survival analyses of time to resolution of persistent (grade 1) and clinically significant (grade 2) VUR in patients with >1 postoperative cystogram.

Results—Of 965 patients, 59 (94 ureters) had persistent VUR (6.1%): 19 grade 1/3, 29 grade 2/3 and 11 grade 3/3. Median age at reimplantation was 1.9 years; 62.7% were female. Preoperative VUR grade was 2/3 in 42.4% and 3/3 in 57.6%; 30.5% had ureteral tapering. Median follow-up was 47.1 months (IQR 19.3–65.3). 26/36 (72.2%) patients resolved; median time to resolution was 20.4 months. 21/32 with grade 2 on postoperative cystogram (65.6%) resolved; median time to resolution was 20.4 months. 10 had persistent VUR at last cystogram; grade 1 or 2 in 9 patients and 3/3 in 1 patient. One had repeat reimplantation for persistent VUR. 7 patients (13%) had postoperative febrile UTI at a median of 37 months postoperatively (IQR 1.7–64.4).

Conclusions—Persistent VUR after reimplantation resolves spontaneously in most children and can be managed non-operatively with good long-term outcomes.

Keywords

Vesico-ureteral reflux; Surgical Procedures; Operative; Follow-up Studies

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Correspondence: Caleb P. Nelson, MD, MPH, Dept. of Urology, Hunnewell 390, Children's Hospital Boston, 300 Longwood Ave, Boston, MA 02115, Phone: 617-355-3338, Fax: 617-730-0474, caleb.nelson@childrens.harvard.edu.

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INTRODUCTION

Ureteral reimplantation remains the gold standard for surgical treatment of primary vesicoureteral reflux (VUR). The technical success rate, based on postoperative screening cystography, is so high that several groups have suggested that routine postoperative cystography is unnecessary.^{1–3} However, most studies have shown that a small percentage of reimplantation procedures fail. Previously reported risk factors for persistent VUR after reimplantation include male gender, high-grade preoperative VUR, dysfunctional voiding, preoperative hydronephrosis, ureteral tapering and younger age.^{3–5} Although most of these children seem to do well, their management represents a therapeutic dilemma. Available alternatives include surveillance, repeat reimplantation, or endoscopic therapy, but there are few studies documenting the natural history among the small group with persistent VUR. The purpose of this study was to describe risk factors, clinical outcomes and long-term resolution in patients with persistent VUR on initial screening cystography after ureteral reimplantation for primary VUR.

METHODS

We performed a retrospective review of all patients with primary VUR (all grades) who underwent open ureteral reimplantation at our institution between January 1990 and December 2002. Data were collected from electronic billing and medical records after approval by the Institutional Review Board. Intravesical and extravesical procedures were included, as were reimplantations requiring ureteral tapering. We excluded all patients with secondary VUR (those with neurogenic bladder or neural tube defects, posterior urethral valves, bladder exstrophy, renal transplant, prune belly syndrome, or ureterocele) as well as repeat, laparoscopic or robotic, and endoscopic procedures.

Surgical outcomes were analyzed among those patients with a routine postoperative screening cystogram (radionuclide cystogram (RNC) or voiding cystourethrogram (VCUG)) performed within 9 months of reimplantation (range 0.4–8.9 months). Patients were excluded if they a) had no postoperative cystogram, or b) had an initial postoperative cystogram >9 months after reimplantation. (Late cystograms are more likely performed for clinical indications (e.g. UTI) and may represent a biased sample. Surgical success was defined as the absence of VUR (grade 0) into the reimplanted ureter(s) on the initial postoperative screening cystogram, while any degree of VUR (grade 1) was defined as persistent VUR.

Among those with persistent VUR, we evaluated demographics, clinical presentation, preoperative and postoperative VUR grades, procedure variables, additional surgical procedures and incidence of postoperative UTI. Toilet-trained patients (>30 months of age) were assessed for any evidence of dysfunctional elimination syndrome (DES).

Preoperative VUR was graded based on the final preoperative cystogram. Since most of these cystograms were RNC's, we elected to use the 3-point RNC scale in order to grade both preoperative and postoperative VUR.⁶ In cases where the final cystogram was a VCUG (typically graded using the 5-point scale based on the International Reflux Study (IRS)), we converted these scores to the 3-point RNC scale as follows: IRS Grade I = RNC grade 1/3, IRS Grade II or III = RNC grade 2/3, IRS grade IV or V = RNC grade 3/3.⁷ In cases of bilateral VUR, the patient was categorized based on the grade on the higher grade side. DES was considered present if voiding symptoms (frequency, urgency, incontinence, voiding postponement), with or without constipation, were addressed in the medical record in children who were at least 30 months of age.⁸ Procedure variables analyzed included intravesical vs. extravesical approach, ureteral tailoring (tapered or excised), and

reimplantation of single system vs. duplex system (considered “duplicated” if at least one duplex system was reimplanted).

In the persistent VUR group, the primary outcome was the long-term resolution of persistent VUR into the reimplanted ureter(s). Resolution was defined as grade 0 VUR on subsequent postoperative cystography following the initial postoperative cystogram. The decision to perform subsequent postoperative cystography was at the discretion of the attending urologist. Because grade 1 VUR is of uncertain clinical significance, we also performed a secondary analysis looking at time to resolution of “clinically significant” VUR (grade 2); in this secondary analysis, resolution was defined as VUR grade 0 or 1 on subsequent cystography. Additional clinical endpoints included incidence of additional anti-reflux surgery and of UTI during the follow-up period. Because VUR may not be clinically significant if it is not associated with postoperative UTI, we also assessed the incidence of UTI in the population with persistent VUR.

Bivariate tests of association were performed using Fisher’s exact test or Wilcoxon rank-sum test as appropriate based on data characteristics. We performed a survival analysis of time to resolution of persistent VUR using Cox proportional hazards regression. In cases of additional anti-reflux procedures on the side of the reimplanted ureter, such patients were censored in the survival analysis at the time of additional surgery. All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC). All tests were two-sided and p-values of ≤ 0.05 were considered significant.

RESULTS

Sample characteristics

We identified 1413 patients who underwent open reimplantation for VUR during the study period, of whom 1076 had primary VUR. 965 of these (89.7%) had an initial postoperative screening cystogram performed within nine months of reimplantation. These patients were more likely to be white (90.1% vs. 70.0%, $p < 0.0001$), have preoperative grade 3/3 VUR (45.5% vs. 28.2%, $p = 0.005$), a duplex system (19.7% vs. 11.7%, $p = 0.04$), than those who did not have an initial postoperative screening cystogram performed within nine months. There was no difference in age, gender, clinical presentation, bilaterality, surgical technique and ureteral tapering between the two groups. 111/1076 (10.3%) patients were excluded because they did not have an initial postoperative cystogram within nine months of reimplantation. Of these 111, 36 (32.4%) had their initial postoperative cystogram more than 9 months after surgery. Of these 36, only one (2.8%) was subsequently diagnosed with persistent VUR (grade 2). 75/111 (67.5%) of the excluded patients never had any postoperative cystography. Three (2.7%) of the excluded patients had a postoperative febrile UTI.

Of the 965 patients included in the study, 906 (93.9%) had no VUR (grade 0) into the reimplanted ureter(s). 59 patients (94 ureters) had persistent VUR (grade 1) into the reimplanted ureter(s) (6.1%).

Most patients with persistent VUR had high-grade VUR on preoperative imaging, and presented with UTI (Table 1). At least one preoperative breakthrough UTI (while on antimicrobial prophylaxis and after VUR diagnosis) occurred in 23/59 patients (39%). 8/34 (23.5%) patients with grade 3/3 preoperative VUR had breakthrough UTI, whereas 15/25 (60%) patients with grade 2/3 preoperative VUR had breakthrough UTI.

Although the patients with persistent VUR were similar to those who underwent successful reimplantation in some ways, there were some differences. There were no differences in

race, preoperative VUR grade, laterality, surgical technique or type of system reimplanted. The persistent VUR group was younger (median age 1.9 vs. 4.7 years, $p<0.001$), more likely to be male (37.3% vs. 25.5%, $p=0.05$), had a higher rate of ureteral tapering (30.5% vs. 7.6%, $p<0.0001$), were more likely to have presented with prenatal hydronephrosis (27.6% vs. 10.8%, $p=0.0005$), and were less likely to have presented with UTI (63.8 vs. 81.3%, $p=0.0005$).

Post-reimplantation VUR

Among the 59 patients with persistent VUR, there was a general correlation between pre- and postoperative VUR grades (Table 2), particularly among those with low-grade VUR preoperatively (grade 2/3). Very few patients with low grade VUR preoperatively had high-grade VUR postoperatively. The distribution of postoperative VUR grades was wider among those with high-grade VUR (grade 3/3) preoperatively.

For 22 of the 59 patients (37.3%) with persistent VUR, no further imaging beyond the initial postoperative screening cystogram was performed; as expected, the majority of these had very low-grade VUR (grade 1/3). The initial postoperative grades were grade 1/3 in 14 patients (63.6%), grade 2/3 in 7 patients (31.8%), and grade 3/3 in 1 patients (4.6%). These 22 patients did not differ from those with subsequent cystography in age, gender, race, presentation, preoperative VUR grade, bilaterality, surgical technique, duplication, or ureteral tapering, but were less likely to have postoperative grade 2/3 or 3/3 VUR compared to those who did have subsequent cystography (20.0% vs. 80.0%, $p<0.0001$). None of the 22 experienced a postoperative febrile UTI at median follow-up of 20.6 months.

Among the 37 patients (62.7%) who did have subsequent postoperative cystography, the initial postoperative VUR grade was grade 1/3 in 5 (13.5%), grade 2/3 in 22 (59.5%) and grade 3/3 in 10 (27.0%). Resolution of VUR (defined as grade 0 VUR) occurred in 26/37 patients (70.3%) at a median postoperative time of 20.4 months [95% CI: 15.2–30.3 months] (Figure 1), including all five of those with initial postoperative grade 1/3 VUR. The 5-year probability of persistent VUR among patients with persistent VUR on initial postoperative screening cystogram was 15.6%. Age, gender, laterality, surgical technique, ureteral tapering, system reimplanted, preoperative or postoperative VUR grade, and presence of DES were not associated with time to resolution.

Evaluating the secondary outcome of “clinically significant” VUR (grade $>1/3$), 21/32 patients (65.6%) had documented resolution at a median postoperative time of 20.4 months [95% CI: 15.2–26.9] (Figure 2). The 5-year probability of persistent VUR in this group was 14.8%. Ten patients had persistent VUR at the last cystogram; grade 1/3 in 3, grade 2/3 in 6 and grade 3/3 in 1.

Only 2 patients in this series underwent additional reimplantation procedures. One who had persistent grade 3/3 VUR had two failed attempts at endoscopic treatment followed by successful bilateral reimplantation 46 months after the initial procedure. Another patient underwent successful contralateral reimplantation for new contralateral VUR (grade 3/3) 30 months after the initial reimplantation (the ipsilateral ureter had already resolved spontaneously, and was not reimplanted).

Postoperative UTI

Of the 59 patients with initial persistent VUR, 7 (11.9%) had at least one documented febrile UTI following reimplantation. Median time from reimplantation to initial postoperative febrile UTI was 37.0 months (IQR 1.7–64.4). Although the incidence of postoperative febrile UTI among those with persistent VUR was higher (11.9%) than among those who

underwent successful reimplantation (6.6%), this difference was not statistically significant ($p=0.1$).

Among the group with UTI, the initial postoperative VUR grades were grade 1/3 in one patient and grade 2/3 in six. Five of the patients had persistent VUR at the most recent check prior to the UTI (median time of cystogram 7.3 months prior to the UTI), but all had resolution of their persistent VUR on subsequent imaging (median 9.8 months post-UTI [IQR 8.2–20.8]). It is uncertain which, if any, of these five patients actually had persistent VUR at the time of the UTI. The other two patients with UTI previously had documentation of VUR resolution at 40 and 16 months postoperatively (at 7 and 24 months prior to the UTI, respectively). The former patient had confirmation of persistent VUR resolution 5 months after the UTI. Age, gender, race, clinical presentation, type of collecting system, laterality, surgical technique, ureteral tapering and preoperative or postoperative VUR grade and DES were not associated with postoperative febrile UTI.

DISCUSSION

Ureteral reimplantation remains the gold standard for surgical treatment of VUR in children, despite recent advances in minimally invasive surgery.⁹ Although technical success rates are high, patients with persistent VUR after reimplantation represent a therapeutic challenge.⁷ In this study we reported a large series of such reimplantation failures and assessed their long-term clinical outcomes.

There are few studies describing the natural history of persistent VUR after ureteral reimplantation.^{1–3} Bisignani and colleagues found that 3/207 (1.4%) reimplanted ureters had persistent VUR that resolved in all cases within 2 years.¹ Barrieras and colleagues noted persistent VUR in 6.8% and 3.2% of patients at 3 and 12 months respectively following reimplantation.³

Although it appears that most children with persistent VUR after reimplantation will not need further intervention, there are selected patients for whom additional anti-reflux procedures are indicated. Several groups have suggested endoscopic management since it avoids the challenges of re-operative reimplantation.^{10–12} Reported success rates for a single dextranomer/hyaluronic acid (DHA) injection for persistent VUR following reimplantation range from 70–83%.^{10–12} Lower DHA success rates have been reported in patients with an initial diagnosis other than primary VUR, in those with persistent voiding dysfunction prior to injection and following tapered reimplantation.^{10–11} Various hypotheses have been suggested to explain why persistent VUR occurs following reimplantation.¹³ It may be secondary to technical issues exacerbated by postoperative edema and/or infection.¹³ Persistent high-grade VUR may be due to the presence of non-compressible distal ureters owing to chronic inflammatory or ischemic changes.¹³ This may explain why tapered reimplantation has been shown to be a risk factor for persistent postoperative VUR in our study and others.⁵

In our cohort, most of the persistent VUR after reimplantation was low-grade, and resolved spontaneously in most patients who had subsequent postoperative cystography. The majority of our patients with persistent VUR after reimplantation did not require any further anti-reflux procedures. We found that neither age, gender, laterality, surgical technique, ureteral tapering, preoperative nor postoperative VUR grade was associated with time to resolution.

The results of this study should be interpreted in light of its limitations, including those inherent in the methodology of a retrospective record review. These single-institution findings over a lengthy period of time may not be generalizable to other settings, institutions, surgeons, or to contemporary practice. A further limitation is that not all

patients had postoperative screening cystography, potentially introducing selection bias. The 89.7% who had postoperative cystography were younger (median age 4.6 vs. 6.4 years, $p=0.0007$), had more preoperative grade 3 VUR (45.5% vs. 28.2%, $p=0.0005$), were more likely to be white (90.1% vs. 70.0%, $p<0.0001$), and were more likely to have a duplex system (19.7% vs. 11.7%, $p=0.04$) than those who did not have cystography. However, there was no difference in age, gender, clinical presentation, surgical technique, bilaterality and ureteral tapering between the two groups. Therefore, the analyzed group is reasonably representative of all patients undergoing reimplantation.

The sample of patients included in the survival analysis is also selected, as it includes only those patients who had >1 postoperative cystogram. It is possible that this introduces bias if, in fact, patients who did not get a subsequent cystogram differ systematically from those who did. It is also important to note, however, that all patients with postoperative grade I VUR who had subsequent imaging had resolution. It seems reasonable to presume that patients with postoperative grade I VUR who did not get subsequent imaging were highly likely to have resolution of their VUR as well. Nonetheless, we cannot be certain of this and it is possible that, had all patients undergone subsequent cystography on a systematic basis, we would have observed a lower rate of VUR resolution. Finally, the power in a time-to-event analysis is determined by the number of events observed, not the number of subjects in a study. Although this series is large by the standards of the literature, the small numbers of patients with the outcomes of interest limit our ability to detect associations.

CONCLUSIONS

In our cohort, most of the persistent VUR after reimplantation was low-grade, and resolved spontaneously in most patients. Few patients with persistent VUR had UTI's or required additional anti-reflux procedures. Persistent VUR after ureteral reimplantation is uncommon and can be managed non-operatively with good long-term clinical outcomes.

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Key of Definitions for Abbreviations

VUR	vesicoureteral reflux
IQR	interquartile range
UTI	urinary tract infection
RNC	radionuclide cystogram
DES	dysfunctional elimination syndrome
IRS	International Reflux Study
DHA	dextranomer/hyaluronic acid

Figure 1.
Probability of Persistent VUR (Grade ≥ 1) among Patients with VUR (Grade ≥ 1) on Initial Postoperative Cystogram

Figure 2.
Probability of Persistent VUR (Grade ≥ 2) among Patients with VUR (Grade ≥ 2) on Initial Postoperative Cystogram

Table 1

Characteristics of patients with persistent VUR after reimplantation

	Persistent VUR (%)
<i>Median age at surgery (years)</i>	
	1.9 [0.8–5.1]
<i>Gender</i>	
Male	22 (37.3%)
Female	37 (62.7%)
<i>Race/Ethnicity</i>	
White/Caucasian	39 (90.7%)
African-American	1 (2.3%)
Asian	1 (2.3%)
Hispanic	2 (4.7%)
<i>Initial presentation</i>	
UTI	37 (63.8%)
Prenatal hydronephrosis	16 (27.6%)
Sibling screen/incidental diagnosis/other	5 (8.6%)
<i>Dysfunctional elimination syndrome (of those >30 months of age)</i>	
Yes	4 (26.7%)
<i>No</i>	11 (73.3%)
<i>Preoperative VUR grade (by patient)</i>	
Grade 2/3	25 (42.4%)
Grade 3/3	34 (57.6%)
<i>Laterality</i>	
Unilateral	24 (40.7%)
Bilateral	34 (59.3%)
<i>Pre-operative Breakthrough UTI</i>	
Yes	23 (39.0%)
No	36 (61.0%)
<i>Surgical technique</i>	
Extravesical	9 (15.3%)
Glenn-Anderson	2 (3.4%)
Politano-Leadbetter	18 (30.5%)
Cohen cross-trigonal	30 (50.9%)
<i>Ureteral tapering (by patient)</i>	
No	40 (69.5%)
Yes	18 (30.5%)
<i>System(s)reimplanted (by patient)</i>	
Unilateral Single	17 (22.8%)

	Persistent VUR (%)
Bilateral Single	26 (44.1%)
Unilateral Duplex	7 (11.9%)
Bilateral Duplex	4 (6.8%)
One Duplex, One Single	5 (8.5%)
<i>Postoperative febrile UTI</i>	
No	52 (88.1%)
Yes	7 (11.9%)

* Fisher's exact test

** Chi-square trend test

[†] Wilcoxon rank-sum test

Table 2

Preoperative VUR Grade (rows) vs. Postoperative VUR Grade (columns)

		Postoperative VUR		
		Grade 1/3	Grade 2/3	Grade 3/3
Postoperative VUR	Grade 1/3	0	0	0
	Grade 2/3	9	12	4
	Grade 3/3	10	17	7